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PART I: FIELD DESORPTION MASS SPECTROMETRY OF ALKALI METAL CRYPTATES. PART II: STEREOCHEMICAL DIFFERENTIATION OF ALCOHOL DERIVATIVES BY VARIOUS MASS SPECTROMETRIC TECHNIQUES.

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PART I
FIELD DESORPTION MASS SPECTROMETRY OF ALKALI METAL CRYPTATES

PART II
STEREOCHEMICAL DIFFERENTIATION OF ALCOHOL DERIVATIVES

BY VARIOUS MASS SPECTROMETRIC TECHNIQUES

BY



AU, Mei-Kuen

A Dissertation
submitted to the Faculty of Graduate Studies
through the Department of
Chemistry in Partial Fulfillment
of the requirements for the Degree
of Doctor of Philosophy at
The University of Windsor

Windsor, Ontario, Canada

1981

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760745

To my parents

ABSTRACT

PART I

Field desorption (FD) mass spectra have been obtained from a series of alkali metal cryptates formed from [2.2.2]-, [2.2.1]- and [2.1.1]-cryptands with Li^+ , Na^+ and K^+ salts of Cl^- , Br^- , I^- , OTs^- and BPh_4^- . Stabilities of these complexes under FD conditions are compared with their thermodynamic stabilities in solution. Differences in these stabilities are attributed to the lack of solvation of ions under FD conditions. A marked anion effect is also observed in FD spectra. This effect is correlated with the recombination energy of the released cation and anion in the gaseous state.

PART II

Acid phthalates from isomeric alicyclic alcohols have been studied by field desorption (FD) and electron impact (EI) mass spectrometry. Isomeric acid phthalates gave identical FD spectra and EI spectra. The use of these methods for distinguishing stereoisomers of this type thus proved to be unsuccessful. However, the field ionization (FI) spectra of cis- and trans-4-t-butylcyclohexyl 9-fluor-

enylmethyl carbonate show distinguishing features. The trans-isomer undergoes a rearrangement reaction which involves mainly the transfer of the benzylic hydrogen to carbonyl oxygen, whereas the cis-isomer transfers either the benzylic hydrogen or a readily available hydrogen from the 2-position in the cyclohexyl ring. This divided pathway gives rise to an additional ion for the cis-isomer (m/z 138) which is the major qualitative difference in the spectra. The EI spectra for both isomers are simple and closely related to each other.

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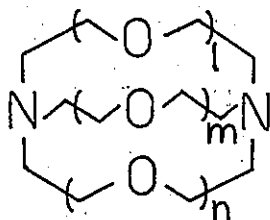
amu	atomic mass unit
AP	appearance potential
b.a.t.	best anode temperature
b.e.t.	best emitter temperature
C	metal cation
CI/D	chemical ionization/desorption
ECP	emitter current programmer
EI	electron impact
EI/D	electron impact/desorption
EIMS	electron impact mass spectrometry
ETR	emitter temperature regulator
eV	electron volt
ED	field desorption
FDMS	field desorption mass spectrometry
FI	field ionization
IR	infrared
kV	kilovolt
L	ligand, cryptand
mA	milliampere
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
THF	tetrahydrofuran
TIC	total ion current

PART I

FIELD DESORPTION MASS SPECTROMETRY OF
ALKALI METAL CRYPTATES

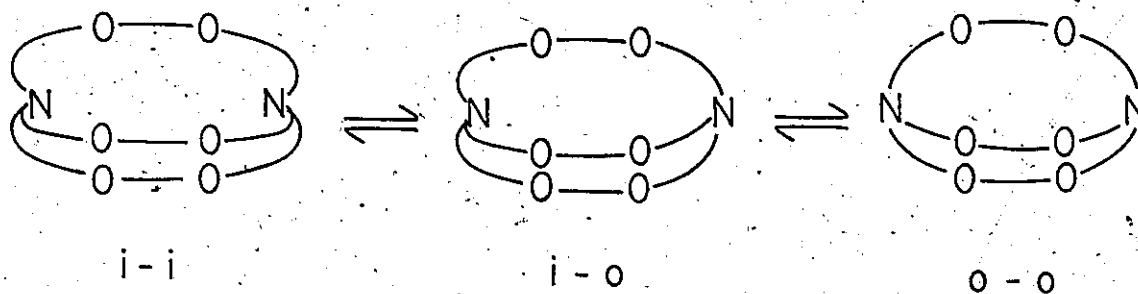
CHAPTER I
INTRODUCTION

Field desorption mass spectrometry (FDMS) has been shown to be a powerful tool for analyzing heat labile, non-volatile compounds.¹ However, the technique has been plagued by unwanted side effect of contaminants, especially alkali metal cations, which are present in most naturally occurring samples. Early work in this laboratory has shown that addition of a complexing agent to the sample in solution prior to FDMS analysis removes the deleterious effects of alkali metal ions, and results in a reproducible, smooth desorption process at relatively low temperatures.^{2,3} Among the complexing agents used, diazapolyoxyamacroyclics (cryptands) showed the strongest binding ability toward alkali metal ions under FD conditions.³ In another aspect, these ligands form very stable alkali metal complexes in solution. The complexation between cryptands and metal cations is well-known and well-studied.⁴ These macrobicyclic ligands share a general formula as shown below.



