1985

Endocyclic Nucleophilic Methyl Transfer

Michael Jerome Mcgarrity

CANADIAN THESES ON MICROFICHE

I.S.B.N.

THESES CANADIENNES SUR MICROFICHE

National Library of Canada
Collections Development Branch

Canadian Theses on
Microfiche Service

Ottawa, Canada
K1A 0N4

Bibliothèque nationale du Canada
Direction du développement des collections

Service des thèses canadiennes
sur microfiche

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us a poor photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de mauvaise qualité.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

ENDOCYCLIC NUCLEOPHILIC METHYL TRANSFER

by

Michael Jerome McGarrity

Department of Chemistry

Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

Faculty of Graduate Studies
The University of Western Ontario
London, Ontario
August, 1984

Volume 1

ABSTRACT

This thesis describes the synthesis of three methyl ω-(dimethylamino)alkanesulfonates and the experiments used to determine the mechanism of their rearrangements to the corresponding ω-(trimethylammonio)alkanesulfonates. Since existence of an intramolecular pathway would represent the first example of an endocyclic methyl transfer, kinetic and double-label crossing experiments were used to determine the molecularity of these rearrangements. Methyl 4-(dimethylamino)butane-1-sulfonate, at concentrations ranging from 0.2 M to 2.0×10^{-4} M in chloroform, was found to form 4-(trimethylammonio)butane-1-sulfonate exclusively via an intermolecular pathway and the results are consistent with an effective molarity of less than 3×10^{-5} M for the endocyclic process. Similarly, the formation of 2-(trimethylammoniomethyl)phenylmethanesulfonate from methyl 2-(dimethylaminiomethyl)phenylmethanesulfonate in benzene with initial ester concentrations ranging from 0.2 M to 5×10^{-4} M was found to occur via intermolecular methyl transfer and these results imply that the effective molarity for the endocyclic process is less than 2×10^{-5} M. For the rearrangement of methyl 2-[2-(dimethylaminomethyl)phenyl]ethanesulfonate to 2-[2-(trimethylammoniomethyl)phenyl]ethanesulfonate in benzene, the crossing experiments provided conclusive proof for the existence of both intramolecular and intermolecular pathways. From the dependence of the intra to intermolecular product ratio on the initial ester concentration, an effec-

tive molarity of 2 x 10^{-3} M was deduced for the intramolecular process. An example of an endocyclic methyl transfer *via* a nine-membered cyclic transition state has, therefore, been shown. Collectively, the results imply that concerted nucleophilic methyl transfer transition states show a marked preference for a linear orientation of the nucleophile, the methyl carbon and the nucleofuge.

Model kinetic studies and an ^{18}O-labelling experiment which made use of an ^{18}O isotope effect on ^{13}C NMR chemical shifts showed that the intermolecular pathway for the rearrangements is a two step process. An intermolecular methyl transfer between two molecules of the amino ester gives an ion pair which then annihilates *via* N-methylation to give two molecules of the betaine.

ACKNOWLEDGEMENTS

I wish to thank Dr. S.M. Loosmore, Dr. J.D. Lock, Dr. J.H. Hillhouse, Dr. M. Aslam, Mr. G.T. Tsang and all other members of our research group for their advice and encouragement. I particularly thank Dr. J.F. King for his support and guidance throughout the course of these studies and Miss D.L. Walker for word processing this thesis.

TABLE OF CONTENTS

VOLUME I

VOLUME II

TABLE OF CONTENTS

LIST OF TABLES

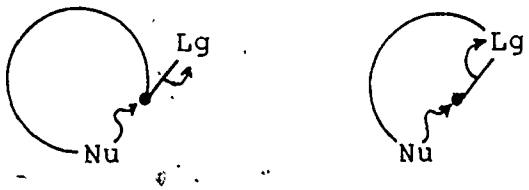
LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES

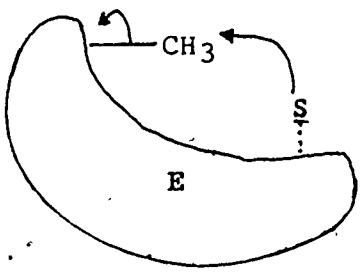
I. General Introduction:

Eschenmoser[1] has defined two different types of intramolecular S_N2 - type displacements. The commonly encountered mode, the exocyclic displacement, is characterized by the expulsion of the leaving group (Lg) from the molecule.



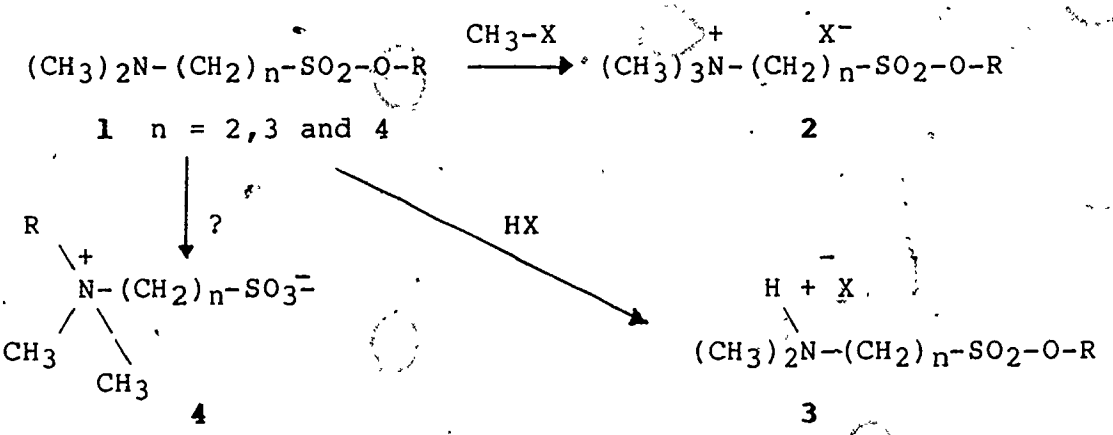
exocyclic endocyclic

In endocyclic displacement, the leaving group remains joined to the nucleophile (Nu) by an array of covalent bonds. The literature contains no adequately proven example of an endocyclic methyl transfer by an S_N2 - type process. Yet, this is a reaction of biochemical importance since it parallels enzyme methylations.[2] That is, enzymic methylation of a substrate (S) involves a transition state in which the enzyme (E), the substrate and the methyl group undergoing displacement are in a cyclic array. A simple example of an endocyclic methyl transfer might then be of value as an enzyme model.

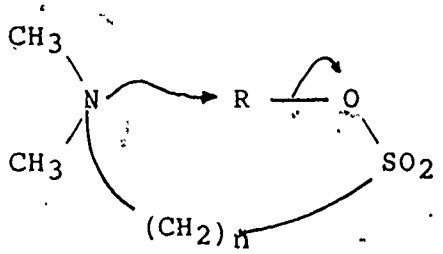


The goal of the studies reported in this thesis was to find the first proved example of an endocyclic nucleophilic methyl transfer.

A new class of compounds, alkyl ω-(dimethylamino)-alkanesulfonates (**1**), were recently prepared in this laboratory and were used as intermediates in the conversion of alcohols to alkyl ω-(trimethylammonio)alkanesulfonate esters, (**2**, "betylates") or to alkyl ω-(dimethylammonio)-alkanesulfonate esters, (**3**, "norbetylates").[3] Since the amino esters, **1**,



contain both an electrophilic alkyl group (R) and a nucleophilic nitrogen, it seemed reasonable to anticipate that, in absence of acids or methylating agents, they would rearrange to the corresponding sulfobetaines, **4**. The simplest mechanism that comes to mind for this rearrangement is, of course, an endocyclic nucleophilic displacement.



Experience obtained during the study of betylate chemistry[3] suggested that methyl ω-(dimethylamino)alkanesulfonates and their corresponding sulfobetaine products would have physical properties which would make them ideally suited for the attainment of the project's goal. The esters would be soluble in nonpolar aprotic solvents and hence complications due to competitive solvolysis would be absent. The high solubility of the betaines in water would simplify product isolation while their low solubility in nonpolar aprotic solvents would be expected to minimize further reactions of the products. The esters could be protected by converting them to the corresponding "norbetylates" by simply treating them with acid. That is, other "norbetylates" with feebly nucleophilic counter ions such as perchlorate and trifluoromethanesulfonate have been found to have reasonable shelf stability. A simple deprotonation with aqueous base would be used to generate solutions of the esters in nonpolar solvents. These solutions would be free of other reagents.

Further discussion requires a brief summary of the pertinent aspects of the physical organic chemistry of reactions involving cyclic transition states. The observed dependence of the ease of ring formation on the ring size was rationalized initially by Prelog[4]. He suggested that this observed dependence was the result of two competing parameters: the strain of the ring being formed (an enthalpic effect) and the probability of encounter of the

terminal functional groups (an entropic effect). The strain in cycloalkanes, as obtained from their heats of combustion, was used to approximate the strain term. The probability of encounter was thought to be highest in three-membered ring formations, to drop off sharply through the common (5-, 6- and 7- membered) ring sizes, to gradually level off through the medium (8-, 9-, 10- and 11-membered) ring sizes and finally to decline very gradually for large ring formations. This simple model indicates that for small rings, the entropic effect will compensate for the large strain inherent in these rings and the closures will not be unusually difficult. Formation of the common rings, for which both terms are favorable, will be facile. Medium ring formation will be most difficult since both terms are unfavourable. Finally, large ring formation will be retarded by the low probability of encounter but aided by the absence of strain. A major deficiency in this model is that it compares transition state ring strain directly with the ring strain of cycloalkanes and in doing so, ignores the structural variations in the former encountered in different reaction mechanisms.

Clearly, a precise index of the ease of ring closure was required. Ruggli[5], with his infinite dilution principle, demonstrated that cylizations are favoured by low substrate concentrations because, under these conditions, the first order cyclization competes more favourably with the second order bimolecular reactions. This led chemists to consider

the relative ease of cyclic reactions in terms of a parameter called on effective molarity (**EM**).[6,7]

$$\mathbf{EM} = \frac{k_1}{k_2} \qquad (1)$$

The **EM** is, by definition, the first order rate constant (k_1) of an intramolecular reaction divided by the second order rate constant (k_2) for the corresponding intermolecular reaction. In practice, the second order rate constant is often obtained from the reaction of suitable model compounds. The term **EM** is used since the units of the parameter are mol L^{-1}.[†] The **EM** is, at identical concentrations of the cyclization substrate and of one of the compounds in the model reaction, the concentration of the second model compound required to achieve equal rates for the model reaction and the cyclization. The parameter corrects the rates of diverse intramolecular reactions for differences in the bimolecular reactivity of the terminal functional groups and thereby provides a common scale for comparing the relative ease of different intramolecular reactions.

Illuminati and Mandolini[6] have examined the dependence of ring size on **EM**'s (**EM** profiles) for a variety of reactions. Their data, along with a list of the surveyed reactions, are shown Figure 1. The most noteworthy feature

---

[†]The same units are obtained when the constant for an intramolecular equilibrium is divided by the constant for an intermolecular equilibrium. An **EM** derived in this manner is referred to as a thermodynamic **EM** whereas one derived from rate constants is a kinetic **EM**. In this thesis, the term **EM** is restricted to kinetic **EM**'s.

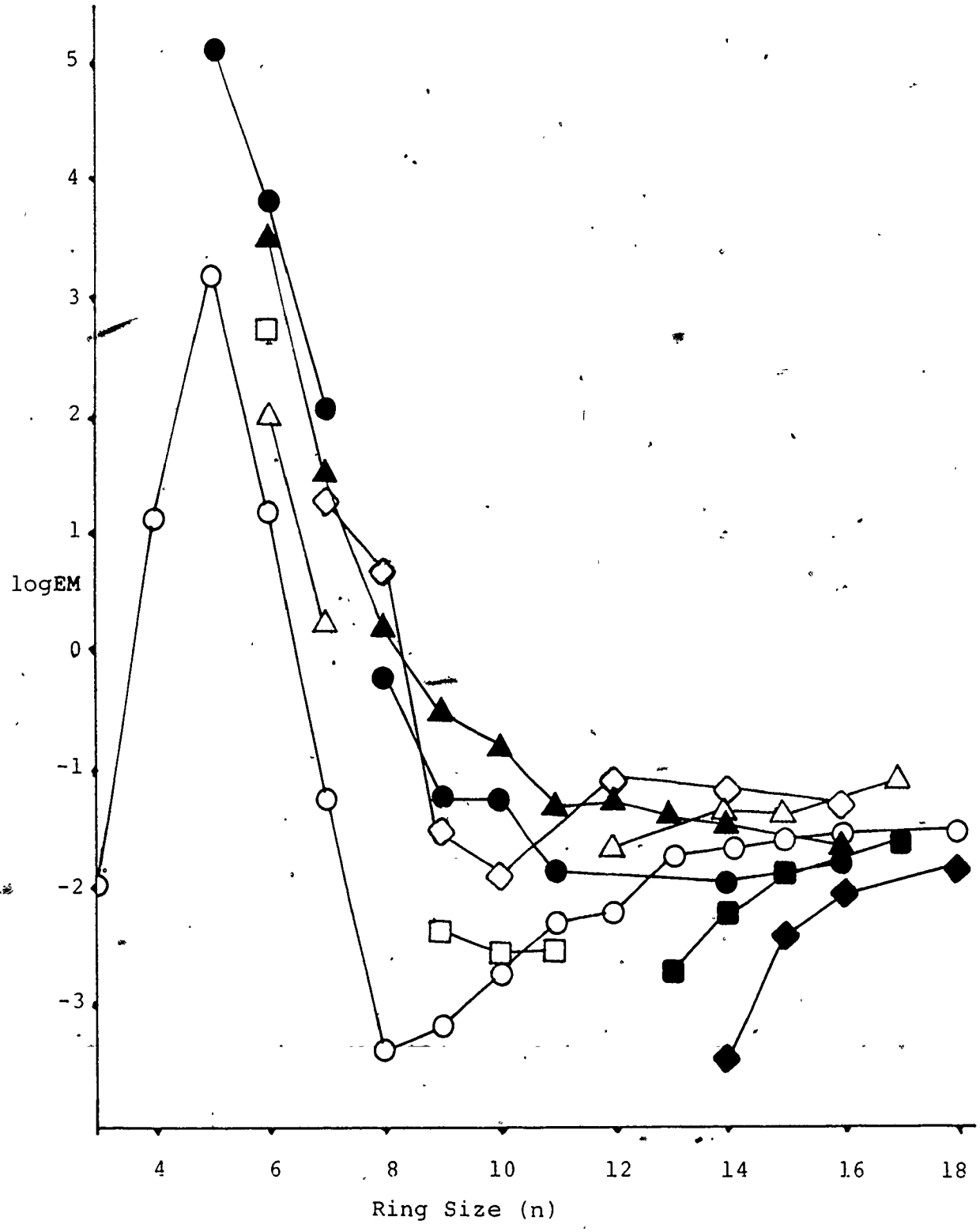


Figure 1: Effective Molarity Profiles

Figure 1 (con't)

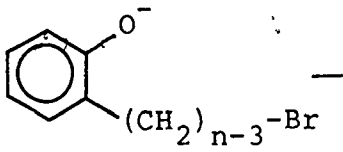
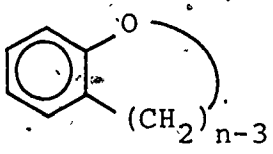
Legend

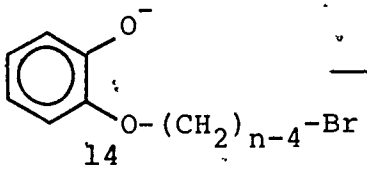
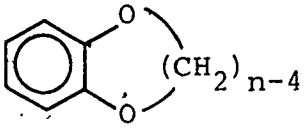
○ $Br-(CH_2)_{n-2}-CO_2^-$ (5) ⟶ $(CH_2)_{n-2}$ lactone (6) (ref. 8)

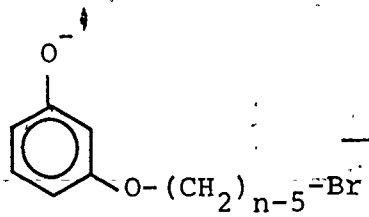
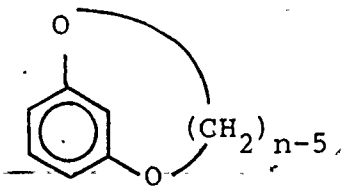
△ $Br-(CH_2)_{n-1}-NH_2$ (7) ⟶ $(CH_2)_{n-1}NH$ (8) (ref. 9,10)

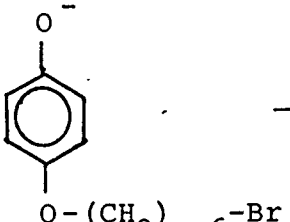
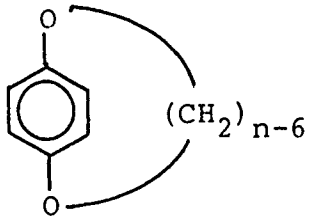
□ $Br-(CH_2)_{n-3}-C(CH_3)_2-CO_2^-$ (9) ⟶ $(CH_2)_{n-3}$ lactone with $C(CH_3)_2$ (10) (ref.6,11)

◇ $\dot{N}^-(CH_2)_{n-2}-N$ (11) ⟷ $N-(CH_2)_{n-2}-\dot{N}^-$ (11) (ref. 12)+

●  (12) ⟶  (13) (ref. 10)

▲  (14) ⟶  (15) (ref. 10)

■  (16) ⟶  (17) (ref. 13)

◆  (18) ⟶  (19) (ref. 13)

+ N= α-naphthyl

of this collection of **EM** profiles is that they converge to a common **EM** of approximately Ø.Ø5 M when the ring size exceeds 2Ø atoms. For this ring size and beyond, the profiles have lost all dependence on either the reaction mechanism or on the structure of the hydrocarbon chain which links the reacting functional groups and the **EM**'s are dependent only on the loss of conformational entropy associated with the formation of the large rings. In the medium and common ring region, the **EM** profiles show a marked dependence on both the reaction mechahism and on the structure of the hydrocarbon chain. By holding one of these variables constant, the effect on the **EM** profile of modifications in the other may be examined. For example, the set of reactions which involve exocyclic nucleophilic substitutions has been used to examine the effects of changes in the hydrocarbon chain on the **EM** profiles characteristic of this mechanism. The effect of replacing an ethylene with an ortho-fused benzene ring is observed through comparison of the profile for the lactonization of **5** to form **6** with that of the formation of the ortho-benz-fused cyclic ether (**13**) from **12**. This structural change results in **EM** enhancement in the common and medium ring regions; the effect being more pronounced in the latter where the **EM** minima seen in the medium ring region for aliphatic substrates has been virtually eliminated. This is in agreement with the synthetic experiences recorded by Ziegler in 1937.[14] The effect of positional changes in the site of benz-fusion is obtained by

comparison of the **EM** profile for the formation of the ortho--benz-fused cyclic diethers (**14** to **15**), with those of the meta- and para-benz-fused analogues (**16** to **17** and **18** to **19** respectively). In contrast to the facile cyclization of the ortho substituted compounds, the meta and para substituted compounds cyclize only in the large ring region and, even there, do so with some difficulty. The downward curvature seen in their **EM** profiles as the ring size is reduced is characteristic of reactions in which strain increases with decreasing ring size. The incorporation of these rigid moieties in the cyclic transition states has produced limiting geometrical constraints. As the ring sizes are reduced, severe distortions of the bond lengths and bond angles in the cyclic arrays are required to span the rigid moieties. The onset of this limitation is rapid with respect to reduction in the ring size and hence, the **EM** profiles plunge.

The **EM** profiles for the exocyclic displacements illustrate two other structural effects. The replacement of a methylene by an oxygen (**12** to **13** versus **14** to **15**) results in **EM** enhancement in the medium ring region. This is attributable to reductions in the transannular repulsions normally encountered in medium ring cyclizations. The incorporation of a gem - dimethyl in an aliphatic backbone results in **EM** enhancements in common ring formations. (compare **5** to **6** with **9** to **10**). The effect gradually decreases with increasing ring size and becomes neglibible in the nine membered cyclic transition states.

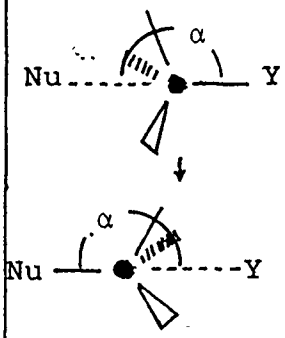
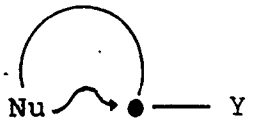
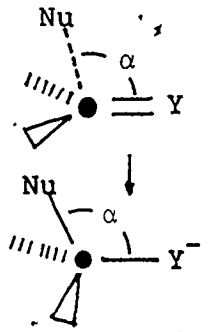
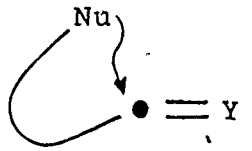
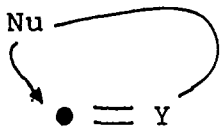
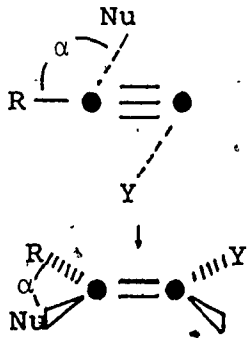
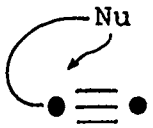
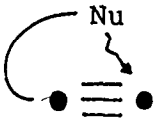
For different cyclic reactions which have in common the same hydrocarbon chains linking the reacting functional groups, differences in the **EM** profiles are the result of differences in the stereochemical requirements of the reaction mechanisms. The reactions of **5** to form **6** and of **7** to form **8** are both exocyclic nucleophilic displacements in which straight hydrocarbons chains link the terminal functional groups. They, therefore, have very similar **EM** profiles.† Comparison of the **EM** profile for **5** to **6** with that of the degenerate election transfer to **11** shows a pronounced difference. That the large minima in the medium ring region of the former is substantially reduced in the latter implies that the stereochemical requirements for election transfer, relative to those for exocyclic displacement, induce less strain.

The **EM**'s of small and common ring sized cyclic reactions are profoundly dependent on the reaction center's stereochemical requirements. Baldwin[15] has devised a set of "Rules for Ring Closure" which are useful for predicting the relative ease of these reactions. These rules are summarized in Table 1. Briefly, a reaction is classified under the following parameters: the number of atoms in the transition state cyclic array, the location of the receptor (**Y**) of the electron pair from the bond being broken (endo for

†The slightly lower values obtained for the common and medium ring lactonizations may be rationalized in terms of the products requiring the less favourable cisoid ester configuration. This, of course, favours the bimolecular reaction and hence reduces the **EM**'s.

Table 1

Baldwin's Rules For Ring Closure

Reaction Center Geometry	Stereochemical Requirements (Subtended Angle , α)	Exo Rules	Endo Rules
tet	 α = 180	 3- to 7-exo-tet favoured	 5- & 6-endo-tet disfavoured
trig	 α = 109°	 3 to 7-exo-trig favoured	 3 to 5-endo-trig disfavoured 6 & 7-endo-trig favoured
dig	 α = 120°	 3 & 4-exo-dig disfavoured 5 to 7-exo-dig favoured	 3 to 7-endo-dig favoured

endocyclic, meaning that **Y** is a member of the cyclic array or exo for exocyclic, meaning that **Y** is not a member of the cyclic array) and the geometry of the reacting center (tet for tetrahedral, trig for trigonal or dig for digonal). The rules then state whether the reaction in question is "favoured" or "disfavoured". The rationale upon which these rules are based is that for each reacting center geometry there is a subtended angle, α , between the nucleophile (**Nu**) and **Y** (or for digonal, between **Nu** and the substituent's single bond to the carbon undergoing attack) which is maintained throughout the reaction. If the cyclic reaction in question can meet the stereochemical requirements imposed by α without resorting to severe bond angle or bond length distortions then the reaction is "favoured". If not, the reaction is "disfavoured". The rules are also applicable to electrophilic and and radical addition reactions involving cyclic transition states. A limiting requirement is that **Nu**, **Y** and the reaction center must all be first row elements since departure from these will result in significant changes in the polarizability of the atoms involved as well as differences in their bond angles and bond lengths.

Most pertinent to this thesis are the rules governing endo- and exo-tet processes. While 3- to 7-exo-tet's are favoured, 5- and 6-endo-tet's are disfavoured. These rules are a consequence of the stereochemical requirements for concerted nucleophilic displacements.

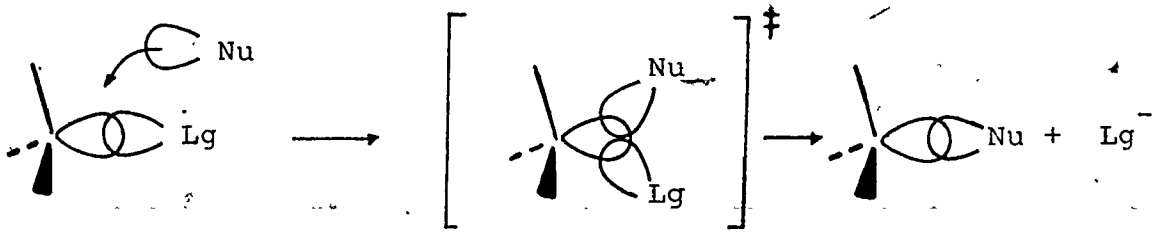
The accepted mechanism for S_N2 reactions is that ori-

ginally proposed by Hughes and Ingold[16] as a means of accounting both for the observed first order dependence of the reactions on both the nucleophile and substrate concentrations and for the observed Walden inversion of the reacting carbons. The reaction is initiated by the attack of

the nucleophile's electron pair on the back lobe of the carbon's sp^3 orbital which is involved in the carbon-leaving group bond. Formation of the bond to the nucleophile is simultaneous with breakage of the bond to the leaving group. The transition state has a trigonal bipyramidal geometry in which the three nonreacting substituents are in the equatorial plane bonded to the central carbon through its sp^2 hybridized orbitals. The incoming nucleophile and the departing leaving group are in the apical positions and are partially bonded to the central carbon's p orbital. A 180° angle between the nucleophile and the leaving group is then considered to be optimal throughout the reaction since it maximizes orbital overlap and minimizes steric repulsions between the apical and equatorial substituents. There is, however, no direct experimental evidence for a 180° trajectory in this mechanism. Nonlinear transition states have

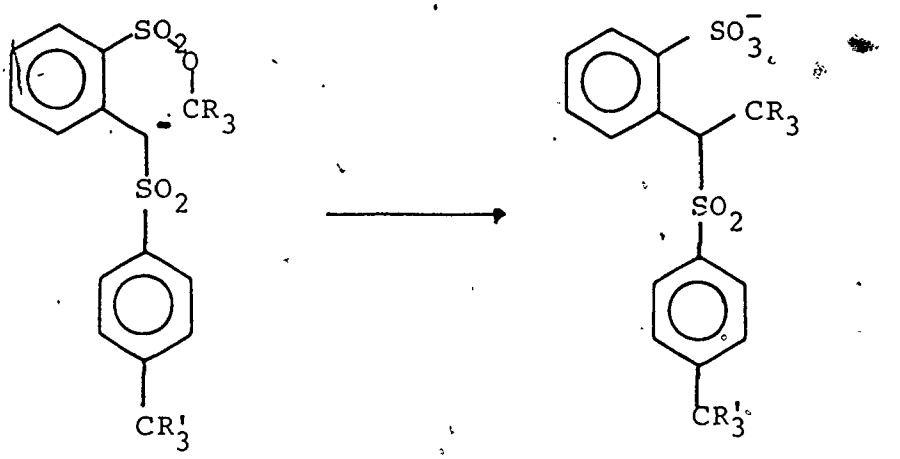
been invoked in force field[17,18] calculations of the minimum energy transition state structures for halide ion displacements on ethyl, n-propyl, isobutyl and neopentyl bromides. Early calculations by de la Mare, et al[17]. suggested a 175° Br-C-Br angle in the transition state structure for the displacement of neopentyl bromide by bromide. Recently, more refined calculations by De Tar, et al[18], have indicated a 143° angle in this transition state structure. De Tar[19] has also calculated the transition state structures for the common ring forming exocyclic nucleophilic displacements of several ω-bromoalkylamines. In these, Br-C-N angles as small as 150° have been invoked. Likewise, Menger's Molecular Orbital calculated transition state structures for 3-exo-tet reactions have indicated nonlinear Nu-C-Lg orientations.[20]

A second mechanism conceivable for S_N2 reactions is the front-face displacement. This mechanism is characterized



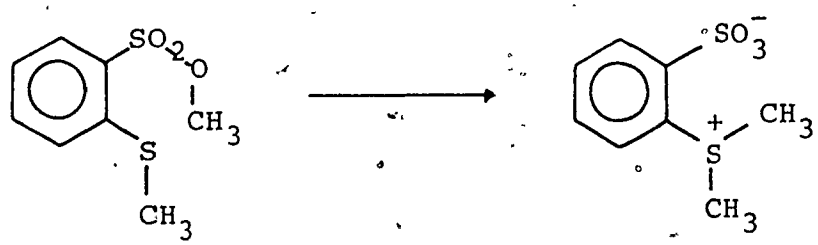
by the attack of the nucleophile on the lobe of the carbon sp^3 orbital which is overlapped with the leaving group orbital. Such a displacement would result in retention of configuration at the reaction center.

That no such displacements on carbon have been observed indicates that this transition state is of higher energy than that of the backside $\underline{S}_N2$ displacement. Eschenmoser, et al[1], reasoned that if this energy difference is small, then selective supression of the backside displacement should result in a front-face $\underline{S}_N2$. This supression is realized in an intramolecular methylation involving a six membered cyclic transition state. For this type of reaction, space filling molecular models indicate that the backside of the methyl group is sterically inaccessible. Eschenmoser examined two such methylations.



20a:R,R'=^{1}H
b:R,R'=^{2}H

21a:R,R'=^{1}H
b:R=^{1}H,R'=^{2}H and R=^{2}H,R'=^{1}H
c:R,R'=^{2}H

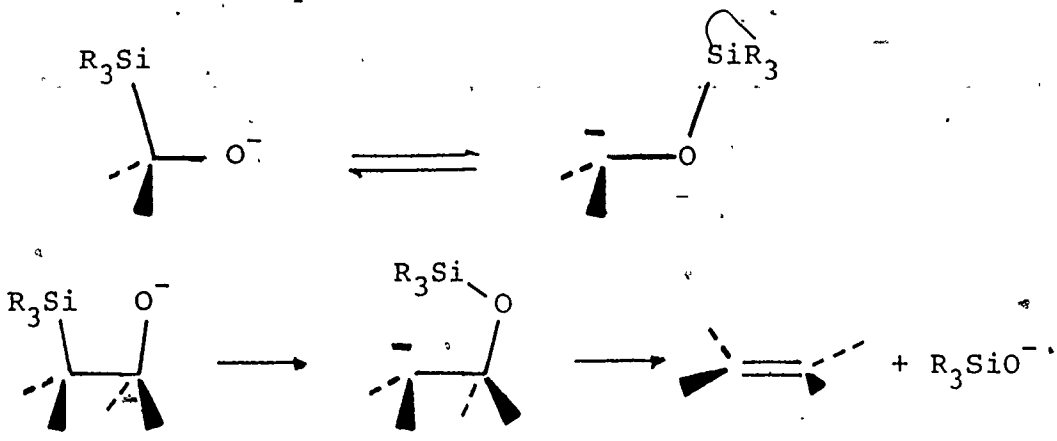


22

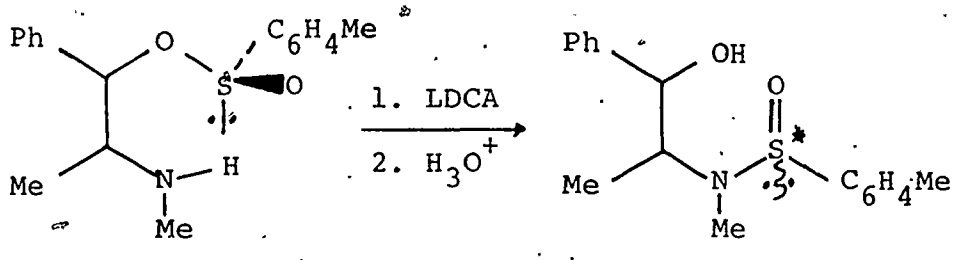
23

Both reactions gave the depicted products readily. To test for intramolecularity in the first reaction, double-label crossing experiments were used. An equimolar mixture of **20a** and **20b** gave, even with initial concentration as low as 5 x 10^{-3} M, exclusively the intermolecular product distribution; a 1:2:1 mixture of **21a**, **21b** and **21c**. Similarly, kinetic studies of the reaction of **22** to form **23** indicated a strict second order rate law. Again, this is indicative of intermolecular methyl transfer. They concluded that S_N2 methylations show a profound preference for backside displacement.

It should be noted in passing that endocyclic nucleophilic displacements have been observed with certain second row element reaction centers. Front-face nucleophilic displacements are well documented for tetravalent silicon derivatives[21]. Some examples, taken from Brook's recent review[22] of organosilicon rearrangements, are shown below. All of these silicon migrations are intramolecular, proceed with retention of configuration on silicon, and are considered to be front-face nucleophilic substitutions.



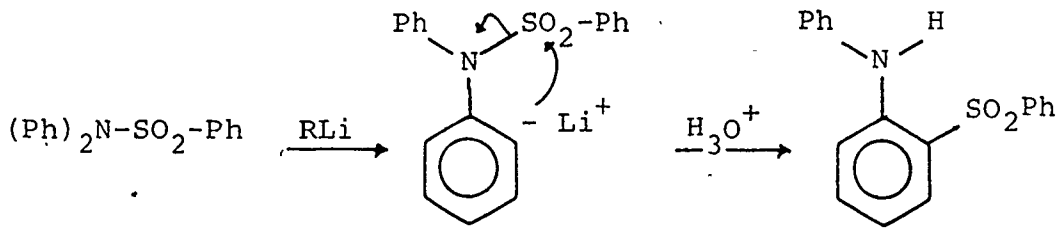
Similarly, retentive bimolecular displacement on sulfinyl sulfur has been documented.[23-27] Wudl and Lee[28] have recently demonstrated an endocyclic nucleophilic sulfinyl transfer. The optically pure R-sulfinate ester (**24**), when treated with lithium dicyclohexylamide, was found to give the sulfinamide (**25**). At high initial concentrations of **24**, the major product was the S isomer, the formation of which is indicative of inversion of the sulfinyl configuration. Low substrate concentrations resulted in the formation of the retention product, **25** R. This is indicative of a front-face intramolecular migration. These results are in agreement with competitive second order bimolecular and first order endocyclic sulfinyl transfers.



24-R

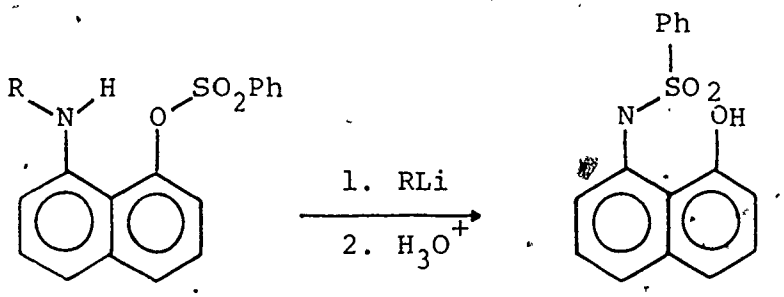
25- R and/or -S

Endocyclic displacement on sulfonyl sulfur has been used, in the absence of any examples of bimolecular front-face displacements, to demonstrate the ability of this reaction center to undergo front-face displacements. Hellwinkel and Supp[29] have shown that the sulfonamide, **26**, when treated with an alkyl lithium reagent, undergoes an intramolecular displacement to give the sulfone, **27**.



26 27

An analogous sulfonyl migration from oxygen in **28** to nitrogen in **29** has been reported by Anderson, et al.[30]



28 29

These endocyclic displacements clearly show the feasibility of front-face displacement on sulfonyl sulfur. Collectively, these second row endocyclic displacements serve to verify Eschenmoser's hypothesis.[1] That is, if front-face displace-

ments transition states are close in energy to those of backside displacements; then the 6-endo-tet should be experimentally observable.

The difficulty of Eschenmoser's 6-endo-tet methyl transfers stands in stark contrast to the ease 6-exo-tet displacements for which **EM**'s ranging from 1Ø to 5 x $1Ø^9$ are known.[7] This contrast is largely the result of a difference between these mechanisms with respect the angle, θ , through which the cyclic arrays are joined in the transition states to the reaction centers. For exo-tet reactions, θ is approxi-

mately 9Ø° and since this angle is only 2Ø° less than that normally found between the substituents on a tetrahedral carbon, the strain encountered in these common ring forming reactions parallels the minimal strain found in common ring cycloalkanes. Hence, these reactions are "favoured". In endo-tet reactions, however, θ is approximately 18Ø°. The resulting linear array of the nucleophile, the reaction center and the leaving group is also longer than two carbon--carbon single bonds. The rest of the cyclic array must then span this linear moiety. In common ring size transition

states, excessive distortions of the bond angles and bond lengths in the spanning array are required. The resulting strain then makes these reactions "disfavoured".

Clearly, if an endocyclic methyl transfer is to be observed, the strain in the spanning moiety of its cyclic transition state must be reduced. One approach is to increase the number of atoms in the cyclic array. The effect of ring size on the strain in cycloalkynes, which have four collinear atoms, should serve as a useful means of accessing the validity of this approach. Table 2 lists the partial heats of hydrogenation of several cycloalkynes. The triple

Table 2

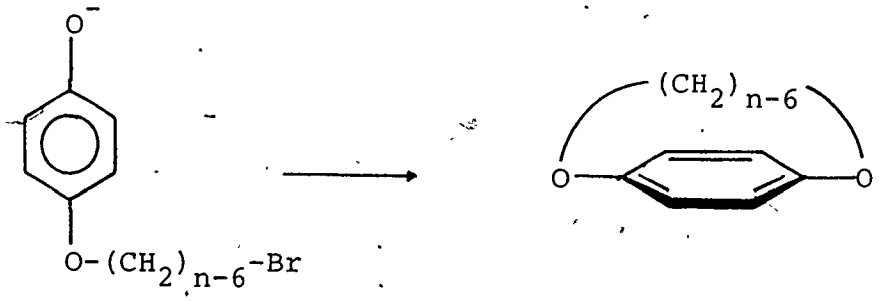
Partial Heats of Hydrogenation of Cycloalkynes[31]

Alkyne	Hydrogenation Product	$-\Delta H$ (kcal mol^{-1})
cyclooctyne	cis - cyclooctene	45.5
cyclononyne	cis - cyclononene	38.3
cyclodecyne	cis - cyclodecene	35.8
cyclododecyne	cis - cyclododecene	35.4
4 - octyne	cis - 4 - octene	35.4

bond induced strain in these compounds is deduced by comparison of their partial heats of hydrogenation with that of 4-octyne.† These data show that ring strain is negligible in ten and larger than ten membered cycloalkynes. Cyclon-

†The use of partial heats of hydrogenation as a measure of ring strain is preferable to the use of the heats of full hydrogenation since the series of cis - cycloalkenes resulting from the former are more similar with respect to transannular repulsions than are the series of cycloalkanes derived from the latter.

onyne is somewhat strained (2.9 kcal mol^{-1}) while cyclooctyne, the smallest isolable cycloalkyne, is heavily strained (10.1 kcal mol^{-1}). The onset of ring strain induced by the collinearity required of the four atoms is very fast with respect to reduction in the ring size. Also, the previously mentioned **EM** profile for the formation of the para-benz-fused cyclic diethers, **18** from **17**, suggests that the above stated thermodynamic argument may be extended to kinetically derived **EM**'s. The hydroquinone segment of **18** has

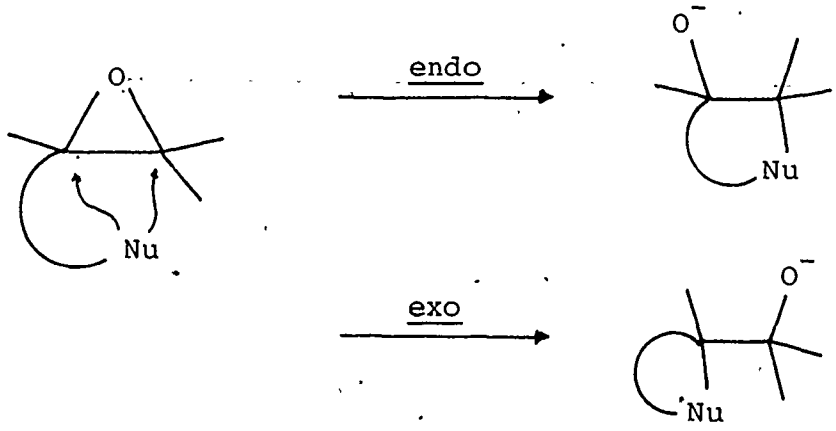


17 18

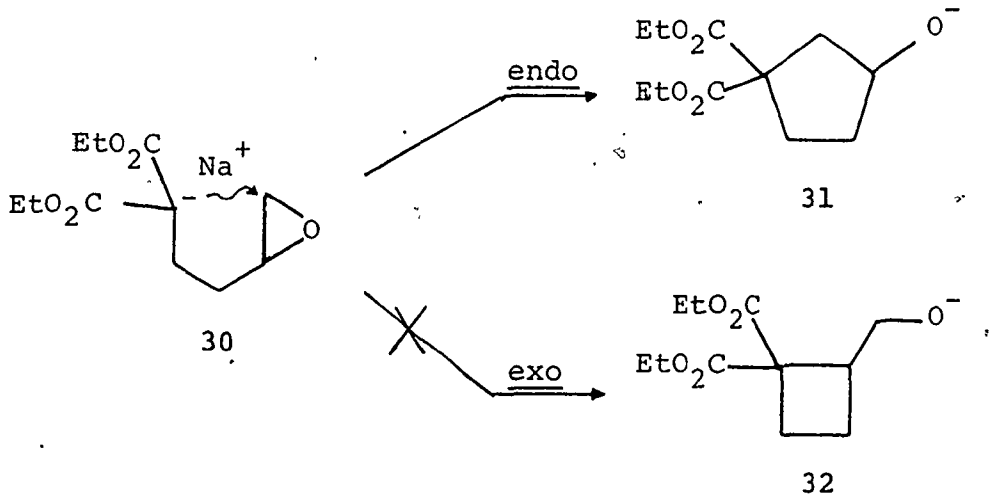
collinear phenyl-oxygen bonds and hence may be treated as a linear array. In this series, formation of the eighteen membered ring is strainless. As the ring size is reduced to the sixteen and fifteen membered homologues, however, increasing strain is encountered and the **EM** profile curves downward accordingly. It drops drastically for the smallest observable cyclization, the fourteen membered ring formation. A smiliar shape is anticipated for the endo-tet methyl transfer **EM** profile. That is, the smallest observable cyclic transition state should be considerably strained and

hence show a low **EM**. The strain induced by the collinearity of the three reacting atoms should disappear over the next two to four larger cyclic transition states and the **EM** profile should rise accordingly. When the transition state ring size reaches approximately twenty atoms, all strain should disappear and hence the previously discussed **EM** common to cyclization in this region (Ø.Ø5 M) should be observed.

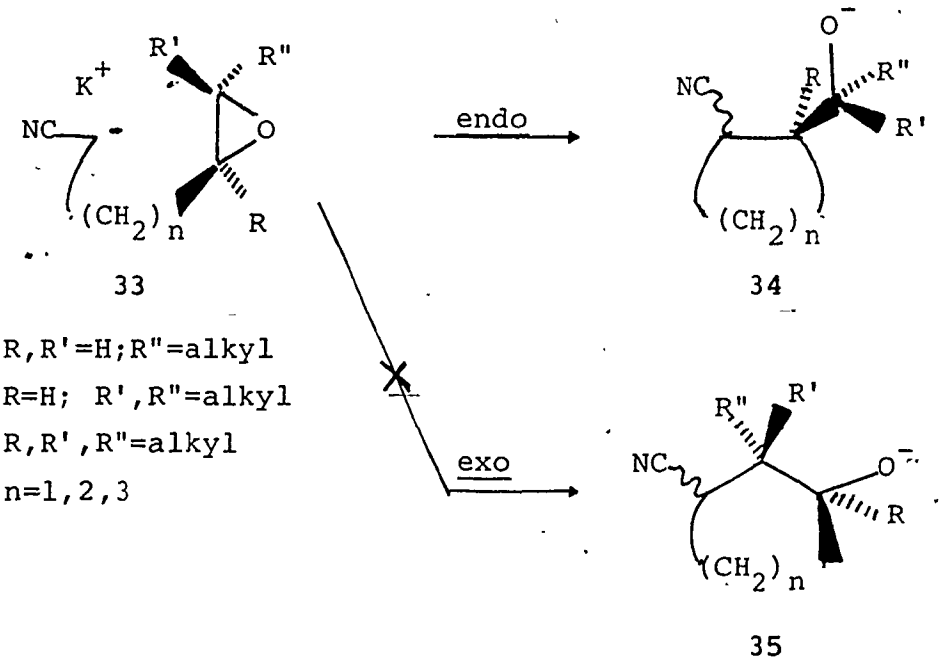
The most chemically interesting member of the series is the smallest one that is capable of overcoming the strain imposed by the collinearity constraint. Certainly, the strain in this transition state will be reduced if the energy required by a bent S_N2 transition state is only marginally higher than that required by a collinear one. That is, a bent S_N2 type transition state should facilitate endocyclic displacements in the most strained ring sizes. Cases in point are the known intramolecular cleavages of epoxides by carbanions. These reactions may occur by either exocyclic displacement in which the smaller ring is formed or by endocyclic displacement which forms the larger ring.



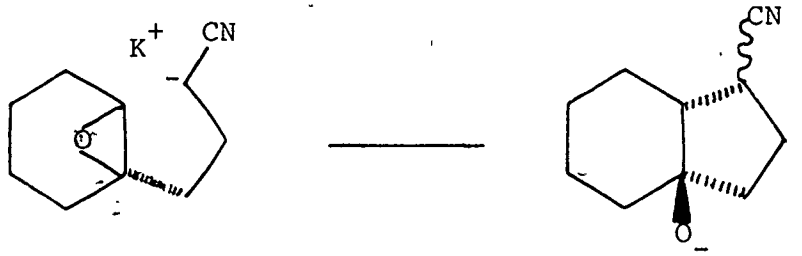
Cruickshank and Fishman reported the first example of an endocyclic epoxide cleavage.[32] The epoxymalonate anion, **30**, was found to give the five membered ring endocyclic displacement product, **31**, rather than the four membered ring exocyclic displacement product, **32.**



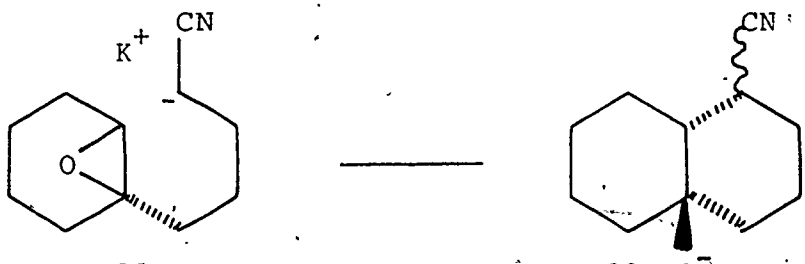
Stork, et al[33,34] examined the cyclization of a variety of epoxynitrile carbanions (**33**) and concluded, based on



the observed regiospecificity, that when both ends of the epoxide are equally substituted, the exocyclic mode which leads to the smaller ring (**34**) is dominant over the endocyclic mode which gives the larger ring (**35**). With the cyclohexylepoxynitrile carbanions, **36** and **38**, however, the endocyclic displacement products, **37** and **39**, are formed exclusively. Also, the second reaction (**38** to **39**) was found to be faster than the first (**36** to **37**). This suggests a

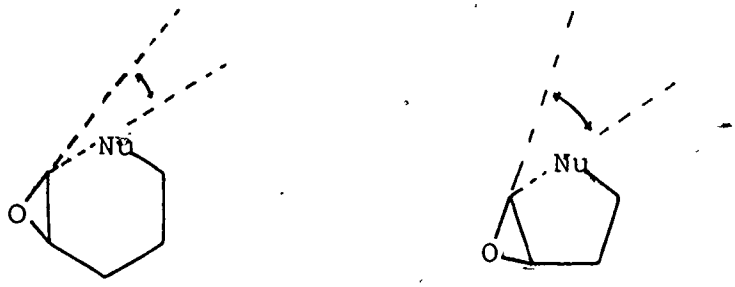


36 37

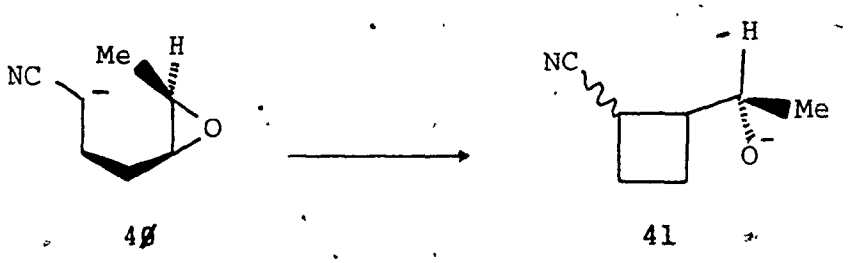


38 39

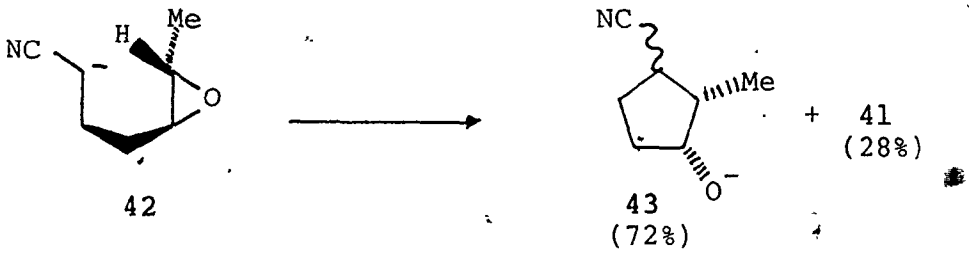
lower **EM** for the former since the bimolecular reactivity of both substrates would be expected to be comparable. Stork, et al[33,34], rationalized this difference in ring closure ease



as being the result of a closer approach to linearity in the three reacting atoms of the transition state in the larger ring forming cyclization. His conclusion that equally substituted epoxides favour exocyclic displacement has been challenged by Lallemand and Onanga[35] who have found that the stereochemistry of the epoxide substitution is important. The cis-epoxynitrile (**40**) gave exclusively the exo-product, **41**, while the trans-epoxynitrile, **42**, gave a mixture of the exo and endo products (**41** and **43**) with **43** being predominant.



40 **41**



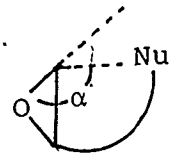
42 **43** (72%)

44 **45**

In agreement with their observation, Durst, et al[36], have reported an endocyclic displacement with an epoxysulfonyl carbanion (**44** to **45**).

Collectively, the epoxy carbanion small and common ring closure results indicate that there is a preference for the exocyclic mode but that this preference is not pronounced.

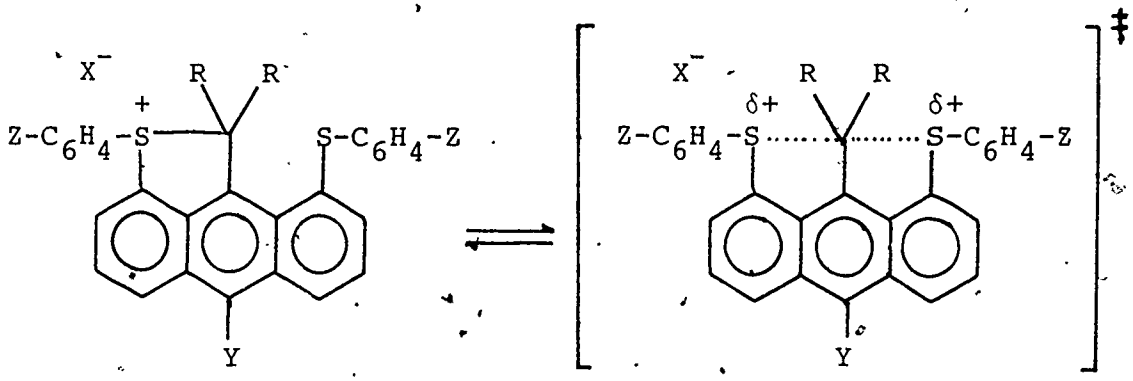
The ease of the 6 and 7-endo-tet epoxide displacements stands in stark contrast to the results obtained by Eschenmoser for 6-endo-tet methyl transfers.[1] Baldwin[15] has accounted for this by envoking a large deviation from linearity in the S_N2 type transition state structure for the epoxide cleavages. He speculates that the subtended angle, α, is somewhere between trigonal carbon's 120° and tetrahedral carbon's 180°. With such an α, the backside of



the carbon undergoing displacement is accessible to the nucleophile in common ring sized endocyclic transition states. Pertinent to this thesis is that endocyclic epoxide cleavages demonstrate that deviation from linearity in endocyclic nucleophilic displacement transition states relieves strain in the rest of the cyclic array..

Skeletal molecular models suggest that an 8-endo-tet

is the smallest endo-tet in which approximate collinearity of the three reacting atoms is attainable in the absence of undue strain in the hydrocarbon backbone. In addition to the previously discussed epoxide reactions, the literature contains two other examples of endocyclic displacements on carbon. That both are 8-endo-tet processes lends credibility to the above molecular model prediction. Martin and Basalay[37], in an attempt to prepare the first example of a hypervalent carbon compound, prepared a series of symmetrical sulfonium ions, **46**. These were found to undergo rapid



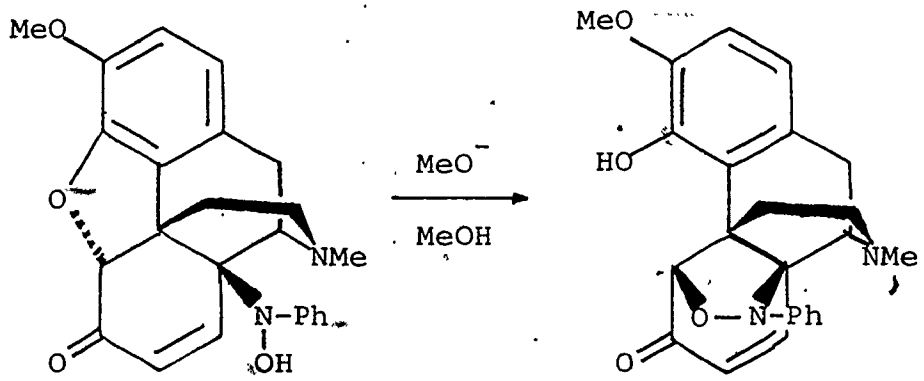
46 47

a: R=H ; b: R=Me
Y=H,Me,Ph
Z=3-Me, 4-Me, 4-t-Bu, 4-Ph
X=BF_4, CF_3CO_2, Cl

degenerate nucleophilic displacement on the benzylic carbon. NMR coalescene temperature determinations were used to monitor the rates of these displacements. After determining the Z and Y substituent effects, the effect of solvent polarity and unsuccessfully attempting to trap any intermediate

benzylic carbonium ion, the authors concluded that the reactions proceeded by a mechanism near the S_N2 extreme. They proposed an approximately 17° deviation from 180° for the S—C—S bond angle in the transition state structure (**47**) and concluded that this was reasonable since severe bond length or bond angle distortions were not required to achieve this 8-endo-tet transition state geometry.

A second 8-endo-tet has recently been reported by Kirby, et al.[38] They found that the hydroxylamine derivative of thebaine (**48**), when treated with methoxide, underwent a rapid endocyclic displacement to give the phenolic compound, **49**. The ability of this backbone to accommodate a collinear

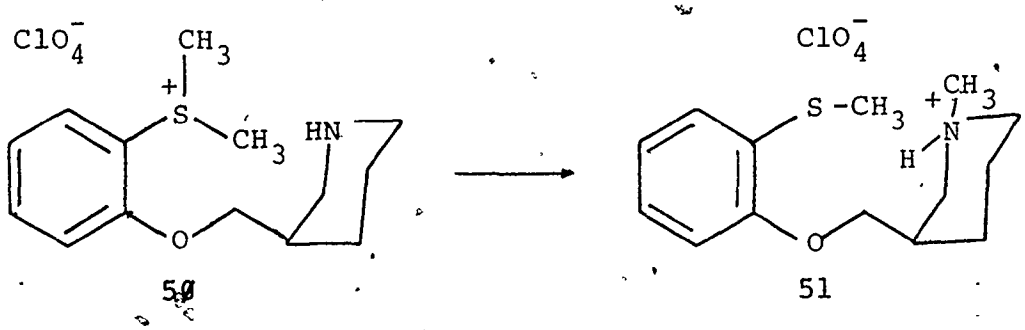


48 49

arrangement of the nucleophilic oxygen atom, the reaction center and the phenoxy oxygen was cited as being responsible for the ease of this displacement. It must be noted, however, that while the ability of α-carbonyl substituents to accelerate S_N2 reactions is well documented,[39-41] their

effect on the trajectory requirements of this mechanism is not.

There is one unsubstantiated claim in the literature of the observation of an endocyclic methyl transfer. Lok and Coward[42] have reported that the amino sulfonium salt, **50**, rearranges via a 9-endo-tet displacement to form the ammonio sulfide, **51**. U.V. kinetic data for this reaction

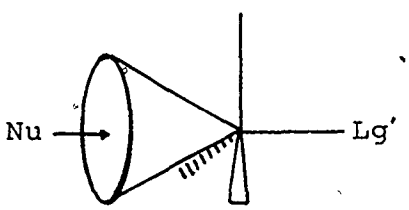


50 51

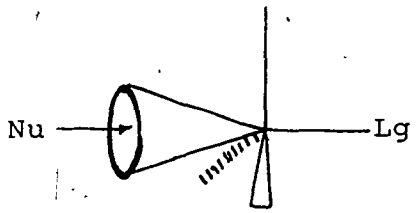
were obtained at low substrate concentrations ($\sim 10^{-4}$M) in aqueous dioxane. Both first and second order plots of these data were nonlinear. The authors assumed that this was the result of competing second order bimolecular and first order endocyclic displacements and, accordingly, assigned an **EM** of 2.9 a 10^{-3}M to the endocyclic methyl transfer. Unfortunately, no attempt was made to verify that, under the kinetic conditions, the product was 51. This result then does not constitute a proof for the first example of an endocyclic methyl transfer but rather, it should be regarded as being merely an encouraging preliminary experiment.

The two proven 8-endo-tets when coupled with the lack

of any analogous 7-endo-tets and with the molecular model considerations suggest that an eight membered cyclic transition state is the smallest one feasible for endocyclic methyl transfer. The **EM** of such a methyl transfer may provide some qualitative information regarding the strictness of the collinearity requirement for S_N2 on methyl groups. Using Menger's terminology,[20] a distinction might be drawn between a narrow and a wide trajectory cone for nucleophilic methyl displacements. That is, an **EM** lower than that normal-



"a wide trajectory cone"



"a narrow trajectory cone"

ly observed for eight membered cyclic transition states with compounds having similar hydrocarbon backbones would be indicative of a more strained transition state and hence imply a narrow trajectory cone. Conversely, a higher **EM** would be indicative of less transition state strain and would imply a wide trajectory cone.

With those arguments in mind, the methyl transfers of three different methyl ω-(dimethylamino)alkanesulfonates were examined using the same experimental approach as that employed by Eschenmoser.[1] At high initial substrate concentrations (~0.2 M), ^{1}H NMR kinetics were used to establish

the rate law. A first order rate law would imply an intramolecular endocyclic methyl transfer while a second order rate law would be indicative of a bimolecular pathway. Double-label crossing experiments were used at lower initial starting material concentrations. An equimolar mixture of the ($^2H_3$)methyl ω-(di($^2H_3$)methylamino)alkanesulfonate and its unlabelled analogue would give after endocyclic transfer, and equimolar mixture of the corresponding fully labelled $\underline{d}_9$- and unlabelled $\underline{d}_0$-(trimethylammonio)alkanesulfonates (or betaines). The intermolecular product would be an equimolar mixture of the $\underline{d}_0$-, $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-betaines. In the event of endocyclic methyl transfer at the ^1H NMR concentrations, the **EM** would be assigned by comparing the observed first order rate constant with a second order rate constant obtained from the reaction of a suitable pair of model compounds. In the event of clean second order ^1H NMR kinetics, crossing experiments using lower initial ester concentrations would be used. From these, an **EM** could be deduced from the dependence of the ratio of the intermolecular to intramolecular products on the initial ester concentrations. In the absence of any sign of the endocyclic reaction at the lowest initial ester concentration, a maximum value for the **EM** would be assigned based on the amount of endocyclic product capable of being disguised by the experimental error inherent in the product ratio determination.

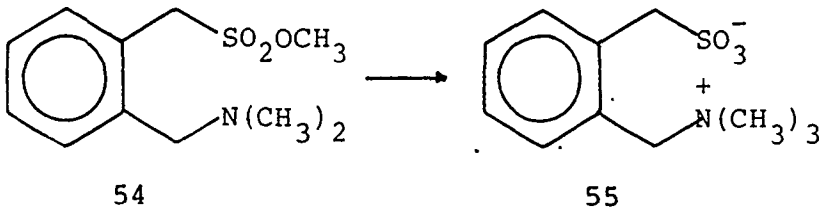
The first reaction examined was the methyl transfer of methyl 4-(dimethylamino)butanesulfonate (**52**) to form

52 53

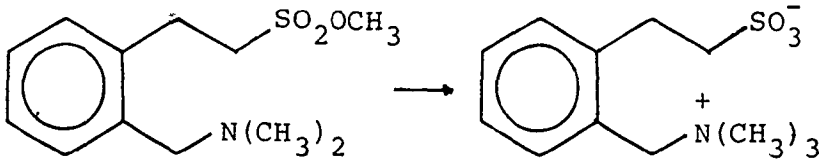
4-(trimethylammonio)butanesulfonate (**53**); potentially an 8-endo-tet process. This reaction was chosen simply because the synthetic precursors to **52** were the same as those of [4]-betylates and hence were readily available. However, as a result of the paucity of **EM** data for straight chain linked eight membered cyclic transition state reactions, the significance of the results would be difficult to determine.

More meaningful results could be obtained with ortho-benz-fused substrates. For other reactions involving substrates with this type of backbone, medium ring strain largely disappears and hence more **EM**'s are known. Also, the chances of success in observing an endocyclic methyl transfer would be improved because of both this absence of medium ring strain and of the favourable entropic contribution of the cisoid arrangement of the ortho chains.[6] The methyl transfers of methyl 2-(dimethylaminomethyl)phenylmethanesulfonate (**54**) to form 2-(trimethylammoniomethyl)phenylmethanesulfonate (**55**) and of methyl 2-[2-(dimethylaminomethyl)phenyl]ethanesulfonate (**56**) to form 2-[2-(trimethylammoniomethyl)phenyl]ethanesulfonate (**57**) were, therefore,

also examined.



54 55

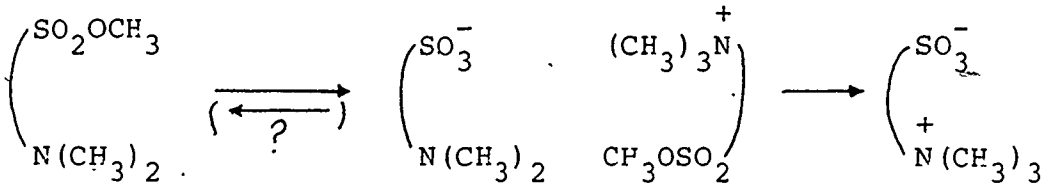


56 57

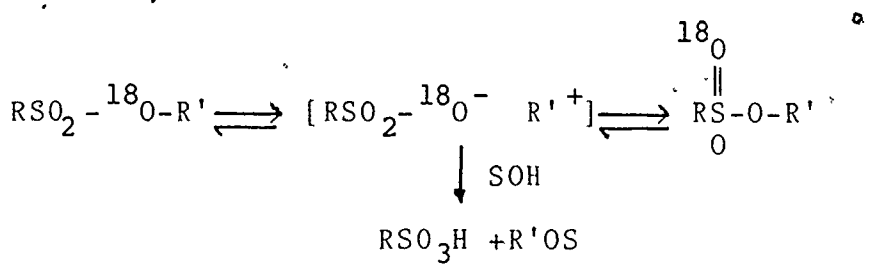
The results of the kinetics and crossing experiments for **52** to **53** are presented and discussed in Section A of the Results and Discussion. Sections B and C deal with the same topics of the reactions of **54** to **55** and **56** to **57** respectively. The mechanism of the bimolecular reaction of these compounds is examined in detail in Section D. Among other things, this section contains a rather novel use of ^{18}O isotope effects on ^{13}C NMR chemical shifts.

For reasons which will be presented in Section D of the Results and Discussion, it was necessary to determine if methyl ω-(dimethylamino)alkanesulfonate esters were involved in internal return during their conversion to ω-(trimethylammonio)alkanesulfonates. Internal return has been observed in the solvolysis of many secondary alkanesulfonate esters and has been used as evidence for the

existence of ion pair intermediates in those reactions.[43,44]



The experiment commonly used to monitor internal return in those reactions involves the incorporation of an ^{18}O label in either the ethereal or the sulfonyl oxygen of the solvolytic starting material. Internal return is indicated by partial equilibration in the position of the label in unreacted starting material recovered from the reaction mixture during the course of the reaction. The ^{18}O content of the



ethereal oxygen of the recovered material is then determined by mass spectroscopic analysis of the alcohol produced by sodium-naphthalene reduction of its ethereal oxygen-sulfur bond. This value, when compared with the mass spectrometrically determined total ^{18}O content of the recovered material, yields the label distribution.[44,45]

The ^{18}O-labelling experiment then seemed to be well suited to the previously described problem. However, in view of the tedious nature of the analytical method and the anticipated experimental difficulties posed by the vola-

the anticipated experimental difficulties posed by the volatility of methanol, a more direct analytical method was deemed necessary. In this regard, an ^{18}O positional analysis based on the recently observed ^{18}O isotope effects in ^{13}C NMR held promise.

The prediction of the existence of ^{18}O-^{13}C NMR isotope effects was made by Raynes and Stanney[46] in 1974. Later, calculations by Jameson indicated that a small upfield shift should be observed; mainly the result of changes in the anharmonic vibrational term of the chemical shielding.[47] In 1979, Darensbourg[48,49] and Van Etten[50] confirmed these predictions with the first experimentally observed ^{18}O-^{13}C NMR isotope effects. Since then, the structural dependence of the magnitude of the effect has been examined for a wide variety of oxygen containing organic compounds.[50-53] In general, it depends on the number of bonds to oxygens, the order of these bonds, the hybridization of the carbon and on the nature of the other substituents on both the carbon and oxygen atoms. For carbonyl carbons, which have received the most attention, the isotope effect ($^1\Delta$) varies between 0.030 and 0.060 ppm and has been found to correlate with the carbon's chemical shift (δ_C)[54]:

$$^1\Delta = 4.16 \times 10^{-2} \text{ ppm} - 4.38 \times 10^{-4} \ \delta_C \qquad (2)$$

Although no isotope effects have thus far been reported for methyl carbons, a variety of effects have been recorded for other sp^3 carbons. Table 3 shows some pertinent values for alcohols, ethers and esters. In the series of alcohol

Table 3

Selected ^{18}O Isotope Effects on sp^3 Carbon ^{13}C NMR Shifts[50-53]

	Isotope Effect (ppm, upfield)
1. Alcohols	
t-butanol	Ø.Ø35
1-phenylethanol	Ø.Ø23
cyclooctanol	Ø.Ø29
cyclohexanol	Ø.Ø22
cyclobutanol	Ø.Ø2Ø
1-octanol	Ø.Ø21
1-hexanol	Ø.Ø22
benzyl alcohol	Ø.Ø19
2. Ethers	
phenetole	Ø.Ø25
p-Bromophenetole	Ø.Ø25
3. Esters	
$Ph-CO-^{18}O-CH_2CH_2CH_3$	Ø.Ø32
$C_6H_{11}-CO-^{18}O-CH_2CH_2CH_3$	Ø.Ø3Ø

isotope effects, the effect decreases on going from tertiary to secondary to primary carbons. The ethers and esters give isotope shifts larger then those observed for primary alcohols. This suggests then that sulfonate esters should give measurable isotope effects as well. If this is true, then the previously discussed internal return analytical problem would be reduced to a simple ^{18}O-^{13}C NMR experiment.

The acceptance by chemists of ^{18}O-^{13}C NMR isotope effects as an experimental tool has been rapid. Biochemical applications include their use in the elucidation of macrolide biosynthetic pathways[55] and in the study of enzyme catalysis mechanisms.[56] Inorganic chemists have used these effects in the study of several metal carbonyl rearrangements.[48,49] Applications in physical organic chemistry have included their use in studies of the rates of acid catalyzed oxygen exchange by alcohols in water,[50] in mechanistic studies of formyl group transfers,[57] and in the determination of a triepoxide rearrangement mechanism.[58] Since the completion of the studies reported in the thesis, these effects have been used in this laboratory to monitor oxygen transfer in the aqueous chlorination of 3-mercaptopropanol.[59]

II Results and Discussion

A. The Formation of 4-(Trimethylammonio)butane-1-sulfonate (53) from Methyl 4-(Dimethylamino)butane-1-sulfonate (52)

1. Introduction:

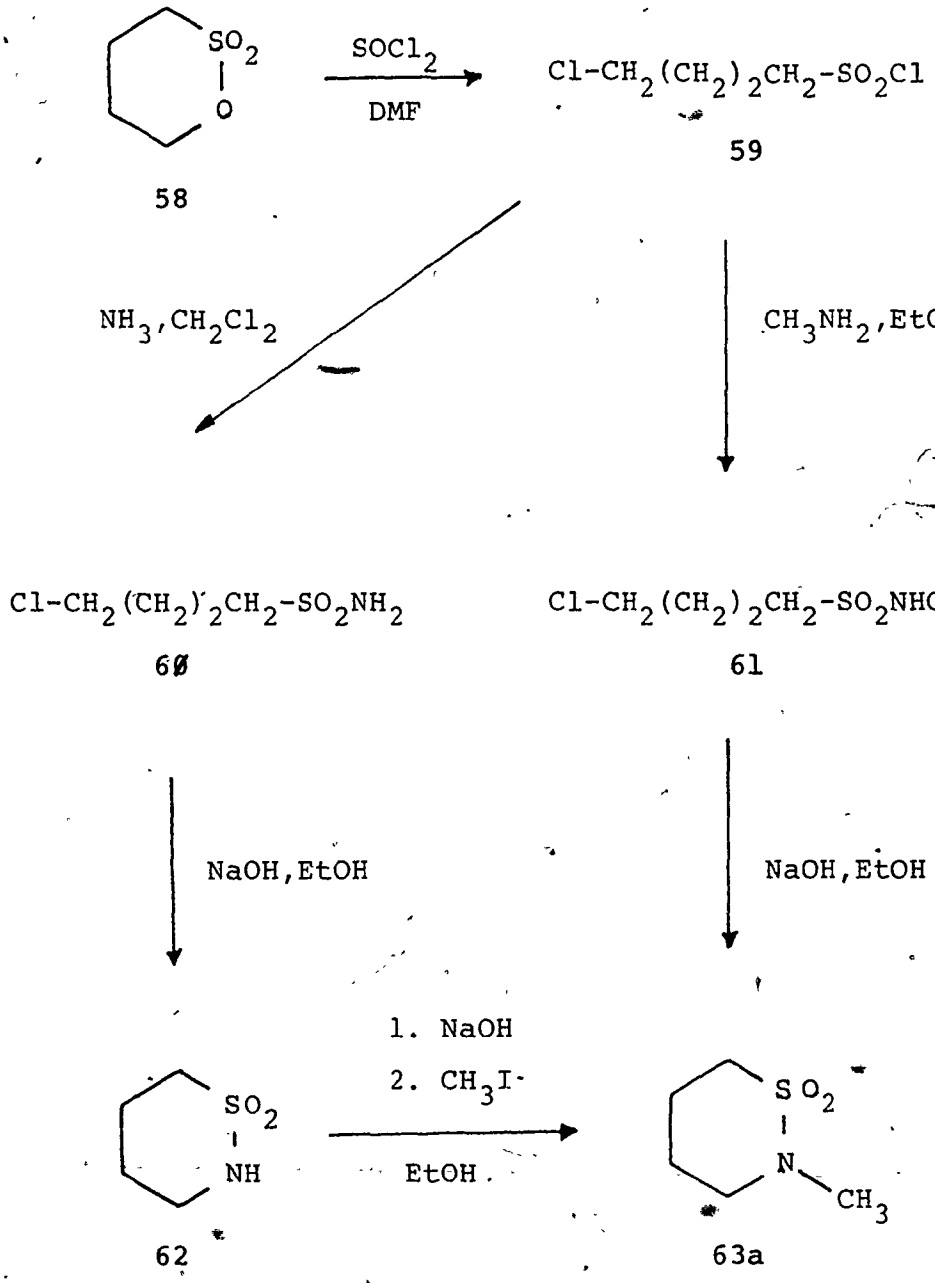
52 53

This section describes the search for an endocyclic pathway in the methyl transfer of **52** to form **53**. It includes, first, the synthetic routes employed in preparing the required compounds and second, the results of the ^1H NMR kinetic experiments and of the double-label crossing experiments used to determine if endocyclic methyl transfer occurs in the formation of **53** from **52**.

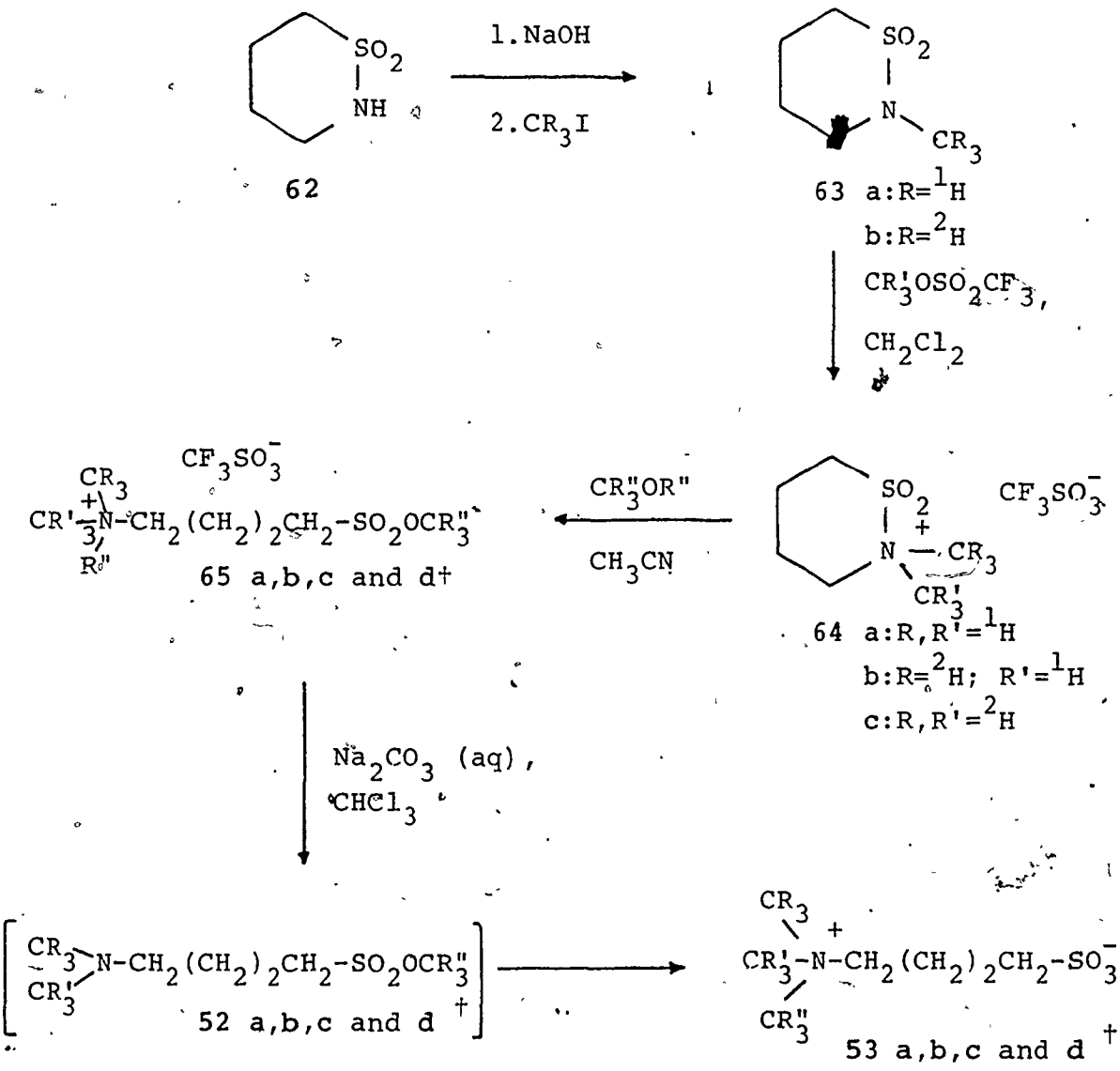
2. Synthesis

The key synthetic intermediates required for the preparation of the compounds used in this section were tetrahydro-2H-1,2-thiazine 1,1-dioxide (1,4-butanesultam, **62**) and 2-methyltetrahydro-2H-1,2-thiazine-1,1-dioxide (N-methyl-1,-4-butanesultam, **63a**). The route used to prepare them is summarized in Scheme 1. 1,4-Butanesultone (**58**), which was prepared in three steps from tetrahydrofuran by the method

of Helberger and Lantermann[60], was cleaved with thionyl chloride in the presence of a catalytic amount of N,N-dimethylformamide to give 4-chlorobutane-1-sulfonyl chloride (**59**) in 85% yield. For the conversion of **59** to the sultams (**62** and **63**), the reaction sequence of Helferich, et al,[61] was used following, as recommended by Kaiser and Knutson[62], procedures similar to those devised by Bliss, et al,[63] for the synthesis of 1,3-propanesultam from 3-chloropropane--1-sulfonyl chloride. Briefly, treatment of **59** with anhydrous ammonia in methylene chloride gave 4-chlorobutane--1-sulfonamide (**60**) in 90% yield. The sulfonamide (**60**) was cyclized with sodium hydroxide in refluxing ethanol to give the sultam, **62**, in 65% yield. The anion of **62** was generated in ethanol with sodium hydroxide and then methylated with methyl iodide to give **63a** in 80% yield. Alternatively, treatment of **59** with methylamine in ether gave, in 90% yield, N-methyl-4-chlorobutane-1-sulfonamide (**61**) which was then cyclized in ethanol with sodium hydroxide to give **63a** in 70% yield. The latter sequence is, of course, advantageous since the number of steps is reduced and the overall yield is improved. Scheme 2 depicts the subsequent use of the sultams, **62** and **63a**. A methylene chloride solution of **63a** and methyl trifluoromethanesulfonate deposited, over the course of 3 days at room temperature, an 80% yield of crystals of the "sultamium" salt, N,N-dimethyltetrahydro-2H-1,-2-thiazinium 1,1-dioxide trifluoromethanesulfonate (**64a**). Methanolysis of **64a** in anhydrous acetonitrile-methanol re-


SO2
O
SOCl2
DMF
Cl-CH2(CH2)2CH2-SO2Cl
59
58
NH3,CH2Cl2
CH3NH2,EtOH
Cl-CH2(CH2)2CH2-SO2NH2
60
Cl-CH2(CH2)2CH2-SO2NHCH3
61
NaOH,EtOH
NaOH,EtOH
1. NaOH
2. CH3I
EtOH
SO2
NH
62
S O2
N
CH3
63a

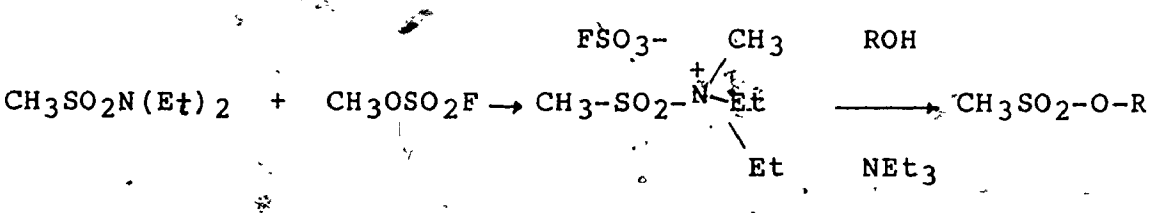
Scheme 1



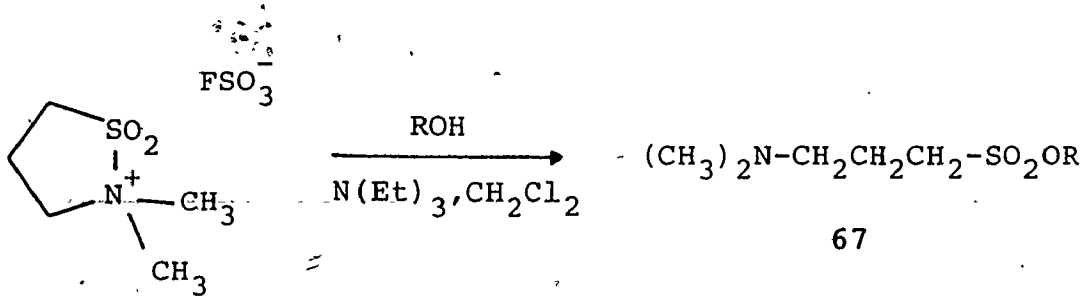
† a:R,R',R"=^{1}H c:R=R"=^{2}H; R'=^{1}H
b:R=R'=^{1}H; R"=^{2}H d:R,R',R"=^{2}H

Scheme 2

sulted in the quantitative formation of the corresponding methyl "norbetylate", 4-(methoxysulfonyl)-N,N-dimethylbutanaminium trifluoromethanesulfonate (**65a**). A similar sequence involving the methylation of N,N-diethylmethanesulfonamide to form the corresponding sulfonylammonium salt followed by the reaction of this salt with a primary or secondary alcohol in the presence of triethylamine has been advocated by King and du Manoir[64] as a useful method of methanesulfonate ester synthesis. Similarly, King, et al,[3] have found



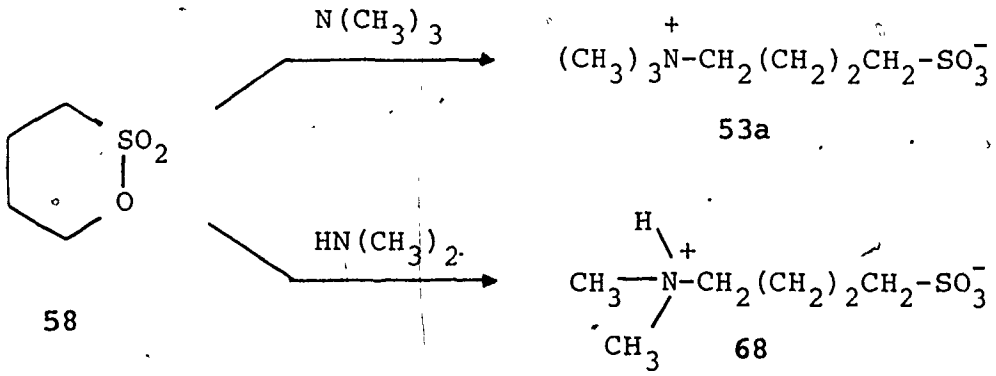
that 2,2-dimethylisothiazolidinium 1,1-dioxide fluorosulfate (**66**) reacts readily with primary and secondary alcohols in the presence of triethylamine to give high yields of alkyl 3-(dimethylamino)propanesulfonate esters (**67**). In contrast to these results,



66 67

only tarry materials were obtained when **64a** was reacted with alcohols in the presence of triethylamine. In the absence of an amine catalyst, however, **64a** was found to

undergo slow cleavage by alcohols in acetonitrile. Specifically, when a 50°C acetonitrile solution initially 3M in **64a** and 3.3M in methanol was monitored by ^{1}H NMR, it was found that the complete conversion of **64a** to **65a** required approximately 10 h. Evaporation of the solvent left **65a** as a clear colourless oil which was judged by ^{1}H NMR to be greater than 98% pure. Methyl 4-(dimethylamino)butanesulfonate (**52a**) was prepared in solution by suspending the "norbetylate" (**65a**) in methylene chloride or chloroform and then washing the suspension with aqueous sodium carbonate. Evaporation of the solvent left an oil which gradually solidified giving a 95% yield of 4-(trimethylammonio)butanesulfonate (**53a**). The structure of **53a** was confirmed by comparison with an authentic specimen of **53a** prepared from 1,4-butane sultone (**58**) and trimethylamine using the procedure of Helferich and Bollert.[65] An authetic specimen of the "norbetaine" (4-(dimethylammonio)butanesulfonate, **68**) was similarly prepared from 1,4-butane sultone (**55**) and dimethylamine[65].



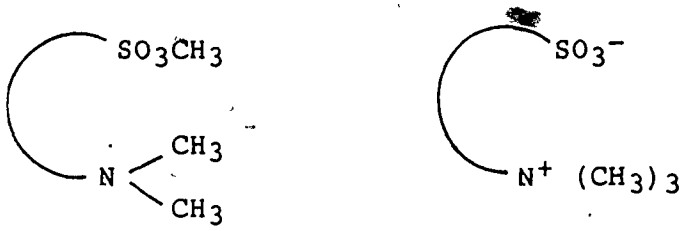
For the crossing experiments, the $\underline{d}_9$-"norbetylate", 4-[($^2H_3$)methoxysulfonyl]-*N*,*N*-di($^2H_3$)methylbutanaminium trifluoromethanesulfonate (**65d**) was required. Its synthesis, as shown in Scheme 2, involved incorporation of the deuterated methyl groups in the last three steps. That is, methylation of the sultam, **62**, with ($^2H_3$)methyl iodide gave the *N*-($^2H_3$)methyl sultam (**63b**) which in turn was methylated with ($^2H_3$)methyl trifluoromethanesulfonate to give the $\underline{d}_6$-"sultamium" salt, **64c**. ($^2H_3$)Methyl trifluoromethanesulfonate was prepared using the procedure described by Gramstad and Haszeldine[66] for the preparation of methyl trifluoromethanesulfonate from methyl iodide and silver trifluoromethanesulfonate with the only change being the use of ($^2H_3$)methyl iodide instead of ordinary methyl iodide. The $\underline{d}_6$-"sultamium" salt, **64c**, was then cleaved with ($^2H_4$)-methanol to give the $\underline{d}_9$-"norbetylate", **65d**.

Samples of each of the $\underline{d}_0$-, $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-betaines (**53a**, **b**, **c** and **d**) were required for control experiments related to the crossing experiments. The $\underline{d}_0$-betaine (**53a**) was on hand and the $\underline{d}_9$-betaine (**53d**) was obtained simply *via* the rearrangement of the $\underline{d}_9$-ester (**52d**) which was prepared by deprotonation of the $\underline{d}_9$-"norbetylate" (**65d**). Deuterium combustion analysis indicated that the ammonio methyls were, on average, at least 95% deuterated. A specimen of $\underline{d}_3$-betaine (**53b**) was prepared analogously from the $\underline{d}_3$ "norbetylate" (**65b**) which was obtained by cleavage of the "sultamium" salt (**64a**) with ($^2H_4$)methanol. Finally,

methylation of **62** with ($^2H_3$)methyl iodide gave the $\underline{d}_3$-N--methylsultam (**63b**) which, on treatment with methyl trifluoromethanesulfonate, gave the $\underline{d}_3$-"sultamium" salt (**64b**). ($^2H_4$)Methanolysis of **64b** gave the $\underline{d}_6$-"norbetylate" (**64c**) which after deprotonation and rearrangement, gave the $\underline{d}_6$-betaine (**53c**).

3. Kinetic Studies

In this section and in Sections B and C, it is assumed that the amino esters, **E**, react by the following two pathways:



E **B** and **C**

$$\mathbf{E} \xrightarrow{k_1} \mathbf{C}$$

$$2\mathbf{E} \xrightarrow{k_2} 2\mathbf{B}$$

C is the betaine derived from the endocyclic first order reaction of **E** and **B** is the betaine formed by the intermolecular second order reaction of **E**. These pathways are assigned the rate constants k_1 and k_2 respectively. The scheme is then described by the following rate laws:

$$\frac{d\mathbf{C}}{dt} = k_1\mathbf{E} \qquad (3)$$

$$\frac{d\mathbf{B}}{dt} = 2k_2\mathbf{E}^2 \qquad (4)$$

$$\text{and } -\frac{d\mathbf{E}}{dt} = k_1\mathbf{E} + 2k_2\mathbf{E}^2 \qquad (5)$$

It follows then that the distinction between these two pathways may in principle be made with a simple kinetic experiment. If the contribution from the second order term in equation (5) is negligible then equation (6) will describe the rate law and the kinetic data will yield a linear first order plot (ln **E** *versus* time). This behaviour would then

$$-\frac{dE}{dt} \simeq k_1 E \qquad (6)$$

be indicative of endocyclic methyl transfer. Conversely, if the contribution of the first order term is negligible then equation (7) will apply and a linear second order plot (1/**E** *versus* time) will be obtained. This would point to

$$-\frac{dE}{dt} \simeq 2k_2 E^2 \qquad (7)$$

intermolecular methyl transfer.