- I [2.2.2]-cryptand
l=m=n=2
- II [2.2.1]-cryptand
l=m=2, n=1
- III [2.1.1]-cryptand
l=2, m=n=1

They are termed [1'm·n]-cryptands, where 1, m and n denote the number of oxygen atoms in each bridge. They possess three-dimensional intramolecular cavities lined with various binding sites, and thus form remarkably stable inclusion complexes (cryptates) with metal cations. The lone pairs of the two nitrogen atoms in the bridgeheads can turn inward or outward with respect to the molecular cavity, and the cryptands can thus exist in three forms: the in-in (i-i), in-out (i-o), and out-out (o-o) forms.^{5,6} The three forms are in equilibrium in solution with the i-i form as the



dominant species. The same stability order holds also for the cryptates.⁶ In solid state, the cryptates exist in the i-i form.^{7,8,9} Modification of the length of the bridges enables stepwise changes in cavity sizes of the ligands. Stabilities of the cryptates in solution depend on goodness of fit of the cations to the molecular cavities of the ligands. Thus, each of these ligands displays high selectivity for a particular cation within the same group in the periodic system. Some of the stability constants of alkali metal cryptates are listed in Table 1.¹⁰

3 =
 Table 1

Stability Constants ($\log K_s$) of Alkali Metal
 Cryptates at 25°C^a

Ligand	Interstitial radius (Å) ^b	Solvent	$\log K_s$		
			Li ⁺ (0.78) ^c	Na ⁺ (0.98) ^c	K ⁺ (1.33) ^c
[2.2.2]	1.4	W	<2	3.9	5.3
		M/W	1.8	7.21	9.75
[2.2.1]	1.1	W	2.5	5.3	3.9
		M/W	4.18	8.84	7.45
[2.1.1]	0.8	W	4.3	2.8	<2
		M/W	7.58	6.08	2.26

a. Key: W, water; M/W, methanol/water 95/5.

b. Estimated cavity size measured by space filling models.
 See ref. 18.

c. Ionic radius.

For every cryptand, the stability constant passes through a maximum when the cationic radius approximates the interstitial radius. Thus [2:2:2]-, [2:2:1]-, and [2:1:1]-cryptands form most stable complexes with K^+ , Na^+ , and Li^+ respectively. The complexation of cryptands I, II, and III with alkali metal cations is accompanied by large favorable enthalpies but unfavorable entropies.¹¹

Changing the solvent from water to an organic solvent increases the stability constants tremendously. As shown in Table 1, transfer of these complexes from water to methanol/water (95/5) mixture increases the stability constants more than 10^3 times. This increase would be too much to come solely from the stronger solvation of the cation in water than in methanol.^{12,13} A study of the solvent effects on cryptate formation in non-aqueous solvents indicated that the ligands are more strongly solvated in water than in non-aqueous solvents.¹⁴ Although decrease of the dielectric constant of the solvent increases the stability of the complexes, the selectivity may remain unchanged with a given group in the periodic table.^{9,15} The anion effect is negligible in polar solvents, however, it may play a role in non-polar solvents.⁹

Kinetic studies of alkali metal cryptates^{16,17} showed that the pronounced selectivity of the cryptands for alkali metal cations was reflected entirely in the dissociation rates of the complexes. Regardless of ligand cavity size, the rate of formation increases monotonically

with increasing cation size. For a given metal cation, the rate of formation increases with increasing ligand size.

This reflects the fact that the larger ligand is more flexible to accommodate the incoming cation.

The extraordinary stabilities of the alkali metal cryptates in solution and under field desorption conditions^{2,3} led us to study an extended set of these complexes in field desorption. In the present work, a series of complexes from cryptands I, II, and III with various Li^+ , Na^+ , and K^+ salts have been studied under field desorption. The spectra obtained are discussed in terms of ease of ionization, and stability relationships, and other aspects of the behavior of complexes in FDMS.

CHAPTER II

TECHNIQUE OF FIELD DESORPTION

The technique of field desorption was first introduced to mass spectrometry by Beckey in 1969¹⁹ and soon showed its power in analyzing biologically and medically important substances. The technique allows mass spectral analysis of polar, non-volatile and thermally labile compounds which are not amenable to other ionization methods.²⁰ The application of field desorption to a vast variety of synthetic and naturally occurring samples has been discussed by Schulten in two recent reviews.^{1,21} The sample to be analyzed is deposited on a field anode which is then introduced into the ion source of the mass spectrometer through a vacuum lock. A high electric field is applied. Thermal energy, transferred by electrical heating of the field anode, may be required before the spectrum can be recorded.

A. Theory

A theoretical model for field evaporation was first developed by Müller²² and Gomer²³, and described by Beckey.²⁰ The schematic energy level diagrams of neutral and ionic adsorption are shown in Figure 1.²⁰ As shown in Figure 1a, in the absence of an electric field, $I - \phi$ is so large that the neutral and ionic curves do not intersect. Ionic desorption can only occur when sufficient energy is trans-

ferred to the adsorbant. In the presence of high electric field, as shown in Figure 1b, the neutral and ionic curves intersect in the attractive portion of the neutral curve. Activation energy for thermal desorption is reduced. Ionic desorption can then take place by quantum mechanical tunneling.

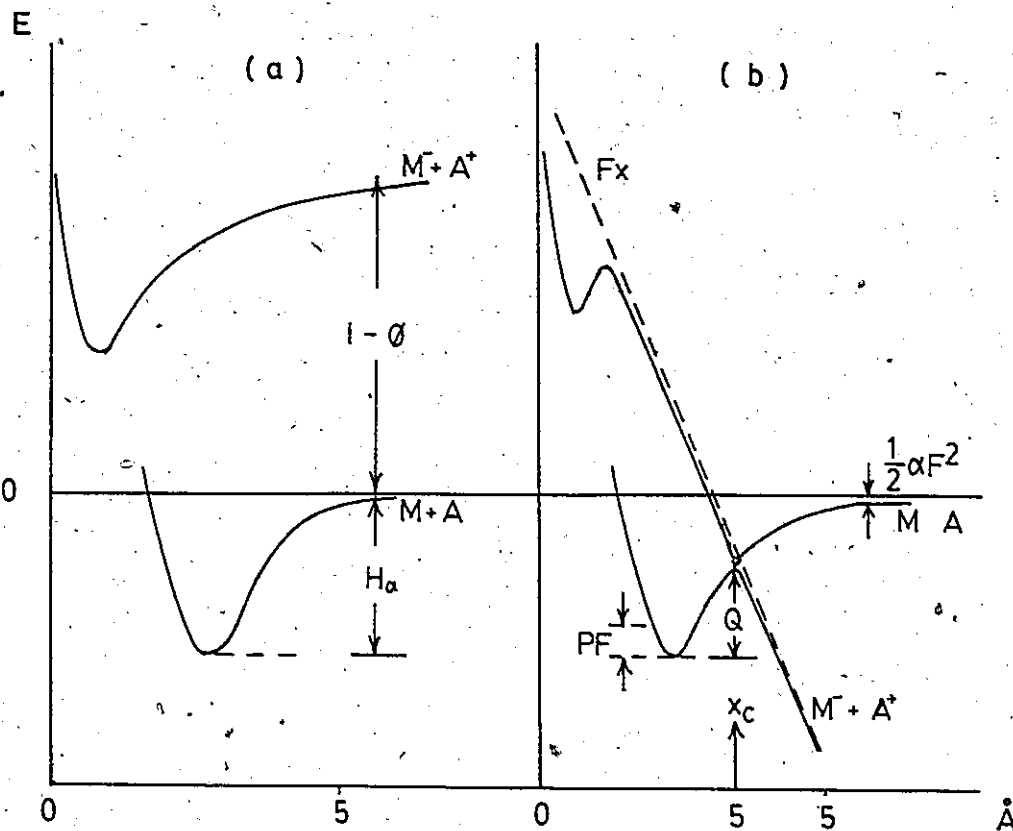


Figure 1. Schematic Energy Level Diagram for Neutral And Ionic Adsorption on A Metal Surface. (a) Zero Field; (b) High Field. A=Adsorbant; M=Metal; I = Ionization Potential; ϕ =Work Function; $\frac{1}{2}\alpha F^2$ = Polarization Energy of Atom in Field; PF =Bond-Field Interaction; H_a = Heat of Adsorption; Q =Activation Energy of Adsorption; x_c = Interaction Point of Ionic And Neutral Curves.

Accumulated FD applications show that some compounds lose a single electron to form a molecular radical ion, M^+ , whereas some compounds instead of losing an electron, form a 'quasi-molecular ion', $[M + H]^+$. The phenomena indicate a complex mechanism which may not be fully explained by the theoretical model proposed.

In 1976, the theory was questioned by Holland, Soltmann, and Sweeley.^{24,25} They investigated the role of high electric field in field desorption. Results of these experiments implied that desorption of ions occurred when no field was applied; that is, the rate of desorption was maintained with or without the high electric field. These workers therefore questioned the role of the high electric field in field desorption and suggested that the desorption was mainly thermal. A new thermal desorption mechanism (thin film ionization mechanism) was then proposed. According to this mechanism, the ionization of a pure organic compound is classified into four stages (Figure 2). In the first stage, the temperature is below best anode temperature (b.a.t.), which is defined as the temperature at which the peak carrying molecular characteristics is highest and the fragmentation is lowest. At this stage, no ions can be detected even in high electric field. In the second stage, the b.a.t. is approached. The organic compound begins to melt. The organic molecules gain mobility to move up to the surface-vacuum boundary. Ions can be formed at this boundary from thermally induced chemical ionization reactions. In the

THIN FILM IONIZATION MECHANISM

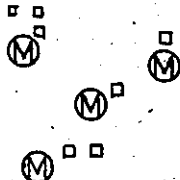
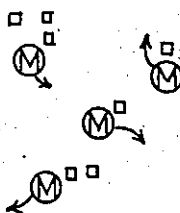
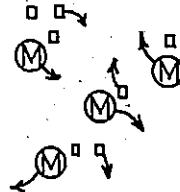
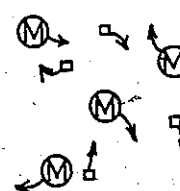
STATE	REACTION TYPE	IONS DETECTED
<p>I Solid State</p> 	None	None
<p>II Semi-fluid</p> 	<p>Solute Mobility</p> $M + M \rightarrow 2M$ $2M \rightarrow M^+ + M^-$ $2M + \ominus \rightarrow (2M + \ominus)^+$	<p>M^+</p> <p>$(nM + \ominus)^+$</p>
<p>III Semi-fluid</p> 	<p>Small Ion Mobility</p> $M + H^+ \rightarrow (M + H)^+$ $M + \ominus \rightarrow (M + \ominus)^+$ $(M + \ominus)^+ + \ominus - H^+ \rightarrow (M + 2\ominus - H)^+$	<p>$(M + H)^+$</p> <p>$(M + \ominus)^+$</p> <p>$(M - (n-1)H + n\ominus)^+$</p>
<p>IV Fluid Lattice</p> 	<p>Thermal Ionization</p> <p>Lattice Ion Mobility</p>	<p>\ominus</p> <p>$\ominus \ominus \ominus$</p> <p>$\ominus \ominus^+$</p> <p>\ominus^+</p>

Figure 2. A Proposed Temperature-dependent Ionization Mechanism in Field Desorption

presence of inorganic salt impurities, a common situation, cationization may also occur. Once these ions are formed, they will be extracted from the surface by the high electric field. In the next stage, which is often indistinguishable from the second stage, temperature is beyond b.a.t. Inorganic salts gain sufficient mobilities and cationization increases. Increased fragmentation is often observed at this elevated temperature. In the final stage, with temperature at its highest, simple ions and cluster ions from the inorganic salts are observed. This thermal ionization mechanism was further supported by the evidence that the best emitter temperature (b.e.t., defined as the optimum emitter temperature for the evaporation of a sample) in EI/D corresponded closely to the b.a.t. in field desorption. However, in this FD mechanism, the high field is still needed to extract the ions formed by thermally induced chemical ionization. Thus the possibility of a field dependent ionization process cannot be excluded. After its publication, the "thin film ionization mechanism" received immediate response from Beckey and Rollgen.²⁶ The debate continues between the two groups.^{27,28} In 1980, a 'field assisted charge transfer' (FACT) mechanism has been proposed.²⁹ According to it, the high electric field is mainly involved in ion generation and ion collection.