Accordingly, the kinetic properties of the formation of **53** from **52** were examined. To generate a solution of the amino ester, **52a**, the "norbetylate", **65a**, was shaken in cold aqueous sodium carbonate and extracted with $CDCl_3$. The extract, after the addition of a precisely measured amount of CH_2Cl_2, was diluted with $CDCl_3$ in a volumetric flask. An aliquot of this solution was transferred to an n.m.r. tube which was then capped and inserted into the probe of the ^1H NMR spectrometer where it remained for the course of the kinetic run. The probe temperature was 37.0°C. At appropriate time intervals, the integrals of the peak assigned to the internal standard (CH_2Cl_2, δ = 5.2 ppm) and of the peak corresponding to the *O*-methyl group of **52a** (δ = 3.8 ppm) were determined and, since the internal standard's concentration was known, were used to calculate the concentration of **52a** at each time interval. From an initial ester concentration of 0.25 *M*, it was possible to follow the reaction to 80% completion. Beyond this, the low intensity of the ester peak led to excessive error in

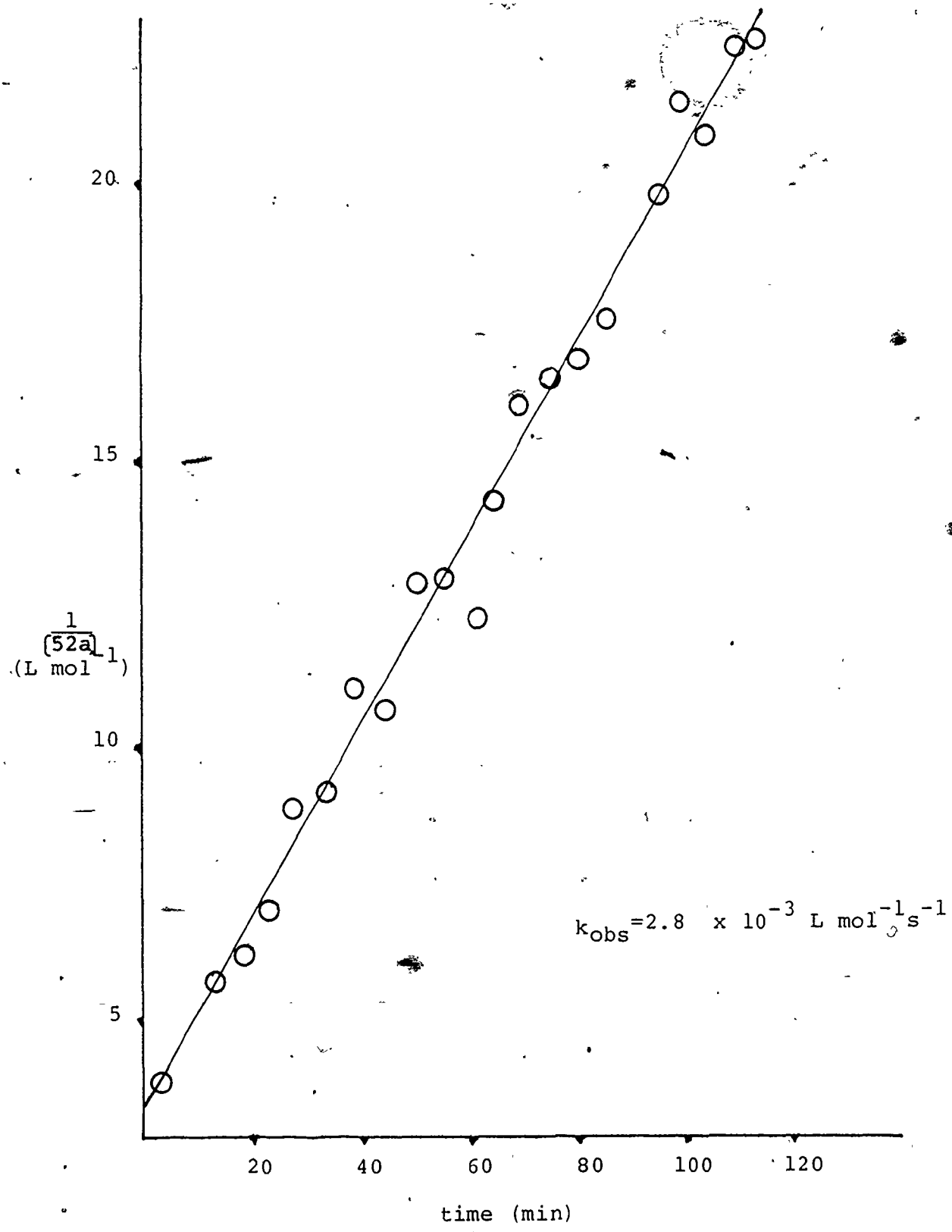


Figure 2: Rate of the Rearrangement of Methyl 4-(Dimethylamino)butane-1-sulfonate (52a) to 4-(Trimethylammonio)butane-1-sulfonate (53a) in $CDCl_3$ at 37.0°C

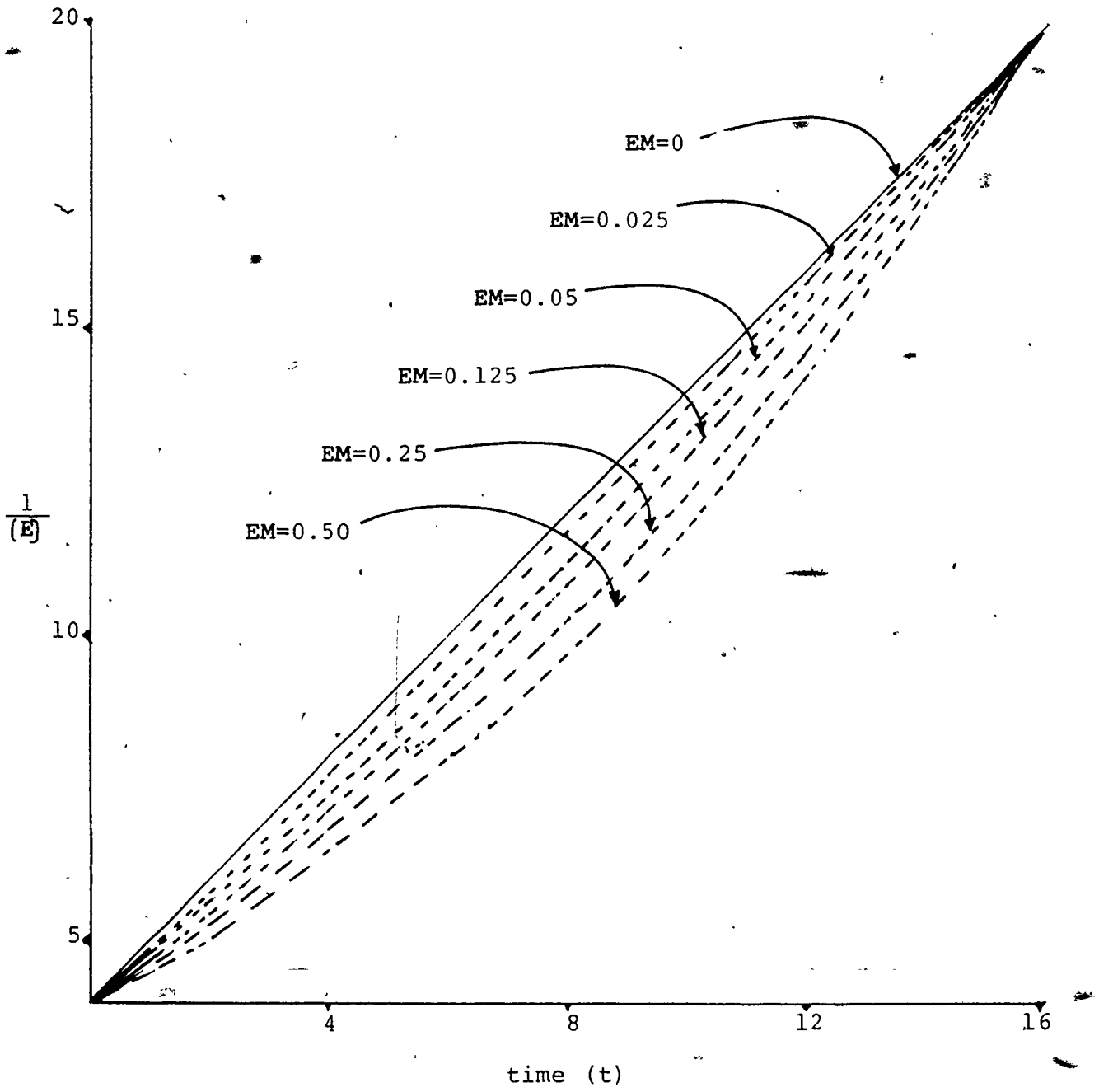


Figure 3: Simulated Mixed First and Second Order Kinetic Curves

the determination of its integrals. The betaine, **53a**, was insoluble in $CDCl_3$ and hence gave no detectable ^1H NMR spectrum.

A second order plot of the kinetic data from the first run (1(a)(i)) is shown in Figure 2. The rate constant (k_{obs} or $2k_2$), as defined by the slope of line deduced by linear least squares regression analysis, was found to be 2.8 x 10^{-3} L $mol^{-1}s^{-1}$. A duplicate run (1(a) (ii)) also gave a linear second order plot and yielded a rate constant of 2.7 x 10^{-3} L $mol^{-1}s^{-1}$. The $\pm$ 5% agreement between these values is acceptable since it represents the range of uncertainty in the concentration of the internal standard. From the linearity of the second order plots, it can be concluded that the formation of **53a** from **52a**, in the ester concentration range of 0.25 M to 0.05 M, occurs predominantly by the intermolecular pathway. The extent to which a first order endocyclic pathway could contribute to the formation of **53a** without inducing detectable curvature in the second order plots can be estimated by calculating, for various **EM**'s, the loss of **52a** as a function of time then examining for curvature the second order plots of these data. When the previously defined overall rate law for the loss of **E** (equation (5)) is integrated and the reciprocal of **E** is expressed as a function of k_1, **EM** and t, equation (8) is obtained. To facilitate comparison, the resulting curves shown in Figure **3**, each of which is characteristic of a particular **EM**, share common initial ester

$$\frac{1}{E} = \frac{e^{k_1 t}}{E_o} + \frac{2}{EM} \ln (e^{k_1 t} - 1) \qquad (8)$$

concentrations (E_o = 0.25 M), endpoints (E_f = 0.05 M) and total reaction times (t_f) where t is any arbitrarily chosen time until such that for EM = 0, t_f = 16.† For each EM, k_1 may be calculated using equation (9) which is simply a rearranged form of equation (8). (The EM and k_1 furnish k_2 via equation (1)).

$$k_2 = \frac{1}{t_f} \ln \left[\frac{E_o (2E + EM)}{E_f (2E_o + EM)} \right] \qquad (9)^*$$

Also, the extent of the contribution of the first order pathway to the formation of the product, when expresed as % C, may be calculated using equation (10). The resulting data

$$\%C = \frac{50EM}{(E_o - E_f)} \ln \left(\frac{2E_o + EM}{2E_f + EM} \right) \qquad (10)^*$$

are summarized in Table 4.

Table 4

Mixed First and Second Order Simulation Data

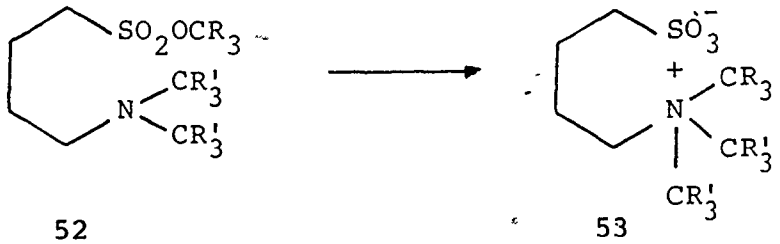
EM	k_1 (t^{-1} x 10²)	k_2 ($L\,mol^{-1}\,t^{-1}$ x 10)	%C	E_o/EM
0	0	10.0	0	
0.025	1.09	4.36	9	10
0.05	1.94	3.79	16	5
0.125	3.67	2.94	32	2
0.25	5.30	2.12	48	1
0.50	6.87	1.37	64	0.5

†If k_2 = 1 then 16 time units are required for 80% reaction from the initial ester concentration of 0.25M.
i.e. 1/(0.05) − 1/(0.25) = 16

*These equations are derived in Appendix 1.

Comparison of the kinetic plot (Figure 2) with the simulated curves (Figure 3) indicates that a reasonable limit to detectable curvature in the kinetic plots is represented by the curve characteristic of **EM** = 0.05 M. This suggests then that the **EM** for the formation of **53a** from **52a** is less than 0.05 M or 20% of the initial ester concentration. That approximately 15% of **53a** could arise from endocyclic methyl transfer and still escape detection indicates that the kinetic method is not a very sensitive way of spotting small contributions of a first order pathway. The reaction of **52a** to **53a** was then examined at lower initial concentrations of **52a** through the use of double-label crossing experiments.

4. Crossing Experiments



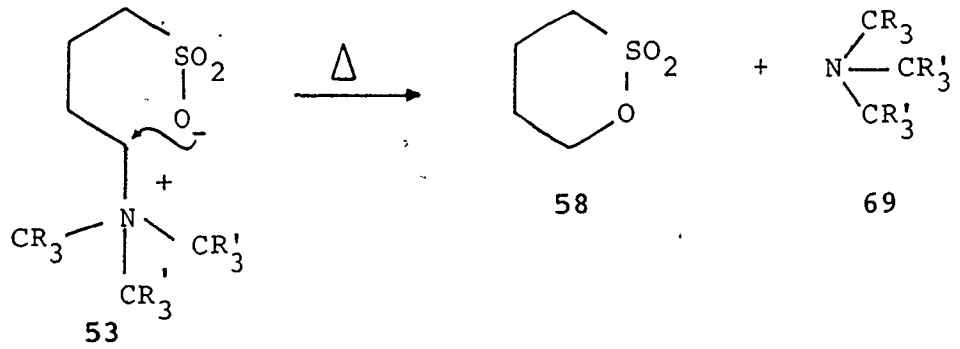
52 53

a:R,R'=^{1}H; **b**:R=^{2}H,R'=^{1}H; **c**:R=^{1}H,R'=^{2}H; **d**:R,R'=^{2}H

The distinction between intramolecular endocyclic methyl transfer and intermolecular methyl transfer in the rearrangement of the amino-ester (**52**) to the betaine (**53**) may be drawn with a double-label crossing experiment. An equimolar mixture of the $\underline{d}_0$-and $\underline{d}_9$-esters (**52a** and **d**) will yield, after endocyclic methyl transfer, an equimolar mixture of the $\underline{d}_0$- and $\underline{d}_9$-betaines (**53a** and **d**). Conversely, intermolecular methyl transfer will result in the formation of an equimolar mixture of the $\underline{d}_0$-, $\underline{d}_3$-, $\underline{d}_6$-and $\underline{d}_9$-betaines (**53a, b, c** and **d**).

This experiment, of course, requires that there be an analytical method available for determining quantitatively the relative amounts of **53a, b, c** and **d** in mixtures of these betaines. Accordingly, the mass spectrometric properties of these compounds were examined. It was found that a probe temperature greater than 300°C was required to obtain a mass spectrum from the $\underline{d}_0$-betaine (**53a**). The resulting complex spectrum contained no parent mass ion (m/e = 195) but rather, contained two dominant peaks: one at m/e = 136 and the other at m/e = 59. 1,4-Butanesultone (**58**) and trimethylamine (**69a**)

respectively would seem to be likely sources of these peaks, and a reasonable explanation for their presence is that they are the products of the thermal decomposition of the betaine by way of an intramolecular exocyclic nucleophilic displacement by the sulfo anion.



53 58 69

a:R,R'=^{1}H; **b**:R=^{2}H,R'=^{1}H; **c**:R=^{1}H,R'=^{2}H; **d**:R,R'=^{2}H

It is interesting to note that this reaction is the reverse of that previously used for the preparation of an authentic sample of **53a**. This implies that at elevated temperatures, the sultone and amine have less free energy than does the betaine. Presumably, the enthalpy lost in the thermolysis is offset by the gains in translational and rotational entropy.†

While in principle the trimethylamine peak would serve adequately for the desired analysis, the presence of other minor peaks in the range that would be occupied by the deuterated amines (m/e = 59 to 68) introduced prohibitive complications. To avoid these, **53a** was subjected to preparative ther-

† Reactions in solution in which two molecules are formed from one typically have gains in entropy of approximately 45 cal K^{-1} $mole^{-1}$ [67]

mal degradation. A sample of **53a** was heated at 340°C for 20 min in a reaction vessel which was being slowly swept with nitrogen. When the effluent gas was bubbled through a saturated solution of picric acid in ether, a yellow precipitate was formed which, after recrystallization, showed no melting point depression when mixed with an authentic sample of trimethylammonium picrate; the thermolysis picrate was obtained in 30% yield. When the tarry residue in the reaction vessel was extracted with $CDCl_3$, the extract gave an ^1H NMR spectrum identical to one obtained from authentic **58**. These results then confirm the structures of the degradation products. When the volatile components of the effluent gas were condensed in a U-tube cooled in frozen pentane and then distilled directly into the mass spectrometer probe, a mass spectrum was obtained that was identical to one obtained from an authentic sample of trimethylamine. In both spectra, the relative intensities of the parent mass ions (m/e = 59) and their M + 1 peaks (m/e = 60) which are due primarily to the natural abundance of ^{15}N and ^{13}C, agreed with the calculated values of 100 and 3.8 respectively within the experimental error of $\pm$ 2 inherent in the spectrometric method. The spectra also contained significant M - 1 peaks for which the source is undoubtedly the iminium ion (**71**) formed by the loss of a hydrogen atom from the parent radical cation, **70**.[68] In the spectra of the deuterated amines, (**69, b, c** and **d**), this fragmentation results in the presence of an M - 2 peak which introduces a complication in the analysis of mixtures of **69 a, b,**

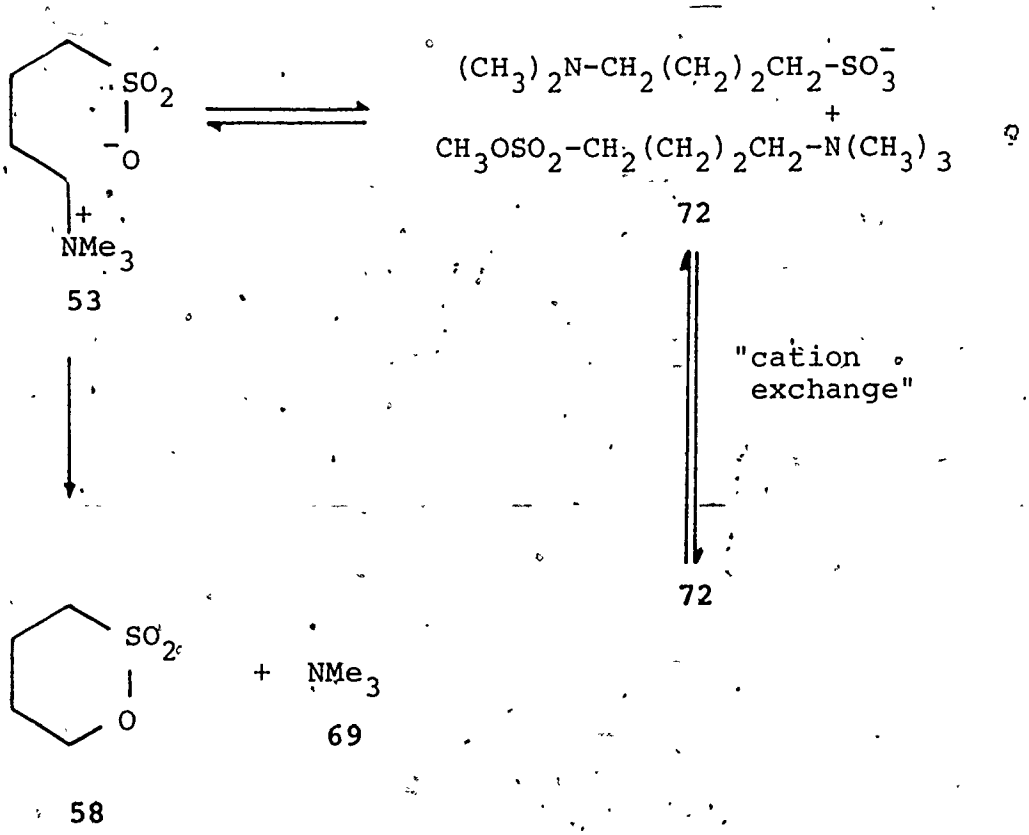
c, and d since these M - 2 peaks will overlap with the

$$\underset{\textbf{70}}{N(CH_3)_3^{+\cdot}} \longrightarrow \underset{\textbf{71}}{(CH_3)_2\overset{+}{N}=CH_2} + H\cdot$$

M + 1 peaks from the amines bearing one less deuterated methyl. As well, all peaks arising from deuterated ions will have corresponding M - 1 peaks caused by the presence of the small amount of protium that results from incomplete deuteration. These M - 1 peaks will further complicate the spectra by causing additional overlap between the amine clusters. To remove the overlap, a computer program (MSP2) which is described in detail in Appendix 2, was devised. It relocates all ^{13}C and ^{15}N M + 1 peaks with their parent ions and then relocates the M - 1 peaks due to incomplete deuteration with their parent ions. The program then sums the corrected M - 2, M - 1 and M peaks for each amine and reports these sums normalized to one of the amines for which it has arbitrarily assigned a value of 100.

As a control experiment, a sample of the $\underline{d}_6$-betaine (**53c**) was thermolyzed. Surprisingly, the resulting mass spectrum contained peaks attributable to the $\underline{d}_0$-, $\underline{d}_3$- and $\underline{d}_9$-amines as well as that of the anticipated $\underline{d}_6$-amine. Analysis of the spectrum revealed a $\underline{d}_0$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ ratio of 2.7:9.7:-100:12.7. A second thermolysis gave a similar ratio (1.0:-13.5:100:14.6). These spectra suggest that during the thermolysis a simultaneous side reaction occurs that serves to partially scramble the ammonio methyls. Whereas trimethylamine is the product of an intramolecular displacement by the

sulfo anion of the betaine on the methylene α to the nitrogen atom, an intermolecular displacement by the sulfo anion on an ammonio methyl would form the ion pair, **72.** The latter reaction would be expected to be reversible since the ion pair consists of an anionic nucleophile and a cationic methylating agent. The exchange of cations between anions would then provide a mechanism for scrambling the ammonio methyls. Because the scrambling of the label in the analysis materially affects the interpetation of the results, it is necessary at this point to describe the approach used to correct for this phenomenon. The pathways taken by each of the labelled betaines



in one such methyl exchange are shown in Figure 4 in which $\mathbf{A}_x$ is the anion (in **72**) bearing x deuterated methyls, **L** is the fraction of the ammonio methyls that are labelled and **U** is the fraction of these that are unlabelled. The $\underline{d}_0$-betaine (**53a**), on formation of **72**, will give exclusively A_0 and similarly, **53d** will give only A_2. Since the chances of a $\underline{d}_3$-betaine (**53b**) losing a CD_3 group are only half those of its losing a CH_3 group, one third of **53b** will lose a CD_3 group to form the unlabelled anions (A_0) while two thirds of **53b** will form $\underline{d}_3$-anions ($\mathbf{A}_1$). Similarly, two thirds of **53c** will form $\mathbf{A}_1$ and one third will form $\mathbf{A}_2$. After cation exchange, each of the anions, $\mathbf{A}_x$, will receive a methyl group from a cation and hence the amount of the betaine with x CD_3 groups that will be formed is given by $\mathbf{UA}_x$ and the amount of betaine with x + 1 deuterated methyls that will be formed is given by $\mathbf{LA}_x$. This may perhaps be shown more clearly by an explicit example. In the thermolysis of the pure $\underline{d}_6$-betaine (**53c**), $\underline{n}$ molecules of **53c** will yield $2\underline{n}/3$ molecules of $\mathbf{A}_1$ and $\underline{n}/3$ molecules of $\mathbf{A}_2$. Since **U** = 1/3 and **L** = 2/3, $2\underline{n}/3$ molecules of $\mathbf{A}_1$ will then yield $(1/3)(2\underline{n}/3) = 2\underline{n}/9$ molecules of **53b** and $(2/3)(2\underline{n}/3) = 4\underline{n}/9$ molecules of **53c**. Similarly, $\underline{n}/3$ molecules of $\mathbf{A}_2$ will give $(1/3)(\underline{n}/3) = \underline{n}/9$ molecules of **53c** and $(2/3)(\underline{n}/3) = 2\underline{n}/9$ molecules of **53d**. A single methyl scramble will thus lead to a 2:5:2 mixture of the $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-betaines.

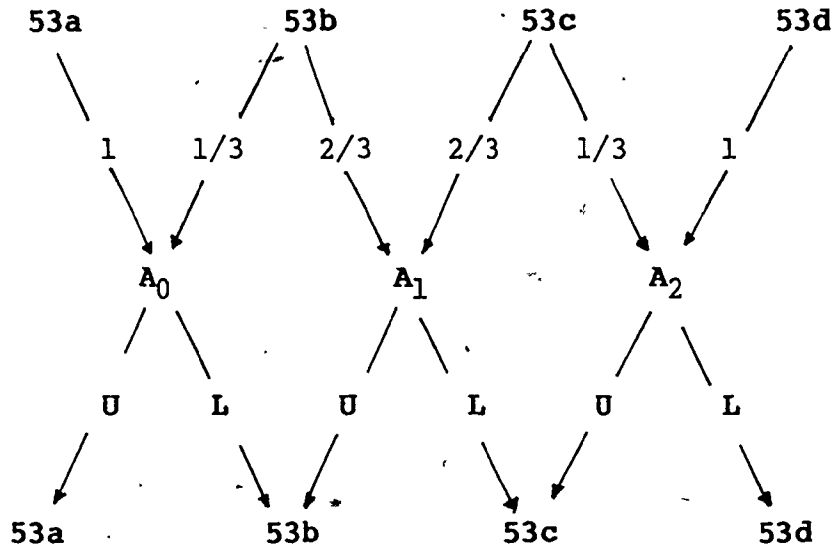


Figure 4: A Single Methyl Scrambling Cycle

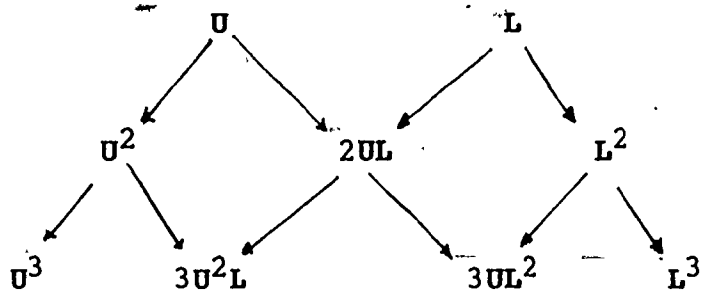


Figure 5: Fork Diagram[69] for the Prediction of the Betaine Statistically Scrambled Label Distribution

After a large number of these single scrambling cycles, all three of the ammonio methyls will be scrambled and hence the statistical distribution of the labelled methyls will be obtained. This distribution is that predicted by the fork diagram shown in Figure 5: $U^3:3U^2L:3UL^2:L^3$ - $\underline{d}_0:\underline{d}_3:\underline{d}_6:\underline{d}_9$. Starting with pure $\underline{d}_6$-betaine, the statistical distribution is thus 1:6:12:8.

Trimethylamine generated during the thermolysis will consist of amine derived from unscrambled betaine and of amine derived from scrambled betaine. The label distribution in the amine generated from unscrambled betaine will be that present in the original betaine mixture while the label distribution of the amine generated from scrambled betaine will be somewhere between the limiting extremes predicted for the single methyl scramble and for the fully scrambled statistical distribution. It follows then that the observed mass spectrum should be simply the sum of the unscrambled and scrambled components. In the previously mentioned $\underline{d}_6$-betaine thermolyses, the mole fraction of the amine mixture that is attributable to amines derived from scrambled betaines may be evaluated for both scrambling extremes. For the single methyl scramble, since the $\underline{d}_3$- and $\underline{d}_9$-amines are derived solely from the scrambled betaines and they represent 4/9 of the scrambled component, the mole fraction of the amine mixture that is derived from scrambled betaine, S_1, can be calculated using equation (11). The two previously mentioned $\underline{d}_6$-betaine

$$S_1 = \frac{9}{4}\frac{(\underline{d}_3 + \underline{d}_9)}{(\underline{d}_3 + \underline{d}_6 + \underline{d}_9)} \qquad (11)$$

thermolysis ratios thus have S_1 values of 0.41 and 0.49 respectively. Similarly, for the statistical scrambling limit, since the $\underline{d}_0$-, $\underline{d}_3$- and $\underline{d}_9$-amines represent 15/27 of the scrambled component, the mole fraction of the amine mixture attributable to scrambled amines, S_2, can be calculated using equation (12). These calculations indicate that S_2 is 0.36 and

$$S_2 = \frac{27\ (\underline{d}_0 + \underline{d}_3 + \underline{d}_9)}{15\ (\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9)} \qquad (12)$$

0.40 respectively for the pair of $\underline{d}_6$-betaine thermolysis mixtures. It may be concluded then that in the first thermolysis, between 36% and 41% of the amine was generated from scrambled betaine and in the second thermolysis, between 40 and 49% was so generated. While in principle, the average number of scrambling cycles could be obtained from the $\underline{d}_0$:$\underline{d}_3$ or $\underline{d}_0$:-$\underline{d}_9$ ratios, the experimental error in these values would render any such conclusions dubious at best.

At this point in the study, the thermolysis procedure was optimized. Based on the assumption that amines produced early in the thermolysis should be less scrambled than those produced later, the time interval during which the betaine was heated was reduced from 20 min to 10 min. Also, to eliminate the experimental difficulties associated with manipulating the small amounts of trimethylamine produced by the thermolysis (< 5 mg), the amine was isolated as its hydrochloride which was obtained by simply bubbling the thermolysis effluent gas through methanolic HCl at -78°C and then removing the methanol and excess HCl by evaporation. A thermolysis of **53a** yielded a sample of trimethylammonium chloride

which gave a mass spectrum identical to one obtained from an authentic sample.

This modified thermolysis procedure was used for the crossing experiment product analysis and for the authentic mixture control experiments. For the latter, mixtures of-**53a**, **b**, **c**, and **d** that correspond to those expected from the crossing experiments were prepared and then thermolyzed. The resulting amine hydrochlorides were analyzed mass spectrometrically to give the amine ratios reported in Table 5. The first two mixtures were those anticipated from completely endocyclic methyl transfer (1:0:0:1-**53a:53b:53c:53d**) while the third and fourth mixtures represent the completely intermolcular product (1:1:1:1-**53a:53b:53c:53d**). The last two mixtures are two that could result from a combination of both pathways. Table 6 shows the trimethylamine ratios derived from the betaines obtained from three crossing experiments. When these are compared with those of the authentic mixture control experiments, they are found to most closely resemble those obtained from the 1:1:1:1-**53a:53b:53c:53d** mixtures. This then leads to the preliminary conclusion that, under the reaction conditions used in the crossing experiments, **53** is formed from **52** predominantly by way of intermolecular methyl transfer. In order to assign a maximum **EM** to the endocyclic process, a detailed analysis of the crossing experiments and the authentic mixture controls is required.

The first feature that emerges from examination of the amine ratios reported in Tables 5 and 6 is that, in all cas-

es, $\underline{d}_0$ is greater than $\underline{d}_9$ and $\underline{d}_3$ is greater than $\underline{d}_6$. This imbalance is most likely the result of a gradual decrease in the amount of amine in the mass spectrometer probe during the time interval required for the acquisition of the spectrum (2 to 5 min) and/or of isotope effects in the thermolysis and in the ionization of the amines. Regardless of its source, if the imbalance is assumed to be linear with respect to m/e, its effects can be eliminated by simply using the sum of the $\underline{d}_0$-and $\underline{d}_9$-amines and the sum of the $\underline{d}_3$-and $\underline{d}_6$-amines in the analysis of the spectra.

In the authentic betaine mixtures, since the component that mimics the endocyclic product is a 1:1-$\underline{d}_0$:$\underline{d}_9$ mixture and the component that mimics the intermolecular product is a 1:1:1:1-$\underline{d}_0$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ mixture, the amount of endocyclic product in these mixtures may be deduced by simply subtracting the sum of the $\underline{d}_3$ and $\underline{d}_6$ species from the sum of the $\underline{d}_0$ and $\underline{d}_9$ species. When expressed as a percentage of the total betaine mixture, the expected % endo (or % excess $\underline{d}_0$, $\underline{d}_9$), C_a,† can be calculated using equation (13). Similarily, the found % endo (or % excess $\underline{d}_0$, $\underline{d}_9$), F_a, can be calculated from the

$$C_a = 100 \left[\frac{(53a + 53d) - (53b + 53c)}{53a + 53b + 53c + 53d} \right] \qquad (13)$$

$$F_a = 100 \left[\frac{(\underline{d}_0 + \underline{d}_9) - (\underline{d}_3 + \underline{d}_6)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9} \right] \qquad (14)$$

---

†The subscript "a" means that the value was obtained from a mixture in which the endocyclic product was a $\underline{d}_0$, $\underline{d}_9$ mixture and that, in this mixture, half of the ammonio methyls were labelled (i.e. U = L = .5)

Table 5
Butane Derivative Authentic Mixture
Thermolysis Control Experiments

Exp't No.	Betaine Ratio 53a	:53b	:53c	:53d	Observed Amine Ratio d_0	d_3	d_6	d_9
1	1	0	0	1	100.0	17.8	15.7	74.6
2	1	0	0	1	100.0	20.0	18.9	82.1
3	1	1	1	1	100.0	116.9	107.1	85.8
4	1	1	1	1	100.0	116.7	107.5	83.8
5	1.2	1	1	1.2	100.0	90.1	78.7	76.3
6	1.4	1	1	1.4	100.0	82.1	70.9	74.2

Table 6
Butane Derivative Crossing Experiment Amine Ratios

Exp't No.	$[52a + 52d]_0$ (M)	Observed Amine Ratio d_0	d_3	d_6	d_9
1	1.0×10^{-2}	100.0	123.0	116.7	84.5
2	1.9×10^{-4}	100.0	115.9	99.8	76.7
3	1.9×10^{-4}	100.0	118.2	102.3	79.9

amine mixtures using equation (14). The C_a and F_a values so-obtained for each of the authentic mixture experiments are

listed in Table 7 and may be compared in terms of the previously discussed scrambling mechanism. Since the amine mixtures were derived from both scrambled and unscrambled betaines, the mole fraction of the amine mixture that is derived from scramble betaine may be determined for both of the previously discussed scrambling extremes.

If statistical scrambling is operative (i.e. all three ammonio methyls are scrambled) then the scrambled amine will be present as a 1:3:3:1-$\underline{d}_0$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ mixture.† The mole fraction of the amine mixture that is attributable to this component, S_{2a}, may then be calculated from F_a and C_a using equation(15) which is derived in Appendix 3.

$$S_{2a} = \frac{C_a - F_a}{5\emptyset + C_a} \qquad (15)$$

For the other scrambling extreme, the single methyl exchange, it may be shown that the scrambled betaines are not present in a constant ratio, but rather, their ratio is dependent on the initial betaine ratio. For example, an initially 1:Ø:Ø:1-**53a:53b:53c:53d** mixture will be converted via a single methyl exchange to a 1:1:1:1 mixture while an initially 1:1:1:1 mixture will be so transformed into a 1:2:2:1 mixture. Fortunately, this presents no difficulties since the mole fraction of the amine mixture that is derived from the single methyl scrambled betaines, S_{1a}, can be calculated directly from C_a and F_a using equation (16) which is also derived in Appendix 3.

† (From $U^3:3U^2L:3UL^2:L^3$ for $U = .5$ and $L = .5$)

Table 7

Butane Derivative Authentic Mixture
Thermolysis Control Experiment Scrambling Corrections:

Exp't No.	C_a	F_a	S_{1a}	C	$C-C_a$
1	100	67.8	0.32	94.8	-5.2
2	100	64.8	0.35	91.1	-8.9
3	0	-9.3	0.28	0.1	0.1
4	0	-9.9	0.30	-0.7	-0.7
5	9.1	2.2	0.18	14.2	5.1
6	16.7	6.5	0.23	19.5	2.8

$$C_a = 100 \left[\frac{(53a + 53d) - (53b + 53c)}{(53a + 53b + 53c + 53d)}\right] \quad (13)$$

$$F_a = 100 \left[\frac{(d_0 + d_9) - (d_3 + d_6)}{(d_0 + d_3 + d_6 + d_9)}\right] \quad (14)$$

$$S_{1a} = \frac{3 \cdot (C_a - F_a)}{100 + 2C_a} \quad (16)$$

(S'_{1a} = average S_{1a} = 0.28)

$$C = \frac{F_a + 100 \cdot (S'_{1a})/3}{1 - 2 \cdot (S'_{1a})/3} \quad (18)$$

$$S_{1a} = \frac{3 \cdot (C_a - F_a)}{100 + 2C_a} \quad (16)$$

From equations (15) and (16), equation (17) can be derived. For each of the thermolyses then, the mole fraction

$$S_{1a} = 1.5\ S_{2a} \qquad (17)$$

of the amine mixture that was formed from scrambled betaines will lie somewhwere between S_{1a} and S_{2a} as calculated from F_a and C_a and since S_{1a} is the larger of the two mole fractions, the corresponding S_{1a} values are listed in Table 7. Examination of these reveals that S_{1a} varies between Ø.35 and Ø.18 and that the average, S'_{1a}, is Ø.28. If S'_{1a} is assumed to be a constant, the set of F_a values may be corrected for this extent of scrambling using equation (18) in which C is the calculated % endo (or % excess $\underline{d}_Ø$,$\underline{d}_9$).† The agreement of ± 1Ø% between C and C_a suggests that if the F_a's obtained

$$C = \frac{3\ F_a + 1ØØ\ S'_{1a}}{3 - 2\ S'_{1a}} \qquad (18)$$

from the crossing experiment ratios are corrected using equation (18) with S'_{1a} = Ø.28, then C should represent, within ± 1Ø%, the true percentage of endocyclic product in the betaine mixtures.

The results of the crossing experiments are summarized in Table 8. For these, an equimolar mixture of the $\underline{d}_Ø$- and $\underline{d}_9$-"norbetylates" (**65a** and **65d**) was shaken with saturated aqueous sodium carbonate then extracted with ethanol-free

---

†If S_{2a} is calculated for each of the authentic mixtures, the average, S'_{2a}, is found to be Ø.19. When this value used in equation (19) which is derived in Appendix 3, the same C's as those reported in Table 7 are obtained.

$$C = \frac{F_a + 5Ø\ S'_{2a}}{1 - S'_{2a}} \qquad (19)$$

Table 8
Butane Derivative Crossing Experiment Results

Exp't No.	Temp. (°C)	Reaction Time (da)	[**52a** + **52d**] (mol L^{-1})	**53**	Yields (%) $HNMe_3Cl^-$	Thermolysis Amine Ratio d_0	d_3	d_6	d_9	F_a (%)	**C** (%)
1	23	21	1.0×10^{-2}	-	33	100.0	123.0	116.7	84.5	-13.0	-4.5
2	61	21	1.9×10^{-4}	55	33	100.0	115.9	99.8	76.7	-10.0	-0.8
3	61	27	1.9×10^{-4}	30	27	100.0	118.2	102.3	79.9	-10.2	-1.1

$$F_a = \text{found \% excess } d_0, d_9 = 100 \left[\frac{(d_0 + d_9) - (d_3 + d_6)}{d_0 + d_3 + d_6 + d_9} \right] \qquad (14)$$

$$C = \text{calculated \% endo} = \frac{3F_a + 100\, S'_{1a}}{3 - 2\, S'_{1a}} \qquad (18)$$

where S'_{1a} is the average mole fraction of the product that was scrambled in the authentic mixture control experiments ($S'_{1a} = 0.28$).

chloroform. The extract was further diluted in a volumetric flask to give a stock solution of the d_0-and d_9-esters (**52a** and **52d**) in which the combined ester concentration ([**52a** + **52d**]) was known.† In the first experiment, an aliquot of a stock solution was transferred to a round-bottom flask which was then stoppered, wrapped in foil, and left for 21 days at room temperature. In experiments 2 and 3, stock solutions were diluted with anhydrous ethanol-free chloroform and then refluxed in the dark for the indicated reaction times. The exclusion of light was only partially successful in preventing solvent decomposition since discoloration of the solvent was observed and the odor of phosgene was detected during the work up. After the indicated reaction times, unreacted **52a** and **52d** were hydrolyzed by simply adding water to the reaction mixture and then refluxing the resulting suspension overnight. After the chloroform and water were removed by distillation, the residue was dissolved in water and washed with ether to remove any organic soluble solvent decomposition products. The aqueous layer was evaporated leaving a mixture of the "norbetaine" and the betaine (**53**). To remove the "norbetaine", the mixture was dissolved in water and passed through a column of deionizing resin.* Evapora-

---

†As a control experiment, an aliquot of one stock solution, when evaporated to dryness, gave a 97% yield of the trimethyl betaine (**53**). The deprotonation procedure was therefore taken to be quantitiative.

*When an aqueous solution of **53a** was passed through a column of deionizing resin (1Ø equiv.) and then evaporated to dryness, 85% of the betaine was recovered. Conversely, similar treatment of **68** resulted in a 4% recovery.

tion of the eluant left the betaine in the indicated yield. In the third crossing experiment, a ^1H NMR spectrum of the crude products in 1 M Na_2CO_3-D_2O indicated the 29% of the mixture was the betaine, in excellent agreement with the isolated yield (30%). Thermolysis of the betaine in the usual manner gave trimethylammonium chloride in the indicated yields. Mass spectrometric analysis of these mixtures gave the reported $\underline{d}_0 : \underline{d}_3 : \underline{d}_6 : \underline{d}_9$ amine ratios and from each, the found % excess $\underline{d}_0$, $\underline{d}_9$, F_a, was calculated using equation (14). These values were then corrected for scrambling ($S'_{1a} = 0.28$) using equation (18) to give the calculated % endo, C, for each crossing experiment. That these are all to close to zero (well within the $\pm$ 10% error inherent in the scrambling correction) indicates that the crossing experiments show no sign whatever of any intramolecular methyl transfer and hence the only reasonable conclusion is that the formation of **53** from **52** occurs via the intermolecular pathway.

If it as assumed that 10% of the product of the crossing experiment that was conducted at the lowest initial ester concentration (E_0) and was allowed to reach the greatest percent reaction was indeed endocyclic product and that its presence was masked by the experimental error ($\pm$ 10%) inherent in the analytical method, then an upper limit to the **EM** of the endocyclic reaction may be calculated using equation (10).† Of course, to use this equation, a value for the final ester concentration (E_f) is required. If it is assumed that all of

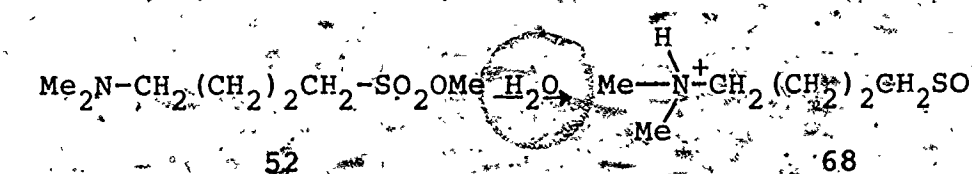
†Equation (10) is derived in Appendix 2.

the "norbetaine" (68) in the crude product mixture was formed

$$\% \text{ endo} = \frac{50EM}{(E_0 - E_f)} \ln\left(\frac{2E_0 + EM}{2E_f + EM}\right) \qquad (10)$$

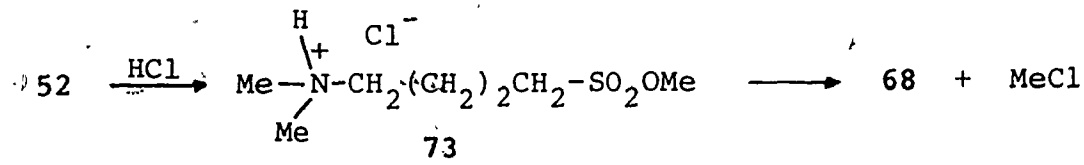
during the quenching hydrolysis, then the extent of conversion of 52 to 53 will equal the betaine yield. For Experiment 2 and 3 in which E_0 and E_f are 1.9×10^{-4} M and 1.1×10^{-4} M respectively (average betaine yield = 42%), equation (10) shows that for less than 10% of the betaine to have been the product of endocyclic methyl transfer, an EM less than 3×10^{-5} M is indicated.

The validity of the assumption that the percent reaction is equal to the betaine yield requires further discussion since comparision of the betaine yields with the reaction times in Experiment 2 and 3 indicates that, at least in Experiment 3, some of the "norbetaine" must have been formed prior to quenching hydrolysis. This second source of the "norbetaine" is probably hydrolysis of the starting material by adventitious moisture and/or protonation of the ester by HCl produced by the solvent decomposition followed by a substrate reagent ion pair (or SRIP)[3] reaction by the resulting "norbetylate" chloride, 73, to give methyl chloride and 68.†



52 68

† Methyl chloride, due to its volatility (bp - 24°C), would be rapidly distilled from the reaction mixture and hence would not react with 52.



52 —HCl→ Me—N⁺(H)—CH₂(CH₂)₂CH₂—SO₂OMe Cl⁻ (Me) → 68 + MeCl

73

Since the second order rate constant for the conversion of **52** to **53** at 61°C in $CHCl_3$ was not determined, the extent of the incursion of these "norbetaine" - producing side reactions cannot be evaluated. The effect on the **EM** assignment must, therefore be considered. Because both side reactions would serve to increase the range of ester concentrations spanned during the formation of the betaine, betaine derived from the first order endocyclic pathway will, therefore be favoured over that formed from the second order intermolecular pathway. This will result in an erroneously high **EM** assignment. Fortunately, since only an upper limit to the **EM** is being assigned, the effect of the side reactions can be ignored because the **EM** limit assigned with the assumed E_f will contain any of this error resulting from the side reaction. It may safely be concluded then that the **EM** for the endocyclic methyl transfer of **52** to form **53** is indeed less than $.3 \times 10^{-5}$ M.

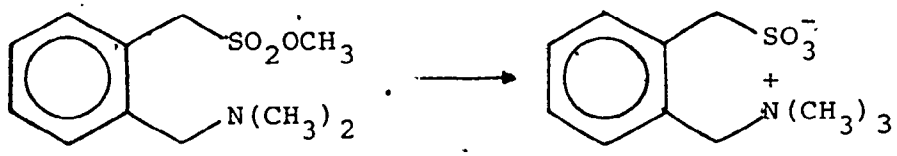
In summary, the crossing experiments show no sign, even at concentrations as low as 1.9×10^{-4} M, of an endocyclic methyl transfer in the conversion of **52** to **53**. When considered in terms of the experimental error, the results are consistent with an **EM** of less than 3×10^{-5} M for the endocyclic process. Although any saturated eight-membered cyclic transi-

tion state is subject to the steric strain usual to such medium rings[4], the fact that this EM is less than 1/10 of that reported[8] for an analogous exocyclic reaction (i.e. the lactonization of 7-bromoheptanoate) indicates that there is very likely additional strain associated with the endocyclic backside S_N2-like reaction in a simple eight member cyclic system. In Baldwin's terminology[15], the 8-endo-tet reaction is probably "disfavoured". While further effort would certainly reduce the experimental error inherent in the methods described in this section of the thesis, it was decided that, in view of the humble conclusions that were drawn from these studies, this effort would be better expended in examining the reaction of a substrate which has a greater potential for undergoing endocyclic methyl transfer.

B. The Formation of 2-(Trimethylammoniomethyl)phenylmethanesulfonate (55) from Methyl 2-(Dimethylaminomethyl)phenylmethanesulfonate (54)

1. Introduction

Since the medium ring effect is virtually absent in the cyclic reactions of many ortho-benz-fused ring systems,[6] it seemed reasonable to anticipate that an 8-endo-tet methyl transfer would also be facilitated by the inclusion of an ortho-benz-fused moiety in its cyclic array. Accordingly, the rearrangement of **54** to **55** was examined.



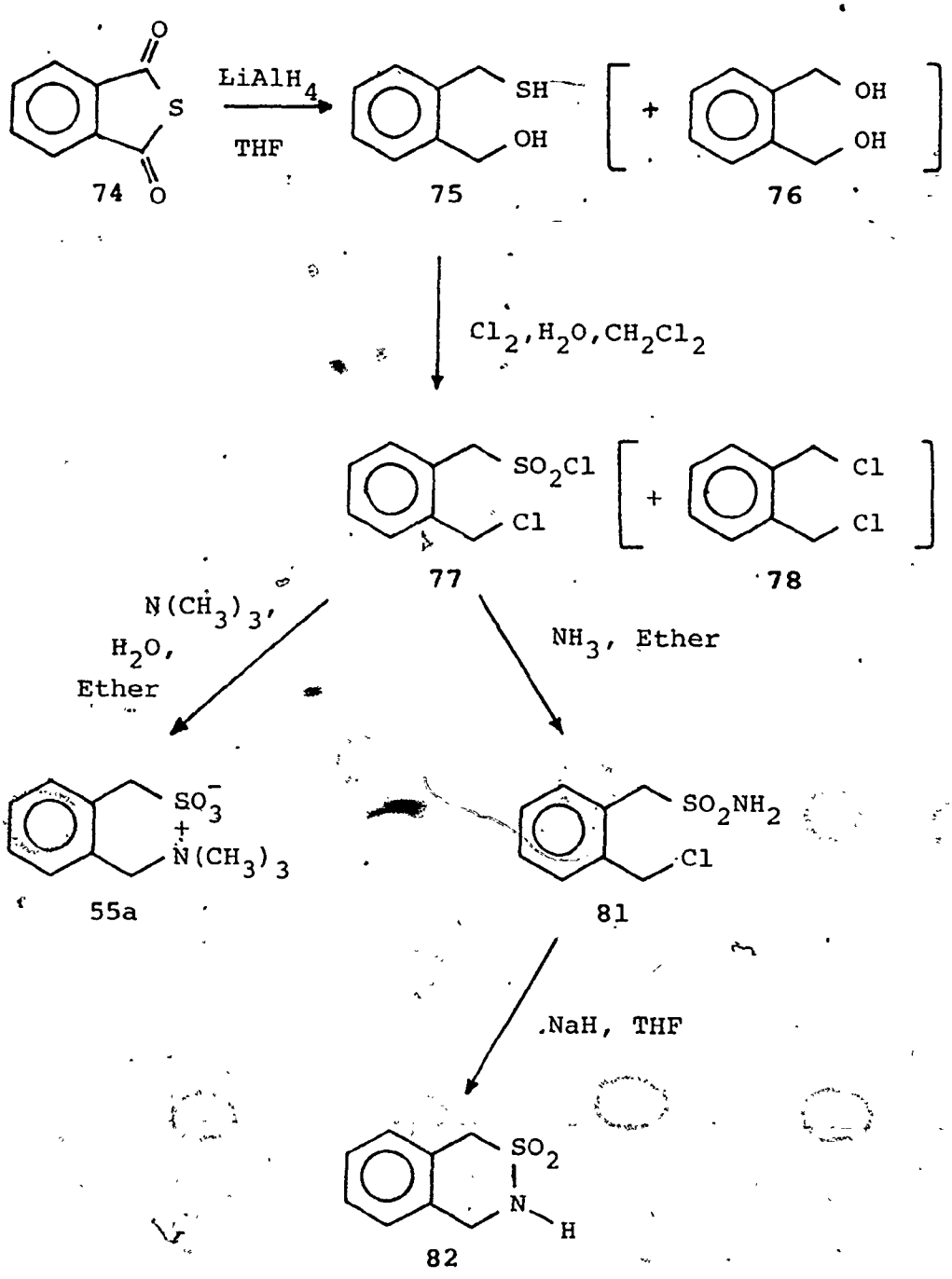
54 **55**

This section describes the kinetic and double-label crossing experiments used to determine the molecularity of the rearrangement of **54** to **55** as well as the synthesis of the compounds used in these experiments. The procedures used in these experiments were somewhat more refined than those discussed in the Section II A. 3 and 4 since the resulting **EM**, (or in the absence of endocyclic methyl transfer, the assigned maximum **EM**) would be more significant simply because there are more **EM** data for 8-membered benz-fused cyclic reactions with which to compare the result. Also, to circumvent the previously mentioned difficulties posed by the decomposition of

chloroform during the crossing experiments, benzene was used as the solvent for the rearrangement of **54** to **55**.

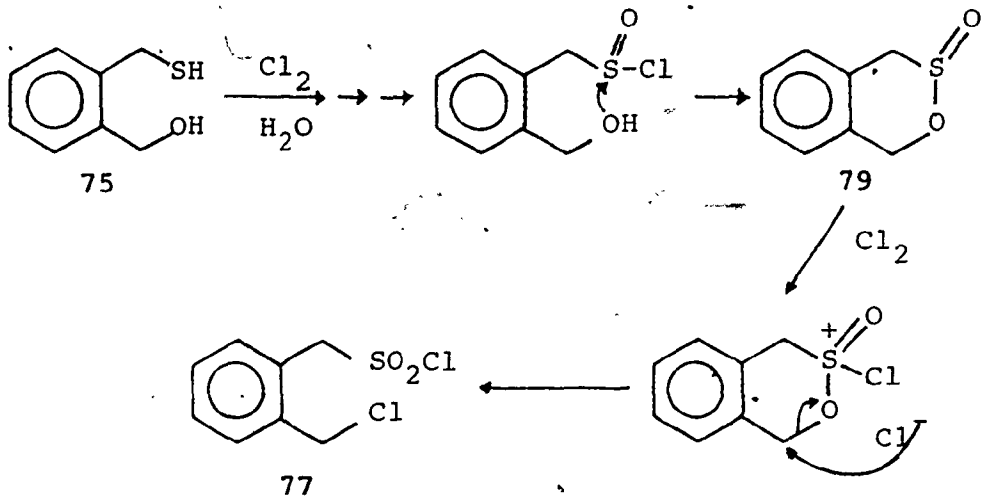
2. Synthesis:

In the previously described synthesis of the butane derivatives, the use of tetrahydro-2H-1,2-thiazine 1,1-dioxide (**62**) as a synthetic intermediate resulted in a particularly efficient sequence with which to introduce the deuterated methyl groups. It seemed reasonable, then, to expect that the analogous ortho-benz-fused sultam, 3,4-dihydro-1H-2,3--benzothiazine 1,1-dioxide (**82**) would be equally useful in the synthesis of the required 2-methylphenylmethane derivatives. The synthesis of the sultam (**82**), is shown in Scheme 3. Following the recommendation of Schlessinger and Ponticello[70], thiophthalic anhydride (**74**) was reduced with excess lithium aluminum hydride in ether to give 2-(mercaptomethyl)phenylmethanol (**75**). Careful examination of the product indicated that it was an approximately equimolar mixture of **75** and 2--(hydroxymethyl)phenylmethanol (**76**). When the reduction was conducted in refluxing tetrahydrofuran, however, a 3:1 mixture of **75** to **76** was obtained and hence no further optimization was attempted. Oxidative chlorination of **75** in a water--methylene chloride suspension at 0°C gave a 90% yield of 2--(chloromethyl)phenylmethanesulfonyl chloride (**77**). Noteworthy in this reaction is the substitution at the benzylic carbon of the hydroxyl group with a chlorine atom. Neighboring group participation by the benzylic hydroxyl via a cyclic intermediate such as the sultine (**79**) would seem to be a rea-

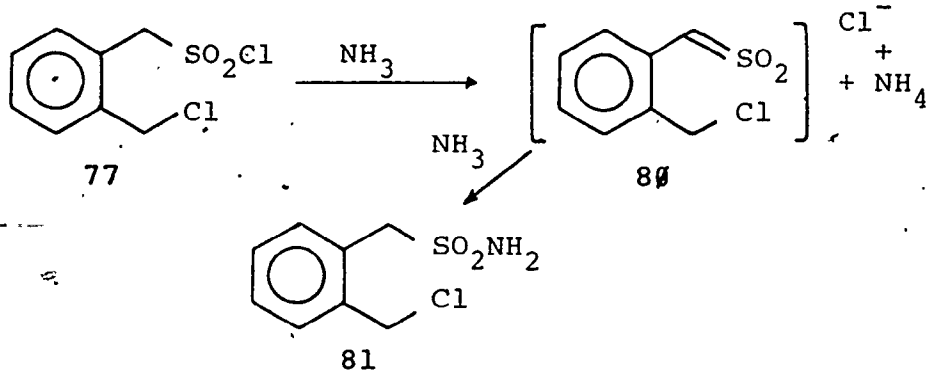

LiAlH4
THF
SH
OH
OH
OH
74
75
76
Cl2, H2O, CH2Cl2
SO2Cl
Cl
Cl
Cl
77
78
N(CH3)3,
H2O,
Ether
NH3, Ether
SO3−
+
N(CH3)3
SO2NH2
Cl
55a
81
NaH, THF
SO2
N
H
82

Scheme 3

sonable mechanism.[59]

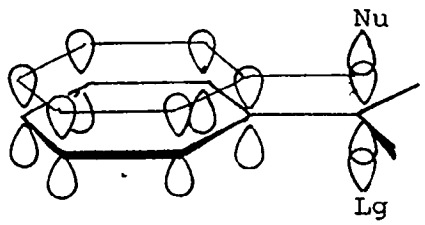


In practice, the mixture **75** and **76** obtained by reduction of **74** was not separated but, rather, was chlorinated directly to give a mixture of 2-(chloromethyl)phenylmethanesulfonyl chloride (**77**) and, apparently, chloro-2-(chloromethyl)phenylmethane (**78**). The structure of **78** was assigned solely on the basis of the ^1H NMR spectrum of the crude mixture; no attempts were made either to isolate or characterize this compound. Simple extraction with pentane removed **78** from the mixture to yield **77** sufficiently pure for synthetic purposes. Treatment of **77** with 2.1 equivalents of ammonia in anhydrous ether gave a 95% yield of 2-(chloromethyl)phenylmethanesulfonamide (**81**). The selective substitution of the sulfonyl chloride over that of the benzylic chloride is undoubtedly the consequence of sulfene (**80**) intermediacy in this reaction.[71]



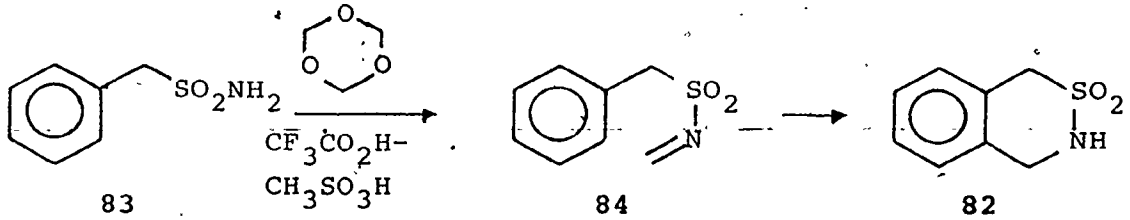
The last step in the synthesis of **82** was the base-catalyzed cyclization of the chlorosulfonamide (**81**). This proved to be more difficult than was anticipated in view of the known facility of other 6-<u>exo</u>-<u>tet</u> ring closures.[6,7] Attempted cyclization of **81** in ethanol with sodium hydroxide following the procedure used for the preparation of 1,4-butane sultam (**62**) gave mainly oligomeric materials. At higher dilution, solvolysis became a major complication. Under carefully optimized conditions, however, a 46% yield of **82** was obtained <u>via</u> slow dropwise addition of the sulfonamide (**81**) in tetrahydrofuran to a refluxing sodium hydride-tetrahydrofuran suspension. The difficulty encountered in the cyclization is probably a result of the stereochemical requirements of nucleophilic displacements on benzylic carbons. In general, that S_N2 reactions on benzylic carbon are facile has been ascribed to orbital overlap between the reaction center's <u>p</u> orbital and the aromatic <u>p</u> orbitals and hence is optimal when the axis joining the nucleophile and the leaving group is perpendicular to the plane of the aromatic ring.[72] Deviations from this transition state structure have recently be-

en shown to be accompanied by an increase in activation energy.[73] For the ring closure resulting in the formation of **82**, molecular models indicate that such a deviation is imposed



on the transition state by the configuration of the hydrocarbon backbone. Since the bimolecular reaction is subject to no such constraint, it is then favoured over the intramolecular reaction relative to 6-<u>endo</u>-<u>tet</u> reactions not involving a benzylic reaction center. The result is then a depression in the **EM** for the formation of **82**.

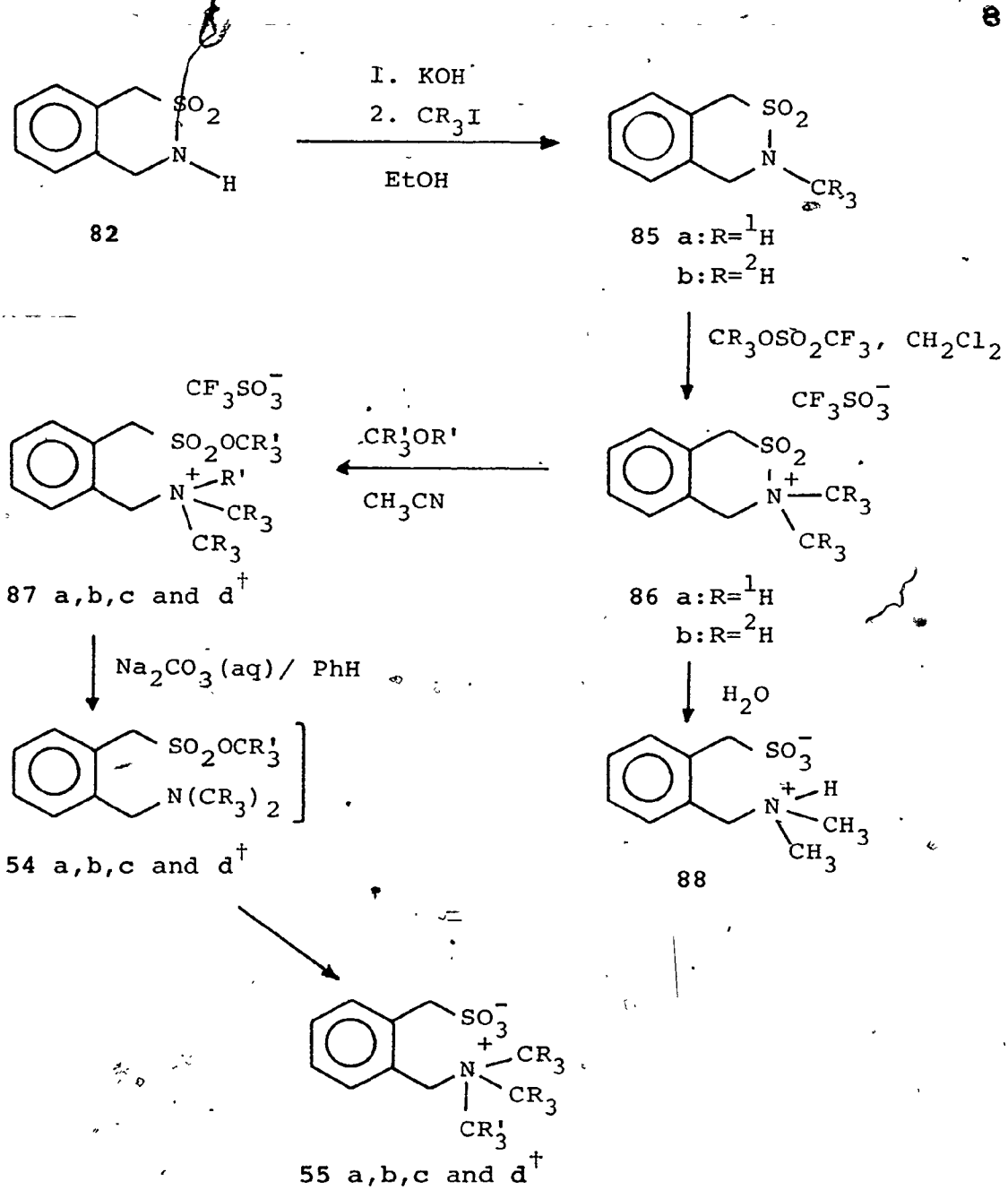
In the literature, there is an apparently more convenient synthesis of **82**. Orazi and Corral[74] have reported that phenylmethanesulfonamide (**83**) reacts with trioxan in 75% methanesulfonic acid-trifluoroacetic acid to give **82** in 67% yield, presumably <u>via</u> an N-sulfonylimine intermediate (**84**).



83 **84** **82**

Unfortunately, this work was overlooked prior the completion of the synthesis of **82** reported herein.

The remaining steps in the synthesis, shown in Scheme 4, parallel those used in the synthesis of the butane derivatives. Treatment of the sultam, **82**, in ethanol with potassium hydroxide and then with methyl iodide gave the N-methyl sultam, 3-methyl-3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxide (**85a**) in 90% yield. Methyl trifluoromethanesulfonate was then used to methylate **85a** to give the "sultamium" salt, 3,3-dimethyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (**86a**) in 85% yield. Methanolysis of **86a** overnight at room temperature in anhydrous acetonitrile-methanol gave the "norbetylate", 2-(methoxysulfonylmethyl)-phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (**87a**) in 75% yield. The "norbetylate", **87a**, was suspended in benzene and washed with aqueous sodium carbonate to give a benzene solution of the aminoester, methyl 2-(dimethylaminomethyl)phenylmethanesulfonate (**54a**). Evaporation of the solvent left an oily residue which solidified to give the betaine, 2-(trimethylammoniomethyl)phenylmethanesulfonate (**55a**), as colourless crystals. The overall yield for the conversion of **87a** to **55a** was 98%. A specimen of **55a** was prepared independently by reacting an ether solution of the chloro sulfonyl chloride (**77**), with aqueous trimethylamine. That this material was identical to that obtained from **87a** confirmed the structural assignment. Also, an authentic sample of the "norbetaine", 2-(dimethylammoniomethyl)phenylmethanesul-



82

85 a:R=^{1}H
b:R=^{2}H

86 a:R=^{1}H
b:R=^{2}H

87 a,b,c and d†

54 a,b,c and d†

88

55 a,b,c and d†

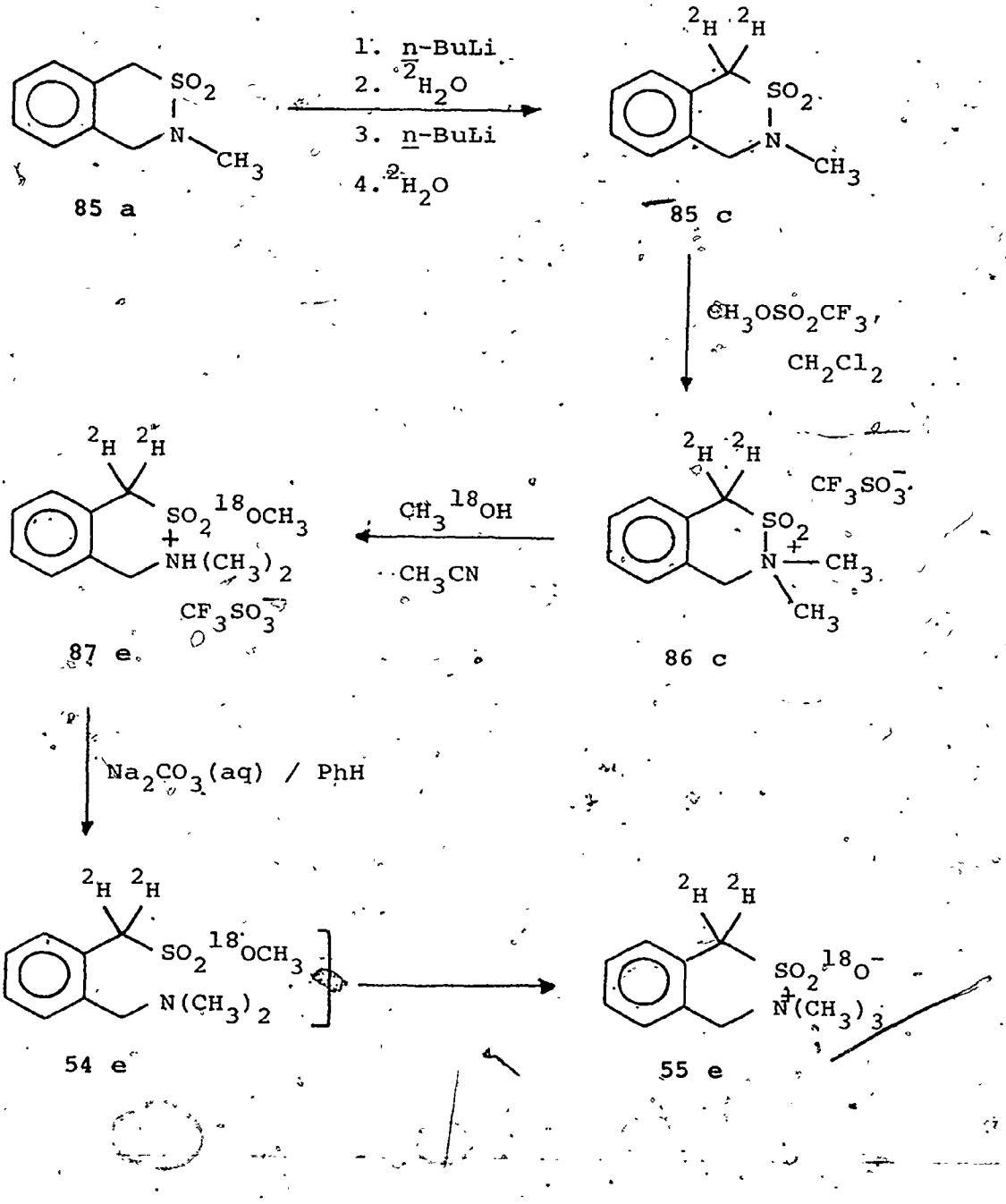
† a:R,R'=^{1}H; b:R=^{1}H,R'=^{2}H; c:R=^{2}H,R'=^{1}H; d:R,R'=^{2}H

Scheme 4

fonate (**88**), was prepared by hydrolysis of the "sultamium" salt (**86a**) in aqueous acetonitrile.

Samples of the $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-"norbetylates", **87b, c** and **d**, were required for the deuterio methyl crossing experiments. The $\underline{d}_3$-"norbetylate" was prepared by ($^2H_4$)methanolysis of the "sultamium" salt, **86a**. For the $\underline{d}_6$- and $\underline{d}_9$-"norbetylates", the sultam (**82**) was methylated with ($^2H_3$)methyl iodide to give the $\underline{N}$-($^2H_3$)methyl sultam (**85b**) which, in turn, was methylated with ($^2H_3$)methyl trifluoromethanesulfonate to give the $\underline{d}_6$-"sultamium" salt, **86b**. Treatment of **86b** with methanol gave the $\underline{d}_6$-"norbetylate", **87c** and, similarly, ($^2H_4$)methanolysis of **86b** gave the $\underline{d}_9$-"norbetylate", **87d**. Controls related to the crossing experiments required the use of authentic samples of the $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-betaines (**55b, c** and **d** respectively). These were each prepared from the corresponding "norbetylates" via deprotonation with sodium carbonate followed by the rearrangements of the corresponding intermediate aminoesters, **54b, c** and **d**. Deuterium combustion analysis of **55d** indicated that the labelled methyls averaged 96% deuteration.

For a different type of crossing experiment, the required starting materials were **87a** and 2-[($^{18}O_1$)methoxysulfonyl ($^2H_2$)methyl]phenyl-$\underline{N}$,$\underline{N}$-dimethylmethanaminium trifluoromethanesulfonate (**87e**). The synthesis of **87e** is shown in Scheme 5. The $\underline{N}$-methylsultam (**85a**), in tetrahydrofuran at -78°C, was treated with excess $\underline{n}$-butyl lithium, warmed to room temperature and quenched with excess D_2O. The product, obtained



85 a

85 c

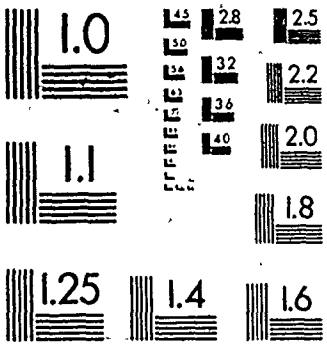
87 e

86 c

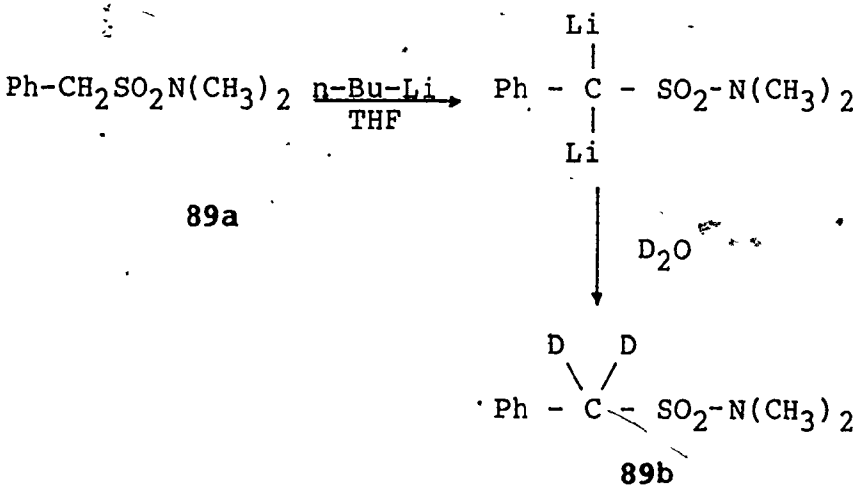
54 e

55 e

Scheme 5


1.0
1.1
1.25
1.4
1.6
2.8
3.2
3.6
4.0
2.5
2.2
2.0
1.8

in 50% yield after purification by chromatography followed by recrystallization, was (1,1-$^2H_2$)-3-methyl-3,4-dihydro-1H--2,3-benzothiazine 2,2-dioxide (**85c**). ^1H NMR indicated that approximately 85% deuteration had occurred at the α -sulfonyl methylene. A second identical exchange cycle resulted in 91% deuteration. In agreement with this result, Kaiser, et al[75], have reported that N,N-dimethylphenylmethanesulfonamide (**89a**), when treated with 2.2 equivalents of n-butyl lithium and then with excess D_2O, underwent 80% deuterium exchange at the α -sulfonyl methylene. This result was considered to be the first evidence for the existence of α-dilithio sulfonamides.



89a **89b**

The d_2-sultam (**85c**), was then methylated in the usual manner with methyl trifluoromethanesulfonate to give the d_2--"sultamium" salt, (1,1-$^2H_2$)-3,3-dimethyl-3,4-dihydro-1H-2,-3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (**86c**). ^1H NMR analysis again showed approximately 90% deuter-

ation at the α-sulfonyl methylene. ($^{18}O_1$)Methanolysis† then gave **87e**. The corresponding betaine, 2-(trimethylammoniomethyl)phenyl($^2H_2$)methane($^{18}O_1$)sulfonate (**55e**), was then prepared from **87e** via $^{18}O_1$-methyl 2-(dimethylaminomethyl)phenyl($^2H_2$)methane($^{18}O_1$)sulfonate (**54e**) in the usual manner.

3. Kinetic Studies

As in Section II A.3, equation (5) was assumed to be the rate law describing the formation of **55** from **54** (or **E**). Again, the first term applies to the first order endocyclic pathway and the second, to the second order intermolecular methyl transfer.

$$-\frac{d\mathbf{E}}{dt} = k_1 \mathbf{E} + 2k_2 \mathbf{E}^2 \qquad (5)$$

A somewhat more elaborate ^1H NMR kinetic procedure was devised for the experiments reported in this section. Briefly, the "norbetylate" (**87**), was deprotonated with aqueous sodium carbonate then extracted into d_6-benzene. After addition of the internal standard (1,1,2,2-tetrachloroethane, δ=5.1 ppm), the ester solution was sealed under nitrogen at -78°C in an NMR tube. An integrated ^1H NMR spectrum was

---

† The ($^{18}O_1$)methanol was prepared using the method of Sawyer-76. Briefly, tri-n-butyl formate (**90**) was hydrolyzed with $H_2{}^{18}O$ (98% ^{18}O) in the presence of a catalytic amount of anhydrous HCl to give ($^{18}O_1$-)n-butyl formate (**91**). Lithium aluminum hydride reduction of this material then gave, in 75% yield, ($^{18}O_1$)-methanol which was later found (see Section II.D) to contain approximately 93% ^{18}O.

$$(CH_3(CH_2)_3\text{-}O)_3\text{-}CH \xrightarrow[HCl]{H_2\,{}^{18}O} CH_3(CH_2)_3\text{-}O\text{-}\overset{\overset{O}{\overset{\|}{}}}{\underset{H}{C}} \xrightarrow[diglyme]{LiAlH_4} CH_3\text{-}{}^{18}O\text{-}H$$

90 **91**

then obtained immediately. The sample was then immersed in a constant temperature bath and a timer was started. At appropriate intervals, the sample was removed from the bath and thermally quenched by immersion in ice water. After the ^1H NMR integral of a peak characteristic of **54** and that of the internal standard peak were recorded, the sample was returned to the bath. The timer was stopped during the interval in which the sample was out of the bath. The reactions were generally followed to 80% completion. At $t = \infty$ (overnight or when no signals due to **54** were detectable), the tube was opened and flushed water which, on evaporation, left a crystalline residue. In all runs, the residue, when examined by ^1H NMR in basic D_2O, was found to be >98% betaine (**55**). The initial ester concentration was calculated from the amount of recovered betaine and the volume of solvent in the NMR tube which was deduced from the weight of water required to fill the tube to the same level as the original ester solution. The initial pair of integrals and the initial ester concentration then furnished the internal standard concentration with which the ester concentrations were calculated from each of the subsequent pairs of integrals. All of the runs reported in Table 6 gave linear second order plots (1/[**E**] *versus* time). The slopes of best fit lines, as deduced by linear least squares regression analysis, provided the observed second order rate constants (k_{obs} or $2k_2$). A typical plot is shown in Figure 6. In view of the time error introduced by the thermal quenching procedure and the error inherent in

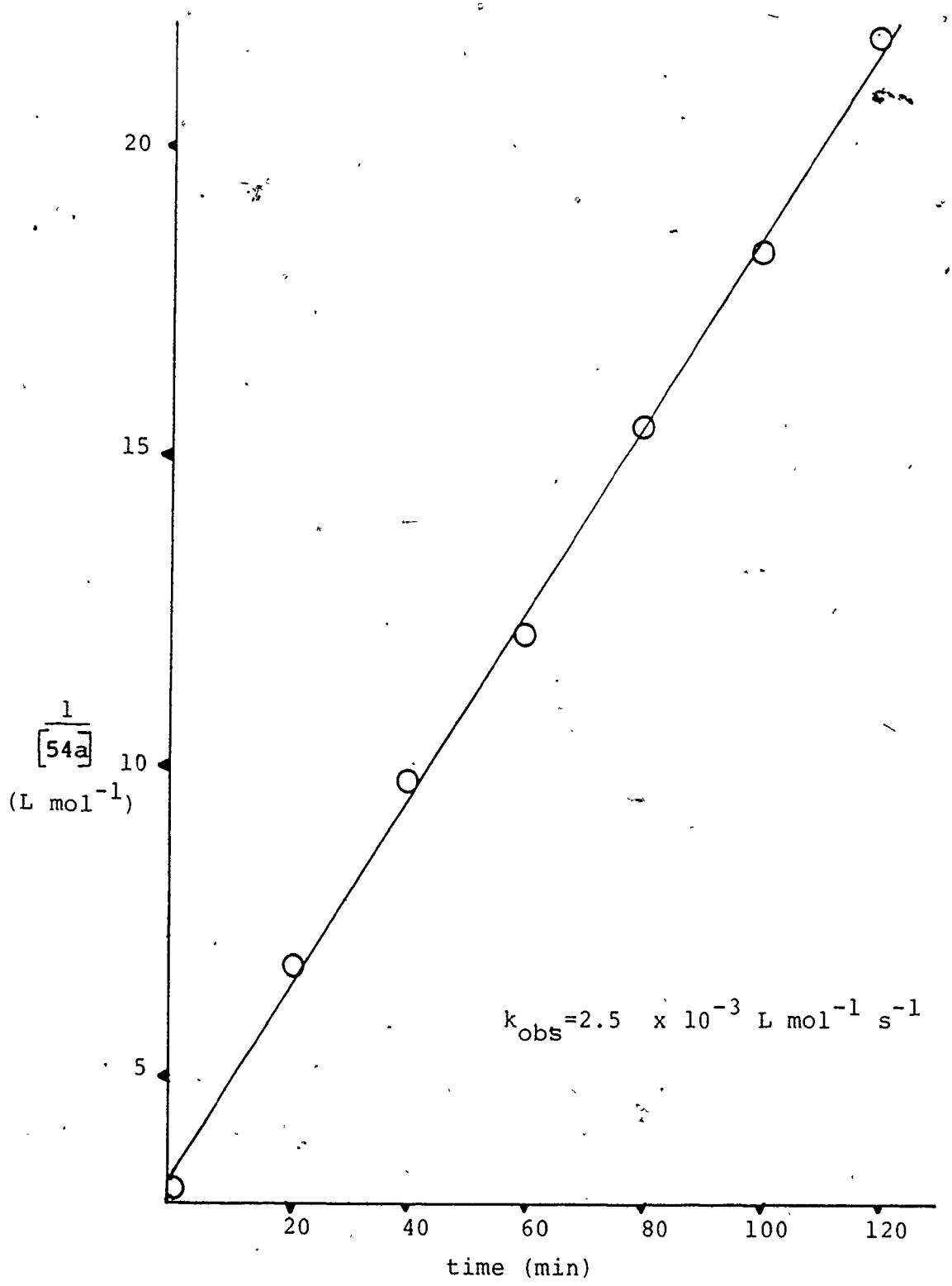


Figure 6: Rate of the Rearrangement of Methyl 2-(Dimethylaminomethyl)phenylmethanesulfonate (**54a**) to 2-(Trimethylammoniomethyl)phenylmethanesulfonate (**55a**) in C_6D_6 at 110.0°C

the solvent volume determination, ± 10% would seem to be a reasonable limit to the reproducibility of these rate constants.

Table 9

2-(Methyl)phenylmethane Derivative Kinetic Results

Exp't No.	Ester	Temp. (°C)	$[Ester]_0$ (M)	k_{obs} ($L\ mol^{-1}s^{-1} \times 10^3$)
2(a)(i)	**54a**	110.0	0.319	2.5
2(a)(ii)	**56a**	110.0	0.172	2.5
2(b)	**54a**	91.0	0.223	1.1
2(c)	**54a**	70.0	0.219	0.35
2(d)	**54a**	37.0	0.307	0.049
2(e)	**54b**	110.0	0.278	2.8
2(f)(i)	**54c**	110.0	0.202	3.2
2(f)(ii)	**54c**	110.0	0.193	3.3
2(g)	**54d**	110.0	0.253	2.8

The observed clean second order kinetics indicates that, between ester concentrations of 0.30 and 0.04 M, the formation of **55** from **54** occurs predominantly by the intermolecular pathway and not by way of endocyclic substitution. The linearity of the kinetic plots when compared with the simulated mixed kinetic curves discussed in Section II.A.3, (Figure 3) is consistent with an **EM** of less than 0.04 M for the endocyclic pathway.

In order to facilitate crossing experiment optimization, the temperature dependence of k_{obs} was determined between 37.0° and 110.0°C. The Eyring plot (ln (k_{obs}/T) versus

$1/T)^{\dagger}$ shown in Figure 7 was constructed. The slope of the linear least squares best fit line gave the activation enthalpy, $\Delta H^{\ddagger}$, and entropy, $\Delta S^{\ddagger}$, which were 12.2 kcal mol^{-1} and -39 cal $K^{-1}\,mol^{-1}$ respectively.

The large negative $\Delta S^{\ddagger}$ is typical of S_N2 reactions in nonpolar aprotic solvents. For example, Reinheimer *et al*[78] have reported $\Delta S^{\ddagger}$'s of -34 and -36 cal $K^{-1}\,mol^{-1}$ for the alkylations of pyridine with ethyl bromide and ethyl iodide respectively in benzene at 80°C. An interesting feature in these data is that, at 37°C, k_{obs} for **54** to **55** in benzene is less than 1/50'th of k_{obs} for **52** to **53** in $CDCl_3$. Part of the rate reduction is due to the lower solvent polarity of benzene relative to chloroform. For example, Lassau and Jungers have reported that the second order rate constant for the methylation of tripropylamine with methyl iodide at 20°C in chloroform is seven times that determined for the same reaction in benzene.[79] The rest of the reactivity reduction must

---

† From ref. (77):

$$k_{obs} = \left[\frac{\kappa T}{h}\right] e^{\Delta S^{\ddagger}/R} \cdot e^{-\Delta H^{\ddagger}/RT}$$

$$\therefore \ln\left[\frac{k_{obs}}{T}\right] = \ln\left[\frac{\kappa}{h}\right] + \frac{\Delta S^{\ddagger}}{R} - \frac{\Delta H^{\ddagger}}{RT}$$

The slope of $\ln\left[\frac{k_{obs}}{T}\right]$ versus $1/T$ equals $-\frac{\Delta H^{\ddagger}}{R}$

and $\Delta S^{\ddagger} = \frac{\Delta H^{\ddagger}}{T} + R \ln\left[\frac{h\, k_{obs}}{\kappa T}\right]$

(In this calculation S was determined for 110.0°C)
where h = Planck's constant; κ = Boltzmann's constant)
R = gas constant; T = temperature (K)

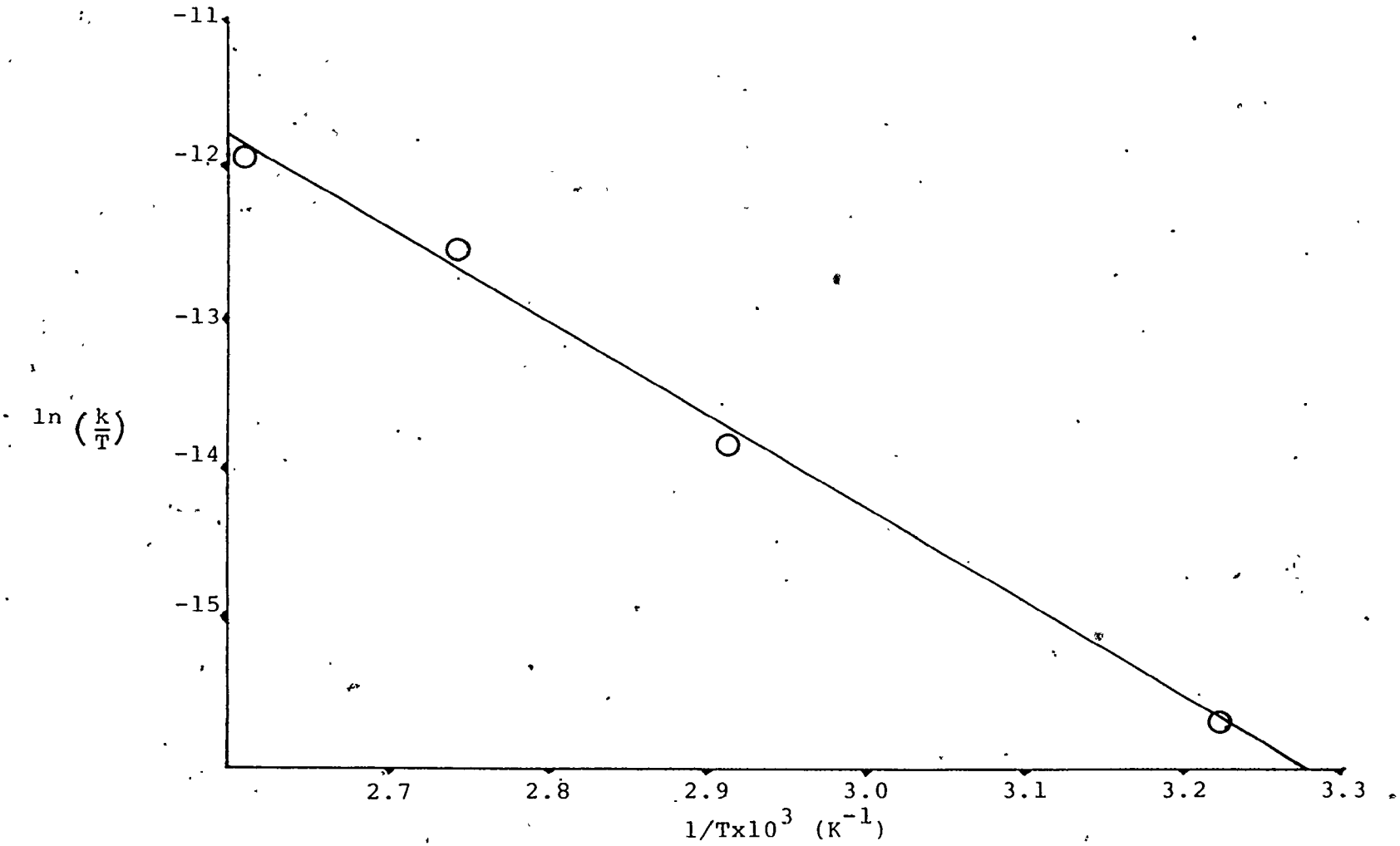


Figure 7: Eyring Plot for the Rearrangement of Methyl 2-(Dimethylaminomethyl)-phenylmethanesulfonate (54a) in C_6D_6

stem from the replacement of the ethylene (in 52) with the ortho-fused benzene ring (in 54). Since the site of the structural change is two bonds away from the amino nitrogen atom and four bonds away from the methoxy carbon atom, a reasonable expectation is that this structural change should modify the reactivity of the former much more than the latter. The nucleophilicity of 54 should be less than that of 52 simply because the aromatic ring is, relative to an ethylene, inductively electron withdrawing. This effect is paralleled by the pKa's of benzyldimethylamine and n-butyldimethylamine which are 8.93 and 10.02 respectively.[80] As well, the steric bulk of the ortho substituted benzene ring in 54 should further reduce the nucleophilicity of the nitrogen atom in 54 relative to that in 52.

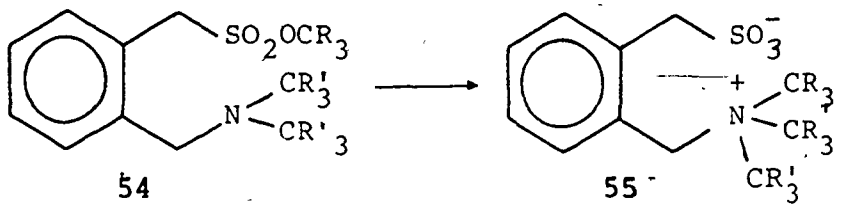
The remaining entries in Table 9 represent attempts to measure the secondary kinetic isotope effects (S.K.I.E.'s) encountered in the rearrangements of 54a, b, c and d.

S.K.I.E.'s in S_N2 reactions have been the subject of numerous studies[81-88] and have been found to be useful in the transition state structural analysis of reactions of this type. Unfortunately, the ±10% error inherent in the second order rate constants reported in Table 9 precludes any such analysis. The results do suggest, however, that the S.K.I.E.'s are rather small and hence may be ignored in the interpretation of the forthcoming double-label crossing experiments.

In summary, the kinetic studies described in this sec-

tion have shown that, between concentrations of 0.3 M and 0.04 M, the formation of 55 from 54 occurs by intermolecular methyl transfer and not by way of endocyclic displacement. The results are consistent with an EM of less than 0.04 M for the endocyclic pathway. The intermolecular reaction has activation parameter typical of S_N2's in nonpolar solvents.

4. Crossing Experiments:



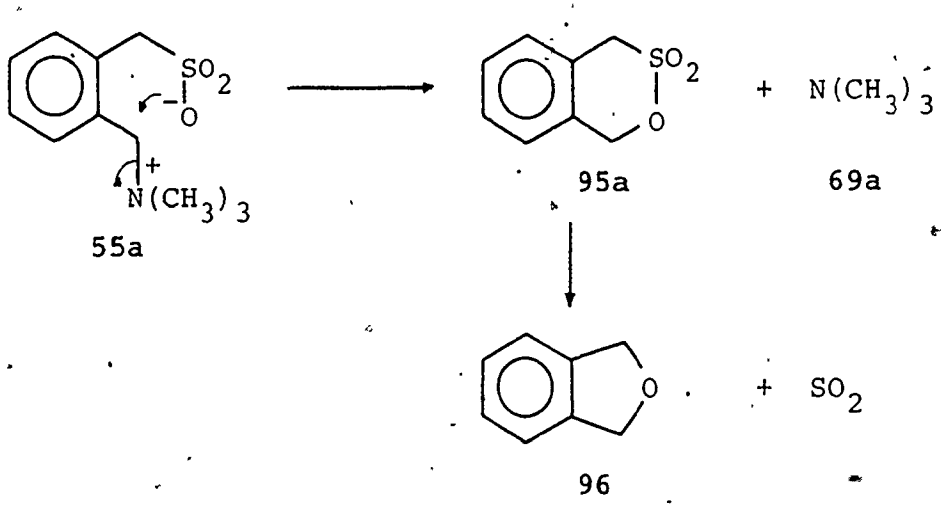
54 55

a:R,R'=^{1}H;**b**:R=^{2}H,R'=^{1}H;**c**:R=^{1}H,R'=^{2}H;**d**:R=R'=^{2}H

At concentrations of **54** lower than those used in the kinetic studies, the molecularity of the rearrangement of **54** to **55** was determined via double-label crossing experiments. In these, an equimolar mixture of the $\underline{d}_0$- and $\underline{d}_9$--esters (**54a** and **d**), was expected to give, after endocyclic methyl transfer, an equimolar mixture of the $\underline{d}_0$- and $\underline{d}_9$-betaines (**55a** and **d**) and, likewise, an equimolar mixture of the $\underline{d}_3$- and $\underline{d}_6$-esters (**54b** and **c**) would be expected to give an equimolar mixture of the $\underline{d}_3$- and $\underline{d}_6$-betaines (**55b** and **c**). (The significance of the apparently redundant latter experiment will emerge shortly). Conversely, intermolecular methyl transfer would be expected to result in the formation of a 1:1:1:1 mixture of the $\underline{d}_0$-, $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-betaines (**55a, b, c** and **d**) from either ester mixture.

The mass spectrometric properties of the betaines were examined in view of determining the relative amounts of each of the betaines in mixtures of **55a, b, c** and **d.** Paralleling the behavior of **53** as described in Section II A.4,

a mass spectrometer probe temperature of 260°C was required to generate a mass spectrum from **55a**; this spectrum contained no molecular ion from **55a** (m/e = 243) but did show ions attributable to trimethylamine (**69a**, m/e = 59), the sultone (1,4-dehydro-2,3-benzoxathiin 3,3-dioxide, **95a**, m/e = 184) and phthalan (**96**, m/e = 120). The required probe temperature and the thermal behavior of **53** suggest that **69a** and **95a** are the products of a 6-exo-tet thermal decomposition of **55a**. Extrusion of sulfur dioxide by **95a** is a likely source of **96**.