In a recent review by Cotter, the nature of the desorption process was discussed in a more objective manner.³⁰ He pointed out that ions as well as neutrals could be desorbed at very high temperature. Some of the experimental

results from the desorption of non-volatile compounds from extended probes may help to clarify the nature of desorption mechanisms. The technique involves the insertion of an extended probe, coated with non-volatile compound, directly into the ion source. The probe is then heated rapidly for desorption to take place. For those experiments using activated emitters as direct solid probes (e.g. EI/D and CI/D), secondary means of ionization are required.^{31,32} Without the secondary means of ionization, neither thermal ionization nor thermally induced cationization have been observed, although very high temperature is reached in a short time.* However, laser experiments show that thermal ionization can occur if high enough temperature is reached in a short period of time.^{34,35} Because of the diverse opinions of various workers and inconsistent results from the desorption from extended probes, more definitive experiments must be directed towards the nature of field desorption process before a conclusive mechanism can be drawn.

B. Problems in FD Technique and Attempts to Overcome Them

Since its introduction in 1969, field desorption has received intensive study. The technique has become the method of choice for mass spectral analysis of non-volatile compounds. Although field desorption has become a standard

*Recently purely thermal desorption spectra of quaternary ammonium salts have been obtained. See ref. 33.

ionization technique in mass spectrometry, the use of this method still suffers from some difficulties. This subject will be discussed in three main categories: reproducibility, alkali metal ion contamination, and ion production, together with attempts that have been tried to overcome these problems.

1. Reproducibility

Production of a field desorption mass spectrum depends on many factors. The primary variables come from the field anodes. In order to create a high electric field and a large surface area, chemically inert microneedles are usually grown on the emitter wire before use. Such a process is called activation. These microneedles also create an uneven local field on the anode. The electric field strength is higher at the tip than at the base. Thus the morphology of these microneedles may have a major effect on the quality of the spectrum produced. Although a standard activation method has been developed, the structure of the microneedles may still vary from anode to anode. Thus an unresolved structural problem is imposed during the activation process. The use of an untreated wire has been suggested, however, it is not widely applied.³⁶

Heating of the anode is another variable. The temperature of the anode is usually described in terms of the heating current (mA) passing through the emitter wire. This heating current does not correspond strictly to the temper-

ature of the ionization zone. The temperature is higher in the middle of the wire than near the posts. Also it is higher at the base of the microneedles and cools off towards the tip. These inhomogenities would cause a change in the appearance of the spectrum. Although the use of an emitter current programmer (ECP)³⁷ can provide linear and reproducible heating rates, the b.a.t. for a given sample may still change with different anodes due to the factors described above. A device called the emitter temperature regulator (ETR)³⁸ has been developed recently to provide constant temperature control of the anode regardless of its configuration. The device can regulate the heating current in either a constant temperature mode or a constant current mode. Thus a more reproducible temperature control for the heating of the anode is made possible.

2. Alkali metal ion contamination

Another serious problem arises from the impurities present in the samples. The presence of trace amounts of alkali metal ions, especially sodium ion, can be detrimental. The general features of the spectra of these alkali metal ion contaminated samples are relatively high anode heating current, fluctuating ion emission current, and in the extreme, the only major peak corresponds to the metal ion. It has been found that gel chromatography,³⁹ dialysis,³⁹ and solvent extraction^{39,40} methods can effectively remove the deleterious effect of contaminating sodium ion. Addition

of a complexing agent to the sample prior to FD analysis has been shown to be beneficial.^{2,3} Also, the use of a matrix material, containing polyhydroxyl functionals, for analyses of organic sodium salts results in a smoother desorption process, a reduced sodium peak and a more reproducible spectrum.⁴¹⁻⁴³

3. Ion production

The ion current produced from field desorption is relatively small compared to other standard ionization techniques. This provides another reason for poor reproducibility of field desorption. The ion production from a certain compound greatly depends on its ionization efficiency. In order to effect ion formation process, alkali metal ion attachment has been found to be useful in some cases.⁴⁴⁻⁴⁷ Addition of an equimolar amount of substituted sodium benzoates to some nucleosides increases the total ionization by 10 to 100 times, with the ion current carried mainly by cationized molecular species.⁴⁸ It has been known that silver ion is readily bound to unsaturated sites. Thus, Ag^+ attachment can serve as an alternative cationization. Addition of Ag^+ to some nucleosides gives intense but complicated spectra, containing mainly cationized molecular species and some clusters of molecular species plus inorganic silver salt.⁴⁹ This Ag^+ attachment technique needs more thorough investigation before it can be applied generally. Doubly-charged alkaline earth metal ions have also been used

successfully for the analysis of certain polymers.^{50, 51}

This method not only enhances the ionization but also expands the mass scale to a range beyond the usual mass limit of most mass spectrometers. This is important for the analysis of high molecular weight substances.

Attempts have also been made to improve the ionization of the sample by precoating a layer of charge transfer complexes onto the anode prior to dipping. The results indicate that there is some kind of conditioning of the anode. The ionization is enhanced by 2 to 5 fold without changing the appearance of the spectrum.⁵² The phenomenon can be explained as the partial transfer of an electron from the sample to the electron acceptor-donor pair without formation of separate ions. Thus, the ionization barrier is reduced.⁵³

CHAPTER III EXPERIMENTAL

A. Instrumental

The mass spectra were recorded with a Varian MAT CH5 DF mass spectrometer equipped with an EI/FI/FD source and an INCOS 2000 data system. Ion source temperature was kept at 50-70°. A potential difference of 11 kV (+3 on field anode and -8 on extraction plate) was applied to the electrodes. The secondary electron multiplier was set at 2 kV for computer acquisition. The magnet was scanned quadratically from 900 to 10 amu in 12 seconds. Field anodes were activated with low benzonitrile vapor pressure at high temperature in a Varian device. Heating of the anode was manipulated by an ECP (Biomedical System Specialties, Model ECP 10) accurate to 0.1 mA.

B. Chemicals

LiCl, LiBr, LiI, NaCl, NaBr, NaI, KCl, KBr, KI, LiOH and KOH were purchased from Fisher Scientific Company. Sodium tosylate (NaOTs) and *p*-toluenesulfonic acid were purchased from Eastman Kodak Company. All these chemicals were used without further purification. NaBPh₄ was purchased from Aldrich Chemical Company and recrystallized from aqueous acetone before use. [2.2.2]-, [2.2.1]-, and [2.1.1]-cryptate were purchased from E. Merck Laboratories Inc. and

used without further purification.

LiOTs and KOTs were prepared by mixing an equimolar amount of the corresponding hydroxide with p-toluenesulfonic acid in water. The salts were recovered by evaporation of water under vacuum at 50°. The residues were then recrystallized from aqueous methanol. Lithium and potassium tetraphenylborates were prepared according to methods described in the literature.⁵⁴

LiBPh₄: To a solution of 0.5 g of NaBPh₄ in 3 ml of tetrahydrofuran (THF) was added a solution of 66 mg LiCl (5% excess) in 2 ml of THF. The precipitated NaCl was removed by centrifugation. LiBPh₄ was recovered by evaporating the solvent. The residue was recrystallized three times from ethylene dichloride/cyclohexane, and then dried under vacuum at 50°C.

KBPh₄: An aqueous solution of NaBPh₄ (ca 5%) was treated with an aqueous solution (ca 5%) containing an equimolar amount of KCl. The insoluble KBPh₄ was filtered and washed with water. The crystals were recrystallized three times from aqueous acetone, then dried under vacuum at 50°.

Cryptates were prepared by mixing an equimolar amount of the corresponding salt with a solution of 50 mg of cryptand in 3 ml of chloroform. The mixture was stirred at room temperature overnight and solvent evaporated. The residue was redissolved in 2 ml of chloroform for FDMS analysis.

CHAPTER IV

RESULTS AND DISCUSSION

In this work, a 3 x 3 x 5 matrix composed of the complexes from cryptands I, II, and III with Li^+ , Na^+ , and K^+ salts of Cl^- , Br^- , I^- , OTs^- , and BPh_4^- was studied. Thirty-nine out of the forty-five complexes were made and studied under FD conditions. The results will be discussed in terms of ease of ionization and stability of these complexes in FD. The study of the anion effect was initiated by some preliminary experiments which showed a strong anion effect on the cationization of nucleosides. These preliminary results will also be discussed.

A. Preliminary Studies on Anion Effects in Field Desorption

Under FD conditions, nucleosides generally desorb smoothly and give reasonably consistent spectra of low intensities. The smooth desorption process is known to be interfered with by contaminating alkali metal ions. The smooth FD process is restored after the contaminating ion is reduced to a tolerable level by special treatment of the sample.

Attempts at cationization of the pure compounds with inorganic salts proved unsuccessful. In contrast, addition of equimolar amounts of substituted sodium benzoates to the

samples was shown to increase the total ion current (TIC) and to result in intense cationized molecular species in some cases.

The major ions containing the molecular species from the cationized spectra of cytidine and some substituted sodium benzoates are listed in Table 2. Addition of sodium ortho-nitro-, meta-nitro-, para-nitro-, and ortho-chloro-benzoate results in a drastic increase in TIC. Both $M+Na$ and $2M+Na$ are observed with larger intensities than the $M+1$ peak in the spectrum of pure cytidine. Cationization is also observed for sodium ortho-methylbenzoate, however, the TIC is not improved.

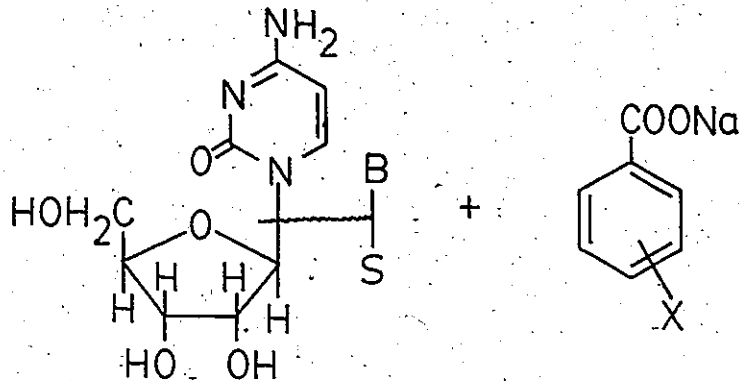
The spectra of adenosine and various sodium benzoates are shown in Table 3. The spectrum of adenosine is also improved by the addition of ortho-nitro substituted salt. However, all the other salts prove to be ineffective and give essentially the same spectrum as untreated adenosine.

The addition of these salts to guanosine results in both cationized and noncationized molecular species. The spectra show no significant increase in TIC but less fragmentation. The spectra of these mixtures are shown in Table 4.