The amine clusters from duplicate mass spectrometric thermolyses of **55a** were found to each consist of a parent ion (m/e = 59), an M + 1 peak due primarily to the natural abundance of ^{15}N and ^{13}C and an M - 1 peak caused by the loss of a hydrogen atom from the parent ion. The observed relative intensities of the M + 1 peaks in the duplicate runs (3.2 and 4.0) agreed with the relative intensity calculated for C_3H_9N (3.8) within the experimental error inherent

in the mass spectrometric method ($\pm$ 2) and the M - 1 peaks were, as in Section II A.4, variable (17.5 and 46.6). Since the remainder of the range of m/e's that would be occupied by the amines generated from mixtures **55a, b, c** and **d** (m/e = 61 to 69) was devoid of extraneous ions, thermolysis of **55** directly in the mass spectrometer probe seemed to be an adequate solution to the problem of analyzing betaine mixtures.

Next, the labelled betaines, **55b, c** and **d**, were examined and the analytical results are recorded in Table 10. For these and for all subsequent betaine mixtures, the spectra were compiled and the overlap between the amine clusters was removed using the procedure described in Section II A.4. Again, the results are reported as the amounts of each of the $\underline{d}_0$-, $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-amines (**69a, b, c** and **d**) normalized to one amine which has been arbitrarily assigned a value of 100. The data in Table 10 clearly show that

Table 10

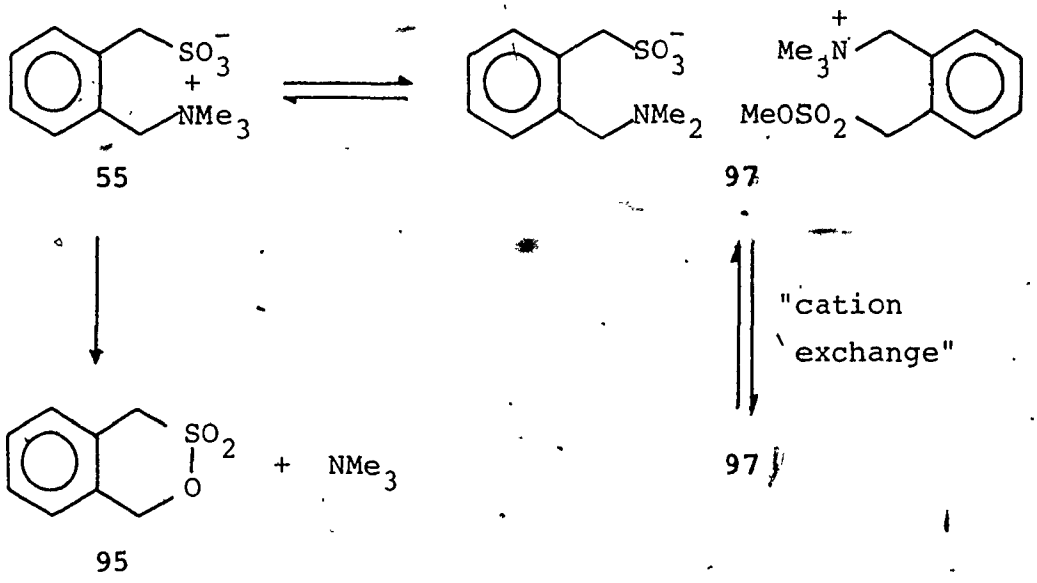
2-Methylphenylmethane Derivative Betaine Thermolysis

Analytical Results

Betaine	Observed Trimethylamine Ratio			
	$\underline{d}_0$	$\underline{d}_3$	$\underline{d}_6$	$\underline{d}_9$
55a	100.0	0	0	0
55b	1.5	100.0	1.0	0
55c	0	0.4	100.0	1.9
55d	0	0	0	100.0

the $\underline{d}_0$- and $\underline{d}_9$-betaines (**55a** and **d**) both yield exclusively

the appropriate amines (**69a** and **69d** respectively). The $\underline{d}_3$- and $\underline{d}_6$-betaines (**55b** and **c**), however, yield, as well as the appropriate amines (**69b** and **c** respectively), small but real amounts of the amines containing one more and one less deuterated methyl than predominant amine. These results are then indicative of partial scrambling of the ammonio methyls during the thermolysis. Paralleling the thermolysis of **53**, this scrambling is probably the result of cation exchange by the ion pair, **97**, that is apparently formed reversibly during the thermolysis of **55** <u>via</u> the intermolecular displacement of an ammonio methyl by a sulfo anion.



The effect of this scrambling pathway on the observed amine ratios is discussed in detail in Section II A.4 and in Appendix 3 and this discussion will not be repeated here. Pertinent, however, is that the $\underline{d}_3$-betaine, after one cation exchange, will be converted into a 2:5:2-**55a:55b:55c** mixture

and after numerous exchanges, will be converted into the stastically scrambled 8:12:6:1-**55a:55b:55c:55d** mixture. It follows then that amine generated during the $\underline{d}_3$-betaine thermolysis will consist both of unscrambled $\underline{d}_3$-amine and of a scrambled amine mixture that will be present in a ratio somewhere between the two above-mentioned extremes. Similarly, the $\underline{d}_6$-betaine, on thermolysis, will yield a mixture of unscrambled $\underline{d}_6$-amine and scrambled amines which will be present in a ratio somewhere between the single exchange derived $\emptyset$:2:5:2-$\underline{d}_\emptyset$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ mixture and the statistically scrambled 1:6:12:8-$\underline{d}_\emptyset$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ mixture. Although in principle, the amine ratios obtained from the $\underline{d}_3$- and $\underline{d}_6$-betaines thermolyses could each be analyzed to determine the fraction of these amines that were derived from scrambled betaine for both of the scrambling extremes, such analyses would be inappropriate since, in both spectra, the sizes of the peaks attributable to scrambled amines do not exceed the experimental error inherent in the mass spectrometric method. It may, however, be concluded that, while the extent of scrambling observed in the thermolysis of **55** is considerably less than that previously observed in the thermolysis of **53**, scrambling in the former is indeed real and, therefore, the amine ratios obtained from crossing experiment product thermolyses must be corrected for this scrambling.

With the need for a scrambling correction in mind, the authentic mixtures of **55a, b, c** and **d** that would be expected to arise from the crossing experiments were prepared

and analyzed mass spectrometically. Since the ensuing discussion of the scrambling correction is rather detailed, in order to place it in its proper perspective, the set of selected authentic mixture control experiment results shown in Table 11 will first be compared with a representive set of $\underline{d}_0,\underline{d}_9$ crossing experiment results which is shown in Table 12. Briefly, the authentic mixtures reported in Table 11 represent, in order, the intermolecular methyl transfer product, the endocyclic product and the product mixture that would result from 20% endocyclic and 80% intermolecular methyl transfer. When the crossing experiment amine ratios are compared with the authentic mixture amine ratios, they are found to most closely resemble the amine ratio obtained from the 1:1:1:1-betaine mixture. The preliminary conclusion that may be drawn is then that, at concentrations of **54** as low as 4.5×10^{-4} M, **55** is formed from **54** by way of intermolecular methyl transfer and not via the endocyclic pathway. In order to assign a maximum **EM** for the endocyclic reaction, a detailed analysis of both the authentic betaine mixture control experiments and of the crossing experiments is required.

In the $\underline{d}_0,\underline{d}_9$ crossing experiments products and in the authentic mixtures that mimic them, the endocyclic product is represented by the amount by which the sum of **55a** and **55d** exceeds the sum of **55b** and **55c**. When expressed as a percentage of the mixture, the expected % endo (or % excess

Table 11

Selected 2-Methylphenylmethane Derivative

Authentic Betaine Mixture Thermolysis Control Experiments

Exp't No.	Betaine Mixture 55a	55b	55c	55d	Observed Amine Ratio d_0	d_3	d_6	d_9
1	1	1	1	1	100.0	100.0	94.6	84.2
2	1	0	0	1	100.0	9.0	9.4	101.2
12	1.5	1	1	1.5	100.0	80.5	82.2	103.3

Table 12

Selected 2-Methylphenylmethane Derivative

Crossing Experiment Results (Benzene, 110°C)

Exp't No.	[54a + 54d]$_0$, (M)	Observed Amine Ratio d_0	d_3	d_6	d_9
1	4.5×10^{-3}	100.0	104.0	97.1	86.7
5	8.9×10^{-4}	100.0	99.0	93.3	88.0
9	4.5×10^{-4}	100.0	117.5	119.8	97.2

$\underline{d}_0$,$\underline{d}_9$), C_a, may be calculated using equation (22).†

$$C_a = 100 \left[\frac{(55a + 55d) - (55b + 55c)}{55a + 55b + 55c + 55d} \right] \qquad (22)$$

Similarly in the amine mixtures generated from these samples, the found % endo (or % excess $\underline{d}_0$,$\underline{d}_9$), F_a, is defined by equation (14).

$$F_a = 100 \left[\frac{(\underline{d}_0 + \underline{d}_9) - (\underline{d}_3 + \underline{d}_6)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9} \right] \qquad (14)$$

As it did in Section II A.4, partial scrambling will cause F_a to be less than C_a for each of these thermolyses and, again, the amine mixtures so generated will be made up of unscrambled and scrambled components. The former will have the same label distribution as did the initial betaine mixture while the latter will have a distribution that lies somewhere between the distribution obtained by scrambling one of the betaine's ammonio methyls and the statistically scrambled 1:3:3:1-$\underline{d}_0$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ distribution that would be the result of the exchange of all three of the betaine's ammonio methyls. The mole fraction of the amine mixture that is attributable to the scrambled component can be calculated assuming either of the scrambling extremes. Equation (16) provides the scrambled mole fraction based on the single methyl exchange assumption (S_{1a}) while Equation (15) provides the scrambled mole fraction based on assumed statistical scrambling (S_{2a}). The true scrambled mole fraction will

†The subscript "a" denotes a parameter derived from a mixture in which the endocyclic product is present as enrichment in the $\underline{d}_0$ and $\underline{d}_9$ species and in which half of the ammonio or amino methyls in the mixture (U=L=0.5) are labelled.

$$S_{1a} = \frac{3\ (C_a - F_a)}{100 + 2\ C_a} \qquad (16)$$

$$S_{2a} = \frac{C_a - F_a}{50 + C_a} \qquad (15)$$

then lie somewhere between S_{1a} and S_{2a}.

The scrambling correction procedure used in Section II A.4 involved simply obtaining an average scrambled mole fraction (S'_{1a}) from the authentic mixture control experiments and then using this value to correct the F_a's obtained from the crossing experiment betaine mixtures. While the error inherent in this method was rather large (± 10%), it was deemed to be acceptable in view of the humble conclusions drawn from those experiments. In this section, since the conclusions were expected to be more significant, a more accurate scrambling correction procedure was desired. Experience gained from preliminary experiments involving the thermolyses of mixtures of **55a**, **b**, **c** and **d** suggested that the day to day variation in the extent of scrambling in these thermolyses (S_{1a} = 0.10 ± 0.10) was comparable to that previously observed in the thermolyses of **53** and that this variation was probably a consequence of poor reproducibility in some unknown variable associated with the mass spectrometer probe conditions. These experiments suggested, however, that S_{1a} was virtually constant (± 0.02) for analyses conducted consecutively. A scrambling correction procedure based on the use of complementary $\underline{d}_0$,$\underline{d}_9$ and $\underline{d}_3$,$\underline{d}_6$ crossing experiments was devised to exploit this feature. A discussion this method requires, first, a brief

description of the properties of $\underline{d}_3,\underline{d}_6$ crossing experiments and of the thermolytic behavior of their resulting betaine mixtures.

Whereas the endocyclic product from a $\underline{d}_0,\underline{d}_9$ crossing experiment is an equimolar mixture of the $\underline{d}_0$- and $\underline{d}_9$-betaines, (**55a** and **d**), a $\underline{d}_3,\underline{d}_6$ crossing experiment's endocyclic product will be an equimolar mixture of the $\underline{d}_3$- and $\underline{d}_6$-betaines (**55b** and **c**). It follows then that in $\underline{d}_3,\underline{d}_6$ crossing experiments products or in authentic mixture that mimic them, the expected % <u>endo</u> (or % excess $\underline{d}_3,\underline{d}_6$), $\mathbf{C}_b$, may be calculated using equation (23).†

$$\mathbf{C}_b = 100\left[\frac{(\mathbf{55b} + \mathbf{55c}) - (\mathbf{55a} + \mathbf{55d})}{\mathbf{55a} + \mathbf{55b} + \mathbf{55c} + \mathbf{55d}}\right] \qquad (23)$$

Similarly, in the amine mixtures derived by thermolyses of these samples, the found % <u>endo</u> (or % excess $\underline{d}_3,\underline{d}_6$), $\mathbf{F}_b$, can be calculated with equation (24).

$$\mathbf{F}_b = 100\left[\frac{(\underline{d}_3 + \underline{d}_6) - (\underline{d}_0 + \underline{d}_9)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \qquad (24)$$

Partial scrambling in these thermolyses will again perturb the amino ratio toward the statistical 1:3:3:1 - $\underline{d}_0:\underline{d}_3:\underline{d}_6:\underline{d}_9$ amine ratio and, therefore, if $\mathbf{C}_b$ is less than 50% then $\mathbf{F}_b$ will be greater than $\mathbf{C}_b$ but if $\mathbf{C}_b$ is greater than 50%, then $\mathbf{F}_b$ will be less than $\mathbf{C}_b$. If the scrambling is assumed to be limited to the exchange of only one ammonio

†The subscript "b" denotes a parameter that is obtained from a mixture in which the endocyclic product is present as enrichment in the $\underline{d}_3$ and $\underline{d}_6$ species and in which half of the ammonio or amino methyls are labelled (U=L=0.5).

methyl, then the mole fraction of the amine mixture that consists of scrambled amines (S_{1b}), can be calculated using equation (25) which is derived in Appendix 3. If, however, the scrambled component is assumed to be present in the statistical distribution that results from the exchange of all three ammonio methyls, then its mole fraction (S_{2b}) can be calculated using equation (26). Again, the actual

$$S_{1b} = \frac{3(F_b - C_b)}{100 - 2C_b} \qquad (25)$$

$$S_{2b} = \frac{C_b - F_b}{50 - C_b} \qquad (26)$$

scrambled mole fraction will lie somewhere between these extremes.

With the following argument, it may be shown that these scrambling equations provide a means through which to compare $\underline{d}_0,\underline{d}_9$ and $\underline{d}_3,\underline{d}_6$ crossing experiments conducted under identical reaction conditions and in so doing, obtain the true percentage of the products that are attributable to the endocyclic pathway (**C**). If the extent of scrambling is the same in both thermolyses, then S_{1a} will equal S_{1b} and S_{2a} will equal S_{2b}. It follows then that equation (16) and (25) may be combined to give equation (27) and similarly (14) and (26) give (28):

If $S_{1a} = S_{1b}$ then,

$$3\,\frac{(C_a - F_a)}{100 + 2C_a} = 3\,\frac{(F_b - C_b)}{100 - 2C_b} \qquad (27)$$

and if $S_{2a} = S_{2b}$ then,

$$\frac{C_a - F_a}{50 + C_a} = \frac{C_b - F_b}{50 - C_b} \qquad (28)$$

Since the crossing experiment products being compared will have been formed under identical reaction conditions, they should, in the absence of isotope effects, have in common the same percentage of endocyclic products and this value, the true percent endo, C, will equal both C_a and C_b. If C is substituted for C_a and C_b in equations (27) and (28), both yield, after rearranging and collecting terms, equation (29). The significance of this equation is that it allows

$$C = \frac{F_a + F_b}{2 + 0.02\,(F_a - F_b)} \qquad (29)$$

C, the true percent <u>endo</u>, to be calculated directly from the F_a and F_b values obtained from $\underline{d}_0$, $\underline{d}_9$ and $\underline{d}_3$, $\underline{d}_6$ crossing experiments which were conducted under identical conditions. Both the total extent of scrambling and the average number of ammonio methyls per betaine involved in this scrambling need not be known to obtain C. The validity of equation (29), of course, hinges on the assumption that consecutive thermolyses share identical extents of scrambling. To test this, excess $\underline{d}_0$, $\underline{d}_9$ and excess $\underline{d}_3$, $\underline{d}_6$ betaine mixtures which shared common C_a and C_b values were prepared and analyzed. The results of these analyses are recorded in Table 13. In the first three experiments, which represent the extremes of the product ratios anticipated from the crossing experiments, the mixtures were prepared by simply weighing out the appropriate amounts of the betaines then combining them. An error of $\pm 5\%$ in C would seem to be a reasonable consequence of this procedure. Experiment 1's mixture is the

Table 13

Authentic 2-Methylphenylmethane Betaine Mixtures Control Experiments

1. Excess $\underline{d}_0, \underline{d}_9$ Mixtures

Exp't No.	C_a % endo	Observed Amine Ratio $\underline{d}_0$	$\underline{d}_3$	$\underline{d}_6$	$\underline{d}_9$	F_a (excess $\underline{d}_0, \underline{d}_9$)
1	0	100.0	100.0	94.6	84.2	-2.7
2	100	100.0	9.0	9.4	101.2	83.3
4	2.5	100.0	93.9	91.3	86.5	0.4
6	5.0	100.0	107.1	107.5	92.4	-5.5
8	7.5	100.0	94.7	90.0	89.0	1.2
10	10.0	100.0	89.6	85.7	91.6	4.4
12	20.0	100.0	80.5	82.2	103.3	11.1

2. Excess $\underline{d}_3, \underline{d}_6$ Mixtures

Exp't No.	C_b % endo	Observed Amine Ratio $\underline{d}_0$	$\underline{d}_3$	$\underline{d}_6$	$\underline{d}_9$	F_b (excess $\underline{d}_3, \underline{d}_6$)
3	100	4.1	100.0	98.8	5.1	91.1
5	2.5	100.0	114.2	113.7	98.8	6.8
7	5.0	100.0	127.4	132.5	107.3	11.2
9	7.5	100.0	126.1	128.2	98.3	12.4
11	10.0	100.0	131.5	133.3	94.3	15.4
13	20.0	100.0	152.6	149.7	96.3	21.3

Table 13 (cont'd)

3. Combined Results

C_a, C_b % endo	Excess $\underline{d}_0$, $\underline{d}_9$ Expt' No.	Excess $\underline{d}_3$, $\underline{d}_6$ Expt' No.	F_a % excess $\underline{d}_0$, $\underline{d}_9$	F_b % excess $\underline{d}_3$, $\underline{d}_6$	C % endo
100	2	3	83.3	91.1	94.6
2.5	4	5	0.4	6.8	3.8
5.0	6	7	-5.5	11.2	3.4
7.5	8	9	1.2	12.4	7.7
10.0	10	11	4.4	15.4	11.1
20.0	12	13	11.1	21.3	18.0

$$C_a = 100\left[\frac{(55a + 55d) - (55b + 55c)}{55a + 55b + 55c + 55d}\right] \quad (22)$$

$$C_b = 100\left[\frac{(55b + 55c) - (55a + 55d)}{55a + 55b + 55c + 55d}\right] \quad (23)$$

$$F_a = 100\left[\frac{(\underline{d}_0 + \underline{d}_9) - (\underline{d}_3 + \underline{d}_6)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \quad (14)$$

$$F_b = 100\left[\frac{(\underline{d}_3 + \underline{d}_6) - (\underline{d}_0 + \underline{d}_9)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \quad (24)$$

$$C = \frac{F_a + F_b}{2} + 0.02\,(F_a - F_b) \quad (29)$$

product that would be formed in both $\underline{d}_0,\underline{d}_9$ and $\underline{d}_3,\underline{d}_6$ crossing experiments in which the methyl transfer was entirely intermolecular. Since F_a is simply $-F_b$, C must be zero and hence this experiment does not serve as test of the descrambling approach. It does, however, show that the extent of scrambling is small and that F_a does not differ greatly from C_a. The excess $\underline{d}_0,\underline{d}_9$ and $\underline{d}_3,\underline{d}_6$ mixtures that are used in experiments 2 and 3 are those that would arise from completely endocyclic methyl transfer in $\underline{d}_0,\underline{d}_9$ and $\underline{d}_3,\underline{d}_6$ crossing experiments. The deviation of F_a and F_b from C_a and C_b clearly follow the pattern expected from partial scrambling and the agreement of C with C_a and C_b ($\pm$ 6%) is acceptable in view of the error associated with the mode of sample preparation. To reduce this source of error, aqueous solution of **55a**, **b**, **c** and **d** were prepared and their concentrations were adjusted until a common U.V. absorbance (1.230 $\pm$ .005, 268.5 nm, 1 cm cells) was obtained. Appropriate volumes of these solutions were dispensed with a burette and then combined and evaporated to dryness to give each of the samples used in the rest of the control experiments. The uncertainty in these mixture compositions is probably less than $\pm$ 1%. The data obtained from these mixtures is listed in Table 13, and as well, the F_a, F_b and C values are illustrated in Figure 8. Since these samples represent mixtures for which C_a or C_b is less than 50%, in all cases, F_a should be less than C_a and F_b should be greater than C_b. This is indeed observed. The most note-

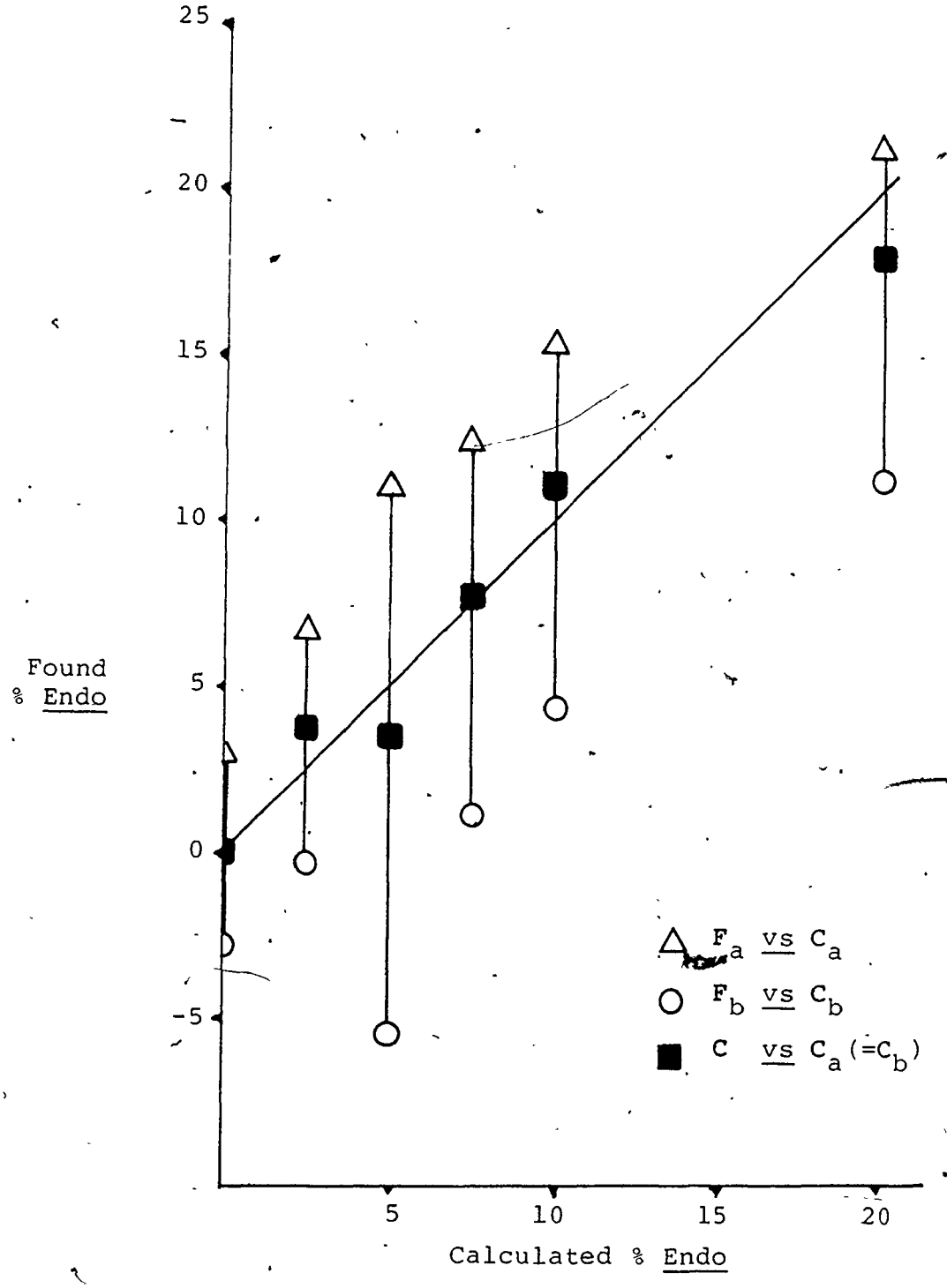


Figure 8: 2-Methylphenylmethane Derivative Authentic Betaine Mixture Control Experiment Results

worthly feature in these data is that, for all pairs, **C** agrees with $\mathbf{C}_a$ (or $\mathbf{C}_b$) to ± 2%. This argues well for the validity of the assumption that the extent of scrambling is effectly held constant within a given $\underline{d}_0$,$\underline{d}_9$ and $\underline{d}_3$,$\underline{d}_6$ pair of thermolyses that are analyzed consecutively.

Another feature of the data in Table 13 that warrants discussion is that, in all of the amine ratios, $\underline{d}_0$ is greater than $\underline{d}_9$ and $\underline{d}_3$ is greater than $\underline{d}_6$. This is probably a consequence of change in the amount of amine present in the probe during the time interval required for the acquisition of the mass spectra and of isotope effects in both the thermolytic degradation of **55** and in the ionization of the amines. The equations used to calculate $\mathbf{F}_a$, $\mathbf{F}_b$ and **C** are based on the assumption that this imbalance is linear with respect to m/e. That **C** agrees with $\mathbf{C}_a$ and $\mathbf{C}_b$ to ± 2% indicates that if any error is induced by this assumption, it is not large. In summary, the combined $\underline{d}_0$,$\underline{d}_9$ and $\underline{d}_3$,$\underline{d}_6$ analytical method is accurate to ± 2% in determining the amount of endocyclic product in authentic mixtures of **55a, b, c** and **d**. The same accuracy will then be expected in the crossing experiment analysis.

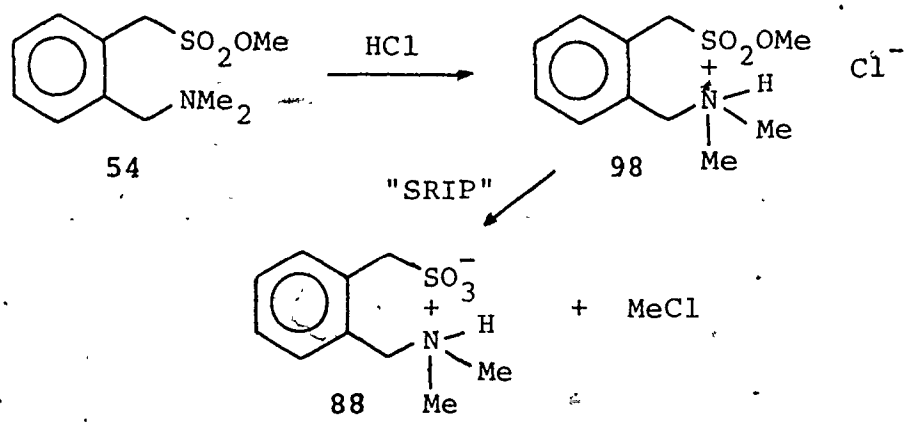
The procedure used in the crossing experiments described in this section is sufficiently different from that used in Section II A.4 that it warrants a separate discussion.

Stock solutions of the $\underline{d}_0$- and $\underline{d}_9$-esters (**54a** and **d**) and of the $\underline{d}_3$- and $\underline{d}_6$-esters (**54b** and **c**) were each prepared by deprotonating mixtures of the corresponding "norbetylates"

(**87a** and **d** or **87b** and **c**) with aqueous sodium carbonate then extracting the mixtures with benzene. The ester solutions were dried over magnesium sulfate, transfered to a dry box and then further dried first over magnesium perchlorate and then over calcium hydride. The solutions were filtered through Celite into volumetric flasks which were then filled to the mark with anhydrous benzene. The rigorous drying procedure was used to preclude the incursion of hydrolytic side reactions in the subsequent crossing experiments. A Karl Fischer titration of 1 mL of the $\underline{d}_0,\underline{d}_9$ stock solution indicated that the solution contained less than 0.2 equivalents of water ($[H_2O] < 1 \times 10^{-3}$ $\underline{M}$). It was necessary to know what the ester concentrations were in the stock solutions and, therefore, an aliquot of each was evaporated to dryness. The residue was stored overnight over Drierite at 50 torr then weighed, dissolved in 1 M Na_2CO_3 in D_2O and examined by ^1H NMR. The samples gave spectra that were consistent with **55** in which half of the ammonio methyls were absent and both spectra were devoid of any peaks ascribable to the "norbetaine" (**88**). These spectra, coupled with the yields, indicated that the conversion of the "norbetylates" to the esters was quantitative and hence the stock solution concentration were calculated directly from the number of moles of the "norbetylates" and the volumes of the stock solutions. Each sample was recovered by rinsing the NMR tubes with water and then passing this aqueous solution through a short column of deionizing resin (Rexyn 300

(^+H,^-OH), in 10 fold excess)† Evaporation of the eluant left the betaine which was then analyzed mass spectrometrically to give the amine ratio reported in Table 14 under the heading Stock 1 (and Stock 2). It should be noted that these samples represent the products of crossing experiments conducted at room temperature in the absence of a solvent.

For each of the crossing experiments summarized in Table 14, an aliquot of the appropriate stock solution was diluted in a volumetric flask with anhydrous benzene. The resulting solution was removed from the dry box and then sealed at -78°C under nitrogen in a flame-dried Carius tube, which was then immersed in a 100°C oil bath for the indicated reaction time. The tube was opened at -78°C and its contents were treated with 1 M HCl (3 equiv.) and then warmed to room temperature. The acid was used to convert unreacted **54** to the corresponding "norbetylate" chloride, **98**, which, based on experience with other "norbetylate" chlorides in



†In a control experiment, 95% of the sample of **55a** was recovered after being passed in water through a column of Rexyn 300 (10 equiv.). Similar treatment of a sample of the "norbetaine" (**88**) resulted in only a 5% recovery.

Table 14

2-Methylphenylmethane Derivative Crossing Experiment Results

1. d_0,d_9 Crossing Experiments

Exp't No.	[54a + 54d]$_0$ (M)	Reaction Time (h)	% Reaction calcd	% Reaction found	Observed Amine Ratio d_0	d_3	d_6	d_9	F_a (%)
(Stock 1)	Neat	12	100	>98	100.0	91.6	84.6	72.3	-1.1
1	4.5×10^{-3}	25	50	44	100.0	104.0	97.1	86.7	-3.7
3	8.9×10^{-4}	41	23.5	26	100.0	95.7	85.7	83.3	-0.5
5	8.9×10^{-4}	120	47	48	100.0	79.0	93.3	88.0	-1.1
7	4.5×10^{-4}	80	24.5	26	100.0	106.5	100.1	94.2	-3.0
					100.0	120.3	120.7	108.4	-7.2
9	4.5×10^{-4}	240	49	53	100.0	117.5	119.8	97.2	-9.2
					100.0	118.8	120.4	108.4	-6.9

$$F_a = 100 \left[\frac{(d_0 + d_9) - (d_3 + d_6)}{d_0 + d_3 + d_6 + d_9} \right]$$

Table 14 (cont'd)

2. d_3, d_6 Crossing Experiments

Exp't No.	[**54b** + **54c**]ø	Reaction Time (h)	% Reaction calcd	% Reaction found	Observed Amine Ratio d_0	d_3	d_6	d_9	F_b (%)
(Stock 2)	Neat	12	100	>98	100.0	101.1	93.5	85.2	2.5
2	4.5×10^{-3}	25	50	46	100.0	100.7	96.3	81.5	4.1
4	8.9×10^{-4}	41	23.5	25	100.0	95.3	88.1	77.3	1.7
6	8.9×10^{-4}	120	47	42	100.0	95.9	87.9	78.1	1.6
8	4.5×10^{-4}	80	24.5	24	100.0	100.8	92.1	80.1	3.4
					100.0	106.1	103.0	88.0	5.3
10	4.5×10^{-4}	240	49	57	100.0	107.2	108.5	85.7	7.5
					100.0	115.8	116.7	104.1	6.5

$$F_b = 100 \left[\frac{(d_3 + d_6) - (d_0 + d_9)}{d_0 + d_3 + d_6 + d_9} \right]$$

this laboratory, would be expected to undergo a substrate reagent ion pair (or SRIP)[3] reaction during the work up with the SRIP products being methyl chloride and the "norbetaine" (88). The mixture was then extracted with water. The organic layer was evaporated to dryness and the residue was weighed then examined in $CDCl_3$ by ^1H NMR. In all of the experiments, a small amount of oily material was obtained (0.1 - 0.4 mg; δ= 1.0 to 2.5 ppm, m). This oil was, in all likelihood, an impurity in the calcium hydride used to dry the stock solutions. The aqueous extract was evaporated to dryness and the residue was stored overnight at 50 torr over phophorus pentoxide in a desiccator. The residue was weighed then dissolved in 1 M Na_2CO_3 in D_2O and examined by ^1H NMR. In all the experiments, the ^1H NMR spectrum was consistent with a mixture the "norbetaine" (88) and the betaine (55) both of which were deficient in half of their ammonio methyl resonances. The lack of any peaks ascribable to the "norbetylate" chloride (97) confirms its anticipated fate. Also, product ratios, expressed as % 55, were obtained from the integrals of these spectra. After each mixture was recovered from the NMR tube, it was passed in water through a column of deionizing resin (10 equiv.). Evaporation of the eluant left the betaine which was weighed and then analyzed mass spectrometrically to give the amine ratio reported in Table 14. The reported found % endo values (F_a and F_b) were calculated from these using equations (14) and (24).

Generally, the weight of the crude product mixture

was approximately 10% (± 20%) greater than the amount calculated from the initial ester concentration, the volume of solvent used and the ^1H NMR betaine:"norbetaine" ratio. This is probably a result of the hygroscopic nature of **88** and the large variation is a result of the error inherent in the weighing procedure. The yields of the betaine obtained prior to the mass spectrometric analysis generally agreed to ± 10% with the NMR product ratios and again the error inherent in the weighing procedure is probably the main source of the discrepancies. It was, therefore, assumed that the NMR product ratio was the best measure of the extent of reaction and hence the found % reaction values in Table 14 are derived from these ratios. An assumption made here is that all of the "norbetaine" ,**88**, present in the product mixture was formed from unreacted starting material in the work-up. The calculated percent reaction was obtained from the integrated second order expression, equation (30).

$$\frac{1}{[\mathbf{54}]_f} = k_{obs} t + \frac{1}{[\mathbf{54}]_\emptyset} \qquad (30)$$

where $[\mathbf{54}]_\emptyset$ is the initial ester concentration, $[\mathbf{54}]_f$ is the apparent final concentration of the ester, k_{obs} is the observed second order rate constant for the conversion of **54** to **55** in benzene at 110°C (2.5×10^{-3} L mol^{-1} s^{-1}) and t is the reaction time in seconds. The agreement between the percent reaction derived from the NMR product ratio and the percent reaction calculated from the rate constant (± 5%) is well within the cumulative errors associated with

the ^1H NMR integrals and the rate constant value. This agreement suggests then that virtually all of **88** is indeed formed from **54** in the work up. It also argues well against the incursion of any unforeseen side reactions.

In keeping with the $\underline{d}_0,\underline{d}_9$ - $\underline{d}_3,\underline{d}_6$ analytical procedure, the F_a and F_b values derived from the pairs of $\underline{d}_0,\underline{d}_9$ and $\underline{d}_3,\underline{d}_6$ crossing experiments that had in common the same reaction times and initial ester concentrations, were used to obtain **C** values *via* equation (29). These data are summarized in Table 15.

That **C** is zero ($\pm$ 2%) for all of the pairs is strong evidence that the formation of **55** from **54**, under the range of concentrations of **54** employed in these crossing experiments, occurs exclusively *via* intermolecular methyl transfer.

It has been assumed in applying the analytical method developed from the authentic betaine mixture control experiments to the betaine product ratios from the crossing experiments that the latter are not perturbed by secondary kinetic isotope effects. However, since the crossing experiments were terminated after 25 or 50% reaction, it follows that if significant S.K.I.E.'s are operative in the intermolecular methyl transfers, then the product ratio's will indeed be perturbed. A brief discussion of the effects of S.K.I.E.'s on the **C** values is, therefore, required. Each intermolecular methyl transfer involves four functional groups that may or may not be labelled. Two of these interact directly with the methyl being displaced while the other two are

Table 15

Combined 2-Methylphenylmethane Crossing Experiment Results

$[E]_0$ (M)	% Reaction (calcd.)	d_0, d_9 Exp't No.	F_a (%)	d_3, d_6 Exp't No.	F_b (%)	C (% endo)	A (% endo)
Neat	00	Stock 1	-1.1	Stock 2	2.5	0.7	0.7
4.5×10^{-3}	50	1	-3.7	2	4.1	0.2	0.2
8.9×10^{-4}	23.5	3	0.5	4	1.7	0.9	0.7
8.9×10^{-4}	47	5	-1.1	6	1.6	0.3	0.4
4.5×10^{-4}	24.5	7	-3.0	8	3.4	0.2	0.2
			-7.2		5.3	-1.1	-0.9
4.5×10^{-4}	49	9	-9.2	10	7.5	-1.0	-0.9
			-6.9		6.5	-0.2	-0.2

$$[E]_0 = [54_a + 54_d]_0 = [54_b + 54_c]_0$$

$$C = \frac{F_a + F_b}{2 + 0.02\,(F_a - F_b)} \qquad (29)$$

$$A = \frac{F_a + F_b}{2} \qquad (30)$$

remote with their bonds to the labelled atoms being eight bonds away from the reaction center. If the remote labels impart no significant S.K.I.E.'s then the intermolecular product ratios for the $\underline{d}_0,\underline{d}_9$ and $\underline{d}_3,\underline{d}_6$ crossing experiments should be identical because the betaines so formed (**55a, b, c** and **d**) are derived from the same set of S.K.I.E.'s, (ie. 1, $k_{\underline{d}_0}/k_{\underline{d}_3}$, $k_{\underline{d}_0}/k_{\underline{d}_6}$ and $k_{\underline{d}_0}/k_{\underline{d}_9}$ respectively)

When these identical product ratios are used in equations (22) and (23), $\mathbf{C}_a$ will equal minus $\mathbf{C}_b$ and, likewise, $\mathbf{F}_a$ will be minus $\mathbf{F}_b$. The average of $\mathbf{F}_a$ and $\mathbf{F}_b$, **A**, will then be zero if no endocyclic methyl transfer has been observed in a complimentary pair of $\underline{d}_0,\underline{d}_9$ and $\underline{d}_3,\underline{d}_9$ and $\underline{d}_3,\underline{d}_6$ crossing experiments.

$$\mathbf{A} = \frac{\mathbf{F}_a + \mathbf{F}_b}{2} \qquad (31)$$

Examination of these averages reported in Table 15 reveals that they, like **C**, are within $\pm$ 2% of zero and hence indicate that the formation of **55** from **54** occurs exclusively <u>via</u> the intermolecular pathway and <u>not</u> via endocyclic methyl transfer.

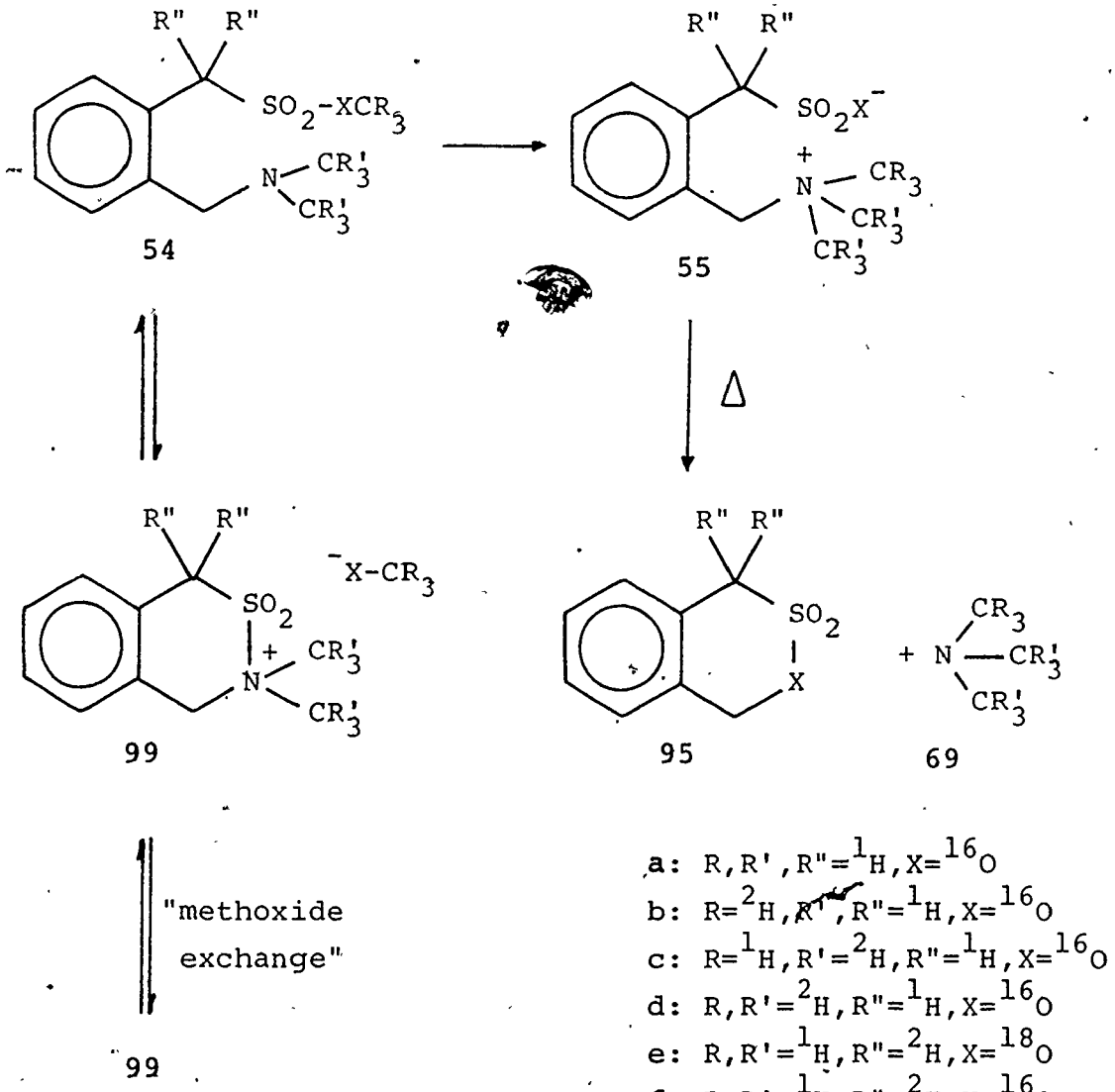
An upper limit for the **EM** of the endocyclic process may be assigned by assuming the crossing experiments conducted to the greatest extent of reaction from the lowest initial ester concentration (Experiments 9 and 10, $[\mathbf{54}]_0 = 4.5 \times 10^{-4}$ <u>M</u>, 50% reaction) did indeed contain endocyclic products and these were masked by the experimental error ($\pm$ 2%).

When the appropriate values are used, equation (10)

indicates that **EM** is less than 2 x 10^{-5} M for the endocyclic methyl transfer of **54** to form **55**.

$$\% \text{ endo} = \frac{50\ \mathbf{EM}}{(\mathbf{E}_0 - \mathbf{E}_f)} \ln\left(\frac{2\ \mathbf{E}_0 + \mathbf{EM}}{2\ \mathbf{E}_f + \mathbf{EM}}\right) \qquad (10)$$

There is one conceivable side reaction of **54** that could mask the presence of endocyclic products in the crossing experiment derived betaine mixtures. As shown in Scheme 6, intramolecular displacement of methoxide from the sulfonyl



a: R,R',R"=^{1}H,X=^{16}O
b: R=^{2}H,R',R"=^{1}H,X=^{16}O
c: R=^{1}H,R'=^{2}H,R"=^{1}H,X=^{16}O
d: R,R'=^{2}H,R"=^{1}H,X=^{16}O
e: R,R'=^{1}H,R"=^{2}H,X=^{18}O
f: R,R'=^{1}H,R"=^{2}H,X=^{16}O
g: R,R',R"=^{1}H,X=^{18}O

Scheme 6

sulfur by the amino nitrogen would result in the formation of the "sultamium" methoxide (**99**). This reaction, in all likelihood, would be reversible since the synthesis of the "norbetylates" (**87**) involved cleavage of the corresponding "sultamium" triflate (**86**) with methanol. Methoxide exchange by **99** would then provide a means through which endocyclic products in the crossing experiment derived betaine mixtures could have escaped detection. For example, the equimolar mixture of **54a** and **d** used in the $\underline{d}_0,\underline{d}_9$ crossing experiments would form **99a** and **d** which would in turn form an equimolar mixture of **99a, b, c** and **d** by way of methoxide exchange. Return of the latter mixture to **54** would then have converted the equimolar mixture of **54a** and **d** to an equimolar mixture of **54a, b, c** and **d**. Similarly this pathway would convert the equimolar mixture of **54b** and **c** used in the $\underline{d}_3,\underline{d}_6$ crossing experiments into the same equimolar mixture of **54a, b, c** and **d**. It follows then that both types of crossing experiments would yield, regardless of the molecularity of the methyl transfer, the equimolar mixture of **55a, b, c** and **d** that has been assumed to be the product of intermolecular methyl transfer.

Although methoxide is generally considered to be a poor leaving group in substitution reactions[88], it must be noted that, under the crossing experiment reaction conditions, the most favorable reaction available to **54**, its second order intermolecular rearrangement, has been suppressed and, therefore, less favorable first order reactions

such as the conversion of **54** to **99** might then occur. This side reaction must, of course, be consistent with all of the previously discussed experimental observations that pertain to the rearrangement of **54** to **55**. For example, that no ^{1}H NMR peaks attributable to **99** were observed in the ^{1}H NMR kinetic spectra requires that **99** be at least 3 kcal mol^{-1} higher in free energy than **54**. Also, the agreement observed in the crossing experiments between the observed percent reaction and the calculated percent reaction (based on exclusive intermolecular methyl transfer) imposes approximately 20% as the upper limit to the amount of **55** that could have been generated by endocyclic methyl transfer. The effect of such a contribution on the previously made maximum **EM** assignment is sufficiently great that the possibility of methoxide exchange <u>via</u> **99** warranted an experimental probe.

Evidence for or against methoxide exchange by **54** <u>via</u> **99** can be obtained with a simple double label crossing experiment. An equimolar mixture of unlabelled **54a** and the methoxy-^{18}O- α-sulfonyl-$^{2}H_2$-labelled ester, **54e** should, in absence of methoxide exchange <u>via</u> **99**, give an equimolar mixture of **55a** and **e**. However, with reversible formation of **99** and its subsequent methoxide exchange, the mixture of **54a** and **e** would be converted to a mixture of **54a, e, f** and **g** which would in turn rearrange to give an equimolar mixture of **55a, e, f** and **g**.

For the required betaine label distribution analysis,

mass spectrometric thermolysis of **55a** was again examined since, in the previously mentioned spectrum of **55a**, a mass ion at m/e = 184 had been detected and its source was thought to be the sultone, **95**. Accordingly, a sample of **55a** was again thermolyzed and the resulting cluster of ions at m/e = 184 was examined. It was found to consist of a parent peak (m/e = 184) and M + 1 peak and an M + 2 peak which had relative intensities of 100, 11.0 and 5.6 respectively. The ± 2% agreement between these and the calculated relative intensities (100, 9.9 and 5.2) based on the natural abundances of ^{13}C and ^{34}S for $C_8H_8O_3S$ lends credibility to the assignment of the source of the mass ion. Since the M + 1 and M + 2 of **95a** would overlap with ions resulting from incomplete labelling in **95e**, they were relocated with their parent ion using the calculations described in Section III E.1. This treatment was used for each of the clusters attributable to labelled **95**. As control experiments, samples of **55e** and of an equimolar mixture of **55a** and **e** were each thermolyzed and there mass spectra obtained. After relocation of the M + 1 and M + 2 peaks, the isotopic label distributions shown in Table 16 were obtained. The presence of the small amounts of the ($^{16}O_1$, $^{1}H_1$, $^{2}H_1$), (^{16}O, $^{2}H_2$) and (^{18}O, $^{1}H_2$) sultones in the products of the thermolysis of **55a** suggests that the analytical method is accurate to ± 2% in determining the label distribution. The pattern obtained from **55e** is in generally in good agreement with that anticipated based on 90% deuterium labelling and 93% $^{18}O_1$

labelling in the "norbetylate" (**87e**) from which **55e** was prepared. The equimolar mixture of **55a** and **55e** clearly gives the pattern that is obtained from the sum of the distributions shown separately by **55a** and **55e**. It may be concluded then that the mass spectrometric analytical procedure is accurate to $^{+}$ 2% in determining the relative amounts of **55a, e, f** and **g** in mixtures of these betaines.

For the proposed crossing experiments, a stock solution of **54a** and **e** in benzene was prepared in the usual manner from the "norbetylates", **87a** and **e**. An aliquot was evaporated to dryness giving a quantitative yield of the betaine which was then thermolyzed and its mass spectrum recorded. After relocation of the M + 1 and M + 2 peaks, the observed label distribution shown in Table 16 under "Stock" was obtained. Two crossing experiment solutions were then prepared from the stock solution ($[\mathbf{54a} + \mathbf{54e}]_{\emptyset}$ = 8.9 x 10^{-4} M and 4.5 x 10^{-4} M for experiments 1 and 2 respectively) and were each allowed to react at 110°C for 120 h. When worked up in the usual way, 54% and 39% yields (as judged by an ^{1}H NMR of the crude betaine mixture) were obtained (calcd yields: 47 and 33%). Thermolysis of the products and analysis of the mass spectra gave the isotopic distribution patterns shown in Table 16. That the distributions are the same for the authentic 1:1 mixture of **55a** and **55e**, the stock product and both of the crossing experiment products indicates clearly that methoxide exchange <u>via</u> **99** does not occur and hence the previously assigned **EM** maximum for the endo-

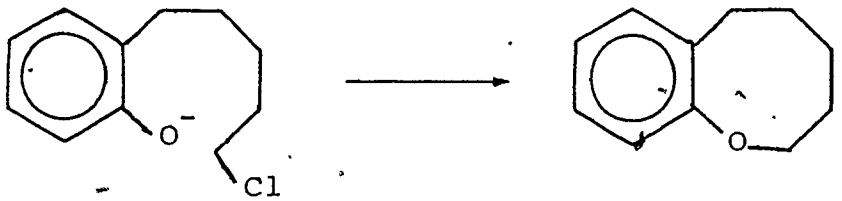
Table 16

$^{18}O_1$, $^{2}H_2$-Crossing Experiment and Related Control Experiment Label Distributions

Labelled 95	Parent m/e	Observed Label Distribution 55a	55e	1:1 55a:55e	Stock	Crossing Exp't 1	Crossing Exp't 2
$^{16}O,^{1}H_2$	184	100.0	4.1	100.0	100.0	100.0	100.0
$^{16}O,^{1}H_1,^{2}H1$	185	1.2	1.3	1.5	1.0	1.0	1.4
$^{18}O,^{1}H_2$ and $^{16}O,^{2}H_2$	186	0.4	11.2	8.6	9.3	8.6	11.9
$^{18}O,^{1}H_1,^{2}H_1$	187	0	14.4	12.4	13.2	11.0	16.3
$^{18}O,^{2}H_2$	188	0	100.0	80.4	76.1	76.3	86.9

cyclic rearrangement of **54** to **55** is valid.

In summary, the crossing experiments described in the section of the thesis indicate that, even at concentrations of **54** as low as 1 x 10^{-4} M, the formation of **55** from **54** occurs by way of intermolecular methyl transfer and not via the endocyclic pathway. When considered in terms of the experimental error, the results are consistent with an **EM** of less than 2 x 10^{-5} M for the 8-endo-tet process. When compared with the **EM** of 0.35 reported for the formation of **101** from **100**[10], an 8 exo-tet process, this result indicates that the transition state for the 8-endo-tet is considerably more strained than is the transition state for the 8-exo-tet reaction. This difference in strain must

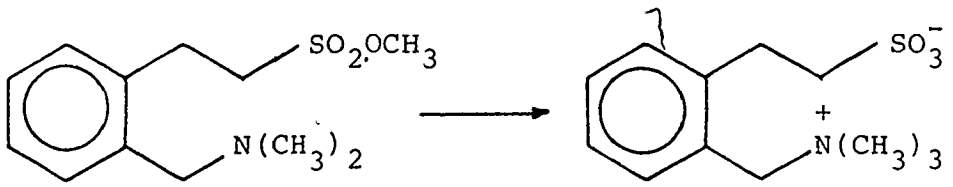


100 **101**

be due, at least in part, to deviation from the ideal 180° orientation of the nucleophile, methyl carbon and nucleofuge in the 8-endo-tet transition state. One way of alleviating this strain is to expand the exo-tet transition state. Accordingly, the potential 9-endo-tet rearrangement of **56** to **57**, was examined next.

C. The Formation of 2-[2-(Trimethylammoniomethyl)phenyl]-ethanesulfonate (**57**) from Methyl 2-[2-(Dimethylaminomethyl)-phenyl]ethanesulfonate (**56**)

1. Introduction:

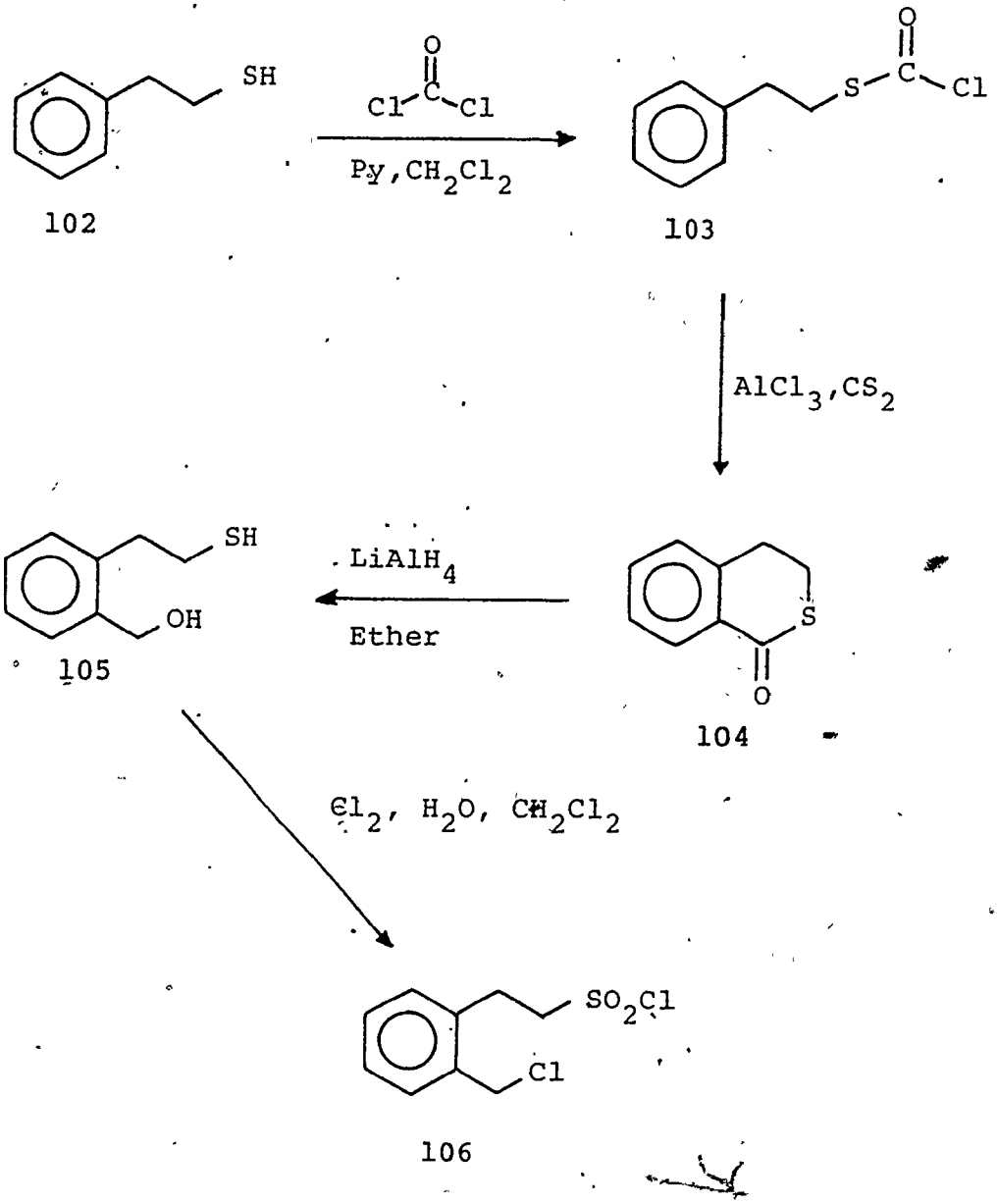


56 **57**

Since the inability to observe 8-endo-tet methyl transfer in the rearrangement of **54** was thought to be a consequence of the excessive transition state ring strain imposed by the S_N2 collinearity requirement, it was anticipated that, for reasons presented in the General Introduction, this strain could at least in part be alleviated by expansion of the transition state cyclic array. In this light, the rearrangement of the ortho-benz-fused amino ester, **56**, a potential 9-endo-tet reaction, was examined. This section contains a description of the kinetic and double-label crossing experiments used to determine its molecularity. The synthesis of the compounds required in these experiments is also described.

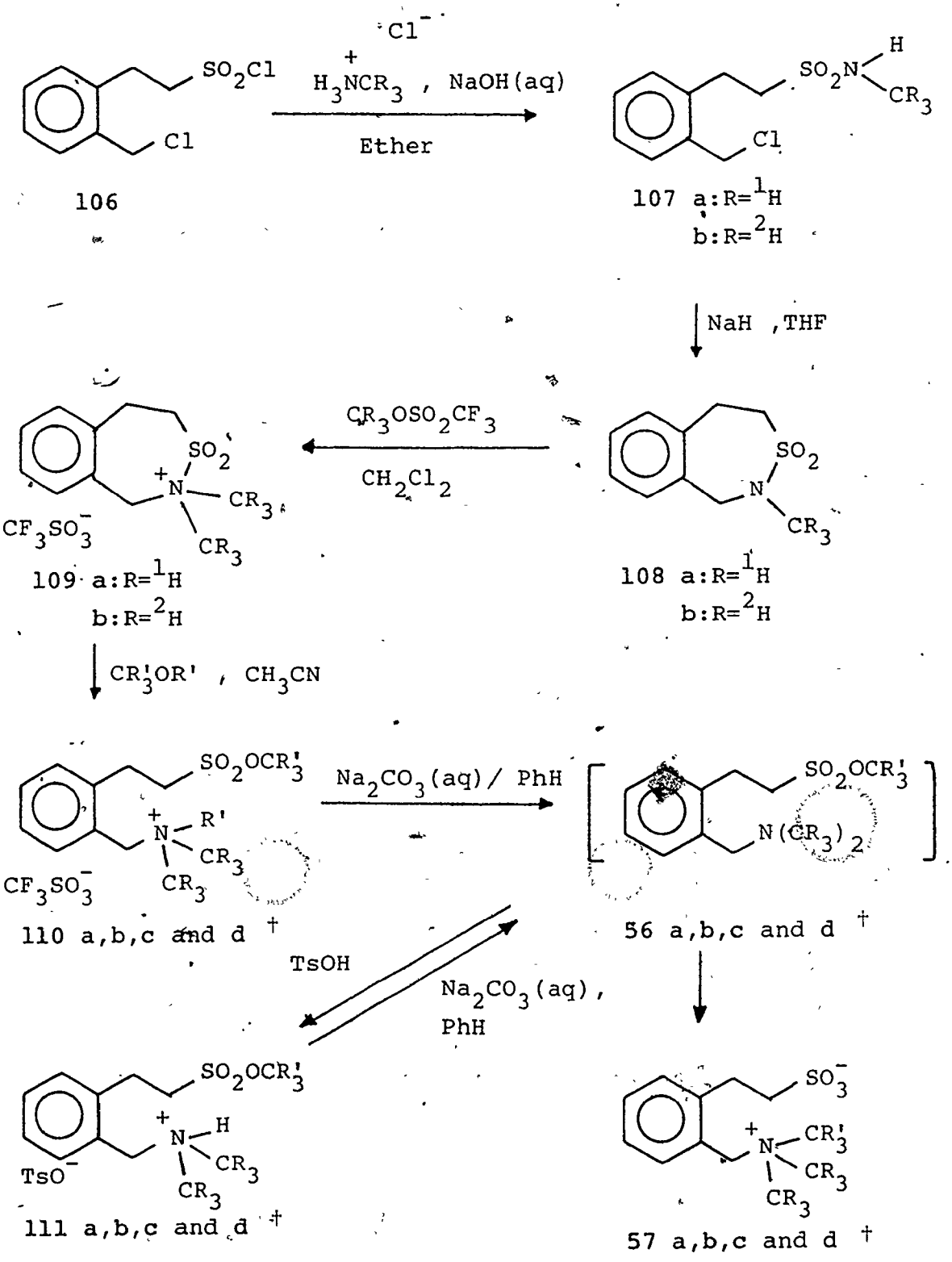
2. Synthesis:

The synthesis of the required 2-(2-methylphenyl)ethane derivatives, shown in scheme 7,8 and 9, followed the same general pattern as those previously described for the preparation of the butane and 2-methylphenylmethane derivatives.



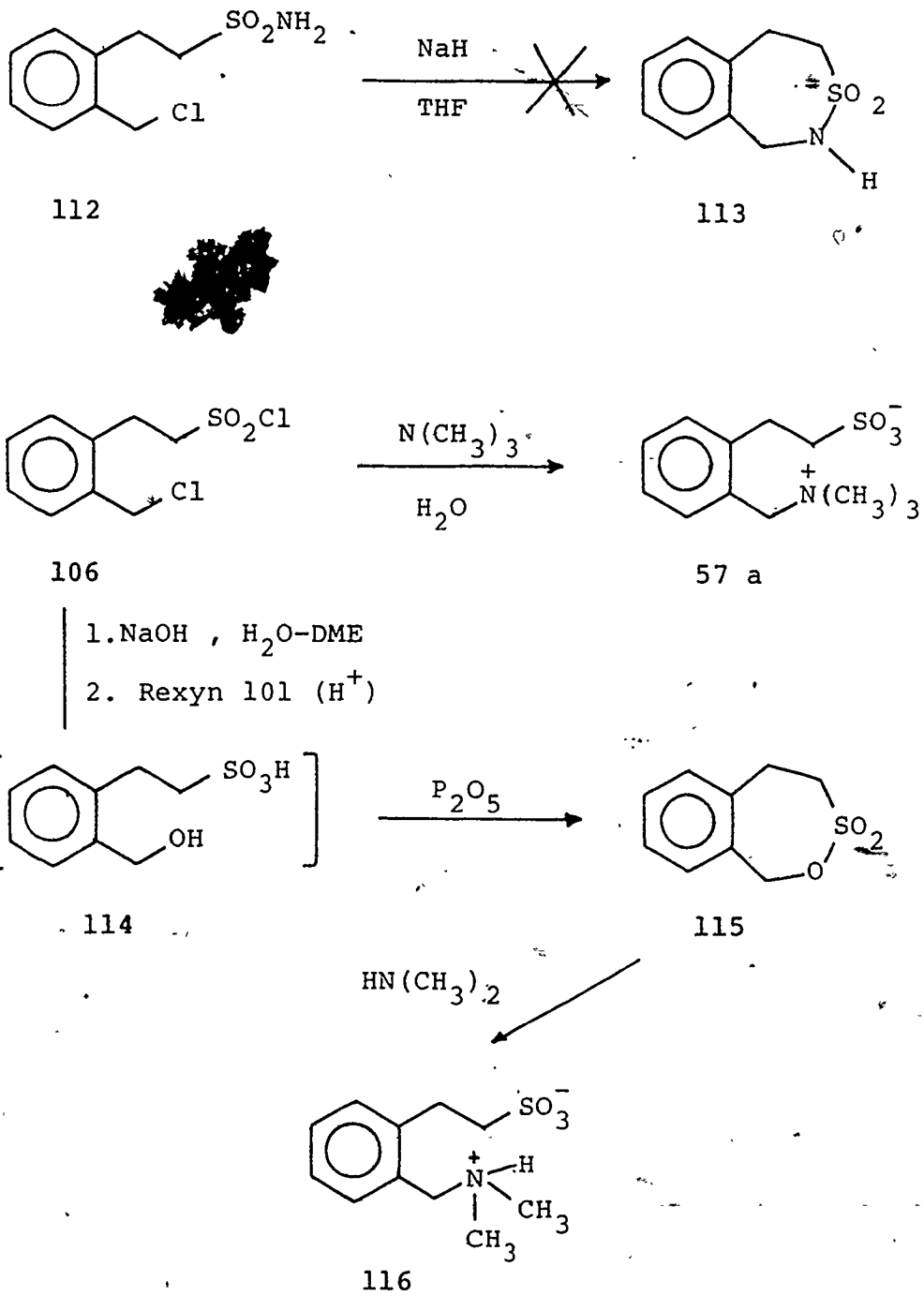
102 103 104 105 106

Scheme 7



† a:R,R'=^{1}H; b:R=^{1}H,R'=^{2}H; c:R=^{2}H,R'=^{1}H; d:R,R'=^{2}H

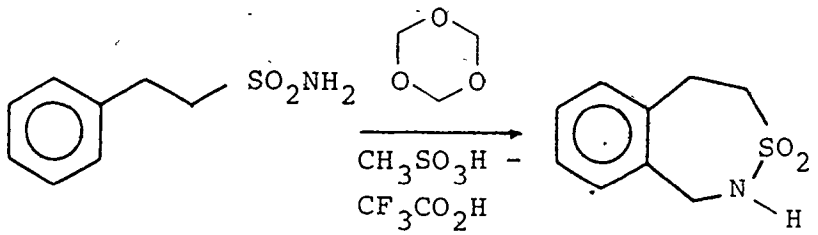
Scheme 8


SO2NH2
Cl
NaH
THF
SO 2
N
H
112
113
SO2Cl
Cl
N(CH3)3
H2O
SO3−
+
N(CH3)3
106
57 a
1.NaOH , H2O-DME
2. Rexyn 101 (H+)
SO3H
OH
P2O5
SO2
O
114
115
HN(CH3)2
SO3−
+
N
H
CH3
CH3
116

Scheme 9

2-Phenylethanethiol (**102**) reacted with phosgene and pyridine to give S-2-phenylethyl thiochloroformate (**103**) in 92% yield. The experimental procedure used in this reaction was that reported by Olah and Schilling[89] for the preparation of a variety of other alkyl thiochloroformates. Aluminum chloride catalyzed intramolecular acylation of **103** gave 3,4-dihydro-1H-2-benzothiin-1-one (**104**) in 85% yield. Lithium aluminum hydride reduction of **104** gave, in 90% yield, 2-(2-mercaptoethyl)phenylmethanol (**105**) which was then chlorinated at 0°C in a water-methylene chloride suspension to give 2-[2-(chloromethyl)phenyl]ethanesulfonyl chloride (**106**) in 97% yield. It was then necessary to effect the conversion of the sulfonyl chloride, **106**, to its N-methylsulfonamide, N-methyl-2-[2-(chloromethyl)phenyl]ethanesulfonamide (**107a**), in the absence of excess methylamine because benzyl chlorides in general are reactive to nucleophilic displacements[72] and this side reaction with methylamine was undesirable. The experimental problem presented by the volatility of methylamine (bp 3°C) was overcome by simply titrating a mixture of the sulfonyl chloride, **106**, and 1.1 equivalents of methylamine hydrochloride in ether with 2.1 equivalents of 1N aqueous sodium hydroxide at 0°C. The resulting yield of **107** from **106** was 95%. Dropwise addition of **107a** in tetrahydrofuran to a refluxing tetrahydrofuran suspension of sodium hydride gave the N-methylsultam, 2-methyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide (**108a**), in 79% yield. Several unsuccessful attempts were made to cyclize

2-(2-chloromethyl)phenylethanesulfonamide (**112**) using the same procedure as that described above. In all cases, only tarry oligomeric products were obtained. Presumably, the reaction of the starting material with anions derived from the sultam (**113**) or from the oligomeric materials predominated. Orazi and Corral[74] have reported the preparation of **113** from the reaction of 2-phenylethanesulfonamide



113

and trioxan in methanesulfonic acid-trifluoroacetic acid. As previously stated, this publication was overlooked at the time the synthesis reported herein was devised.

The N-methylsultam, **108a**, reacted with methyl trifluoromethanesulfonate to give the "sultamium" salt, 2,2-dimethyl-1,2,4,5-tetrahydro-3,2,-benzothiazepinium 3,3-dioxide trifluoromethanesulfonate (**109a**) in 80% yield. Relative to the "sultamium" salt from the 2-methylphenylmethane series, **86**, **109a** was less reactive to methanol. A 1 M solution of **109a** and methanol (1.5 equivalents) in acetonitrile, when monitored by ^{1}H NMR, was found to require 40 h at 40°C to reach completion. Under these conditions, approximately one third of the desired product, 2-[2-(methoxysulfonyl)-ethyl]phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (**110a**) underwent further reaction with methanol

to form 2-[2-(dimethylammoniomethyl)phenyl]ethanesulfonate (**116**), trifluoromethanesulfonic acid and presumably dimethylether. The latter, presumably because of its volatility, was not directly observed. The use of less than 1.5 equivalents of methanol resulted in the presence of unreacted **109a** subsequent to the complete consumption of the methanol. To isolate the "norbetylate", the crude mixture was shaken with aqueous base and extracted with methylene chloride to give, in the extract, methyl 2-[2-(dimethylaminomethyl)phenyl]ethanesulfonate (**56a**). The extract was treated with p-toluenesulfonic acid and evaporated to dryness leaving the "norbetylate" tosylate (**111a**) as the residue. The overall yield of recrystallized **111a** from **109a** was 50%.

To generated **56a** in solution, **111a** was suspended in benzene and washed with aqueous sodium carbonate. Evaporation of the benzene left an oil which rapidly solidified giving the betaine, 2-[2-trimethylammoniomethyl)phenyl]-ethanesulfonate (**57a**), in quantitative yield. As illustrated in Scheme 9, a specimen of **57a** was also prepared by treating the chloro-sulfonyl chloride (**106**) with aqueous trimethylamine. An independent synthesis of the "norbetaine", 2-[2--(dimethylammoniomethyl)phenyl]ethanesulfonate (**116**), was was also devised. After base catalyzed hydrolysis of **106**, the crude product was passed through a strong acid ion exchange column (Rexyn 101). Evaporation of the eluant left 2-[2-(hydroxymethyl)phenyl]ethanesulfonic acid (**114**) as a brown viscous oil which was not characterized but rather

was left for one week at 50 torr over phosphorus pentoxide. Recrystallization of this material gave the sultone, 4,5-dihydro-1H-2,3-benzoxathiepin 3,3-dioxide (**115**) in 50% yield. Dimethylamine reacted readily with **115** to give the "norbetaine" (**116**) in 99% yield.

As with the previous two ring systems, the crossing experiments and related controls required samples of the $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-"norbetylates" (**111b, c** and **d**) and the corresponding $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-betaines (**57b, c** and **d**). The preparation of these compounds is shown in Scheme 8.

($^2H_4$)Methanolysis of the $\underline{d}_0$-"sultamium" salt, **109a**, gave the $\underline{d}_3$-"norbetylate" which was isolated as its tosylate salt, **111b**. The synthesis of the $\underline{d}_6$- and $\underline{d}_9$-"norbetylates" started with reaction of the chloro-sulfonyl chloride (**106**) with ($^2H_3$)methanaminium chloride and aqueous sodium hydroxide to give the $\underline{N}$-($^2H_3$)methylsulfonamide, **107b**. Cyclization of **107b** gave the $\underline{N}$-($^2H_3$)methylsultam, **108b**, which in turn was methylated with ($^2H_3$)methyl trifluoromethanesulfonate to give the $\underline{d}_6$-"sultamium" salt, **109b**. Methanolysis of **109b** gave the $\underline{d}_6$-"norbetylate" which was isolated as its tosylate salt (**111c**) and ($^2H_4$)methanolysis of **109b** gave the $\underline{d}_9$ "norbetylate" which, again, was isolated as its tosylate **111d**. The deuterated betaines (**57b, c** and **d**) were each prepared in the usual manner from the corresponding "norbetylates" (**111b, c** and **d** respectively). Deuterium combustion analysis of the $\underline{d}_9$-betaine (**57d**) indicated an average of 95% deuteration in the labelled methyls.

3. Kinetics

The kinetic studies of the reaction of **56** to form **57** mimic those of the previously discussed reactions of **52** and **54** in that the assumed rate law is again that described by equation (5) in which the first term pertains to the endocyclic methyl transfer and the second to the intermolecular pathway.

$$-\frac{d\mathbf{E}}{dt} = k_1\mathbf{E} + 2k_2\mathbf{E}^2 \qquad (5)$$

The procedure used to generate a benzene-$\underline{d}_6$ solution of **56** from the "norbetylate" (**111**) and to monitor by ^{1}H NMR the decline of its concentration as a function of time was identical to that used in the kinetic studies of the methyl transfer of **54** which were described in detail in Section II B.3. As before, the reactions were generally followed to 80% completion and, at t =∞, ^{1}H NMR analysis confirmed that over 98% of the product was indeed the betaine (**57**). The kinetic data from all of the runs reported in Table 17 gave linear second order plots (1/**E** versus time). A typical plot is illustrated in Figure 9. The reported observed second order rate constants, k_{obs}'s (or $2k_2$'s), were obtained from the slopes of the linear least squares best fit lines.

The adherence of the methyl transfer to a strict second order rate law indicates that, between ester concentrations of 0.2 and 0.02 M, the formation of **57** occurs predominantly by way of the intermolecular pathway and not via endocyclic

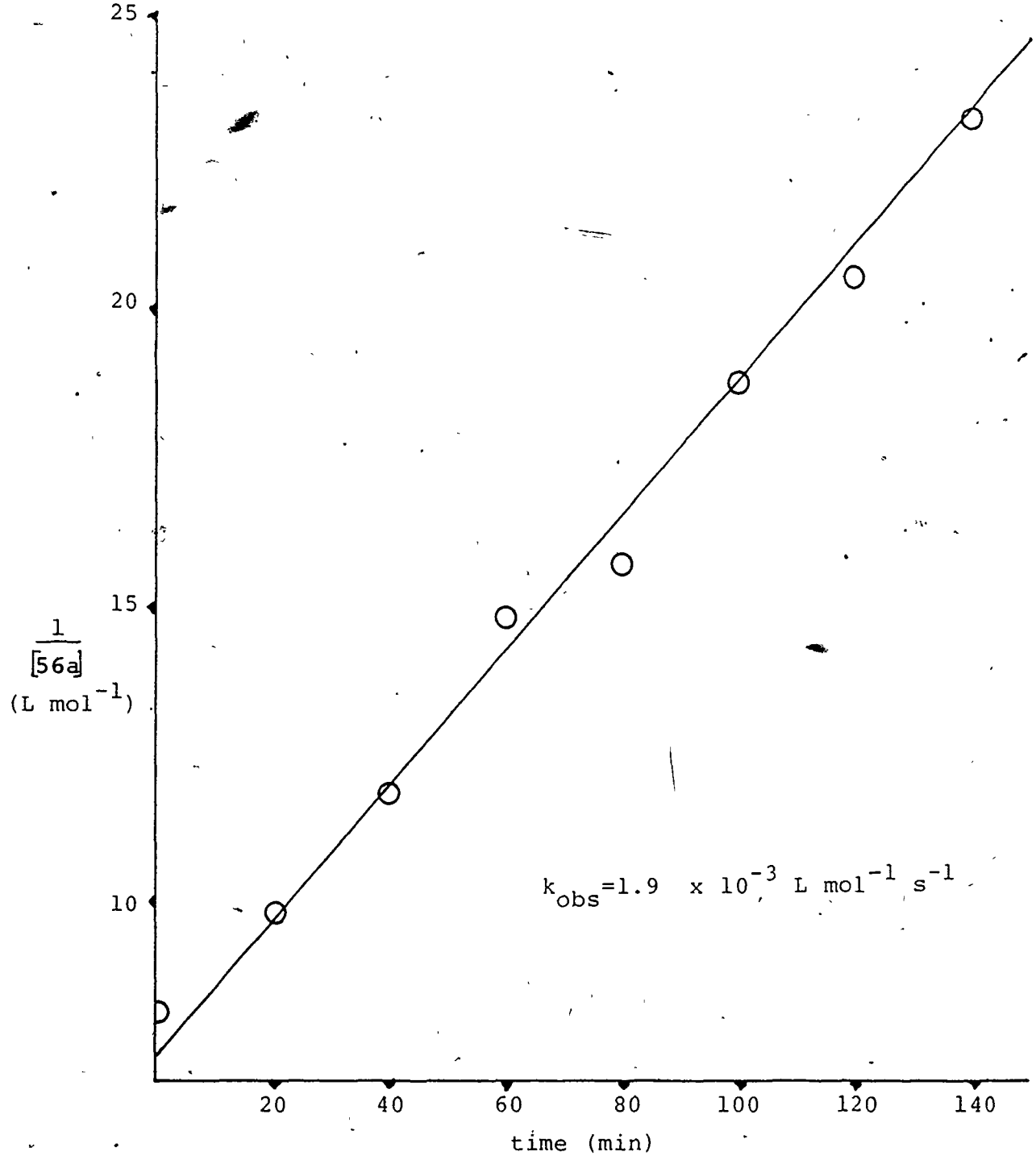


Figure 9: Rate of the Rearrangement of Methyl 2-[2-(Dimethylaminomethyl)phenyl]ethanesulfonate (**56a**) to 2-[2-(Trimethylammoniomethyl)phenyl]ethanesulfonate (**57a**) in C_6D_6 at 110°C

Table 17

2-[2-(Methyl)phenyl]ethane Derivative Kinetic Results

Experiment No.	Ester	Temperature (°C)	$[E]_0$, (M)	k_{obs} (L $mol^{-1}s^{-1}$ x 10^3)
2(h)(i)	**56a**	110.0	0.124	1.9
2(h)(ii)	**56a**	110.0	0.132	2.1
2(i)	**56a**	92.0	0.176	0.55
2(j)	**56a**	60.0	0.215	0.072
2(k)	**56a**	37.0	0.153	0.0089
2(e)	**56b**	110.0	0.161	2.1
2(m)	**56c**	110.0	0.156	1.9
2(n)	**56d**	110.0	0.159	2.2

nucleophilic substitution. The linearity of the kinetic plots, when compared with the simulated mixed first and second order curves shown in Figure 3 (Section II A.3) is consistent with an **EM** of less than 0.04 M for the endocylic process.

The kinetic results summarized in Table 17 serve as a means with which to compare the intermolecular reaction of **56** with that of **54**. To determine the activation parameter of the former, the Eyring plot shown in Figure 10 was constructed. The slope of the linear least squares best fit line furnished an enthalpy of activation, $\Delta H^{\ddagger}$, of 16.5 kcal mol^{-1} and from this, the entropy of activation, $\Delta S^{\ddagger}$ (at 110°C), was calculated to be -29 cal K^{-1} mol^{-1}. That these bear a strong resemblance to the activation parameters determined for the reaction of **54a** ($\Delta H^{\ddagger}$ = 12.2 kcal mol^{-1} and $\Delta S^{\ddagger}$ = -39 cal K^{-1} mol^{-1}) suggests that the re-

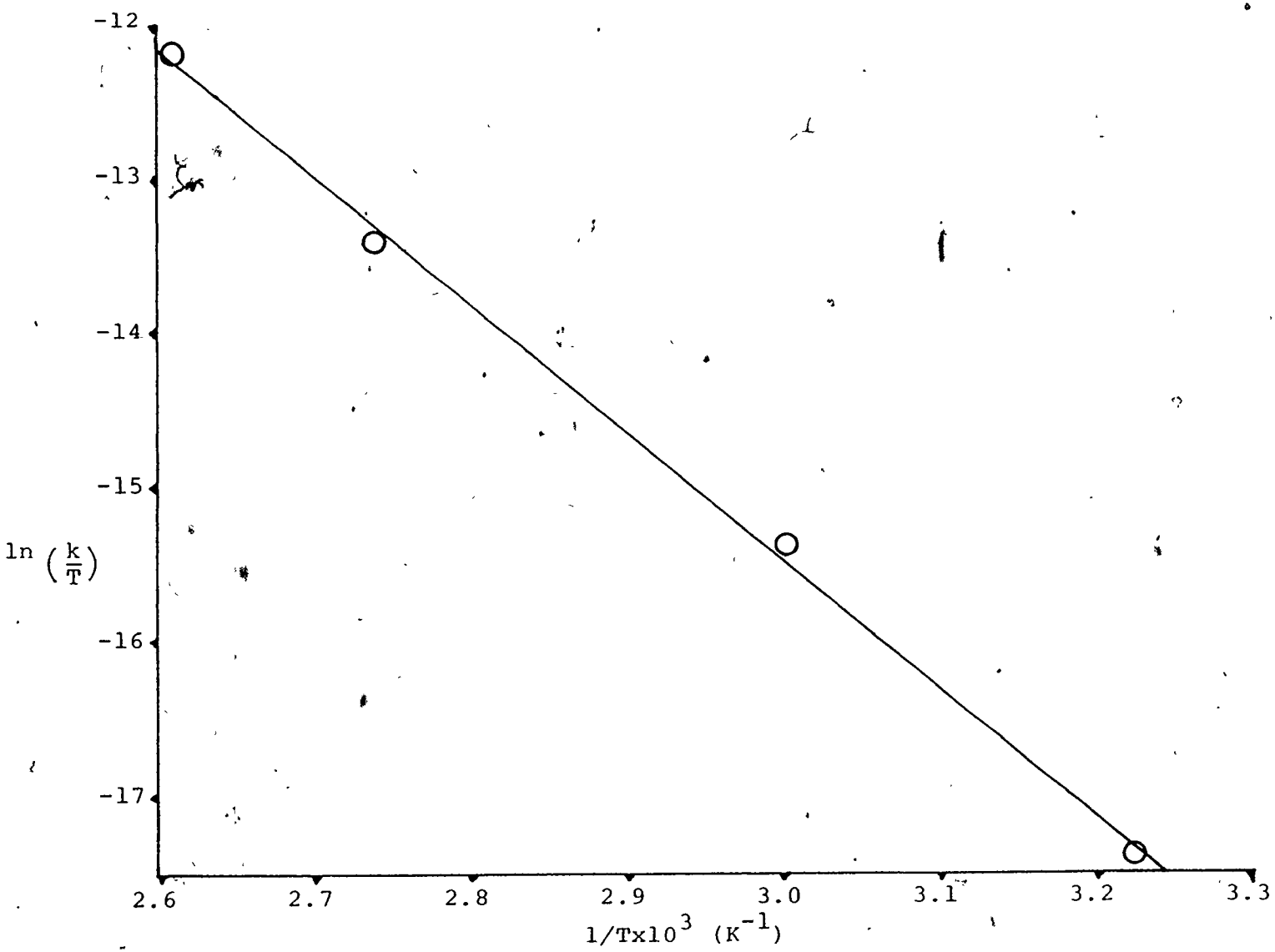
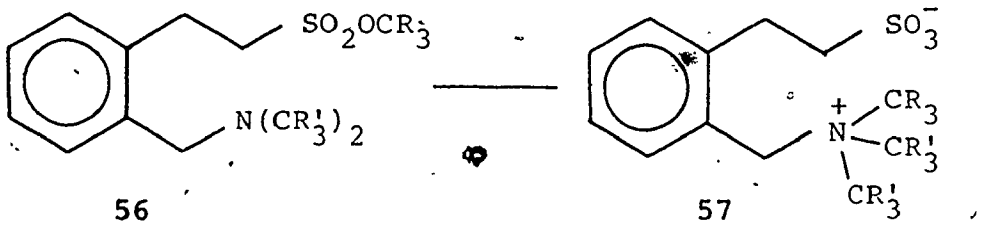


Figure 10: Eyring Plot for the Rearrangement of Methyl 2-[2-(Dimethylaminomethyl)phenyl]ethanesulfonate in C_6D_6

actions are mechanistically similar. The remaining rate constants reported in Table 17 were obtained in an attempt to measure the secondary kinetic isotope effects encountered in the rearrangements of 56 b, c and d and, as in Section II.B.3, the ±10% error in the rate constants precludes any transition state structural interpretation based on these values. They do, however, suggest that any error induced by ignoring these isotope effects in the forthcoming crossing experiment discussion will be minimal.

4. Crossing Experiments



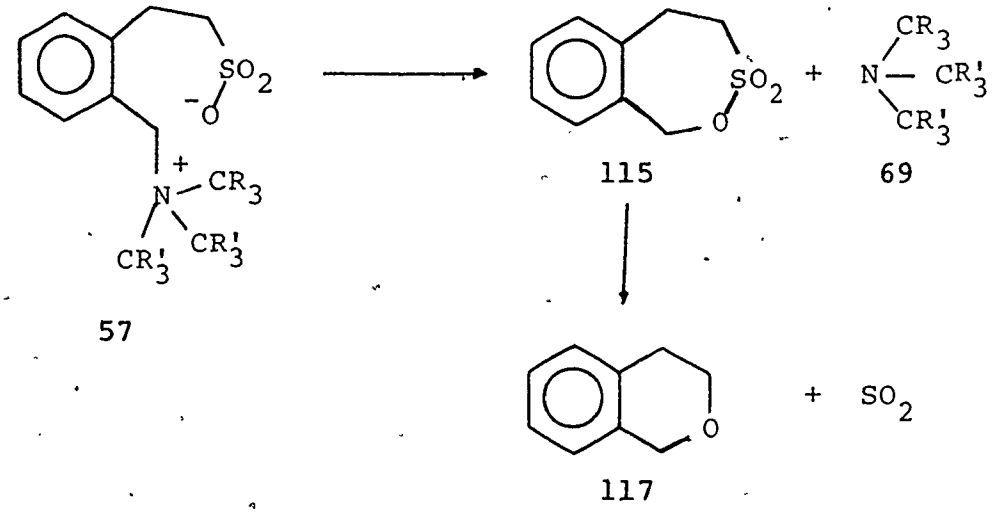
56 57

a: R,R'= ^{1}H, **b:**R=^{2}H,R'=^{1}H; **c:**R=^{1}H,R'=^{2}H; **d:**R,R'=^{2}H

At lower concentrations of **56** than those used in the kinetic experiments, evidence was sought for endocyclic methyl transfer in the rearrangement of **56** to form **57** via double-label crossing experiments. In these, endocyclic methyl transfer by an equimolar mixture of **56a** and **d** (a $\underline{d}_0,\underline{d}_9$-crossing experiment) would give an equimolar mixture of **57a** and **d** and likewise, **56b** and **c** (a $\underline{d}_3,\underline{d}_6$-crossing experiment) would give **57b** and **c.** Both ester mixtures would give an equimolar mixture of **57a, b, c** and **d** as the result of intermolecular methyl transfer.

The mass spectrometric analytical procedure used to determine the relative amounts of **57a, b, c** and **d** in mixtures of these betaines directly parallels that described in Section II B.4 for the analysis of the **55a, b, c** and **d** mixtures. To obtain a mass spectrum of **57a,** a probe temperature of 240°C was required and the resulting spectrum contained no parent mass ion but rather, showed fragments at m/e =

59, 134 and 198 for which trimethylamine (**69a**), 1H-3,4-dihydrobenzoxine (**117**) and the sultone (**115**) are the likely sources. Based on the precedents set in Sections II A.4 and II B.4, a plausible explanation for the formation for these compounds is that the betaine (**57a**) on thermolysis, undergoes a 7-exo-tet displacement of trimethylamine from its benzylic methylene by the sulfo anion to give the sultone and subsequent extrusion of sulfur dioxide by the sultone gives the ether (**117**).



a:R,R'=^{1}H; **b**:R=^{2}H,R'=^{1}H; **c**:R=^{1}H,R'=^{2}H; **d**:R,R'=^{2}H

Duplicate analyses of the amine fragment from **57a** indicated that it consisted of an M - 1 peak (m/e = 58), a parent mass ion (m/e = 59) and an M + 1 peak (m/e = 60) in the relative intensities of 35.5:100:3.4 and 5.0:100:4.2 respectively. As before, the relative intensities of the M +

1 peaks agreeded within the mass spectrometric error of ± 2% with the anticipated M + 1 intensity (3.8) as calculated from the natural abundances of ^{13}C and ^{15}N in C_3H_9N. The M - 1 peaks caused by the loss of a hydrogen atom from the parent ion were variable in relative intensity. As well, the range of m/e's from 62 to 69 was devoid of extraneous peaks and hence the previously described method for determining the relative amount of **69a, b, c** and **d** (i.e. $\underline{d}_0$, $\underline{d}_3$, $\underline{d}_6$, $\underline{d}_9$) in mixtures of these amines was used for all mass spectra.

The deuterated betaines (**57b, c** and **d**) were then analyzed and the results are reported in Table 18. The presence

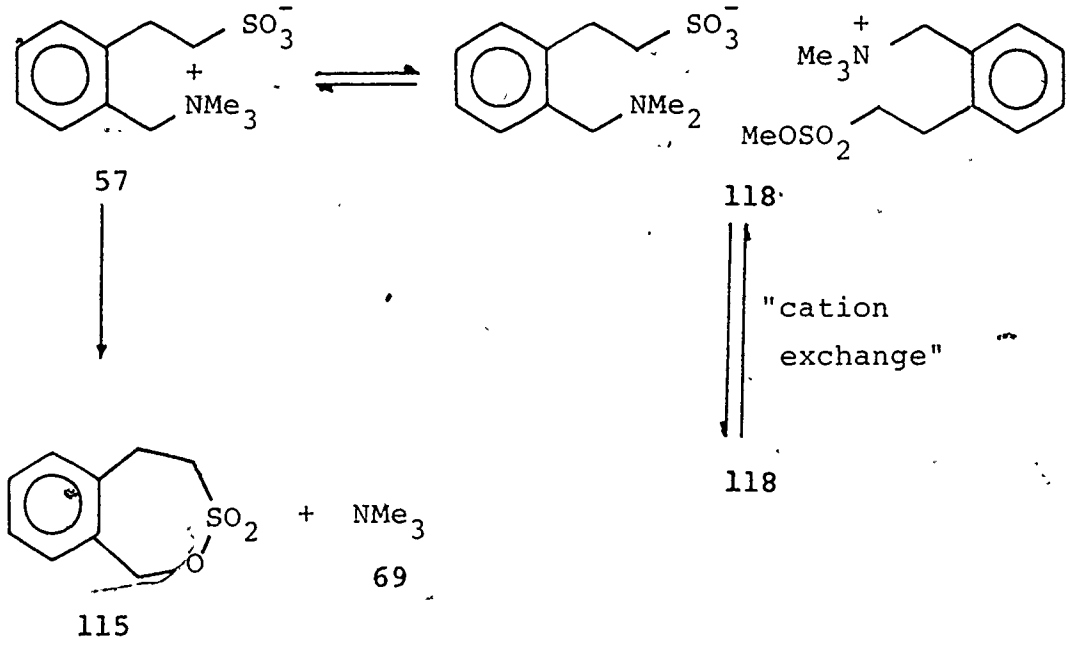
Table 18

2-(2-Methylphenyl)ethane Derivative Betaine
Mass Spectrometric Analysis Results

	Observed Amine Mixture			
Betaine	$\underline{d}_0$	$\underline{d}_3$	$\underline{d}_6$	$\underline{d}_9$
57a	100.0	0.0	0.0	0.0
57b	0.3	100.0	0.4	0.0
57c	0.0	1.0	100.0	0.8
57d	0.0	0.0	(0.4)	100.0

of small amounts of the $\underline{d}_0$- and $\underline{d}_6$-amines in the spectrum obtained from **57b** and of the $\underline{d}_3$- and $\underline{d}_9$-amines in the spectrum from **57c** is indicative of partial methyl scrambling during the thermolysis. In the absence of any other reasonable explanation, partial scrambling is probably the result of cation exchange by the ion pair, **118**, which, apparently,

is formed reversibly *via* intermolecular methyl transfer by **57** during its thermal degradation.



As in Section II B.4, this side reaction introduces complications that require a rather detailed treatment. To place this discussion in perspective, a brief summary of the results of the authentic betaine mixture thermolysis control experiments and of the crossing experiments is in order. The results obtained using selected authentic mixtures containing an excess of the d_0- and d_9-betaines are listed in Table 19 and indicate that while the observed amine ratios are not identical to the betaine ratios from which they were derived, they do show a fair correlation. This is, a reduction in the amounts of **57b** and **c** relative

Table 19

Selected 2-(2-Methylphenyl)ethane Derivative Authentic Betaine Mixture Thermolysis Results

Exp't No.	Authentic Betaine Mixture 57a	57b	57c	57d	Observed Amine Mixture d_0	d_3	d_6	d_9
1	1	1	1	1	100.0	98.5	99.8	87.1
11	1.5	1	1	1.5	100.0	70.2	67.8	91.9
4	3	1	1	3	100.0	33.3	32.7	83.7
2	1	0	0	1	100.0	1.4	1.0	86.0

Table 20

Selected 2-(2-Methylphenyl)ethane Derivative d_0, d_9 Crossing Experiment Results (Benzene, 110° c, 20% Reaction)

Exp't No.	[56a + 56d]$_0$ (M)	Observed Amine Ratio d_0	d_3	d_6	d_9
8	2.2×10^{-2}	100.0	113.0	114.6	136.0
10	8.9×10^{-3}	100.0	99.8	101.8	130.0
12	6.7×10^{-3}	100.0	77.5	75.3	107.7
14	4.5×10^{-3}	100.0	69.2	67.3	102.2

to **57a** and **d** clearly results in a similar reduction in the amounts of the $\underline{d}_3$- and $\underline{d}_6$-amines relative to the $\underline{d}_0$- and $\underline{d}_9$-amines. The selected $\underline{d}_0,\underline{d}_9$ crossing experiments results listed in Table 20 show that when the initial ester concentration was 2.2×10^{-2} M, an amine mixture in which the sum of the $\underline{d}_0$- and $\underline{d}_9$-amines approximately equalled the sum of the $\underline{d}_3$- and $\underline{d}_6$-amines was obtained. This is indicative of virtually exclusive intermolecular methyl transfer in the conversion of **56** to **57**. Reduction of the initial concentration of **56**, however, resulted in a reduction in the amounts of the thermolysis derived $\underline{d}_3$- and $\underline{d}_6$-amines relative to the $\underline{d}_0$- and $\underline{d}_9$- amines. This is precisely the behavior expected if **57** is being formed from **56** via both the second order intermolecular and the first order endocyclic pathways. It follows then that these results may be regarded as preliminary evidence that **57** is formed from **56**, at least in part, via endocyclic methyl transfer. A rigorous proof of this conclusion and a subsequent **EM** assignment for the endocyclic pathway requires a detailed discussion of the full set of the authentic betaine mixture control experiments and of the full set of crossing experiments.

Following the approach used in Section II B.4 to cope with the scrambling side reaction, complementary pairs of authentic mixtures of **57a, b, c** and **d** were prepared such that in each pair, one of the mixtures was enriched in **57a** and **d** and hence corresponded to the product mixture that would be obtained from a partially endocyclic $\underline{d}_0,\underline{d}_9$ crossing

experiment and the other was enriched to the same extent with **57b** and **c** and hence corresponded to the partially endocyclic $\underline{d}_3,\underline{d}_6$ crossing experiment product mixture. For the $\underline{d}_0,\underline{d}_9$ enriched mixtures, the percentage of the mixture that corresponds to the endocyclic product, C_a, is calculated from equation (32) and in the amine mixture obtained after thermolysis, the apparent percentage that corresponds to the endocyclic product, F_a, is defined be equation (14).

$$C_a = 100 \left[\frac{(\mathbf{57a} + \mathbf{57d}) - (\mathbf{57b} + \mathbf{57c})}{\mathbf{57a} + \mathbf{57b} + \mathbf{57c} + \mathbf{57d}}\right] \qquad (32)$$

$$F_a = 100 \left[\frac{(\underline{d}_0 + \underline{d}_9) - (\underline{d}_3 + \underline{d}_6)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \qquad (14)$$

Equations (33) and (24) describe the analogous values, C_b and F_b, for the mixtures enriched in the $\underline{d}_3$- and $\underline{d}_6$-betaines.

$$C_b = 100 \left[\frac{(\mathbf{57b} + \mathbf{57c}) - (\mathbf{57a} + \mathbf{57d})}{\mathbf{57a} + \mathbf{57b} + \mathbf{57c} + \mathbf{57d}}\right] \qquad (33)$$

$$F_b = 100 \left[\frac{(\underline{d}_3 + \underline{d}_6) - (\underline{d}_0 + \underline{d}_9)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \qquad (24)$$

If the extent of scrambling in the thermolysis is the same for a given pair of mixtures in which C_a equals C_b, then the true percent endo, **C**, as defined by equation (29), must equal C_a and C_b. To test the validity of equation (29)

$$C = \frac{F_a + F_b}{2 + 0.02(F_a - F_b)} \qquad (29)$$

and to determine the accuracy of this analytical method, authentic mixtures of **57a, b, c** and **d** were prepared and thermolyzed. The results of these experiments are shown in Table 21.

In the first five experiments, equimolar aqueous solutions of **57a, b, c** and **d** were prepared and used to make

Table 21

2-(2-Methylphenyl)ethane Derivative Authentic Betaine Mixture Thermolysis Control Experiment Results

1. Excess $\underline{d}_0$,$\underline{d}_9$ Mixtures:

Exp't No.	C_a (% endo)	Observed Amine Ratio $\underline{d}_0$	$\underline{d}_3$	$\underline{d}_6$	$\underline{d}_9$	F_a (% excess $\underline{d}_0$,$\underline{d}_9$)
1	0	100.0	98.5	99.8	87.1	-2.9
2	100	100.0	1.4	1.0	86.0	97.4
4	50	100.0	33.3	32.7	83.7	47.1
6	0	100.0	99.7	99.1	92.3	-1.7
7	5.0	100.0	88.1	87.3	92.2	4.6
9	10.0	100.0	86.9	84.6	96.6	6.8
11	20.0	100.0	70.2	67.8	91.9	17.2
13	40.0	100.0	44.3	42.3	87.3	36.8

2. Excess $\underline{d}_3$,$\underline{d}_6$ Mixtures:

Exp't No.	C_b (% endo)	Observed Amine Ratio $\underline{d}_0$	$\underline{d}_3$	$\underline{d}_6$	$\underline{d}_9$	F_b (% excess $\underline{d}_3$,$\underline{d}_6$)
3	100	0.9	100.0	99.6	0.8	98.3
5	50	36.6	100.0	102.6	31.7	49.6
8	5.0	100.0	106.3	103.4	88.7	5.3
10	10.0	86.2	100.0	100.8	79.8	9.5
12	20.0	71.4	100.0	96.8	68.1	18.0
14	40.0	47.4	100.0	96.9	41.1	38.0

Table 21 (cont'd)
2-(2-Methylphenyl)ethane Derivative Authentic Betaine Mixture
Thermolysis Control Experiment Results

3. Combines Results:

C_a, C_b (% endo)	Excess $\underline{d}_0$, $\underline{d}_9$ Expt' No.	Excess $\underline{d}_3$, $\underline{d}_6$ Expt' No.	F_a % excess $\underline{d}_0$, $\underline{d}_9$	F_b % excess $\underline{d}_3$, $\underline{d}_6$	C % endo
100	2	3	97.4	98.3	98.7
50	4	5	47.1	49.6	49.6
5	7	8	4.6	5.3	5.0
10	9	10	6.8	9.5	8.4
20	11	12	17.2	18.0	17.8
40	13	14	36.8	38.0	37.9

$$C_a = 100\left[\frac{(57a + 57d) - (57b + 57c)}{57a + 57b + 57c + 57d}\right] \quad (32)$$

$$C_b = 100\left[\frac{(57b + 57c) - (57a + 57d)}{57a + 57b + 57c + 57d}\right] \quad (33)$$

$$F_a = 100\left[\frac{(\underline{d}_0 + \underline{d}_9) - (\underline{d}_3 + \underline{d}_6)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \quad (14)$$

$$F_b = 100\left[\frac{(\underline{d}_3 + \underline{d}_6) - (\underline{d}_0 + \underline{d}_9)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \quad (24)$$

$$C = \frac{F_a + F_b}{2 + 0.02\,(F_a - F_b)} \quad (29)$$

1:0:0:1, 0:1:1:0, and 1:0:0:1-**57a:b:c:d** solutions which were then mixed in the appropriate volumes. Evaporation left the authentic betaine mixtures which were then analyzed. For the remaining control experiments, aqueous solutions of each of the betaines (**57a, b, c** and **d**) were prepared and their concentrations were adjusted to a common U.V. absorbance (0.973 ± .005 at 267 nm in 1 cm quartz cells). After the appropriate volumes of these were dispensed by burette and combined, the resulting solutions were evaporated to dryness and the residues were thermolyzed. Examination of the resulting amine ratios reveals that, as in Section II A.4 and II B.4, $\underline{d}_0$ is generally greater than $\underline{d}_9$. Again, this probably the result both of isotope effects and of a decline in the amount of amine present in the probe during time interval required for the acquisition of the spectra and is hence assumed to be linear with respect to m/e. More importantly, the pairs of F_a and F_b values which are plotted in Figure 11, all yield **C**'s that agree to ± 3% with C_a (or C_b). This, of course, demonstrates that over the entire range of mixtures that are anticipated from the crossing experiments, (0% <u>endo</u> to 100% <u>endo</u>) the analytical procedure is accurate to ± 3% in determining the percentage of the products derived from the endocyclic pathway. This then will be the assumed accuracy in the analysis of the crossing experiment derived betaine mixtures.

The procedure used for the crossing experiments was virtually identical to that described in Section II B.4

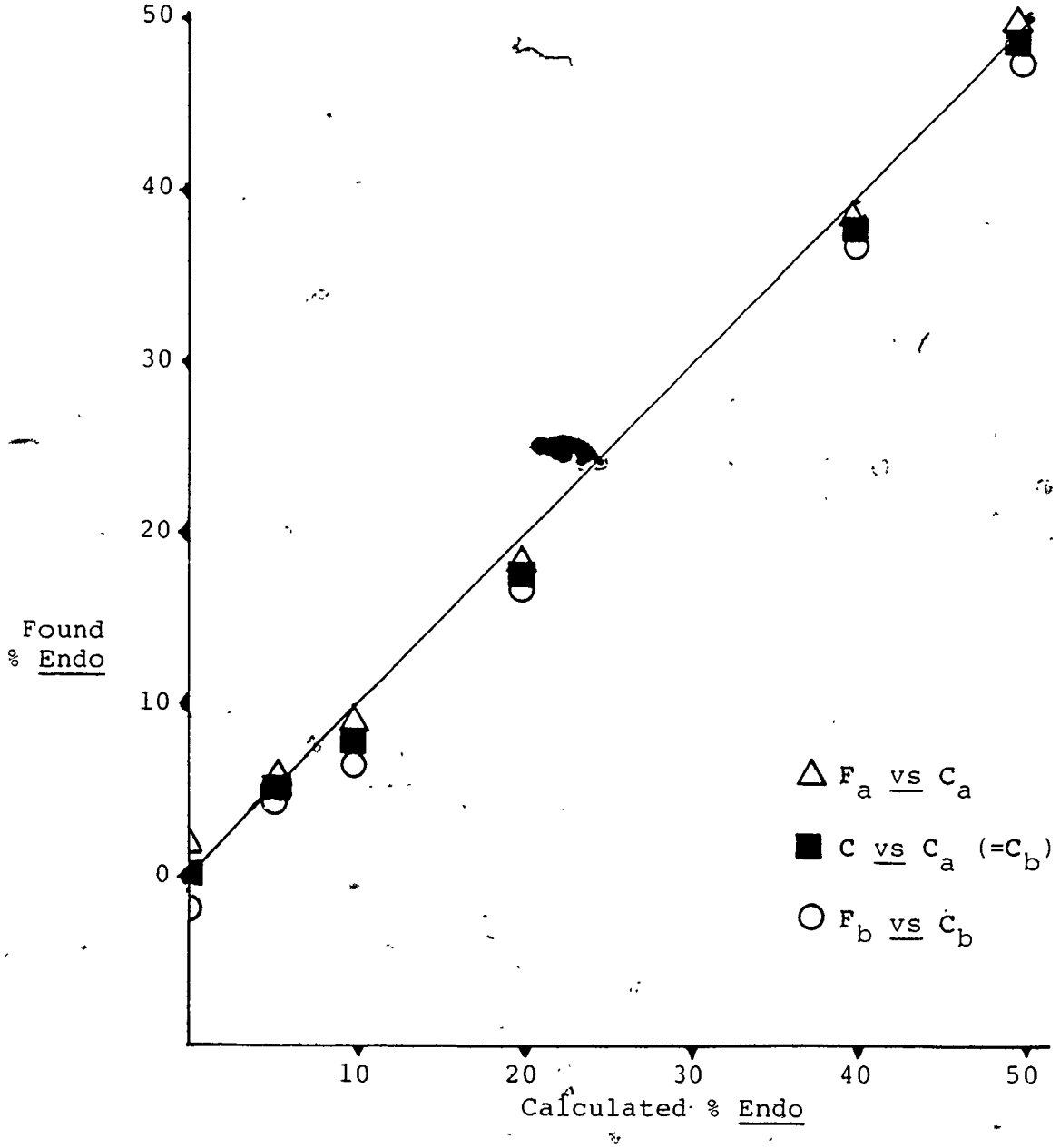


Figure 11: 2-(2-Methylphenyl)ethane Derivative Authentic Betaine Mixture Control Experiment Results

for the analogous experiments with **54**. Stock benzene solutions of **56a** and **d** (for $\underline{d}_0$,$\underline{d}_9$ crossing experiments) or of **56b** and **c** (for $\underline{d}_3$,$\underline{d}_6$ crossing experiments) were prepared by deprotonating the corresponding "norbetylates" (**111a** and **d** or **111b** and **c**) and from each, an aliquot was taken and evaporated to dryness. After being stored overnight over Drierite at 50 torr, the residue was weighed then examined by ^{1}H NMR in 1 $\underline{M}$ Na_2CO_3/D_2O. All residues were found to be at least 98% betaine (**57**). Each sample was recovered and then passed in water through a column of deionizing resin (Rexyn 300 ($^+$H,$^-$OH), 20 equiv.).† Evaporation of the eluant left a residue which was analyzed mass spectrometrically to give the amine ratio reported in Table 22. The corresponding $\mathbf{F}_a$ and $\mathbf{F}_b$ values were calculated directly from these using equation (14) or (24). The appropriate $\mathbf{F}_a$ and $\mathbf{F}_b$ values were then used to calculate **C** using equation (29). Since these samples are the products of crossing experiments conducted in the absence of a solvent, the betaine mixtures would be expected to be those derived from the intermolecular pathway. With the exception of stock 4, the $\mathbf{F}_a$ and $\mathbf{F}_b$ values are all within $\pm$ 2% zero and the **C**'s calculated from stocks 2 and 3 and from 6 and 7 are within 0.5% of zero. These results clearly indicate that the products were derived exclusively from the intermolecular

†A control experiment showed that 80% of a sample of **57a** was recovered after being passed in water through a column of deionizing resin (Rexyn 300 ($^+$H, $^-$OH), 20 equiv.). Less than 1% of a sample of the "norbetaine" (**116**) was recovered after similar treatment.

Table 22

2-(2-Methylphenyl)ethane Derivative
Stock Solution Analysis Results

Stock	d_X, d_Y	% Yield	Observed Amine Ratio d_0	d_3	d_6	d_9	F_a (% excess d_0, d_9)	F_b (% excess d_3, d_6)	% C endo
1	d_0, d_9	100	100.0	87.8	81.2	71.8	-0.8	-	-
2	d_0, d_9	102	100.0	107.9	106.8	109.7	-1.2	-	
3	d_3, d_6	94	100.0	97.4	97.9	89.7	-	1.4	0.1
4	d_0, d_9	105	100.0	122.8	129.0	118.0	-7.2	-	
5	d_3, d_6	93	100.0	92.3	88.1	82.8	-	0.6	3.6
6	d_0, d_9	105	100.0	101.8	98.3	98.2	-0.5	-	
7	d_3, d_6	103	100.0	94.9	95.4	85.6	-	1.3	0.4

F_a = found % excess d_0, d_9 as calculated using equation (14)

F_b = found % excess d_3, d_6 as calculated using equation (24)

C = observed % endo as calculated using equation (29)

pathway and that the extent of scrambling in the thermolyses was small. The discrepancy shown by the F_a value from stock 4 illustrates that the thermolysis procedure does occasionally, for unknown reasons, give a heavily scrambled amine mixture. To guard against error so induced, all subsequent pairs of F_a and F_b values that differed by more than 10% were discarded. The yields reported in Table 22 were obtained by comparing the weight of the residue with that calculated from the volume of the aliquot and the stock solution concentration for which a value was assigned based on the assumption that conversion of the "norbetylate" to the amino ester was quantitative. That the observed yields are all within the $\pm$ 10% experiment error inherent in the yield determination verifies this assumption.

The crossing experiment solutions were prepared, sealed in Carius tubes and allowed to react at 110.0°C for the reaction times specified in Tables 23 and 24. The tubes were then opened and the reactions were quenched with 1 N HCl (2 equiv.). As before this step was expected to convert any unreacted amino ester to the "norbetylate" chloride, **119**, which would then be converted, via a SRIP reaction, to the "norbetaine", **116**. Using the previously discussed procedure, the organic soluble products and the water soluble products were separated, isolated and weighed. When the former were examined by ^{1}H NMR in $CDCl_3$, the spectra indicated the presence of a oily material (^{1}H NMR: δ = 1.5 to 2.0 ppm, m) which, as before, was thought to be an impurity

Table 23

2-(2-Methylphenyl)ethane Derivative d_0, d_9-Crossing Experiment Results

Exp't No.	[56]ø	Reaction Time	% Reaction Calcd	% 57 Found	Yield of 115 %	Observed Amine Ratio d_0	d_3	d_6	d_9	F_a (% excess d_0, d_9)
1	4.5×10^{-3}	14 da	98	85	5	100.0	73.1	72.8	89.9	13.1
2	2.2×10^{-3}	14 da	97	87	28	100.0	69.9	70.5	91.0	15.3
3	2.2×10^{-3}	20.5 da	99	80	22	100.0	77.9	79.0	97.7	11.5
4	8.9×10^{-4}	14	90	86	26	100.0	71.2	75.6	100.8	15.5
5	8.9×10^{-4}	20.5 da	96	75	41	100.0	92.5	99.3	114.8	5.6
6	4.5×10^{-2}	45 min	20	19	ø	100.0	100.1	103.6	121.4	2.7
						100.0	101.1	97.4	110.4	2.7
8	2.2×10^{-2}	85 min	20	17	ø	100.0	113.0	114.6	136.0	1.8
						100.0	113.2	113.7	130.2	ø.7
10	8.9×10^{-3}	3.5 h	20	19	ø	100.0	99.8	101.8	130.0	6.6
						100.0	83.6	78.0	99.9	10.6
12	6.7×10^{-3}	4.7 h	21	18	ø	100.0	77.5	75.3	107.7	15.3
						100.0	84.6	87.0	121.5	12.7
14	4.5×10^{-3}	6.0 h	20	17	2	100.0	69.2	67.3	102.2	19.4
						100.0	73.6	74.1	115.4	18.7
16	2.2×10^{-3}	13.5 h	25	29	18	100.0	68.6	69.2	99.6	18.3
						100.0	77.3	80.3	114.4	15.2
18	8.9×10^{-4}	13.0 h	16	10	38	100.0	97.3	100.1	125.8	6.7
						100.0	95.7	102.3	135.2	8.6
20	$4,5 \times 10^{-3}$	1.3 h	5	5	ø	100.0	81.0	81.3	126.4	16.5
						100.0	74.0	74.4	116.5	18.6

Table 23 (cont'd)

2-(2-Methylphenyl)ethane Derivative
d_0, d_9-Crossing Experiment Results

Exp't No.	[56]ø	Reaction Time	% Reaction Calcd	% 57 Found	Yield of 115 %	Observed Amine Ratio d_0	d_3	d_6	d_9	F_a (% excess d_0, d_9)
22	4.5×10^{-3}	2.7 h	10	10	ø	100.0	71.5	71.1	112.0	19.6
						100.0	71.9	69.3	114.6	20.6
24	4.5×10^{-3}	4.9 h	16.5	12	ø	100.0	90.6	90.9	115.8	8.6
						100.0	71.8	71.6	108.3	18.4
26	4.5×10^{-3}	7.0 h	23	17	ø	100.0	76.2	74.9	107.6	15.8
						100.0	87.2	88.3	105.5	8.6
28	8.9×10^{-4}	29.0 h	30	36	38	100.0	76.4	81.5	115.2	15.4
						100.0	82.2	86.4	113.2	11.7
30	8.9×10^{-4}	49.0 h	45	65	38	100.0	93.2	98.6	121.7	7.2
						100.0	91.4	96.9	123.3	8.5

Table 24

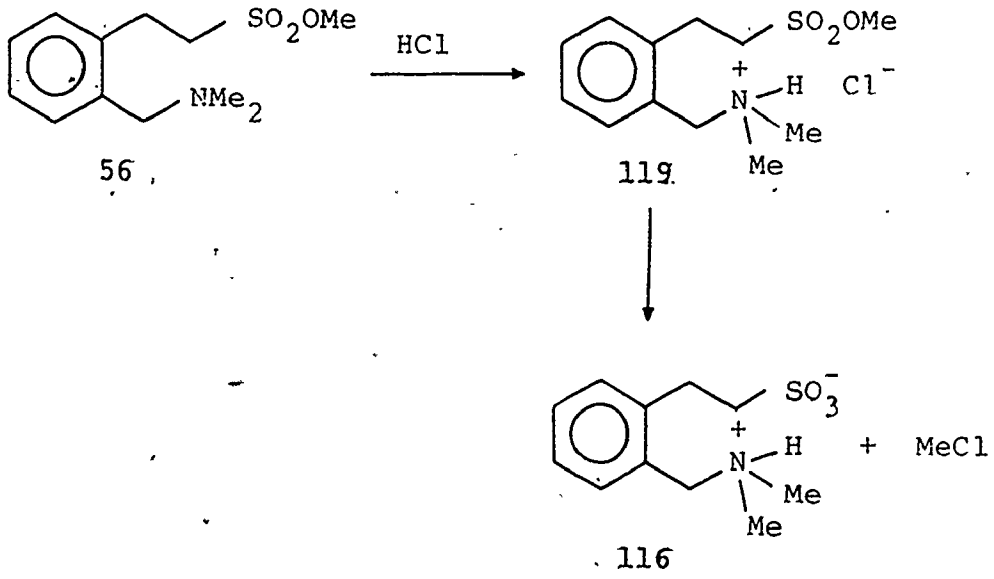
2-(2-Methylphenyl)ethane Derivative
d_3, d_6-Crossing Experiment Results

Exp't No.	[56]ø	Reaction Time	% Reaction Calcd	% 57 Found	Yield of 105 %	Observed Amine Ratio $d_ø$	d_3	d_6	d_9	F_b (% excess d_3, $d_ø$)
7	4.5×10^{-2}	45 min	20	16	ø	100.0	104.4	110.2	93.0	5.3
						100.0	95.1	99.8	83.0	3.2
9	2.2×10^{-2}	85 min	20	18	ø	100.0	106.5	110.9	92.0	6.2
						100.0	98.2	100.3	79.2	5.1
11	8.9×10^{-3}	3.5 h	20	16	ø	100.0	129.0	133.7	95.3	14.7
						100.0	120.0	119.6	85.3	12.8
13	6.7×10^{-3}	4.7 h	21	17	ø	100.0	145.9	149.7	96.0	20.3
						100.0	139.6	143.2	96.8	17.9
15	4.5×10^{-3}	6.0 h	20	20	2	100.0	131.1	128.8	81.0	17.9
						100.0	135.3	139.8	90.6	18.1
17	2.2×10^{-3}	13.5 h	25	25	5	100.0	155.0	158.1	104.9	20.9
						100.0	133.0	132.7	99.7	14.3
19	8.9×10^{-4}	13.0 h	16	10	15	100.0	103.4	135.5	70.2	16.8
						100.0	117.1	148.6	85.3	17.8
21	4.5×10^{-3}	1.3 h	5	8	ø	100.0	141.4	147.2	93.6	19.7
						100.0	135.5	138.5	87.9	18.7
23	4.5×10^{-3}	2.7 h	10	13	ø	100.0	138.8	142.9	89.3	19.6
						100.0	146.0	155.4	101.2	20.0
25	4.5×10^{-3}	4.9 h	16.5	14	ø	100.0	141.9	141.6	86.9	20.5
						100.0	143.5	144.0	91.9	20.0
27	4.5×10^{-3}	7.0 h	23	17	6	100.0	144.5	142.9	88.4	20.8
						100.0	140.7	139.1	87.7	19.7

Table 24 (cont'd)

2-(2-Methylphenyl)ethane Derivative
d_3, d_6-Crossing Experiment Results

Exp't No.	[56]ø	Reaction Time	% Reaction Calcd	% 57 Found	Yield of 105 %	Observed Amine Ratio $d_ø$	d_3	d_6	d_9	F_b (% excess $d_3, d_ø$)
29	8.9×10^{-4}	29.0 h	30	36	25	100.0	128.7	140.8	98.6	15.2
						100.0	138.1	149.6	110.8	15.4
31	8.9×10^{-4}	49.0 h	45	65	28	100.0	133.2	140.1	104.7	14.4
						100.0	131.4	138.2	105.1	13.6



56 119 116

extracted from the calcium hydride used in the stock solution drying procedure. In all crossing experiments with reaction times of 6 h or more, in addition to the oily material, the ^1H NMR spectra indicated the presence of what appeared to be the sultone (**115**). When the IR spectra of several of these residues were obtained, they were found to contain all of the IR bands shown by an authentic specimen of **115** and when the combined organic residue from the first five crossing experiments was recrystallized, the specimen so obtained showed no mp depression when mixed with authentic **115**. It may, therefore, be concluded that **115** is a reaction product in crossing experiments with reaction times of

6 h or more. The sultone yields were estimated† and are reported in Tables 23 and 24. Examination of these indicates that they increase with the reaction time.

The water soluble products were weighed, then dissolved in 1 M Na_2CO_3/D_2O and examined by ^1H NMR. The spectra were consistent with a mixture of the betaine (**57**) and the "nor-betaine" (**116**) in which both were deficient in half of their ammonio methyl resonances. The betaine product ratio, expressed in Tables 23 and 24 as % **57**, was calculated from the integrals of these spectra. It must be noted, however, that in the spectra of the products from crossing experiments in which the yield of **115** was greater than 10%, an additional singlet (δ = 3.0 ppm, T-60) was observed. As will be seen shortly, this peak was due to the presence of a tetramethylammonium ion. Each sample was recovered and passed as an aqueous solution through a column of deionizing resin. Evaporation of the eluant left a residue which was weighed and then analyzed mass spectrometrically to give the reported

---

†A crude estimate of the yield of the sultone was made using equation (34) in which $W_\emptyset$ is the weight of the organic

$$\% \text{ yield of } \mathbf{115} = 100 \; \frac{W_\emptyset - V_s [\text{oil}]_s}{198 \; V_f \; [\mathbf{56}]_\emptyset} \qquad (34)$$

soluble residue, V_s is the volume of stock solution used in the crossing experiment, $[\text{oil}]_s$ is the average concentration of oil observed in the crossing experiments reported in this section that produced no sultone and in the crossing experiments described in Section II B.4 (0.4 mg. mL^{-1}), V_f is the crossing experiment solution volume, $[\mathbf{56}]_\emptyset$ is the initial ester concentration and 198 is the molecular weight of **115**. In view of the somewhat variable nature of $[\text{oil}]_s$, ± 5% would seem to be a reasonable limit to the accuracy of the yields of **115**.

amine ratio from which F_a or F_b was calculated using equation (14) or (24).

As a consequence of the hygroscopic nature of **116**, the weight of the crude water soluble products was generally 10± 20% higher than the corresponding theoretical weight calculated from the observed product ratio and the number of moles of **56** used in the experiment. The yields obtained after the product mixtures were passed through deionizing resin were consistently low simply because of the weak but real affinity of the resin for **57**. It follows then that the observed ^1H NMR betaine ratio, expressed as % **57** found, best represents the extent of reaction. For the purpose of comparison, calculated percent reactions were required. These were obtained from equation (35) via equation (8) which is the integrated form of the assumed rate law described by equation (5).

$$-\frac{d[\mathbf{56}]}{dt} = k_1[\mathbf{56}] + 2k_2[\mathbf{56}]^2 \qquad (5)$$

$$\frac{1}{[\mathbf{56}]_f} = \frac{e^{k_1 t}}{[\mathbf{56}]_\emptyset} + \frac{2}{\mathbf{EM}}(e^{k_1 t} - 1) \qquad (8)$$

$$\%\ \text{reaction (calcd)} = 100\left[\frac{[\mathbf{56}]_\emptyset - [\mathbf{56}]_f}{[\mathbf{56}]_\emptyset}\right] \qquad (35)$$

In these, $[\mathbf{56}]_\emptyset$ is the initial ester concentration, $[\mathbf{56}]_f$ is the final ester concentration, t is the reaction time, **EM** is the effective molarity which is defined by equation (1) (for reasons that will be presented shortly, a value of 2×10^{-3} M was used for the **EM**), $2k_2$ is the observed

$$\mathbf{EM} = \frac{k_1}{k_2} \qquad (1)$$

second order rate constant obtained from the ^1H NMR kinetics (2.0×10^{-3} L mol^{-1} s^{-1}) and k_1 is the first order rate constant calculated from equation (1) ($k_1 = 2 \times 10^{-6}$ s^{-1}). The calculated % reaction values are reported in Tables 23 and 24. In the preliminary† $\underline{d}_0$, $\underline{d}_9$ crossing experiments numbered 1 through 5, the reactions were driven essentially to completion from initial ester concentrations ranging from 4.5×10^{-3} M to 8.9×10^{-4} M. The F_a's obtained from analysis of resulting betaine mixtures clearly indicates the presence of enrichment in the $\underline{d}_0$ and $\underline{d}_9$ betaines (**57a** and **57d**). This then is direct evidence for a least partial endocyclic methyl transfer in the formation of **57** from **56**.

An **EM** for the endocyclic process may be calculated using equation (10) which is derived from the assumed mixed

$$C_{calc} = \text{calcd \% } \underline{\text{endo}} = \left(\frac{50\ \mathbf{EM}}{[\mathbf{56}]_0 - [\mathbf{56}]_f}\right) \ln\left(\frac{2[\mathbf{56}]_0 + \mathbf{EM}}{2[\mathbf{56}]_f + \mathbf{EM}}\right) \quad (10)$$

first and second order rate law described by equation (5).

Equation (10) predicts that for a constant percent reaction, there is a curve of C_{calc} $\underline{vs}$ $[\mathbf{56}]_0$ that is characteristic of a given **EM**. In practice, the use of a logarithmic scale for [**56**] and for the **EM** values is preferred because this allows concentration ranges of several orders of magnitude to be plotted without encountering compression along the abscissa of the plots. Figure 12 shows the calculated % $\underline{\text{endo}}$ (C_{calc}) versus $[\mathbf{56}]_0$ curves that are obtained from

---

†These experiments were conducted prior to the development of the $\underline{d}_0$, $\underline{d}_9$ - $\underline{d}_3$, $\underline{d}_6$ descrambling procedure and hence their interpretation requires the assumption that $F_a = C$.

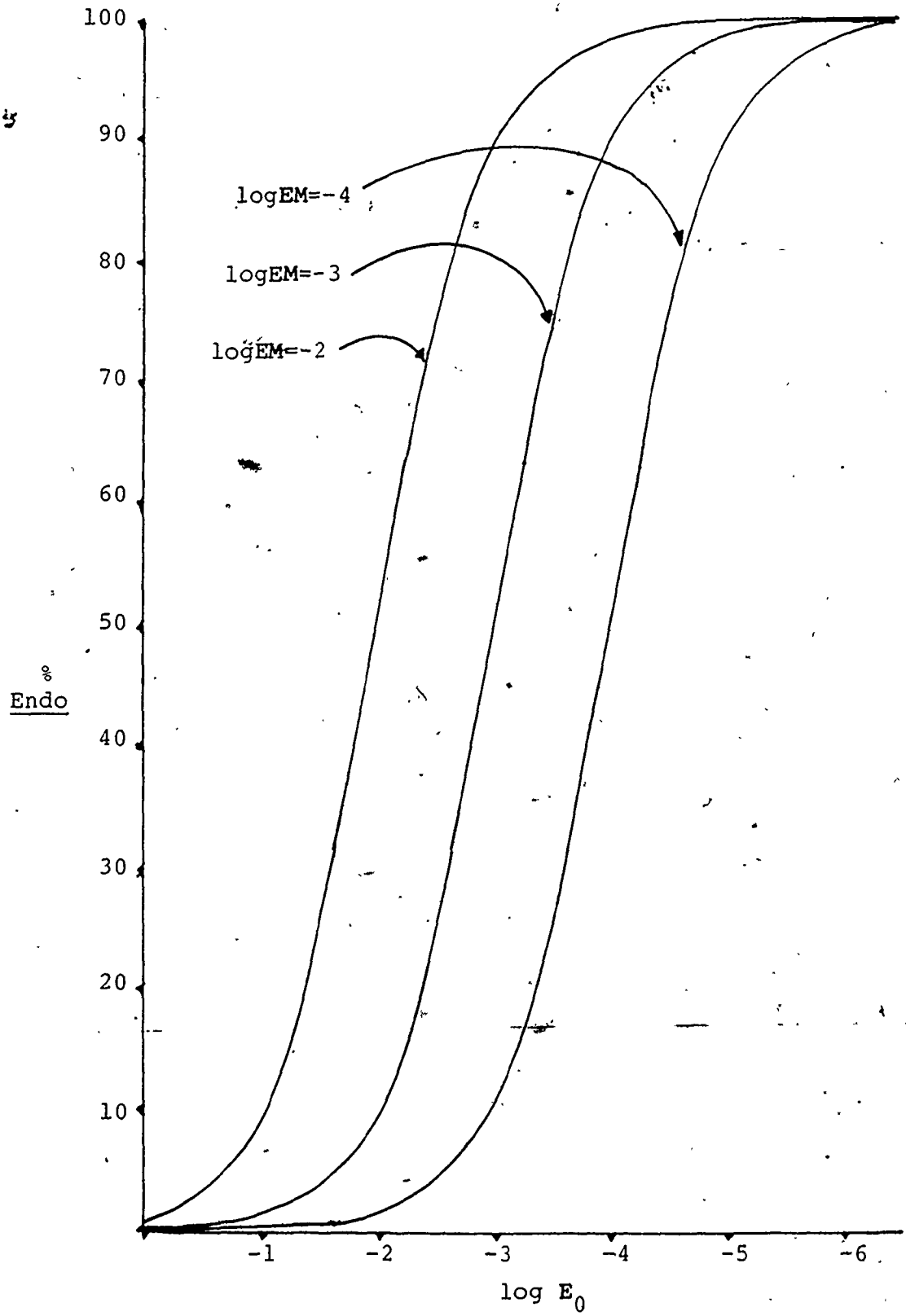


Figure 12: Calculated % Endo (C_{calc}) versus log $[56]_0$
Effective Molarity Curves (85% Reaction)

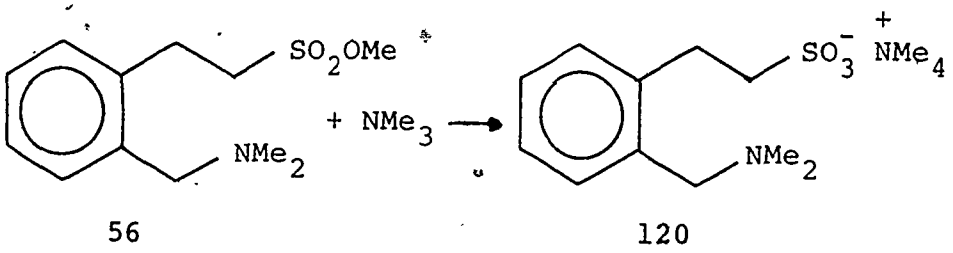
equation (10) for log EM's of -2, -3 and -4 (85% reaction).

In the first five crossing experiments, the observed % endo (**C**) clearly did not increase as the initial concentration of **56** was reduced. It must, therefore, be concluded that the conversion of **56** to **57**, under these conditions; does not obey the rate law shown in equation (5). Two other anomalies are apparent: the observed % **57** is 10 to 15% lower than that anticipated from the calculated % reaction and the presence of both the sultone, **115** and the extraneous singlet in the ^1H NMR of the water soluble products are unaccounted for.

A plausible source of **115** is the same 7-exo-tet displacement of trimethylamine that was used in the mass spectrometric thermolysis. Since these experiments were

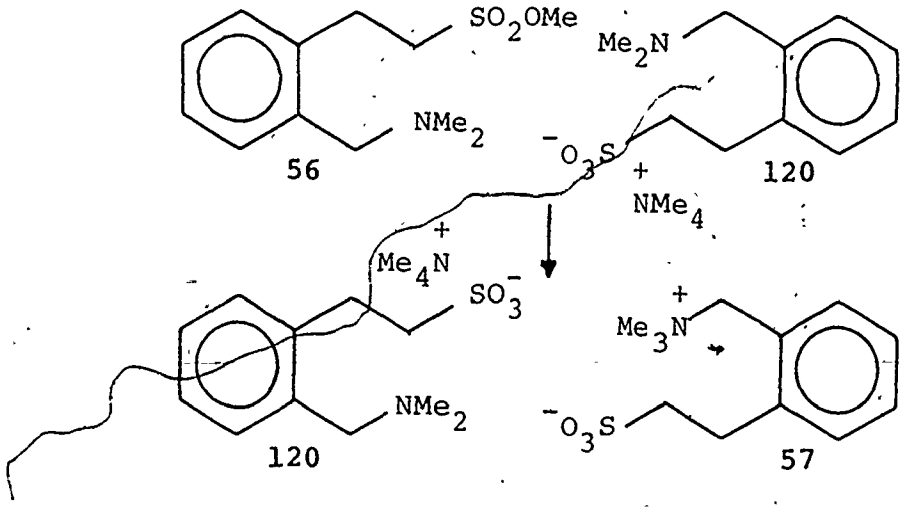
57

conducted in Carius tubes, the trimethylamine so produced could not distill from the reaction mixture but rather, would be partitioned between the gas and liquid phases. The amine in the liquid phase would then be methylated by **56** to give the ion pair, **120**.



56 120

The accumulation of a significant amount of **120** during the course of the conversion of **56** to **57** is then a reasonable consequence of the thermal degradation of **57.** Once generated, **120** would be expected to participate in the conversion of **56** to **57.** That is, methylation of **120** by **56** gives **57** and **120.** This reaction would then serve as a catalytic



second order intermolecular pathway for the formation of **57** from **56.** The second order rate constant for this process, k_3, would be expected to be similar to k_2 since the nucleo-

philicities of **120** and **56** should be comparable. The overall rate law must then be modified to include a third term:

$$\frac{d[57]}{dt} = k_1[56] + 2k_2[56]^2 + k_3[120][56] \qquad (36)$$

Noteworthy also is that, since this reaction is intermolecular, its crossing experiment product is the same 1:1:1:1 - **57a:b:c:d** betaine mixture that is formed by the noncatalytic intermolecular pathway. In the crossing experiments, the endocyclic process must then compete with both intermolecular pathways and hence, in the presence of a significant amount of **120**, the observed % endo will be indicative of an **EM** that is erroneously low. As well, the dependence of **C** versus log $[56]_\emptyset$ would not be expected to follow the curve defined by equation (10). In summary then, the proposed side reactions successfully amount for the formation of the sultone, **115**, for the observation of the extraneous singlet (δ = 3.0 ppm, $^+NMe_4$) in the ^1H NMR spectra of the crude betaine mixtures and for the lack of agreement between the observed % endo (**C**) and log $[56]_\emptyset$ values obtained from the first five crossing experiments with the above mentioned C_{calc} versus log $[56]_\emptyset$ curves.

While a mathematical description of this reaction scheme is, in principle, possible and hence the true **EM** could be obtained from the first five crossing experiment's product ratios, in practice, the number of variables in such a treatment would render the **EM** assignment dubious at best. Rather, a property of the catalytic second order reaction may be exploited to simplify the reaction scheme. That is, at

the onset of the reaction, no **12Ø** is present in the reaction mixture and hence the reaction, at this time, should obey the originally assumed rate law (equation (5)). The betaine isolated from crossing experiments reaction mixtures prior to the accumulation of a significant amount of **12Ø** should be the product of the originally assumed rate law and hence the curve of **C** versus log [**56**]$_Ø$ should provide, via equation (1Ø), a common **EM**.

Accordingly, a series of complementary pairs of $d_Ø$,d_9 and d_3,d_6 crossing experiments (6 through 19) were quenched after approximately 2Ø% reaction. In these, the usual scrambling correction (equation (29)) was used and their combined results are summarized in Table 25. Also since the derived **C**'s would be used in curve fitting, the thermolytic analyses were conducted in duplicate and the pair of **C**'s obtained at each concentration was averaged to give the average observed % endo, **C'**. Figure 13 is the plot of **C'** versus log [**56**]$_Ø$ derived from these experiments. The curves drawn on this plot are those calculated from equation (1Ø) for 2Ø% reaction and log **EM**'s of -2.5, -2.7 and -2.9. Inspection of this plot indicates that when the initial ester concentration is greater than or equal to $4.5 \times 1Ø^{-3}$ M, **C'** versus log [**56**]$_Ø$ fits the curve defined by log **EM** = -2.7 and all points clearly fall between the curves defined by log **EM** equals -2.5 and -2.9. However, the experiments using initial ester concentrations lower than $4.5 \times 1Ø^{-3}$ M and reaction times longer than 6 h give **C'** values whose deviation

Table 25

2-(2-Methylphenyl)ethane Derivative
Combined d_0, d_6 Crossing Experiment Results (Approximately 20% Reaction)

[56]ø	% Reaction (Calcd)	Average Yield of 115 (%)	d_0, d_9 Expt' No.	d_3, d_6 Expt' No.	F_a	F_b	C	Average C'	C (Calcd)
4.5×10^{-2}	20	0	6	7	2.7	5.3	4.1	3.5	2.4
					2.7	3.2	3.0		
2.2×10^{-2}	20	0	8	9	1.8	6.2	4.2	3.6	4.8
					0.7	5.1	3.0		
8.9×10^{-3}	20	0	10	11	6.6	14.7	11.6	11.8	11.1
					10.6	12.8	12.0		
6.7×10^{-3}	21	0	12	13	15.3	20.3	18.7	17.4	14.4
					12.7	17.9	16.1		
4.5×10^{-3}	20	2	14	15	19.4	17.9	18.4	18.4	19.9
					18.7	18.1	18.3		
2.2×10^{-3}	25	12	16	17	18.3	20.9	20.1	17.4	34.3
					15.2	14.3	14.6		
8.9×10^{-4}	16	26	18	19	6.7	16.8	13.1	13.8	55.0
					8.6	17.8	14.5		

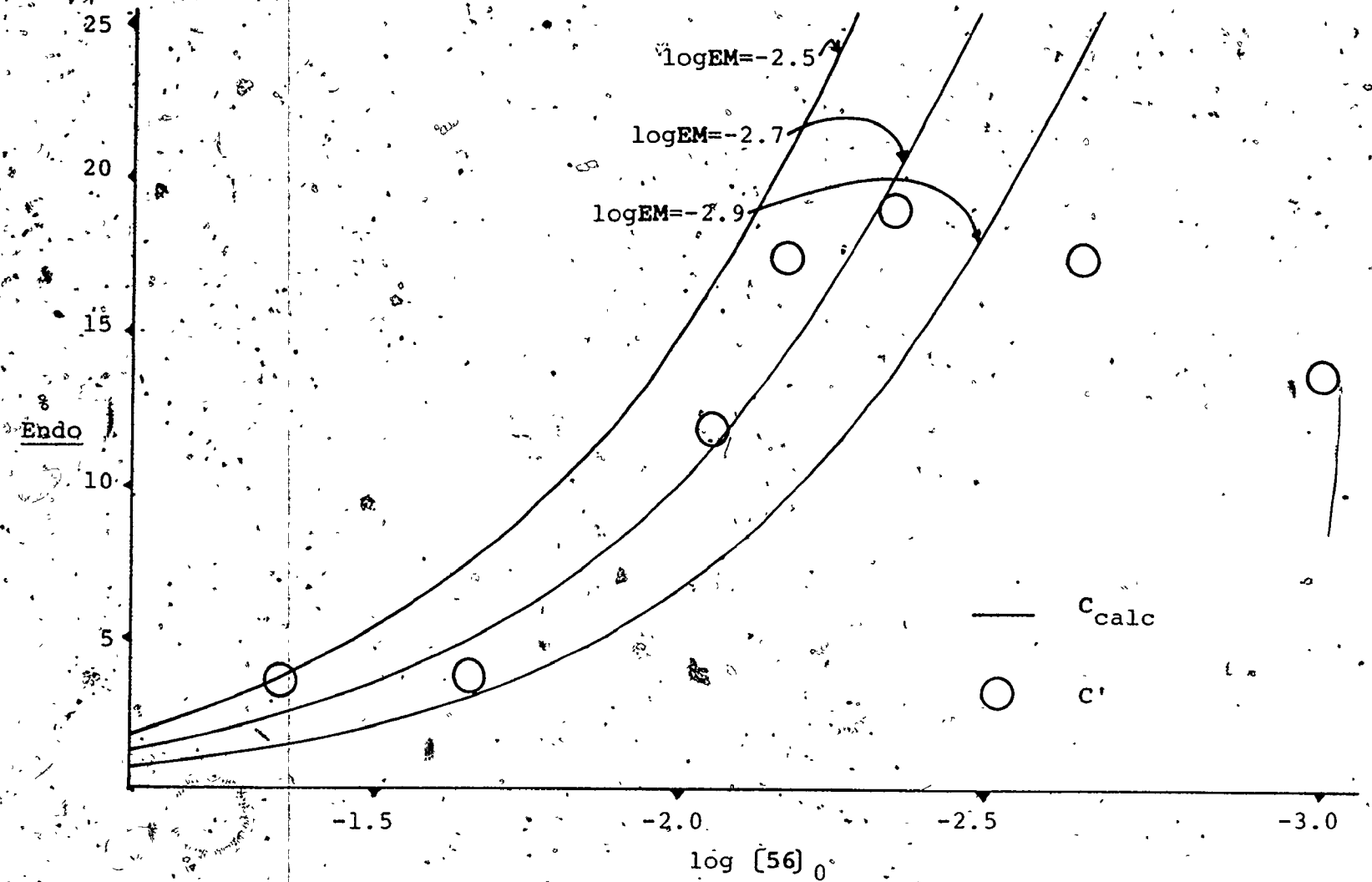


Figure 18: Observed Average % Endo and Calculated % Endo versus log $[56]_0$ Effective Molarity Curves (20% Reaction)

from the log **EM** equals -2.7 curve increases with decreasing initial concentration. Inspection of the average yields of **115** listed in Table 25 indicates that the last **C'** that fits the above curve coincides precisely with the appearance of a trace of **115** ($\simeq$ 2%) in the reaction products and that progressively larger yields of **115** produce progressively larger deviations of **C'** from the C_{calc} versus [**56**]ø curve characteristic of log **EM** $\triangleq$ -2.7. These results then suggest that the appearance of the sultone in the reaction products coincides with the generation of a significant amount of **120** which in turn contributes significantly to the formation of **57** from **56**. When no sultone is detected, however, the catalytic second order pathway apparently makes no significant contribution to the formation of **57** from **56** and hence, in these reactions, the assumed rate law shown in equation (5), is obeyed and the results are consistent with a log-**EM** of -2.7 $\pm$ .2 for the endocyclic process.

If the conclusion that in the absence of a detectable amount of sultone, the contribution from **120** to the formation of **57** from **56** is negligible, is correct, then a series of crossing experiments sharing the same initial ester concentrations that are quenched at different percent reactions up to the percent at which the sultone is first observed should all yield the same **EM** via equation (10). Accordingly, Experiments 20 through 27, which share an initial ester concentration of 4.5×10^{-3} M, were conducted and quenched at approximately 5, 10, 15, 20 and 25% reaction. The F_a, F_b and

Table 26

2-(2-Methylphenyl)ethane Derivative
Combined d_0,d_9-d_3,d_6 Crossing Experiment Results
(Variable Percent Reaction)

[56]$_0$	% Reaction Calcd	Average Yield of 115 %	d_0,d_9 Expt No.	d_3,d_6 Expt No.	% Excess F_a d_0,d_9	% Excess F_b d_3,d_6	C (% endo)	Average C (% endo)	C (Calcd)
4.5×10^{-3}	5	0	20	21	16.5	19.7	18.7	18.7	18.6
					18.6	18.7	18.7		
4.5×10^{-3}	10	0	22	23	19.6	19.6	19.6	19.9	19.0
					20.6	20.0	20.2		
4.5×10^{-3}	16.5	0	24	25	8.6	20.5	-	19.5	19.5
					18.4	20.0	19.5		
4.5×10^{-3}	20	2	14	15	19.4	17.9	18.4	18.3	19.9
					18.7	18.1	18.3		
4.5×10^{-3}	23	3	26	27	15.8	20.8	19.3	19.3	20.1
					8.6	19.7	-		
8.9×10^{-4}	16	26	18	19	6.7	16.8	13.1	13.8	55.0
					8.6	17.8	14.5		
8.9×10^{-4}	30	31	28	29	15.4	15.2	15.3	14.7	57.3
					11.7	15.4	14.1		
8.9×10^{-4}	45	33	30	31	7.2	14.4	11.6	11.6	59.3
					8.5	13.6	11.6		

derived C' values are summarized in Table 28. That C′ agrees with C_{calc} (which was obtained from equation (10) assuming log **EM** = -2.5) to ± 2% verifies the above conclusions.

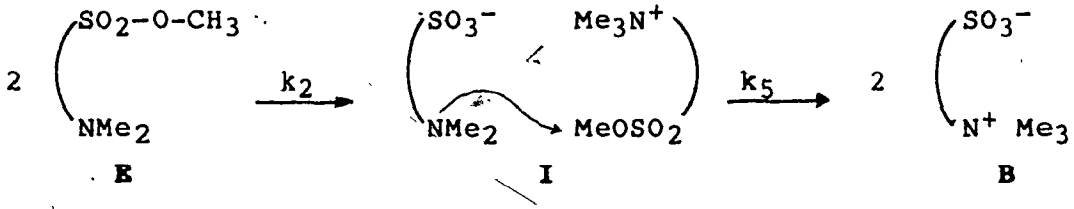
Table 26 also lists the results of a similar series of crossing experiments that shared an initial ester concentration of 8.9×10^{-4} M and were quenched after varing reaction times. In these, a consistent yield of approximately 30% for **115** was observed and no correlation between C′ and C_{calc} (from equation 10) is evident. These results serve simply to confirm the conclusions drawn from the first five d0,d9 crossing experiments.

In summary, the crossing experiments described in this section represent indisputable proof of the first example of an endocyclic methyl transfer. The results are consistent with an **EM** of 2×10^{-3} M for the endocyclic rearrangement of **56** to **57**.

D. The Bimolecular Reaction Mechanism

1. Introduction:

In the previous three sections, it was assumed that the bimolecular methylations occurred by the mechanism shown below.

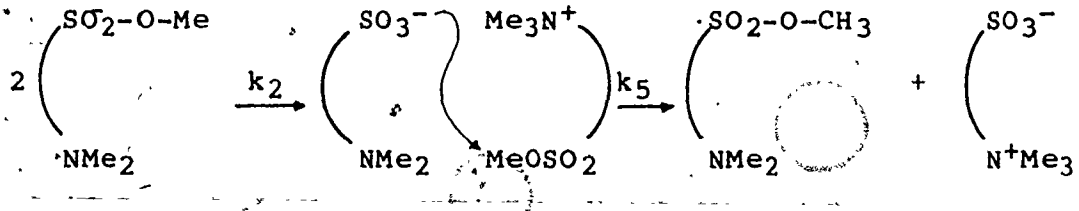


E **I** **B**

Two molecules of the ester (**E**) react in the rate determining step to form an ion pair (**I**). The ion pair then rapidly reacts *via* N-methylation to give two molecules of the betaine (**B**). In this section of the thesis, evidence is presented in support of this assumption.

2. N- versus O-Methylation:

A reasonable alternative to the assumed mechanism is one in which the ion pair annihilates by way of O-methylation.



E **I** **E** **B**

While tertiary amines in aqueous media are much more nucleophilic than alkylsulfonate anions,[90] no such behaviour has been documented for nonpolar aprotic media. In fact, under reaction conditions very similar to those used in

the crossing experiments, betylate sulfonates (**121**) readily give sulfonic esters (**122**).[91] In addition, methyl transfer

$$\underset{\textbf{121}}{R\text{-}O\text{-}SO_2\text{-}CH_2CH_2N^+Me_3\ R'SO_3^-} \xrightarrow[\text{reflux}]{\text{PhH or PhMe}} \underset{\textbf{122}}{R\text{-}O\text{-}SO_2\text{-}R'} + Me_3N^+\text{-}CH_2CH_2SO_3^-$$

R = Hexadecyl, 2-octyl, butyl; R' = Methyl, R-tolyl

to the sulfo anion (O-methylation) is a Hughes - Ingold "type 1" S_N reaction[16,92] and hence would be expected to be subject to a small rate increase with a decrease in solvent polarity, while N-methylation is a "type 2" displacement in which there is an increase in charge separation on formation of the transition state and which should therefore show a "large" decrease in rate with lowering solvent polarity. The result is that, in the absence of more quantitive information, the relative nucleophilicities of the sulfo anion and the tertiary amine in chloroform (or benzene) cannot be safely predicted from their behaviour in water.

Model Kinetic Studies:

A key difference between the mechanisms is that annihilation of one molecule of **I** by N-methylation gives two molecules of **B**, whereas O-methylation results in the formation of one **E** and one **B**. Consequently, the loss of **E** when **I** reacts by N-methylation will be twice as fast as when **I** undergoes the O-methylation process. This difference then appears as a factor of two in their rate laws.

N-methylation; $-\frac{dE}{dt} = 2k_2E^2$, $k_{obs} = 2k_2$ (37)

O-methylation; $-\frac{dE}{dt} = k_2E^2$, $k_{obs} = k_2$ (38)

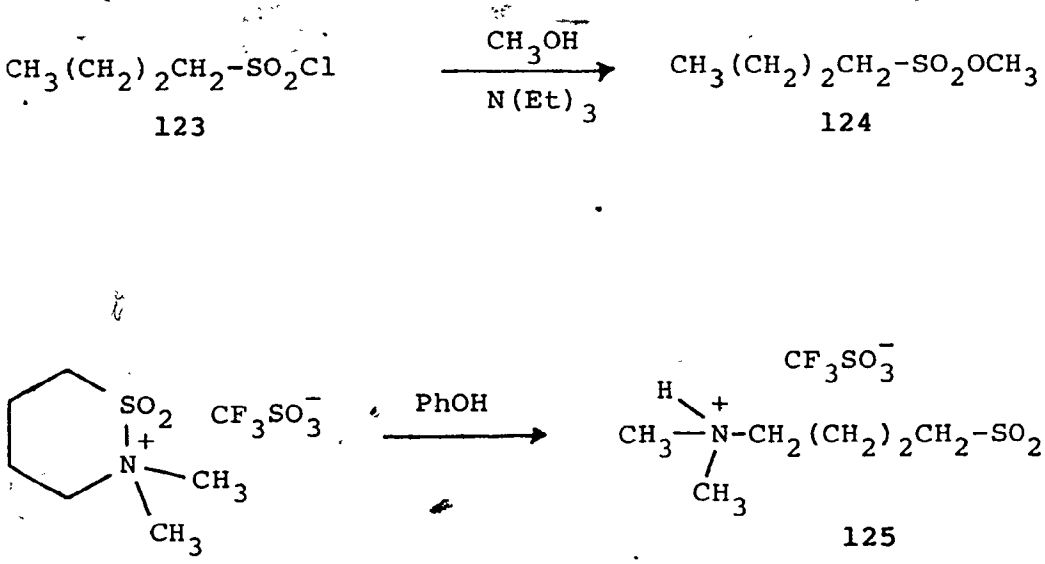
It follows then that the second order rate constant for the bimolecular reaction of two suitable model compounds, k_m, will equal k_2 and hence should provide a means of distinguishing between the mechanisms. If k_m is half k_{obs} then N-methylation has occurred and conversely, if k_m equals k_{obs} then O-methylation is the mechanism. With this in mind, suitable model compounds were prepared and the second order rate constants for their reactions were determined.

Synthesis of the Model Compounds:

The structures, (and when required, the synthesis) of the model compounds are shown in schemes 10 and 11. For the butane system, two models were prepared. Methyl 1-butanesulfonate (**124**) was obtained by reacting butanesulfonyl chloride (**123**) with methanol and triethylamine[93]. Phenolysis of the "sultamium" salt (**64a**) gave the phenyl "norbetylate" (**125**) which when deprotonated with aqueous potassium hydroxide gave phenyl 4-(dimethylamino)butanesulfonate (**126**).

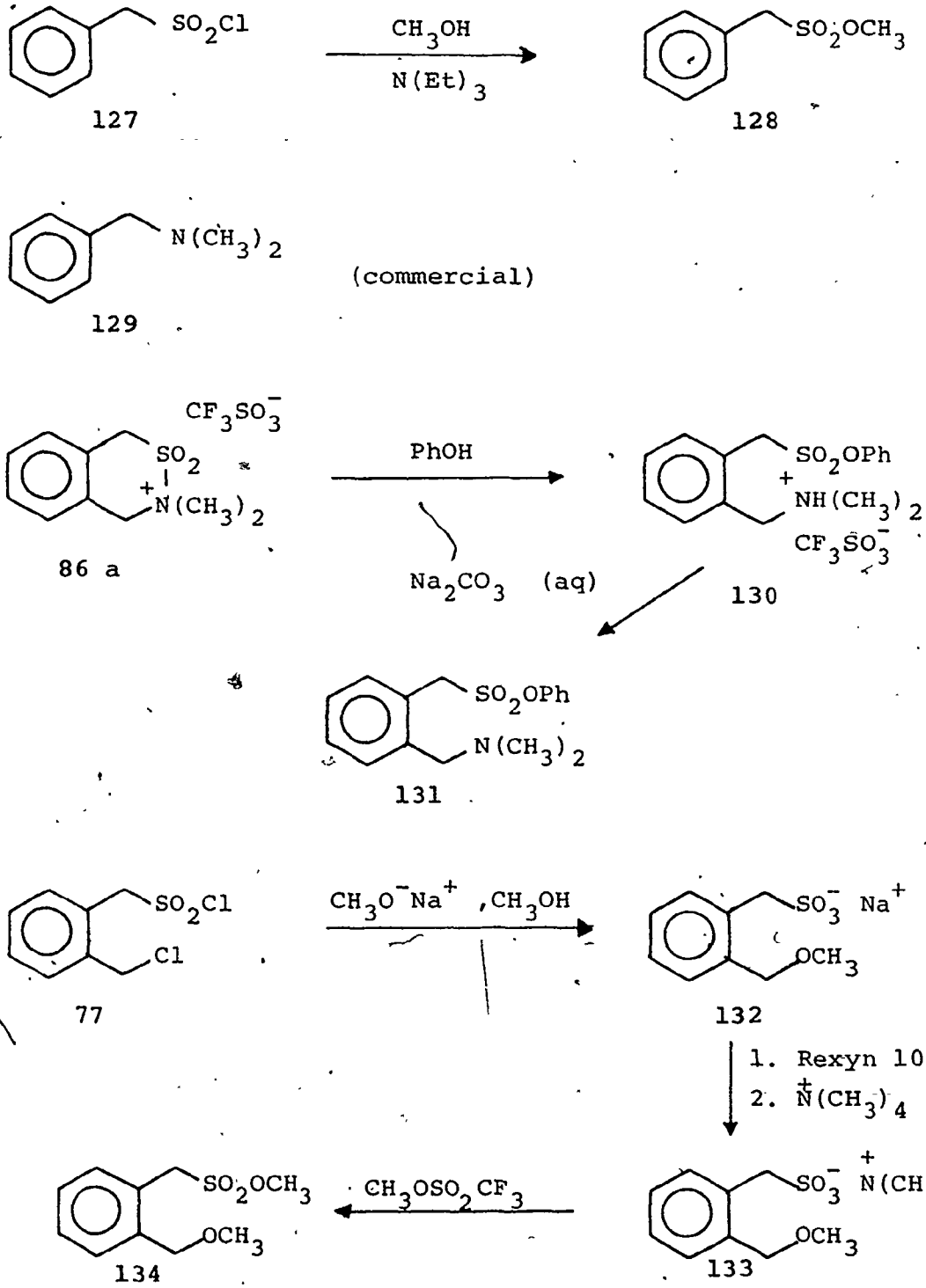
For reasons which will be given shortly, the 2-methylphenylmethane system prompted the synthesis of more than one pair of model compounds. The simplest model ester, methyl phenylmethanesulfonate (**128**), was prepared by reacting phenylmethanesulfonyl chloride (**127**) with methanol and triethylamine[94]. N,N-Dimethylbenzylamine (**129**) was obtained commercially. Phenolysis of the "sultamium" salt, **86a**, gave the corresponding phenyl "norbetylate" (**130**) which on treatment with aqueous sodium carbonate gave phenyl 2-(di-

Model Butane Derivatives:



Scheme 10

Model 2-Methylphenylmethane Derivatives:



Scheme 11

methylaminomethyl)phenylmethanesulfonate (**131**). The last model, methyl 2-(methoxymethyl)phenylmethanesulfonate (**134**), required a more elaborate synthesis. The chloro-sulfonyl chloride, **77**, on treatment with sodium methoxide in methanol gave sodium 2-(methoxysulfonylmethyl)phenylmethanesulfonate (**132**) which was protonated by elution through a strong acid ion exchange resin (Rexyn 101, ^{+}H) then neutralized with tetramethylammonium hydroxide to give the corresponding tetramethylammonium salt, **133**. Methyl trifluoromethanesulfonate converted **133** to the desired model ester, **134**.

^{1}H NMR Kinetic Method

These kinetic runs were conducted using the following general procedure: a solution of the model amine and an internal standard (CH_2Cl_2, 1,1,2,2,-tetrachloroethane or p-di-t-butylbenzene) in $CDCl_3$ or benzene-d_6 was prepared in a volumetric flask and then used to dissolve the model ester. From the ^{1}H NMR spectrum obtained immediately after mixing, the concentrations of the model ester and the internal standard were obtained based on the known initial amine concentration. The reactions were then monitored by ^{1}H NMR under the same conditions as those used to determine k_{obs} for the corresponding methyl ω-dimethylaminoalkanesulfonate ester. At appropriate time intervals, the integral of a peak from one of the model compounds and that from the internal standard peak were obtained. These values then gave the concentrations of the monitored model versus time. The concentrations of the other model were determined

by simply subtracting the amount of consumed monitored model from the initial concentration of the other model. The slope of a linear least squares best-fit line from a plot of $\frac{1}{[A]_0-[B]_0} \ln\left(\frac{[A]}{[B]}\right)$ versus time gave the model second order rate constant (k_m). A typical plot is shown in Figure 14. Generally, excessive noise due to the decreasing spectrum amplitude and to the marginal solubility of the reaction product precluded the acquisition of data beyond 80% reaction. The rate constants were reproducible to ± 10% with the major source of error being uncertainty in the initial substrate concentrations.

Model Kinetics Results and Discussion:

The kinetic results obtained from the butane derivatives are summarized in Table 27. The average k_m for the reaction of 124 with 126 (1.4×10^{-3} L $mol^{-1}s^{-1}$) is exactly half of the average k_{obs} for the reaction of methyl 4-(dimethylamino)butanesulfonate (**52a**; 2.8 L $mol^{-1}s^{-1}$). This result is then evidence supporting the N-methylation mechanism. It must be noted that in these model reactions, the ω-substituent effects were expected to be negligible[95]. Indeed, the 4-phenoxysulfonyl substituent was used in the model amine, not to modify the nucleophilicity of the model but rather simply to facilitate its handling by reducing its volatility.

In the hopes of extending this conclusion to the reactions of the benz-fused amino esters, the kinetic results shown in Table 28 were obtained. The simplest models, **128**

Table 27

Butane Derivative Model Kinetic Results

Exp't No.	Model Amine	Initial Conc.(M)	Model Ester	Initial Conc.(M)	Observed Second Order Rate Constant (k_m) (L $mol^{-1}s^{-1}$)
1.(b)(i)	**126**	0.566	**124**	0.491	1.4×10^{-3}
1.(b)(ii)	**126**	0.587	**124**	0.392	1.3×10^{-3}

Table 28

2-Methylphenylmethane Derivative Model Kinetic Results

Exp't No.	Model Amine	Initial Conc.(M)	Model Ester	Initial Conc.(M)	Observed Second Order Rate Constant (k_m) (L $mol^{-1}s^{-1}$)
2(o)	**129**	0.137	**128**	0.156	6×10^{-2}
2(p)	**131**	0.136	**128**	0.178	2.3×10^{-3}
2(q)(i)	**131**	0.178	**134**	0.128	3.1×10^{-3}
2(q)(ii)	**131**	0.178	**134**	0.228	3.4×10^{-3}

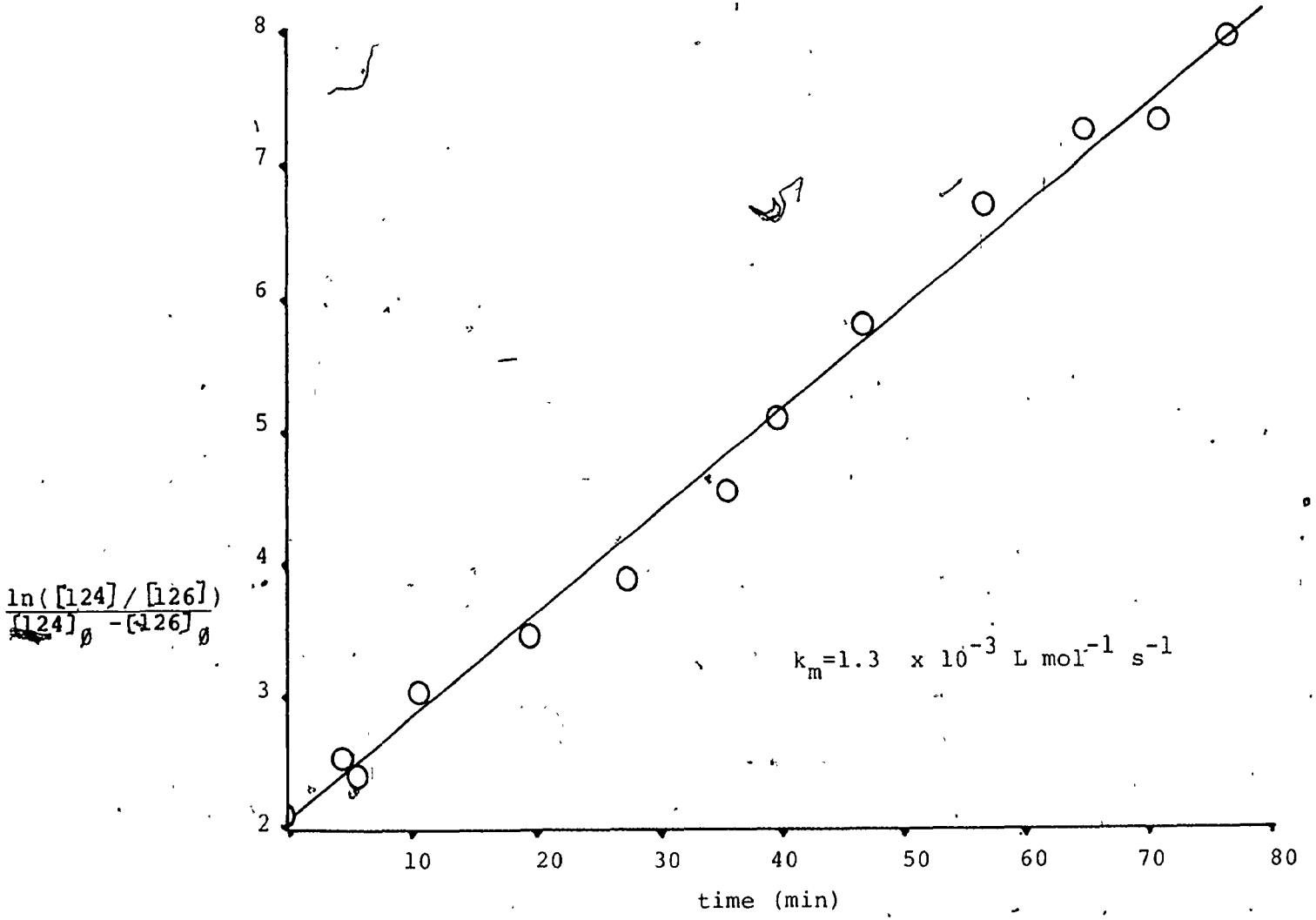
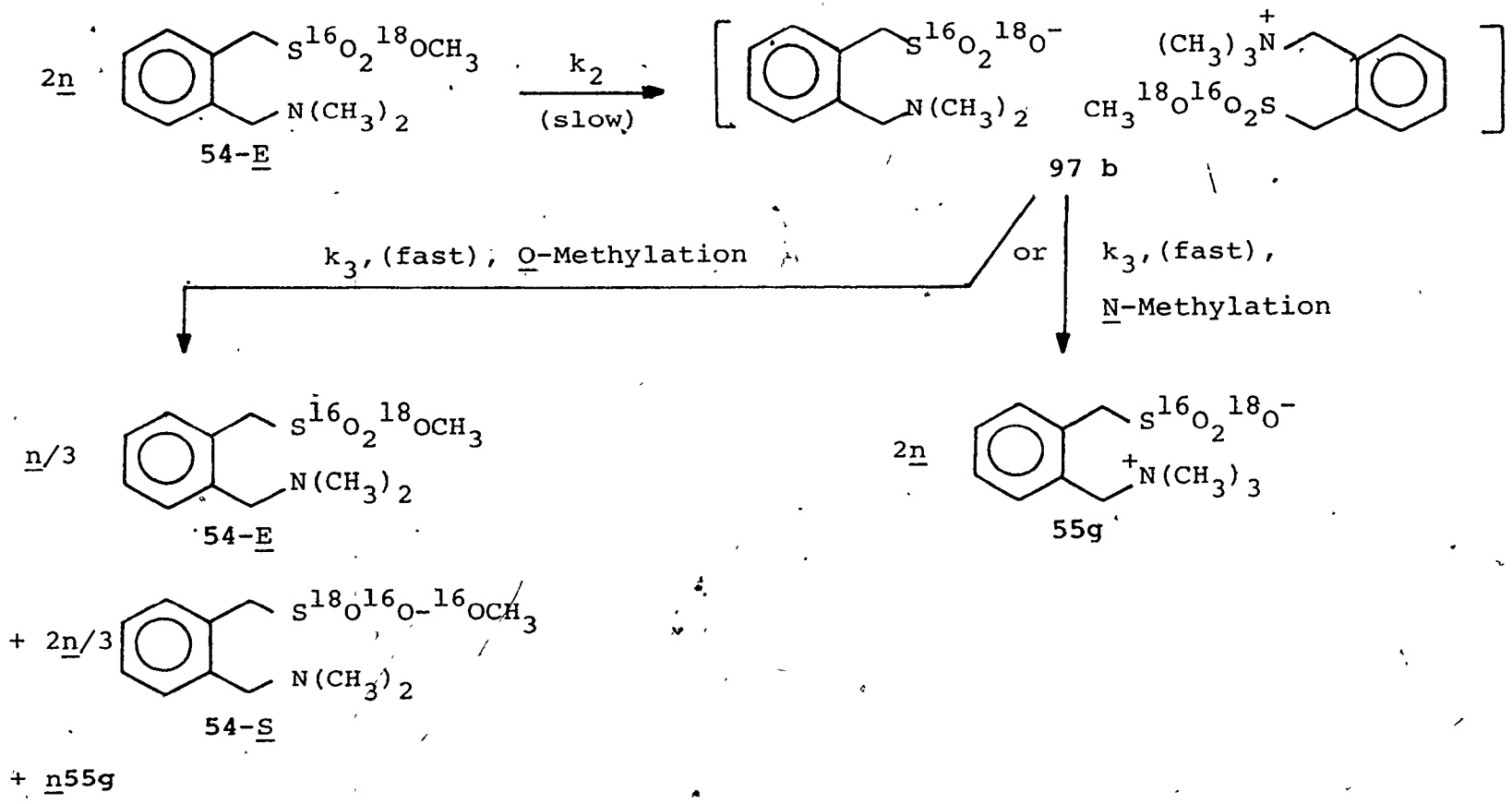


Figure 14: Rate of the Methylation of Phenyl 4-(Dimethylamino)-butane-1-sulfonate (126) with Methyl Butanesulfonate (124) in $CDCl_3$ at 37.0°C

and 129, reacted rapidly yielding a rate constant at leas an order of magnitude greater than k_{obs} for the reactio of methyl 2-(dimethylaminomethyl)phenylmethanesulfonat (54a) obtained under similar conditions. The model reactio was so fast that an accurate determination of k_m could no be made. This result indicates that the effect of the orth substituents on the reactivity of these model compounds is significant. In the next experiment, a phenoxysulfonyl-methyl substituent was incorporated in the ortho positio of the model amine. For the reaction of 128 with 131, k_m was found to be slightly less than k_{obs} but not half k_o ($k_{obs} = 2.5 \times 10^{-3}$ L mol^{-1} s^{-1} for the rearrangement of 54a). Next, k_m for the reaction of the ortho-subsituted amine, 131, with a model ester bearing an ortho-2-methoxymethyl substituent, 134, was determined. Its value was slightly greater than k_{obs}. Collectively, the lack of agreement between the ortho-benz-fused k_m's with either k_{obs} or half k_{obs} is best interpreted as an indication that, the sensitivity of these reactions to ortho-substituent effects is sufficiently great to render the model kinetic method useless for solving the mechanistic problem at hand. Instead, an ^{18}O-labelling experiment was used.

b. ^{18}O-Label Experiments

The distinction between the N-and O-methylation mechanisms for the ortho-benz-fused amino ester reactions was drawn with a simple ^{18}O-label experiment. As shown in scheme 12, 2n molecules of the ester bearing an ethereal ^{18}O-label,


2n
$S^{16}O_2{}^{18}OCH_3$
$N(CH_3)_2$
54-E
k_2
(slow)
$S^{16}O_2{}^{18}O^-$
$N(CH_3)_2$
$(CH_3)_3{}^+N$
$CH_3{}^{18}O^{16}O_2S$
97 b
k_3,(fast); O-Methylation
or
k_3,(fast),
N-Methylation
n/3
$S^{16}O_2{}^{18}OCH_3$
$N(CH_3)_2$
54-E
2n
$S^{16}O_2{}^{18}O^-$
$^+N(CH_3)_3$
55g
+ 2n/3
$S^{18}O^{16}O-{}^{16}OCH_3$
$N(CH_3)_2$
54-S
+ n55g

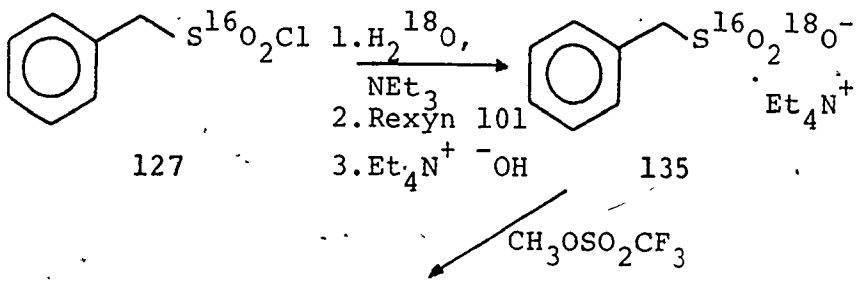
Scheme 12

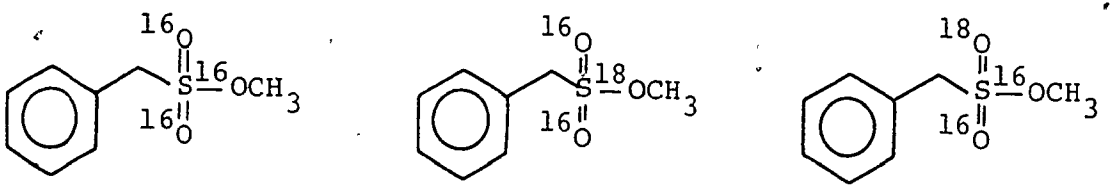
54-E, give n of the ion pair intermediate, **97b**. Annihilation of **97b** via N-methylation gives 2n molecules of the betaine, **55g**. The position of the ^{18}O-label in the unreacted starting material will then remain unchanged throughout the course of the reaction. However, if n **97b** reacts via O-methylation, then the products will be n/3 molecules of **54**-E, 2n/3 molecules of the sulfonyl labelled ester, **54**-S and n molecules of the betaine, **55g**. The result of return from **97b** to **54** is then that the site of the ^{18}O-label in **54** will gradually change during the reaction. The extent to which O-methylation contributes to the annihilation of **97b** may therefore be determined by monitoring the position of the ^{18}O-label in **54** as the reaction proceeds. The recently discovered ^{18}O isotope effects in ^{13}C NMR which discussed in Part I, appeared to be ideal for conducting this analysis.

Control Experiments

Since the literature lacks any examples of ^{18}O isotope effects in the ^{13}C NMR chemical shifts of alkanesulfonate esters, it was first necessary to establish the existence of such effects. With that end in mind, phenylmethanesulfonyl chloride (**127**) was hydrolyzed with $H_2{}^{18}O$ (97.5% ^{18}O) in the presence of triethylamine. The product was protonated via elution through a strong acid ion exchange column and then neutralized with tetraethylammonium hydroxide to give tetraethylammonium phenylmethane($^{18}O_1$)sulfonate (**135**). Methyl trifluoromethanesulfonate was used to convert **135** into a mixture of methyl (sulfonyl-$^{18}O_1$)phenylmethanesul-

fonate (**128**-S), methyl (C-^{18}O)phenylmethanesulfonate (**128**-E) and unlabelled methyl phenylmethanesulfonate, **128**-U. In the absence of an isotope effect in the methylation,



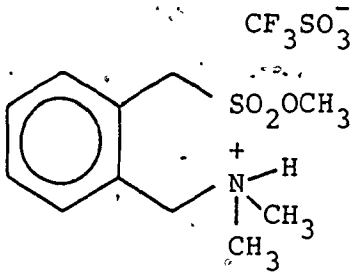


128-U 128-E 128-S

the product was then approximately 10% **128**-U, 30% **128**-E and 60% **128**-S. A ^{13}C NMR spectrum of this material in $CDCl_3$ showed the anticipated splitting of the peak assigned to the methyl carbon (δ = 56.6 ppm). The methyl resonances consisted of two peaks with the upfield (1.7 Hz at 50.3 M Hz) peak being approximately half the size of the downfield peak. This, of course, indicates that the ^{18}O-^{13}C NMR isotope effect is small but measurable.

To show the existence of comparable effects in the spectra of ^{18}O-labelled methyl "norbetylates" three mixtures of **87**-E,-S and -U were prepared and the ^{13}C NMR spectra

of their methyl peaks were obtained. In addition, the extent



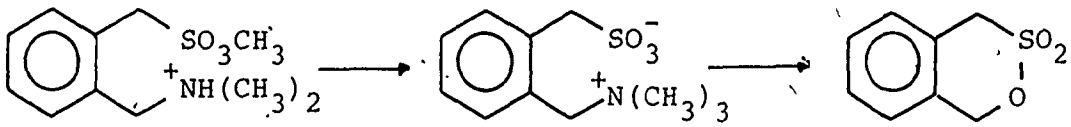
87

E: $RS^{16}O_2-{}^{18}OCH_3$

S: $RS^{18}O^{16}O-{}^{16}OCH_3$

U: $RS^{16}O_2-{}^{16}OCH_3$

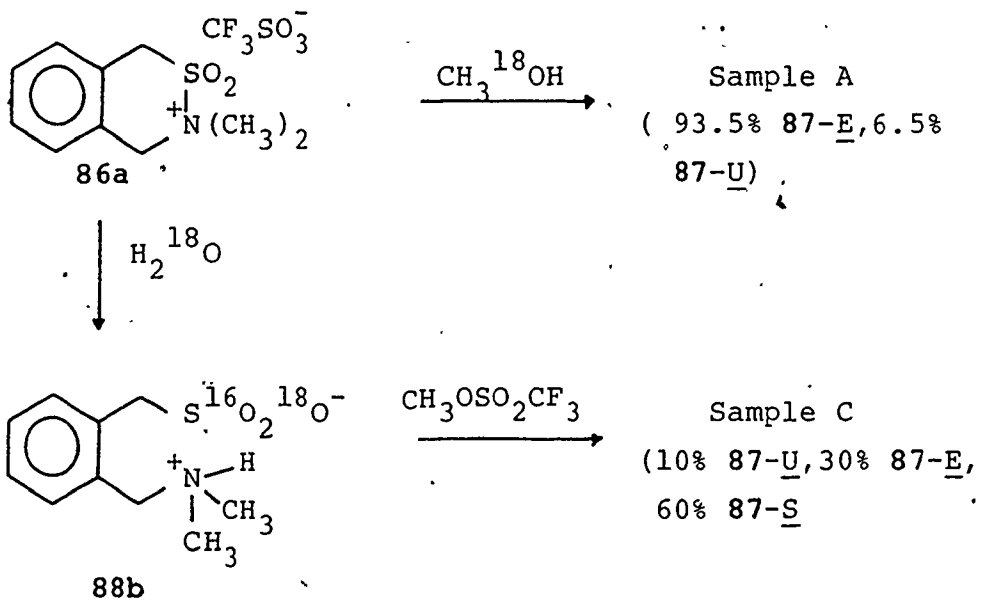
of ^{18}O-labelling in these mixtures was determined using the following procedure: the "norbetylate" mixtures were converted to the corresponding ^{18}O-labelled betaine, **55g**. Thermolysis of the betaine in the probe of the mass spectrometer gave the sultone (**95g**) and trimethylamine. Using a procedure described in the experimental section, the sultone mass spectrometric cluster was examined and gave, within ± 2%, the total ^{18}O content.



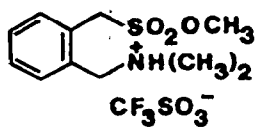
87 $CF_3SO_3^-$ 55 95

Sample A was prepared by ^{18}O-methanolysis of the "sultamium" salt, **86a**, and was found to be 93.5% ^{18}O-labelled. It was, therefore, a mixture consisting of approximately 95% **87**-E and 5% **87**-U. Equimolar portions of sample A and **87**-U were then mixed to give Sample B which was found to be 50% ^{18}O--labelled. The "sultaminum" salt, **86a**, was hydrolyzed with

$H_2{}^{18}O$ (97.5% ^{18}O) to give 2-(dimethylammoniomethyl)phenylmethane($^{18}O_1$)sulfonate (**88b**) which in turn was reacted with methyl trifluoromethanesulfonate to give Sample C. Mass spectrometric analysis indicated that Sample C was 90% ^{18}O--labelled. Hence, assuming the absence of an isotope effect in the methylation, Sample C consisted of 10% **87**-U, 30% **87**-E and 60% **87**-S. The ^{13}C NMR spectra of the methoxy carbons in these samples, obtained at 50.3 MHz in 50% CD_3CN -



CD_3NO_2, are shown in Figure **15**. They clearly indicate that the R-$S^{16}O_2$-^{18}O CH_3 signal is about 1.7 Hz upfield from that of the R-$S^{16}O_2$-^{16}O CH_3 and the R-$S^{18}_{O}{}^{16}O$-^{16}O CH_3 resonances which themselves are indistinguishable. These results then show that any scrambling of the ^{18}O-label in unreacted **54**-E during the course of its conversion to **55g** would be easily detected.

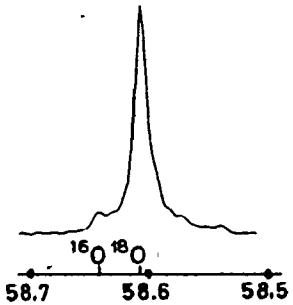


87

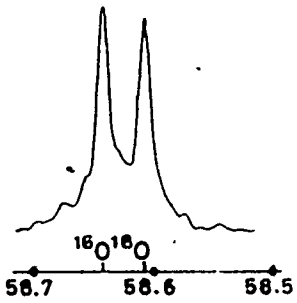
E: $RS^{16}O_2-^{18}OCH_3$

S: $RS^{18}O^{16}O-^{16}OCH_3$

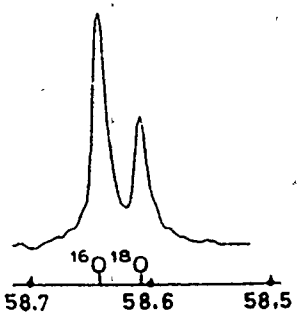
U: $RS^{16}O_2-^{16}OCH_3$



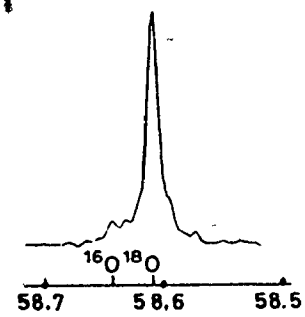
Sample A
(87-E 95%, 87-U 5%)



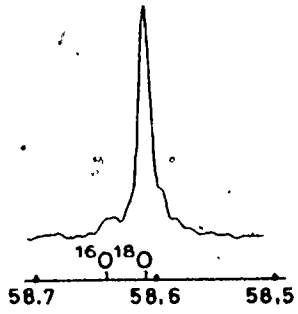
Sample B
(87-E 50%, 87-U 50%)



Sample C
(87-E 30%, 87-S 60%,
87-U 10%)



Recovered after 33%
reaction



Recovered after 66%
reaction

Figure 15: ^{13}C NMR Spectra of the ^{18}O-Containing 2-(Methoxysulfonylmethyl)phenyl-N,N--dimethylmethanaminium Trifluoromethanesulfonate Samples Methoxy Carbons

Recovered Unreacted Starting Material Experiments

In a manner identical to that used to prepare the stock solutions used in the deuterated methyl crossing experiments. Sample A (0.5 mmol) was used to prepare a 2.0 x 10^{-2} M benzene solution of the ester (93.5% **54**-E and 6.5% **54**-U). After 3.2 h in a sealed tube at 110°C (33% reaction as calculated using k_{obs} = 2.5 x 10^{-3} L mol^{-1} s^{-1}) the solution was recovered and then washed with aqueous sodium carbonate to remove the betaine. The benzene layer, which contained the unreacted starting material, was treated with trifluoromethanesulfonic acid (0.33 mmol). Removal of the solvent gave a 66% yield of the "norbetylate". After recrystallization, the material gave the ^{13}C NMR spectrum shown in Figure 15. Mass spectrometric analysis indicated that the sample was 93.5% mono-^{18}O-labelled. When a duplicate experiment was quenched after 12.6 h (calculated for 66% reaction), the "norbetylate" was recovered in 32% yield and its ^{13}C NMR spectrum is shown in Figure 15. Again, mass spectrometric analysis of the betaine generated from the recovered sample showed that it was 93.5% mono-^{18}O-labelled. With the simple computer simulation described in Appendix 4, one can show that if the ion pair, **97b**, annihilates by O-methylation, then unreacted starting material that was initially 93.5% **54**-E and 6.5% **54**-U will, after 33% reaction, be 69% **54**-E, 23.5% **54**-S and 7.5% **54**-U. The "norbetylate" derived from the latter mixture would then be expected to give a pair of O-CH_3 ^{13}C NMR resonances in which

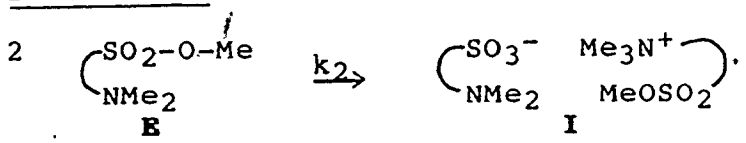
the upfield ^{18}O-CH_3 peak (from **87**-E) would be approximately two and a half times larger than the downfield ^{16}O-CH_3 peak (from **87**-S and **87**-U). Similarly, the simulation indicates that the unreacted starting material would consist, after 66% reaction, of 47% **54**-E, 44% **54**-S and 9% **55**-U, and hence the "norbetylate" derived from this mixture would give-^{16}O-CH_3 and ^{18}O-CH_3 ^{13}C NMR resonances of approximately equal size. Conversely, a derivation included in Appendix 4 indicates that if **97b** annihilates by N-methylation then the composition of the unreacted starting material will not change during the course of its conversion to **55**. That the ^{13}C NMR spectra of Sample A and of the two recovered samples show no significant differences is then clear evidence that no scrambling of the ^{18}O-label in the starting material has occurred during the reaction. Therefore, it may be concluded that **97b** reacts exclusively via N-methylation and hence the observed second order rate constant (k_{obs}) is indeed $2k_2$.

3. Chain Propagation Pathways

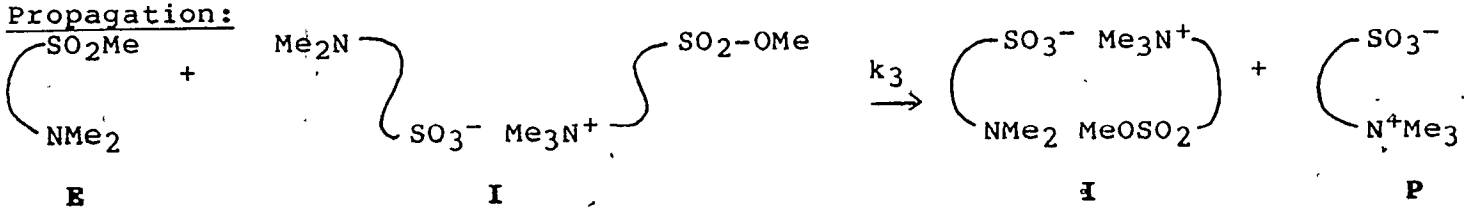
One aspect of the bimolecular reaction mechanism that has not yet been addressed is the possibility of a reaction occurring between the ion pair intermediate (**I**) and the starting material (**E**). Such a reaction would lead to either of the two possible chain propagation mechanisms illustrated in scheme 13. Both chains are initiated by the bimolecular reaction of the ester (**E**) to give the ion pair (**I**). This reaction is second order and hence will be assigned a second

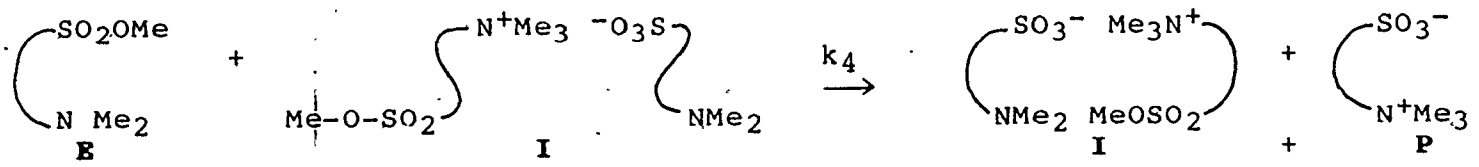
Ion Pair Chain Propagation:

Initiation:

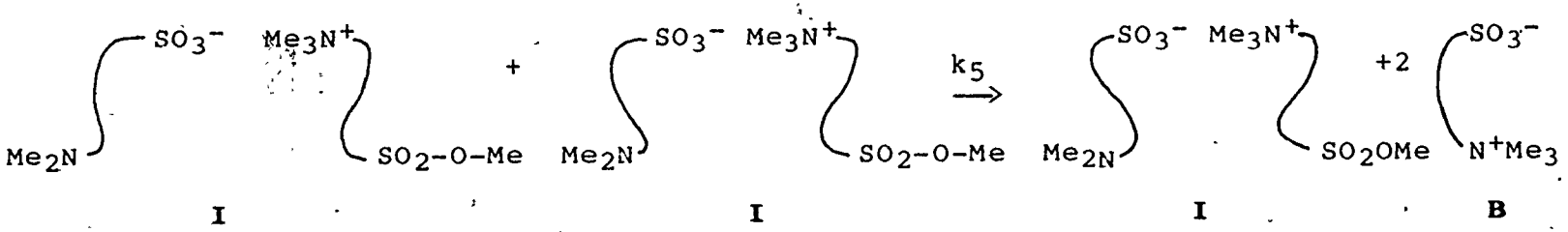


Propagation:

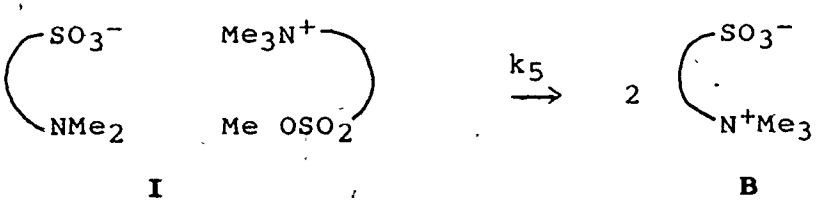




Second Order Termination:



or First Order Termination:



Scheme 13

order rate constant, k_2. The two possible second order reactions of **I** with **E** are the propagation steps in both chains. The methylation of **I** by **E** will be assigned the second order rate constant k_3 and the methylation of **E** by **I**, k_4. These reactions each generate one molecule of **I** and one of the propagation derived betaine, **P**. The chain is then terminated by either first or second order annihilation of **I**. The former gives two molecules of the betaine, **B**, while the latter gave two molecules of **B** plus one of **I**. The rate constant k_5 will be used to describe both, its order being dependant on the context of its usage. Since the two terminations result in different overall rate laws and product ratios, they will be considered separately. Since the **EM** estimates made earlier in this thesis are based on the assumption that the product is only **B**, the key feature that must be examined in both chains is their behavior with respect to their product ratios (ie. **P** to **B**).