From these results, a significant anion effect on the cationization of nucleosides is obvious. However, we are not able to correlate the observations with simple chemical and physical parameters. These observations lead us to search for the existence of an anion effect in the stability of

Table 2

Field Desorption Mass Spectra of Cytidine and
Substituted Sodium Benzoate Mixtures

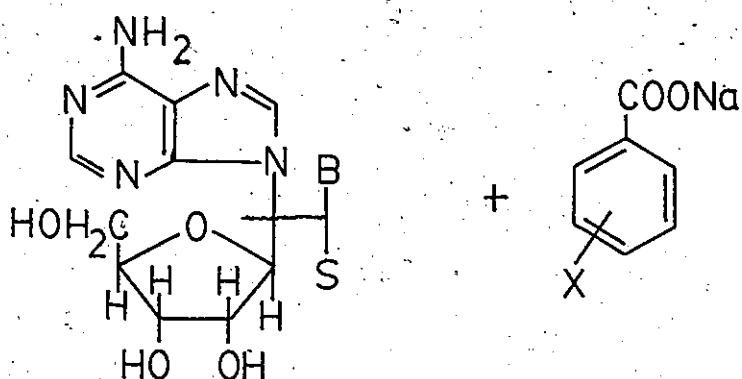


	Pure sample	X				
		<i>o</i> -NO ₂	<i>m</i> -NO ₂	<i>p</i> -NO ₂	<i>o</i> -Cl	<i>o</i> -CH ₃
<u>b.a.t./TIC^a</u>	18/2	19/216	19/147	16/34	20/99	14/<1
Ions						
S	15					
M	10					
M+1	100	1				
M+Na		82	100	100	99	100
2M+Na		100	55	42	100	
M+2Na+ArCOO		56	41	17	28	
M+3Na+2ArCOO		23	6		6	
2M+2Na+ArCOO		9	10		14	

- a. TIC = total ion current in arbitrary unit;
b.a.t. = best anode temperature in mA.

Table 3

Field Desorption Mass Spectra of Adenosine
and Substituted Sodium Benzoate Mixtures



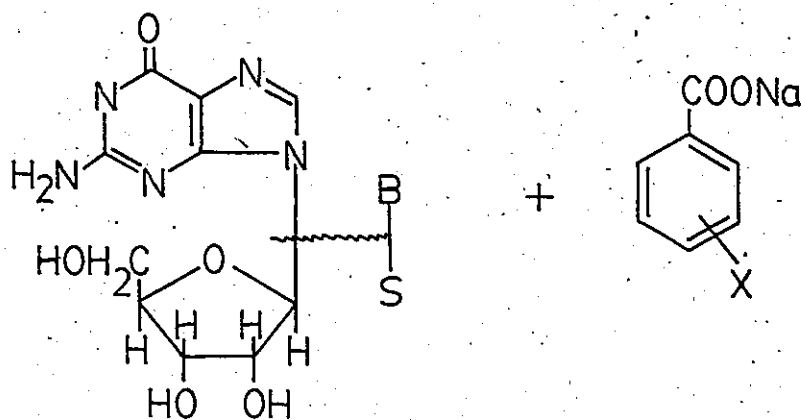
	Pure sample	X				
		<i>o</i> -NO ₂	<i>m</i> -NO ₂	<i>p</i> -NO ₂	<i>o</i> -Cl	<i>o</i> -CH ₃
b.a.t./TIC ^a	19/1	17.5/43	17/1	18/1	18.5/1	18/1
Ions						
S	13		2	5		
M	95		100	100	100	100
M+ 1	100		44	47	22	
M + Na		100		2		
2M + Na		3				
M + 2Na + ArCOO		1				
M + 3Na + 2ArCOO		2				

a. TIC = total ion current in arbitrary unit;

b.a.t. = best anode temperature in mA.

Table 4

Field Desorption Mass Spectra of Guanosine
and Substituted Sodium Benzoate Mixtures



	Pure sample	X				
		<i>o</i> -NO ₂	<i>m</i> -NO ₂	<i>p</i> -NO ₂	<i>o</i> -Cl	<i>o</i> -CH ₃
b.a.t./TIC ^a	18/7	19.5/7	21/8	21/4	19.5/6	18/2
Ions						
Na				67		
BH	8					
M+1	100	100	100	42	20	
M+Na		47	22	100	100	100
M+2Na-1				27	12	
2M+Na					2	

a. TIC = total ion current in arbitrary unit;

b.a.t. = best anode temperature in mA.

cryptates under FD conditions.

B. Field Desorption Mass Spectra of Alkali Metal Cryptates

Among the thirty-nine cryptates studied, three of them, I·KCl, I·LiCl, and II·KCl, failed to give FD spectra. The spectra of the remaining thirty-six complexes are presented in Tables 5, 6 and 7 according to the classification of the ligands. The TIC are also presented for comparison. The unit of TIC represents ca 1,000 ions recorded by the computer under the conditions described in the experimental section. Due to poor ion statistics and, sometimes, unstable desorption behavior, scan to scan reproducibility drops rapidly at low TIC (<1) values. The b.a.t. is also listed in terms of anode heating current (mA). All of the complexes studied give clean and simple spectra except [2.2.2]-cryptand with KCl and LiCl, and [2.2.1]-cryptand with KCl from which no spectra were obtained. The FD spectra of the alkali metal [2.2.2]-cryptates are listed in Table 5. Of the thirteen complexes, almost all of them give the cryptate cation $(L+C)^+$ as the dominant ion, with I·NaBr as the only exception. From this exception together with the failure to obtain the FD spectra of I·LiCl and I·KCl, the operation of an anion effect seems likely. Minor peaks are recorded for $L+C\pm 1$ and $L+C\pm 2$. After the adjustment for ^{13}C , ^{18}O , ^{41}K , and ^6Li isotopes, only $L+C-2$, corresponding to the loss of two hydrogen atoms, remains significant. This apparent loss of two hydrogen atoms from the ligand is

Table 5

FD Spectra of Complexes of Alkali Metal Salts with
[2.2.2]-Cryptand (I)^a

complex(mA) ^b	TIC ^c	L	L+1	L + C			others		
				-2	-1	+1		+2	
I·KBr(16)	1	16		2	1	100	13	8	L-2(19)
I·KI(20)	2	4		1		100	16	9	
I·KOTs(19)	52			8	6	100	22	10	
I·KBPh ₄ (21)	38				2	100	21	10	
I·NaCl(12)	1		1	5	4	100	15	2	
I·NaBr(16)	2	100	23		5	12	2		L-2(4)
I·NaI(18)	3	2		3	1	100	21	2	
I·NaOTs(14)	34		1	2	1	100	20	3	d
I·NaBPh ₄ (20)	13			2	1	100	22	4	
I·LiBr	75	1			8	100	19	3	
I·LiI	73			1	9	100	21	4	L+2C ²⁺ (18)
I·LiOTs(14)	5	11	6		15	100	8	4	
I·LiBPh ₄ (17)	77				1	100	19	2	

(cont'd)

Table 5 (cont'd)

FD Spectra of Complexes of Alkali Metal Salts with

[2.2.2]-Cryptand (I)^a

- a. L = ligand, [2.2.2]-cryptand; C = metal cation.
- b. anode heating current
- c. TIC = total ion current in arbitrary units.
- d. m/z 523 (1); assigned to $L + 2C + OTs - 70$, where loss may be C_4H_6O .

further supported by the L-2 peak in the spectra of I·KBr and I·NaBr.

The anion shows up only in the spectrum of I·NaOTs at m/z 523, which is assigned to L+2C+OTs-70 where the loss could be C₄H₆O. Some more examples of the ions of this kind will be seen in the spectra of the complexes from [2.2.1]-cryptand.

The accomodation of two small Li⁺ ions to the oversized ligand appears only in the spectrum of I·LiI as L+2C²⁺ (relative abundance 18%). The existence of this doubly charged ion is supported by the appearance of an isotope peak at one-half mass unit higher throughout the scans. However, this ion is missing in the spectra of lithium [2.2.2]-cryptates with other anions.

The spectra of alkali metal [2.2.1]-cryptates are presented in Table 6. The general features of these spectra resemble those from the [2.2.2]-cryptates. Fifteen of these complexes were made and only II·KCl failed to give a spectrum. In the remaining fourteen complexes of this set, II·KBr and II·KI fail to give L+C as the dominant ion. After correcting for isotopes, there remain significant L+C±1 ions which correspond to the gain or loss of a hydrogen atom. The L+C-2 ion is still apparent in the lithium complexes and in some of the intense spectra of sodium complexes.

The protonation of the ligand, a well known reaction in solution, is observed in the spectra of II·KOTs and

Table 6

 FD Spectra of Complexes of Alkali Metal Salts with
 [2.2.1]-Cryptand (II)^a

complex (mA) ^b	TIC ^c	L		L + C		others
		-1	+1	-	+1 +2	
II·KBr(16)	11		100 18	2		
II·KI(12-18) ^d	1		100	100		
II·KOTs(13)	4	1	8 5	7	25 15	e
II·KBPh ₄ (12)	5			100 34	20	
II·NaCl(11)	2		24 1	100 17	1	
II·NaBr(17)	3		30 10	100 18	1	
II·NaI(18)	123			5 1	100 21	f
II·NaOTs(13)	65			1	100 25	g
II·NaBPh ₄ (19)	165			1	100 18	3
II·LiCl(14)	2		15 9	2 23	100	
II·LiBr(13)	12			6 16	100 23	2
II·LiI(22)	5			1 7	100 18	
II·LiOTs(17)	178	1	1	2 11	100 17	3 L + I ²⁺ (11)
II·LiBPh ₄ (18)	118			1 3	100 19	2

(cont'd)

Table 6 (cont'd)

FD Spectra of Complexes of Alkali Metal Salts with
[2.2.1]-Cryptand (II)^a

- a. L = ligand, [2.2.1]-cryptand; C = metal cation.
- b. anode heating current.
- c. TIC = total ion current in arbitrary units.
- d. average of 5 scans.
- e. m/z 505(49), 506(8), 507(3); assigned to L + 2H + OTs.
 m/z 557(11); assigned to 2L + C - 146, where loss may be $2 \times C_{4H_7O}$.
 m/z 536(3); assigned to L + 2C + OTs - 45, where loss may be C_2H_5O .
 m/z 459(19); assigned to 3C + 2OTs.
- f. m/z 837(6); not reproducible; assigned to 2L + 2C + I.
- g. At 20 mA and above salt clusters Na_3OTs_2 and Na_2OTs dominate the spectrum.

II·LiOTs. In the spectrum of II·KOTs, a peak is observed at m/z 505 which is assigned to $L+2H+OTs$. The existence of tosylate anion is confirmed by the relatively high m/z 507 when a sulfur atom is present in the ion. Ions at m/z 557 and 536 represent additional examples of ligand decomposition. The former ion is assigned to $2L+C-146$ where loss may be $2 \times (C_4H_7O)$. The latter ion is assigned to $L+2C+OTs-45$ where loss may be C_2H_5O . The $(L+1)^{2+}$ ion in the spectrum of II·LiOTs is another example for the protonation of the ligand. Formation of this ion can be rationalized as the protonation and ionization of the ligand at the same time.