The Second Order Terminated Chain

The chain propagation characterized by the second order termination obeys, if a steady state assumption is used for **I**, the following rate law:

$$-\frac{d\mathbf{E}}{dt} = 2k_2\mathbf{E}^2 + (k_3 + k_4)\ \frac{k_2}{k_5}\cdot{}^5\mathbf{E}^2 \qquad (39)^\dagger$$

The first term, $2k_2\mathbf{E}^2$, describes the rate of formation of **B** and the second, **P**. Since both are second order in **E**, the product ratio, as expressed in terms of **B/T**, where **T** is

† For a derivation, see Appendix 5

the total product formed (i.e. **P** + **B**), is independent of **E**. If the assumption is made that the effects of the ω-substituents on the reacting functional groups are negligible, then $k_2 \simeq k_3 \simeq k_4 \simeq k_5$. **B** must then be half of **T** and hence the previously assigned **EM** values will be low by a factor of two.

$$\frac{\mathbf{B}}{\mathbf{T}} = \frac{2k_2}{2k_2 + (k_3 + k_4)\ \frac{k_2}{k_5} \cdot 5} \qquad (40)^{\dagger}$$

There are, however, several predictable features of this mechanism which are inconsistent with the previously discussed experimental observations. The first is that the model rate constants, k_m, should have been one quarter of k_{obs} not one half. This is clearly contradicted by the results obtained in the butane derivative model studies, and even with the model 2-methylphenylmethane derivatives, k_m fell generally around k_{obs} not one quarter k_{obs}. In addition, this mechanism predicts a build up of the ion pair, **I**, and in none of the amino-ester kinetic runs was any detected. It should be noted that the solubility of **I** should parallel that of the products from the model kinetic runs and peaks from these were clearly visible in the ^1H NMR spectra obtained during these experiments. Hence, if a significant amount of **I** was present in the kinetic reaction mixtures, its ^1H NMR spectrum would be observed. On the basis of these inconsistencies, the chain propagation mech-

† For the derivations, see Appendix 5.

anism with a second order termination may be excluded.

The First Order Terminated Chain

The chain propagation mechanism characterized by the first order termination has the following overall rate law:

$$-\frac{dE}{dt} = 2k_2E^2 + (k_3 + k_4)\frac{k_2}{k_5}E^3 \qquad (41)^{\dagger}$$

Again, the first term, $2k_2E^2$, describes the rate of formation of B and the second, of P. The product ratio (B/T) is dependent on the initial and final concentrations of the starting material (E_0 and E respectively) and is described by equation (42). Evaluation of this expression

$$\frac{B}{T} = \frac{2}{(E_0 - E)\left(\frac{k_3 + k_4}{k_5}\right)} \ln\left[\frac{2 + \left(\frac{k_3 + k_4}{k_5}\right)E_0}{2 + \left(\frac{k_3 + k_4}{k_5}\right)E}\right] \qquad (42)^{\dagger}$$

requires a value for $(k_3 + k_4)/k_5$. However, in this case, since k_3 and k_4 are second order rate constants and k_5 is a first order rate constant, k_3, k_4 and k_5 may not be assumed to be equal. If the intrinsic reactivity of the functional groups involved in each of these reactions is assumed to be identical then $(k_3 + k_4)/k_5$ may be estimated indirectly. The estimate is made by treating the propagation steps as two step processes. The first step is an equilibrium between

$$I + E \overset{K}{\rightleftharpoons} [I \cdot E]_{CA} \xrightarrow{k_{2c} + k_{3c}} I + P$$

---

†For a derivation, see Appendix 5.

the dissociated reactants (I and E) and a solvent caged species ($[I\ E]_{CA}$) and hence may be assigned an equilibrium constant, K. The caged species then reacts to give I and

$$K = \frac{[I\ E]_{CA}}{[I][E]} \qquad (43)$$

P <u>via</u> two kinetically first order reactions which will be assigned the rate constants k_{3c} and k_{4c}. We now have two expressions which describe the rate of formation of P:

$$\frac{dP}{dt} = (k_3 + k_4)[I][E] \qquad (44)$$

and

$$\frac{dP}{dt} = (k_{3c} + k_{4c})[I\ E]_{CA} \qquad (45)$$

and, since

$$K[I][E] = [I\ E]_{CA},$$

$$\frac{dP}{dt} = (k_{3c} + k_{4c})K[I][E]$$

therefore, $(k_{3c} + k_{4c})K = k_3 + k_4$

Using the intrinsic reactivity assumption,

$$k_{3c} \simeq k_{4c} \simeq k_5$$

therefore, $K = \frac{(k_3 + k_4)}{(k_{3c} + k_{4c})} = \frac{(k_3 + k_4)}{2k_5}$

therefore, $2K = \frac{(k_3 + k_4)}{k_5}$. (46)

Equation (46) may then be substituted into equation (42) to give equation (47) which describes the product ratio (B/T) in terms of E_0, E and K.

$$\frac{B}{T} = \frac{\ln\left[\frac{1 + K\ E_0}{1 + K\ E}\right]}{K(E_0 - E)} \qquad (47)$$

A simple thermodynamic argument may be used to estimate K. The enthalpy change in the equilibrium will be assumed to be negligible because no colvent bonds are being made or broken, and because, the solvation energy change will be very small since the process is occurring in a non polar solvent and there is no change in the total charge. A conservative estimate of approximately 10 cal K^{-1} mol^{-1} for the entropy loss associated with the formation of $[\mathbf{I}\ \mathbf{E}]_{CA}$ can be made based on data reported for the reversible formation of hydrogen bonded or charge transfer complexes.[96,97] This then implies that K should be approximately 0.01. When this value and the initial and final ester concentrations typically used in the kinetic runs ($\mathbf{E}_0$ = 0.2 M and $\mathbf{E}_f$ = 0.04 M) are used, equation (47) indicates that 99.9% of **T** is **B**. At the lower ester concentrations used in the crossing experiments, even less **P** should be produced since **P** is the product of a third order process which, at these concentrations, will compete less favourably with the second order formation of **B**. Indeed, for **P** to constitute 10% of the kinetic run products (a reasonable limit imposed by the observed linearity of the second order kinetic plots) K must exceed 1.0 which is very unlikely. It may, therefore, be concluded that while the first order terminated chain propagation mechanism is reasonable, the contribution of the propagation steps to the total product formed is negligible under the reaction conditions employed in these studies. It follows then that the rate law for the bimolecular

conversion of the amino esters to the betaines is indeed that originally assumed in the EM estimates:

$$-\frac{dE}{dt} = 2k_2E^2 \qquad (7)$$

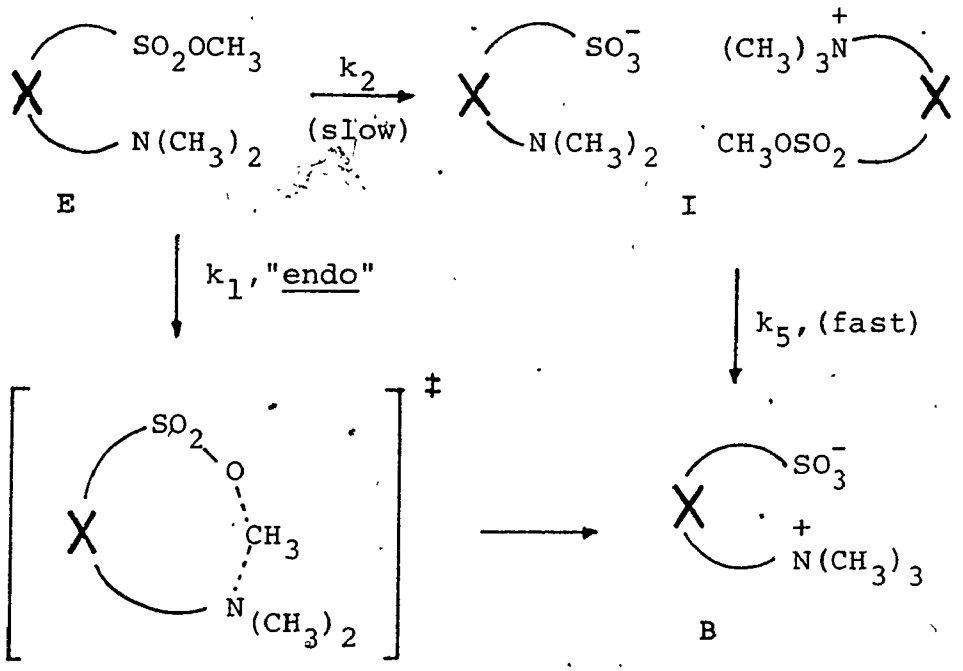
E. Summary and Conclusions:

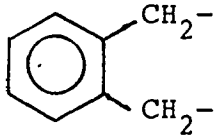
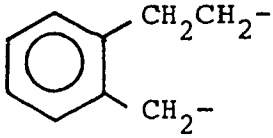
The mechanisms of the rearrangements of three methyl ω-(dimethylamino)alkanesulfonates (E; 52, 54 and 56) to their corresponding sulfobetaines (B; 53, 55 and 57) have been studied in detail in nonpolar aprotic media and the conclusions are summarized in scheme 14. At concentrations of E between 0.3 and 0.04 M, ^{1}H NMR kinetics have shown that all three reactions occur *via* an intermolecular pathway which obeys the rate law described by equation (7). The activation parameters determined for the reactions of 54

$$-\frac{dE}{dt} = 2k_2 E^2 \qquad (7)$$

and 56 were found to be those typical of S_N2 reactions in nonpolar media. Through the use of model kinetic studies for the rearrangement of 52 and an ^{18}O-labelling experiment for the rearrangement of 54, it has been shown that the bimolecular rearrangements occur *via* two step processes. In the first and rate determining step, 2 molecules of E yield are ion pair (I) which, in the second fast step, is converted, by way of N-methylation, to two molecules of B.

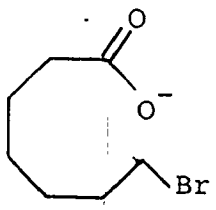
Since the primary goal of these studies was to find an endocyclic methyl transfer, the rearrangements of 52, 54 and 56 were examined at lower initial ester concentrations *via* double-label crossing experiments. For the rearrangement of 52, these showed no sign of any products attributable to endocyclic methyl transfer even when the initial ester concentration was as low as 1.9×10^{-4} M. This observation,



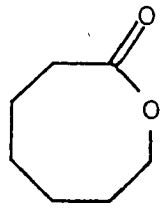
X	E	I	B	Solvent	EM (k_1/k_2, M)
$-CH_2(CH_2)_2CH_2-$	52	72	53	$CHCl_3$	$< 3\times10^{-5}$
	54	97	55	C_6H_6	$< 2\times10^{-5}$
	56	118	57	C_6H_6	2×10^{-3}

Scheme 14

when interpreted in terms of the experimental error inherent in the analytical procedure used in these crossing experiments, indicated that the **EM** for the 8-endo-tet conversion of **52** to **53** is less than 3×10^{-5} M. When compared to the **EM** of 5.7×10^{-4} M reported for the cyclization of **5** to form **6**, [8] (a typical 8-exo-tet reaction) this result indicates simply that the 8-endo-tet transition state is more strained than is the 8-exo-tet transition state. Crossing



5



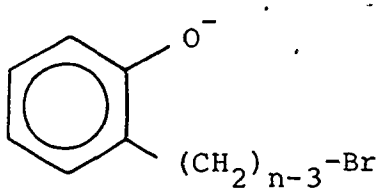
6

experiments using initial ester concentrations as low as 4.5×10^{-4} M again showed no sign of any endocyclic methyl transfer in the conversion of the ortho-benz-fused ester, **54**, to its corresponding sulfobetaine, **55**. From the analytical error in these experiments, a maximum **EM** of 2×10^{-5} M was assigned to the 8-endo-tet reaction of **54**.

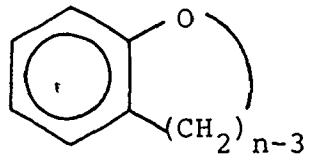
The rearrangement of the higher homologue of **54**, **56** to **57** was then examined and these crossing experiments provided conclusive evidence for the existence of both endocyclic and intermolecular pathways in this reaction. From the observed dependence of the ratio of intramolecular to intermolecular products on the initial ester concentrations,

an **EM** of 2 x 10^{-3} M was deduced for the 9-endo-tet methyl transfer. This constitutes the first proven example of an endocyclic nucleophilic methyl transfer.

Comparison of the **EM** of the 8 and 9-endo-tet reactions of **54** and **56** respectively with those reported for the ortho--benz-fused cyclic ether forming 8 and 9-exo-tet processes[10] shown below, indicates that the 8 and 9 endo-tet transition states are more strained than are the exocyclic counterparts. In Baldwin's terminology, 8 and 9 endo-tet reactions are then "disfavoured" relative to 8 and 9-exo-tet reactions. The additional strain inherent in the endocyclic



100



101

n=8 , **EM**= 0.35 (8-exo-tet)

n=9 , **EM**= 0.056 (9-exo-tet)

transition states must be due, at least in part, to deviation from the ideal 180° orientation of the nucleophile, the methyl carbon and the leaving group in these concerted nucleophilic displacements. Furthermore, that the **EM** for the 8-endo-tet reactions is less that 1/100th of **EM** for the 9-endo-tet process indicates that a sizeable strain increase results from reducing the size of the transition state cyclic array by only one methylene. This suggests that S_N2 type

displacements on methyl carbons have a pronounced preference for the above mentioned linear transition state geometry. These results then suggest that, in Menger's terminology[20], S_N2 methylations proceed via a rather narrow trajectory cone.

ENDOCYCLIC NUCLEOPHILIC METHYL TRANSFER

by

Michael Jerome McGarrity

Department of Chemistry

Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

Faculty of Graduate Studies
The University of Western Ontario
London, Ontario
August, 1984

Volume 2

TABLE OF CONTENTS

VOLUME II

* * *

III EXPERIMENTAL

A. Instruments and General Procedures

Melting points were determined on a Kofler hot stage and are uncorrected. Refractive indices were determined with a Bausch and Lomb–Abbe refractometer. The IR spectra were obtained with either a Beckman IR 4520 or a Perkin-Elemer 621 spectrophotometer using, unless otherwise specified, 0.1 mm KBr cells and were calibrated with polystyrene (1601.8 cm^{-1}). The ^{1}H NMR spectra were obtained with a Varian XL100 NMR spectrometer, or when specified, a Varian T60 NMR spectrometer. All chemical shifts are expressed in ppm downfield from tetramethylsilane. The ^{13}C NMR spectra were obtained with a Varian XL200 NMR spectrometer with all chemical shifts expressed in ppm downfield from tetramethylsilane. The U.V. spectra were obtained from a Varian Cary 219 spectrophotometer using 1 cm pathlength quartz cells. A Varian MAT311A was used for all mass spectra. Elemental analysis were obtained from Micro Analysis Laboratories Limited (Markham, Ontario); Deuterium Analysis from J. Nemeth (Urbana, Illinois).

Benzene, methylene chloride, tetrahydrofuran, ethanol and methanol were all distilled from calcium hydride and stored over molecular sieves (Fisher, 3Å, grade 564, 8-13 mesh). Chloroform was washed with water (x3) then distilled from lithium aluminum hydride. Acetonitrile and carbon disulfide were distilled from phosphorus pentoxide. Acetone was distilled through a Vigreux column (30 cm) and stored

of 3Å molecular sieves. All other solvents were reagent grade. Triethylamine (Eastman) was distilled from calcium hydride prior to use. Methyl trifluoromethanesulfonate (Aldrich) was also distilled prior to use. ($^2H_3$)Methyl iodide was prepared from ($^2H_4$)methanol (Merck, Sharpe and Dohme, 99% $^2H_4$), red phosphorus and iodine.[98] ($^{18}O_1$)Methanol was prepared from $H_2{}^{18}O$ (Merck, Sharpe and Dohme, 97.5% ^{18}O) by the method of Sawyer.[76] All other reagents were commercially available, and unless otherwise specified, obtained from Fisher Scientific Company. These materials were not further purified prior to use.

Solvents were evaporated under reduced pressure using a rotary evaporator connected to a water aspirator. Small scale distillations (< 100 mg) were conducted in a cold finger sublimation apparatus with two wells (each 2 cm long, 1 cm wide) in the bottom, one for use as the still pot and the other as the receiver; the cold finger was arranged to allow the liquid to drip directly into the receiving well. The distance between the tip of the cold finger and the lowest portion of the liquid being distilled was 3 cm.

($^2H_3$)Methyl Trifluoromethanesulfonate

Silver trifluoromethanesulfonate was prepared from trifluoromethanesulfonic acid (Aldrich) and silver carbonate by the method of Haszeldine and Kidd.[99] The salt was recrystallized from anhydrous ether-carbon tetrachloride and, in the dark, dried overnight *in vaccuo* over phosphorus pentoxide.

($^2H_3$)Methyl iodide (99% D, 14.4 g, 0.1 mol) was added dropwise with stirring over 20 min. to silver trifluoromethanesulfonate which was cooled to -78°C. The resulting green paste was stirred at room temperature for 2 h. A red oil was distilled from the reaction mixture at 50 torr and collected in a trap cooled by a dry-ice-acetone bath. The oil was distilled to give the title compound as a clear colourless oil (16.5 g, 96%), bp 97-98°C; n_D^{20} 1:3266; IR (CH_2Cl_2) ν_{max}: 2189(m), 2138(w), 2099(w), 1406(s), 1209(s), 1148(s), 1081(s), 995(s), 782(s), 606(s) cm^{-1}.

B. Preparation of Compounds Used in Sections III C,D and E

1. Butane Derivatives:

1,4-Butane Sultone (**58**)

1,4-Butane sultone was prepared in 70% yield from tetrahydrofuran via 4-chloro-1-acetoxybutane[100] by the method of Helberger and Lantermann.[60] The compound was obtained as a clear colourless oil, bp 112-113°C(0.5 torr), (lit[60] bp 149-150°C(13 torr)); n_D^{20} 1.4638, (lit[101] n_D^{20} 1.4640); ^1H NMR($CDCl_3$) δ : 1.7-2.0(m,2H), 2.1-2.4(m,2H), 3.16(t,3H), 4.53(t,3H); IR (CH_2Cl_2) ν_{max}: 3054(m), 2963(m), 1400(m), 1353(s), 1190(s), 1170(s), 1160(m), 998(s), 910(s), 825(s) cm^{-1}.

4-Chloro-1-butanesulfonyl Chloride, (**59**)

1,4-Butane sultone (**58**, 50 g, 0.36 mmol) was refluxed for 1 week with dimethylformamide (10 mL) in thionyl chloride (200 mL). After the excess thionyl chloride was removed

by distillation, the residual oil was poured onto ice (200 gm) then extracted with methylene chloride (2 x 100 mL). The extract was dried over magnesium sulfate and evaporated to dryness to give a clear colourless oil (75 g). Fractional distillation through a short Vigreux column gave, after a short forerun of dimethylformanide, **59** as a clear colourless oil (60 g, 85%), bp 97-98°C(1.0 torr), (lit[102] bp 110--112°C(1-1.5 torr)); n_D^{20} 1.4910,; ^{1}H NMR($CDCl_3$) δ : 1.8-2.4-(m,4H), 3.62(t,2H), 3.76(5,2H); IR (CH_2Cl_2) ν_{max}: 3058(w), 2962(m), 1441(m), 1372(s), 1162(s), 581(s) cm^{-1}. The spectra were identical to those obtained from a sample of **59** prepared in low yield by the method of Helferich and Kleb.[102]

4-Chloro-1-butanesulfonamide (**60**)

Anhydrous ammonia was slowly bubbled through a -78°C solution of 4-chloro-1-butanesulfonyl chloride (**59**, 30 g 0.15 mmol) in methylene chloride (250mL) until no further formation of precipitate was observed (1 h). After the mixture was stirred overnight at room temperature, the solvent was removed by evaporation and the residue was extracted with hot anhydrous ether (4 x 100 mL). The extract was dried over magnesium sulfate and then evaporated to dryness to give a faintly brown tinted oil (24 g, 90%). This material was not further purified. ^{1}H NMR ($CDCl_3$) δ : 1.97(m,4H), 3.20(m,2H), 3.62(m,2H), 5.3(br s,2H); IR(CH_2Cl_2) ν_{max}: 3425(s), 3336(m), 3267(s), 3052(m), 2958(m), 1535(m), 1383-(s), 1149(s), 890(m), cm^{-1}. These spectra were identical to those obtained from an authentic sample of **60** prepared

in low yeild by the method of Helferich, et al[61].

N-Methyl-4-chloro-1-butanesulfonamide (**61**)

4-chlorobutanesulfonyl chloride (**59**, 59 g, 0.3 mol) in ether (200 mL) was added dropwise with stirring over 1 h to 0°C 40% aqueous methylamine (200 mL, excess). The layers were separated and the aqueous phase extracted with ether (2 x 100 mL). The combined ether layer was washed with saturated aqueous sodium carbonate (300 mL) then with brine (100 mL) and dried over magnesium sulfate. Removal of the solvent by evaporation followed by azeotropic drying with benzene (2 x 100 mL) left the title compound as a clear golden oil (48.5 g, 90%) which was not further purified. ^{1}H NMR($CDCl_3$) δ: 1.95(m,4H), 2.79(s,3H), 3.07(m,2H), 3.60-(m,2H), 4.9(br s,1H); IR (CH_2Cl_2) ν_{max}: 3386(s), 3301(m), 3054(m), 2953(s), 1395(m), 1320(s), 1255(m), 1147(s), 1072(s) and 841(s) cm^{-1}.

Tetrahydro-2H-1,2-thiazine 1,1-Dioxide (**62**)

4-chloro-1-butanesulfonamide (**60**, 29.5 g, 0.17 mol) in absolute alcohol (150 mL) was added dropwise over 1.5 h to a stirred refluxing solution of sodium hydroxide (7.5 g, 0.19 mol) in absolute alcohol (150 mL). The reaction mixture was refluxed for an additional hour then neutralized with hydrochloric acid (1 M), filtered and then evaporated to dryness. The residue was extracted with methylene chloride (2 x 200 mL) which was then removed by evaporation to give a brown solid (24 g). Recrystallization from chloroform-petroleum ether (bp 30-60°C) gave **62** as off-white ne-

edles (16 g, 65%), mp 113-114°C, (lit[61] mp 115°C); ^{1}H NMR-($CDCl_3$) δ: 1.63(m,2H), 2.22(m,2H), 3.12(t,2H), 3.42(t,2H), 4.5(br,s,1H); IR (CH_2Cl_2) ν max: 3340(m), 3052(m), 2957(m), 1397(m), 1331(s), 1179(m), 1150(s), 1032(w), 849(w) cm^{-1}.

2-Methyltetrahydro-2H-1,2-thiazine 1,1 Dioxide (**63a**)

N-Methyl-4-chloro-1-butanesulfonamide (**61**, 48 g, 0.26 mol) in absolute alcohol (150 mL) was added dropwise over 5 h to a stirred refluxing solution of sodium hydroxide (11.2 g, 0.28 mol) in absolute alcohol (500 mL). After the mixture was refluxed for 2 h, the solvent was removed by evaporation. The oily residue was extracted with hot anhydrous ether (50 mL). The extract was washed with 5% aqueous sodium hydroxide (500 mL), dried over magnesium sulfate and evaporated to dryness to give a golden oil (32 g) which was then distilled under reduced pressure to give **63a** as a clear colourless oil (30 g, 77%), bp 108-110°C(0.7 torr). Two additional distillations gave the analytical specimen, n_D^{20} 1.4878; ^{1}H NMR($CDCl_3$) δ: 1.58-1.83(m,2H), 2.06-2.30(m,2H), 2.80(s,3H), 3.01(t,2H), 3.34(t,2H); IR (CH_2Cl_2) ν max: 3057(m), 2955(s), 2869(m), 2818(w), 1460(m), 1443(m), 1334(s), 1320(s), 1292(s), 1217(m), 1160(m), 1139-(s), 920(s) cm^{-1}; Anal. Calcd. for $C_5H_{11}NO_2S$: C,40.25; H,7.43; N,9.39; S,21.49. Found: C,40.45; H,7.61; N,9.20; S,21.32.

2-($^2H_3$) Methyltetrahydro-2H-1,2-thiazine-1,1-Dioxide (**63b**)

Tetrahydro-2H-1,2-thiazine-1,1-dioxide (**62**, 6.75 g, 50 mmol) in absolute alcohol (75 mL) was treated with sodium

hydroxide (2.2 g, 55 mmol) and ($^2H_3$)methyl iodide (99% D, 10 g, 70 mmol) then stored overnight at room temperature. The solvent was removed by evaporation and the residue extracted with methylene chloride (50 mL). The extract was washed with 5% aqueous sodium hydroxide (50 mL) dried over magnesium sulfate and evaporated to dryness to give a brown oil which was distilled under reduced pressure yielding **63b** as a clear colourless oil (6.0 g, 79%), bp 94-96°C(0.4 torr); n_D^{20} 1.4873; ^1H NMR($CDCl_3$) δ : 1.65-1.86(m,2H), 2.05--2.34(m,2H), 3.03(t,2H), 3.34(t,2H); IR (CH_2Cl_2) ν max: 3055-(m), 2956(s), 2864(m), 2221(w), 2070(m), 1441(m), 1340(s), 1321(s), 1292(s), 1201(s), 1167(s), 1141(s), 1092(m), 933(m) cm^{-1}.

A sample of 2-methyltetrahydro-2H-1,2-thiazine-1,1-dioxide (**63a**) prepared in this manner from tetrahydro-2H-1,2--thiazine 1,1-dioxide (**62**) and methyl iodide gave ^1H NMR and IR spectra identical to that obtained from the analytical specimen of **63a**.

2,2-Dimethyltetrahydro-2H-1,2-thiazinium 1,1-Dioxide Trifluoromethanesulfonate (**64a**)

A mixture of 2-methyltetrahydro-2H-1,2-thiazine-1,1-dioxide (**63a**, 3.0 g, 20 mmol) and methyl trifluoromethanesulfonate (4.1 g, 25 mmol) in anhydrous methylene chloride (50 mL) was kept at room temperature in a drybox for 3 da. The product, after filtration and washing with anhydrous ether, was obtained as colourless plates (5.6 g, 90%), mp 142-143°C. Two recrystallizations in the dry-box from anhy-

drous acetonitrile–ether gave the analytical specimen: mp 143-144°C; ^{1}H NMR(CD_3CN) δ : 2.20(m,4H), 3.34(s,6H), 3.87-(t,2H), 4.17(t,2H); IR (CH_3CN) ν max: 3040(w), 2975(w), 2927(w), 1380(s), 1267(s), 1223(m), 1177(w), 1154(s), 1021-(w), 993(w), 978(w), 903(w), 849(w), 812(w), 727(w) cm^{-1}. Anal. Calcd. for $C_7H_{14}F_3NS_2O_5$: C,26.83; H,4.50; F,18.19; N,4.47; S,20.47. Found: C,27.05; H,4.68; F,17.93; N,4.29; S,20.61.

2,2-Di($^2H_3$)Methyltetrahydro-2H-1,2-thiazinium 1,1-Dioxide Trifluoromethanesulfonate (**64c**)

A mixture of 2-($^2H_3$)methyltetrahydro-2H-1,2-thiazine 1,1-dioxide (**63b**, 1.5 g, 10 mmol) and ($^2H_3$)methyl trifluoromethanesulfonate (1.8 g, 11 mmol) in anhydrous methylene chloride (20 mL) was kept at room temperature in a drybox for 3 da. The product, after filtration and washing with anhydrous ether, was obtained as colourless plates (2.6 g, 80%), mp 141-142°C; ^{1}H NMR(CD_3CN) δ : 2.20(m,4H), 3.87-(t,2H), 4.17(t,2H); IR (CH_3CN) ν max: 2978(w), 2940(w), 2920(w), 2288(w), 2241(w), 1380(s), 1273(m), 1267(s), 1201-(w), 1180(m), 1156(s), 1028(m), 995(w), 931(w), 918(w), 810(m), 725(m) cm^{-1}.

4-(Methoxysulfonyl)-N,N-dimethyl-1-butanaminium Trifluoromethanesulfonate (**65a**)

A mixture of 2,2-dimethyltetrahydro-2H-1,2-thiazinium--1,1-dioxide trifluoromethanesulfonate (**64a**, 4.5 g, 14.5 mmol) and anhydrous methanol (0.6 g, 18 mmol) in anhydrous acetonitrile (5 mL) was stirred overnight at 50°C. Removal

of the solvent by evaporation left **65a** a clear colourless viscous oil (5.0 g, 99%), n_D^{20} 1.4368; ^{1}H NMR(CD_3CN) δ: 1.75-1.95(m,solvent obscurred), 2.85(d,6H), 3.00-3.55(m,4H), 3.83(s,3H); IR (neat film) ν_{max}: 3450(s), 3053(m), 2956(w), 1463(m), 1348(s), 1250(vs), 1160(s), 1025(s), 982(s), 822(m), cm^{-1}. A portion of the crude material (100 mg) was shaken in ice cold saturated aqueous sodium carbonate (20 mL) then extracted with methylene chloride (2 x 10 mL). The extract was dried over sodium sulfate and added to a 0°C saturated solution of picric acid in ethanol (100 mL). The yellow precipitate was collected by filtration then recrystallized twice from methylene chloride-pentane to give an analytical speciment of 4-(methoxysulfonyl)-N,N-dimethyl-1-butanaminium picrate, mp 117-118°C; Anal. Calcd. for $C_{13}H_{20}N_4O_{10}S$: C,36.79; H,4.75; N,13.20; S,7.56. Found: C,36.77; H,4.77; N.13.30; S,7.34.

4-[($^2H_3$)Methoxysulfonyl]-N,N-di($^2H_3$)methyl-1-butanaminium Trifluoromethanesulfonate (**65d**)

A mixture of 2.2-di($^2H_3$)methyltetrahydro-2H-1,2-thiazinium trifluoromethanesulfonate (**64c**, 2.0 g, 6.4 mmol) and ($^2H_4$)methanol (Merck, Sharpe and Dohme, 99% D, 0.32 mL, 8 mmol) in anhydrous acetonitrile (4 mL) was stirred at 50°C overnight. Removal of the solvent by evaporation gave **65d** as a clear colourless oil (2.2 g, 97%), n_D^{20} 1.4343, ^{1}H NMR (CD_3CN) δ: 1.73-2.0(m,solvent obscurred), 2.93-3.36-(m,4H); IR (neat film) ν_{max}: 3450(s), 3048(m), 2739(w), 2260(w), 2182(w), 1451(w), 1348(s), 1250(vs), 1160(s), 1020-

(s), 987(s), 843(m) cm^{-1}.

4-(Trimethylammonio)-1-butanesulfonate (**53a**)

1,4-Butane sultone (**58** 12.4 g, 0.09 mol) was reacted with trimethylamine (Eastman, 15 mL, excess) in absolute alcohol (200 mL) using the method of Helferich and Bollert[65] to give **53a** as white crystals (12.1, 68%), mp 345°C(dec) (lit[65] mp 300°C(dec)); ^1H NMR(D_2O) δ: 1.71-2.15(m,4H), 2.99(t,2H), 3.14(s,9H), 3.40(t,2H); IR(nujol mull) ν_{max}: 3040(m), 1481(m), 1376(m), 1165(vs), 1040(s), 963(s), 910(s), 795(m), cm^{-1}.

4(Methoxysulfonyl)-N,N-dimethyl-1-butanaminium trifluoromethanesulfonate (**65a**, 345 mg, 1 mmol) was suspended in ice-cold saturated aqueous sodium carbonate (50 mL) and extracted with methylene chloride (3 x 25 mL). The extract was dried over magnesium sulfate and then evaporated to dryness to give a clear colourless oil which solidified on standing overnight in a desiccator over Drierite (233 mg, 96%). A specimen recrystallized from absolute alcohol gave ^1H NMR and IR spectra identical to that obtained from authentic **53a** and a mixed melting point determination showed no depression.

4-[($^2H_3$)methyldimethylammonio]-1-butanesulfonate (**53b**)

A mixture of 2,2-dimethyltetrahydro-2H-1,2-thiazinium--1,1-dioxide trifluoromethanesulfonate (**64a**, 900 mg, 3 mmol) and anhydrous ($^2H_3$)methanol (Merck, Sharpe and Dohme, 99% D, 140 μL, 3.5 mmol) in anhydrous acetonitrile (5 mL) was stirred at 50°C overnight. Removal of the solvent left

4-[($^2H_3$)methoxysulfonyl]-dimethyl-1-butanaminium trifluoromethanesulfonate (**65b**) as a clear colourless oil (990 mg, 99%), ^1H NMR(CD_3CN T60) δ: 1.7-2.0(m,solvent obscurred), 2.9(s,6H), 3.0-3.4(m,4H). This compound was not further characterized. The oil was shaken in cold saturated aqueous sodium carbonate (50 mL) and extracted with methylene chloride (3 x 35 mL). The extract was dried over magnesium sulfate and evaporated to dryness. The residue crystallized on standing overnight at room temperature in a desiccator over Drierite to give **53b** as a white solid (460 mg, 95% from **65b**) which was then recrystallized from absolute alcohol-methanol to give **53b** as white crystals (395 mg, 68%), ^1H NMR(D_2O) δ: 1.7-2.15(m,4H0, 2.98(t,2H), 3.13(s,6H), 3.39(t,3H); IR (nujol mull) ν_{max}: 3029(m), 2275(w), 1481(m), 1383(m), 1165(vs), 1039(s), 1001(w), 986(w), 943(w), 921(w), 837(w), 794(w), cm^{-1}.

4-[Di($^2H_3$)methylmethylammonio]-1-butanesulfonate (**53c**)

A mixture of 2-($^2H_3$)methyltetrahydro-2H-1,2-thiazine-1,-1-dioxide (**63b**, 1.6 g, mmol) and methyl trifluoromethanesulfonate (1.7 g, 11 mmol) in anhydrous methylene chloride (20 mL) was kept in the drybox for 2 da. 2-($^2H_3$)methyl-2-methyltetrahydro-2H-1,2-thiazinium-1,1-dioxide trifluoromethanesulfonate (**64b**), after collection by filtration and washing with anhydrous ether, was obtained as colourless plates (2.7 g, 83%). ^1H NMR(CD_3CN,T60) δ: 2.2(m,4H), 3.4-(s,3H), 3.9(t,2H), 4.2(t,2H). This material was not further characterized. A mixture of **64b** (1.5 g, 5 mmol) and ($^2H_4$)-

methanol (Merck, Sharpe and Dohme, 99% D, 270 µL, 5.8 mmol) in anhydrous acetonitrile (5 mL) was stirred at 53°C for 15 h in the drybox. Removal of the solvent by evaporation gave 4-[($^2H_3$)methoxylsulfonyl]-N-($^2H_3$)methyl-N-methyl-1--butanaminium trifluoromethanesulfonate (**65c**) as a clear colourless oil (1.7 g, 100%), ^1H NMR(CD_3CN,T60) δ : 1.7-2.0-(m,solvent obscurred), 1.8(s,3H), 3.0-3.4(m,4H). This material was not further characterized.

A sample of **65c**(400 mg, 1.15 mmol) was shaken with ice-cold saturated aqueous sodium carbonate (25 mL) and extracted with methylene chloride (2 x 20 mL). After the solvent was removed by evaporation, the residue was left-overnight in a desiccator over Drierite to give a white solid (220 mg, 95%) which was recrystallized from absolute alcohol-methanol to give the title compound as white crystals (170 mg, 73%), ^1H NMR(D_2O) δ : 1.70-2.15(m,4H), 2.99(t,2H), 3.13(s,3H), 3.39(t,2H); IR (Nujol Mull) ν_{max}: 3029(w), 2275(m), 1385(m), 1170(vs), 1038(s), 977(m), 910(w), 851(w), 830(m), 792(m) cm^{-1}.

4-[Tri($^2H_3$)methylammonio]-1-butanesulfonate (**53d**)

4-[($^2H_3$)methoxysulfonyl]-di($^2H_3$)methyl-1-butanaminium trifluoromethanesulfonate (**65d**, 250 mg, 0.7 mmol) was shaken with ice-cold saturated aqueous sodium carbonate (20 mL) then extracted with methylene chloride (2 x 20 mL). The extract was dried over magnesium sulfate, evaporated to dryness and left overnight in a desiccator over Drierite. The crude white solid (147 mg, 98%) was recrystallized three

times from absolute alcohol-methanol and then dried in vaccuo at 170°C for 8 h to furnish the analytical specimen, ^{1}H NMR (D_2O) δ: 1.70-2.15(m,4H), 2.99(t,2H), 3.39(t,2H): IR (nujol mull) ν_{max}: 2278(m), 1382(m), 1170(vs), 1068(m), 1040(s), 839(w), 793(m) cm^{-1}; Deuterium Anal. Calcd: 52.9 atom % excess D. Found: 50.4 atom % excess D.

4-(Dimethylammonio)-1-butanesulfonate (**68**)

1,4-Butane sultone (**58**, 1.4 g, 10 mmol) was reacted with dimethylamine (Eastman, 2 mL, excess) in methanol (25 mL) using the method of Helferich and Bollert[65] to give the title compound (**68**) as white crystals (1.5 g, 93%), mp 235-240°C(dec), (lit[65] mp 237-243°C(dec)); ^{1}H NMR(D_2O) δ: 1.70-1.95(m,4H), 2.89(s,6H), 2.94(t,2H), 3.18(t,2H); (1N NaOD/D_2O,T60) δ: 1.4-1.8(m,4H), 2.2(s,6H), 2.3(t,2H), 2.9(t,2H); IR (nujol mull) ν_{max}: 3028(w), 2725(s,br s), 1491(m), 1211(s), 1160(s), 1032(s) cm^{-1}.

Methyl 1-Butanesulfonate (**124**)

Triethylamine (Eastman, 7.7 mL, 55 mmol) in methylene chloride (40 mL) was added dropwise over 45 min. to a stirred 0°C solution of 1-butanesulfonyl chloride (**123** Eastman, 7.7 g, 50 mmol) and methanol (4 mL, 0.1 mol) in methylene chloride (100 mL). The mixture was stirred at room temperature for 1 h then washed with ice cold 5% aqueous sulfuric acid (3 x 100 mL) and water (100 mL). The organic layer was dried over magnesium sulfate and evaporated to dryness to give a yellow oil which was then distilled under reduced pressure to give **124** as a clear colourless oil (7.2 g, 95%),

bp 68-70°C(1.0 torr), (lit[103] bp 62°C (0.7 torr)); n_D^{20} 1.4308, (lit[103] n_D^{20} 1.4303); ^{1}H NMR($DCCl_3$) δ: 0.97(t,3H), 1.30-2.05(m,4H), 3.15(t,2H), 3.91(s,3H); IR (CH_2Cl_2) ν_{max}: 3058(m), 2961(s), 2877(m), 1452(m), 1350(s), 1160(s), 990(s), 819(s) cm^{-1}.

Phenyl 4-(Dimethylamino)-1-butanesulfonate (131)

A mixture of 2,2-dimethyltetrahydro-2H-1,2-thiazinium 1,1-dioxide trifluoromethanesulfonate (3.1 g, 10 mmol) and phenol (3 g, 30 mmol) was stirred at 120°C for 2 da. The excess phenol was removed by sublimination under reduced pressure (120°C, 50 torr). The residue was dissolved in 5N sulfuric acid (75 mL) and washed with ether (2 x 10 mL). The aqueous layer was made basic to litmus paper with 5N potassium hydroxide (100 mL) and extracted with methylene chloride (3 x 25 mL). The extract was dried over magnesium sulfate and evaporated to dryness to give 131 as a clear colourless oil (2.0 g, 70%). A small portion decomposed on attempted distillation (140°C, 0.005 torr). n_D^{20} 1.5076; ^{1}H NMR($CDCl_3$) δ: 1.47-1.78(m,2H), 1.82-2.40(m) and 2.22(s,-10H), 3.26(t,2H), 7.18-7.53(m,5H); IR ($CHCl_3$) ν_{max}: 3032(w), 2951(m), 2864(m), 2823(m), 2778(m), 1587(m), 1487(s), 1466-(m), 1373(s), 1145(vs), 868(vs), 689(m) cm^{-1}.

A small portion (200 mg) was added to a saturated solution of picric acid in anhydrous ether (100 mL). The copious yellow precipitate was collected by filtration and recrystallized from absolute alcohol. Two recrystallizations from chloroform-methylene chloride gave an analytical specimen

of 4-(Phenoxysulfonyl)-N,N-dimethyl-1-butanaminium picrate, mp 114-115'C; Anal. Calcd for $C_{18}H_{22}N_4O_1OS$: C,44.44; H,4.56; N,11.52; S,6.59. Found: C,44.22; H,4.62; N,11.36; S,6.47.

2. 2-Methylphenylmethane Derivatives

Thiophthalic Anhydride (74)

Thiophthalic anhydride, (74, 62 gm) was prepared in 55% yield from phthalic anhydride and sodium sulfide by the method of Reissert and Holle.[104] The malodorous compound was obtained as yellow needles, mp 113-114°C (lit[104] 114°C); ^1H NMR($CDCl_3$) δ: 7.8-8.2(m,4H); IR (CH_2Cl_2) ν_{max}: 3056(w), 2984(w), 1791(w), 1738(w), 1701(s), 1659(w), 1594(w), 1417-(w), 955(m) cm^{-1}.

2-(Mercaptomethyl)phenylmethanol (75)

Under nitrogen, thiophthalic anhydride (74, 30 g, 0.18 mol) in anhydrous tetrahydrofuran (200 mL) was added dropwise over 1 h to a stirred refluxing suspension of lithium aluminium hydride (20 g, 0.55 mol) in anhydrous tetrahydrofuran (1 L). The mixture was refluxed for an additional 4 h, cooled in ice and treated dropwise with water (50 mL). The grey paste was poured into ice-cold 4N sulfuric acid (1 L) then extracted with ether (4 x 500 mL). The extract was dried of magnesium sulfate and evaporated to dryness. Further azeotropic drying with benzene (2 x 100 mL) gave a clear foul-smelling yellow oil (27 g). T.L.C. with 1:2 ethyl acetate-petroleum ether (bp 30-60°C) on silica gel (E. Merck, silica gel 60-F-254, 0.25 mm thickness) showed two spots (R_f = 0.35 and 0.05). Using the flash chromato-

graphy technique[105], a portion of the crude reaction product (1.5 g) was passed, at a rate of 5 cm min^{-1}, through a silica gel column (E. Merck, silica get 60, 230-400 mesh, 3.5 cm x 15 cm) with 1:2 ethyl acetate-petroleum ether (bp 30 -60° C). The compound giving the T.L.C. spot of R_f = 0.35 was collected between 200 mL and 500 mL of eluant (as judged by T.L.C.). The second compound (R_f = 0.05) was stripped from the column with ethyl acetate (500 mL). Evaporation of the solvent from the first retained fraction left a yellow oil (750 mg) which was subjected to a second flash chromatographic cycle then distilled under reduced pressure in a cold finger apparatus to give an analytical specimen of **75** as a clear colourless pungent oil (500 mg), bp 80-82°C-(0.0005 torr); n_D^{20} 1.6019; ^{1}H NMR($CDCl_3$) δ: 1.83(t,J=7Hz,1H), 2.68(br s,1H), 3.80(d,J=7Hz,2H), 4.72(s,2H), 7.28(br s,4H); IR($CHCl_3$) ν_{max}: 3600(s), 3445(m,br), 3069(w), 3007(s), 2948(w), 2887(w), 2579(w), 1490(w), 1452(m), 1385(w), 1240-(w), 1181(w), 1099(w), 1003(s) cm^{-1}; Anal. Calcd for-$C_8H_{10}OS$:C162.30; H,6.54; S,20.79. Found: C,62.35; H,6.66; S,20.88. The second fraction was evaporated to dryness to give an orange solid (300 mg) which was recrystallized from ether-pentane to give white needles, mp 67-68.5°C. This compound gave ^{1}H NMR and IR spectra identical to those obtained from an authentic sample of 2-(hydroxymethyl)phenylmethanol, (**76**).[106] A mixed melting point determination showed no depression. The crude reaction product, judged by ^{1}H NMR(T60) to be a 3:1 mixture of **75** and **76**, was used

without further purification for the preparation of 2--(chloromethyl)phenylmethanesulfonyl chloride (77). The yield of the **76** was then approximately 75%.

2-(Chloromethyl)phenylmethanesulfonyl chloride (**77**)

Chlorine was bubbled through a mechanically stirred 0°C mixture of 3:1-2-(mercaptomethyl)phenylmethanol (**76**): 2-(hydroxymethyl)phenylmethanol (**77**) (35 g), methylene chloride (500 mL) and water (500 mL) until the formation of greenish yellow crystals was observed (45 min). The mixture was warmed to room temperature and the two layers were separated. The upper aqueous layer was extracted with methylene chloride (2 x 250 mL). The combined organic layer and extract was dried over magnesium sulfate and evaporated to dryness to give a yellow oil (41 g). The oil was washed with pentane (2 x 200 mL), dissolved in ether (500 mL), decolourized with Norite and filtered through a silica gel pad. Evaporation of the ether gave a clear faintly yellow tinted oil (32 g, 77% based on the original quantity of **75**).

A small portion of this material (1.5 g) was washed with petroleum ether (bp 30-60°C, 2 x 50 mL), dissolved in benzene, decolourized with Norite and passed down a short column of silica gel. Removal of the solvent by evaporation then further drying *in vaccuo* gave an analytical specimen of 2-(chloromethyl)phenylmethanesulfonyl chloride (**77**) as a clear colourless oil, n_D^{20} 1.5801, ^{1}H NMR($CDCl_3$) δ: 4.78-(s,2H), 4.15(s,2H), 7.45(br s,4H); IR ($CHCl_3$) ν_{max}: 3070(w),

3035(m), 1499(m), 1464(m), 1456(m), 1379(s), 1270(m), 1171-(s), 851(m), 670(m), 626(s) cm^{-1}; Anal. Calcd for $C_8H_{18}C_{12}O_2S$: C,40.18; H,3.37; Cl,29.65; S,13.41. Found: C,40.40; H,3.46; Cl,29.90; S,13.70.

2-(Chloromethyl)phenylmethanesulfonamide (**81**)

From an addition funnel cooled by a dry-ice-acetone jacket, ammonia (3.0 g, 0.18 mol) in anhydrous ether (500 mL) was added dropwise over 20 min to a stirred -10°C solution of 2-(chloromethyl)phenylmethanesulfonyl chloride (**77**, 20 g, 0.084 mol) in anhydrous ether (75 mL). The reaction mixture was stirred at room temperature for 20 min and then shaken with 2N sulfuric acid (1 L). The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 250 mL). The combined organic layers were dried over magnesium sulfate and evaporated to dryness to give a pink tinted crystalline solid (17.5 g, 95%), mp 163-166°C. Three recrystallizations from methylene chloride gave the analytical specimen as colourless plates, mp 167-168°C, ^1H NMR (50% $CDCl_3$:CD_3CN) δ: 4.54(s,2H), 4.87(s,2H), 5.33(br s,2H), 7.46(br s,4H); IR (nujol mull) ν_{max}: 3306(s), 3231(s), 3108(m), 1565(m), 1450(w), 1325(s), 1301(m), 1152-(s), 1136(s), 936(s), 774(s), 672(s) cm^{-1}; Anal. Calcd for $C_8H_{10}ClNO_2S$; C,43.79; H,4.59; Cl,15.99; N,6.31; S,14.72.

3,4 Dihydro-1H-2,3-benzothiazine 2,2-Dioxide (**82**)

Sodium hydride (B.D.H., 50% dispersion in oil, 6.6 g, 0.135 mol) was rinsed with pentane (3 x 200 mL) under nitrogen in a flame dried 1 L three neck flask equipped

with a pressure equalizing addition funnel, a condenser and a nitrogen inlet. After the addition of anhydrous tetrahydrofuran (500 mL), the suspension was stirred at reflux for 3 h while 2-(chloromethyl)phenylmethanesulfonamide (**81**, 10 g, 0.045 mol) in dry tetrahydrofuran (200 mL) was added dropwise. The reaction mixture was refluxed for an additional 2 h, then cooled in ice and treated dropwise with concentrated hydrochloric acid (12 mL). Evaporation of the solvent left a dark green gum which was extracted with methylene chloride (3 x 100 mL). The extract was washed with 1 N aqueous sodium bicarbonate (100 mL), dried over magnesium sulfate and evaporated to dryness to give a light green crystalline solid (6.8 g, 82%). Flash chromatography through silica gel (E. Merck, silica gel 60, 240-400 mesh) with 40% ethyl acetate-petroleum ether (bp 30-60°C) gave **82** as off white crystals (3.8 g, 46%). Recrystallization from water-methanol then from chloroform-methylene chloride (x2) gave the analytical specimen, mp 142-143°C(lit[74] 142-143°C); ^{1}H NMR(CD_3CN) δ: 4.31(s,2H), 4.51(d,J=8Hz,2H), 5.5(br s,1H), 7.0-7.4(m,4H); IR (CH_2C_{12}) ν_{max}: 3341(m), 3059(m), 1493(w), 1449(w), 1392(m), 1337(s), 1191(w), 1178(w), 1161(s), 1132-(m), 1059(w), 1036(w), 890(w), 866(w), 834(m), 657(m) cm^{-1}. Anal. Calcd for $C_8H_9NO_2S$: C,52.44; H,4.95; N,7.64; S,17.50. Found: C,52.38; H,4.98; N,7.53; S,17.64.

3-Methyl-3,4-dihydro-1H-2,3-benzothiazine 2,2-Dioxide (**85a**)

3,4-Dihydro-1H-2,3-benzothiazine-2,2-dioxide (**82**, 5 g, 27 mmol) and potassium hydroxide (3.0 g, 54 mmol) were

dissolved in absolute alcohol (500 mL), treated with methyl iodide (5.0 ml) and left overnight at room temperature. Removal of the solvent by evaporation left a yellow gum which was dissolved in 30% ethyl acetate-methylene chloride and filtered through a short column of basic alumnia (Fisher, Brockman Activity 1, 80-200-mesh). Evaporation of the filtrate to dryness gave **85a** as white crystals (4.0 g, 89%), mp 73-75°C. Three recrystallizations from ether-petroleum ether (bp 30-60°C) gave the analytical specimen, mp 76-77°C, (lit[74] mp 74-75°C); ^{1}H NMR($CDCl_3$) δ 2.92(s,3H), 4.33(s,2H), 4.58(s,2H), 7.0-7.2(m,4H); IR ($CHCl_3$) ν_{max}: 3030(m), 2971-(w), 2938(w), 2819(w), 1352(s), 1327(m), 1180(w), 1160(s), 1132(s), 992(m), 895(m), 864(w), 819(m), 657(m) cm^{-1}; Anal. Calcd for $C_9N_{11}NO_2S$: C,54.80; H,5.62; N,7.10; S,16.26. Found: C,54.39; H,5.73; N,6.91; S,16.43.

3-($^2H_3$)Methyl-3,4-dihydro-1H-2,3-benzothiazine 2,2-Dioxide (**85b**)

The title compound, **85b** was obtained as white crystals (2.7 g, 96%) from 3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxide (**82**, 2.6 g, 14 mmol), potassium hydroxide (1.5 g, 28 mmol) and ($^2H_3$)methyl iodide (99% D,2.0 mL) using the procedure described for the preparation of its undeuterated isomer, **85a**. ^{1}H NMR($CDCl_3$) δ 4.57(s,2H), 4.33(s,2H), 7.0-7.2-(m,4H); IR ($CHCl_3$) ν_{max}: 3030(m), 2938(w), 2227(w), 2123(w), 2071(w), 1352(s), 1327(m), 1163(s), 1132(s), 1069(w), 1051-(w), 881(w), 848(w), 811(w), 649(m) cm^{-1}.

(1,1-$^{2}H_2$)-3-Methyl-3,4-dihydro-1H-2,3-benzothiazine 2,2-Dioxide (85c).

A solution of 3-methyl-3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxide (85a, 400 mg, 2 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred under nitrogen at -78°C in a flame dried 3 neck flask equipped with a nitrogen inlet, a condenser and a rubber septum. After n-butyl lithium (Aldrich 2.3 M in hexane, 4.4 mL, 10 mmol) was injected into the solution, the mixture was warmed to room temperature over 25 min. The resulting dark red solution was quenched with D_2O (5 mL) at such a rate as to maintain reflux. After the vigorous reaction subsided, the solvent was removed by evaporation. The residue was eluted through a short column of Basic Alumnia (Fisher, Brockman Activity 1, 80-200 mesh) in 1:1 ethyl acetate-methylene chloride (100 mL). Evaporation of the eluant followed by recrystallization of the residue from ether-hexane gave colourless needles (200 mg, 50%) ^{1}H HMR($CDCl_3$) δ:2.91(s,3H), 4.31(m,0.29H), 4.59(s,2H) 7.0-7.2(m,4H). The integral of the peak corresponding to the α-sulfonyl methylene, (δ = 4.31, 10 mm) when compared with that of the peak from the α-N methylene (δ = 4.59, 68 mm) indicated 85% deuteration at the former position. A second cycle, conducted on half the above scale, yielded, after recrystallation, 85c as colourless needles (100 mg, 25% overall), ^{1}H NMR($CDCl_3$) δ: 2.91(s,3H), 4.31(m,-0.19H), 4.59(s,2H), 7.0-7.2(m,4H). The integral ratio of the above mentioned methylenes (7:75) was in agreement with

91% deuteration at the α- sulfonyl methylene. IR ($CHCl_3$) ν_{max}: 3018(m), 2965(w), 2934(w), 2817(w), 1349(s), 1168(s), 1152(m), 1119(w), 1109(w), 1094(w), 995(m), 870(w), 819(w), 790(m), 730(m), 652(s) cm^{-1}.

3,3-Dimethyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-Dioxide Trifluoromethanesulfonate (**86a**)

A mixture of 3-methyl-3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxide (**85a**, 2.9 g, 15 mmol) and methyl trifluoromethanesulfonate (4.9 g, 30 mmol) in anhydrous methylene chloride (7 mL) was prepared under nitrogen in a dry-box and left there for 7 da. The crystalline product was collected by filtration and washed with anhydrous ether (2 x 30 mL) to give **86a** as pink tinted plates (5.1 g). Recrystallation from anhydrous acetonitrile-ether gave **86a** as colourless plates (4.6 g, 85%), mp 144-145°C. Two additional recrystallizations from anhydrous acetonitrile-ether gave the analytical specimen, mp 146-147°C; ^1H NMR(CD_3CN)δ: 3.33(s,6H), 5.11(s,2H), 5.48(s,2H), 7.3-7.7(m,4H); IR (nujol mull) ν_{max}: 3041(m), 1390(s), 1280(s), 1248(s), 1173(s), 1155(s), 1030(s), 1011(w), 961(m), 950(m), 940(m), 758(m) cm^{-1}. Anal. Calcd for $C_{11}H_{14}F_3NO_5S_2$: C,36.56; H,3.91; F,15.77; N,3.88; S,17.75. Found: C,36.73; H,4.13; F,15.51; N,3.81; S,17.49.

3,3-Di($^2H_3$)Methyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-Dioxide Trifluoromethanesulfonate (**86b**)

Treatment of 3-($^2H_3$)methyl-3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxide (**85b**, 2.8g, 12.5 mmol) with ($^2H_3$)methyl

trifluoromethanesulfonate (4.2 g, 25 mmol) in methylene chloride (7 mL) using the procedure described for the preparation of **86a**, gave the title compound, **86b**, after recystallization, as colourless plates (4.0 g, 87%), ^{1}H NMRδ: 5.11(s,2H), 5.47(s,2H), 7.3-7.7(m,4H); IR (nujol mull) ν_{max}: 2289(m), 1390(s), 1280(s), 1248(s), 1173(s), 1155(s), 1099(w), 1061(w), 1030(s), 960(m), 940(m), 856(m), 840(m), 762(m), 750(m) cm^{-1}.

(1,1-$^2H_2$)-3,3-Dimethyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-Dioxide Trifluoromethanesulfonate (**86c**)

Treatment of (1,1-$^2H_2$)-3-methyl-3,4-dihydro-1H-2,3-benzothiazine 2,2-dioxide (**85c**, 100 mg, 0.5 mmol) with methyl trifluoromethanesulfonate (170 µL, 1.5 mmol) in methylene chloride (3 mL), using the procedure described for the preparation of **86a**, gave the title compound, **86c**, as colourless plates (159 mg, 88%), ^{1}H NMR(CD$_3$CN)δ: 3.33(s,6H), 5.10(s,2H), 5.47(m,22H), 7.3-7.7(m,4H). Comparision of the integral of the peak from the sulfonyl methylene (δ = 5.47, 7 mm) with that of the α-N methylene (δ = 5.10, 65 mm) indicated that **65c** was 89% deuterated at the α-sulfonylmethylene. IR (KBr pellet) ν_{max}: 3036(m), 2195(m), 2117(m), 1387(s), 1280(s), 1241(s), 1171(s), 1150(s), 1023(s), 1009(w), 952(m), 942(m), 932(m), 773(m), 751(s), 729(m) cm^{-1}.

2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium Trifluoromethanesulfonate (**87a**)

A mixture of 3,3-dimethyl-3,4-dihydro-1H-2,3-benzothia-

zinium 2,2-dioxide trifluoromethanesulfonate (**86a**, 2.8 g, 8 mmol) and anhydrous methanol (640 μL, 16 mmol) in anhydrous acetonitrile was stirred overnight at room temperature. Evaporation of the solvent left a tan solid which was recrystallized with Norite from anhydrous acetone-ether to give **87a** as colourless needles (2.4 g, 76%) mp 112-114°C. Two recrystallization from anhydrous acetone-ether gave the analytical specimen , mp 114-115°C, ^{1}H NMR(CD_3CN) δ: 2.86-(d, J=5Hz, 6H), 3.93(s,3H), 4.24(d, J=65Hz, 2H), 4.70(s,2H), 7.59(s,4H); IR (nujol mull) ν_{max}: 3140(s), 3051(w), 1348(s), 1271(s), 1187(w), 1155(s), 1038(s), 999(s), 941(w), 750, 713(w), 645(m) cm^{-1}. IR (KBr pellet) ν_{max}: 3140(s), 2975(m), 2936(m), 2820(s,br), 1475(m), 1361(s), 1265(s), 1150(s), 1030(s), 985(s), 931(m), 899(s), 851(w), 814(s), 786(m), 755(m), 740(m), 705(m), 641(s) cm^{-1}. Anal. Calcd for $C_{12}H_{18}F_3NO_6S_2$: C,36.64; H,4.61; F,14.49; N,3.56; S,16.30. Found: C,36.82; H,4.70; F,14.28; N,3.42; S,16.11.

Isotopically Substituted Analogues of 2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium Trifluoromethanesulfonate (**87 b,c,d** and **e**)

The procedure described for the preparation of **87a** was used to make the following compounds:

(i) 2-[(^{2}H$_3$)Methoxylsulfonylmethyl]phenyl-N,N-dimethylmethanaminium Trifluoromethanesulfonate (**87b**, 1.6 g, 73%) was prepared from 3,3-dimethyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (2.0 g, 5.5 mmol) and (^{2}H$_4$)methanol (Merck, Sharpe and Dohme, 99% D, 500

μL), ^{1}H NMR(CD_3CN) δ: 2.86(m,6H), 4.44(m,2H), 4.71(s,2H), 7.59(s,4H); IR (nujol mull) ν_{max}: 3050(w), 2338(m), 2281(w), 2190(w), 2138(w), 2100(w), 1348(s), 1271(s), 1155(s), 1109-(w), 1087(w), 1038(s), 999(s), 940(m), 822(m), 692(m), 645(m) cm^{-1}.

(ii) 2-(Methoxysulfonylmethyl)phenyl-N,N-di($^2H_3$methyl)-methanaminium Trifluoromethanesulfonate (**87c**, 1.5 g) was prepared in 83% yield from 3,3-di($^2H_3$)methyl-3,4-dihydro-1H--2,3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (**86b**, 1.7 g, 4.5 mmol) and methanol (450 μL). ^{1}H NMR(CD_3-CN)δ: 3.93(s,3H), 4.24(dJ=6.5Hz,2H), 4.70(s,2H), 7.59(s,4H); IR (nujol mull) ν_{max}: 3037(s), 2296(m), 1348(s), 1271(s), 1155(s), 1126(w), 1112(w), 1097(w), 1038(s), 997(s), 870(w), 822(m), 778(w), 736(m), 713(m), 645(m) cm^{-1}.

(iii) 2-[($^2H_3$)Methoxysulfonylmethyl]phenyl-N,N-di($^2H_3$)-methylmethanaminium Trifluoromethanesulfonate (**87d**, 1.9 g) was prepared in 79% yield from 3,3-di($^2H_3$)methyl-3,4-dihydro-1H-2,3-benzothiazinium trifluoromethanesulfonate (**86b**, 2.3 g, 6.0 mmol) and ($^2H_4$)methanol (Merck, Sharpe and Dohme, 99% d, 550 μL). ^{1}H NMR(CD_3CN) δ: 4.24(m,2H), 4.70(s,2H), 7.59(s,4H); IR (nujol mull) ν_{max}: 2352(m), 2296(m), 2270(m), 2190(w), 2140(w), 2100(w), 1348(s), 1271(s), 1155(s), 1089-(w), 1038(s), 999(s), 867(w), 820(m), 785(w), 773(w), 733(m), 692(m), 645(m) cm^{-1}.

(iv) 2-[($^{18}O_1$)Methoxysulfonyl($^2H_2$)methyl]phenyl-N,N-di-methylmethanaminium Trifluoromethanesulfonate (**87e**, 105 mg) was prepared in 66% yield from (1,1-$^2H_2$)-3,3-dimethyl-3,-

4-dihydro-1H-2,3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (**86c**, 150 mg, 0.4 mmol) and ($^{18}O_1$methanol (30 μL, 0.8 mmol) ^{1}H NMR(CD_3CN) δ: 2.86(d,J=5Hz,6H), 3.93-(s,3H), 4.24(d,J=6.5Hz,2H), 4.70(m,0.23H), 7.59(s,4H); IR (KBr pellet) ν_{max}: 3080(br s), 2959(w), 2820(w), 2790(br s), 2240(w), 1475(m), 1364(m), 1351(m), 1265(s), 1150(s), 1030(s), 949(s), 821(m), 795(s), 776(m), 758(m), 640(s), 501(s).

2-(Trimethylammoniomethyl)phenylmethanesulfonate (**55a**)

Method A

2-(Chloromethyl)phenylmethanesulfonyl chloride (**77**, 1.2 g, 5 mmol) in ether (25 mL) was added dropwise over 10 min to a stirred 0°C 1N aqueous solution of trimethylamine (Eastman, 50 mL, excess). After the mixture was stirred at room temperature for 2 h, the phases where separated. The aqueous phase was passed through a column of deionizing resin (Fisher, Rexyn 300 ($^+$H,$^-$OH), 50 m equiv). Evaporation of the eluant to dryness left white crystals (1.1 g, 91%). Three recrystallizations from absolute alcohol gave the analytical specimen as white needles, mp 280-283°C(dec), ^{1}H NMR(D_2O) δ: 3.13(s,9H), 4.41(s,2H), 4.70(s,obscured), 7.59(s,4H); IR (KBr pellet) ν_{max}: 3031(m), 2961(w), 1482(m), 1450(w), 1410(w), 1387(w), 1180(s), 1039(s), 971(w), 928(w), 879(w), 793(m), 716(w), 630(m), 577(w), 525(w) cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_3S$: C,54.30; H,7.04; N,5.76; S,13.18. Found: C,54.51; H,7.02; N,5.71; S,13.22.

Method B

2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (**87a**, 120 mg, 0.3 mmol) was shaken with ice cold saturated aqueous sodium carbonate then extracted with methylene chloride (3 x 10 mL). The extract was dried over magnesium sulfate and evaporated to dryness to give a viscous oil which solidified on standing overnight at room temperature over Drierite in a desiccator. The solid was passed (in water, 50 mL) through a column of deionizing resin (Fisher, Rexyn 300 (^{+}H,^{-}OH), 2 m equiv). Evaporation of the eluant left white crystals (70 mg, 94%). A small amount was recrystallized from absolute alcohol, mp 285-289°C(dec), mixed mp with the analytical specimen of **55a** from Method A showed no depression. The ^{1}H NMR and IR spectra were identical to those obtained from the analytical specimen.

Isotopically Substituted Analogues of 2-(Trimethylammoniomethyl)phenylmethanesulfonate (**55b, c, d** and **e**)

These were prepared via Method B from the appropriate isotopically substituted analogues of 2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate, (**87b, c, d** and **e**)

(i) 2-(($^{2}H_3$)Methyldimethylammoniomethyl)phenylmethanesulfonate (**55b**, 46 mg) was prepared in 85% yield from 2-[($^{2}H_3$)-methoxysulfonylmethyl]phenyl N,N-dimethylmethanaminium trifluoromethanesulfonate (**87b**, 89 mg, 0.22 mmol), ^{1}H NMR(D_2O)δ: 3.12(s,6H); 4.43(s,2H), 4.7(s,obscured), 7.59(s,4H); IR (KBr pellet) ν_{max}: 3030(m), 2955(w), 2280(w), 2090(w),

1481(m), 1450(w), 1417(w), 1382(w), 1200(vs), 1039(s), 943-(w), 920(s), 856(w), 790(m), 704(m), 631(m), 577(m), 520(w).

(ii) 2-(Di($^2H_3$)Methylmethylammoniomethyl)phenylmethanesulfonate (**55c**, 29 mg) was prepared in 72% yield from 2--(methoxysulfonylmethyl)phenyl-N,N-di($^2H_3$)methylmethanaminium trifluoromethanesulfonate (**87c**, 60 mg, 0.15 mmol), ^1H NMR(D_2O) δ: 3.13(s,3H), 4.42(s,2H), 4.7(s,obscured), 7.59-(s,4H); IR (KBr Pellet) ν_{max}: 3028(m), 2965(w), 2277(m), 2080(m), 1480(w), 1465(w), 1450(m), 1428(w), 1382(w), 1195(s), 1031(s), 968(w), 923(w), 850(w), 784(m), 760(w), 728(w), 699(m), 627(s), 571(m), 518(w) cm^{-1}.

(iii) 2-Tri($^2H_3$)methylammoniomethyl)phenylmethanesulfonate (**55d**, 210 mg) was prepared in 83% yield from 2-[($^2H_3$)methoxysulfonylmethyl]phenyl-N,N-di($^2H_3$)methylmethanaminium trifluoromethanesulfonate, (**87d**, 402 mg). Two additional recrystallizations from absolute alcohol followed by drying overnight in vaccuo over phosphorus pentoxide at 110°C gave the analytical specimen as white needles, mp 280-283°C(dec), ^1H NMR(D_2O) δ: 4.42(s,2H), 4.7(s,obscured), 7.59(s,4H). IR (KBr pellet) ν_{max}: 3020(w), 2290(m), 2087(m), 1498(w), 1472(w), 1463(w), 1431(w), 1399(m), 1202(s), 1041(s), 859(w), 807(w), 792(m), 759(w), 728(w), 693(w), 625(s), 577(s), 523(s) cm^{-1}. Deuterium Anal. Calcd 52.9 atom % excess D. Found: 50.9 atom % excess D.

(iv) 2-(Trimethylammoniomethyl)phenyl($^2H_2$)methane($^{18}O_1$)sulfonate (**55e**, 18 mg) was prepared in 96% yield from 2-[($^{18}O_1$)--methoxysulfonyl($^2H_2$)methyl]phenyl-N,N-dimethylmethanaminium

trifluoromethanesulfonate (**87e**, 30 mg, 0.075 mmol). The ^{1}H NMR was not obtained, IR (KBr pellet) ν_{max}: 3030(m), 2965(w), 2240(w), 2158(w), 1483(s), 1450(w), 1412(w), 1385-(w), 1180(s), 1039(s), 971(m), 920(w), 892(s), 879(w), 793-(m), 735(m), 720(m), 710(m), 619(m), 555(m) cm^{-1}.

2-(Dimethylammoniomethyl)phenylmethanesulfonate (**88**)

3,3-Dimethyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (**86a**, 290 mg, 0.8 mmol) and water (700 μL) in acetonitrile (7 mL) was left overnight at room temperature. The resulting white precipitate was collected by filtration to give crude as a white solid (165 mg, 90%). Three recrystallizations from methanol-water followed by drying overnight in vaccuo over phosphorus pentoxide at 110°C gave the analytical specimen, mp 345-350° C-(dec); ^{1}H NMR(1N DCl in D_2O)δ: 2.92(s,6H), 4.40(s,2H), 4.47-(s,2H), 7.55(s,4H); ^{1}H NMR(1N NaOD in D_2O) δ: 2.21(s,4H), 3.63(s,2H), 4.30(s,2H), 7.39(s,4H); IR (KBr Pellet): 3032-(m), 2991(m), 2720(s,br), 1212(s), 1173(s), 1028(s), 941(m), cm^{-1} Anal. Calcd fro $C_{10}H_{15}NO_3S$: C,52.38; H,6.59; N,6.11; S,13.98. Found: C,52.21; H,6.43; N,6.24; S,13.92.

Methyl Phenylmethanesulfonate (**128**)

Anhydrous triethylamine (Eastman, 17 mL, 0.12 mol) in anhydrous ether (100 mL) was added dropwise over 20 min to a stirred 0°C solution of phenylmethanesulfonyl chloride (19 g, 0.1 mol) and methanol (5 mL, 0.12 mol) in anhydrous ether (250 mL). The mixture was stirred for 20 min at room temperature then washed with 2N sulfuric acid (100 mL) and

brine (100 mL). The ether layer was dried over magnesium sulfate and evaporated to dryness to give white crystals (17 g). Recrystallization from petroleum ether (bp 80-110°C) gave colourless needles (14 g, 77%), mp 61-62° (lit[107] mp 61-61°C); ^{1}H NMR($CDCl_3$) δ: 3.74(s,3H), 4.34(s,2H), 7.40(s,5H); IR ($CHCl_3$) ν_{max}: 3018(m), 2949(w), 1491(m), 1450(m), 1358-(s), 1266(m), 1165(s), 991(s), 877(m), 808(m), 689(s), cm^{-1}.

Phenyl 2-(Dimethylaminomethyl)phenylmethanesulfonate (**131**)

A mixture of 3,3-dimethyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (**86a**, 500 mg, 1.4 mmol) and phenol (500 mg) in a stoppered 10 mL round bottom flask, was heated at 75°C for 24 h. The excess phenol was removed by azeotropic distillation with water (3 x 50 mL). The residue was shaken with saturated aqueous sodium carbonate (25 mL) and extracted with methylene chloride (3 x 25 mL). The extract was dried over magnesium sulfate and evaporated to dryness to give an off-white solid (350 mg) which was recrystallized with Norite from hexanes to give clear colourless needles (245 mg, 56%), mp 91-92°C. Two recrystallizations from petroleum ether gave the analytical specimen, mp 92-93°C; ^{1}H NMR($CDCl_3$) δ: 2.12(s,6H0, 3.53(s,2H), 4.08(s,2H), 7.1-7.4(m,9H), IR (KBr pellet) ν_{max}: 3058(m), 2956(m), 2836(m), 2769(m), 1589(m), 1487(s), 1468(m), 1451(m), 1365(s), 1248(m), 1140(s), 1013(s), 910(m), 858(s), 782(s), 687(m), 617(m), 563(s), 521(s) cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_3S$: C,62.93; H,6.27; N,4.59; S,10.50. Found: C,62.62; H,6.19; N,4.41; S,10.31.

Methyl 2-(Methoxymethyl)phenylmethanesulfonate (134)

Sodium (1.6g, 0.07 mol) was added to anhydrous methanol (40 mL). 2-(Chloromethyl)phenylmethanesulfonyl chloride (77, 4.6g, 0.02 mol) in anhydrous methanol (20 mL) was added dropwise with stirring over 20 min to the 0° C methoxide solution. The mixture was stirred overnight at room temperature, filtered and evaporated to dryness to give a brown solid which was dissolved in water (50 mL) and passed through a column of strong acid ion exchange resin (Fisher, Rexyn 101 ($^{+}$H), 0.3 equiv). The eluant was made basic to litmus paper by the addition of 10% aqueous tetramethylammonium hydroxide (Eastman) then evaporated to dryness to give a brown gum. After azeotropic drying with benzene (2x50 mL), the residue was recrystallized with Norite from isopropanol--ether to give tetramethylammonium 2-(methoxymethyl)phenylmethanesulfonate (133) as hygroscopic off white plates. The Plates were dried over phosphorus pentoxide at 50 torr for 2 da then dissolved in methylene chloride (25 mL). The solution was cooled to 0° C, treated methyl trifluoromethanesulfonate (5 mL, excess) and left at room temperature for 3 h. After the mixture was washed with 1N aqueous sodium carbonate (25 mL), toluene (10 mL) was added and the solvent removed by evaporation. The residual brown oil (2.2g) was dissolved in anhydrous ether, treated with Norite and filtered through a silica gel pad. Evaporation left 134 as a clear faintly yellow tinted oil (2.0g, 49%). A small portion decomposed slowly at 140° C (0.001 torr) on attempted

distillation. No further purification was employed. ^1H NMR($CDCl_3$) δ 3.38(s,3H), 3.77(s,3H), 4.58(s,2H), 4.61(s,2H), 7.37(s,3H); IR (KBr pellet) ν_{max}: 2924(m), 1334(s), 1158(s), 1140(s), 979(s), 778(s), 610(m) cm^{-1}.

3. 2-(2-Methylphenyl)ethane Derivatives:

2-Phenylethanethiol] (102)

2-Phenylethanethiol was prepared by a method similar to that described by Frank and Smith[108]. A solution of 2-phenylethanol (Sigma, 122 g, 1 mol) and thiourea (80 g, 1.05 mol) in 48% aqueous hydrogen bromide (550 g, 3.0 mol) was refluxed for 36 h then cooled in an ice bath and treated with 25% aqueous sodium hydroxide (3 mol). The mixture was refluxed for 4 h then made acidic with 48% aqueous hydrogen bromide whereupon a red oil floated to the surface of the reaction mixture. The phases were separated and the lower aqueous layer extracted with ether (3 x 100 mL). The organic phases were combined and dried over Drierite. Evaporation of the solvent left a clear brown oil which was distilled under reduced pressure through a 30 cm Vigreux column to give, as the main fraction, 2-phenylethanethiol (102) as a clear, colourless foul smelling oil. (120 g, 86%), bp 97-99°C(10 torr), (lit[109] bp 104°(17 torr); ^{1}H NMR-($CDCl_3$) δ: 1.34(5,1H), 2.5-3.0(m,4H), 7.0-7.2(m,5H); IR ($CHCl_3$) ν_{max}: 3062(m), 3005(s), 2936(m), 2848(m), 2563-(w), 1603(s), 1496(s), 1452(s), 691(s), 483(w) cm-1.

S-2-Phenylethanethiochloroformate (103)

In a well ventilated fume hood, a 2L round bottom flask containing 2-phenylethanethiol (102, 115 g, 0.82 mol) in methylene chloride (1L) was cooled in an ice-salt-acetone bath. Phosgene was condensed in the flask until the weight of the flask and its contents had increased by 100 g. An-

hydrous pyridine (66 mL, 0.9 mol) in methylene chloride (150 mL) was added dropwise over 1 h to the stirred solution. The resulting white suspension was stirred for 1 h at room temperature then washed with ice-water (3 x 500 mL) and dried over magnesium sulfate. Removal of the solvent by evaporation left a yellow oil (160 g) which was distilled under reduced pressure to give S-2-phenylethylthiochloroformate (**103**) as a clear colourless oil (152 g, 92%), (bp 97--98°C(0.8 torr). A small portion was distilled through a short Vigreux column to give the analytical specimen as a clear colourless oil, bp 103-104°C(3 torr), (lit[120] bp 135°C(10 torr)); n_D^{20} 1.5584 (lit[120] n_D^{20} 1.5590); ^{1}H NMR-($CDCl_3$) δ: 2.82-3.01(m,2H), 3.05-3.25(m,2H), 7.1-7.4(m,5H); IR($CHCl_3$) ν_{max}: 3060(m), 3002(m), 2924(m), 2847(m), 1761(s), 1666(s), 1491(m), 1455(m), 836(s), 689(m), 569(m) cm^{-1}; Anal. Calcd for C_9H_9ClOS: C,53.86; H,4.52; Cl,17.67; S,-15.97. Found: C,53.88; H,4.38; Cl,17.90; S,15.81.

3,4-Dihydro-1H-2-benzothiin-1-one (**104**)

Aluminum chloride (45 g, 0.35 mol) was suspended in anhydrous carbon disulfide (500 mL) under nitrogen in a flame dried 2L three neck round bottom flask equipped with a condenser, a mechanical stirring device and a pressure equalizing addition funnel. S-2-phenylethylthiochloroformate (**103**, 40 g, 0.2 mol) in anhydrous carbon disulfide (50 mL) was added dropwise to the stirred suspension at such a rate as to maintain reflux. The mixture was stirred at room temperature for 3 h then cooled in an ice bath and treated

dropwise with water until the ensuing reaction subsided. The resulting pink suspension was poured into water (500 mL) and the layers separated. The aqueous layer was extracted with methylene chloride (3 x 300 mL).

The combined organic phase was dried over magnesium sulfate and evaporated to dryness to give the title compound as a hot-pink crystalline solid (28 g, 85%). A small portion was recrystallized twice with Norite from ether-petroleum ether (bp 30-60°C) to give the analytical specimen as colourless needles, mp 60-61°C (lit[111] 60-61.5°C) ^{1}H NMR($CDCl_3$) δ: 3.1-3.4(m,4H), 7.2-7.6(m,3H), 7.9-8.0(m,1H); IR($CHCl_3$) ν_{max}: 2996(w), 2923(w), 2823(w), 1632(s), 1596(m), 1445(w), 1422(w), 1271(m), 1179(w), 1097(w), 982(s), 861(m) cm^{-1}; Anal. Calcd for C_9H_8OS: C,65.82; H,4.90; S,19.52. Found: C,65.52; H,4.76; S,19.65.

2-(2-Mercaptoethyl)phenylmethanol (**105**)

3,4-Dihydro-1H-2-benzothiin-1-one (**104**, 27 g, 0.165 mol) in anhydrous ether (300 mL) was added dropwise at such a rate as to maintain reflux to a stirred suspension of lithium aluminum hydride (11.5 g, 0.31 mol) in anhydrous ether (300 mL). The mixture was refluxed for 2 h then cooled in an ice bath and treated dropwise with ice cold 30% aqueous sulfuric acid (500 mL). The layers were separated and the aqueous layer extracted with ether (3 x 200 mL). The combined organic phase was dried over magnesium sulfate, decolourized with Norite and evaporated to dryness to give white crystals (25.8 g, 94%). An analytical specimen was prepared

by sublimation (70°C,(0.5 torr)); mp 38-40°C; ^{1}H NMR($CDCl_3$) δ: 1.42(s,1H), 2.14(s,1H), 2.6-3.1(m,4H), 4.70(s,2H), 7.1--7.5(m,4H); IR ($CHCl_3$) ν_{max}: 3602(s), 3440(br,s), 2998(s), 2932(m), 2879(w), 2568(w), 1490(s), 1450(s), 1380(m), 1218-(s), 995(s), 691(m), 606(m) cm^{-1}; Anal. Calcd for $C_9H_{12}OS$: C,64.24; H,7.19; S,19.06. Found: C,64.31; H,7.38; S,19.21.

2-[2-(Chloromethyl)phenyl]ethanesulfonyl Chloride (106)

A mixture of 2-(2-mercaptoethyl)phenylmethanol (22 g, 0.13 mol) in methylene chloride (500 mL) and water (250 mL) was stirred vigorously with a mechanical stirrer at °0C. Anhydrous chlorine was bubbled into the mixture until the formation of greenish yellow crystals was observed (30 min). The mixture was then warmed to room temperature and the two layers separated. The aqueous layer was extracted with methylene chloride (2 x 200 mL). The combined organic phase was dried over magnesium sulfate and evaporated to dryness to give the title compound, 106, as off-white crystals (38 g, 97%). A small portion was recrystallized twice from petroleum ether (bp 30-60°C) to give the analytical specimen as white needles, mp 63-64°C; ^{1}H NMR($CDCl_3$) δ: 3.3-3.6(m,2H), 3.9-4.2(m,2H), 4.68(s,2H), 7.1-7.5(m,4H); IR($CHCl_3$)ν_{max}: 3024(m), 2975(m), 2923(w), 1603(w), 1496(m), 1462(m), 1381(s), 1261(m), 1242(m), 1167(s), 968(m), 670(s), 618(m) cm^{-1}; Anal. Calcd for $C_9H_{10}Cl_2O_2S$: C,42.70; H,3.98; Cl,28.01; S,12.67. Found: C,42.62; H,4.10; Cl,27.92; S,-12.81.

N-Methyl-2-[2-(chloromethyl)phenyl]ethanesulfonamide (107a)

2-[2-(chloromethyl)phenyl]ethanesulfonyl chloride (**106**, 11.4 g, 0.045 mol) in methylene chloride (600 mL) was left over anhydrous potassium carbonate for 20 min. then filtered into a 1 L round bottom flask where it was cooled in an ice bath and treated with anhydrous methanaminium chloride (3.4 g, 0.05 mol) then 2N aqueous sodium hydroxide (5 mL). The flask was stoppered and the mixture stirred at 0°C for 1.5 h then at room temperature for 2 h. The mixture was washed with 1 N aqueous sulfuric acid (2 x 500 mL) then water (500 mL). The organic phase was dried over magnesium sulfate and evaporated to dryness to give **107a** as off-white crystals (10.6 g, 95%), mp 73-77°C. Two recrystallizations with Norite from ether-petroleum ether (bp 30-60°C) gave the analytical specimen as colourless needles, mp 80-81°C; ^{1}H NMR($CDCl_3$) δ : 2.78(d,3H), 3.1-3.5(m,4H), 4.67(br s,3H), 7.19-7.42(m,4H); IR ($CHCl_3$) ν_{max}: 3400(m), 3303(m), 3024(m), 2976(w), 2941(w), 1491(w), 1452(m), 1394(s), 1320(s), 1144-(s), 1071(s), 969(m), 837(s) cm^{-1}; Anal. Calcd for $C_{10}H_{14}ClNO_2S$: C,48.48; H,5.70; Cl,14.31; N,5.65; S,12.94. Found: C,48.71; H,5.87; Cl,14.22; N,5.61; S,12.78.

N-($^2H_3$)Methyl-2-[2-(chloromethyl)phenyl]ethanesulfonamide (**107b**)

Using the procedure described for the preparation of N-methyl-2-[2-(chloromethyl)phenyl]ethanesulfonamide, (**107a**), the title compound (**107b**, 6.9 g) was prepared in 91% yield from 2-[2-(chloromethyl)phenyl]ethanesulfonyl chloride (**106**, 8.8 g, 0.03 mol), ($^2H_3$)methanaminium chloride (Merck, Sharpe

and Dohme, 99% D, 2.4 g, 0.033 mol) and 1 N aqueous sodium hydroxide (7.5 mL) in methylene chloride (500 mL). ^{1}H NMR-($CDCl_3$) δ: 3.05-3.26(m,4H), 4.2-4.6(br s,1H), 4.65(s,2H), 7.20-7.45(m,4H); IR ($CHCl_3$) ν_{max}: 3400(m), 3298(w), 3021(m), 2968(w), 2221(w), 2071(w), 1493(m), 1451(m), 1390(s), 1321-(s), 1147(s), 1113(s), 1032(m), 811(m) cm^{-1}.

2-Methyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-Dioxide (**108a**)

Sodium hydride (B.D.H., 50% dispersion in oil, 2 g) was washed with pentane (3 x 100 mL) under nitrogen in a flame-dried 1 L 3-neck round bottom flask equipped with a pressure equalizing addition funnel, a condenser and a nitrogen inlet. After the addition of anhydrous tetrahydrofuran (500 mL), the suspension was refluxed and treated dropwise with stirring over 1.5 h with N-methyl-1-[2-(chloromethyl)phenyl]ethanesulfonamide (**107a**, 3.0 g, 12 mmol) in anhydrous tetrahydrofuran (100 mL). The mixture was refluxed overnight then water (5 mL) was added dropwise. Evaporation of the solvent left a green gum which was extracted with methylene chloride (3 x 100 mL). The extract was washed with water, dried over magnesium sulfate and evaporated to dryness to give a tan solid which was passed through short column of basic alumnia (Fisher Brockman Activity 1, 60-100 mesh, 3 cm x 10 cm) with 4:1 - methylene chloride--ethyl acetate (250 mL). Evaporation of the eluant gave the title compound, **108a**, as colourless cubes (2.0 g, 79%). Recrystallization from 50% methylene chloride-ethyl acetate

gave the analytical specimen, mp 160°C(sublimes); ^{1}H NMR-($CDCl_3$) δ: 2.56(s,3H), 3.19(br s,4H), 4.43(br s,2H), 7.32-(s,4H); IR ($CHCl_3$) ν_{max}: 3021(m), 2936(w), 2809(w), 1494(m), 1456(m), 1351(s), 1335(s), 1305(m), 1281(m), 1177(m), 1152-(s), 1133(s), 1117(m), 973(s), 923(s), 909(m), 869(w), 839(w) cm^{-1}; Anal. Calcd for $C_{10}H_{13}NO_2S$: C,56.85; H,6.20; N,6.63; S,15.18. Found: C,57.02; H,6.16; N,6.71; S,15.32.

2-($^2H_3$)Methyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-Dioxide (**108b**)

N-($^2H_3$)Methyl-2-[2-(chloromethyl)phenyl]ethanesulfonamide (**107b**, 2.5 g, 30 mmol) was reacted with sodium hydride (B.D.H., 50% dispersion in oil, 1.5 g) in anhydrous tetrahydrofuran (600 mL) and purified using the procedure described for the preparation of 2-Methyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3 dioxide (**108a**). The title compound, **108b** was obtained as colourless crystals (1.85 g, 85%), ^{1}H NMR-($CDCl_3$) δ: 3.18(br s,4H), 4.42(br s,2H), 7.31(s,4H); IR ($CHCl_3$) ν_{max}: 3022(m), 2941(w), 2219(w), 1068(w), 1494(w), 1456(m), 1352(s), 1305(m), 1282(w), 1273(w), 1179(w), 1155-(s), 1133(m), 1069(w), 1048(w), 923(w), 910(w), 886(w), 869(w), 839(m) cm^{-1}.

2,2-Dimethyl-1,2,4,5-tetrahydro-3,2-benzothiazepinium 3,3-Dioxide Trifluoromethanesulfonate (**109a**)

A mixture of 2-methyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide (**108a**, 1.5 g, 7.5 mmol) and methyl trifluoromethanesulfonate (2.5 mL, 22 mmol) in anhydrous methylene chloride (5 mL) was left for 4 da in a drybox. The

resulting crystalline precipitate was collected by filtration, washed with anhydrous ether and recrystallized with Norite from anhydrous acetonitrile-ether to give the title compound, **109a**, as colourless plates (2.25 g, 80%), mp 171-173°C. A second recrystallization in the drybox gave the analytical specimen, mp 173-174°C; ^{1}H NMR(CD_3CN) δ : 3.10-(s,6H0, 3.24(m,2H), 4.28(m,2H), 4.91(br s,2H), 7.40-7.75-(m,4H); IR (kBr pellet) ν_{max}: 3026(w), 2960(m), 2897(m), 1458(m), 1382(s), 1250(s), 1160(s), 1022(s), 991(w), 881(m), 827(w), 781(w), 749(m), 706(s), 630(m) cm^{-1}; Anal. Calcd for $C_{12}H_{16}F_3NO_5S_2$: C,38.39; H,4.30; F,15.18; N,3.73; S,1708. Found: C,38.41, H,4.36; F,15.13; N,3.82; S,17.29.

2,2-Di($^2H_3$)methyl-1,2,4,5-tetrahydro-3,2-benzothiazepinium 3,3-Dioxide Trifluoromethanesulfonate (**109b**)

The title compound (**109b**, 1.35 g) was prepared in 70% yield from 2-($^2H_3$)methyl-1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide (**108b**, 1.1 g 5 mmol) and ($^2H_3$)methyl trifluoromethanesulfonate (1.7 g, 10 mmol) in anhydrous methylene chloride (5 mL) using the procedure described for the preparation of 2,2-dimethyl-1,2,4,5-tetrahydro-3,2--benzothiazepinium 3,3-dioxide trifluoromethanesulfonate (**109a**). The product was obtained as colourless plates, mp 170-171°C, ^{1}H NMR(CD_3CN) δ : 3.45(m,2H), 4.28(m,2H), 4.89(br s,2H), 7.38-7.75(m,4H); IR (kBr pellet) ν_{max}: 2960-(m), 2890(m), 2273(w), 1456(m), 1395(s), 1250(s), 1160(s), 1087(m), 1052(m), 1022(s), 928(w), 918(w), 795(m), 770(m), 713(m), 693(m), 630(m) cm^{-1}.

2-[2-(Methoxysulfonyl)ethyl]phenyl-N,N-dimethylmethanaminium p-Toluenesulfonate (**111a**)

In a drybox under nitrogen, a mixture of 2,2-dimethyl--1,2,4,5-tetrahydro-3,2-benzothiazepinium 3,3-dioxide trifluoromethanesulfonate (**109a**, 2.6 g, 7 mmol) and anhydrous methanol (475 µL) in anhydrous acetonitrile (7 mL) was kept at 40°C for 40 h. After removal of the solvent by evaporation, the residual oil was shaken with ice-cold saturated aqueous sodium carbonate (50 mL) and extracted with methylene chloride (2 x 25 mL). The extract was dried over magnesium sulfate, diluted with acetonitrile (10 mL) and treated with p-toluenesulfonic acid monohydrate (Eastman, 1.4 g, 7 mmol). Evaporation of the solvent left a tan solid which was recrystallized twice from anhydrous acetonitrile-ether to give the title compound, **111a**, as colourless crystals (1.7 g, 58%). An additional recrystallization in the drybox gave the analytical specimen, mp 103-104°C, ^{1}H NMR(CD_3CN) δ: 2.35(s,3H), 2.84(d,6H), 3.30(m,4H), 3.77(s,3H), 4.34-(d,2H), 7.1-7.8(m,8H); IR (KBr Pellet) ν_{max}: 3500(m,br), 3020(m), 2700(s,br), 1465(m), 1200(vs,br), 1120(m), 1029(s), 938(m), 809(m), 791(m), 748(m), 680(s) cm^{-1}.

Anal. Calcd for $C_{19}H_{27}NS_2O_6$: C,53.13; H,6.37; N,3.26; S,-14.93. Found: C,53.21; H,6.41; N,3.36; S,14.99.

Isotopically Substituted Analogues of 2-[2-(methoxysulfonyl)-ethyl]phenyl-N,N-dimethylmethanaminium p-Toluenesulfonate, (**111b**, **111c** and **111d**).

(a) 2-[2-[($^2H_3$)Methoxysulfonyl]ethyl]phenyl-N,N-dimethyl-

methaminium p-toluenesulfonate (**111b**, 575 mg) was obtained as colourless plates in 45% yield from 2,2-dimethyl-1,2,4,5-tetrahydro-3,2-benzothiazepinium 3,3-dioxide trifluoromethanesulfonate (**109a**, 1.1 g, 3mmol), ($^2H_4$) methanol (270 μL) and p-toluenesulfonic acid monohydrate (600 mg); ^1H NMR-($CDCl_3$) δ: 2.35(s,3H), 2.84(d,6H), 3.29(m,4H), 4.05(br s,1H), 4.34(d,2H), 7.1-7.8(m,8H); IR (KBr Pellet) ν_{max}: 3500(m,br), 3020(m), 2700(s,br), 1470(m), 1200(s,br), 1118-(m), 1030(s), 938(m), 809(m), 768(s), 749(m), 680(s) cm^{-1}.

(b) 2-[2-(Methoxysulfonyl)ethyl]phenyl-N,N-di($^2H_3$)methylmethanaminium p-Toluenesulfonate (**111c**, 1.4 g) was obtained as colourless plates in 70% yield from 3,3-di($^2H_3$)methyl-1,-2,4,5-tetrahydro-3,2-benzothiazepinium 3,3-dioxide trifluoromethanesulfonate (**109b**, 1.7 g, 4.5 mmol), methanol (400 μL) and p-toluenesulfonic acid monohydrate (900 mg), ^1H NMR($CDCl_3$) δ: 2.34(s,3H), 3.33(m,4H), 3.77(s,3H), 4.30(d,-2H), 7.1-7.8(m,8H); IR (KBr Pellet) ν_{max}: 3500(m,br), 3020-(m), 2700(s,br), 1200(vs,br), 1119(m), 1031(s), 807(m), 792(m), 751(m), 746(m), 708(w), 680(s) cm^{-1}.

(c) 2-[-2[($^2H_3$)Methoxysulfonyl]ethyl]phenyl-N,N-di($^2H_3$)methylmethaminium p-Toluenesulfonate (**111d**, 1.1 g) was obtained as colourless plates in 42% yield from 2,2-di($^2H_3$)methyl-1,-2,4,5-tetrahydro-3,2-benzothiazepinium 3,3-dioxide trifluoromethanesulfonate (**109b**, 2.6 g, 6 mmol), ($^2H_4$)methanol (550 μL) and p-toluenesulfonic acid monohydrate (1.2 g). ^1H NMR($CDCl_3$) δ: 2.34(s,3H), 3.33(m,4H), 3.77(s,3H), 4.30-(d,2H), 7.1-7.8(m,8H); IR (KBr Pellet) ν_{max}: 3500(m,br),

3020(m), 2700(s,br), 1200(vs,br), 1121(w), 1030(s), 809(m), 765(s), 750(m), 736(m), 706(m), 608(s), cm^{-1}.

2-[2-(Trimethylammonio methyl)phenyl]ethanesulfonate (**57a**)

Method A:

Trimethylamine(Eastman, 2.5 g, .04 mol) in water (50 mL) was added dropwise over 20 min. to a stirred 0°C solution of 2-[2-(chloromethyl)phenyl]ethanesulfonyl chloride (**106**, 1.26 g, 5mmol) in ether (25 mL). The mixture was stirred at room temperature for 3 h and the layers separated. The aqueous phase was passed through a column of deionizing resin (Fisher Rexyn 300 (^{+}H,^{-}OH), 50 mequiv). The eluant was evaporated to dryness to give a white solid (11 g, 85%) which was recrystallized from absolute alcohol (30 mL) to give the title compound as white needles, mp 250-252° (dec), ^{1}H NMR(D_2O)δ : 3.14(s,9H0, 3.21(s,4H), 4.63(s,obscured), 7.52(m,4H); IR (KBr Pellet) ν_{max}: 3026(m), 3010(m), 1498(m), 1485(m), 1466(m), 1434(m), 1195(s), 1060(s), 949(m), 944(m), 901(m), 810(s), 791(s), 637(s) cm^{-1}, Anal. Calcd for $C_{12}H_{19}NO_3S$: C,56.00; H,7.44; N,5.44; S,12.46. Found: C,56.11; H,7.52; W,5.37, S,12.64.

Method B:

2-[2-(Methoxysulfonyl)ethyl]phenyl-N,N-dimethylmethaminium p-toluenesulfonate (**111a**, 150 mg, 0.35 mmol) was shaken in ice cold aqueous sodium carbonate (25 mL) and extracted with methylene chloride (2 x 25 mL). The extract was dried over magnesium sulfate and evaporated to dryness to give a clear oil which solidified when stored over Drierite in

a desiccator overnight. The solid was passed, in water (50 mL), through a column of deionizing resin (Fisher Rexyn 300 (^{+}H,^{-}OH), 3.5 mequiv). Evaporation of the eluant to dryness gave a white crystalline solid which was recrystallized from absolute alcohol to give the title compound as white needles, (71 mg, 79%) mp 150-152°C(dec), mixed mp with a sample from Method A showed no depression. The ^{1}H NMR(D_2O) and IR (KBr Pellet) spectra were identical to those obtained from the analytical specimen of **57a** prepared by Method A.

Isotopically Substituted Analogues of 2-[2-(Trimethylammoniomethyl)phenyl]ethanesulfonate (**57b, 57c** and **57d**)

These compounds were prepared using Method B.

(a) 2-[2-(($^{2}H_3$)Methyldimethylammoniomethyl]phenyl]ethanesulfonate (**57b**, 54 mg) was prepared in 83% yield from 2-[2-[($^{2}H_3$)methoxysulfonyl]ethyl]phenyl-N,N-dimethylmethaminium p-toluene sulfonate (**111b**, 108 mg, 0.25 mmol), mp 250-255°C(dec); ^{1}H NMR(D_2O) δ : 3.13(s,6H0, 3.20(s,4H), 4.62(s,-obscured), 7.52(m,4H); IR (KBr pellet) ν_{max}: 3027(w), 3011-(m), 2291(m), 2106(w), 1494(s), 1459(m), 1431(m), 1195(s), 1059(s), 983(w), 964(m), 949(m), 874(w), 848(m), 801(s), 637(s) cm^{-1}.

(b) 2-[2-[Di($^{2}H_3$)methylmethylammoniomethyl]phenyl]ethanesulfonate (**57c**, 105 mg) was prepared in 75% yield from 2-[2-(methoxysulfonylmethyl)phenyl]-N,N-di($^{2}H_3$)methylmethanaminium p-toluenesulfonate (**111c**, 230 mg, 0.53 mmol), mp 250-255°C(dec); ^{1}H NMR(D_2O) δ: 3.12(s,3H), 3.20(s,4H),

4.61(s,obscured), 7.52(m,4H); IR (KBr pellet) ν_{max}: 3026(w), 3010(m), 2288(m), 2100(w), 1466(m), 1438(w), 1196(s), 1058-(s), 990(w), 946(m), 870(m), 840(m), 799(s), 635(s) cm^{-1}.

(c) 2-[2-[Tri($^2H_3$)methylammoniomethyl]phenyl]ethanesulfonate (**57d**, 120 mg) was prepared in 90% yield from 2-[2-[-($^2H_3$)methoxysulfonyl]ethyl]phenyl-N,N-di($^2H_3$)methylmethanaminium p-toluenesulfonate (**111d**, 220 g, 0.5 mmol). A second recrystallization followed by drying in vaccuo at 100 °C overnight gave the analytical specimen, mp 250-255° C(dec); ^1H NMR(D_2O) δ : 3.21(s,4H), 3.61(s,obscured), 7.52(m,4H); IR (KBr Pellet) ν_{max}: 3009(m), 2293(m), 2096(m), 1493(m), 1462(m), 1454(m), 1442(w), 1195(s), 1057(s), 849(m), 841(m), 833(m), 797(s), 635(s) cm^{-1}. Deuterium Anal. Cald 47.4 atom % excess D. Found: 45.0 atom % excess D.

4,5-Dihydro-1H-2,3-benzoxathiepin 3,3-Dioxide (**115**)

A mixture of 2-[2-(chloromethyl)phenyl]ethanesulfonyl chloride (**106**, 2.0 g, 8 mmol) and sodium hydroxide (1.1 g, 28 mmol) in 20% aqueous dimethoxyethane (100 mL) was stirred overnight at room temperature. The resulting yellow solution was passed through a column of strong acid ion exchange resin (Fisher, Rexyn 101 (^+H), 75 mequiv). Removal of the solvent by evaporation left a brown viscous oil which slowly crystallized while standing for one week over phosphorus pentoxide at 50 torr. The black solid was filtered in methylene chloride through a silcia gel pad. Evaporation of the filtrate to dryness gave off-white crystals (900 mg, 55%). Two recrystallizations with Norite from anhydrous

ether gave the analytical specimen as colourless plates, mp 115-116°C; ^{1}H NMR($CDCl_3$) δ : 330(s,4H), 5.31(s,2H), 7.37-(m,4H); IR ($CHCl_3$) ν_{max}: 3028(m), 1497(m), 1459(m), 1373(s), 1358(s), 1163(s), 934(s) cm^{-1}. Anal. Calcd for $C_9H_{10}O_3S$: C,54.73; H,5.06; S,16.10. Found: C,54.91; H,5.20; S,16.21.

2-[2-(Dimethylammoniomethyl)phenyl]ethanesulfonate (**116**)

A solution of 4,5-dihydro-1H-2,3-benzoxathiepin 3,3-dioxide (**115**, 300 mg, 1.5 mmol) and dimethylamine (Eastman, 5 mL, excess) in absolute alcohol (50 mL) was left at room temperature overnight. Evaporation to dryness gave white crystals (360 mg, 99%). Three recrystallization from anhydrous ethanol gave the analytical specimen as white needles, mp 226-230°C(dec); ^{1}H NMR(1M Na_2CO_3 in D_2O) δ : 2.34(s,6H), 3.13(s,4H), 3.63(s,2H), 7.35(s,4H); ^{1}H NMR(1M DCl in D_2O) δ: 2.93(s,6H), 3.10(s,4H), 4.43(s,2H), 7.47(s,4H); IR (KBr pellet) ν_{max}: 3480(s,br), 3010(m), 2965(w), 2922(w), 1460-(s), 1201(s), 1135(s), 1022(s), 932(s), 766(s), cm^{-1}; Anal. Calcd for $C_{11}H_{17}NO_3S$: C,54.29; H,7.04; N,5.76; S,13.19. Found: C,54.21; H,7.14; N,5.63; S,13.31.

C. Kinetic Studies:

All kinetic runs were followed by ^1H NMR using a Varian T60 NMR spectrometer. The concentration of unreacted starting material, as determined from the integral of one of its peaks relative to that of an inert internal standard, was monitored with respect to time. For the reactions of the methyl ω-dimethylaminoalkanesulfonate esters for which the ^1H NMR spectral data are shown in Table 29, the reciprocal of the concentration of unreacted starting material was plotted versus time. Treatment of these data by linear least squares regression gave the best-fit line, its correlation coefficient (r) and the slope of line from which the observed rate constant, k_{obs}, was calculated. In all runs, the least squares line agreed with that drawn by inspection. For the reactions of the model compounds (methyl alkanesulfonate esters with dimethylalkylamines) values calculated from $\ln([A]/[B])/([A]_0-[B]_0)$ were plotted against time. The linear least squares slope gave the observed rate constant (k_{obs}) and its correlation coefficient (r). Again, the calculated best fit line was in agreement with that drawn by inspection. For runs less than 24 h in duration, time was measured with a Precision Scientific Timer. A Windert Digital Chronometer was used for runs longer than 24 h. Unless otherwise specified, the sample was immersed in a constant temperature bath during the intervals between analysis. For temperatures less than 100°C, a water bath equipped with a Haake H.J. recirculating heater

was used. An oil bath equipped with A. B. Braun 1460 recirculating heater was used for runs greater than 100° C. The initial concentrations at room temperature (23° C), either known from the mode of solution preparation or calculated from the known solvent volume and product yield, were corrected for thermal expansion by division by the thermal expansion factor (X_T).

Table 29

Methyl ω-Dimethylaminoalkanesulfonate
^{1}H NMR Data

Ester	Solvent	^{1}H NMR Spectrum, (δ, T-60)
52a	$CDCl_3$	1.5-1.8 (m, 2H), 1.8-1.4 (m) and 2.2 (s) (10H), 3.3 (t, 2H), 3.8 (s, 3H)
54a	C_6D_6	2.2 (6H), 3.3 (s, 3H), 3.5 (s, 2H), 4.7 (s, 2H), 7.0 (s, 4H)
54b	C_6D_6	2.2 (6H0, 3.5 (s, 2H), 4.7 (s, 2H), 7.0 (s, 4H)
54c	C_6D_6	3.3 (s, 3H), 3.5 (s, 2H), 4.7 (s, -2H), 7.0 (s, 4H)
54d	C_6D_6	3.5 (s, 2H), 4.7 (s, 2H), 7.0 (s, 4H)
56a	C_6D_6	2.0 (s, 6H), 3.1 (s, 2H), 3.2-3.3- (m, 4H), 3.4 (s, 3H), 7.0 (s, 4H)
56b	C_6D_6	2.0 (s, 6H0, 3.1 (s, 2H), 3.2-3.3- (m, 4H), 7.0 (s, 4H)
56c	C_6D_6	3.1 (s, 2H), 3.2-3.3 (m, 4H0, 3.4 (s, 3H), 7.0 (s, 4H)
56d	C_6D_6	3.1 (s, 2H), 3.2-3.3 (m, 4H), 7.0 (s, 4H)

Solvent Thermal Expansion Factor, X_T

In the kinetic and the crossing experiments described in this thesis, values for the initial substate concentration were required. At room temperature, (23°C), those values were known or could be easily obtained. However, since many of the experiments were conducted in sealed glass tubes at temperatures greater than 23°C, it was necessary to correct the initial room temperature substrate concentrations for dilution via thermal solvent expansion. The temperature dependance of the specific volume (the reciprocal of density) of a variety of solvents has been described quantitatively by Partington[112] with the following empirical expression

$$\upsilon_T = \upsilon_\emptyset (1 + aT + bT^2 + cT^3)$$

where υ_T is the specific volume at T°C, $\upsilon_\emptyset$ is the specific volume at ∅°C and a,b and c are empirical coefficients. Since for a sample of a liquid,

$$\upsilon_{T_1} V_{T_1} = \upsilon_{T_2} V_{T_2}$$

where V_{T1} is the volume of the liquid at T_1°C and V_{T_2} is the volume at T_2°C.

Rearranging

$$V_{T_2} = \frac{\upsilon_{T_2}}{\upsilon_{T_1}} V_{T_1}$$

Since all temperature conversions in this thesis involve one 23°C temperature,

Define $X_T = \frac{\upsilon_T}{\upsilon_{23^\circ}}$

At any temperature, T°C,
$V_T = X_T V_{23^\circ C}$

If the effect of a solute, Z, is negligible, then
$[Z]_T = \frac{[Z]_{23^\circ}}{X_T}$

Pertinent to these experiments, Partington[112] gives the following data.

For Benzene:

$v_0 = 1.1121$ mL g^{-1}
$a = 1.17626 \times 10^{-3}$ deg^{-1}
$b = 1.27755 \times 10^{-6}$ deg^{-1}
$c = 1.11221 \times 10^{-8}$ deg^{-3}

For Chloroform:

$v_0 = 0.65565$ mL g^{-1}
$a = 1.107146 \times 10^{-3}$ deg^{-1}
$b = 4.6647 \times 10^{-6}$ deg^{-2}
$c = -1.17432 \times 10^{-8}$ deg^{-3}

Example:

For benzene at 110.0°C, $X_T = 1.1243$.

Therefore $V_{110°C} = X_T V_{23°C}$

For a 50 mL aliquot (at 23°C),

$$V_{110°C} = 56.2 \text{ mL}$$

In one of the crossing experiments, when 50.0 mL (at 23°C) of a benzene solution of the substrate was sealed in a Caruis tube with an internal diameter of 1.8 cm and then heated to 110°C, the solvent level increased by 2.5 cm. Using Volume = height x π x radius^2, this corresponds to increase in solvent volume of 6.4 mL. The volume at 110°C was then 56.4 mL. The agreement between the value based on X_T and that determined shows that both the effect of the solute and the increased pressure in the Caruis tube are negligible.

1. Butane Derivatives

(a) Rate of Formation of 4-(Trimethylammonio)-1-butanesulfonate (**53a**) from Methyl 4-(Dimethylamino)-1-butanesulfonate (**52a**) at 37.0°C in $CDCl_3$.

(i) 4-(Methoxysulfonyl)-*N*,*N*-dimethyl-1-butanaminium trifluoromethanesulfonate (**65a**, 690 mg, 2 mmol) was shaken with ice-cold saturated aqueous sodium carbonate (3mL) and extracted with $CDCl_3$ (4 x 1 mL). The extract was dried over magnesium sulfate and filtered into a 5.0 mL volumetric flask which contained methylene chloride (40.0 μL, 0.625 mmol). The flask was then filled to the mark with $CDCl_3$. An aliquot (1 mL) was transferred to an NMR tube which was then capped and inserted into the probe of the ^1H NMR spectrometer where it remained for the duration of the kinetic run. The probe temperature was 37.0°C. The integral of the *O*-methyl peak of **52a** (I_E, δ = 3.8 ppm) and that of the internal standard, methylene chloride (I_S, δ = 5.2 ppm) were obtained at the indicated times.

$$[\mathbf{52a}] = \frac{2\ I_E\ [CH_2Cl_2]}{3\ I_S \times X_T} = \frac{2\ I_E \times 0.125}{3\ I_S \times 1.0193} = \frac{I_E}{I_S} \times 8.176 \times 10^{-2}$$

Kinetic Data

Time (min.)	I_s (mm)	I_E (mm)	[52a](M)	1/[52a](L mol^{-1})
2.0	12	36	0.245	4.1
12.2	17	36	0.173	5.8
18.0	17	33	0.159	6.3
22.6	15	26	0.142	7.1
27.3	18	25	0.114	8.8
33.6	18	24	0.109	9.2
38.8	18	20	0.091	11.1
44.3	16	18.5	0.095	10.6
50.7	18	17	0.077	13.0
55.2	17	16	0.077	13.0
61.5	17	17	0.082	12.2
65.0	16.5	14	0.069	14.4
69.4	17	13	0.063	16.0
74.9	17.5	13	0.061	16.5
80.7	16.5	12	0.060	16.8
86.5	16.5	11.5	0.057	17.6
95.4	17	10.5	0.051	19.8
99.1	17.5	10	0.047	21.4
103.9	17	10	0.048	20.8
109.2	16.5	9	0.045	22.4
113.0	17.5	9.5	0.044	22.5
121.6	17.5	8.5	0.040	25.2
133.6	16.5	8.0	0.040	25.2

$k_{obs} = 2.8 \times 10^{-3}$ L mol^{-1} s^{-1} ($r = 0.9945$)

(ii) A second kinetic run was conducted using the same method. The following quantities were used: 4-(Methoxysulfonyl)-N,N-dimethyl-1-butanaminium trifluoromethane sulfonate (65a, 180 mg, 0.52 mmol), $CDCl_3$ (1.0 mL with a 1.0 mL volumetric flask) and methylene chloride (8.0 µL, 0.125 mmol).

$$[52a] = \frac{2}{3}\frac{I_E\,[CH_2Cl_2]}{I_S \times X_T} = \frac{I_E}{I_S} \times 8.176 \times 10^{-2}\ M$$

Kinetic Data

Time (min)	I_S(mm)	I_E(mm)	[52a](M)	1/[52a](L mol^{-1})
0	24	70	0.238	4.2
8	23	50	0.178	5.6
16	24	40	0.136	7.3
24	20	31	0.127	7.9
32	21	28	0.109	9.2
40	22.5	25	0.091	11.0
48	21.5	21.5	0.082	12.2
56	22	20	0.074	13.5
64	30	23	0.063	16.0
72	28	21.5	0.063	15.9
80	28	19	0.055	18.0
88	28.5	18	0.052	19.4
96	27	16.5	0.050	20.0
104	26.5	15.5	0.049	20.9
112	27	15	0.045	22.0
120	27	14	0.042	23.6
128	28.5	14	0.040	24.9
136	28	13	0.038	26.4
144	27.5	12	0.036	28.0

$k_{obs} = 2.7 \times 10^{-3}$ L mol^{-1} s^{-1} ($r = 0.9982$)

(b) Rate of Methylation of Phenyl 4-(Dimethylamino)-1-butanesulfonate (126) with Methyl 1-Butanesulfonate (124) in $CDCl_3$ at 37.0°C:

(i) Methyl 1-butanesulfonate (124, 76 mg, 0.50 mmol) and methylene chloride (6.5 μL) were dissolved in $CDCl_3$ (0.75 mL) in a 1.0 mL volumetric flask. Phenyl 4-(dimethylamino)-1-butanesulfonate (126, 148 mg, 0.575 mmol) was added and the flask filled to the mark with $CDCl_3$. The solution was transferred to an NMR tube which was then capped and placed in the probe of the NMR spectrometer where it remained for the duration of the kinetic run. The probe temperature was 37.0°C. The integral of the O-methyl peak in 124 (I_E δ = 3.9 ppm) and that of the internal standard, methylene chloride (I_S, δ = 5.2 ppm) were obtained at the indicated times. The initial concentrations of 124 and 126 were those calculated from the amounts added divided by X_T.

$$[124] = \frac{I_E}{I_S} \times C$$

From t = 0, $C = 7.766 \times 10^{-2}$ M

$$[126] = [124] + .0750 \text{ M}$$

Kinetic Data

Time (min)	I_S(mm)	I_E(mm)	[124](M)	[126](M)	$\frac{1}{[126]_0-[124]_0}$	$\ln\frac{[126]}{[124]}$
0	11	58	.491	.566		1.9
6.5	14.5	63	.404	.479		2.3
11.4	15.5	49	.294	.369		3.0
15.2	15.5	42	.252	.327		3.5
19.0	15	37	.230	.305		3.8
23.5	15	31	.192	.267		4.4
27.3	16	31.5	.183	.258		4.6
34.0	15	27	.167	.242		4.9
39	18	29	.150	.225		5.4
45.5	19	29	.142	.217		5.7
51	18.5	25	.126	.201		6.2
56	20	22.5	.105	.180		7.2
60	18	18	.093	.168		7.9
64	26	24	.086	.161		8.4
69.5	24	22.5	.087	.163		8.3
75	25	23	.086	.161		8.4
80	24	21	.081	.156		8.7
85.5	23	19	.077	.152		9.1
92.5	25	18	.067	.142		10.0
98	24.5	17	.065	.140		10.3
103	30	19	.059	.134		11.0
108	29	17	.055	.130		11.5

$k_{obs} = 1.4 \times 10^{-3}$ L mol^{-1} s^{-1} ($r = .9945$)

(ii) The same method as that described for Run A was used. The following quantities were used: Methyl-1-butanesulfonate (124, 90.6 mg, 0.6 mmol), Phenyl 4-(dimethylamino)-1-butanesulfonate (126, 103 mg, 0.40 mmol), methylene chloride (10 μL).

$$[124] = \frac{2}{3}\frac{I_E}{I_S}[CH_2Cl_2] = \frac{I_E}{I_S} \times 0.1047$$

$$[126] = [124] - 0.1950_{6}\underline{M}$$

Time (min)	I_S (mm)	I_E (mm)	[124] (M)	[126] (M)	$\frac{1}{([124]_0 - [126]_0)} \ln \frac{[124]}{[126]}$
0	--	--	.587	.392	2.1
4.5	16.5	78	.495	.300	2.6
5.5	15	75	.523	.328	2.4
10.5	18.5	87	.492	.297	2.6
15.0	17.5	73	.437	.242	3.0
20	19.5	74	.397	.202	3.5
28	18.5	65	.368	.173	3.9
36	19	60	.331	.136	4.6
40	20	59	.309	.114	5.1
47	20	55	.288	.093	5.8
57	20	51	.267	.072	6.7
65	19.5	48	.258	.063	7.3
71	20	49	.256	.061	7.3
77	19.5	46	.247	.052	8.0

$k_{obs} = 1.3 \times 10^{-3}$ L mol^{-1} s^{-1} ($r = .9960$)

2. 2-Methylphenylmethane and 2-(2-Methylphenyl)ethane Derivatives:

General Procedure for Runs 2(a) through 2(n)

The "norbetylate" (0.15 mmol) was shaken in cold aqueous sodium carbonate (0.5 mL) and extracted with d_6-benzene (2 x 0.3 mL). After addition of the internal standard, 1,1,2,2-tetrachloroethane, the solution was dried over magnesium sulfate and filtered into an NMR tube which was then sealed under nitrogen at -78° C. The sample was then inserted into the NMR probe. Immediately upon melting, an integrated NMR spectrum was obtained. The sample was then immersed in a bath at the specified temperature and the timer started. For kinetic runs less than 24 h in duration, at the indicated times, the sample was removed from the bath, thermally quenched in an ice bath, analyzed by NMR and returned to the bath. The timer was stopped for the duration of the analytical interval. For runs longer than 24 h, thermal quenching and timer stoppage were omitted. The reaction was followed by comparison of the integral of the specified peak of the starting material (I_E) with that of 1,1,2,2-tetrachloroethane (I_S, δ = 5.0 ppm). In all runs, at t = ∞, the NMR spectrum showed only the 1,1,2,2-tetrachloroethane peak and that due to the isotopic impurity of the solvent (δ = 7.2 ppm). After the kinetic run, the height of the solvent in the NMR tube was measured at room temperature with a ruler calibrated to 1.0 mm. The tube was then opened and its contents flushed with methanol (3 x 2 mL) into a

tared 25 mL round bottom flask containing water (10 mL). The mixture was evaporated to dryness then further dried by standing overnight at 50 torr in a vacuum desiccator. The amount of betaine obtained was taken as the original quantity of starting material since, in all cases, the residue gave an NMR spectrum (D_2O) identical to that obtained from an authentic sample of corresponding betaine. The original solvent volume at 23°C was obtained from the weight of water required to fill the NMR tube to the recorded level (ρ_{H2O} = 1.000 g mL^{-1}). This volume was then corrected for thermal expansion using X_T, and the initial concentration of the starting material ($[Ester]_\emptyset$) calculated as follows:

$$[Ester]_\emptyset = \frac{\text{moles of Betaine}}{(\text{Volume at } 23^\circ C) \times X_T}$$

During the run,

$$[Ester] = C \frac{I_E}{I_S}$$

$$C = \frac{I_S [Ester]_\emptyset}{I_E}$$

(a) Rate of Formation of 2-(Trimethylammoniomethyl)phenyl-methanesulfonate (55a) from Methyl 2-(Dimethylaminomethyl)-phenylmethanesulfonate (54a) in ($^2H_6$) Benzene at 110.0°C:

(i) "norbetylate": 2-(Methoxysulfonylmethyl)phenyl-N,N--dimethylmethanaminium trifluoromethanesulfonate(87a): 62 mg, 0.16 mmol.

Solution Volume (110.0°C): 329 μL (Volume at 23°C = 292 μL; X_T = 1.1243)

Yield of Betaine (55a): 25.5 mg, 0.105 mmol

$[54a]_0$ = 0.3190 M C = 6.156×10^{-2} M

1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[54a](M)	1/[54a](L mol^{-1})
0	22	114	0.319	3.1
20	34	81	0.147	6.8
40	55	91	0.102	9.8
60	56	75	0.082	12.1
80	62	65	0.065	15.5
100	62	55	0.055	18.3
120	63	47	0.046	21.8

$k_{obs} = 2.5 \times 10^{-3}$ L mol^{-1} s^{-1} (r_s = 0.9989)

(ii) "Norbetylate": 2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate(87a): 60 mg, 0.15 mmol.

Solution Volume (110.0°C) = 704 μL (Volume at 23°C = 626 μL; X_T = 1.1243)

Yield of Betaine (54a): 29.5 mg, 0.115 mmol

$[54a]_0$ = 0.1723 M C = 0.0475 M

1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[54a](M)	1/[54a](L mol^{-1})
0	27	98	0.172	5.8
10	35	100	0.136	7.4
30	42	88	0.100	10.1
50	54	90	0.079	12.6
75	70	89	0.060	16.6
100	67	69	0.049	20.5
125	67.5	60	0.042	23.7
150	62	47	0.036	27.8
180	66	41	0.030	33.9

k_{obs} = 2.5 x 10^{-3} L mol^{-1} s^{-1} (r = 0.9983)

(b) Rate of Formation of 2-(Trimethylammoniomethyl)phenylmethanesulfonate (55a) from Methyl 2-(Dimethylaminomethyl)-phenylmethanesulfonate (54a) in ($^2H_6$) Benzene at 91.0°C:

"Norbetylate": 2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesufonate(87a): 61.3 mg, 0.156 mmol.

Solution Volume (91.0°C): 623 μL (Volume at 23°C = 570 μL; X_T = 1.09328)

Yield of Betaine (55a): 34.2 mg; 0.139 mmol

$[54a]_0$ = 0.3190 M C = 0.0976 M

1,1,2,2-Tetrachloroethane: 20 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S (mm)	I_E (mm)	[54a](M)	1/[54a](L mol^{-1})
0	49	112	0.223	4.5
20	50	81	0.158	6.3
40	63	84	0.130	7.7
60	68	75	0.108	9.3
80	64	60	0.092	10.9
100	83	68	0.080	12.5
122	81	62	0.075	13.4
140	81	57	0.069	14.6
160	81	50	0.060	16.6
180	83	48	0.056	17.7
200	87	47	0.053	19.0
221	83	41	0.048	20.7

k_{obs} = 1.2 x 10^{-3} L mol^{-1} s^{-1} (r = .9986)

(c) Rate of Formation of 2-(Trimethylammoniomethyl)phenylmethanesulfonate (55a) from Methyl 2-(Dimethylaminomethyl)-phenylmethanesulfonate (54a) in ($^2H_6$) Benzene at 70.0°C:

"Norbetylate": 2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate(87a): 58.6 mg, 0.149 mmol.

Solution Volume (70.0°C): 602 µL (Volume at 23°C = 567 µL; X_T = 1.0618).

Yield of Betaine (55a): 32.0 mg, 0.132 mmol

$[54a]_0$ = 0.2185 M C = 0.06615 M

1,1,2,2-Tetrachloroethane: 15 µL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_s (mm)	I_E (mm)	[54a](M)	1/[54a](L mol^{-1})
0	33	109	0.219	4.6
38	31	94	0.201	5.0
111	47	99	0.139	7.2
245	65	98	0.100	10.0
360	65	81	0.082	12.1
450	64	70	0.072	13.8
550	69	65	0.062	16.1
655	71	57	0.053	18.8
765	70	52	0.049	20.4

$k_{obs} = 3.5 \times 10^{-4}$ L mol^{-1} s^{-1} (r = 0.9987)

(d) Rate of Formation of 2-(Trimethylammoniomethyl)phenylmethanesulfonate (55a) from Methyl 2-(Dimethylaminomethyl)-phenylmethanesulfonate (54a) in ($^2H_6$) Benzene at 37.0°C:

"Norbetylate": 2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate(87a): 72.8 mg, 0.185 mmol.

Solution Volume (37.0°C): 509 μL (Volume at 23°C = 500 μL; X_T = 1.0174)

Yield of Betaine (55a): 38.0 mg, 0.156 mmol

$[54a]_0$ = 0.3069 M C = 0.1083 M

1,1,2,2-Tetrachloroethane: 20 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[54a](M)	1/[54a](L mol^{-1})
0	36	102	0.307	3.3
4	43	100	0.252	4.0
14.5	58	91	0.170	5.9
49.5	92	72	0.085	11.8
63	91	58	0.069	14.5
82	92	48	0.057	17.7
112	89	35	0.043	23.5
140	85	28	0.036	28.0

k_{obs} = 4.9 x 10^{-5} L mol^{-1} s^{-1} (r = 0.9998)

(e) Rate of Formation of 2-[($^2H_3$)Methyldimethylammoniomethyl]phenylmethanesulfonate(55b) from ($^2H_3$)Methyl 2-(Dimethylaminomethyl)phenylmethanesulfonate (54b) in ($^2H_6$) Benzene at 110.0°C:

"Norbetylate": 2-[($^2H_3$)Methoxysulfonylmethyl]phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate(87b): 59 mg, 0.149 mmol.

Solution Volume (110.0°C): 381 μL (Volume at 23°C = 339 μL; X_T = 1.1243)

Yield of Betaine (55b): 26.1 mg, 0.106 mmol

$[54b]_0$ = 0.2781 M C = 0.05285 M

1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[54b](M)	1/[54b](L mol^{-1})
0	19	100	0.278	3.5
20	29.5	76	0.136	7.3
40	51	91	0.094	10.6
60	49	68	0.073	13.6
80	53	57	0.057	17.6
100	54	49	0.048	20.9
120	54	42	0.041	24.3

k_{obs} = 2.9 x 10^{-3} L mol^{-1} s^{-1} (r = 0.9997)

(f) Rate of Formation of 2-[Di($^2H_3$)methylmethylammonio-methyl]phenylmethanesulfonate(55c) from Methyl 2-[Di($^2H_3$)-methylaminomethyl)phenylmethanesulfonate (54c) in ($^2H_6$) Benzene at 110.0°C:

"Norbetylate": 2-(Methoxysulfonylmethyl)phenyl-N,N-di-($^2H_3$)methylmethanaminium trifluoromethanesulfonate(87c): 66 mg, 0.165 mmol.

Solution Volume (110.0°C): 573 µL (Volume at 23°C = 510 µL; X_T = 1.1243)

Yield of Betaine (55c): 28.9 mg, 0.116 mmol

$[54c]_0$ = 0.2023 M C = 0.1116 M

1,1,2,2-Tetrachloroethane: 5 µL

Peak Monitored: δ = 3.3 ppm, s, 3H($-SO_3-CH_3$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[54c](M)	1/[54c](L mol^{-1})
0	32	58	0.202	4.9
20	50	53	0.118	8.5
40	55	38	0.077	13.0
60	83	44	0.059	16.9
80	93	43	0.052	19.4
100	90	33	0.041	24.4
120	78	24.5	0.035	28.5

k_{obs} = 3.3 x 10^{-3} L mol^{-1} s^{-1} (r = 0.9982)

Run (ii)

"Norbetylate" (87c): 63.4 mg, 0.159 mmol.

Solution Volume (110.0°C): 596 μL (Volume at 23°C = 530 μL; X_T = 1.1243)

Yield of Betaine (55c): 28.6 mg, 0.115 mmol

$[54c]_0$ = 0.1925 M C = 0.1892 M

1,1,2,2-Tetrachloroethane: 8 μL

Peak Monitored: δ = 3.3 ppm, s, 3H($-SO_3-CH_3$)

Kinetic Data:

Time (min)	I_s (mm)	I_E (mm)	[54c](M)	1/[54c](L mol^{-1})
0	57	58	0.193	5.2
20	79	45	0.108	9.3
35	97	44	0.086	11.7
45	98	35	0.068	14.8
63	102	32	0.059	16.9
75	100	27	0.051	19.6
92.5	100	24	0.045	22.0
105	106	21	0.038	26.7
120	97	17	0.033	30.2

k_{obs} = 3.4×10^{-3} L mol^{-1} s^{-1} (r= 0.9947)

(g) Rate of Formation of 2-[Tri($^2H_3$)methylammoniomethyl)-phenylmethanesulfonate(55d) from ($^2H_3$)Methyl 2-[Di($^2H_3$)-methylaminomethyl]phenylmethanesulfonate (54d) in ($^2H_6$) Benzene at 110.0°C:

"Norbetylate": 2-[($^2H_3$)Methoxysulfonylmethyl]phenyl-N,N-di-($^2H_3$)methylmethanaminium, trifluoromethanesulfonate(87d): 66 mg, 0.164 mmol.

Solution Volume (110.0°C): 514 µL (Volume at 23°C = 457 µL; X_T = 1.1243)

Yield of Betaine (55d): 32.8 mg, 0.130 mmol

$[54d]_0$ = 0.2529 M C = 0.06323 M

1,1,2,2-Tetrachloroethane: 5 µL

Peak Monitored: δ = 3.5 ppm, s, 2H(R-CH_2-N)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[54d](M)	1/[54d](L mol^{-1})
0	20	80	0.253	4.0
20	29	70	0.153	6.6
40	30	43	0.091	11.0
60	22	27	0.078	12.9
80	30	29.5	0.062	16.1
100	29	22	0.048	20.5
120	30	19	0.040	25.0

k_{obs} = 2.9 x 10^{-3} L mol^{-1} s^{-1} (r = 0.9944)

(h) Rate of Formation of 2-[2-(Trimethylammoniomethyl)-phenyl]ethanesulfonate (57a) from Methyl 2-[2-(Dimethylaminomethyl)phenyl]ethanesulfonate (56a) in ($^2H_6$) Benzene at 110.0°C:

(i) "Norbetylate": 2-[2-(Methoxysulfonyl)ethyl]phenyl-N,N-dimethylmethanaminium 4-methylbenzenesulfonate(111a): 50.2 mg, 0.117 mmol.

Solution Volume (110.0°C): 717 μL (Volume at 23°C = 638 μL; X_T = 1.1243)

Yield of Betaine (57a): 22.9 mg, 0.195 mmol

$[56a]_0$ = 0.1241 M C = 0.07420 M

1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[56a](M)	1/[56a](L mol^{-1})
0	52	87	0.124	8.1
20	66	90	0.101	9.9
40	84	96	0.085	11.8
60	89	81	0.068	14.8
80	84	72	0.064	15.7
100	88	63	0.053	18.8
120	81	53	0.049	20.6
140	86	50	0.043	23.2
160	84	42	0.037	27.0

k_{obs} = 1.9 x 10^{-3} L mol^{-1} s^{-1}

(ii) "Norbetylate" (111a): 60.0 mg, 0.140 mmol.

Solution Volume (110.0°C): 503 μL (Volume at 23°C = 447 μL; X_T = 1.1243)

Yield of Betaine (57a): 17.1 mg, 0.0655 mmol

$[56a]_0$ = 0.1321 M C = 0.03844 M

1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S (mm)	I_E (mm)	[56a](M)	1/[56a](L mol^{-1})
0	32	110	0.132	7.6
10	35	106	0.116	8.6
30	42	104	0.095	10.5
50	51	106	0.080	12.5
75	57	91	0.061	16.3
100	74	95	0.049	20.3
125	74	81	0.042	23.8
150	66	67	0.039	25.6
180	67	60	0.034	29.1

k_{obs} = 2.1 x 10^{-3} L mol^{-1} s^{-1} (r = 0.9970)

(i) Rate of Formation of 2-[2-(Trimethylammoniomethyl)-phenyl]ethanesulfonate (57a) from Methyl 2-[2-(Dimethylaminomethyl)phenyl]ethanesulfonate (56a) in ($^2H_6$) Benzene at 92.0°C:

"Norbetylate": 2-[2-(Methoxysulfonyl)ethyl]phenyl-N,N-dimethylmethanaminium 4-methylbenzenesulfonate(111a): 70 mg, 0.163 mmol.

Solution Volume (92.0°C): 718 μL (Volume at 23°C = 656 μL; X_T = 1.09484)

Yield of Betaine (57a): 32.5 mg, 0.1263 mmol

$[56a]_0$ = 0.1759 M C = 0.05244 M

1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[56a](M)	1/[56a](L mol^{-1})
0	31	104	0.176	5.7
15	33	97	0.154	6.5
30	33	86	0.137	7.3
45	43.5	105	0.127	7.9
60	41	93	0.119	8.4
75	46.5	98	0.111	9.1
90	47	103	0.115	8.7
105	50	98	0.103	9.7
120	48	92	0.101	10.0
135	50	91	0.095	10.5
150	52	86	0.087	11.5
165	48	80	0.087	11.4
180	48	77	0.084	11.9

k_{obs} = 5.5 x 10^{-4} L mol^{-1} s^{-1} (r = 0.9881)

(j) Rate of Formation of 2-[2-(Trimethylammoniomethyl)-phenyl]ethanesulfonate (57a) from Methyl 2-[2-(Dimethylaminomethyl)phenyl]ethanesulfonate (56a) in ($^2H_6$) Benzene at 60.0°C:

"Norbetylate": 2-[2-(Methoxysulfonyl)ethyl]phenyl-N,N-dimethylmethanaminium 4-methylbenzenesulfonate(111a): 54.9 mg, 0.128 mmol.

Solution Volume (60.0°C): 553 µL (Volume at 23°C = 528 µL; X_T = 1.04776)

Yield of Betaine (57a): 30.6 mg, 0.1189 mmol

$[56a]_0$ = 0.2151 M C = 0.1112 M

1,1,2,2-Tetrachloroethane: 15 µL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S (mm)	I_E (mm)	[56a](M)	1/[56a](L mol^{-1})
0	45	87	0.215	4.7
7.5	59	77	0.145	6.9
17.6	86	92	0.119	8.4
24.2	67	61	0.101	9.9
32.0	75	58	0.086	11.6
41.0	80	47	0.065	15.3
47.5	72	41	0.063	15.8
55	77	38	0.055	18.2
66.5	77	31	0.045	22.3

k_{obs} = 7.2 x 10^{-5} L mol^{-1} s^{-1} (r = 0.9932)

(k) Rate of Formation of 2-[2-(Trimethylammoniomethyl)-phenyl]ethanesulfonate (57a) from Methyl 2-[2-(Dimethylaminomethyl)phenyl]ethanesulfonate (56a) in ($^2H_6$) Benzene at 37.0°C:

"Norbetylate": 2-[2-(Methoxysulfonyl)ethyl]phenyl-N,N-dimethylmethanaminium 4-methylbenzenesulfonate(111a): 55 mg, 0.128 mmol.

Solution Volume (37.0°C): 672 μL (Volume at 23°C = 661 μL; X_T = 1.01738)

Yield of Betaine (57a): 26.5 mg, 0.1030 mmol

$[56a]_0$ = 0.1533 M C = 0.05169 M

1,1,2,2-Tetrachloroethane: 15 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S (mm)	I_E (mm)	[56a](M)	1/[56a](L mol^{-1})
0	29	86	0.153	6.5
27	34	95	0.144	6.9
41	40	103	0.133	7.5
55	36	84	0.121	8.3
88.5	45	95	0.109	9.2
112.5	38	74	0.101	9.9
142	45	81	0.093	10.8
192	57	98	0.089	11.3
210	58	90	0.080	12.5
259.5	68	84	0.064	15.7

k_{obs} = 8.9 x 10^{-6} L mol^{-1} s^{-1} (r = 0.9789)

(1) Rate of Formation of 2-[2-(($^2H_3$)Methyldimethylammoniomethyl)phenyl]ethanesulfonate (57b) from ($^2H_3$)Methyl 2-[2-(Dimethylaminomethyl)phenyl]ethanesulfonate (56b) in ($^2H_6$) Benzene at 110.0°C:

"Norbetylate": 2-[2-(($^2H_3$)Methoxysulfonyl)ethyl]phenyl-N,N-dimethylmethanaminium 4-methylbenzenesulfonate(111b): 56.5 mg, 0.131 mmol.

Solution Volume (110.0°C): 713 μL (Volume at 23°C = 634 μL; X_T = 1.1243)

Yield of Betaine (57b): 29.9 mg, 0.1149 mmol

$[56b]_0$ = 0.1611 M C = 0.0707 M

1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 2.0 ppm, s, 6H($-N(CH_3)_2$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[56b](M)	1/[56b](L mol^{-1})
0	50	114	0.161	6.2
20	65	101	0.110	9.1
40	66	85	0.091	11.0
60	83	91	0.078	12.9
80	80	74	0.065	15.3
100	83	63	0.054	18.7
120	82	57	0.049	20.4
140	83	51	0.043	23.0
160	81	45	0.039	25.5
180	83	40	0.034	29.4

k_{obs} = 2.1 x 10^{-3} L mol^{-1} s^{-1} (r = 0.9973)

(m) Rate of Formation of 2-[2-(Di($^2H_3$)methyl-N-methylammonio-methyl)phenyl]ethanesulfonate (57c) from Methyl 2-[2-(Di-($^2H_3$)methylaminomethyl)phenyl]ethanesulfonate (56c) in ($^2H_6$) Benzene at 110.0°C:

"Norbetylate": 2-[2-(Methoxysulfonyl)ethyl]phenyl-N,N-di-($^2H_3$)methylmethanaminium 4-methylbenzenesulfonate(111c): 55.7 mg, 0.128 mmol.

Solution Volume (110.0°C): 686 μL (Volume at 23°C = 610 μL; X_T = 1.1243)

Yield of Betaine (57c): 28.2 mg, 0.1071 mmol

$[56c]_0$ = 0.1561 M C = 0.04990 M

1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 3.2-3.3 m, m, 4H($Ph-CH_2-CH_2-SO_2-$)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[56c](M)	1/[56c](L mol^{-1})
0	31	97	0.156	6.4
20	41	96	0.117	8.6
40	65	115	0.088	11.3
60	62	93	0.075	13.4
80	83	104	0.063	16.0
100	80	90	0.056	17.8
120	85	80	0.047	21.3
140	79	75	0.047	21.1
160	78	63	0.040	24.8

$k_{obs} = 1.9 \times 10^{-3}$ L mol^{-1} s^{-1} (r = 0.9946)

(n) Rate of Formation of 2-[2-(Tri($^2H_3$)methylammoniomethyl)-phenyl]ethanesulfonate (57d) from ($^2H_3$)Methyl 2-[2-(Di($^2H_3$)-methylaminomethyl)phenyl]ethanesulfonate (56d) in ($^2H_6$) Benzene at 110.0°C:

"Norbetylate": 2-[2-(($^2H_3$)Methoxysulfonyl)ethyl]phenyl-N,N-di($^2H_3$)methylmethanaminium 4-methylbenzenesulfonate(111c): 53.5 mg, 0.122 mmol.

Solution Volume (110.0°C): 671 μL (Volume at 23°C = 597 μL; $\bar{X}_T$ = 1.1243)

Yield of Betaine (57d): 28.4 mg, 0.1066 mmol

$[56d]_0$ = 0.1589 M C = 0.05921 M

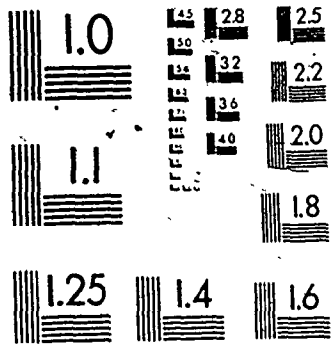
1,1,2,2-Tetrachloroethane: 10 μL

Peak Monitored: δ = 3.2-3.3 ppm, m, 4H(Ph-CH_2-CH_2-SO_2-)

Kinetic Data:

Time (min)	I_S(mm)	I_E(mm)	[56d](M)	1/[56d](L mol^{-1})
0	38	102	0.159	6.3
20	46	96	0.124	8.1
40	63	104	0.098	10.2
60	58	79	0.081	12.4
80	61	66	0.064	15.6
100	60	55	0.054	18.4
120	59	49	0.049	20.3
140	61	43	0.042	24.0
160	59	37	0.037	26.9
180	57	33	0.034	29.2

k_{obs} = 2.2 x 10^{-3} L mol^{-1} s^{-1} (r = 0.99761)


1.0
1.1
1.25
1.4
1.6
2.8
3.2
3.6
4.0
2.5
2.2
2.0
1.8

(o) Rate of Methylation of Benzyldimethylamine (129) with Methyl Phenylmethanesulfonate (128) in ($^2H_6$) Benzene at 110.0°C:

A solution of benzyldimethyamine (129, 118.3 mg, 0.875 mmol) and 1,1,2,2 tetrachloroethane (50 µL) in ($^2H_6$)benzene was prepared in a 5.0 mL volumetric flask then used to fill a 1.0 mL volumetric flask which contained methyl phenylmethanesulfonate (128, 28.6 mg, 0.154 mmol). The latter solution was transferred to an NMR tube which was then sealed at -78°C under nitrogen. After an NMR spectrum was obtained, the tube was immersed in a 110°C oil bath for 15 min. A second NMR spectrum indicated that the reaction was approximately 90% complete. The initial concentrations of 129 and 128 were those prepared corrected for thermal expansion (X_T = 1.1243). The final concentrations of 129 and 128 were obtained by comparison for the integral for the peak assigned to the aminomethyls in 129 (I_A, δ= 2.0 ppm, s, 6H) and that of the ∝-sulfonyl methylene in 128 (I_E, δ= 3.8 ppm, s, 2H) with that of 1,1,2,2-tetrachloroethane (I_S, =5.0 ppm, s). From the first NMR spectrum;

$$[129]_0 = 0.0508 \frac{I_A}{I_S} \text{ and } [128]_0 = 0.1633 \frac{I_E}{I_S}$$

Kinetic Data

Time (min)	I_S (mm)	I_A (mm)	I_E (mm)	[129](M)	[128](M)	$\frac{\ln([129]/[128])}{[129]_0-[128]_0}$
0	31	95	26	0.137	0.156	6.8
15	33	20	2	0.010	0.031	60.7

k_{obs} 6×10^{-2} L mol^{-1} s^{-1}

(p) Rate of Methylation of Phenyl 2-(Dimethylaminomethyl)phenylmethanesulfonate (131) with Methyl Phenylmethanesulfonate (128) in ($^2H_6$)Benzene at 110.0°C:

A solution of phenyl 2-(dimethylaminomethyl)phenylmethanesulfonate (131, 61 mg, 0.20 mmol) and p-di-t-butylbenzene (5 mg) in ($^2H_6$)benzene was prepared in a 1.0 mL volumetric flask. Approximately half was transferred to an NMR tube which contained methyl phenylmethanesulfonate (128, 23.8 mg, 0.13 mmol). The tube was then sealed at -78°C under nitrogen. The sample was handled during the kinetic run using the method described in the general procedure for Run B1 through Run B14. The reaction was monitored by comparison of the integral for the aminomethyl peak from 131 (I_A, δ = 2.0 ppm, s, 6H) with that of the t-butyl peak from p-di-t-butylbenzene (I_S, δ = 1.4, s, 18H). The initial concentration of 128 was simply that prepared corrected for solvent expansion (X_T = 1.1243).

$$[131] = C \frac{I_A}{I_S}$$

from t = 0, C = 5.930×10^{-2}

at t = ∞, [131] = 0.0419 M

$\therefore$ [128] = [131] - 0.0419 M

Kinetic Data

Time (min)	I_s (mm)	I_A (mm)	[131]	[128]	$\frac{\ln([131]/[128])}{[131]_0 - [128]_0}$
0	17	51	0.178	0.136	6.4
20	25	53	0.126	0.086	9.7
40	31	53	0.101	0.060	12.7
60	33	49	0.088	0.046	15.4
80	34	43	0.075	0.033	19.5
100	31	41	0.074	0.032	20.1
120	34	39	0.068	0.026	22.9
∞	34	24	0.042	0	-

$k_{obs} = 2.3 \times 10^{-3}$ L mol^{-1} s^{-1} ($r = 0.9914$)

(q) Rate of Methylation of Phenyl 2-(Dimethylaminomethyl)-phenylmethanesulfonate (131) with Methyl 2-(Methoxymethyl)-phenylmethanesulfonate (134) in ($^2H_6$)Benzene at 110.0°C:

A solution of phenyl 2-(dimethylaminomethyl)phenylmethanesulfonate (131, 61 mg, 0.20 mmol) and p-di-t-butylbenzene (7.6 mg) in ($^2H_6$)benzene was prepared in a 1.0 mL volumetric flask then dispensed equally into two NMR tubes each containing methyl 2-(methoxymethyl)phenylmethanesulfonate (134, 18 mg, 0.078 mmol for Run (i) 31 mg 0.135 mmol, for Run (ii)). The tubes were then sealed at -78°C under nitrogen. The samples were manipulated during the kinetic runs using the method described in the general procedure for Run 2(a) through Run 2(n). In both runs, the initial concentration of 131 was that prepared corrected by division by X_T. Both reactions were followed by comparison of the integral for the aminomethyl peak from 131 (I_A, δ= 2.0 ppm, s, 6H) with that of the t-butyl peak from p-di-t-butylbenzene (I_S, δ= 1.4 ppm, s, 18H)

Run (i)

$$[131] = C \frac{I_A}{I_S}$$

from t = 0, C = 0.1198 M

$$[131]_\infty = 0.0503 \text{ M}$$

$$\therefore [134] = [131] - 0.0503 \text{ M}$$

Kinetic Data

Time (min)	I_S (mm)	I_A (mm)	[131]	[134]	$\frac{\ln([131]/[134])}{[131]_0-[134]_0}$
0	66	98	0.178	0.128	6.6
20	70	74	0.127	0.076	10.1
40	88	75	0.102	0.052	13.5
60	110	80	0.087	0.037	17.1
80	116	74	0.076	0.026	21.4
100	89	53	0.071	0.021	24.3
120	115	63	0.066	0.015	28.9
	100	42	0.050	-	-

$k_{obs} = 3.1 \times 10^{-3}$ L mol^{-1} s^{-1} ($r = 0.9991$)

Run (ii)

$[131] = C \frac{I_A}{I_S}$

from t = 0, C = 0.1241 M

For [134], the integral obtained from the peaks from the benzylic methylenes in 134 (δ = 4.4 ppm, s, 2H and δ = 4.6 ppm, s, 2H), 65 mm, was compared with that of the amino methyls in 131, 76 mm, at t = 0.

$[134]_0 = \frac{(65/4)}{(76/6)} [131]_0 = 0.2282$ M

[134] = [131] + 0.0503 M

Kinetic Data

Time (min)	I_S(mm)	I_A(mm)	[131]M	[134]M	$\frac{\ln([134]/[131])}{[134]_0-[131]_0}$
0	53	76	0.178	0.228	5.0
20	89	67	0.093	0.144	8.6
40	111	51	0.057	0.107	12.6
60	117	37	0.039	0.090	16.4
80	113	27.5	0.030	0.081	19.5
100	116	19	0.020	0.071	24.8
120	117	14	0.015	0.065	29.4

$k_{obs} = 3.4 \times 10^{-3}$ L mol^{-1} s^{-1} (r = 0.9977)

D. Deuterated Methyl Crossing and Related Control Experiments

1. Mass Spectrometric Methods

This section of the experimental contains numerous mass spectra of mixtures of N,N-dimethylmethanamine (**69a**, d_0), N,N-dimethyl($^2H_3$)methanamine (**69b**, d_3), N,N-di($^2H_3$)methylmethanamine (**69c**, d_6) and N,N-di($^2H_3$)methyl($^2H_3$)methanamine (**69d**, d_9). These mixtures were prepared by preparative thermolysis of mixtures of 4-(trimethylammonio)-1-butanesulfonate (**53a**) and its deuterio methyl isomers (**53b,c** and **d**) or by thermolysis in the probe of the mass spectrometer of mixtures of 2-(trimethylammoniomethyl)phenylmethanesulfonate (**55a**) and its deuterio methyl isomers (**55b,c** and **d**) or 2-[2-(trimethylammoniomethyl)phenyl]ethanesulfonate (**57a**) and its deuterio methyl isomers (**57b,c** and **d**). The spectra were obtained using an ionization energy of 18 ev at a resolution of approximately 1,000. The range from m/e equals 57 to 69 was scanned repeatedly with each scan being recorded on Kodak Lithographic paper. The peak heights were measured with a ruler calibrated to 1mm and summed for each m/e. The full spectrum of the mixture obtained from Butane Derivative Crossing Experiment 3 is shown below as a typical spectrum.

m/e / Scan #	Peak Heights (mm) 1	2	3	4	5	Total
58	58	57.5	58	56	54	283.5
59	117	113	113	114	113	570
60	21	20	21	20	20	102
61	58	56	54	54	53	275
62	134	132	134	129	127	656
63	34	36	37	33	34	174
64	34	35	34	32	32	167
65	118	113	113	110	108	562
66	47	46	46	43	45	227
67	6	7	6	6	5	30
68	90	88	89	86	83	436
69	3	3	3	4	3	16

The sums were processed using the computer program MSP2 which is described in detail in Appendix 1. The program normalizes the spectrum, removes overlaps occurring between amine peaks, calculates the sum of the peak heights for each amine then calculates the percent excess of $\underline{d}_0$ and $\underline{d}_9$ (or $\underline{d}_3$ and $\underline{d}_6$) as defined by the following equations:

$$F_a = \%\ \text{excess}\ \underline{d}_0,\ \underline{d}_9 = 100 \left[\frac{(\underline{d}_0 + \underline{d}_9) - (\underline{d}_3 + \underline{d}_6)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \qquad (14)$$

or

$$F_b = \%\ \text{excess}\ \underline{d}_3,\ \underline{d}_6 = 100 \left[\frac{(\underline{d}_3 + \underline{d}_6) - (\underline{d}_0 + \underline{d}_9)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_c + \underline{d}_9}\right] \qquad (24)$$

The example shown above yields the following normalized spectrum and relative abandances.

m/e	Intensity	Amine Product Ratio
58	49.7	
59	100.0	$\underline{d}_0$ = 100.0
60	17.9	
61	48.2	
62	115.1	$\underline{d}_3$ = 118.2
63	30.5	
64	29.3	
65	98.6	$\underline{d}_6$ = 102.3
66	39.8	
67	5.3	
68	76.5	$\underline{d}_9$ = 79.9
69	2.8	

F_a = -28.0 % excess $\underline{d}_0$, $\underline{d}_9$

In this section, the normalized spectra, the relative abundances of the amines and the percent excess $\underline{d}_0$, $\underline{d}_9$ (or $\underline{d}_3$, $\underline{d}_6$) are reported for each of the thermolyses.

Authentic Samples:

(i) Trimethylamine

A sample of commercial trimethylamine (Eastman) was distilled at room temperature into the probe of the mass spectrometer. The following spectrum was obtained:

m/e	Intensity (10 scans)
57	0
58	21.0
59	100.0
60	6.2
61	0

(ii) Trimethylammonium Chloride

Anhydrous hydrochloric acid was bubbled into trimethyl-

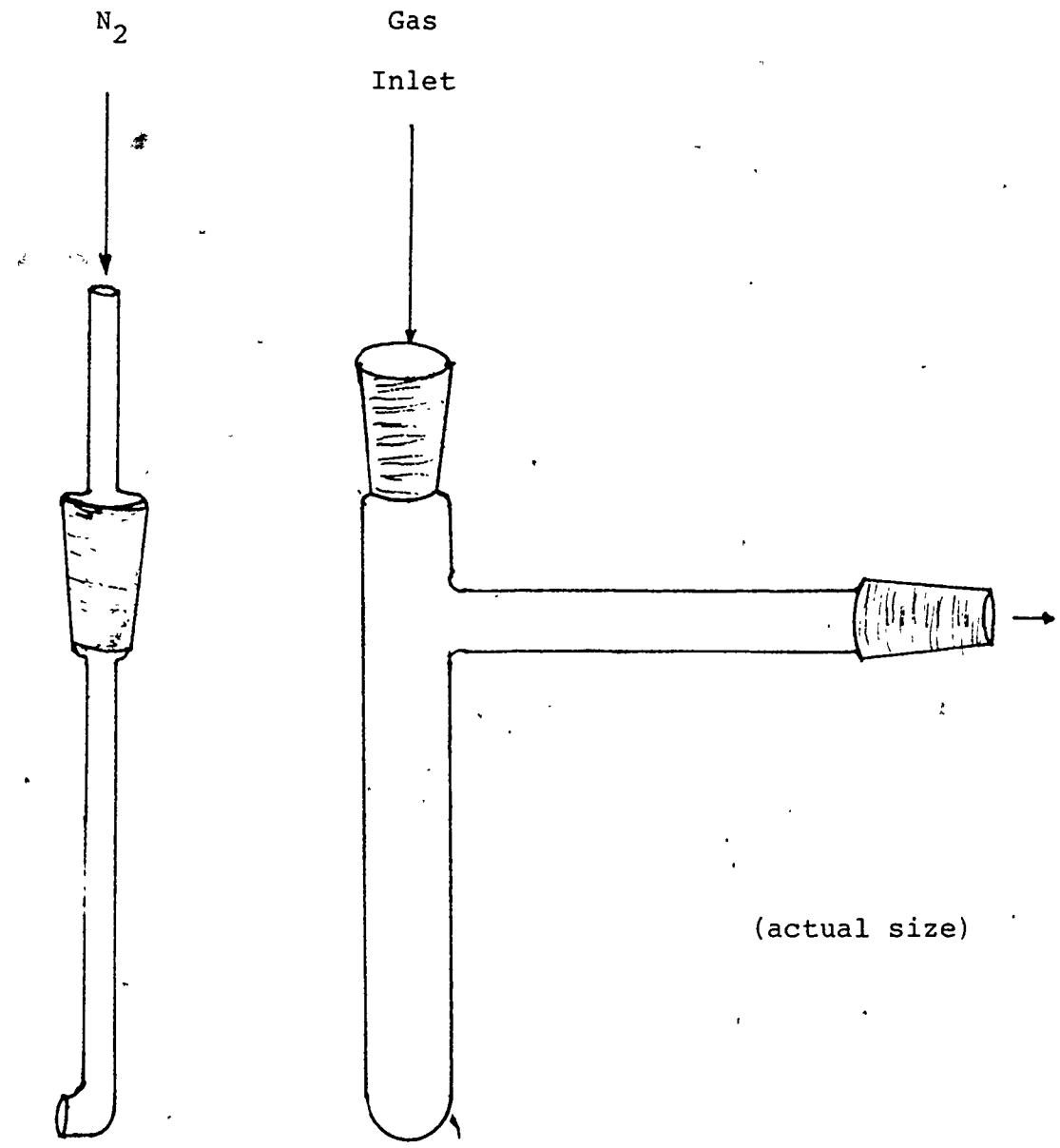


Figure 16

Preparative Betaine Thermolysis Apparatus

amine in anhydrous ether at 0°C. The white precipitate was collected by filtration, azeotroped to dryness with benzene, and injected, as a concentrated methanol solution, into the probe (at 60.0°C) of the mass spectrometer. The following spectrum was obtained:

m/e	Intensity (10 scans)
57	0
58	55.3
59	100.0
60	4.2
61	0

2. Butane Derivatives:

General Thermolysis Procedures:

A concentrated methanol solution of the betaine was evaporated to dryness in the reaction vessel shown in Figure 16. The appropriate trap was then connected to the apparatus. With nitrogen being slowly passed through the apparatus, the reaction vessel was heated with a 340°C Wood's metal bath for approximately 20 min. (10.0 min. for Method B). During the thermolysis, the contents of the reaction vessel slowly changed from a white crystalline solid to a brown oil containing a suspended black amorphous solid.

Method A: The effluent gas was passed through a U-tube equipped with a stopcock at each end. The U-tube was cooled with frozen pentane during the thermolysis. After, the stopcocks were closed and the apparatus dismantled. The contents of the U-tube were then distilled at room temper-

ature into the probe of the mass spectrometer.

Method B: The effluent gas and anhydrous hydrochloric acid were bubbled simultaneously through a methanol trap (25 mL) which was cooled to -78°C with a dry-ice-acetone bath. After the thermolysis, the methanol was removed by evaporation. Benzene was added and then removed by evaporation to give trimethylamine hydrochloride as a hydroscopic white solid. A concentrated methanol solution of this material was injected into the probe of the mass spectrometer which was thermally equilibrated at 60°C.

Method C: The effluent gas was bubbled through a 0°C saturated solution of picric acid in anhydrous ether (50 mL). The resulting yellow precipitate was collected by filtration.

Thermolysis of 4-(Trimethylammonio)-1-butanesulfonate (**53a**)

Product Characterization

A sample of 4-(trimethylammonio)-1-butanesulfonate (**53a**,100 mg) was thermolyzed using Method C. The crude yellow precipitate (41 mg, 30%) was recrystallized from absolute alcohol to give trimethylammonium picrate as yellow needles. mp 214-215°C (lit[113] mp = 216°C). An authentic sample of trimethylammonium picrate (prepared from Eastman trimethylamine and picric acid then purified by recrystallization from absolute alcohol), when mixed with the above thermolysis product, showed no melting point depression. The residue in the reaction vessel was extracted with C_DCl_3 and the extract gave an ^1H NMR spectrum identical to that

obtained from an authentic sample of 1,4-butane sultone.

Method A Thermolysis:

Two thermolyses using Method A gave the following mass spectra:

1.

m/e	Intensity	(10 scans)
57	0	
58	22.5	
59	100.0	
60	5.6	
61	0	

2.

m/e	Intensity	(10 scans)
57	0	
58	20.9	
59	100.0	
60	4.2	
61	0	

Method B Thermolysis:

A thermolysis using Method B gave trimethylammonium chloride which gave the following mass spectrum:

m/e	Intensity	(10 scans)
57	0	
58	69.9	
59	100.0	
60	4.2	
61	0	

Thermolysis of 4-(Di($^2H_3$)methyl)ammonio-1-butanesulfonate (53c)

The Method A thermolysis of 4-(Di($^2H_3$)methyl)ammonio-1--butanesulfonate (**53c**,100 mg) was performed in duplicate.

The following mass spectra were obtained:

(a)	m/e	Intensity	(10 scans)
	58	1.0	
	59	2.2	$\underline{d}_0$ = 2.7
	60	0.5	
	61	1.5	
	62	9.6	$\underline{d}_3$ = 9.7
	63	7.2	
	64	10.4	
	65	100.0	$\underline{d}_6$ = 100.0
	66	6.3	
	67	0.9	
	68	11.1	$\underline{d}_9$ = 12.7
	69	0.8	

(b)	m/e	Intensity	(10 scans)
	58	1.2	
	59	0	$\underline{d}_0$ = 1.0
	60	1.3	
	61	0	
	62	13.2	$\underline{d}_3$ = 13.5
	63	2.6	
	64	5.3	
	65	100.0	$\underline{d}_6$ = 100.0
	66	4.6	
	67	1.1	
	68	13.1	$\underline{d}_9$ = 14.6
	69	1.1	

Authentic Mixtures Control Experiments

In the first two control experiments, the betaines, in the amounts indicated, were dissolved in methanol and evaporated to dryness. The residue was thermolyzed by Method B to give the amine hydrochloride in the indicated yield. For the remaining control experiments, two mixtures were prepared. 4-(Trimethylammonio)-1-butanesulfonate (**53a**, 48.8 mg), 4-(($^2H_3$)methyldimethylammonio)-1-butanesulfonate (**53b**, 49.6 mg), 4-(di($^2H_3$)methyl-N-methylammonio)-1-butanesulfonate (**53c**, 50.3 mg) and 4-(tri($^2H_3$)methylammonio-1-butanesulfonate (**53d**, 51.1 mg) were dissolved in methanol (10 mL). Evaporation to dryness gave a 1:1:1:1-d_0:d_3:d_6:d_9 authentic sample. Similarly, a 1:0:0:1-d_0:d_3:d_6:d_9 sample was prepared from **53a** (24.2 mg) and **53d** (25.3 mg). The indicated amounts of these mixtures were combined, dissolved in methanol, evaporated to dryness and then thermolyzed by Method B to give the amine hydrochloride in the indicated yield.

In the ensuing tables the compositions of the authentic mixtures are expressed as % excess d_0, d_9 as defined by equation (13).

$$C_a = 100 \left[\frac{(\mathbf{53a} + \mathbf{53d}) - (\mathbf{53b} + \mathbf{53c})}{\mathbf{53a} + \mathbf{53b} + \mathbf{53c} + \mathbf{53d}}\right] \qquad (13)$$

Control Experiment 1:

C_a = 100% excess d_0, d_9

Mixture: **53a**(d_0): 39 mg

53d(d_9): 42 mg

Thermolysis yield: 17 mg

Mass spectrum

m/e	Intensity	(3 scans)
58	37.3	
59	100.0	d_0 = 100
60	6.7	
61	5.4	
62	16.2	d_3 = 17.8
63	4.0	
64	3.7	
65	15.6	d_6 = 15.7
66	26.2	
67	3.8	
68	70.9	d_9 = 74.6
69	3.7	

F_a = 67.8% excess d_0, d_9

Control Experiment 2:

C_a = 100% excess $\underline{d_0}$, $\underline{d_9}$

Mixture: **53a**($\underline{d_0}$): 39 mg

53d($\underline{d_9}$): 42 mg

Thermolysis yield: 8 mg

Mass spectrum

m/e	Intensity	(5 scans)
58	50.1	
59	100.0	$\underline{d_0}$ = 100
60	6.3	
61	8.4	
62	19.1	$\underline{d_3}$ = 20.0
63	5.7	
64	5.6	
65	19.0	$\underline{d_6}$ = 18.9
66	38.1	
67	4.7	
68	79.7	$\underline{d_9}$ = 82.1
69	3.1	

F_a = 64.8% excess $\underline{d_0}$, $\underline{d_9}$

Control Experiment 3:

C_a = Ø% excess $\underline{d}_Ø$, $\underline{d}_9$

Mixture: 1:1:1:1-$\underline{d}_Ø$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$: 3Ø mg

Thermolysis yield: 8 mg

Mass spectrum

m/e	Intensity	(4 scans)
58	43.1	
59	1ØØ.Ø	$\underline{d}_Ø$ = 1ØØ
6Ø	15.8	
61	4Ø.3	
62	115.2	$\underline{d}_3$ = 116.9
63	28.3	
64	26.5	
65	1Ø3.4	$\underline{d}_6$ = 1Ø7.1
66	37.1	
67	4.9	
68	83.4	$\underline{d}_9$ = 85.8
69	3.Ø	

F_a = -9.3% excess $\underline{d}_Ø$, $\underline{d}_9$

Control Experiment 4:

C_a = 0% excess d_0, d_9

Mixture: 1:1:1:1-d_0:d_3:d_6:d_9: 30 mg

Thermolysis yield: 5 mg

Mass spectrum

m/e	Intensity	(4 scans)
58	45.3	
59	100.0	d_0 = 100
60	16.4	
61	43.1	
62	114.2	d_3 = 116.7
63	30.7	
64	28.2	
65	102.4	d_6 = 107.5
66	39.2	
67	4.8	
68	80.1	d_9 = 83.8
69	3.2	

F_a = -9.9% excess d_0, d_9

Control Experiment 5:

C_a = 9.1% excess d_0, d_9

Mixture: 1:1:1:1-d_0:d_3:d_6:d_9: 30 mg

1:0:0:1-d_0:d_3:d_6:d_9: 3 mg

Thermolysis yield: 6 mg

Mass spectrum

m/e	Intensity	(4 scans)
58	42.3	
59	100.0	d_0 = 100
60	12.5	
61	30.5	
62	89.1	d_3 = 90.1
63	20.5	
64	18.6	
65	77.0	d_6 = 78.7
66	32.1	
67	3.6	
68	74.5	d_9 = 76.3
69	2.6	

F_a = 2.2% excess d_0, d_9

Control Experiment 6:

C_a = 16.7% excess $\underline{d}_0$, $\underline{d}_9$

Mixture: 1:1:1:1-$\underline{d}_0$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$: 30 mg

1:0:0:1-$\underline{d}_0$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$: 6 mg

Thermolysis yield: 5.5 mg

Mass spectrum

m/e	Intensity	(4 scans)
58	31.0	
59	100.0	$\underline{d}_0$ = 100
60	9.5	
61	21.1	
62	80.9	$\underline{d}_3$ = 82.1
63	14.0	
64	13.1	
65	69.4	$\underline{d}_6$ = 70.9
66	23.0	
67	3.4	
68	72.4	$\underline{d}_9$ = 74.2
69	2.8	

F_a = 6.5% excess $\underline{d}_0$,$\underline{d}_9$

Crossing Experiments

Stock Solution Preparation:

A mixture of 4-(methoxysulfonyl)-N,N-dimethyl-1-butanaminium trifluoromethanesulfonate (**65a**, 431 mg, 1.25 mmol) and 4-(($^2H_3$)methoxysulfonyl)-N,N-di($^2H_3$)methyl-1-butanaminium trifluoromethanesulfonate (**65d**, 445 mg, 1.25 mmol) was shaken in ice-cold saturated aqueous sodium carbonate (40 mL) then extracted with chloroform (3 x 75 mL). The combined extract was dried over magnesium sulfate then filtered into a 250 mL volumetric flask which was then filled to the mark with anhydrous chloroform.

Crossing Experiment Procedure:

An aliquot of the stock solution (V_S) was transferred to a flame-dried round bottom flask (100 mL for Experiment 1, 5L for Experiments 2, 3 and 4) where it was diluted to the specified volume (V_S) with anhydrous ethanol free chloroform. The reaction vessel was then placed in a heating mantle, wrapped in aluminium foil and fitted with a condenser which was vented through an oil bubble seal terminated with a Drierite column. After the reaction mixture was refluxed for the specified reaction time, water (0.1 x V_S) was added and then the reflux was continued overnight. The solvent was distilled leaving a yellow tinted solid which was dissolved in water (50 mL) and washed with methylene chloride (2 x 50 mL). Evaporation of the aqueous phase to dryness gave an off-white solid, the weight of which is given as the crude yield. The residue was dissolved in 1.0 M N_aOD

in D_2O and its ^1H NMR spectrum recorded. The ratio of betaine (**53**) to "norbetaine" (**68**) was obtained by comparison of the integral of the peak from the ammonio methyls in **53** ($I_{T,\delta}$ = 3.1 ppm, S, 4.5H) with that of the peak from the amino methyls in 68 ($I_{D,\delta}$ = 2.2 ppm, s, 3H). The crude product was then dissolved in water (10 mL) and passed through a short column of deionizing resin (Fisher Rexyn 300 (H^+,OH^-), 10 equiv.). The column was rinsed with water (40 mL) and then the combined eluant was evaporated to dryness to give white crystals of **53**, the weight of which is given as the pure yield. Thermolysis using method B gave trimethylammonium chloride in the indicated amount. This material was analyzed by mass spectroscopy.

The initial concentration at 23°C was obtained by correcting the stock concentration for the dilution. This was corrected for expansion at 61°C using the Method described in the Kinetic Section of the experiment (X_T = 1.0538).

1. Deionizing Resin

4-(Trimethylammonio)-1-butanesulfonate (**53a**, 160 mg) was dissolved in water (10 mL) then passed down a column of deionizing resin (Fisher Rexyn 300 (H^+,OH^-), wet capacity 0.8 mequiv. mL^{-1}, 1.5 mL). The column was rinsed with water (40 mL). The combined eluant was evaporated to dryness to give **53a** as white crystals (135 mg).

4-(Dimethylammonio)-1-butanesulfonate (**68a**, 180 mg), when treated using the procedure described above, gave a residue of only 7 mg.

2. Stock Concentration Control:

An aliquot of the stock solution used for Crossing Experiment 2 (50.0 mL) was evaporated to dryness. The residue crystallized on standing to give the betaine, **53**, as white crystals (98 mg, 97%).

Crossing Experiment 1

Solution Preparation:

[stock] = 1.0×10^{-2} M

V_s = 50.0 mL V_f = 50.0 mL

[**53a** + **53d**]$_0$ at 23°C = 1.0×10^{-2} M

Reaction Time: 21 da (room temperature)

Yields:

Crude: 98 mg (thermolyzed directly)

Thermolysis: 16 mg (33%)

Mass Spectrum

m/e	Intensity	(6 scans)
58	56.6	
59	100.0	$\underline{d}_0$ = 100.0
60	21.9	
61	56.6	
62	118.5	$\underline{d}_3$ = 123.0
63	38.8	
64	37.6	
65	111.6	$\underline{d}_6$ = 116.7
66	48.1	
67	5.8	
68	80.1	$\underline{d}_9$ = 84.5
69	3.2	

F_a = -13.0% excess $\underline{d}_0$,$\underline{d}_9$

Crossing Experiment 2

Solution Preparation:

[stock] = 1.0×10^{-2} M

V_s = 100.0 mL V_f = 5.0 L

[**53a** + **53d**]$_0$ at 23°C = 2.0×10^{-4} M

[**53a** + **53d**]$_0$ at 61.0°C = 1.9×10^{-4} M

Reaction Time: 21 da (at 61.0°C)

Yields:

Crude: 210 mg

Pure: 110 mg (55%)

Thermolysis: 18 mg (33%)

Mass Spectrum

m/e	Intensity	(6 scans)
58	63.1	
59	100.0	$\underline{d}_0$ = 100.0
60	21.7	
61	58.6	
62	112.9	$\underline{d}_3$ = 115.9
63	37.3	
64	34.4	
65	96.2	$\underline{d}_6$ = 99.8
66	50.1	
67	4.7	
68	72.0	$\underline{d}_9$ = 76.7
69	2.8	

F_a = -10.0% excess $\underline{d}_0$, $\underline{d}_9$

Crossing Experiment 3

Solution Preparation:

[stock] = 1.0×10^{-2} M

V_s = 100.0 mL V_f = 5.0 L

[**53a** + **53d**]$_0$ at 23°C = 2.0×10^{-4} M

[**53a** + **53d**]$_0$ at 61.0°C = 1.9×10^{-4} M

Production Ratio:

^{1}H NMR Data: I_T = 84 I_D = 135

Calcd % **53**: 29%

Yields:

Crude: 191 mg

Pure: 60 mg (30%)

Thermolysis: 8 mg (27%)

Mass Spectrum

m/e	Intensity	(6 scans)
58	49.7	
59	100.0	d_0 = 100.0
60	17.9	
61	48.2	
62	115.1	d_3 = 118.2
63	30.5	
64	29.3	
65	98.6	d_6 = 102.3
66	39.8	
67	5.3	
68	76.5	d_9 = 79.9
69	2.8	

F_a = -10.2% excess d_0, d_9

3. 2-Methylphenylmethane Derivatives

Thermolysis Procedure

A methanol solution of the betaine was injected into the mass spectrometer probe which was equilibrated at approximately 260±20°C.

Betaines:

(i) 2-(Trimethylammoniomethyl)phenylmethanesulfonate (**55a,d$_0$**).

Full spectrum

m/e	Intensity	(9 scans)
58	17.5	
59	100.0	
60	3.2	
119	53.7	
120	15.9	
121	4.8	
122	1.3	
184	17.8	
185	1.2	
186	2.1	

Partial spectrum

m/e	Intensity	(5 scans)
57	0.0	
58	46.6	
59	100.0	
60	4.0	
61	0.0	

2-(($^2H_3$)Methyldimethylammoniomethyl)phenylmethanesulfonate (53b, d_3)

m/e	Intensity	(4 scans)
58	1.3	
59	1.1	d_0 = 1.5
60	10.7	
61	40.0	
62	100.0	d_3 = 100
63	3.9	
64	0.5	
65	0.8	d_6 = 1.0
66	0.2	
67	0.0	
68	0.0	d_9 = 0
69	0.0	

2-(Di($^2H_3$)methylammoniomethyl)phenylmethanesulfonate (53c, d_6)

m/e	Intensity	(6 scans)
58	0.0	
59	0.0	d_0 = 0.0
60	0.2	
61	0.3	
62	1.0	d_3 = 0.4
63	29.5	
64	32.0	
65	100.0	d_6 = 100
66	5.3	
67	0.5	
68	0.9	d_9 = 1.9
69	0.1	

2-(Tri($^2H_3$)methylammoniomethyl)phenylmethanesulfonate (53d, d_9)

m/e	Intensity	(5 scans)
63	0.0	
64	0.0	
65	1.0	$d_6 = 3 \times 10^{-3}$
66	35.2	
67	4.5	
68	100.0	$d_9 = 100$
69	3.9	

Authentic Betaine Mixtures

Authentic mixtures of the betaines **53a**, **b**, **c** and **d** were prepared by two different methods. In the first three experiments the indicated amounts of the betaines were weighed out, combined, then dissolved in methanol (5 mL). The solvent was removed by evaporation and the residue analyzed mass spectrometrically. For, the rest of the control experiments, the authentic mixtures were prepared volumetrically. Stock solutions were prepared by adding water, via a burette, to the betaines using the following quantities:

$\underline{d}_0$: 44.3 mg of **53a** in 82.8 mL H_2O

$\underline{d}_3$: 43.8 mg of **53b** in 80.8 mL H_2O

$\underline{d}_6$: 42.8 mg of **53c** in 78.1 mL H_2O

$\underline{d}_9$: 43.1 mg of **53d** in 77.6 mL H_2O.

The betaine concentrations were then adjusted by further dilution, or by addition of more of the betaine, to a common absorbance of 1.230 $\pm$ .005 at 268.5 mm in 1.0 cm quartz U.V. cells. Aliquots (50.0 mL) of each of these solutions were transferred by pipette into 250 mL volumetric flasks which were then filled to the mark with water. The indicated volumes of the solutions ($V\underline{d}_X$) were dispensed via a burette and combined. The water was removed by evaporation and the residue analyzed mass spectrometrically. In experiments 3, 12 and 13, the aliquots ($V\underline{d}_X$) were taken by transfer pipette from the U.V calibrated solutions before the latter were diluted. For the experiments that mimic the $\underline{d}_0$,$\underline{d}_9$ crossing experiment products, the amount by which **55a** and

55d exceed **55b** and **55c** in the authentic mixture, Ca, is calculated with equation (22) and the amount by which the $\underline{d}_0$ and $\underline{d}_9$ amines exceed the $\underline{d}_3$ and $\underline{d}_6$ amines is calculated with equation (14).

$$C_a = 100 \left[\frac{(55a + 55d) - (55b + 55c)}{55a + 55b + 55c + 55d}\right] \quad (22)$$

$$F_a = 100 \left[\frac{(\underline{d}_0 + \underline{d}_9) - (\underline{d}_3 + \underline{d}_6)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \quad (14)$$

Similarily, for the samples enriched in **55b** and **55c** relative to **55a** and **55d**, C_b and F_b are calculated from equations (23) and (24) respectively.

$$C_b = 100 \left[\frac{(55b + 55c) - (55a + 55d)}{55a + 55b + 55c + 55d}\right] \quad (23)$$

$$F_b = 100 \left[\frac{(\underline{d}_3 + \underline{d}_6) - (\underline{d}_0 + \underline{d}_9)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9}\right] \quad (24)$$

Control Experiment 1:

C_a = Ø% excess $d_Ø$, d_9

Mixture: $d_Ø$, (**53a**) : 6.1 mg
d_3, (**53b**) : 6.2 mg
d_6, (**53c**) : 6.2 mg
d_9, (**53d**) : 6.3 mg

Mass spectrum

m/e	Intensity	(5 scans)
58	21.8	
59	100.Ø	$d_Ø$ = 100.Ø
6Ø	8.1	
61	18.3	
62	99.3	d_3 = 100.Ø
63	14.Ø	
64	13.Ø	
65	92.4	d_6 = 94.6
66	18.9	
67	3.6	
68	83.1	d_9 = 84.2
69	3.Ø	

F_a = -2.7% excess $d_Ø$, d_9

Control Experiment 2:

C_a = 100% excess d_0, d_9

Mixture: d_0, (53a) : 7.0 mg

d_9, (53d) : 7.3 mg

Mass spectrum

m/e	Intensity	(5 scans)
58	24.0	
59	100.0	d_0 = 100.0
60	4.3	
61	2.1	
62	8.5	d_3 = 9.0
63	1.9	
64	1.9	
65	8.8	d_6 = 9.4
66	21.6	
67	4.3	
68	98.2	d_9 = 101.2
69	3.7	

F_a = 83.3% excess d_0, d_9

Control Experiment 3:

C_b = 100% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: $\underline{d}_3$, (53b) : 7.0 mg

$\underline{d}_6$, (53c) : 7.1 mg

Mass spectrum

m/e	Intensity (5 scans)	
58	0.4	
59	4.2	$\underline{d}_0$ = 4.1
60	2.2	
61	9.2	
62	100.0	$\underline{d}_3$ = 100.0
63	8.3	
64	7.8	
65	97.5	$\underline{d}_6$ = 98.8
66	4.6	
67	0.4	
68	4.3	$\underline{d}_9$ = 5.1
69	0.2	

F_b = 91.1% excess $\underline{d}_3$, $\underline{d}_6$

Control Experiment 4:

C_a = 2.5% excess $\underline{d}_0$, $\underline{d}_9$

Mixture: $V\underline{d}_0$ = 25.63 mL
$V\underline{d}_3$ = 24.38 mL
$V\underline{d}_6$ = 24.38 mL
$V\underline{d}_9$ = 25.63 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	2.8	
59	100.0	$\underline{d}_0$ = 100.0
60	4.8	
61	3.6	
62	91.9	$\underline{d}_3$ = 93.9
63	4.6	
64	3.8	
65	89.0	$\underline{d}_6$ = 91.3
66	5.2	
67	3.2	
68	83.9	$\underline{d}_9$ = 86.5
69	3.4	

F_a = 0.4% excess $\underline{d}_0$, $\underline{d}_9$

Control Experiment 5:

C_b = 2.5% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: $V\underline{d}_0$ = 24.38 mL
$V\underline{d}_3$ = 25.63 mL
$V\underline{d}_6$ = 25.63 mL
$V\underline{d}_9$ = 24.38 mL

Mass spectrum

m/e	Intensity	(6 scans)
58	5.0	
59	100.0	$\underline{d}_0$ = 100.0
60	5.4	
61	5.3	
62	113.1	$\underline{d}_3$ = 114.2
63	8.0	
64	8.0	
65	108.0	$\underline{d}_6$ = 113.7
66	8.8	
67	4.0	
68	95.5	$\underline{d}_9$ = 98.8
69	3.1	

F_b = 6.8% excess $\underline{d}_3$, $\underline{d}_6$

Control Experiment 6:

C_a = 5.0% excess d_0, d_9

Mixture: Vd_0 = 26.25 mL
Vd_3 = 23.75 mL
Vd_6 = 23.75 mL
Vd_9 = 26.25 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	8.0	
59	100.0	d_0 = 100.0
60	5.7	
61	8.5	
62	105.3	d_3 = 107.1
63	8.9	
64	8.1	
65	103.3	d_6 = 107.5
66	9.1	
67	4.0	
68	91.0	d_9 = 92.4
69	2.9	

F_a = 5.5% excess d_0 , d_9

Control Experiment 7:

C_b = 5.0% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: $V\underline{d}_0$ = 23.75 mL
$V\underline{d}_3$ = 26.25 mL
$V\underline{d}_6$ = 26.25 mL
$V\underline{d}_9$ = 23.75 mL

Mass spectrum

m/e	Intensity	(6 scans)
58	12.8	
59	100.0	$\underline{d}_0$ = 100.0
60	9.1	
61	15.6	
62	122.7	$\underline{d}_3$ = 127.4
63	16.1	
64	15.2	
65	123.0	$\underline{d}_6$ = 132.5
66	18.5	
67	6.0	
68	100.3	$\underline{d}_9$ = 107.3
69	3.8	

F_b = 11.2% excess $\underline{d}_3$, $\underline{d}_6$

Control Experiment 8:

C_a = 7.5% excess $\underline{d}_0$: $\underline{d}_9$

Mixture: $V\underline{d}_0$ = 26.88 mL

$V\underline{d}_3$ = 23.13 mL

$V\underline{d}_6$ = 23.13 mL

$V\underline{d}_9$ = 26.88 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	3.7	
59	100.0	$\underline{d}_0$ = 100.0
60	4.8	
61	3.8	
62	93.4	$\underline{d}_3$ = 94.7
63	5.0	
64	3.9	
65	87.9	$\underline{d}_6$ = 90.0
66	5.7	
67	3.2	
68	86.6	$\underline{d}_9$ = 89
69	3.3	

F_a = 1.2% excess $\underline{d}_0$, $\underline{d}_9$

Control Experiment 9:

C_b = 7.5% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: $V\underline{d}_0$ = 23.13 mL

$V\underline{d}_3$ = 26.88 mL

$V\underline{d}_6$ = 26.88 mL

$V\underline{d}_9$ = 23.13 mL

Mass spectrum

m/e	Intensity	(6 scans)
58	2.7	
59	100.0	$\underline{d}_0$ = 100.0
60	5.9	
61	4.9	
62	122.5	$\underline{d}_3$ = 126.1
63	7.6	
64	6.4	
65	122.4	$\underline{d}_6$ = 128.2
66	7.4	
67	4.7	
68	93.4	$\underline{d}_9$ = 98.3
69	4.0	

F_b = 12.4% excess $\underline{d}_3$, $\underline{d}_6$

Control Experiment 10:

C_a = 10% excess d_0, d_9

Mixture: Vd_0 = 25.50 mL
Vd_3 = 22.50 mL
Vd_6 = 22.50 mL
Vd_9 = 27.50 mL

Mass spectrum

m/e	Intensity	(4 scans)
58	9.6	
59	100.0	d_0 = 100.0
60	5.9	
61	8.5	
62	87.5	d_3 = 89.6
63	8.4	
64	6.8	
65	82.2	d_6 = 85.7
66	10.9	
67	4.0	
68	88.2	d_9 = 91.6
69	3.5	

F_a = 4.4% excess d_0, d_9

Control Experiment 11:

C_b = 10% excess d_3, d_6

Mixture: Vd_0 = 22.50 mL
Vd_3 = 27.50 mL
Vd_6 = 27.50 mL
Vd_9 = 22.50 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	15.7	
59	100.0	d_0 = 100.0
60	9.0	
61	17.7	
62	129.0	d_3 = 131.5
63	15.7	
64	14.8	
65	128.4	d_6 = 133.3
66	18.4	
67	4.6	
68	90.1	d_9 = 94.3
69	3.5	

F_b = 15.4% excess d_3, d_6

Control Experiment 12:

C_a = 20% excess d_0, d_9

Mixture: Vd_0 = 3.0 mL
Vd_3 = 2.0 mL
Vd_6 = 2.0 mL
Vd_9 = 3.0 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	9.7	
59	100.0	d_0 = 100.0
60	7.5	
61	9.1	
62	75.7	d_3 = 80.5
63	8.5	
64	8.1	
65	76.8	d_6 = 82.2
66	12.4	
67	5.5	
68	97.8	d_9 = 103.3
69	4.0	

F_a = 11.1% excess d_0, d_9

Control Experiment 13:

C_b = 20% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: $V\underline{d}_0$ = 2.0 mL

$V\underline{d}_3$ = 3.0 mL

$V\underline{d}_6$ = 3.0 mL

$V\underline{d}_9$ = 2.0 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	10.5	
59	100.0	$\underline{d}_0$ = 100.0
60	8.1	
61	14.6	
62	149.6	$\underline{d}_3$ = 152.6
63	13.4	
64	11.6	
65	146.1	$\underline{d}_6$ = 149.7
66	14.6	
67	3.7	
68	93.1	$\underline{d}_9$ = 96.3
69	3.5	

F_b = 21.3% excess $\underline{d}_3$, $\underline{d}_6$

(c) Crossing Experiments

Stock Solution Prepartion:

For $\underline{d}_0$,$\underline{d}_9$ crossing experiments, an equimolar mixture of 2-(methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (**87a**) and 2-(($^2H_3$)methoxysulfonylmethyl)phenyl-N,N-di($^2H_3$)methylmethanaminium trifluoromethanesulfonate (**87d**) or for $\underline{d}_3$,$\underline{d}_6$ crossing experiments; 2-(($^2H_3$)methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (**87b**) and 2-(methoxysulfonylmethyl)phenyl-N,N-di($^2H_3$)methylmethanaminium trifluoromethanesulfonate (**87c**)) was shaken with ice-cold aqueous saturated sodium carbonate (30 mL) then extracted with benzene (3 x 1/4 of the final solution volume, V_f). The combined extract was dried over magnesium sulfate and then transferred to the dry box where it was further dried, first by standing for 20 min over anhydrous magnesium perchlorate, then over calcium hydride for 30 min. The solution was filtered through Celite into a volumetric flask (of volume V_f) which was then filled to the mark with anhydrous benzene.

Stock Solution Analyses

An aliquot of the stock solution (V_A) was taken with a Mohr pipette and evaporated to dryness in a tared 25 mL round bottom flask. The oily residue crystallized after standing overnight at 50 torr over Drierite in a vacuum desiccator. After weighing to obtain the crude yield, the sample was dissolved in 1.0 M sodium carbonate in D_2O and its ^1H NMR spectrum recorded. In both stock solutions,

the spectrum was consistent only with that of the betaine (55) in which half of the N-methyls were deuterated. The sample was then passed in water (10 mL) through a short column of deionizing resin (Rexyn 300 (H^+, OH^-) 10 equiv). After rinsing the column with water (40 mL), the combined eluant was evaporated to dryness. The residue was transferred in methanol to a tared 5 dram vial where, after removal of the methanol by evaporation, the pure yield was obtained. The sample was then analyzed mass spectrometrically.

Crossing Experiment Procedure

In the dry box, an aliquot (V_s) of the specified stock solution was transferred to a volumetric flask (of volume V_f) which was then filled to the mark with anhydrous benzene. The solution was sealed at -78° C under nitrogen in a flame-dried Carius tube. The tube was then immersed in an oil bath maintained at 110.0° C ($\pm$0.1) by a B. Braun Thermomix 1460 recirculating heater. After the specified reaction time, the tube was cooled to -78° C and then opened. The contents were treated with 1M aqueous hydrochloric acid (3 equiv.), warmed to room temperature and then extracted with water (2 x 25 mL). The organic layer was dried over magnesium sulfate and evaporated to dryness in a tared 50 mL round bottom flask to give an oily residue in the indicated amount. This residue, in all experiments, gave an ^1H NMR spectrum in $CDCl_3$ consisting of a broad poorly resolved multiplet (δ= 1.0 to 2.5 ppm).

The combined aqueous layers were transferred to a tared

50 mL round bottom flask, evaporated to dryness and further dried by standing overnight at 50 torr over phosphorus pentoxide in a vacuum desiccator. After weighing to obtain the crude yield, the hydroscopic solid was dissolved in 1 M sodium carbonate in D_2O and examined by ^1H NMR. The ratio of betaine (**55**) to the "norbetaine" (**88**), expressed as % **55**, was obtained by comparison of the integral of the peak ascribed to the aromatic protons in the betaine (I_T, δ = 7.6 ppm, s, 4H) with that of the "norbetaine" (I_D, δ = 7.3, s, 4H). The crude product was dissolved in water (10 mL) and passed down a short column of deionizing resin (Rexyn 300 (^+H, ^-OH, 10 equiv.). After rinsing the column with water (40 mL), the combined eluant was evaporated to dryness to give a white crystalline solid which was then transferred in methanol to a tared 5 dram vial. Removal of the methanol by evaporation left the purified product, the weight of which is given as the pure yield. The sample was then analyzed by mass spectrometrically.

The initial starting material concentration ($[\mathbf{E}]_0$) at 23°C was obtained by correcting the stock solution for the dilution. This valve was then corrected for thermal expansion at 110°C in the manner described in the kinetic section of the experimental. (X_T = 1.1243). The indicated calculated percent reaction is based on the integrated second order rate expression;

$$\frac{1}{[\mathbf{E}]_t} - \frac{1}{[\mathbf{E}]_0} = k_{obs}t \qquad (30)$$

where t is the reaction time and k_{obs} is the known second

order rate constant (2.5×10^{-3} L mol^{-1} s^{-1})

$$\% \text{ reaction} = 100 \left(1 - \frac{[E]_t}{[E]_0} \right) \qquad (48)$$

The calculated crude yield is the weight of crude product calculated from the moles of starting material and the product ratio indicated by ^1H NMR. The percent pure yield is the overall percent conversion of the starting material to pure product.

Control Experiments:

Deionizing Resin:

2-(Trimethylammonimethyl)phenylmethanesulfonate (**55a**, 11 mg) in water (5 mL) was passed down a short column of deconizing resin (Fisher A.C.S. Certified Analytical Grade Rexyn 300 (^+H, ^-OH), 20 equiv.). The column was rinsed with water (45 mL) and the combined eluant evaporated to dryness to give **55a** as white crystals (10.5 mg).

2-(Dimethylammoniomethyl)phenylmethanesulfonate (**88**, 25 mg) was subjected to the same treatment. The combined eluant, on evaporation to dryness, gave only a trace (0.2 mg) of a white powder.

Water content:

An aliquot (1.0 mL) of stock solution 1 was injected into an Aquavolt Automatic Karl Fisher Titrator. The total water content was 18 μg and, therefore, the concentration of water was (1×10^{-3} M).

Stock Solution 1

Solution Preparation:

Substrates: **87a** (d_0) : 49.2 mg, 0.125 mmol
87d (d_9) : 50.3 mg, 0.125 mmol

V_f = 50.0 mL

[stock] = 5.0×10^{-3} M

Analysis

V_A = 5.0 mL

Yields: Crude : 6.4 mg (calcd = 6.3 mg)
Pure : 5.8 mg

Mass spectrum:

m/e	Intensity	(5 scans)
58	50.8	
59	100.0	d_0 : 100.0
60	13.9	
61	35.6	
62	92.6	d_3 : 91.6
63	25.1	
64	22.4	
65	84.2	d_6 : 84.6
66	35.2	
67	3.3	
68	72.1	d_9 : 72.3
69	2.6	

F_a = -1.1% excess d_0, d_9

Stock Solution 2

Solution Preparation:

Substrates: **87b** ($\underline{d}_3$) : 49.6 mg, 0.125 mmol

87c ($\underline{d}_6$) : 49.9 mg, 0.125 mmol

V_f = 50.0 mL

[stock] = 5.0×10^{-3} M

Analysis

V_A = 5.0 mL

Yields: Crude : 6.4 mg (calcd = 6.3 mg)

Pure : 4.8 mg

Mass spectrum:

m/e	Intensity	(5 scans)
58	72.0	
59	100.0	$\underline{d}_0$: 100.0
60	20.0	
61	57.1	
62	101.0	$\underline{d}_3$: 101.1
63	38.2	
64	34.6	
65	93.0	$\underline{d}_6$: 93.5
66	60.3	
67	5.0	
68	82.0	$\underline{d}_9$: 85.2
69	3.2	

F_b = 2.5% excess $\underline{d}_3$, $\underline{d}_6$

Crossing Experiment 1:

Solution Preparation:

Stock Solution 1 ($\underline{d_0}$, $\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 7.5 mL V_f = 7.5 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 25 h (calcd % reaction = 50)

Products

(a) Organic Residue: 0.1 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 28 I_D = 36

% 55 = 44%

Yields: Crude: 13.0 mg (calcd. = 9.1 mg)

Pure : 4.4 mg (47%)

Mass spectrum

m/e	Intensity	(6 scans)
58	71.5	
59	100.0	d_0 = 100.0
60	20.5	
61	59.2	
62	102.9	d_3 = 104.0
63	40.2	
64	35.8	
65	95.6	d_6 = 97.1
66	60.9	
67	4.7	
68	84.1	d_9 = 86.7
69	3.0	

F_a = -3.7% excess $\underline{d_0}$, $\underline{d_9}$

Crossing Experiment 2:

Solution Preparation:

Stock Solution 2 ($\underline{d}_3$, $\underline{d}_6$) [stock] = $5.0\times10^{-3}\underline{M}$

V_s = 7.5 mL V_f = 7.5 mL

$[E]_\emptyset$ at 23°C = $5.0\times10^{-3}\underline{M}$ $[E]_\emptyset$ at 110.0°C = $4.5\times10^{-3}\underline{M}$

Reaction Time = 25 h (calcd % reaction = 50)

Products

(a) Organic Residue: 0.2 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 38 I_D = 44

% 55 = 46%

Yields: Crude: 12.5 mg (calcd. = 9.1 mg)

Pure : 4.1 mg (44%)

Mass spectrum

m/e	Intensity	(5 scans)
58	74.6	
59	100.0	$\underline{d}_\emptyset$ = 100.0
60	21.6	
61	59.3	
62	99.1	$\underline{d}_3$ = 100.7
63	40.9	
64	36.3	
65	95.9	$\underline{d}_6$ = 96.3
66	60.6	
67	4.8	
68	77.9	$\underline{d}_9$ = 81.5
69	2.8	

F_b = 4.1% excess $\underline{d}_3$, $\underline{d}_6$

Crossing Experiment 3:

Solution Preparation:

Stock Solution 1 ($\underline{d}_0$, $\underline{d}_9$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 41 h (calcd % reaction = 23.5)

Products

(a) Organic Residue: 0.4 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 28 I_D = 80

% 55 = 26%

Yields: Crude: 10.2 mg (calcd. = 11.8 mg)

Pure : 2.8 mg (23%)

Mass spectrum

m/e	Intensity	(6 scans)
58	74.4	
59	100.0	$\underline{d}_0$ = 100.0
60	19.9	
61	55.0	
62	96.1	$\underline{d}_3$ = 95.7
63	33.1	
64	33.1	
65	88.4	$\underline{d}_6$ = 85.7
66	60.4	
67	4.4	
68	81.5	$\underline{d}_9$ = 83.3
69	2.6	

F_a = 0.5% excess $\underline{d}_0$, $\underline{d}_9$

Crossing Experiment 4:

Solution Preparation:

Stock Solution 2 ($\underline{d}_3$, $\underline{d}_6$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 41 h (calcd % reaction = 23.5)

Products

(a) Organic Residue: 0.4 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 15 I_D = 44

% 55 = 25%

Yields: Crude: 11.0 mg (calcd. = 11.8 mg)

Pure : 3.1 mg (25%)

Mass spectrum

m/e	Intensity	(5 scans)
58	76.1	
59	100.0	$\underline{d}_0$ = 100.0
60	20.4	
61	56.2	
62	95.4	$\underline{d}_3$ = 95.3
63	39.0	
64	33.7	
65	87.2	$\underline{d}_6$ = 88.1
66	57.1	
67	4.5	
68	75.5	$\underline{d}_9$ = 77.3
69	2.6	

F_b = 1.7% excess $\underline{d}_3$, $\underline{d}_6$

Crossing Experiment 5:

Solution Preparation:

Stock Solution 1 ($\underline{d_0}$, $\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 120 h (calcd % reaction = 47)

Products

(a) Organic Residue: 0.3 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 40 I_D = 43

% 55 = 48%

Yields: Crude: 13.2 mg (calcd. = 12.0 mg)

Pure : 4.6 mg (37%)

Mass spectrum

m/e	Intensity	(5 scans)
58	70.3	
59	100.0	$\underline{d_0}$ = 100.0
60	19.5	
61	55.8	
62	97.6	$\underline{d_3}$ = 99.0
63	39.0	
64	33.5	
65	91.7	$\underline{d_6}$ = 93.3
66	63.2	
67	4.7	
68	83.1	$\underline{d_9}$ = 88.0
69	2.8	

F_a = 1.1% excess $\underline{d_0}$, $\underline{d_9}$

Crossing Experiment 6:

Solution Preparation:

Stock Solution 2 ($\underline{d_3}$, $\underline{d_6}$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 120 h (calcd % reaction = 47)

Products

(a) Organic Residue: 0.2 mg, oil

(b) Aqueous Residue:

^1H NMR Integrals: I_T = 44 I_D = 55

% 55 = 42%

Yields: Crude: 9.0 mg (calcd. = 12.0 mg)

Pure : 5.2 mg (42%)

Mass spectrum

m/e	Intensity	(5 scans)
58	74.5	
59	100.0	$\underline{d_0}$ = 100.0
60	20.7	
61	55.9	
62	94.9	$\underline{d_3}$ = 95.9
63	37.5	
64	32.9	
65	87.8	$\underline{d_6}$ = 87.9
66	57.1	
67	4.4	
68	75.7	$\underline{d_9}$ = 78.1
69	2.8	

F_b = 1.6% excess $\underline{d_3}$, $\underline{d_6}$

Crossing Experiment 7:

Solution Preparation:

Stock Solution 1 (d_0, d_9) [stock] = 5.0×10^{-3} M

V_S = 5.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 5.0×10^{-4} M $[E]_0$ at 110.0°C = 4.5×10^{-4} M

Reaction Time = 80 h (calcd % reaction = 24.5)

Products

(a) Organic Residue: 0.4 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 15 I_D = 43

% 55 = 26%

Yields: Crude: 8.1 mg (calcd. = 5.9 mg)

Pure : 1.7 mg (27%)

Mass spectrum 1			Mass spectrum 2		
m/e	Intensity	(6 scans)	m/e	Intensity	(6 scans)
58	63.9		58	4.0	
59	100.0	d_0 = 100.0	59	100.0	d_0 = 100.0
60	18.8		60	5.3	
61	51.8		61	5.7	
62	108.0	d_3 = 106.5	62	118.1	d_3 = 120.3
63	37.1		63	7.6	
64	31.6		64	6.5	
65	100.6	d_6 = 100.1	65	116.1	d_6 = 120.7
66	57.1		66	7.9	
67	4.8		67	4.9	
68	93.8	d_9 = 94.2	68	104.2	d_9 = 108.4
69	3.4		69	4.2	
F_a = -3.0% excess d_0, d_9			F_a = -7.2% excess d_0, d_9		

Crossing Experiment 8:

Solution Preparation:

Stock Solution 2 ($\underline{d}_3$, $\underline{d}_6$) [stock] = 5.0×10^{-3}M

V_s = 5.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 5.0×10^{-4}M $[E]_0$ at 110.0°C = 4.5×10^{-4}M

Reaction Time = 80 h (calcd % reaction = 24.5)

Products

(a) Organic Residue: 0.3 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 13 I_D = 42

% 55 = 24%

Yields: Crude: 8.0 mg (calcd. = 5.9 mg)

Pure : 1.7 mg (27%)

Mass spectrum 1			Mass spectrum 2		
m/e	Intensity	(6 scans)	m/e	Intensity	(5 scans)
58	64.2		58	3.9	
59	100.0	$\underline{d}_0$ = 100.0	59	100.0	$\underline{d}_0$ = 100.0
60	18.4		60	4.4	
61	50.9		61	3.8	
62	100.4	$\underline{d}_3$ = 100.8	62	105.8	$\underline{d}_3$ = 106.1
63	34.2		63	5.2	
64	29.9		64	3.9	
65	92.0	$\underline{d}_6$ = 92.1	65	102.0	$\underline{d}_6$ = 103.0
66	50.7		66	5.5	
67	4.1		67	3.1	
68	77.8	$\underline{d}_9$ = 80.1	68	86.8	$\underline{d}_9$ = 88.0
69	3.0		69	3.1	

F_b = 3.4% excess $\underline{d}_3$, $\underline{d}_6$ F_b = 5.3% excess $\underline{d}_3$, $\underline{d}_6$

Crossing Experiment 9:

Solution Preparation:

Stock Solution 1 ($\underline{d_0}$, $\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 5.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 5.0×10^{-4} M $[E]_0$ at 110.0°C = 4.5×10^{-4} M

Reaction Time = 240 h (calcd % reaction = 49)

Products

(a) Organic Residue: 0.2 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 27 I_D = 24

% 55 = 53%

Yields: Crude: 7.3 mg (calcd. = 6.4 mg)

Pure : 4.0 mg (65%)

Mass spectrum 1			Mass spectrum 2		
m/e	Intensity	(5 scans)	m/e	Intensity	(5 scans)
58	75.0		58	2.6	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	10.7		60	6.3	
61	24.3		61	5.1	
62	115.9	$\underline{d_3}$ = 117.5	62	114.5	$\underline{d_3}$ = 118.8
63	19.0		63	8.3	
64	21.3		64	7.0	
65	114.5	$\underline{d_6}$ = 119.8	65	112.8	$\underline{d_6}$ = 120.4
66	23.6		66	7.0	
67	6.0		67	7.6	
68	95.5	$\underline{d_9}$ = 97.2	68	100.4	$\underline{d_9}$ = 108.4
69	3.2		69	4.3	
F_a = -9.2% excess $\underline{d_0}$, $\underline{d_9}$			F_a = -6.9% excess $\underline{d_0}$, $\underline{d_9}$		

Crossing Experiment 10:

Solution Preparation:

Stock Solution 2 ($\underline{d}_3$, $\underline{d}_6$) [stock] = 5.0×10^{-3} M

V_s = 5.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 5.0×10^{-4} M $[E]_0$ at 110.0°C = 4.5×10^{-4} M

Reaction Time = 240 h (calcd % reaction = 49)

Products

(a) Organic Residue: 0.4 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 39 I_D = 30

% 55 = 57%

Yields: Crude: 5.6 mg (calcd. = 6.5 mg)

Pure : 4.1 mg (66%)

Mass spectrum 1			Mass spectrum 2		
m/e	Intensity	(5 scans)	m/e	Intensity	(5 scans)
58	33.0		58	12.1	
59	100.0	$\underline{d}_0$ = 100.0	59	100.0	$\underline{d}_0$ = 100.0
60	11.0		60	8.1	
61	27.4		61	12.9	
62	108.1	$\underline{d}_3$ = 107.2	62	112.8	$\underline{d}_3$ = 115.8
63	19.8		63	11.8	
64	25.1		64	11.8	
65	104.1	$\underline{d}_6$ = 108.5	65	111.8	$\underline{d}_6$ = 116.7
66	24.6		66	13.9	
67	4.6		67	5.6	
68	87.8	$\underline{d}_9$ = 85.7	68	100.8	$\underline{d}_9$ = 104.1
69	3.2		69	4.0	

F_b = 7.5% excess $\underline{d}_3$, $\underline{d}_6$ F_b = 6.5% excess $\underline{d}_3$, $\underline{d}_0$

4. 2-(2-Methylphenyl)ethyl Derivatives:

Thermolysis Procedure:

A methanol solution of the betaine was injected into the mass spectrometer probe which was equilibrated at 240±20° C.

(a) Betaines

(i) 2-[2-(Trimethylammoniomethyl)phenyl]ethanesulfonate (**57a**,d0)

Full spectrum:

m/e	Intensity	(9 scans)
58	32.5	
59	100.0	
60	3.4	
105	8.9	
106	1.2	
116	2.3	
117	18.0	
118	3.2	
133	55.2	
134	58.1	
135	5.4	
198	10.8	
199	1.2	

Partial spectrum:

m/e	Intensity	(4 scans)
57	0.0	
58	5.0	
59	100.0	
60	4.2	
61	0.0	

(ii) 2-[2-(($^2H_3$)Methyldimethylammoniomethyl)phenyl]ethanesulfonate (**57b**, $\underline{d}_3$)

m/e	Intensity	(4 scans)
58	0.3	
59	1.3	$\underline{d}_0$ = 0.3
60	4.7	
61	19.5	
62	100.0	$\underline{d}_3$ = 100
63	4.0	
64	0.2	
65	1.0	$\underline{d}_6$ = 0.4
66	0.4	

(iii) 2-[2-(Di($^2H_3$)methyl methylammoniomethyl)phenyl]ethanesulfonate (**57c**, $\underline{d}_6$)

m/e	Intensity	(6 scans)
62	1.4	$\underline{d}_3$ = 1.0
63	9.4	
64	12.2	
65	100.0	$\underline{d}_6$ = 100.0
66	3.8	
67	0.1	
68	1.0	$\underline{d}_9$ = 0.8
69	0.1	

(iv) 2-[2-(Tri($^2H_3$)methylammoniomethyl)phenyl]ethanesulfonate (**57d**, $\underline{d}_9$)

m/e	Intensity	(5 scans)
65	1.5	
66	28.2	$\underline{d}_6$ = Ø.4
67	4.7	
68	100.0	$\underline{d}_9$ = 100.0
69	3.5	

Authentic Betaine Mixtures:

Authentic mixtures of the betaines **57a** ($\underline{d}_Ø$), **57b** ($\underline{d}_3$), **57c** ($\underline{d}_6$) and **57d** ($\underline{d}_9$) were prepared using the following two methods.

Method A

Carefully weighed samples of the betaines **57a** ($\underline{d}_Ø$, 21.1 mg), **57b** ($\underline{d}_3$, 21.4 mg), **57c** ($\underline{d}_6$, 21.6 mg) and **57d** ($\underline{d}_9$, 21.9 mg) were each dissolved in water in 50 mL volumetric flasks. An aliquot (25.0 mL) of each solution was taken by transfer pipette and combined to give a 1:1:1:1 - $\underline{d}_Ø$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ stock betaine solution. The remaining $\underline{d}_Ø$- and $\underline{d}_9$-betaine solutions were combined in a 100 mL volumetric flask which was then filled to the mark with water to give a stock 1:Ø:Ø:1 - $\underline{d}_Ø$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ solution. A stock Ø:1:1:Ø - $\underline{d}_Ø$:$\underline{d}_3$:$\underline{d}_6$:$\underline{d}_9$ solution was prepared in the same manner from the remaining $\underline{d}_3$- and $\underline{d}_6$-solutions. Aliquots of each of these stock solutions, specified as V(1:1:1:1), V(1:Ø:Ø:1) and V(Ø:1:1:Ø), were taken by transfer pipette, combined and evaporated to dryness. The residue was analyzed mass spectrometrically. This method was used for experiments 1 through 5.

Method B

The indicated amount of water was dispensed from a burette to weighed samples of the betaines:

57a ($\underline{d}_0$, 30.8 mg) in 76.1 mL H_2O

57b ($\underline{d}_3$, 30.7 mg) in 75.0 mL H_2O

57c ($\underline{d}_6$, 31.2 mg) in 75.4 mL H_2O

57d ($\underline{d}_9$, 32.6 mg) in 77.9 mL H_2O

The concentrations of these solutions were adjusted, either by the addition of more of the betaine, or by further dilution, to a common absorbance of $0.973 \pm .005$ at 267 nm in 1 cm path length quartz U.V. cells. Aliquots (50 mL) of each of the solutions were transferred by pipette to 250 mL volumetric flasks which were then filled to the mark with water. The indicated volumes ($V\underline{d}_x$) were then dispensed via a burette, combined and evaporated to dryness. The residue was examined mass spectrometrically. This method was used for experiments 6 through 14. In the experiments in which the amount of **57a** and **57d** is greater than **57b** and **57c**, the mixture composition is expressed as $\mathbf{C}_a$ (% excess $\underline{d}_0$,$\underline{d}_9$) as described by equation (32). Similarly, the composition of the observed amine mixture is expressed as $\mathbf{F}_a$ % excess $\underline{d}_0$,$\underline{d}_9$ as defined by equation.

$$\mathbf{C}_a = 100 \left[\frac{(\mathbf{57a} + \mathbf{57d}) - (\mathbf{57b} + \mathbf{57c})}{\mathbf{57a} + \mathbf{57b} + \mathbf{57c} + \mathbf{57d}} \right] \qquad (32)$$

$$\mathbf{F}_a = 100 \left[\frac{(\underline{d}_0 + \underline{d}_9) - (\underline{d}_3 + \underline{d}_6)}{\underline{d}_0 + \underline{d}_3 + \underline{d}_6 + \underline{d}_9} \right] \qquad (14)$$

For the mixtures enriched in **57b** and **57c** relative to **57a** and **57d**, $\mathbf{C}_b$ and $\mathbf{F}_b$ are defined by equations (33) and

(24) respectively.

$$C_b = 100 \left[\frac{(57b + 57c) - (57a + 57d)}{57a + 57b + 57c + 57d}\right] \quad (33)$$

$$F_b = 100 \left[\frac{(d_3 + d_6) - (d_0 + d_9)}{d_0 + d_3 + d_6 + d_9}\right] \quad (24)$$

Control Experiment 1

C_a = 0% excess d_0, d_9

Mixture: V(1:1:1:1) = 10.0 mL

Mass spectrum

m/e	Intensity	(6 scans)
58	32.7	
59	100.0	d_0 = 100.0
60	10.6	
61	25.4	
62	98.6	d_3 = 98.5
63	18.8	
64	18.1	
65	99.8	d_6 = 99.8
66	28.4	
67	4.3	
68	85.8	d_9 = 87.1
69	3.2	

F_a = -2.9% excess d_0, d_9

Control Experiment 2

C_a = 100% excess $\underline{d_0}$, $\underline{d_9}$

Mixture: V(1:0:0:1) = 10.0 mL

Mass spectrum

m/e	Intensity	(6 scans)
58	35.7	
59	100.0	$\underline{d_0}$ = 100.0
60	3.9	
61	0.4	
62	1.3	$\underline{d_3}$ = 1.4
63	0.2	
64	0.2	
65	1.9	$\underline{d_6}$ = 1.0
66	27.6	
67	4.1	
68	84.4	$\underline{d_9}$ = 86.0
69	3.1	

F_a = 97.4% excess $\underline{d_0}$, $\underline{d_9}$

Control Experiment 3

C_b = 100% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: V(0:1:1:0) = 10.0 mL

Mass spectrum

m/e	Intensity (9 scans)	
58	0.2	
59	1.0	$\underline{d}_0$ = 0.9
60	5.3	
61	20.5	
62	100.0	$\underline{d}_3$ = 100.0
63	15.5	
64	14.2	
65	98.8	$\underline{d}_6$ = 99.6
66	3.9	
67	0.1	
68	0.7	$\underline{d}_9$ = 0.8
69	0,04	

F_b = 98.3% excess $\underline{d}_3$, $\underline{d}_6$

Control Experiment 4

C_a = 50% excess d_0, d_9

Mixture: V(1:1:1:1) = 5.0 mL

V(1:0:0:1) = 10.0 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	29.8	
59	100.0	d_0 = 100.0
60	5.7	
61	8.2	
62	33.1	d_3 = 33.3
63	5.7	
64	5.6	
65	33.1	d_6 = 32.7
66	22.8	
67	3.9	
68	82.5	d_9 = 83.7
69	3.0	

F_a = 47.1% excess d_0, d_9

Control Experiment 5

C_b = 50% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: V(1:1:1:1) = 5.0 mL

V(0:1:1:0) = 10.0 mL

Mass spectrum

m/e	Intensity	(7 scans)
58	14.6	
59	36.4	$\underline{d}_0$ = 36.6
60	9.7	
61	32.1	
62	98.9	$\underline{d}_3$ = 100.0
63	23.6	
64	22.5	
65	100.0	$\underline{d}_6$ = 102.6
66	14.8	
67	16.0	
68	30.9	$\underline{d}_9$ = 31.7
69	1.1	

F_b = 49.6% excess $\underline{d}_3$, $\underline{d}_6$

Control Experiment 6

C_a = 0% excess d_0, d_9

Mixture: Vd_0 = 10.0 mL

Vd_3 = 25.0 mL

Vd_6 = 25.0 mL

Vd_9 = 25.0 mL

Mass spectrum

m/e	Intensity	(6 scans)
58	58.9	
59	100.0	d_0 = 100.0
60	15.6	
61	47.4	
62	99.5	d_3 = 99.7
63	34.3	
64	30.4	
65	97.3	d_6 = 99.1
66	54.6	
67	4.9	
68	89.2	d_9 = 92.3
69	3.3	

F_a = -1.7% excess d_0, d_9

Control Experiment 7

C_a = 5% excess d_0, d_9

Mixture: Vd_0 = 26.25 mL

Vd_3 = 23.75 mL

Vd_6 = 23.75 mL

Vd_9 = 26.25 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	17.7	
59	100.0	d_0 = 100.0
60	6.6	
61	12.8	
62	88.1	d_3 = 88.1
63	9.8	
64	9.6	
65	86.9	d_6 = 87.3
66	17.0	
67	3.9	
68	90.4	d_9 = 92.2
69	3.5	

F_a = 4.6% excess d_0, d_9

Control Experiment 8

C_b = 5% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: $V\underline{d}_0$ = 23.75 mL

$V\underline{d}_3$ = 26.25 mL

$V\underline{d}_6$ = 26.25 mL

$V\underline{d}_9$ = 23.75 mL

Mass spectrum

m/e	Intensity	
58	27.1	
59	100.0	$\underline{d}_0$ = 100.0
60	9.8	
61	24.1	
62	105.2	$\underline{d}_3$ = 106.3
63	17.7	
64	15.7	
65	102.4	$\underline{d}_6$ = 103.4
66	24.6	
67	4.0	
68	87.2	$\underline{d}_9$ = 88.7
69	3.3	

F_b = 5.3% excess $\underline{d}_3$, $\underline{d}_6$

Control Experiment 9

C_a = 10% excess $\underline{d}_0$, $\underline{d}_9$

Mixture: $V\underline{d}_0$ = 27.50 mL

$V\underline{d}_3$ = 22.50 mL

$V\underline{d}_6$ = 22.50 mL

$V\underline{d}_9$ = 27.50 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	42.8	
59	100.0	$\underline{d}_0$ = 100.0
60	12.4	
61	30.7	
62	85.0	$\underline{d}_3$ = 86.9
63	22.5	
64	19.3	
65	83.0	$\underline{d}_6$ = 84.6
66	41.9	
67	4.6	
68	93.3	$\underline{d}_9$ = 96.6
69	3.5	

F_a = 6.8% excess $\underline{d}_0$, $\underline{d}_9$

Control Experiment 10

C_b = 10% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: $V\underline{d}_0$ = 22.50 mL

$V\underline{d}_3$ = 27.50 mL

$V\underline{d}_6$ = 27.50 mL

$V\underline{d}_9$ = 22.50 mL

Mass spectrum

m/e	Intensity	(6 scans)
58	47.5	
59	100.0	$\underline{d}_0$ = 86.2
60	16.4	
61	44.3	
62	114.6	$\underline{d}_3$ = 100.8
63	33.1	
64	29.4	
65	115.3	$\underline{d}_6$ = 100.8
66	44.6	
67	4.7	
68	89.8	$\underline{d}_9$ = 79.8
69	3.4	

F_b = 9.5% excess $\underline{d}_3$, $\underline{d}_6$

Control Experiment 11

C_a = 20% excess d_0, d_9

Mixture: Vd_0 = 30.0 mL

Vd_3 = 20.0 mL

Vd_6 = 20.0 mL

Vd_9 = 30.0 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	53.2	
59	100.0	d_0 = 100.0
60	11.8	
61	29.7	
62	70.1	d_3 = 70.2
63	21.2	
64	19.1	
65	67.6	d_6 = 67.8
66	47.6	
67	4.6	
68	89.0	d_9 = 91.9
69	3.5	

F_a = 17.2% excess d_0, d_9

Control Experiment 12

C_b = 20% excess d_3, d_6

Mixture: Vd_0 = 20.0 mL

Vd_3 = 30.0 mL

Vd_6 = 30.0 mL

Vd_9 = 20.0 mL

Mass spectrum

m/e	Intensity	(6 scans)
58	40.5	
59	71.6	d_0 = 71.4
60	15.5	
61	44.5	
62	100.0	d_3 = 100.0
63	31.9	
64	28.2	
65	96.0	d_6 = 96.8
66	38.7	
67	3.3	
68	66.2	d_9 = 65.1
69	2.2	

F_b = 18.0% excess d_3, d_6

Control Experiment 13

C_a = 40% excess d_0, d_9

Mixture: Vd_0 = 35.0 mL

Vd_3 = 15.0 mL

Vd_6 = 15.0 mL

Vd_9 = 35.0 mL

Mass spectrum

m/e	Intensity	
58	26.6	
59	100.0	d_0 = 100.0
60	6.2	
61	9.5	
62	44.2	d_3 = 44.3
63	7.1	
64	6.3	
65	42.4	d_6 = 42.3
66	20.7	
67	3.9	
68	86.8	d_9 = 87.3
69	3.3	

F_a = 36.8% excess d_0, d_9

Control Experiment 14

C_b = 40% excess $\underline{d}_3$, $\underline{d}_6$

Mixture: $V\underline{d}_0$ = 15.0 mL

$V\underline{d}_3$ = 35.0 mL

$V\underline{d}_6$ = 35.0 mL

$V\underline{d}_9$ = 15.0 mL

Mass spectrum

m/e	Intensity	(5 scans)
58	7.5	
59	47.6	$\underline{d}_0$ = 47.4
60	4.7	
61	13.5	
62	100.0	$\underline{d}_3$ = 100.0
63	10.2	
64	9.7	
65	96.6	$\underline{d}_6$ = 96.9
66	8.9	
67	2.0	
68	40.3	$\underline{d}_9$ = 41.1
69	1.6	

F_b = 38.0% excess $\underline{d}_3$, $\underline{d}_6$

Crossing Experiments

The procedure used for these crossing experiments is essentially the same as that used for the 2-methylphenylmethane derivatives. The starting materials were, for the $\underline{d}_0,\underline{d}_9$ crossing experiments, 2-[2-(methoxymethyl)ethyl]phenyl-dimethylmethanaminium p-toluenesulfonate (111a) and 2-[2-($^2H_3$)methoxysulfonyl)ethyl]phenyl-di($^2H_3$)methylmethanaminium p-toluenesulfonate (111d), or, for the $\underline{d}_3,\underline{d}_6$ crossing experiments, 2-[2-($^2H_3$)methoxysulfonyl)ethyl]phenyl-dimethylmethanaminium p-toluenesulfonate (111b) and 2-[2-(methoxysulfonyl)ethyl]phenyl-di($^2H_3$)methylmethanaminium p-toluenesulfonate (111c).

With the exception of those mentioned below, all symbols and abreviations in the ensuing tables have the same meaning as defined for the 2-methylphenylmethane derivative crossing experiments.

The calculated percent reaction was obtained from equation (35) in which $[56]_0$ is the intial ester concentration

$$\% \text{ reaction calcd} = 100\left[\frac{[56]_0 - [56]_f}{[56]_0}\right] \qquad (35)$$

and $[56]_f$ is the final ester concentration as calculated from equation (8) in which t is the reaction time in seconds,

$$\frac{1}{[56]_f} = \frac{e^{k_1 t}}{[56]_0} + \frac{(e^{k_1 t}-1)}{EM} \qquad (8)$$

EM is the assumed effective molarity (2.0×10^{-3} mol L^{-1})

and k_1 is the first order rate constant (2×10^{-6} s^{-1}).†

The organic soluble residues gave ^{1}H NMR spectra consistent with the same previously mentioned "oil" (^{1}H NMR ($CDCl_3$) δ: 1.0 - 1.5, (br m)).

In the experiments with reaction times of 6 or more h, the spectra contained, as well as the "oil"'s multiplet, all of the peaks that were found in the ^{1}H NMR of 4,5-dihydro-1H-2,3-benzoxathiepin ("sultone", **115**). The IR spectra of these mixtures also contained all of **115**'s bands. The combined organic residue from experiments 1 through 5 was recrystallized from ether-petroleum ether (bp 30-60°C) with Norite to give white needles (3 mg), mp 113-115°C. Mixed mp with an authentic specimen of **115** showed no depression. The presence of **115** in the organic residues of crossing experiments is indicated as "sultone" in the ensuing tables. An estimate of the yields of **115** was made by correcting the weights of the organic residues, $W_\emptyset$, for the weight of oil present in each. The average concentration of oil was deduced by dividing the total weight of oil isolated from all of the experiments in this section in which no **115** was observed plus all oil isolated from the 2-methylphenylmethane derivative crossing experiment organic residues by the total volume of stock solutions used in these experiments (11.9 mg/278 mL = 40 mgL^{-1}). Equation (34) then gives the sultone yield where V_S in the volume of stock solution

† Equation (8) is derived in Appendix 1.

$$\% 115 = 100 \left[\frac{W_0 - V_s (40\ mgL^{-1})}{198\ V_f\ [56]_0} \right] \quad (34)$$

used, 198 is the molecular weight of 115, V_f is the final solution volume and $[56]_0$ is the crossing experiment initial ester concentration.

The ^1H NMR product ratio, expressed as % 57 was obtained by the comparison of the integral of the peak ascribed to the aromatic protons in the betaine (I_T, δ = 7.5 S,4H) with that of the "norbetaine" (I_D, δ = 7.3, S,4H). In experiments 14, 15, 20 and 21, the ^1H NMR spectrum were of sufficiently poor resolution that these peaks were inseparable. Instead, the integral of the multiplet ascribed to the ammonio methyls and the ethyl group in the betaine (I'_T, δ = 3.2 - 3.1 ppm,m,-9.5H) was compared with that of the N-methyls in the "norbetaine" (I'_D, δ = 2.2 ppm,3H). In the spectra obtained from experiments with reaction times greater than 6h, a singlet (δ = 3.0 ppm,T-60) was also observed.

Deionizing Resin Control Experiment:

2-[2-(Trimethylammoniomethyl)phenyl]ethanesulfonate (57a, 44 mg) in water (5 mL) was passed through a short column of deionizing resin (Fisher Rexyn 300 (^+H, OH), 20 eq). After rinsing the column with water, the combined eluant was evaporated to dryness to give 57a as white crystals (30 mg). A second idential cycle left 23 mg of 57a.

2-[2-(Dimethylammoniomethyl)phenyl]ethanesulfonate (57a, 30 mg) was subjected to a single cycle of the above manipulation. Evaporation of the eluant to dryness gave only a trace of white powder as a residue (<0.2 mg).

Stock Solution 1

Solution Preparation

Substrates: **111a** (d_0): 53.7 mg, 0.125 mmol

111d (d_9): 54.8 mg, 0.125 mmol

V_f = 50.0 mL

[stock] = 5.0×10^{-3} M

Analysis

V_A = 8.5 mL

Yields: Crude: 11.0 mg (calcd = 11.1 mg)

Pure : - (not obtained)

Mass spectrum

m/e	Intensity	(5 scans)
58	44.9	
59	100.0	d_0 = 100.0
60	12.6	
61	32.0	
62	86.6	d_3 = 87.8
63	21.7	
64	20.3	
65	79.7	d_6 = 81.2
66	32.1	
67	3.7	
68	70.0	d_9 = 71.8
69	2.5	

F_a = 0.8 % Excess d_0, d_9

Stock Solution 2

Solution Preparation

Substrates: **111a** (d_0): 53.7 mg, 0.125 mmol
111d (d_9): 54.8 mg, 0.125 mmol

V_f = 5.0 mL

[stock] = 5.0×10^{-2} M

Analysis

V_A = 365 μL

Yields: Crude: 4.9 mg (calcd = 4.8)
Pure : 4.2 mg

Mass spectrum

m/e	Intensity	(6 scans)
58	66.0	
59	100.0	d_0 = 100.0
60	19.6	
61	57.1	
62	106.6	d_3 = 107.9
63	40.5	
64	36.9	
65	105.2	d_6 = 106.8
66	71.5	
67	6.1	
68	106.1	d_9 = 109.7
69	4.1	

F_a = -1.2 % Excess d_0, d_9

Stock Solution 3

Solution Preparation

Substrates: **111b** ($\underline{d}_3$): 54.1 mg, 0.125 mmol

111c ($\underline{d}_6$): 54.5 mg, 0.125 mmol

V_f = 5.0 mL

[stock] = 5.0×10^{-2} M

Analysis

V_A = 375 μL

Yields: Crude: 4.6 mg (calcd = 4.9 mg)

Pure : 3.9 mg

Mass spectrum

m/e	Intensity	(7 scans)
58	60.0	
59	100.0	$\underline{d}_0$ = 100.0
60	17.1	
61	47.3	
62	95.6	$\underline{d}_3$ = 97.4
63	35.1	
64	31.3	
65	94.8	$\underline{d}_6$ = 97.9
66	54.9	
67	5.0	
68	85.7	$\underline{d}_9$ = 89.7
69	3.1	

F_b = 1.4 % Excess $\underline{d}_3$,$\underline{d}_6$

Stock Solution 4

Solution Preparation

Substrates: **111a** ($\underline{d_0}$): 107.4 mg, 0.25 mmol

111d ($\underline{d_9}$): 109.7 mg, 0.25 mmol

V_f = 50.0 mL

[stock] = 1.0×10^{-2} M

Analysis

V_A = 4.5 mL

Yields: Crude: 12.4 mg (calcd = 11.8 mg)

Pure : 11.1 mg

Mass spectrum

m/e	Intensity	(5 scans)
58	57.4	
59	100.0	$\underline{d_0}$ = 100.0
60	21.1	
61	57.6	
62	119.2	$\underline{d_3}$ = 122.8
63	44.3	
64	41.8	
65	123.2	$\underline{d_6}$ = 129.0
66	69.1	
67	8.5	
68	109.6	$\underline{d_9}$ = 118.0
69	3.9	

F_a = -7.2 % Excess $\underline{d_0}$,$\underline{d_9}$

Stock Solution 5

Solution Preparation

Substrates: **111b** ($\underline{d}_3$): 108.2 mg, 0.25 mmol

111c ($\underline{d}_6$): 108.9 mg, 0.25 mmol

V_f = 50.0 mL

[stock] = 1.0×10^{-2} M

Analysis

V_A = 4.5 mL

Yields: Crude: 11.0 mg (calcd = 11.8 mg)

Pure : 10.6 mg

Mass spectrum

m/e	Intensity	(6 scans)
58	73.5	
59	100.0	$\underline{d}_0$ = 100.0
60	19.1	
61	54.1	
62	91.3	$\underline{d}_3$ = 92.3
63	38.3	
64	33.5	
65	86.1	$\underline{d}_6$ = 88.1
66	61.6	
67	5.0	
68	77.9	$\underline{d}_9$ = 82.8
69	2.7	

F_b = -0.6 % Excess $\underline{d}_3$, $\underline{d}_6$

Stock Solution 6

Solution Preparation

Substrates: **111a** (d_0): 107.4 mg, 0.25 mmol

111d (d_9): 109.7 mg, 0.25 mmol

V_f = 100.0 mL

[stock] = 5.0×10^{-3} M

Analysis

V_A = 6.2 mL

Yields: Crude: 8.5 mg (calcd = 8.1 mg)

Pure : 8.0 mg

Mass spectrum

m/e	Intensity	(5 scans)
58	49.8	
59	100.0	d_0 = 100.0
60	15.3	
61	40.2	
62	101.0	d_3 = 101.8
63	28.9	
64	26.0	
65	96.9	d_6 = 98.3
66	49.9	
67	4.9	
68	94.6	d_9 = 98.2
69	3.4	

F_a = -0.5% Excess d_0,d_9

Stock Solution 7

Solution Preparation

Substrates: **111b** ($\underline{d}_3$): 108.2 mg, 0.25 mmol

111c ($\underline{d}_6$): 108.9 mg, 0.25 mmol

V_f = 100.0 mL

[stock] = 5.0×10^{-3} M

Analysis

V_A = 6.9 mL

Yields: Crude: 9.3 mg (calcd = 9.0 mg)

Pure : 8.1 mg

Mass spectrum

m/e	Intensity	(6 scans)
58	46.0	
59	100.0	$\underline{d}_0$ = 100.0
60	13.5	
61	34.5	
62	25.7	$\underline{d}_3$ = 94.9
63	25.7	
64	23.8	
65	94.1	$\underline{d}_6$ = 95.4
66	39.2	
67	4.5	
68	83.7	$\underline{d}_9$ = 85.6
69	3.0	

F_b = 1.3 % Excess $\underline{d}_3$, $\underline{d}_6$

Crossing Experiment 1

Solution Preparation:

Stock Solution 1 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 10.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 14 da (calcd % reaction = 98)

Products

(a) Organic Residue: 0.9 mg, oil and sultone (5%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 38 I_D = 7

%57 = 85

Yields: Crude: 12.4 mg (calcd = 13.0 mg)

Pure: 4.2 mg (31%)

Mass Spectrum

m/e	Intensity (5 scans)	
58	70.6	
59	100.0	$\underline{d_0}$ = 100.0
60	16.5	
61	41.3	
62	71.0	$\underline{d_3}$ = 73.0
63	30.5	
64	26.9	
65	71.3	$\underline{d_6}$ = 72.8
66	64.3	
67	5.1	
68	84.1	$\underline{d_9}$ = 89.9
69	3.0	

F_a = 13.1% excess $\underline{d_0}$,$\underline{d_9}$

Crossing Experiment 2

Solution Preparation:

Stock Solution 1 (d_0,d_9) [stock] = 5.0×10^{-3} M

V_S = 5.0 mL V_F = 10.0 mL

$[E]_0$ at 23°C = 2.5×10^{-3} M $[E]_0$ at 110.0°C = 2.2×10^{-3} M

Reaction Time = 14 da (calcd % reaction = 97)

Products

(a) Organic Residue: 1.6 mg, oil and sultone (28%)

(b) Aqueous Residue:

^1H NMR Integrals: I_T = 21 I_D = 3

%57 = 87

Yields: Crude: 6.0 mg (calcd = 6.5 mg)

Pure: 2.2 mg (34%)

Mass Spectrum

m/e	Intensity (5 scans)	
58	29.3	
59	100.0	d_0 = 100.0
60	7.7	
61	16.6	
62	69.9	d_3 = 69.9
63	12.2	
64	11.7	
65	70.6	d_6 = 70.5
66	25.1	
67	4.0	
68	90.6	d_9 = 91.0
69	3.2	

F_a = 15.3% excess d_0,d_9

Crossing Experiment 3

Solution Preparation:

Stock Solution 1 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 5.0 mL V_f = 10.0 mL

$[E]_0$ at 23°C = 2.5×10^{-3} M $[E]_0$ at 110.0°C = 2.2×10^{-3} M

Reaction Time = 20.5 da (calcd % reaction = 99)

Products

(a) Organic Residue: 1.3 mg, oil and sultone (22%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 37 I_D = 9

%57 = 80

Yields: Crude: 8.0 mg (calcd = 6.5 mg)

Pure: 2.5 mg (38%)

Mass Spectrum

m/e	Intensity (5 scans)	
58	62.9	
59	100.0	d_0 = 100.0
60	15.5	
61	39.4	
62	76.0	d_3 = 77.9
63	29.6	
64	26.1	
65	77.2	d_6 = 79.0
66	62.4	
67	5.6	
68	92.2	d_9 = 97.7
69	3.4	

F_a = 11.5% excess $\underline{d_0}$,$\underline{d_9}$

Crossing Experiment 4

Solution Preparation:

Stock Solution 1 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 14 da (calcd % reaction = 90.1)

Products

(a) Organic Residue: 3.0 mg, mimly sultone (26%)

(b) Aqueous Residue:

^1H NMR Integrals: I_T = 36 I_D = 6

%57 = 86

Yields: Crude: 10.1 mg (calcd = 13.0 mg)

Pure: 1.5 mg (11%)

Mass Spectrum

m/e	Intensity (5 scans)	
58	39.8	
59	100.0	$\underline{d_0}$ = 100.0
60	10.6	
61	22.4	
62	70.5	$\underline{d_3}$ = 71.2
63	17.8	
64	16.8	
65	74.6	$\underline{d_6}$ = 75.6
66	38.4	
67	5.0	
68	99.0	$\underline{d_9}$ = 100.8
69	3.6	

F_a = 15.5% excess $\underline{d_0}$,$\underline{d_9}$

Crossing Experiment 5

Solution Preparation:

Stock Solution 1 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 20.5 da (calcd % reaction = 96)

Products

(a) Organic Residue: 4.5 mg, sultone (41%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 39 I_D = 13

%57 = 75

Yields: Crude: 11.3 mg (calcd = 12.9 mg)

Pure: 0.7 mg (5%)

Mass Spectrum

m/e	Intensity (5 scans)	
58	72.7	
59	100.0	$\underline{d_0}$ = 100.0
60	19.9	
61	53.5	
62	90.5	$\underline{d_3}$ = 92.5
63	40.5	
64	37.3	
65	98.7	$\underline{d_6}$ = 99.3
66	83.0	
67	6.9	
68	109.8	$\underline{d_9}$ = 114.8
69	3.8	

F_a = 5.6% excess $\underline{d_0}$,$\underline{d_9}$ = 5.6

Crossing Experiment 6

Solution Preparation:

Stock Solution 2 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-2}

V_s = 2.0 mL V_f = 2.0 mL

[E]ø at 23°C = 5.0×10^{-2} M [E]ø at 110.0°C = 4.5×10^{-2} M

Reaction Time = 45 min (calcd % reaction = 20)

Products

(a) Organic Residue: 0.4 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 31 I_D = 130

%57 = 19

Yields: Crude: 27.5 mg (calcd = 25.0 mg)

Pure: 3.6 mg (14%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(5 scans)	m/e	Intensity	(6 scans)
58	65.6		58	48.9	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	20.7		60	14.3	
61	56.8		61	39.7	
62	102.5	$\underline{d_3}$ = 106.1	62	100.7	$\underline{d_3}$ = 101.1
63	40.5		63	27.9	
64	36.7		64	25.0	
65	99.8	$\underline{d_6}$ = 103.6	65	96.9	$\underline{d_6}$ = 97.4
66	81.6		66	52.9	
67	6.9		67	5.6	
68	114.0	$\underline{d_9}$ = 121.4	68	108.1	$\underline{d_9}$ = 110.4
69	4.0		69	3.9	
F_a = 2.7% excess $\underline{d_0}$,$\underline{d_9}$			F_a = 2.7% excess $\underline{d_0}$,$\underline{d_9}$		

Crossing Experiment 7

Solution Preparation:

Stock Solution 3 ($\underline{d}_3,\underline{d}_6$) [stock] = 5.0×10^{-2} M

V_S = 2.0 mL V_f = 2.0 mL

[E]ø at 23°C = 5.0×10^{-2} M [E]ø at 110.0°C = 4.5×10^{-2} M

Reaction Time = 45 min (calcd % reaction = 20)

Products

(a) Organic Residue: 0.7 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 14 I_D = 74

%57 = 16

Yields: Crude: 25.1 mg (calcd = 24.8 mg)

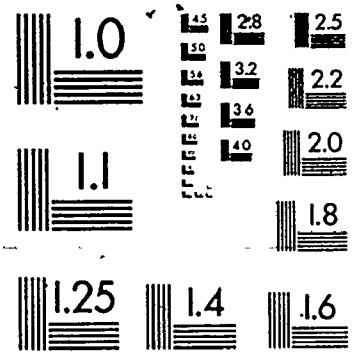
Pure: 3.5 mg (14%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (7 scans)		m/e	Intensity (6 scans)	
58	56.5		58	53.5	
59	100.0	$d_ø$ = 100.0	59	100.0	$d_ø$ = 100.0
60	16.7		60	14.9	
61	48.1		61	40.6	
62	102.9	d_3 = 104.4	62	94.6	d_3 = 95.1
63	36.7		63	31.5	
64	33.1		64	27.6	
65	107.5	d_6 = 110.2	65	98.3	d_6 = 99.8
66	52.2		66	44.8	
67	5.5		67	4.5	
68	90.4	d_9 = 93.0	68	80.3	d_9 = 83.0
69	3.3		69	3.0	

F_b = 5.3% excess $\underline{d}_3,\underline{d}_6$ F_b = 3.2% excess $\underline{d}_3,\underline{d}_6$

5 5

OF / DE



Crossing Experiment 8

Solution Preparation:

Stock Solution 2 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-2} M

V_S = 2.0 mL V_f = 4.0 mL

$[E]_0$ at 23°C = 2.5×10^{-2} M $[E]_0$ at 110.0°C = 2.2×10^{-2} M

Reaction Time = 85 min (calcd % reaction = 20)

Products

(a) Organic Residue: 0.5 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 23 I_D = 113

%57 = 17

Yields: Crude: 26.1 mg (calcd = 24.9 mg)

Pure: 3.3 mg (13%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(7 scans)	m/e	Intensity	(6 scans)
58	66.6		58	67.0	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	21.7		60	33.0	
61	60.0		61	60.8	
62	110.7	$\underline{d_3}$ = 113.0	62	110.6	$\underline{d_3}$ = 113.2
63	44.7		63	45.6	
64	40.6		64	40.7	
65	111.7	$\underline{d_6}$ = 114.6	65	109.9	$\underline{d_6}$ = 113.7
66	89.6		66	86.1	
67	8.4		67	8.9	
68	129.5	$\underline{d_9}$ = 136.0	68	122.5	$\underline{d_9}$ = 130.2
69	4.8		69	4.9	
F_a = 1.8% excess $\underline{d_0}$,$\underline{d_9}$			F_a = 0.7% excess $\underline{d_0}$,$\underline{d_9}$		

Crossing Experiment 9

Solution Preparation:

Stock Solution 3 ($\underline{d_3}$,$\underline{d_6}$) [stock] = 5.0×10^{-2} M

V_s = 2.0 mL V_f = 4.0 mL

$[E]_0$ at 23°C = 2.5×10^{-2} M $[E]_0$ at 110.0°C = 2.2×10^{-2} M

Reaction Time = 85 min (calcd % reaction = 20).

Products

(a) Organic Residue: 0.3 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 17 I_D = 79

%57 = 18

Yields: Crude: 25.5 mg (calcd = 24.9 mg)

Pure: 3.3 mg (13%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(7 scans)	m/e	Intensity	(5 scans)
58	57.5		58	63.8	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	18.3		60	18.3	
61	48.0		61	49.8	
62	105.5	$\underline{d_3}$ = 106.5	62	96.9	$\underline{d_3}$ = 98.2
63	36.9		63	37.3	
64	33.4		64	32.6	
65	109.0	$\underline{d_6}$ = 110.9	65	98.8	$\underline{d_6}$ = 100.3
66	52.5		66	50.2	
67	5.2		67	4.6	
68	89.5	$\underline{d_9}$ = 92.0	68	77.0	$\underline{d_9}$ = 79.2
69	3.4		69	2.8	
F_b = 6.2% excess $\underline{d_3}$,$\underline{d_6}$			F_b = 5.1% excess $\underline{d_3}$,$\underline{d_6}$		

Crossing Experiment 10

Solution Preparation:

Stock Solution 4 (d_0,d_9) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 5.0 mL

$[E]_0$ at 23°C = 1.0×10^{-2} M $[E]_0$ at 110.0°C = 8.9×10^{-3} M

Reaction Time = 3.5 h (calcd % reaction = 20)

Products

(a) Organic Residue: 0.3 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 13 I_D = 57

%57 = 19

Yields: Crude: 14.5 mg (calcd = 12.5 mg)

Pure: 1.5 mg (11%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(6 scans)	m/e	Intensity	(7 scans)
58	47.9		58	43.6	
59	100.0	d_0 = 100.0	59	100.0	d_0 = 100.0
60	14.8		60	11.9	
61	37.4		61	28.9	
62	99.4	d_3 = 99.8	62	83.3	d_3 = 83.6
63	27.6		63	20.9	
64	25.9		64	17.5	
65	102.1	d_6 = 101.8	65	77.8	d_6 = 78.0
66	60.3		66	45.0	
67	6.6		67	5.1	
68	127.4	d_9 = 130.0	68	95.2	d_9 = 99.9
69	4.8		69	3.3	
F_a = 6.6% excess d_0,d_9			F_a = 10.6% excess d_0,d_9		

Crossing Experiment 11

Solution Preparation:

Stock Solution 5 ($\underline{d}_3,\underline{d}_6$) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 5.0 mL

$[E]_\emptyset$ at 23°C = 1.0×10^{-2} M $[E]_\emptyset$ at 110.0°C = 8.9×10^{-3} M

Reaction Time = 3.5 h (calcd % reaction = 20)

Products

(a) Organic Residue: 0.3 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 12 I_D = 65

%57 = 16

Yields: Crude: 9.5 mg (calcd = 12.5 mg)

Pure: 2.0 mg (15%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (5 scans)		m/e	Intensity (6 scans)	
58	58.0		58	48.0	
59	100.0	$\underline{d}_\emptyset$ = 100.0	59	100.0	$\underline{d}_\emptyset$ = 100.0
60	20.2		60	16.7	
61	60.3		61	46.6	
62	127.6	$\underline{d}_3$ = 129.0	62	118.4	$\underline{d}_3$ = 120.0
63	43.6		63	34.5	
64	40.4		64	30.5	
65	132.7	$\underline{d}_6$ = 133.7	65	117.0	$\underline{d}_6$ = 119.6
66	55.4		66	42.3	
67	5.3		67	4.6	
68	92.9	$\underline{d}_9$ = 95.3	68	82.3	$\underline{d}_9$ = 85.3
69	3.5		69	3.2	
F_b = 14.7% excess $\underline{d}_3,\underline{d}_6$			F_b = 12.8% excess $\underline{d}_3,\underline{d}_6$		

Crossing Experiment 12

Solution Preparation:

Stock Solution 4 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 1.0×10^{-2} M

V_S = 5.0 mL V_f = 6.7 mL

$[E]_0$ at 23°C = 7.5×10^{-3} M $[E]_0$ at 110.0°C = 6.7×10^{-3} M

Reaction Time = 4.7 h (calcd % reaction = 21)

Products

(a) Organic Residue: 0.1 mg, oil

(b) Aqueous Residue:

^1H NMR Integrals: I_T = 13 I_D = 58

%57 = 18

Yields: Crude: 12.1 mg (calcd = 12.5 mg)

Pure: 1.4 mg (11%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(5 scans)	m/e	Intensity	(6 scans)
58	23.9		58	45.1	
59	100.0	d_0 = 100.0	59	100.0	d_0 = 100.0
60	7.8		60	11.6	
61	14.8		61	27.1	
62	77.2	d_3 = 77.5	62	88.0	d_3 = 84.6
63	10.9		63	21.3	
64	10.7		64	19.4	
65	75.1	d_6 = 75.3	65	89.8	d_6 = 87.0
66	24.9		66	42.8	
67	4.7		67	6.6	
68	106.5	d_9 = 107.7	68	127.8	d_9 = 121.5
69	3.5		69	5.3	
F_a = 15.3% excess $\underline{d_0}$,$\underline{d_9}$			F_a = 12.7% excess $\underline{d_0}$,$\underline{d_9}$		

Crossing Experiment 13

Solution Preparation:

Stock Solution 5 ($\underline{d_3}$,$\underline{d_6}$) [stock] = 1.0×10^{-2} M

V_S = 5.0 mL V_f = 6.7 mL

$[E]_\emptyset$ at 23°C = 7.5×10^{-3} M $[E]_\emptyset$ at 110.0°C = 6.7×10^{-3} M

Reaction Time = 4.7 h (calcd % reaction = 21)

Products

(a) Organic Residue: 0.7 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 12.5 I_D = 62

%57 = 17

Yields: Crude: 11.0 mg (calcd = 12.4 mg)

Pure: 2.1 mg (16%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (7 scans)		m/e	Intensity (scans)	
58	6.9		58	58.9	
59	100.0	$d_\emptyset$ = 100.0	59	100.0	$d_\emptyset$ = 100.0
60	5.5		60	23.5	
61	9.4		61	63.7	
62	144.9	d_3 = 145.9	62	138.9	d_3 = 139.6
63	9.3		63	49.0	
64	8.7		64	45.1	
65	147.6	d_6 = 149.7	65	139.6	d_6 = 143.2
66	9.9		66	59.6	
67	3.8		67	5.9	
68	94.6	d_9 = 96.0	68	91.4	d_9 = 96.8
69	3.3		69	3.4	
F_b = 20.3% excess $\underline{d_3}$,$\underline{d_6}$			F_b = 17.9% excess $\underline{d_3}$,$\underline{d_6}$		

Crossing Experiment 14

Solution Preparation:

Stock Solution 6 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 10.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 6.0 h (calcd % reaction = 20)

Products

(a) Organic Residue: 0.6 mg, oil plus a trace of sultone (2%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 52 I_D = 28

%57 = 17

Yields: Crude: 10.7 mg (calcd = 12.4 mg)

Pure: 2.1 mg (16%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(6 scans)	m/e	Intensity	(5 scans)
58	35.6		58	63.7	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	8.5		60	14.3	
61	19.5		61	36.6	
62	69.7	$\underline{d_3}$ = 69.2	62	73.6	$\underline{d_3}$ = 73.6
63	14.3		63	27.4	
64	12.7		64	24.2	
65	67.4	$\underline{d_6}$ = 67.3	65	73.8	$\underline{d_6}$ = 74.1
66	35.8		66	72.2	
67	4.5		67	6.0	
68	100.2	$\underline{d_9}$ = 102.2	68	111.6	$\underline{d_9}$ = 115.4
69	3.5		69	4.1	

F_a = 19.4% excess $\underline{d_0}$,$\underline{d_9}$ F_a = 18.7% excess $\underline{d_0}$,$\underline{d_9}$

Crossing Experiment 15

Solution Preparation:

Stock Solution 7 ($\underline{d}_3$,$\underline{d}_6$) [stock] = 5.0×10^{-3} M

V_s = 10.0 mL V_f = 10.0 mL

$[E]_\emptyset$ at 23°C = 5.0×10^{-3} M $[E]_\emptyset$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 6.0 h (calcd % reaction = 20)

Products

(a) Organic Residue: 0.6 mg, oil plus a trace of sultone (2%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 69 I_D = 33

%57 = 20

Yields: Crude: 11.5 mg (calcd = 12.5 mg)

Pure: 2.0 mg (15%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (6 scans)		m/e	Intensity (5 scans)	
58	48.9		58	64.2	
59	100.0	$\underline{d}_\emptyset$ = 100.0	59	100.0	$\underline{d}_\emptyset$ = 100.0
60	18.3		60	23.9	
61	50.2		61	66.1	
62	130.8	$\underline{d}_3$ = 131.1	62	136.4	$\underline{d}_3$ = 135.3
63	35.9		63	51.4	
64	33.7		64	45.3	
65	127.5	$\underline{d}_6$ = 128.8	65	138.6	$\underline{d}_6$ = 139.8
66	41.5		66	58.1	
67	4.4		67	5.2	
68	78.3	$\underline{d}_9$ = 81.0	68	88.7	$\underline{d}_9$ = 90.6
69	2.7		69	3.5	
F_b = 17.9% excess $\underline{d}_3$,$\underline{d}_6$			F_b = 18.1% excess $\underline{d}_3$,$\underline{d}_6$		

Crossing Experiment 16

Solution Preparation:

Stock Solution 4 (d_0,d_9) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 15.0 mL

$[E]_0$ at 23°C = 2.5×10^{-3} M $[E]_0$ at 110.0°C = 2.2×10^{-3} M

Reaction Time = 13.5 h (calcd % reaction = 25)

Products

(a) Organic Residue: 1.5 mg, oil and sultone (18%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 19 I_D = 47

%57 = 29%

Yields: Crude: 11.4 mg (calcd = 8.7 mg)

Pure: 2.5 mg (19%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (6 scans)		m/e	Intensity (5 scans)	
58	68.0		58	65.9	
59	100.0	d_0 = 100.0	59	100.0	d_0 = 100.0
60	13.9		60	15.8	
61	35.7		61	40.0	
62	69.7	d_3 = 68.6	62	76.6	d_3 = 77.3
63	26.6		63	30.4	
64	23.9		64	28.2	
65	69.6	d_6 = 69.2	65	79.2	d_6 = 80.3
66	65.6		66	74.6	
67	5.4		67	6.8	
68	97.5	d_9 = 99.6	68	108.8	d_9 = 114.4
69	3.1		69	4.1	
F_a = 18.3% excess d_0,d_9			F_a = 15.2% excess d_0,d_9		

Crossing Experiment 17

Solution Preparation:

Stock Solution 5 ($\underline{d}_3$,$\underline{d}_6$) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 15.0 mL

$[E]_\emptyset$ at 23°C = 2.5×10^{-3} M $[E]_\emptyset$ at 110.0°C = 2.2×10^{-3} M

Reaction Time = 13.5 h (calcd % reaction = 25)

Products

(a) Organic Residue: 0.6 mg, oil and sultone (5%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 18 I_D = 53

%57 = 25%

Yields: Crude: 9.5 mg (calcd = 12.5 mg)

Pure: 2.5 mg (19%)

Mass Spectrum 1

m/e	Intensity	(5 scans)
58	65.8	
59	100.0	$\underline{d}_\emptyset$ = 100.0
60	27.5	
61	80.7	
62	153.2	$\underline{d}_3$ = 155.0
63	60.9	
64	53.2	
65	154.5	$\underline{d}_6$ = 158.1
66	71.2	
67	6.1	
68	100.5	$\underline{d}_9$ = 104.9
69	3.4	

F_b = 20.9% excess $\underline{d}_3$,$\underline{d}_6$

Mass Spectrum 2

m/e	Intensity	(6 scans)
58	64.0	
59	100.0	$\underline{d}_\emptyset$ = 100.0
60	23.9	
61	68.5	
62	131.5	$\underline{d}_3$ = 133.0
63	49.7	
64	45.8	
65	128.2	$\underline{d}_6$ = 132.7
66	65.7	
67	6.0	
68	94.4	$\underline{d}_9$ = 99.7
69	3.5	

F_b = 14.3% excess $\underline{d}_3$,$\underline{d}_6$

Crossing Experiment 18

Solution Preparation:

Stock Solution 4 (d_0,d_9) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 13.0 h (calcd % reaction = 16)

Products

(a) Organic Residue: 4.0 mg, oil and sultone (38%)

(b) Aqueous Residue:

^{1}H NMR Integrals: $I_T = 7$ $I_D = 65$

%57 = 10%

Yields: Crude: 10.0 mg (calcd = 12.4 mg)

Pure: 0.9 mg (7%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(5 scans)	m/e	Intensity	(5 scans)
58	67.1		58	51.1	
59	100.0	d_0 = 100.0	59	100.0	d_0 = 100.0
60	18.1		60	13.7	
61	51.3		61	37.8	
62	97.3	d_3 = 97.3	62	97.1	d_3 = 95.7
63	37.6		63	29.5	
64	35.1		64	27.3	
65	99.8	d_6 = 100.1	65	102.9	d_6 = 102.3
66	83.0		66	65.4	
67	7.0		67	7.6	
68	121.8	d_9 = 125.8	68	132.7	d_9 = 135.2
69	4.1		69	5.1	
F_a = 6.7% excess d_0,d_9			F_a = 8.6% excess d_0,d_9		

Crossing Experiment 19

Solution Preparation:

Stock Solution 5 ($\underline{d}_3,\underline{d}_6$) [stock] = 1.0×10^{-2} M

V_S = 5.0 mL V_f = 50.0 mL

$[E]_\emptyset$ at 23°C = 1.0×10^{-3} M $[E]_\emptyset$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 13.0 h (calcd % reaction = 16)

Products

(a) Organic Residue: 1.7 mg, oil and sultone (15%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 8 I_D = 71

%57 = 10 %

Yields: Crude: 10.1 mg (calcd = 12.4 mg)

Pure: 1.4 mg (11%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(6 scans)	m/e	Intensity	(6 scans)
58	135.0		58	94.1	
59	100.0	$\underline{d}_\emptyset$ = 100.0	59	100.0	$\underline{d}_\emptyset$ = 100.0
60	27.9		60	24.1	
61	79.2		61	65.3	
62	138.8	$\underline{d}_3$ = 103.4	62	141.2	$\underline{d}_3$ = 117.1
63	62.3		63	52.1	
64	117.6		64	86.2	
65	144.0	$\underline{d}_6$ = 135.5	65	155.9	$\underline{d}_6$ = 148.6
66	70.7		66	60.0	
67	5.6		67	6.5	
68	90.9	$\underline{d}_9$ = 70.2	68	102.1	$\underline{d}_9$ = 85.3
69	3.4		69	3.6	
F_b = 16.8% excess $\underline{d}_3,\underline{d}_6$			F_b = 17.8% excess $\underline{d}_3,\underline{d}_6$		

Crossing Experiment 20

Solution Preparation:

Stock Solution 6 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_s = 50.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 1.3 h (calcd % reaction = 5)

Products

(a) Organic Residue: 0.5 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 84 I_D = 57

%57 = 5

Yields: Crude: 62.9 mg (calcd = 61.7 mg)

Pure: 2.6 mg (4%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(6 scans)	m/e	Intensity	(6 scans)
58	61.8		58	60.6	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	15.2		60	13.8	
61	38.9		61	36.3	
62	81.0	$\underline{d_3}$ = 81.0	62	72.8	$\underline{d_3}$ = 74.0
63	28.6		63	26.6	
64	25.8		64	24.3	
65	81.7	$\underline{d_6}$ = 81.3	65	72.8	$\underline{d_6}$ = 74.4
66	75.6		66	71.1	
67	6.7		67	6.0	
68	123.0	$\underline{d_9}$ = 126.4	68	111.1	$\underline{d_9}$ = 116.5
69	4.6		69	4.0	
F_a = 16.5% excess $\underline{d_0}$,$\underline{d_9}$			F_a = 18.6% excess $\underline{d_0}$,$\underline{d_9}$		

Crossing Experiment 21

Solution Preparation:

Stock Solution 7 ($\underline{d_3}$,$\underline{d_6}$) [stock] = 5.0×10^{-3} M

V_s = 50.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 1.3 h (calcd % reaction = 5)

Products

(a) Organic Residue: 1.1 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 64 I_D = 47

%57 = 8

Yields: Crude: 56.4 mg (calcd = 61.8 mg)

Pure: 1.8 mg (3%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (6 scans)		m/e	Intensity (6 scans)	
58	51.4		58	45.5	
59	100.0	d_0 = 100.0	59	100.0	d_0 = 100.0
60	20.0		60	17.3	
61	58.7		61	49.1	
62	139.7	d_3 = 141.4	62	134.9	d_3 = 135.5
63	45.3		63	38.2	
64	40.1		64	34.0	
65	143.2	d_6 = 147.2	65	135.9	d_6 = 138.5
66	50.7		66	41.6	
67	5.1		67	4.3	
68	89.9	d_9 = 93.6	68	86.1	d_9 = 87.9
69	3.2		69	3.0	
F_b = 19.7% excess $\underline{d_3}$,$\underline{d_6}$			F_b = 18.7% excess $\underline{d_3}$,$\underline{d_6}$		

Crossing Experiment 22

Solution Preparation:

Stock Solution 6 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 5.0×10^{-3} M

V_S = 20.0 mL V_f = 20.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 2.7 h (calcd % reaction = 10)

Products

(a) Organic Residue: 0.4 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 7 I_D = 65

%57 = 10%

Yields: Crude: 21.1 mg (calcd = 24.8 mg)

Pure: 1.3 mg (5%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(5 scans)	m/e	Intensity	(6 scans)
58	40.7		58	50.4	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	8.8		60	11.7	
61	22.5		61	28.0	
62	73.2	$\underline{d_3}$ = 71.5	62	72.4	$\underline{d_3}$ = 71.9
63	16.4		63	19.4	
64	15.4		64	17.2	
65	72.0	$\underline{d_6}$ = 71.1	65	71.7	$\underline{d_6}$ = 69.3
66	42.0		66	55.6	
67	5.4		67	6.3	
68	111.8	$\underline{d_9}$ = 112.0	68	111.7	$\underline{d_9}$ = 114.6
69	3.9		69	3.9	
F_a = 19.6% excess $\underline{d_0}$,$\underline{d_9}$			F_a = 20.6% excess $\underline{d_0}$,$\underline{d_9}$		

Crossing Experiment 23

Solution Preparation:

Stock Solution 7 ($\underline{d_3}$,$\underline{d_6}$) [stock] = 5.0×10^{-3} M

V_S = 20.0 mL V_f = 20.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 2.7 h (calcd % reaction = 10)

Products

(a) Organic Residue: 0.5 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 11 I_D = 77

%57 = 13

Yields: Crude: 21.8 mg (calcd = 24.8 mg)

Pure: 1.4 mg (5%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (5 scans)		m/e	Intensity (6 scans)	
58	36.0		58	48.7	
59	100.0	d_0 = 100.0	59	100.0	d_0 = 100.0
60	12.8		60	21.1	
61	38.8		61	58.9	
62	141.2	d_3 = 138.8	62	141.7	d_3 = 146.0
63	29.6		63	47.9	
64	27.2		64	40.8	
65	143.2	d_6 = 142.9	65	148.4	d_6 = 155.4
66	32.3		66	52.1	
67	4.3		67	5.9	
68	89.6	d_9 = 89.3	68	96.1	d_9 = 101.2
69	2.9		69	3.7	
F_b = 19.6% excess $\underline{d_3}$,$\underline{d_6}$			F_b = 20.0% excess $\underline{d_3}$,$\underline{d_6}$		

Crossing Experiment 24

Solution Preparation:

Stock Solution 4 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 1.0×10^{-2} M

V_S = 5.0 mL V_f = 10.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 4.9 h (calcd % reaction = 16.5)

Products

(a) Organic Residue: 0.6 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 9 I_D = 66

%57 = 12

Yields: Crude: 10.9 mg (calcd = 12.4 mg)

Pure: 1.3 mg (10%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(6 scans)	m/e	Intensity	(6 scans)
58	75.6		58	53.2	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	19.9		60	11.8	
61	53.9		61	30.5	
62	89.5	$\underline{d_3}$ = 90.6	62	71.7	$\underline{d_3}$ = 71.8
63	39.2		63	22.5	
64	35.8		64	19.7	
65	89.8	$\underline{d_6}$ = 90.0	65	71.5	$\underline{d_6}$ = 71.6
66	88.4		66	56.4	
67	6.8		67	5.7	
68	109.3	$\underline{d_9}$ = 115.8	68	104.6	$\underline{d_9}$ = 108.3
69	3.9		69	4.0	

F_a = 8.6% excess $\underline{d_0}$,$\underline{d_9}$ F_a = 18.4% excess $\underline{d_0}$,$\underline{d_9}$

Crossing Experiment 25

Solution Preparation:

Stock Solution 5 ($\underline{d}_3$,$\underline{d}_6$) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 10.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 4.9 h (calcd % reaction = 16.5)

Products

(a) Organic Residue: 0.2 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 12 I_D = 72

%57 = 14%

Yields: Crude: 12.1 mg (calcd = 12.4 mg)

Pure: 1.3 mg (10%)

Mass Spectrum 1

m/e	Intensity (5 scans)	
58	63.9	
59	100.0	$\underline{d}_0$ = 100.0
60	24.6	
61	72.6	
62	139.8	$\underline{d}_3$ = 141.9
63	52.2	
64	47.0	
65	138.7	$\underline{d}_6$ = 141.6
66	57.4	
67	5.0	
68	83.7	$\underline{d}_9$ = 86.9
69	2.9	

F_b = 20.5% excess $\underline{d}_3$,$\underline{d}_9$

Mass Spectrum 2

m/e	Intensity (6 scans)	
58	54.2	
59	100.0	$\underline{d}_0$ = 100.0
60	20.9	
61	62.2	
62	142.5	$\underline{d}_3$ = 143.5
63	45.8	
64	40.8	
65	141.3	$\underline{d}_6$ = 144.0
66	51.6	
67	5.1	
68	88.7	$\underline{d}_9$ = 91.9
69	3.2	

F_b = 20.0% excess $\underline{d}_3$,$\underline{d}_6$

Crossing Experiment 26

Solution Preparation:

Stock Solution 4 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 1.0×10^{-2} M

V_S = 5.0 mL V_f = 10.0 mL

$[E]_0$ at 23°C = 5.0×10^{-3} M $[E]_0$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 7.0 h (calcd % reaction = 23)

Products

(a) Organic Residue: 0.2 mg, oil plus a trace of sultone (<1%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 13 I_D = 65

%57 = 17%

Yields: Crude: 13.3 mg (calcd = 12.4 mg)

Pure: 1.7 mg (13%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity	(5 scans)	m/e	Intensity	(5 scans)
58	80.4		58	53.7	
59	100.0	$\underline{d_0}$ = 100.0	59	100.0	$\underline{d_0}$ = 100.0
60	17.3		60	14.2	
61	48.0		61	37.3	
62	76.2	$\underline{d_3}$ = 76.2	62	86.6	$\underline{d_3}$ = 87.2
63	33.2		63	28.0	
64	31.2		64	25.7	
65	75.2	$\underline{d_6}$ = 74.9	65	86.6	$\underline{d_6}$ = 88.3
66	85.4		66	57.8	
67	6.2		67	6.1	
68	103.4	$\underline{d_9}$ = 107.6	68	104.1	$\underline{d_9}$ = 105.5
69	3.5		69	3.9	
F_a = 15.8% excess $\underline{d_0}$,$\underline{d_9}$			F_a = 8.6% excess $\underline{d_0}$,$\underline{d_9}$		

Crossing Experiment 27

Solution Preparation:

Stock Solution 5 ($\underline{d}_3$,$\underline{d}_6$) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 10.0 mL

$[E]_\emptyset$ at 23°C = 5.0×10^{-3} M $[E]_\emptyset$ at 110.0°C = 4.5×10^{-3} M

Reaction Time = 7.0 h (calcd % reaction = 23)

Products

(a) Organic Residue: 0.8 mg, oil plus a trace of sultone (6%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 14 I_D = 68

%57 = 17%

Yields: Crude: 10.5 mg (calcd = 12.4 mg)

Pure: 2.0 mg (15%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (5 scans)		m/e	Intensity (6 scans)	
58	74.3		58	52.7	
59	100.0	$\underline{d}_\emptyset$ = 100.0	59	100.0	$\underline{d}_\emptyset$ = 100.0
60	28.0		60	20.4	
61	84.6		61	58.6	
62	143.8	$\underline{d}_3$ = 144.5	62	140.0	$\underline{d}_3$ = 140.7
63	61.1		63	43.2	
64	53.5		64	37.8	
65	140.7	$\underline{d}_6$ = 142.9	65	137.0	$\underline{d}_6$ = 139.1
66	67.6		66	46.5	
67	6.3		67	5.1	
68	82.8	$\underline{d}_9$ = 88.4	68	85.7	$\underline{d}_9$ = 87.7
69	2.9		69	3.3	

F_b = 20.8% excess $\underline{d}_3$,$\underline{d}_6$ F_b = 19.7% excess $\underline{d}_3$,$\underline{d}_6$

Crossing Experiment 28

Solution Preparation:

Stock Solution 4 (d_0,d_9) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 50.0 mL

[E]ø at 23°C = 1.0×10^{-3} M [E]ø at 110.0°C = 8.9×10^{-4} M

Reaction Time = 29.0 h (calcd % reaction = 30)

Products

(a) Organic Residue: 4.0 mg, oil plus sultone (38%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 22 I_D = 39

%57 = 36

Yields: Crude: 11.0 mg (calcd = 12.6 mg)

Pure: 1.0 mg (8%)

Mass Spectrum 1

m/e	Intensity (6 scans)	
58	80.8	
59	100.0	d_0 = 100.0
60	18.0	
61	48.1	
62	76.2	d_3 = 76.4
63	37.3	
64	33.0	
65	81.6	d_6 = 81.5
66	91.6	
67	6.8	
68	110.6	d_9 = 115.2
69	3.8	

F_a = 15.4% excess d_0,d_9

Mass Spectrum 2

m/e	Intensity (6 scans)	
58	54.0	
59	100.0	d_0 = 100.0
60	14.4	
61	35.1	
62	81.3	d_3 = 82.2
63	26.8	
64	24.9	
65	85.8	d_6 = 86.4
66	52.7	
67	6.9	
68	115.4	d_9 = 113.2
69	4.7	

F_a = 11.7% excess d_0,d_9

Crossing Experiment 29

Solution Preparation:

Stock Solution 5 ($\underline{d_3}$,$\underline{d_6}$) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 50.0 mL

$[E]_\emptyset$ at 23°C = 1.0×10^{-3} M $[E]_\emptyset$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 29.0 h (calcd % reaction = 30)

Products

(a) Organic Residue: 2.7 mg, oil plus sultone (25%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 21 I_D = 37

%57 = 36

Yields: Crude: 10.6 mg (calcd = 12.6 mg)

Pure: 4.5 mg (29%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (5 scans)		m/e	Intensity (6 scans)	
58	77.0		58	59.5	
59	100.0	$\underline{d}_\emptyset$ = 100.0	59	100.0	$\underline{d}_\emptyset$ = 100.0
60	25.8		60	22.9	
61	74.4		61	61.2	
62	131.8	$\underline{d}_3$ = 128.7	62	140.5	$\underline{d}_3$ = 138.1
63	55.9		63	49.0	
64	60.3		64	50.7	
65	138.8	$\underline{d}_6$ = 140.8	65	145.3	$\underline{d}_6$ = 149.6
66	70.1		66	61.2	
67	6.2		67	8.1	
68	101.3	$\underline{d}_9$ = 98.6	68	109.7	$\underline{d}_9$ = 110.8
69	3.3		69	4.1	
F_b = 15.2% excess $\underline{d}_3$,$\underline{d}_6$			F_b = 15.4% excess $\underline{d}_3$,$\underline{d}_6$		

Crossing Experiment 30

Solution Preparation:

Stock Solution 4 ($\underline{d_0}$,$\underline{d_9}$) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 49.0 h (calcd % reaction = 45)

Products

(a) Organic Residue: 4.0 mg, oil and sultone (38%)

(b) Aqueous Residue:

^1H NMR Integrals: I_T = 33 I_D = 18

%57 = 65

Yields: Crude: 11.0 mg (calcd = 12.8 mg)

Pure: 1.8 mg (14%)

Mass Spectrum 1

m/e	Intensity	(5 scans)
58	65.0	
59	100.0	d_0 = 100.0
60	18.0	
61	47.5	
62	92.4	d_3 = 93.2
63	37.7	
64	35.2	
65	95.3	d_6 = 98.6
66	79.5	
67	7.6	
68	114.6	d_9 = 121.7
69	4.1	

F_a = 7.2% excess $\underline{d_0}$,$\underline{d_9}$

Mass Spectrum 2

m/e	Intensity	(6 scans)
58	61.6	
59	100.0	d_0 = 100.0
60	16.7	
61	44.7	
62	90.4	d_3 = 91.4
63	34.9	
64	30.4	
65	96.1	d_6 = 96.9
66	76.7	
67	6.5	
68	117.4	d_9 = 123.3
69	4.5	

F_a = 8.5% excess $\underline{d_0}$,$\underline{d_9}$

Crossing Experiment 31

Solution Preparation:

Stock Solution 5 ($\underline{d}_3$,$\underline{d}_6$) [stock] = 1.0×10^{-2} M

V_s = 5.0 mL V_f = 50.0 mL

$[E]_0$ at 23°C = 1.0×10^{-3} M $[E]_0$ at 110.0°C = 8.9×10^{-4} M

Reaction Time = 49.0 h (calcd % reaction = 45)

Products

(a) Organic Residue: 3.0 mg, oil and sultone (28%)

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 30 I_D = 16

%57 = 65

Yields: Crude: 11.2 mg (calcd = 12.8 mg)

Pure: 1.9 mg (15%)

Mass Spectrum 1			Mass Spectrum 2		
m/e	Intensity (6 scans)		m/e	Intensity (6 scans)	
58	68.5		58	64.1	
59	100.0	$\underline{d}_0$ = 100.0	59	100.0	$\underline{d}_0$ = 100.0
60	25.2		60	23.4	
61	71.5		61	66.7	
62	132.3	$\underline{d}_3$ = 133.2	62	130.0	$\underline{d}_3$ = 131.4
63	55.2		63	51.2	
64	48.7		64	46.8	
65	138.2	$\underline{d}_6$ = 140.1	65	134.9	$\underline{d}_6$ = 138.2
66	72.6		66	69.0	
67	5.0		67	6.4	
68	100.9	$\underline{d}_9$ = 104.7	68	99.5	$\underline{d}_9$ = 105.1
69	3.6		69	3.9	

F_b = 14.4% excess $\underline{d}_3$,$\underline{d}_6$ F_b = 13.6% excess $\underline{d}_3$,$\underline{d}_9$

E. ^{18}O-$^{2}H_2$ Crossing Experiments

1. Mass Spectrometric Method

This section of the experimental contains mass spectra of mixtures of $^{18}O_1$ - (1,1-$^{2}H_2$)-1,4-dihydro-3,2-benzoxathiin 2,2-dioxide (**95e**) and its partially or unlabelled isomers. These were generated by thermolysis of mixtures of 2-(trimethylammoniomethyl)phenyl($^{2}H_2$)methane($^{18}O_1$)sulfonate (**55e**) and its partially or unlabelled isomers in the probe of the mass spectrometer. The spectra were recorded using the same technique as that described previously for the probe thermolysis of 2-(trimethylammoniomethyl)phenylmethane sulfonate **55a** and its deuterio methyl isomers (**55b**, **c**[*] and **d**). In this section, the range of m/e = 184 to m/e = 190 was scanned. For example, the full mass spectrum obtained in the first ^{18}O - $^{2}H_2$ crossing experiment is shown on the following page.

Sample--Total Spectrum:

	Peak Heights (mm)							
m/e	Scan 1	2	3	4	5	6	Total	Normalized
184	114	106	99	90	87	81	577	100
185	12.6	11.7	11.1	10.1	9.0	8.8	63.3	10.9
186	19.0	15.8	15.7	13.6	12.9	12.0	89.0	15.4
187	18.5	15.2	16.1	13.4	12.9	11.8	87.9	15.2
188	90	86	79	72	68	56	45.1	78.2
189	9.9	8.7	8.3	7.3	7.0	6.8	48.0	8.3
190	4.8	4.5	4.3	3.7	3.8	3.5	24.6	4.3

Calculation of the Label Distribution

In these spectra the following species were present:

Species	(m/e)
$C_8H_8{}^{16}O_3S$ ($^{16}\underline{O}, \underline{d}_0$)	184
$C_8H_7D{}^{16}O_3S$ ($^{16}\underline{O}, \underline{d}_1$)	185
$C_8H_6D_2{}^{16}O_3S$ ($^{16}\underline{O}, \underline{d}_2$)	186
$C_8H_8{}^{16}O_2{}^{18}OS$ ($^{18}\underline{O}, \underline{d}_0$)	186
$C_8H_7D{}^{16}O_2{}^{18}OS$ ($^{18}\underline{O}, \underline{d}_1$)	187
$C_8H_6D_2{}^{16}O_2{}^{18}OS$ ($^{18}\underline{O}, \underline{d}_2$)	188

Since the calculated isotopic cluster for **95** is 100, 9.9 and 5.2 for M, M + 1 and M + 2, the resulting overlap between these labelled species must be removed in order to determine their relative abundances. This may be accomplished sequentially, starting at m/e = 184, using the following equations:

$$P(m) = O(m) - 0.099\ P(m-1) - 0.052\ P(m-2)$$

$$T(m) = P(m) + 0.099\ P(m) + 0.052\ P(m)$$

where, at m/e = m, O(m) is the observed peak height, P(m) is the part of that peak height due to the parent peak from the species of m molecular weight, 0.099 P(m-1) is the M

+ 1 peak from the species of molecular weight (m-1) and Ø.Ø52 P(m-2) the the M + 2 of the species of m-2 molecular weight. T(m) is the sum of the peak heights for the isotopic cluster having m as the parent peak. The T(m) values are then normalized and reported adjacent to the appropriate species. Using the same example as above;

m/e	Intensity	T(m)	Normalized Abundances	Species
184	1ØØ	115.1	1ØØ----->	$^{16}O,d_Ø$
185	1Ø.9	1.2	1.Ø--->	$^{16}O,d_1$
186	15.4	11.6	8.6--->	$^{18}O,d_Ø+^{16}O,d_2$
187	15.2	16.3	11.Ø--->	$^{18}O,d_1$
188	78.2	87.8	76.3--->	$^{18}O,d_2$
189	8.3	Ø.1	-	
19Ø	4.3	Ø.33	-	

2. $^{18}O_1$-$^{2}H_2$ Betaine Thermolysis Control Experiments

Thermolysis Procedure:

A methanol solution of the betaine was injected into the probe of the mass spectrometer which was equilibrated at 260 ± 20°C.

(a) Betaines:

(i) 2-(Trimethylammoniomethyl)phenylmethanesulfonate, (**55a**):

Mass spectrum: (6 scans)

m/e	Intensity		Species and Abundances	
184	100	--->	^{16}O, d_0	100
185	11.0	--->	^{16}O, d_1	1.2
186	5.6	--->	^{16}O, d_2+^{18}O,d_0	0.4
187	0			

(ii) 2-(Trimethylammoniomethyl)phenyl($^{2}H_2$)methane($^{18}O_1$)sulfonate, (**55e**):

Mass Spectrum: (6 scans)

m/e	Intensity		Species and Abundances	
184	4.0	--->	^{16}O, d_0 =	4.1
185	1.7	--->	^{16}O, d_1 =	1.3
186	11.3	--->	^{16}O, d_2+^{18}O,d_0 =	11.2
187	15.2	--->	^{18}O, d_1 =	14.4
188	100.0	--->	^{18}O, d_2 =	100.0
189	10.5			
190	5.5			

(b) Authentic Betaine Mixture Control:

From a burette, water (49.7 mL) was added to 2-(trimethylammoniomethyl)phenylmethanesulfonate (**55a**, 19.1 mg). Similarly, 2-(trimethylammoniomethyl)phenyl($^{2}H_2$)methane

($^{18}O_1$)sulfonate (**55e**, 10.8 mg) was dissolved in 30.0 mL of water. The concentration of the first solution was adjusted by dilution and by the addition of **55a** until both solutions had a common absorbance of 0.960 ($\pm$.005) at 268 nm in 1 cm pathlength quartz U.V. cells. An aliquot of each solution (10.0 mL) was taken by transfer pipette. The aliquots were combined and the resulting solution evaporated to dryness. The residue was examined mass spectrometrically.

Mass Spectrum (7 scans)

m/e	Intensity	Species and Abundances		
184	100.0	---> ^{16}O, d_0	=	100.0
185	11.4	---> ^{16}O, d_1	=	1.5
186	13.9	---> $^{16}O_2$+^{18}O, d_0	=	8.6
187	13.3	---> ^{18}O, d_1	=	12.4
188	82.0	---> ^{18}O, d_2	=	80.4
189	8.7			
190	4.8			

3. $^{18}O - {}^{2}H_2$ Crossing Experiments

The procedure used for these crossing experiments was exactly the same as that used for the deuterio methyl crossing experiments involving 2-methylphenylmethyl derivatives. The substrates were 2-[($^{18}O_1$)methoxysulfonyl($^{2}H_2$)methyl]-phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (87e) and 2-(methoxysulfonylmethyl)phenyldimethylmethanaminium trifluoromethanesulfonate (87a). The range of m/e = 184 to 190 was analyzed mass spectrometrically.

^{18}O-$^{2}H_2$ Crossing Experiment Stock Solution

Solution Preparation:

Substrates: **87a** (d_0,^{16}O): 24.8 mg, 0.0625 mmol

87e (d_2,^{18}O): 25.0 mg, 0.0625 mmol

V_f = 25.0 mL

[stock] = 5.0×10^{-3} M

Analysis:

V_A = 4.7 mL

Yields: Crude: 6.0 (calcd. 6.0)

Pure: 5.1 mg

Mass Spectrum (6 scans)

m/e	Intensity		Species and Abundances		
184	100.0	--->	$^{16}O,d_0$	=	100.0
185	10.6	--->	$^{16}O,d_1$	=	1.0
186	14.6	--->	$^{16}O,d_2$+$^{18}O,d_0$	=	9.3
187	14.2	--->	$^{18}O,d_1$	=	13.2
188	77.9	--->	$^{18}O,d_2$	=	76.1
189	8.1				
190	4.2				

Crossing Experiment 1

Solution Preparation:

V_S = 10.0 mL V_f = 50.0 mL

[**54**]$_0$ at 23°C = 1.0 x 10^{-3} M [**54**]$_0$ at 110°C = 8.9 x 10^{-4} M

Reaction Time: 120 h (calcd. % reaction = 47)

Products:

(a) Organic Residue: 0.4 mg, oil

(b) Aqueous Residue:

^{1}H NMR Integrals: I_T = 33 I_D = 28

therefore: %**55** = 54

Yields: Crude: 12.5 mg

Pure: 6.1 mg

Mass Spectrum (6 scans)

m/e	Intensity		Species and Abundances		
184	100.0	--->	^{16}O,d_0	=	100.0
185	10.9	--->	^{16}O,d_1	=	1.0
186	15.4	--->	^{18}O,d_0+^{16}O,d_2	=	8.6
187	15.2	--->	^{18}O,d_1	=	11.0
188	78.2	--->	^{18}O,d_2	=	76.3
189	8.3				
190	4.3				

Crossing Experiment 2

Solution Preparation:

[stock] = 5.0×10^{-3} M

V_s = 10 mL V_f = 100.0 mL

$[54]_0$ at 23°C = 5.0×10^{-4} M $[54]_0$ at 110°C = 4.5×10^{-4} M

Reaction Time: 120 h (calcd. % reaction = 33)

Products:

(a) Organic Residue: 0.2 mg, oil

(b) Aqueous Residue:

^1H NMR Integrals: I_T = 29 I_D = 50

therefore: %55 = 39

Yields: Crude: 13.3 mg

Pure: 3.9 mg

Mass Spectrum (7 scans)

m/e	Intensity		Species and Abundances		
184	100.0	--->	$^{16}O, d_0$	=	100.0
185	11.3	--->	$^{16}O, d_1$	=	1.4
186	17.2	--->	$^{16}O, d_2 + ^{18}O, d_0$	=	11.9
187	17.5	--->	$^{18}O, d_1$	=	16.3
188	89.1	--->	$^{18}O, d_2$	=	86.9
189	9.9				
190	5.0				

F. ^{13}C NMR-^{18}O-Isotope Effect Experiments

1. ^{13}C NMR Procedure

The ^{13}C NMR spectra were obtained at 50.3 M Hz with a Varian XL200 spectrometer under conditions of complete proton decoupling. Unless otherwise specified, the samples were examined as 0.5 M nitromethane-d_3: acetonitrile-d_3 (1:1) solutions in 5.0 mm tubes. The operating conditions were: 2K Hz sweep width (sp^3 region), 5-8K transients, 30° pulse, 2 s repetition rate and 32K transforms.

2. Mass Spectrometric ^{18}O Analyses

The ^{18}O content in the labelled "norbetylates" was determined using the following procedure. The "norbetylate" was converted to 2-(-trimethylammoniomethyl)phenylmethane ($^{18}O_1$)surfonate, **55g**, using the procedure described for the preparation of the corresponding unlabelled betaine, **55a** (Method B). The labelled betaine, **55g**, was then injected, as a concentrated methanol solution, into the probe of the mass spectrometer which was thermally equilibrated to 240±20°C. The fragment attributable to $^{18}O_1$-1,4-dihydro--3,2-benzoxathiin 2,2-dioxide, **95g**, (m/e = 184 to 188) was examined mass spectrometrically using the method described in the ^{18}O-$^{2}H_2$ crossing experiments section. Since the calculated isotopic cluster for $C_8H_8{}^{16}O_3S$ is 100, 9.9 and 5.2 for m/e = 184, 185 and 186, overlap occurrs between the M + 2 for $C_8H_8{}^{16}O_3S$ and the parent peak for $C_8H_8{}^{18}O{}^{16}O_2S$ at m/e = 186. The M + 2 contribution to the total peak height at m/e = 186 is 0.052 times the peak height at m/e

= 184. The total contribution from $C_8H_8{}^{16}O_3S$ is then the sum of the peak heights for m/e = 184 and 185 plus 0.052 times the peak height at m/e = 184. The total $C_8H_8{}^{18}O^{16}O_2S$ contribution is then the sums of the peak heights for m/e = 186, 187 and 188 minus 0.052 times the peak height at m/e = 184. The ^{18}O content, expressed as $\%^{18}O_1$, was calculated using equation (49) where P(X) is the observed peak height at X m/e.

$$\%^{18}O_1 = 100 \left[\frac{P(186)+P(187)+P(188)-0.052\ P(184)}{P(184)+P(185)+P(186)+P(187)+P(188)}\right] \qquad (49)$$

3. Substrate Preparations

Methyl Phenylmethane($^{18}O_1$)sulfonate†

A 100 mL three neck round-bottom flask equipped with a nitrogen inlet and a pressure equalizing addition funnel was flame dried under nitrogen and then charged with $H_2{}^{18}O$ (Merck, Sharpe & Dohme, 97.5% excess ^{18}O, 120 μL, 5.5 mmol) and a solution of phenylmethanesulfonyl chloride (Eastmann, 1.0 g, 5 mmol) in anhydrous methylene chloride (30 mL). The mixture was stirred at 0°C and treated dropwise over 20 min. with anhydrous triethylamine (1.5 mL, 11 mmol) in anhydrous methylene chloride (5 mL). After the mixture was stirred at room temperature for 20 min., the solvent was removed by evaporation. The residue was passed through a strong acid ion exchange column (Rexyn 101, 50 meq's) in 30% aqueous dimethoxyethane (50 mL). The eluant was

---

†ie. A mixture composed of approximately 0.1 **128**-U, 0.6 **128**-S and 0.3 **128**-E.

neutralized with 10% aqueous tetraethylammonium hydroxide then evaporated to dryness. The residue was dissolved in 50% acetonitrile-benzene (50 mL), evaporated to dryness (x2) and then left overnight in vaccuo over phosphorus pentoxide. The resulting tan plates were dissolved in anhydrous methylene chloride (50 mL) and treated with methyl trifluoromethanesulfonate (3.4 mL, 30 mmol). The solution was left for 1 h at room temperature then washed with water (2 x 50 mL). The organic layer was dried over magnesium sulfate and evaporated to dryness to give a red oil which, on crystallization from hexane with cocoanut charcoal, gave the title compound as white needles (450 mg, 49%), mp 62-63°C. The ^{1}H NMR ($CDCl_3$) was identical to that obtained from methyl phenylmethanesulfonate (**128**). IR ($CHCl_3$) ν_{max}: 3020(m), 2980(w), 1490(m), 1349(s), 1270(m), 1165(s), 989(s), 957(m), 890(m), 815(s), 690(s) cm^{-1}. ^{13}C NMR ($CDCl_3$) δ: 55.9(CH_2), 56.6(CH_3), 127.7(CH), 128.8(CH), 128.9(CH), 130.5(CH). The peak assigned to the methyl carbon (δ = 56.6 ppm) was found to be a 2.5:1 doublet, the smaller peak being 1.7 H_z upfield of the larger peak.

2-[($^{18}O_1$)Methoxysulfonylmethyl]phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (**87**-E)

Using the procedure described for the preparation of 2-(Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (**87a**), 3,3-dimethyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (**86a**, 1.1 g, 3 mmol) was reacted with ($^{18}O_1$)methanol (200

μL, 4.5 mmol) to give the title compound as white needles (950 mg, 80%). The ^1H NMR (CD_3CN) was identical to that obtained for **87a**. The IR (KBr pellet) differed from the of **87a** only between 1,000 and 900 cm^{-1} where two bands, 986 (vw) and 955(s) were observed. ^{13}C NMR of the methyl carbon showed a singlet with a small shoulder 1.7 H_Z downfield. This partial spectrum is shown in Figure 15. A small portion (25 mg, 0.063 mmol) was converted to 2-(trimethylammoniomethyl)phenylmethane($^{18}O_1$)sulfonate (**55f**, 13 mg, 82%) which thermolized in the probe of the mass spectrometer to give the following spectrum.

m/e	Intensity	(12 scans)
184	6.6	
185	1.1	
186	100.0	
187	9.9	
188	5.5	$\%^{18}O_1$ = 93.5

<u>$^{18}O_1$-2-(Methoxysulfonyl methyl)phenyl-dimethylmethanaminium Trifluoromethanesulfonate</u>†

In the drybox, 3.3-dimethyl-3,4-dihydro-1H-2,3-benzothiazinium 2,2-dioxide trifluoromethanesulfonate (**86a**, 325 mg, 0.9 mmol) in anhydrous acetonitrile (10 mL) was treated with $H_2{}^{18}O$(Merck, Sharpe and Dohme, 97% excess ^{18}O, 150 μL), stoppered and left overnight at room temperature. The precipitate was collected by filtration and triturated with ice cold methanol to give 2-(dimethylammoniomethyl)-phenylmethane($^{18}O_1$)sulfonate, as white crystals (185 mg,

†A mixture of approximately 0.1 **87**-<u>U</u>, 0.6 **87**-<u>S</u> and 0.3 **87**-<u>E</u>.

89%). Without further purification, the crystals were stirred in methyl trifluoromethanesulfonate (3 mL) at 55°C for 24 h. After toluene (20 mL) was added, the solution was evaporated to dryness to give a white solid (310 mg) which was recrystallized from anhydrous acetone-ether to give the title mixture as white needles (270 mg, 76% (from 86a)). The ^{1}H NMR (CD_3CN) was identical to that obtained from the unlabelled analogue, 87a. The IR (KBr pellet) differed only between 1,000 and 900 cm^{-1} where two bands, 985(s) and 953(m) were observed. The ^{13}C NMR methoxymethyl resonances are shown in Figure 15. A small portion (25 mg, 0.063 mmol) was converted to 2-(trimethylammoniomethyl)phenylmethane($^{18}O_1$)sulfonate (55f, 14.2 mg, 87%) which, on thermolysis in the probe of the mass spectrometer, gave the following spectrum:

m/e	Intensity	(8 scans)
184	14.2	
185	1.7	
186	100.0	
187	9.8	
188	5.6	$\%^{18}O_1 = 87.3$

4. Authentic Mixture Control Experiments

A mixture of 2-(methoxysulfonylmethyl)phenyl-dimethylmethanaminium trifluoromethanesulfonate (87a or 87-U, 53 mg, 0.135 mmol) and 2-[($^{18}O_1$)methoxysulfonylmethyl]phenyl-dimethylmethanaminium trifluoromethanesulfonate (87-E, 54 mg, 0.135) was dissolved in 50% CD_3CN-CD_3NO_2(450 μL) and examined by ^{13}C NMR to give the partial spectrum shown

in Figure 15. The spectrum shows two methyl carbon peaks of equal intensity separated by 1.7 H_z. The solvent was removed by evaporation and the white crystalline residue was examined by IR (KBr pellet). The spectrum differed from that of **87a** only between 1,000 and 900 cm^{-1} where two bands, 986(m) and 955(m), were observed. A portion of the residue (25 mg, 0.063 mmol) was converted to 2-(trimethylammoniomethyl)phenylmethane [$^{18}O_1$] sulfonate (14.4 mg, 90%). Thermolysis in the probe of the mass spectrometer gave the following spectrum:

m/e	Intensity	(8 scans)
184	88.0	
185	9.1	
186	100.0	
187	9.9	$\%^{18}O_1$ = 52.2
188	5.2	

5. Recovered Starting Material Experiments

(i) After 33% Reaction

2-[($^{18}O_1$)Methoxysulfonylmethyl)phenyl-N,N-dimethylmethanaminium trifluoromethanesulfonate (**87**-E, 198 mg, 0.5 mmol) was shaken in cold aqueous saturated sodium carbonate and extracted with benzene (3 x 7 mL). The extract was dried over magnesium sulfate, transfered to the drybox and further dried for 20 min over anhydrous magnesium perchlorate then over calcium hydride for 20 min. The solution was filtered through Celite into a 25.0 mL volumetric flask which was then filled to the mark with anhydrous benzene. The reaction mixture was sealed at -78°C under nitrogen in a flame dried

Carius tube which was then immersed in a 110.0°C oil bath for 3.2 h. (This is the time necessary for 33% reaction based on a second order rate constant, k_{obs}, of 2.5 x 10^{-3} L $mol^{-1}s^{-1}$ and an initial substrate concentration of 1.8 x 10^{-2} M at 110°C). The tube was opened at -78°C and the contents, after warming to room temperature, were washed with ice-cold saturated aqueous sodium carbonate (25 mL). The organic layer was dried over magnesium sulfate and treated with anhydrous trifluoromethanesulfonic acid (30 μL, 0.33 mmol). Evaporation of the solvent left a brown solid (130 mg, 66%) which, after recrystallization from anhydrous acetone-ether with Norite, gave the unreacted starting material as colourless plates (81 mg, 41%). This material gave identical ^1H NMR and IR spectra to those obtained from the starting material. The ^{13}C NMR spectrum of the methyl carbon is shown in Figure 15. A portion of the recovered crystals (30 mg, 0.076 mmol) was converted to 2-(trimethylammoniomethyl)phenylmethane ($^{18}O_1$) sulfonate (17 mg, 91%) which, on thermolysis in the probe of the mass spectrometer, gave the following mass spectrum.

m/e	Intensity	(11 scans)
184	6.6	
185	1.1	
186	100.0	
187	9.8	
188	5.7	$\%^{18}O_1$ = 93.5

(b) After 66% Reaction

A second experiment was conducted on twice the previous

scale (ie. 1 mmol of **54** in 50.0 mL benzene) using the same procedure. The reaction time was 12.6 h (calcd. for 66% reaction assuming an initial substrate concentration of 1.8×10^{-2} M at 110 °C). After the reaction was quenched with trifluoromethanesulfonic acid (30 μL, 0.33 mmol), the solvent was removed by evaporation to leave a brown solid (125 mg, 32%) which, on recrystallization from anhydrous acetone-ether, gave colourless plates (85 mg, 21%). The ^{1}H NMR and IR were identical to those of the starting material. The ^{13}C NMR of the methyl carbon shown in Figure 15. A small portion of the recovered crystals (25 mg, 0.063 mmol) was converted to 2-(trimethylammoniomethyl)phenylmethane($^{18}O_1$)sulfonate (**55f**, 14 mg, 88%) which, on thermolysis in the probe of the mass spectrometer, gave the following mass spectrum:

m/e	Intensity (10 scans)	
184	6.6	
185	1.2	
186	100.0	
187	9.9	
188	5.5	$\%^{18}O_1 = 93.5$

Appendix 1: Mixed First and Second Order Rate Law Derivations:

$$E \longrightarrow B + C$$

For the above reaction scheme, the following equations apply:

$$\frac{dC}{dt} = k_1 E \qquad (3)$$

$$\frac{dB}{dt} = 2k_2 E^2 \qquad (4)$$

$$-\frac{dE}{dt} = k_1 E + 2k_2 E^2 \qquad (5)$$

$$EM = \frac{k_1}{k_2} \qquad (6)$$

It may be shown that,

1. at any time t;

$$\frac{1}{E_t} = \frac{e^{k_1 t}}{E_\emptyset} + \frac{2(e^{k_1 t} - 1)}{EM} \qquad (8)$$

2. $$k_1 = \frac{1}{t_f} \ln \left[\frac{E_\emptyset (EM + 2E_f)}{E_f (EM + 2E_\emptyset)} \right] \qquad (9)$$

3. The percent of the total product that is C is:

$$\% C = \frac{50\ EM}{(E_\emptyset - E_f)} \ln \left(\frac{2E_\emptyset + EM}{2E_f + EM} \right) \qquad (10)$$

Derivation of Equation (8):

Rearranging equation (5),

$$\frac{dE}{k_1 E + 2k_2 E^2} = -dt$$

$$\int_{E_\emptyset}^{E_f} \frac{dE}{E(k_1 + 2k_2 E)} = \int_0^t -dt$$

$$-\frac{1}{k_1} \ln\left(\frac{k_1 + 2k_2 E_f}{E_f}\right) + \frac{1}{k_1} \ln\left(\frac{k_1 + 2k_2 E_\emptyset}{E_\emptyset}\right) = -t$$

therefore, $$\ln\left[\left(\frac{k_1 + 2k_2 E_f}{E_f}\right)\left(\frac{E_\emptyset}{k_1 + 2k_2 E_\emptyset}\right)\right] = k_1 t \quad (1.1)$$

$$\ln\left[\frac{k_1 E_\emptyset + 2k_2 E_f E_\emptyset}{k_1 E_f + 2k_2 E_f E_\emptyset}\right] = k_1 t$$

$$\left(\frac{k_1 E_\emptyset + 2k_2 E_f E_\emptyset}{k_1 E_f + 2k_2 E_f E_\emptyset}\right) = e^{k_1 t}$$

$$\left[\frac{k_1 E_\emptyset + 2k_2 E_f E_\emptyset}{E_f(k_1 + 2k_2 E_\emptyset)}\right] = e^{k_1 t}$$

$$\frac{k_1 E_\emptyset}{E_f} + 2k_2 E_\emptyset = (k_1 + 2k_2 E_\emptyset)\, e^{k_1 t}$$

$$\frac{k_1 E_\emptyset}{E_f} = (k_1 + 2k_2 E_\emptyset)\, e^{k_1 t} - 2k_2 E_\emptyset$$

$$\frac{1}{E_f} = \left(\frac{k_1}{k_1 E_\emptyset} + \frac{2k_2 E_\emptyset}{k_1 E_\emptyset}\right) e^{k_1 t} - \frac{2k_2}{k_1}$$

$$\frac{1}{E_f} = \frac{e^{k_1 t}}{E_\emptyset} + \frac{2k_2}{k_1}(e^{k_1 t} - 1)$$

and since $k_1 = k_2EM$ (2)

$$\frac{1}{E_f} = \frac{e^{k_1 t}}{E_0} + \frac{2}{EM}(e^{k_1 t} - 1) \quad (8)$$

Derivation of Equation (9):

From Equation (1.1);

$$k_1 = \frac{1}{t}\ln\left[\frac{E_0(k_1 + 2k_2E_f)}{E_f(k_1 + 2k_2E_0)}\right]$$

since $k_1 = k_2EM$

$$k_1 = \frac{1}{t}\ln\left|\frac{E_0(k_2EM + 2k_2E_f)}{E_f(k_2EM + 2k_2E_0)}\right|$$

therefore $$k_1 = \frac{1}{t}\ln\left|\frac{E_0(EM + 2E_f)}{E_f(EM + 2E_0)}\right| \quad (9)$$

Derivation of Equation (10):

From Equations (4) and (5)

$$\frac{\frac{dC}{dt}}{\frac{dE}{dt}} = \frac{dC}{dE} = \frac{k_1E}{k_1E + 2k_2E^2}$$

$$= \frac{k_1}{k_1 + 2k_2E}$$

therefore $$dC = \frac{k_1 dE}{k_1 + 2k_2E}$$

Substituting $k_1 = k_2EM$

$$dC = \frac{k_2EMdE}{k_2EM + 2k_2E}$$

$$= \frac{EMdE}{EM + 2E}$$

$$\int_0^C dC = \int_{E_0}^{E_f} \frac{EMdE}{EM + 2E}$$

$$C = -\frac{EM}{2}\ln(EM + 2E_f) + \frac{EM}{2}\ln(EM + 2E_0)$$

$$= \frac{EM}{2} \ln\left(\frac{EM + 2E_{\emptyset}}{EM + 2E_f}\right)$$

By definition;

$$\% C = 100 \left(\frac{C}{E_{\emptyset} - E_f}\right)$$

$$\text{therefore } \% C = \frac{50EM}{(E_{\emptyset} - E_f)} \ln\left(\frac{EM + 2E_{\emptyset}}{EM + 2E_f}\right) \qquad (10)$$

Appendix 2: Deuterated Trimethylamine

. Mass Spectral Numercial Manipulations:

A necessary task in the interpretation of the crossing experiments described in Sections II A.4, B.4 and C.4 was the quantitative mass spectrometric differentration of $\underline{d}_0$-, $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-trimethylamine in mixtures of these compounds. The two major peaks in the mass spectrum of the $\underline{d}_0$-amine are the parent mass ion (m/e = 59) and the M - 1 peak (m/e = 58). The source of the latter is the fragment formed by the loss of a hydrogen atom from the parent radical cation. It follows then that $\underline{d}_9$-trimethyl amine will give an M - 2 peak caused by the loss of a deuterium atom. Both M - 1 and M - 2 peaks will be observed in the spectra of the $\underline{d}_3$- and $\underline{d}_6$-amines. The natural abundance of ^{13}C and ^{15}N will give rise to M + 1 peaks for each of the previous mentioned M, M - 1 and M - 2 peaks. Also, incomplete deuteration of the labelled methyls in the $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-amines will result in small M - 1 peaks from each of the peaks in these clusters. The resulting overlap between spectrally adjacent amine clusters must, therefore, be removed.

Since all of the ions in these spectra have three carbons and one nitrogen, the intensity of all of the M + 1's will be 3.77 relative to 100 for the corresponding ^{12}C, ^{14}N ion (the contribution of the natural abundance of deuterium to the M + 1 (0.01) is negligible and hence is ignored). The M + 1 induced overlap can be removed by relocating

the M + 1 peak with the corresponding $^{12}C,^{14}N$ ion using the following sequence: For the peak at m/e = 58, the M + 1 value is calculated (Ø.Ø377 times the m/e = 58 peak height), added to the m/e = 58 peak height and subtracted from the m/e = 59 peak height. The M + 1 from the remaining m/e = 59 peak height is then calculated and treated analogously. This sequence is then repeated consecutively for all other m/e's through m/e = 68. This results in a set of corrected peak heights in which the value at each m/e represents the peak height due to both the ion of that molecular weight and to its $^{13}C,^{15}N$ M + 1.

The overlap resulting from incomplete deuteration in the $\underline{d}_3$-, $\underline{d}_6$- and $\underline{d}_9$-amines can be removed, again, by relocating the so caused M - 1 peaks with the peaks from corresponding fully deuterated ions. Since after the relocation of the $^{13}C,^{15}N$ M + 1 peaks, the remaining peak at m/e = 67 is due solely to isotopic impurity in the $\underline{d}_9$ parent ion, its height provides an index of the amount of isotopic impurity in the deuterated methyls. A constant, **I**, may be calculated using equation (2.1). **I** represents the

$$\mathbf{I} = \frac{1}{9}\,\frac{(\text{height of m/e} = 67)}{(\text{height of m/e} = 68)} \qquad (2.1)$$

magnitude of the isotopic impurity per deuterium. Equation (2.2) gives the height of the M - 1 peaks relative to their corresponding fully deuterated M peaks. **Z** is the number

$$(\text{height of M} - 1) = (\text{height of M})\ \mathbf{I}\ \mathbf{Z} \qquad (2.2)$$

of deuteriums in M. To relocate the M - 1 peaks with their M peaks, the following sequence is employed. The value

for I is calculated as above. The M - 1 is then calculated for m/e = 68, added to m/e = 68 and subtracted from m/e = 67. The peak at m/e = 66 then gives its M - 1 which is treated analogously. The sequence is then repeated consecutively through m/e = 60. The resulting set of peak heights then represents, for each m/e, the total peak height of the fully deuterated $^{14}N,^{12}C$ ion of that molecular weight, its $^{15}N,^{13}C$ M + 1 and its M - 1 due to incomplete deuteration. The relative amount of the $\underline{d}_0$-amine in the mixture is then the sum of the corrected peak heights for m/e = 58 and 59. The total $\underline{d}_3$-amine is given by the sum of m/e = 60, 61 and 62; the $\underline{d}_6$-amine is the sum of m/e = 63, 64 and 65 and the $\underline{d}_9$-amine is given by the sum of m/e = 66, 67 and 68.

Program MSP2:

The BASIC computer program, MSP, was devised to perform the above described manipulations. The measured peak heights are input as a one-dimensional matrix, A(x), in which the element x corresponds to the peak height at (x + 57) m/e. (MAT A) line 60). A(x) is then normalized with respect to the most abundant amine (as chosen by inspection) to give the matrix, B(x), (lines 70 to 110). The $^{13}C,^{14}N$ M + 1's are then relocated using a loop (lines 120 to 150). For each x, the M + 1 is calculated and stored in a matrix, M(x), (line 130). M(x-1) is then subtracted from B(x) and M(x) is added to the residual peak height, (line 140). The loop gives a matrix, C(x), in which the $^{13}C,^{15}N$

M + 1's have been relocated with their corresponding $^{12}C,^{14}N$ ions. The next step in the program is the relocation of the M - 1's caused by incomplete deuteration in the labelled methyls. The constant, **I**, is calculated from C(10) and C(11), (line 170). (For spectra in which m/e = 67 and 68 are weak, an **I** is provided (line 190) based on the average deuterium combustion analysis results obtained from the betaines **53d**, **55d**, and **57d**). The number of deuterium atoms present in the fully deuterated ion at each m/e is stored as a one dimensional matrix, Z(x), (lines 200 and 210). The relocation of the M - 1's is effected in a loop (lines 220 to 250). For each C(x), the M - 1 from C(x + 1) is subtracted to give H(x), (line 230). The M - 1 is then calculated for and added to H(x) to give the matrix element, D(x), (line 240). After completion of the loop, matrix D(x) then represents, for each m/e, the peak height due to the ion of that molecular weight, its M + 1 from $^{13}C,^{15}N$ natural abundances and its M - 1 caused by incomplete deuteration. C(x) and D(x) are then normalized (lines 270 and 290). A loop is used to print, for each x, the corresponding m/e, A(x), B(x), C(x) and D(x) under the headings M/E, CRUDE, NORMAL, M + 1'D and ISO'D, (lines 370 to 410). The sums of the peak heights for each amine are then obtained such that the $\underline{d}_0$-amine is P(1), the $\underline{d}_3$-amine is P(2), the $\underline{d}_6$-amine is P(3) and the $\underline{d}_9$-amine is P(4), (lines 300 to 320). These values, after being normalized with respect to the previously chosen amine (lines 420 and 430), are

printed under the headings D_0, D_3, D_6 and D_9, (lines 450 and 460). Finally, the program compares the sum of the $\underline{d}_0$- and $\underline{d}_9$-amines with that of the $\underline{d}_3$-and $\underline{d}_6$-amines, (line 480). The difference between these sums is then divided by the sum of all of the amines, multiplied by 100 and printed beside the heading "% x's D0,D9 =" (or "% x's D3, D6 =", depending on which pair is more abundant), (lines 490 through 530).

```
10 REM MSP2 MASS SPEC PROGRAM
20 PRINT " N*ME3  MASS SPEC PROGRAM"
30 DIM A(15),B(15),C(15),D(15),H(15),M(15),P(15),Z(15)
40 M(0)=H(13)=0
50 PRINT" INPUT PEAK HEIGHTS (58,59,60,...,69)"
60 MAT INPUT A
70 PRINT" NORMALIZE TO D",
80 INPUT N
90 N2=N+2
100 N3=100/A(N2)
110 MAT B = (N3)*A
120 FOR X=1 TO 12
130 M(X)=(B(X)-M(X-1))*0.0377
140 C(X)=B(X)-M(X-1)+M(X)
150 NEXT X
160 IF C(10)<3 THEN 190
170 I=C(10)/(9*C(11))
180 GO TO 200
190 I=4.77/900
200 MAT READ Z(15)
210 DATA 0,0,2,3,3,5,6,6,8,9,9,0,0,0,0
220 FOR X=12 TO 1 STEP -1
230 H(X)=C(X)-Z(X+1)*I*H(X+1)
240 D(X)=H(X)+Z(X)*I*H(X)
250 NEXT X
260 N4=100/C(N2)
270 MAT C=(N4)*C
280 N5=100/D(N2)
290 MAT D=(N5)*D
300 P(1)=D(1)+D(2)
310 P(2)=D(3)+D(4)+D(5)
320 P(3)=D(6)+D(7)+D(8)
330 P(4)=D(9)+D(10)+D(11)+D(12)
340 PRINT
350 PRINT
360 PRINT
370 PRINT "M/E";TAB(5);"CRUDE","NORMAL","M+1'D","ISO'D"
380 PRINT
390 FOR X=1 TO 12
400 PRINT 57+X;TAB(5);A(X),B(X),C(X),D(X)
410 NEXT X
420 N6=100/P(N/3+1)
430 MAT P =(N6)*P
440 PRINT
450 PRINT "D0","D3","D6","D9"
460 PRINT P(1),P(2),P(3),P(4)
470 PRINT
480 IF(P(1)+P(4))<(P(2)+P(3)) THEN 520
490 W=100*(P(1)+P(4)-P(2)-P(3))/(P(1)+P(2)+P(3)+P(4))
500 PRINT "% X'S D0,D9=" W
510 GO TO 540
520 W=100*(P(2)+P(3)-P(1)-P(4))/(P(1)+P(2)+P(3)+P(4))
530 PRINT "% X'S D3,D6=" W
540 END
```

```
N*ME3  MASS SPEC PROGRAM
INPUT PEAK HEIGHTS (58,59,60,...,69)
?283.5,570,102,275,656,174,167,562,227,30,436,16
NORMALIZE TO D                ?0
```

M/E	CRUDE	NORMAL	M+1'D	ISO'D
58	283.5	49.7368	50.6873	50.7661
59	570	100	100	100
60	102	17.8947	14.4667	13.8486
61	275	48.2456	48.6222	47.537
62	656	115.088	115.454	116.854
63	174	30.5263	26.757	26.664
64	167	29.2982	28.8494	26.4313
65	562	98.5965	99.393	101.205
66	227	39.8246	36.8385	38.5713
67	30	5.26316	3.97492	0
68	436	76.4912	77.8031	81.9051
69	16	2.80702	-7.25179E-2	-7.26307E-2

D0	D3	D6	D9
100	118.223	102.344	79.8613

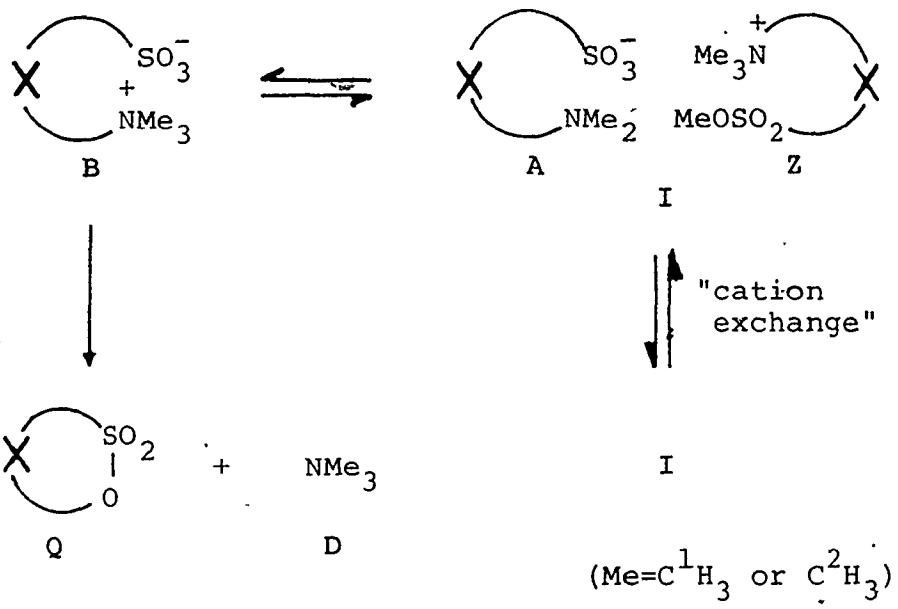
```
% X'S D3,D6= 10.1656
```

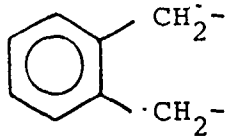
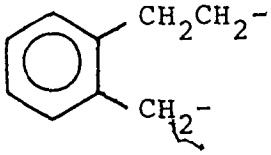
Appendix 3: Betaine Thermolysis Scrambling Derivations

A. Introduction:

The interpretation of the double-label crossing experiments described in Sections II A.4, B.4 and C.4 required a method for determing the relative amounts of the $\underline{d}_0$-, $\underline{d}_3$-, $\underline{d}_6$- and d_9-betaines (**B**) in mixtures of these compounds. As shown in Scheme 15. The betaines were each found to give the corresponding sultone (**Q**) and trimethylamine (**D**) as thermolysis products. However, when the amine mixtures were analyzed mass spectrometrically, their $\underline{d}_0:\underline{d}_3:\underline{d}_6:\underline{d}_9$ ratios were found to be different from the $\underline{d}_0:\underline{d}_3:\underline{d}_6:\underline{d}_9$ ratios of the betaine mixtures from which they were derived. This suggested that partial scrambling of the ammonio methyls was occurring during the course of the thermal betaine degradation. This appendix describes a general mechanism for the scrambling side reaction. From this mechanism, the equations used to predict the original betaine ratios from the observed amine ratios are derived.

As illustrated in Scheme 15, the betaine (**B**), on thermolysis, undergoes an intramolecular displacement of trimethylamine (**D**) to form the sultone (**Q**). Concurrent with this process is the reversible methyl transfer from **B** to **B** to form the ion pair (**I**) which consists of an anion (**A**) and a cation (**Z**). The exchange of cations by anions then provides the step through which the betaine ammonio methyls are ultimately scrambled. In the ensuing discussion, the term "cycle" will be used to denote a sequence consisting



X	B	Q
$-CH_2(CH_2)_2CH_2-$	53	58
	55	95
	57	115

Scheme 15

of the formation of **I** from **B**, the exchange of cations by **A** and then the return of **I** to form 2**B**. The "cycle" will be assumed to be pseudo first order in **B** and the amine producing thermolytic reaction will be assumed to be first order in **B**. Kinetic isotope effects will be assumed to be nil in the entire reaction sequence.

B. Betaine Label Distribution:

The effect of the intermolecular methyl exchange pathway on the label distribution in the betaine mixture will be examined first. In this treatment, both intermolecular equilibria will be considered to be irreversible processes. **B**, **A** and **D** will be referred to as BX_i, AX_i and DX_i such that X refers to the number of deuterated methyls in **B**, **A** or **D** and $_i$ denotes the number of cycles that the given species has completed. For example, Al_2 is the anion which has completed two exchange cycles and bears one deuterated methyl. BT_i will refer to the total amount of betaine which has completed i cycles and DT_i will represent the total amine generated from BT_i. Also, **U** will refer to the fraction of ammonio methyls that are unlabelled as defined by equation (3.1) and **L** will denote the fraction that are labelled.

$$U = \frac{3B\emptyset\emptyset + 2B1\emptyset + B2\emptyset}{BT\emptyset} \qquad (3.1)$$

$$L = 1-U \qquad (3.2)$$

The exchange pathways taken by the initial betaine mixture are illustrated in Figure 17. $B\emptyset\emptyset$, since it bears only unlabelled methyls, will form $A\emptyset\emptyset$ exclusively. Similarly $B3\emptyset$ will form only $A2\emptyset$. Since the chances of a $\underline{d}_3$-betaine

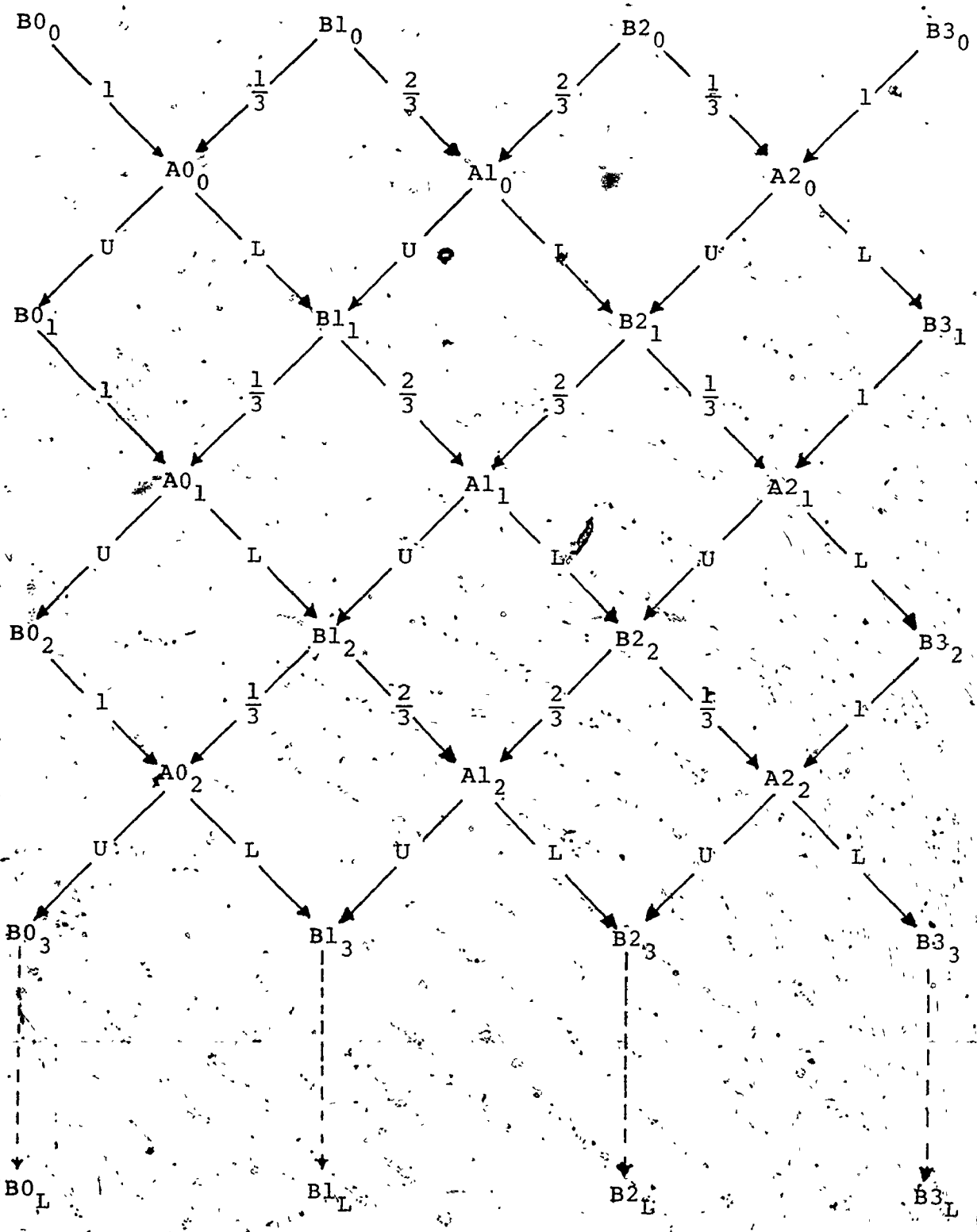


Figure 17

Multicycle Betaine Scrambling Pathway Diagram

losing a CH_3 group are twice as high as they are of losing a CD_3 group, $\underline{n}$ $B1_0$ will form $\underline{n}/3$ of AO_0 and $2\underline{n}/3$ of $A1_0$. Similarly $\underline{n}$ $B2_0$ will form $2\underline{n}/3$ of $A1_0$ and $\underline{n}/3$ of $A2_0$. After cation exchange, the anions will then react with cations to form the betaine. Since U represents the fraction of cations that are unlabelled and L represents the fraction that are labelled, $\underline{n}AO_0$ will yield $\underline{n}U$ of BO_1 and $\underline{n}L$ of $B1_1$ Similarly $\underline{n}A1_0$ will give $\underline{n}U$ of $B1_1$ and $\underline{n}L$ of $B2_1$ while $\underline{n}A2_0$ will yield $\underline{n}U$ of $B2_1$ and $\underline{n}L$ of $B3_1$. The betaines BO_1, $B1_1$ $B2_1$ and $B3_1$ will then repeat the cycle to give BO_2, $B1_2$, $B2_2$ and $B3_2$. After numerous cycles, the statistically scrambled betaine ratio ($U^3:3U^2L:3UL^2:L^3$ as predicted *via* the fork diagram shown in Figure 5, Section II A.4) will obtained. This ratio will be designated $\underline{BO}_L$: $\underline{B1}_L$: $\underline{B2}_L$: $\underline{B3}_L$.

Of interest to this discussion is the betaine distribution within each cycle and its dependence on the initial betaine distribution. The second reaction in a given cycle is described by equation (3.3) and

For X = 0 to 3;

$$\frac{BX}{BT}_{i+1} = U\frac{AX}{AT}_1 + L\frac{A(X-1)}{AT}_i \qquad (3.3)$$

The first reaction is described by equation (3.4).

For X = 0 to 3;

$$\frac{AX}{AT}_i = \frac{(3-X)BX}{3BT}_i + \frac{(1+X)B(X+1)}{3BT}_i \qquad (3.4)$$

Equation (3.4) may then be substituted into equation (3.3) to give equation (3.5) which expresses the distribution of a given betaine with respect to its cycle (BX_{i+1}/BT_{i+1})

as a function of the betaine distribution in the previous cycle (BX_i/BT_{i+1}).

For X = Ø to 3;

$$\frac{BX_{i+1}}{BT_{i+1}} = \frac{U}{3BT_i}\left[(3-X)BX_i + (1+X)B(X+1)_i\right] + \frac{L}{3BT_i}\left[(4-X)B(X-1)_i + XBX_i\right] \quad (3.5)$$

It follows that the initial betaine ratio will give, via equation (3.5), the betaine ratio obtained after one exchange. Similarly, the latter ratio may then be transformed into the second cycle distribution which in turn will give the third cycle distribution. Since these manipulations are rather tedious, a simple computer program, BSD, was devised to perform them. The program and the sets of betaine distributions obtained from a variety of initial betaine ratios are listed at the end of this Appendix.

C. Amine Product Mixtures:

It is necessary at this point to discuss the relationship between the betaine ratios that occur during the thermolysis and the observed amine ratios. At any given time during the thermolysis, the total betaine (BT_T) will consist of the sum of unscrambled (i = Ø) and scrambled components (i = 1,2,3...) in which each will be present in its appropriate label distribution. (a_i are coefficients such that their sum equals one). Since trimethylamine is being generated from each of these components via a first order pathway, each of the betaine components will produce an amine com-

$$BT_T = a_ØBT_Ø + a_1BT_1 + a_2BT_2 \ldots a_LBT_L \quad (3.6)$$

ponent bearing the same label distribution. That is;

For X = Ø to 3;

$$\frac{\mathbf{BX}_i}{\mathbf{BT}_i} = \frac{\mathbf{DX}_i}{\mathbf{DT}_i}$$

The amine mixture will then be the sum of these "cyclic" components:

$$\mathbf{DT}_T = b_Ø\mathbf{DT}_Ø + b_1\mathbf{DT}_1 + b_2\mathbf{DT}_2 \ldots b_2\mathbf{DT}_2 \qquad (3.7)$$

(b_i are coefficients such that their sum equals one)

In the ensuing manipulation of the amine ratios, it will be assumed that the amine consists of an unscrambled component and a scrambled component. Furthermore, it will be assumed that the scrambled amine component will consist of either single cycle scrambled amines or of statistically scrambled amines. The unscrambled component ($\mathbf{DT}_Ø$) will have the same label distribution as the unscrambled betaine ($\mathbf{BT}_Ø$);

For X = Ø to 3;

$$\frac{\mathbf{DX}_Ø}{\mathbf{DT}_Ø} = \frac{\mathbf{BX}_Ø}{\mathbf{BT}_Ø}$$

The single cycle scrambled amine ($\mathbf{DT}_1$) will be that derived from single scrambled betaine ($\mathbf{BT}_1$) and it will hence have the same label distribution as does the single scrambled betaine;

For X = Ø to 3;

$$\frac{\mathbf{DX}_1}{\mathbf{DT}_1} = \frac{\mathbf{BX}_1}{\mathbf{BT}_1}$$

The second type of scrambled amine component ($\mathbf{DT}_L$) will be that derived from statistically scrambled betaine ($\mathbf{BT}_L$) and therefore;

For X = Ø to 3;

$$\frac{DX_L}{DT_L} = \frac{BX_L}{BT_L}$$

The first treatment ($DT_T = (1 - Y)DT_Ø + YDT_Ø$) will overestimate the extent of scrambling in the amine mixture while the second ($DT_T = (1 - Y)DT_Ø + YDT_L$) will underestimate the extent of scrambling. ($Y \leq 1$)

D. Pure d_6-Betaine Scrambling Equations

1. Single Methyl Scrambling

If it is assumed that the scrambling in the thermolysis of the pure d_6-betaine is limited to one cycle then the following applies:

$$DT_T = (1 - S_1)DT_Ø + S_1DT_1 \qquad (3.8)$$

where S_1 is the mole fraction of the mixture that is attributable to scrambled amines. Since the label distribution in $DT_Ø$ is simply $D2_Ø$ and the distribution in DT_1 as predicted by Program BSD is 2:5:2 for $D1_1:D2_1:D3_1$ then the d_3-and d_6-amines in the mixture represent 4/9 of the scrambled component.

therefore $S_1 = \frac{9\ (D1_T + D3_T)}{4 \qquad DT_T} = \frac{9\ (d_3 + d_9)}{4\ (d_3 + d_6 + d_9)}$ (11)

2. Statistical Scrambling

$$DT_T = (1 - S_2)\ DT_Ø + S_2\ DT_L \qquad (3.9)$$

The above equation represents the composition of the amine mixture derived from the d_6-betaine if it is assumed that the scrambled component is present in the statistical label distribution; S_2 is the mole fraction of the amine mixture that is attributable to the scrambled component.

Since this component will be present in a 1:6:12:8-DO_L:$D1_L$:-$D2_L$:$D3_L$ mixture ($U3:3U^2L:3L^2U:L^3$ for $U = 1/3$ and $L = 2/3$), the $\underline{d}\emptyset$,$\underline{d}_3$ and $\underline{d}_9$-amines will comprise 15/27 of this component and therefore:

$$S_2 = \frac{27\,(D\emptyset_T + D1_T + D3_T)}{15 \qquad DT_T}$$

$$= \frac{27\,(\underline{d}\emptyset + \underline{d}_3 + \underline{d}_9)}{15\,(\underline{d}\emptyset + \underline{d}_3 + \underline{d}_6 + \underline{d}_9)} \qquad (12)$$

E. Crossing Experiment Product Thermolysis Scrambling Equations:

1. Excess $\underline{d}\emptyset$,$\underline{d}_9$ Mixtures:

In the excess $\underline{d}\emptyset$,$\underline{d}_9$ crossing experiment products and in the authentic mixtures that mimic them, the endocyclic product is present as a 1:1 -$\underline{d}\emptyset$:$\underline{d}_9$ betaine mixture while the intermolecular product is present as a 1:1:1:1-$\underline{d}\emptyset$:$\underline{d}_3$:$\underline{d}_6$:-$\underline{d}_9$ betaine mixture. It follows then that the true percentage of these mixtures that is attributable to the endocyclic product, C_a, is that defined by equation (13). In the scrambled amine mixture, the found % endo, F_a is defined by equation (14).

$$C_a = 100 \left[\frac{(B\emptyset_\emptyset + B3_\emptyset) - (B1_\emptyset + B2_\emptyset)}{BT_\emptyset}\right] \qquad (13)$$

$$F_a = 100 \left[\frac{(D\emptyset_T + D3_T) - (D1_T + D2_T)}{DT_T}\right] \qquad (14)$$

Equations that link C_a to F_a via scrambling corrections are then required.

(a) Single Methyl Scrambling.

If it is assumed that the amine mixture is made up

of unscrambled and single methyl scrambled components, then the mole fraction of the mixture that is attributable to the scrambled component, S_{1a}, is described by equation (16).

$$S_{1a} = 3\left[\frac{(C_a - F_a)}{100 + 2C_a}\right] \qquad (16)$$

This is derived as follows:

Since for X = 0 to 3,

$$\frac{BX_0}{BT_0} = \frac{DX_0}{DT_0}$$

equation (13) may be rewritten in terms of DX. To simplify the ensuing derivations, two new parameters will be defined:

$$C_a = \frac{100}{DT_0}\left[(D0_0 + D3_0) - (D1_0 + D2_0)\right] \qquad (3.10)$$

$$G_i = \frac{D0_i + D3_i}{DT_i} \qquad (3.11)$$

$$H_i = \frac{D1_i + D2_i}{DT_i} \qquad (3.12)$$

Equations (3.10) then becomes Equation (3.13);

$$C_a = 100(G_0 - H_0) \qquad (3.13)$$

and (14) becomes (3.14);

$$F_a = 100(G_T - H_T) \qquad (3.14)$$

A relationship between G_0 and G_1 and between H_0 and H_1 are required. Inspection of the betaine distribution generated from Program BDS (for mixtures in which U = L = .5) that are shown at the end of this Appendix reveals that BX_{i+1}/BT_{i+1} is always somewhere between BX_i/BT_i and BX_L/BT_L. Indeed, BX_{i+1}/BT_{i+1} is always two thirds of the way toward BX_L/BT_L. It follows then that the amine components

$$\frac{BX_{i+1}}{BT_{i+1}} = \frac{BX_i}{BT_i} - \frac{2}{3}\left[\frac{BX_i}{BT_i} - \frac{BX_L}{BT_L}\right]$$

will also have this property. (Equation (3.15).

$$\frac{DX_{i+1}}{DT_{i+1}} = \frac{DX_i}{DT_i} - \frac{2}{3}\left[\frac{DX_i}{DT_i} - \frac{DX_L}{DT_L}\right] \qquad (3.15)$$

$$= \frac{DX_i}{3DT_i} + \frac{2DX_L}{3DT_L}$$

Since the statistical distribution for $U = L = .5$ is 1:3:3:1, then $D\emptyset_L/DT_L = D3_L/DT_L = 1/8$ and $D1_L/DT_L = D2_L/DT_L = 3/8$. Equation (3.15) may then be solved for X = Ø to 3 and i = 1.

$$\frac{D\emptyset_1}{DT_1} = \frac{D\emptyset_\emptyset}{3DT_\emptyset} + \frac{1}{12}$$

$$\frac{D1_1}{DT_1} = \frac{D1_\emptyset}{3DT_\emptyset} + \frac{1}{4}$$

$$\frac{D2_1}{DT_1} = \frac{D2_\emptyset}{3DT_\emptyset} + \frac{1}{4}$$

$$\frac{D3_1}{DT_1} = \frac{D3_\emptyset}{3DT_\emptyset} + \frac{1}{12}$$

therefore, from equations (3.11) and (3.12)

$$G_1 = \frac{G_\emptyset}{3} + \frac{1}{6} \qquad (3.16)$$

$$H_1 = \frac{H_\emptyset}{3} + \frac{1}{2} \qquad (3.17)$$

These may then be used in conjunction with the single scrambling expression for the amine composition (3.8) to give F_a as a function of $G_\emptyset$, $H_\emptyset$ and S_{1a} (equation (3.16):

$$\frac{DX_T}{DT_T} = (1-S_{1a})\frac{DX_\emptyset}{DT_\emptyset} + S_{1a}\frac{DX_1}{DT_1} \qquad (3.8)$$

And Since: $F_a = 100\ (G_T - H_T)$

$$F_a = 100\left[\left((1-S_{1a})G_\emptyset + S_{1a}G_1\right) - \left((1-S_{1a})H_\emptyset + S_{1a}H_1\right)\right]$$

$$= 100\left[\left((1-S_{1a})G_\emptyset + S_{1a}\left(\frac{G_\emptyset}{3}+\frac{1}{6}\right)\right) - \left((1-S_{1a})H_\emptyset + S_{1a}\left(\frac{H_\emptyset}{3}+\frac{1}{2}\right)\right)\right]$$

$$= 100\left[\left(G_0\left(1-\frac{2}{3}S_{1a}\right)+\frac{S_{1a}}{6}\right) - \left(H_0\left(1-\frac{2}{3}S_{1a}\right)+\frac{S_{1a}}{2}\right)\right]$$

$$= 100\left[\left(G_0-H_0\right)\left(1-\frac{2}{3}S_{1a}\right)-\frac{S_{1a}}{3}\right]$$

therefore, $F_a = C_a\left(1-\frac{2}{3}S_{1a}\right)-\frac{100}{3}S_{1a}$ (3.18)

Rearrangement then gives (16) and (18).

$$S_{1a} = \frac{3\,(C_a - F_a)}{100 + 2C_a} \tag{16}$$

$$C_a = \frac{3F_a + 100S_{1a}}{3 - 2S_{1a}} \tag{18}$$

(b) Statistical Scrambling

If the scrambled component of the amine mixture is assumed to be present in the statistical distribution and its mole fraction is denoted S_{2a}, then the mixture composition is described by equation (3.19). It must be shown

$$DT_T = (1-S_{2a})DT_0 + S_{2a}DT_L \tag{3.19}$$

that equation (15) is true.

$$S_{2a} = \frac{C_a - F_a}{50 + C_a} \tag{15}$$

As previously shown;

$$C_a = 100\ (G_0 - H_0)$$

$$F_a = 100\ (G_T - H_T)$$

and $F_a = 100\left[\left((1-S_{2a})G_0+S_{2a}G_L\right) - \left((1-S_{2a})H_0+S_{2a}H_L\right)\right]$ (3.20)

Expressions for G_L and H_L are needed.

Since for $U = L = .5$, $D0_L:D1_L:D2_L:D3_L = 1:3:3:1$

and $G_L = \frac{D0_L + D3_L}{DT_L}$

$$G_L = \frac{1}{4} \tag{3.21}$$

$$H_L = \frac{D1_L + D2_L}{DT_L}$$

$$= \frac{3}{4} \qquad (3.22)$$

Substituting into (3.20);

$$F_a = 100\left[\left((1-S_{2a})G_0 + \frac{S_{2a}}{4}\right) - \left((1-S_{2a})H_0 + 3\frac{S_{2a}}{4}\right)\right]$$

$$= 100\left[(G_0-H_0)(1-S_{2a}) - \frac{S_{2a}}{2}\right]$$

$$F_a = C_a(1-S_{2a}) - 50S_{2a} \qquad (3.23)$$

Rearranging,

$$S_{2a} = \frac{C_a - F_a}{50 + C_a} \qquad (15)$$

and

$$C_a = \frac{F_a + 50S_{2a}}{(1 - S_{2a})} \qquad (19)$$

(c) Proof that $S_{1a} = 1.5S_{2a}$ (Equation (17)

$$S_{1a} = \frac{3(C_a - F_a)}{100 + 2C_a} \qquad (16)$$

$$= \frac{3(C_a - F_a)}{2(50 + C_a)}$$

Substituing Equation (15)

$$S_{1a} = \frac{3}{2}S_{2a} \qquad (17)$$

2. Excess d_3, d_6 Crossing Experiment Products:

In the excess d_3, d_6 crossing experiments products and in the corresponding authentic betaine mixture control experiments, the endocyclic product is present as a 1:1-d_3:d_6-mixture and the intermolecular product is present as a 1:1:1:1-d_0:d_3:d_6:d_9 mixture. The true percent endo, C_b,

in these mixtures is then defined by equation (22) and in the thermolysis derived amine mixture, the found percent endo, F_b, is defined by equation (24).

$$C_b = 100\left[\frac{(B1_0 + B2_0) - (B0_0 + B3_0)}{BT_0}\right] \quad (22)$$

$$F_b = 100\left[\frac{(D1_T + D2_T) - (D0_T + D3_T)}{DT_T}\right] \quad (24)$$

These may be rewritten as functions of H_i and G_i (see equation (3.10) through (3.13))

$$C_b = 100(H_0 - G_0) \quad (3.24)$$

$$F_b = 100(H_T - G_T) \quad (3.25)$$

(a) Single Methyl Scrambling:

If it is assumed that the scrambling is limited to one methyl exchange, then DT_T is composed of an unscrambled component (DT_0) and a single scrambled component (DT_1). If the mole fraction of the mixture attributable to scrambled amines is S_{1b}, then the composition of the entire amine mixture is described by equation (3.26).

$$DT_T = (1-S_{1b})DT_0 + S_{1b}(DT_1) \quad (3.26)$$

It must be shown that equation (26) is true.

$$S_{1b} = \frac{3(F_b - C_b)}{100 - 2C_b} \quad (26)$$

Since $$H_1 = \frac{H_0}{3} + \frac{1}{2} \quad (3.16)$$

and $$G_1 = \frac{G_0}{3} + \frac{1}{6} \quad (3.17)$$

(see equations (3.11), (3.12))

and

$$F_b = 100\left[\left((1-S_{1b})H_\emptyset + S_{1b}H_1\right) - \left((1-S_{1b})G_\emptyset + S_{1b}G_1\right)\right]$$

therefore

$$F_b = 100\left[\left((1-S_{1b})H_\emptyset + S_{1b}\left(\frac{H_\emptyset}{3}+\frac{1}{2}\right)\right) - \left((1-S_{1b})G_\emptyset + S_{1b}\left(\frac{G_\emptyset}{3}+\frac{1}{6}\right)\right)\right]$$

$$= 100\left[\left((1-\frac{2S_{1b}}{3})H_\emptyset + \frac{S_{1b}}{2}\right) - \left((1-\frac{2S_{1b}}{3})G_\emptyset + \frac{S_{1b}}{6}\right)\right]$$

$$= 100\left[(1-\frac{2S_{1b}}{3})(H_\emptyset - G_\emptyset) + \frac{S_{1b}}{3}\right]$$

$$F_b = C_b(1-\frac{2S_{1b}}{3}) + \frac{100S_{1b}}{3} \qquad (3.24)$$

Rearranging,

$$S_{1b} = \frac{3(F_b - C_b)}{100 - 2C_b} \qquad (26)$$

and

$$C_b = \frac{3F_b - 100S_{1b}}{3 - 2S_{1b}} \qquad (3.28)$$

(b) Statistical Scrambling:

If it is assumed that the scrambled component is statistically scrambled and its mole fraction of the mixture is S_{2b}, then total amine composition is expressed with equation (3.28). It must be shown that equation (26) is true.

$$DT_T = (1-S_{2b})DT_\emptyset + S_{2b}DT_L \qquad (3.29)$$

$$S_{2b} = \frac{(F_b - C_b)}{50 - C_b} \qquad (26)$$

again;

$$C_b = 100(H_\emptyset - G_\emptyset) \qquad (3.24)$$

and

$$F_b = 100(H_T - G_T) \qquad (3.25)$$

$$H_T = (1-S_{2b})H_\emptyset + S_{2b}H_L$$

$$G_T = (1-S_{2b})G_\emptyset + S_{2b}G_L$$

and since $G_L = \frac{1}{4}$ and $H_2 = \frac{3}{4}$

$$F_b = 100\left[\left((1-S_{2b})H\emptyset + \frac{3S_{2b}}{4}\right) - \left((1-S_{2b})G\emptyset + \frac{S_{2b}}{4}\right)\right]$$

$$= 100\left[(1-S_{2b})(H\emptyset - G\emptyset) + \frac{S_{2b}}{2}\right]$$

therefore $F_b = C_b(1-S_{2b}) + 50\,S_{2b}$ (3.30)

Rearranging,

$$S_{2b} = \frac{(F_b - C_b)}{50 - C_b} \quad (26)$$

and

$$C_b = \frac{F_b - 50S_{2b}}{(1 - S_{2b})} \quad (3.31)$$

3. Combined $d\emptyset, d9$-$d3, d6$ Crossing Experiments Derivations:

It must be shown that for complementary pair of experiments in which one is excess $d\emptyset, d9$ and the other is excess $d3, d6$ and both have the same percent endo, ($C_a = C_b$) then regardless of whether the scrambling is single or statistical, (provided it is the same in both thermolyses; i.e. $S_{1a} = S_{1b}$ or $S_{2a} = S_{2b}$), the true percent endo, C, may be gleaned from the F_a and F_b values using equation (29):

$$C = \frac{F_a + F_b}{2 + 0.02(F_a - F_b)} \quad (29)$$

a) Single Methyl Scrambling

Since $C_a = C_b$ then,

$$C = \frac{3F_a + 100S_{1a}}{3 - 2S_{1a}} = \frac{3F_b - 100S_{1b}}{3 - 2S_{1b}} \quad (18)\ \&\ (3.28)$$

Since $S_{1a} = S_{2a}$;

$$3F_a + 100S_{1a} = 3F_b - 100S_{1b}$$

therefore $S_{1a} = S_{1b} = \frac{3}{200}(F_b - F_a)$ (3.32)

Substituting (3.32) into (18),

$$C = \frac{3F_a + 100\left(\frac{3(F_b - F_a)}{200}\right)}{3 - 2\left(\frac{3(F_b - F_a)}{200}\right)}$$

$$= \frac{F_a + 0.05(F_b - F_a)}{1 - 0.01(F_b - F_a)}$$

$$C = \frac{F_a + F_b}{2 + 0.02(F_a - F_b)} \qquad (29)$$

(b) Statistical Scrambling:

Since $C_a = C_b$

$$C = \frac{F_a + 50S_{2a}}{(1 - S_{2a})} = \frac{F_b - 50S_{2b}}{(1 - S_{2b})} \qquad (19) \text{ \& } (3.31)$$

therefore since $S_{2a} = S_{2b}$,

$$F_a + 50S_{2a} = F_b - 50S_{2b}$$

therefore $$S_{2a} = S_{2b} = \frac{F_b - F_a}{100} \qquad (3.33)$$

Substituting (3.33) into (19);

$$C = \frac{F_a + 50\left(\frac{(F_b - F_a)}{100}\right)}{1 - \left(\frac{(F_b - F_a)}{100}\right)}$$

$$= \frac{F_a + .5F_b - .5F_a}{1 - 0.01(F_b - F_a)}$$

$$= \frac{F_a + F_b}{2 - 0.02(F_b - F_a)} \qquad (29)$$

E. Betaine Scrambling Distribution Program - BSD

The initial betaine ratio (B0ø:B1ø:B2ø:B3ø) is input as B5, B6, B7 and B8 (Line 65). These values are then normalized and become Bø, Bl, B2 and B3 such that Bø + Bl + B2 + B3 = 1. (Lines 65 through 100). U and L are then calculated (Lines 110 and 120). The column headings I, B /BT, Bl/BT, B2/BT and B3/BT are printed and under these, ø , Bø, Bl, B2 and B3 are printed (Lines 130 and 140). The loop (Lines 150 to 260) then performs, for each I, a scrambling cycle. In each cycle, B5, B6, B7 and B8 a generated via a single scrambling cycle (Lines 160 to 190) from Bø, Bl, B2 and B3. These are then renamed Bø, Bl, B2 and B3 (Lines 200 to 230) and then printed under the above mentioned headings (Line 250). The new Bø, Bl, B2 and B3 values are then sent through another cycle (Line 260). After 5 of these cycles have been completed, the statistical distribution is calculated from U^3, $3U^2L$, $3UL^2$ and L^3 and then printed out. (Lines 270, 280, 290, 300, and 330).

```
10REM:BETAINE SCRAMBLING DISTRIBUTION ----BSD
50 PRINT"INITIAL BETAINE RATIO = B0:B1:B2:B3",
60 INPUT B5,B6,B7,B8
65 T=B5+B6+B7+B8
70 B0=B5/T
80 B1=B6/T
90 B2=B7/T
100 B3=B8/T
110 U=(3*B0+2*B1+B2)/3*(B0+B1+B2+B3)
120 L=1-U
122 PRINT
123 PRINT
130 PRINT" I","B0/BT","B1/BT","B2/BT","B3/BT"
135 PRINT
140 PRINT" 0",B0,B1,B2,B3
150 FOR I=1 TO 5
160 B5=U*(B0 + B1/3)
170 B6=U*(2*B1/3 +2*B2/3) + L*(B0 + B1/3)
180 B7=U*(B2/3 + B3) + L*(2*B1/3 + 2*B2/3)
190 B8=L*(B3 + B2/3)
200 B0=B5
210 B1=B6
220 B2=B7
230 B3=B8
240 PRINT
250 PRINT I,B0,B1,B2,B3
260 NEXT I
270 B0=U*U*U
280 B1=3*U*U*L
290 B2=3*U*L*L
300 B3=L*L*L
310 PRINT
320 PRINT
330 PRINT" L",B0,B1,B2,B3
340 END
```

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?0,1,0,0

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0	1	0	0
1	0.222222	0.555556	0.222222	0
2	0.271605	0.481481	0.222222	2.46914E-2
3	0.288066	0.45679	0.222222	3.29218E-2
4	0.293553	0.44856	0.222222	3.56653E-2
5	0.295382	0.445816	0.222222	3.65798E-2
L	0.296296	0.444444	0.222222	0.037037

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?0,0,1,0

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0	0	1	0
1	0	0.222222	0.555556	0.222222
2	2.46914E-2	0.222222	0.481481	0.271605
3	3.29218E-2	0.222222	0.45679	0.288066
4	3.56653E-2	0.222222	0.44856	0.293553
5	3.65798E-2	0.222222	0.445816	0.295382
L	0.037037	0.222222	0.444444	0.296296

INIIIAL BETAINE RATIO = B0:B1:B2:B3 ?1,1,1,1

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0.25	0.25	0.25	0.25
1	0.166667	0.333333	0.333333	0.166667
2	0.138889	0.361111	0.361111	0.138889
3	0.12963	0.37037	0.37037	0.12963
4	0.126543	0.373457	0.373457	0.126543
5	0.125514	0.374486	0.374486	0.125514
L	0.125	0.375	0.375	0.125

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?1,0,0,1

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0.5	0	0	0.5
1	0.25	0.25	0.25	0.25
2	0.166667	0.333333	0.333333	0.166667
3	0.138889	0.361111	0.361111	0.138889
4	0.12963	0.37037	0.37037	0.12963
5	0.126543	0.373457	0.373457	0.126543
L	0.125	0.375	0.375	0.125

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?0,1,1,0

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0	0.5	0.5	0
1	8.33333E-2	0.416667	0.416667	8.33333E-2
2	0.111111	0.388889	0.388889	0.111111
3	0.12037	0.37963	0.37963	0.12037
4	0.123457	0.376543	0.376543	0.123457
5	0.124486	0.375514	0.375514	0.124486
L	0.125	0.375	0.375	0.125

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?2,1,1,2

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0.333333	0.166667	0.166667	0.333333
1	0.194444	0.305556	0.305556	0.194444
2	0.148148	0.351852	0.351852	0.148148
3	0.132716	0.367284	0.367284	0.132716
4	0.127572	0.372428	0.372428	0.127572
5	0.125857	0.374143	0.374143	0.125857
L	0.125	0.375	0.375	0.125

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?1,2,2,1

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0.166667	0.333333	0.333333	0.166667
1	0.138889	0.361111	0.361111	0.138889
2	0.12963	0.37037	0.37037	0.12963
3	0.126543	0.373457	0.373457	0.126543
4	0.125514	0.374486	0.374486	0.125514
5	0.125171	0.374829	0.374829	0.125171
L	0.125	0.375	0.375	0.125

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?3,1,1,3

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0.375	0.125	0.125	0.375
1	0.208333	0.291667	0.291667	0.208333
2	0.152778	0.347222	0.347222	0.152778
3	0.134259	0.365741	0.365741	0.134259
4	0.128086	0.371914	0.371914	0.128086
5	0.126029	0.373971	0.373971	0.126029
L	0.125	0.375	0.375	0.125

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?1,3,3,1

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0.125	0.375	0.375	0.125
1	0.125	0.375	0.375	0.125
2	0.125	0.375	0.375	0.125
3	0.125	0.375	0.375	0.125
4	0.125	0.375	0.375	0.125
5	0.125	0.375	0.375	0.125
L	0.125	0.375	0.375	0.125

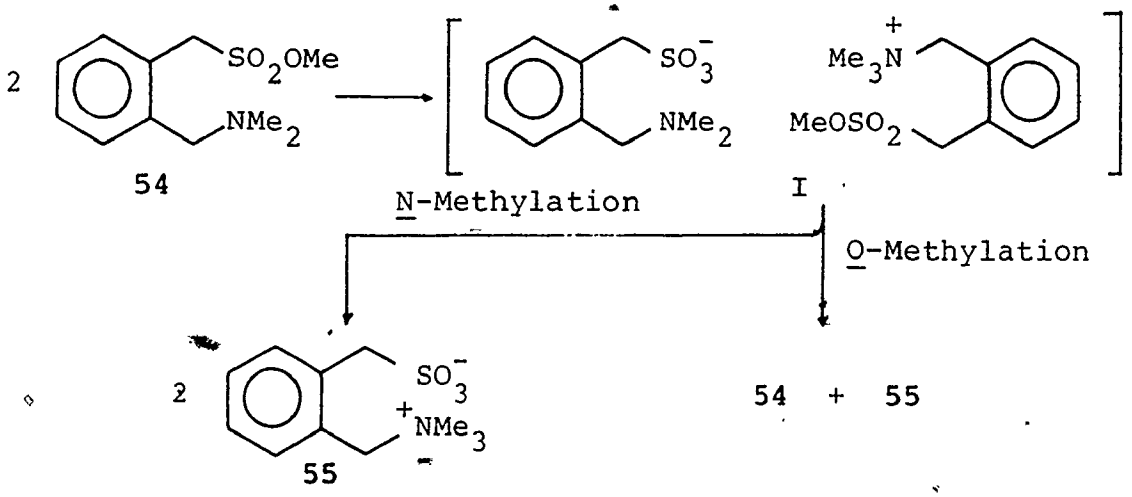
INITIAL BETAINE RATIO = B0:B1:B2:B3 ?1,4,4,1

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0.1	0.4	0.4	0.1
1	0.116667	0.383333	0.383333	0.116667
2	0.122222	0.377778	0.377778	0.122222
3	0.124074	0.375926	0.375926	0.124074
4	0.124691	0.375309	0.375309	0.124691
5	0.124897	0.375103	0.375103	0.124897
L	0.125	0.375	0.375	0.125

INITIAL BETAINE RATIO = B0:B1:B2:B3 ?4,1,1,4

I	B0/BT	B1/BT	B2/BT	B3/BT
0	0.4	0.1	0.1	0.4
1	0.216667	0.283333	0.283333	0.216667
2	0.155556	0.344444	0.344444	0.155556
3	0.135185	0.364815	0.364815	0.135185
4	0.128395	0.371605	0.371605	0.128395
5	0.126132	0.373868	0.373868	0.126132
L	0.125	0.375	0.375	0.125

Appendix 4: Ion Pair Annihilation: N versus O-Methylation Derivations and Computer Simulation Program:



E: $RS^{16}O_2{}^{-18}OMe$

S: $RS^{18}O^{16}O{}^{-16}OMe$

U: $RS^{16}O_2{}^{-16}OMe$

In the above reaction scheme, the formation of **55** from **54** follows a strict second order rate law. Two n molecules of **54** react in the rate determing first step to form n ion pairs (nI). There are two possible fast second steps: O-methylation or N-methylation. N-methylation gives simply 2n molecules of **55** while O-methylation give n of **54** and n of **55**. To distinguish between these mechanisms, a mixture of the ethereal ^{18}O-labelled ester, **54**-E (93.5%) and the unlabelled ester, **54**-U (6.5%) was prepared and then allowed to react. The distribution of the ^{18}O-label in samples of **54** that were recovered during the course of its conversion

to **55** was determined by ^{13}C NMR. Since the method could distinguish **54**-E from **54**-S or **54**-U but not **54**-S from **54**-U, the results were interpreted in terms of % **54**-E as defined by equation (4.1). Obviously, the ^{18}O-label distribution

$$\% \ \mathbf{54}\text{-E} = 100 \ \frac{\mathbf{54}\text{-E}}{\mathbf{54}\text{-E} + \mathbf{54}\text{-U} + \mathbf{54}\text{-S}} \qquad (4.1)$$

must be predicted for each of the annihilation mechanisms before the results can be interpreted.

N-Methylation:

For the N-methylation, a mathematical solution for % **54** versus % reaction can be readily derived.

$$-\frac{dE}{dt} = k_1E^2 + k_2EU \qquad (4.2)$$

$$-\frac{dU}{dt} = k_3U^2 + k_2EU \qquad (4.3)$$

therefore,

$$\frac{dE}{dU} = \frac{k_1E^2 + k_2EU}{k_3U^2 + k_2EU} \qquad (4.4)$$

In the absence of kinetic isotope effects;

$$k_1 = k_2 = k_3$$

therefore,

$$\frac{dE}{dU} = \frac{E^2 + EU}{U^2 + EU} \qquad (4.5)$$

$$= \frac{E(E + U)}{U(E + U)} = \frac{E}{U} \qquad (4.6)$$

$$\int_{E_0}^{E_f} \frac{dE}{E} = \int_{U_0}^{U_f} \frac{dU}{U} \qquad (4.8)$$

$$\ln \frac{E_f}{-E_0} = \ln \frac{U_f}{U_0} \qquad (4.9)$$

In the interest of simplicity, **54**-E, **54**-S and **54**-U will be referred to as E, S and U respectively.

therefore, $$\frac{E_f}{E_\emptyset} = \frac{U_f}{U_\emptyset} \qquad (4.10)$$

therefore, $$U_f = \frac{E_f U_\emptyset}{E_\emptyset} \qquad (4.11)$$

$$\% E_f = 100 \left[\frac{E_f}{E_f + U_f} \right] \qquad (4.1)$$

Substituting (4.11) into (4.1)

$$\% E_f = 100 \left[\frac{E_f}{E_f + \frac{E_f U_\emptyset}{E_\emptyset}} \right] = 100 \left[\frac{1}{1 + \frac{U_\emptyset}{E_\emptyset}} \right]$$

Since $U_\emptyset$ and $E_\emptyset$ are constants, % E_f is constant and therefore will not change during the reaction.

O-Methylation:

Since return from **I** to **54** occurs in this mechanism, the original mixture of **54**-E and **54**-U will be converted gradually into a mixture of **54**-E, -S and-U. All bimolecular combinations of these esters must then be considered for the first step. These combinations and the designations of the ion pairs so formed are shown in Table 30. Also included are the average number of ^{18}O-labels in the ion pair's sulfo anion and the distribution of products formed via the reaction of the ion pairs. For example, the reaction between E + U yields an ion pair, **I4** in which only half of the sulfo anions are labelled. Half of these ion pairs react to form **54**-U and **55**. Of the other half of **I4**, one third give **54**-E (plus **55**) and two thirds give **54**-S (plus **55**). To cope with this scheme, the computer simulation program OIPA was devised.

The simulation is based on the assumption that for

Table 30
O-Methylation Ion Pair Annihilation Reaction Pathways

Combination of **54**	Ion Pair	Sulfo Anion Label, $^{18}O_x$	Products **54** (+ **55**)
E + E	I1	1	E/3 + 2S/3
S + S	I2	1	E/3 + 2S/3
E + S	I3	1	E/3 + 2S/3
E + U	I4	Ø.5	E/6 + S/3 + U/2
S + U	I5	Ø.5	E/6 + S/3 + U/2
U + U	I6	Ø	U

the second order rate law:

$$-\frac{dA}{dt} = kA^2$$

over an infinitesimal time interval, Δt,

$$A = kA^2 \Delta t$$

and, therefore, over a longer time interval,

$$\int_{A\emptyset}^{A_j} dAj = \sum_{j=\emptyset}^{j=1} kA^2_j \Delta t$$

The program starts with the input of the initial concentration of **54** (A), the % ^{18}O-labelling (Z), the step size (T) and the total number of interations ("IT's" or X), (line 5Ø). The initial concentrations of E, S and U are then calculated (line 12Ø). A loop then performs the simulation (lines 15Ø to 36Ø). The ion pairs (I1 through I6) are generated from E, S and U (lines 16Ø through 21Ø) over the small time interval (T). The ion pairs are then partitioned into the annihilation products E, S and U as well as the betaine, B. The total amounts of E, S, U and B1

are then adjusted accordingly (lines 220 through 260). The rest of the loop controls the printout. B2 sums the amount of B1 generated since the last printout (line 270). If B2 is greater than a specified percent reaction, L (line 130), it is reset to zero (line 30) and the total percent reaction (P1 in line 310), the percent of unreacted ester that is comprised by E (P2, line 320), by S (P3, line 330) and by U (P4, line 340) are calculated and printed out along with the total number of interations (K) under the headings "% Reaction", "% E", "% S", "% U" and "IT's", (lines 110 and 350). If B2 is less than or equals to the specified percent reaction print interval, then the print sequence is by passed (line 290) and a new interation is initiated (line 360). When the limit assigned to the total number of interations is obtained (K = X) then the simulation is terminated (lines 280 and 370).

```
10 PRINT"O-18 ESTER DISTRIBUTION - O-METHYLATION (DIPA)"
20 PRINT
30 PRINT
40 PRINT"[54]O,%O-18,STEP SIZE,IT'S ?",
50 INPUT A,Z,T,X
60 E=A*Z/100
70 S=0
80 U=A*(1-Z/100)
90 PRINT
100 PRINT
110 PRINT"% REACTION","%E","%S","%U","IT'S"
120 PRINT"0",Z,"0",100-Z,"0"
130 L=A/6
140 I1=I2=I3=I4=I5=I6=B=B1=B2=0
150 FOR K=1 TO X
160 I1=E*E*T
170 I2=S*S*T
180 I3=E*S*T
190 I4=E*U*T
200 I5=S*U*T
210 I6=U*U*T
220 B=I1+I2+I3+I4+I5+I6
230 E=E-2*I1-I3-I4+(I1+I2+I3)/3 +(I4+I5)/6
240 S=S-2*I2-I3-I5+2*(I1+I2+I3)/3 +(I4+I5)/3
250 U=U-2*I6-I4-I5+(I4+I5)/2 + I6
260 B1=B1+B
270 B2=B2+B
280 IF K=X THEN 310
290 IF B2<=L THEN360
300 B2=0
310 P1=100*B1/A
320 P2=100*E/(A-B1)
330 P3=100*S/(A-B1)
340 P4=100*U/(A-B1)
350 PRINT P1,P2,P3,P4,K
360 NEXT K
370 END
```

```
[54]O,%O-18,STEP SIZE,IT'S ? ?2E-2,93.5,.02,10000

% REACTION      %E            %S            %U            IT'S
0               93.5          0             6.5           0
 16.6782         81.5877       11.4225       6.98983       565
 33.3482         68.8306       23.6454       7.52402       1504
 50.0175         56.6172       35.2412       8.14164       3190
 66.6856         46.3477       44.6703       8.98188       6686
 74.6409         42.3612       48.0729       9.56583       10000
```

Appendix 5: Chain Propagation Derivations:

1. Second Order Termination:

Initiation:

$$2\,\mathbf{E} \xrightarrow{k_2} \mathbf{I}$$

Propagation:

$$\mathbf{I} + \mathbf{E} \xrightarrow{k_3} \mathbf{I} + \mathbf{P} \qquad \text{(Methylation by E)}$$

$$\mathbf{I} + \mathbf{E} \xrightarrow{k_4} \mathbf{I} + \mathbf{P} \qquad \text{(Methylation of E)}$$

Termination:

$$2\mathbf{I} \xrightarrow{k_5} \mathbf{I} + \mathbf{B}$$

In the above scheme, E is the amino ester, I is the ion pair intermediate, P is the betaine generated by chain propagation and B is the betaine generated in the termination step. T is the sum of P and B. This section includes a derivation of the overall rate law ($-dE/dt =$) and a general expression for the product ratio (B/T).

Rate Law:

The process will obey the following rate law:

$$-\frac{d\mathbf{E}}{dt} = 2k_2\mathbf{E}^2 + (k_3 + k_4)\mathbf{IE}$$

Assuming a steady state in I:

$$\frac{d\mathbf{I}}{dt} = 0 = k_2\mathbf{E}^2 - k_5\mathbf{I}^2 \qquad (5.1)$$

therefore, $\mathbf{I} = \left(\frac{k_2}{k_5}\right)^{.5}\mathbf{E}$

therefore, $-\frac{d\mathbf{E}}{dt} = 2k_2\mathbf{E}^2 + (k_3 + k_4)\left(\frac{k_2}{k_5}\right)^{.5}\mathbf{E}^2 \qquad (39)$

Product Ratio (B/T):

From (5.1),

$$\frac{dB}{dt} = 2k_5I^2 = 2k_2E^2$$

and

$$\frac{dI}{dt} = -\frac{dE}{dt}$$

therefore,

$$\frac{dB}{dE} = \frac{2k_2E^2}{2k_2E^2 + (k_3 + k_4)\left(\frac{k_2}{k_5}\right)^{.5}E^2}$$

$$= \frac{2k_2}{2k_2 + (k_3 + k_4)\left(\frac{k_2}{k_5}\right)^{.5}} \qquad (40)$$

2. First Order Termination

Initiation:

$$2\ E \xrightarrow{k_2} I$$

Propagation:

$$I + E \xrightarrow{k_3} I + P \qquad \text{(Methylation by E)}$$

$$I + E \xrightarrow{k_4} I + P \qquad \text{(Methylation of E)}$$

Termination:

$$I \xrightarrow{k_5} 2B$$

Again, expressions are needed for the overall rate law (-dE/dt =) and the product ratio (B/T).

Rate Law:

$$-\frac{dE}{dt} = 2k_2E^2 + (k_3 + k_4)IE \qquad (5.1)$$

Assuming a steady state for I;

$$-\frac{dI}{dt} = 0 = k_2E^2 - k_5T$$

therefore, $I = \frac{k_2E^2}{k_5}$

therefore, $$-\frac{dE}{dt} = 2k_2E^2 + (k_3 + k_4)\left(\frac{k_2}{k_5}\right)E^3 \qquad (41)$$

Product Ratio (B/T):

$$\frac{dB}{dt} = 2k_5I$$

and since $k_5I = k_2E^2$

$$\frac{dB}{dt} = 2k_2E^2$$

therefore, $$\frac{dB}{-dE} = \frac{2k_2E^2}{2k_2E^2 + (k_3 + k_4)\left(\frac{k_2}{k_5}\right)E^3}$$

$$= \frac{2}{2 + \left(\frac{k_3 + k_4}{k_5}\right)E}$$

$$\int_0^B dB = -2\int_{E_\emptyset}^{E_f} \frac{dE}{2 + \left(\frac{k_3 + k_4}{k_5}\right)E}$$

$$B = \frac{2}{\left(\frac{k_3 + k_4}{k_5}\right)} \ln\left[\frac{2}{2 + \left(\frac{k_3 + k_4}{k_5}\right)E}\right]\Bigg|_{E_\emptyset}^{E_f}$$

$$= \frac{2}{\left(\frac{k_3 + k_4}{k_5}\right)} \ln \frac{2 + \left(\frac{k_3 + k_4}{k_5}\right)E_\emptyset}{2 + \left(\frac{k_3 + k_4}{k_5}\right)E_f}$$

and since $T = E_\emptyset - E_f$

$$\frac{B}{T} = \frac{2}{(E_\emptyset - E_f)\left(\frac{k_3 + k_4}{k_5}\right)} \ln\left[\frac{2 + \left(\frac{k_3 + k_4}{k_5}\right)E_\emptyset}{2 + \left(\frac{k_3 + k_4}{k_5}\right)E_f}\right] \qquad (41)$$

REFERENCES

1. L. Tenud, A. Farooq, J. Seibl and A. Eschenmoser, Helv. Chim. Acta, **53**, 2059 (1970)

2. M.F. Hegazi, R.T. Borchardt and R.L. Schowen, J. Am. Chem. Soc., **101**, 4359 (1979) and references cited therein

3. J.F. King, S.M. Loosmore, M. Aslam, J.D. Lock and M.J. McGarrity, J. Am. Chem. Soc., **104**, 7108 (1982)

4. V. Prelog in "Perspectives in Organic Chemistry", Sir A. Todd, Ed., Interscience Publishers, New York, 1956, pp 96-133

5. P. Rüggli, Liebigs Ann. Chem., **412**, 1 (1917)

6. G.I. Illuminati and L. Mandolini, Acc. Chem. Res., **14**, 95 (1981)

7. A.J. Kirby, Advan. Phys. Org. Chem., **17**, 183 (1982)

8. C. Galli, G. Illuminati, L. Mandolini and P. Tamborra, J. Am. Chem. Soc., **99**, 2591 (1977)

9. G. Salomon, Trans. Faraday Soc., **32**, 153 (1936)

10. G. Illuminati, L. Mandolini and B. Masci, J. Am. Chem. Soc., **99**, 6308 (1977)

11. C. Galli, G. Giovannelli, G. Illuminati and L. Mandolini, J. Org. Chem., **44**, 1258 (1979)

12. K. Shimada and M. Szwarc, J. Am. Chem. Soc., **97**, 3313 and 3321 (1975)

13. A.D. Cort, L. Mandolini and B. Masci, J. Org. Chem., **45**, 3923 (1980)

14. K. Ziegler, A. Luttringhaus and K. Wohlgemuth, Liebigs Ann. Chem., **528**, 162 (1937)

15. J.E. Baldwin, J. Chem. Soc. Chem. Comm., 734 (1976)

16. E.D. Hughes and C.K. Ingold, J. Chem. Soc., 244 (1935)

17. P.B.D. de la Mare, L. Fowden, E.D. Hughes, C.K. Ingold and J.D.H. Mackie, J. Chem. Soc., 3200 (1955)

18. D.F. De Tar, D.F. McMullen and N.P. Luthra, J. Am. Chem. Soc., **100**, 2484 (1978)

19. D.F. De Tar and N.P. Luthra, J. Am. Chem. Soc., **102**, 4505 (1980)

20. F.M. Menger, Tetrahedron, **39**, 1013 (1983)

21. L.H. Sommers, "Stereochemistry, Mechanism and Silicon", McGraw Hill, New York, 1965

22. A.G. Brook and A.R. Bassindale in "Rearrangements in the Ground and Excited States", Volume 2, P. de Mayo, Ed., Academic Press, Toronto, 1981, pp 149-221 and references cited therein

23. D.S. Garwood, M.R. Jones and D.F. Cram, J. Am. Chem. Soc., **95**, 1925 (1973)

24. B.W. Christensen, J. Chem. Soc. Chem. Comm., 597 (1971)

25. S. Oae, M. Yokoyama, M. Kise and N. Furukowa, Tetrahedron Lett., 4131 (1968)

26. M. Mikolajcyzk and J. Drabowica, J. Chem. Soc. Chem. Comm., 775 (1974)

27. T.J. Maricich and V.L. Hoffman, J. Am. Chem. Soc., **96**, 7770 (1974)

28. F. Wudl and T.B.K. Lee, J. Am. Chem. Soc., **95**, 6349 (1973)

29. D. Hellwinkel and M. Supp., Chem. Ber., **109**, 3749 (1976)

30. K.K. Anderson, G.Gowda, L. Jewell, P. McGraw and B.T. Phillips, J. Org. Chem., **47**, 1884 (1982)

31. R.B. Turner, A.D. Jarrett, P. Goebel and B.J. Mallon, J. Am. Chem. Soc., **95**, 790 (1973)

32. P.A. Cruickshank and M. Fishman, J. Org. Chem., **34**, 4060 (1969)

33. G. Stork, L.D. Cama and D.R. Coulson, J. Am. Chem. Soc., **96**, 5268 (1974)

34. G. Stork and J.F. Cohen, J. Am. Chem. Soc., **96**, 5270 (1974)

35. J.Y. Lallemand and M. Onanga, Tetrahedron Lett., 585 (1975)

36. J.M. Decesare, B. Corbel, T. Durst and J.F. Blount, Can. J. Chem., **59**, 1415 (1981)

37. J.C. Martin and R.J. Basalay, J. Am. Chem. Soc., **95**,

2572 (1973)

38. G.W. Kirby, K.W. Bentley, P. Horsewood and S. Singh, J. Chem. Soc. Perkin 1, 3064 (1979)

39. P.D. Bartlett and E.N. Trachenberg, J. Am. Chem. Soc., **80**, 5808 (1958)

40. F.G. Bordwell and W.T. Brannen, Jr., J. Am. Chem. Soc., **86**, 4645 (1964)

41. A. Halvorsen and J. Songstad, J. Chem. Soc. Chem. Comm., 327 (1978)

42. R. Lok and J.K. Coward, Bioorg. Chem., **5**, 169 (1976)

43. H.L. Goering and R.W. Thies, J. Am. Chem. Soc., **90**, 2967 and 2968 (1968)

44. H.L. Goering and B.E. Jones, J. Am. Chem. Soc., **102**, 1628 (1980) and references cited therein

45. W.D. Closson, P. Wriede and S. Bank, J. Am. Chem. Soc., **88**, 1581 (1966)

46. W.T. Raynes and G. Stanney, J. Magn, Reson., **14**, 378-380 (1974)

47. C.J. Jameson, J. Chem. Phys., **66**, 4983 (1977)

48. D.J. Darensbourg, J. Organometal. Chem., **174**, C70 (1979)

49. D.J. Darensbourg and B.J. Baldwin, J. Am. Chem. Soc., **101**, 6447 (1979)

50. J.M. Risley and R.L. Van Etten, J. Am. Chem. Soc., **101**, 252 (1979)

51. J.C. Vedevas, J. Am. Chem. Soc., **102**, 374 (1980)

52. J. Diakur, T.T. Nakashima and J.C. Vederas, Can. J. Chem., **58**, 1311 (1980)

53. J.M. Risley and R.L. Van Etten, J. Am. Chem. Soc., **102**, 4609 (1980)

54. J.R. Everett, Org. Magn. Reson., **19**, 86 (1982)

55. D.E. Crane, H. Hasler and T-C Liang, J. Am. Chem. Soc., **103**, 5960 and 5962 (1981)

56. J.M. Risley, F. Kuo and R.L. Van Etten, J. Am. Chem. Soc., **105**, 1647 (1983)

57. G.K. Smith, W.T. Meuller, L.J. Slicker, C.W. De Brosse and S.J. Benkovic, J. Biochem., **21**, 2870 (1982)

58. S.A. Benner, J.E. Maggio and H.E. Simmons III, J. Am. Chem. Soc., **103**, 1581 (1981)

59. J.F. King, S. Skonieczny, K.C. Khemani and J.B. Stothers, J. Am. Chem. Soc., **105**, 6514 (1983)

60. J.H. Helberger and H. Lantermann, Liebigs Ann. Chem., **586**, 158 (1954)

61. B. Helferich, K. Geist and H. Plumpe, Liebigs Ann. Chem., **651**, 41 (1962)

62. E.M. Kaiser and P.L.A. Knutson, J. Org. Chem., **40**, 1342 (1975)

63. A.D. Bliss, W.K. Cline, E.C. Hamilton and O.J. Sweeting, J. Org. Chem., **28**, 3537 (1963)

64. J.F. King and J.R. du Manior, J. Am. Chem. Soc., **97**, 2566 (1975)

65. B.V. Helferich and V. Bollert, Liebigs Ann. Chem., **647**, 37 (1961)

66. T. Gramstad and R.N. Haszeldine, J. Chem. Soc., 173 (1956)

67. M.I. Page and W.P. Jencks, Proc. Nat. Acad. Sci. USA., **68**, 1678 (1971)

68. H. Budzikiewicz, C. Djerassi and D.H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day Inc., San Francisco, 1967, pp 297-327

69. K.D. Trivedi, "Probability and Statistics with Reliability, Queuing and Computer Science Applications", Prentice-Hall Inc., Englewood Cliffs, New Jersey, 1982, Chapters 1 and 2.

70. R.H. Schlessinger and I.S. Ponticello, J. Chem. Soc. Chem. Comm., 1013 (1969)

71. J.F. King, Acc. Chem. Res., **8**, 10 (1975)

72. M.J.S. Dewar and R.C. Dougherty, "The PMO Theory of Organic Chemistry", Plenum Press, New York, 1975, pp 256 ff

73. J.F. King and G.T.Y. Tsang, J. Chem. Soc. Chem. Comm., 1131 (1979)

74. O.O. Orazi and R.A. Corral, J. Chem. Soc. Chem. Comm., 470 (1976)

75. E.M. Kaiser, L.E. Solter, R.A. Schwarz, R.D. Beard and C.R. Hauser, J. Am. Chem. Soc., **93**, 4237 (1971)

76. C.B. Sawyer, J. Org. Chem., **37**, 4225 (1972)

77. F. Daniels and R.A. Alberty, "Physical Chemistry", 3 Ed., Whiley and Sons Inc., New York, 1964, p 760

78. J.D. Reinheimer, J.D. Harley and W.W. Meyers, J. Org. Chem., **28**, 1573 (1963)

79. C. Lassau and J-C. Jungers, Bull. Soc. Chim. Fr., **7**, 2678 (1968)

80. H.K. Hall, Jr., J. Am. Chem. Soc., **79**, 5441 (1957)

81. V.J. Shiner, Jr., H.R. Mahler, R.H. Baker, Jr. and R.R. Hiatt, Ann. N.Y. Acad. Sci., **84**, 583 (1960)

82. V.J. Shiner, Jr. in "Isotope Effects in Chemical Reactions", C.J. Collins and N.S. Bowman, Eds., Van Nostrand Reinhold, New York, 1970, Chapter 2

83. L. Melander and W.H. Saunders, Jr., in "Reaction Rates of Isotopic Molecules", Wiley and Sons Inc., Toronto, 1980, Chapter 6

84. J.A. Llewellyn, R.E. Robertson and J.M.W. Scott, Can J. Chem., **38**, 222 (1960)

85. A. Seltzer and A.A. Zavitsas, Can. J. Chem., **45**, 2023 (1917)

86. C.H. Gray, J.K. Coward, K.B. Schowen and R.L. Schowen, J. Am. Chem. Soc., **101**, 4351 (1979)

87. E.S. Lewis, Tetrahedron, **5**, 143 (1959)

88. T.H. Lowry and K.S. Richardson, "Mechanism and Theory in Organic Chemistry", Second Ed., Harper and Row, Publishers, New York, 1981 p 339

89. G.A. Olah and P. Schilling, Liebigs Ann. Chem., **761**, 89 (1972)

90. C.G. Swain and C.B. Scott, J. Am. Chem. Soc., **75**, 141 (1953)

91. J.F. King and M. Alsam, Tetrahedron Lett., 3573 (1981)

92. C.K. Ingold, "Structure and Mechanism in Organic Chemis-

try", Second Ed., Cornell University Press, Ithaca, New York, 1969 pp 457 ff

93. E.P. Panov, V.M. Kostyuchenko, Yu. G. Skripnik, S.P. Zolotukhin and R.V. Visgert, Zh. Org. Chim., **12**, 824 (1976)

94. W.E. Truce, R.W. Cambell and G.D. Madding, J. Org. Chem., **32**, 308 (1967)

95. H.D. Holtz and L.M. Stock, J. Am. Chem. Soc., **87**, 2404 (1965)

96. J.E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963, pp 52-53

97. E.M. Arnett, L. Joris, E. Mitchell, T.S.S.R. Murty, T.M. Gorrie and P.R. Schleyer, J. Am. Chem. Soc., **92**, 2365 (1970)

98. N. Solimene and B.P. Daily, J. Chem. Phys., **23**, 124 (1955)

99. R.N. Haszeldine and J.M. Kidd, J. Chem. Soc., 4228 (1954)

100. J.B. Cloke and F.J. Pilgrim, J. Am. Chem. Soc., **61**, 2667 (1939)

101. Aldrich Chemical Company, Milwaukee, Wisc.

102. B. Helferich and K.G. Kleb, Liebigs Ann. Chem., **635**, 91 (1960)

103. F. Asinger, B. Fell and A. Commichau, Chem. Ber., **98**, 2154 (1965)

104. F. Reissert and H. Holle, Chem. Ber., **44**, 3027 (1911)

105. W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., **43**, 2923 (1978)

106. J. du Manior, private communication

107. C.K. Ingold, E.H. Ingold and F.R. Shaw, J. Chem. Soc., 813 (1927)

108. R.L. Frank and P.V. Smith, J. Am. Chem. Soc., **68**, 2103 (1946)

109. J.A. King and F.H. McMillan, J. Am. Chem. Soc., **68**, 634 (1946)

110. Stauffer Chemical Co., Chem. Abst., **60**, P11902b (1964)

111. W.C. Lumma, Jr., G.A. Dutra and C.A. Voeker, J. Org. Chem., **35**, 3442 (1970)

112. J.R. Partington, "An Advanced Treatise on Physical Chemistry", Longmans, Green and Company, Ltd., London, 1951, Vol. 2, p 53

113. A.I. Vogel, "Practical Organic Chemistry", Second Ed., Longmans, Green and Company, Ltd., Toronto, 1951, p 632

END

08-11-85

FIN