For the final set of these complexes only nine members were attempted. The spectra of all five Li complexes and representative Na and K complexes are listed in Table 7. Although $(L+C)^+$ is still the dominant ion in these spectra, only III·LiBPh₄ and III·LiI give relatively intense spectra. The $L+C-2$ ion appears again in the spectra of III·LiBr and III·LiI. Accommodation of the potassium ion to this undersized ligand is surprisingly good. The complexation of K^+ to two molecules of [2.1.1]-cryptand is seen in the spectrum of III·KBPh₄ as $(2L+C)^+$ (relative abundance 20%).

Table 7

 FD Spectra of Complexes of Alkali Metal Salts with
 [2.1.1]-Cryptand (III)^a

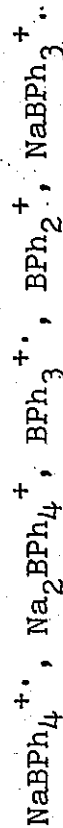
complex(mA) ^b	TIC ^c	L	L+1	L + C			others
				-2	-1	+1 +2	
III·KBPh ₄ (14)	4	12	3	100	14	6	2L+C(20)
III·NaCl(15)	6	1	8	1	100	11	3
III·NaI(18)	1	3		100	11	2	
III·NaBPh ₄ (19)	10	1		100	23	2	d
III·LiCl(17)	3	19	2	6	100	16	2
III·LiBr(19)	8			4	100	14	1
III·LiI(23)	20			3	100	16	2
III·LiOTs(22)	3			8	100	18	2
III·LiBPh ₄ (21)	39			3	100	16	2

a. L = ligand, [2.1.1]-cryptand; C = metal cation.

b. anode heating current.

c. TIC = total ion current in arbitrary units.

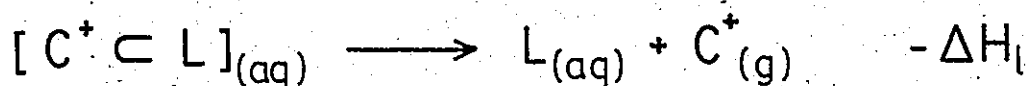
d. Above 20 mA several ions corresponding to portions of the salt are found:



C. Loss of Selectivity of Cryptands in Field Desorption

Perhaps the most surprising result from the FD spectra of the complexes studied is the lack of correlation with the selectivity of the ligand in solution; i.e., toward the particular cation that most nearly fits into its cavity. Thus in solution, [2.2.2]-, [2.2.1]- and [2.1.1]-cryptands display high selectivity toward K^+ , Na^+ and Li^+ respectively. In FD, this "best fit" selectivity is reflected only in the average anode heating current of the complexes. Using the mathematical inclusion symbol, \subset , to represent all complexes with common cation and cryptand, the value of the average anode heating current for $[K^+ \subset 2.2.2]$ complexes is 19 mA, compared to 16 mA for both Na^+ and Li^+ complexes of the same ligand. The value for $[Na^+ \subset 2.2.1]$ is only 1 to 2 mA higher than for the other complexes in the same set. The value for $[Li^+ \subset 2.1.1]$ is 2 mA higher than for $[Na^+ \subset 2.1.1]$ and 6 mA higher than for the $[K^+ \subset 2.1.1]$ complex in this set. However, in terms of ease of ionization (from TIC) and stability (from relative abundance of L and L+C peaks) of the complexes in FD, the "misfits" are held as well as the "bestfits" as long as the ligand is big enough to include the cation completely. Thus $[Li^+ \subset 2.2.2]$ is as stable as $[K^+ \subset 2.2.2]$, in spite of the stability constant of the K^+ complex in solution is more than 10^3 times bigger than that of the Li^+ complex. In solution, stability and selectivity result from a balance between ligation and solvation of the cation since

for the same ligand, the solvation energy of the cryptate cations remains the same. The dissociation process in FD can thus be approximated by the reverse of the ligation reaction:



The thermodynamic parameters of this reaction are presented in Table 8. The selectivity is not found in the entropies of ligation (ΔS_l) which are essentially constant for every ligand regardless of the cation. However, the enthalpies of ligation (ΔH_l) increase with small cations. Thus for every ligand, transfer of a Li^+ from the ligand cavity to the gas phase costs 20 kcal/mol more than the same process for Na^+ which in turn costs 17 kcal/mol more than for K^+ , regardless of the stability of the complexes in solution. Thus the selectivity of the cryptands must come mainly from the solvation of the cation in solution, and the loss of selectivity of these ligands in FD condition is related to a lack of solvation of the extruded cation.

Table 8

Enthalpy (ΔH_1) and Entropy (ΔS_1) of Ligation
of Alkali Metal Cations by Cryptands I-III

Ligand	Thermodynamic parameter ^a	Cations		
		Li ⁺	Na ⁺	K ⁺
I [2.2.2]	$-\Delta H_1$	-	113	97
	$-\Delta S_1$	-	33	31
II [2.2.1]	$-\Delta H_1$	132	111	93
	$-\Delta S_1$	21.6	19.8	21.7
III [2.1.1]	$-\Delta H_1$	137	111	-
	$-\Delta S_1$	25	29	-

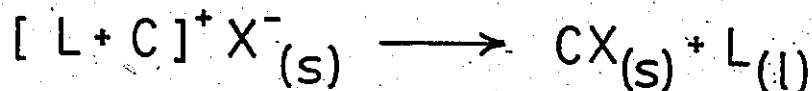
a. ΔH_1 : enthalpy of ligation, in kcal/mol.

ΔS_1 : entropy of ligation, in entropy unit, e.u.

D. Anion Effect on the Stabilities of Alkali Metal Cryptates
in Field Desorption

From Tables 5-7, a marked anion effect is observed in the FD spectra of the cryptates. The average anode heating current increases in the series Cl⁻ to Br⁻ to I⁻ from 14 to 16 to 19 mA respectively. In addition the generally low TIC and high relative abundance of L⁺ ion in

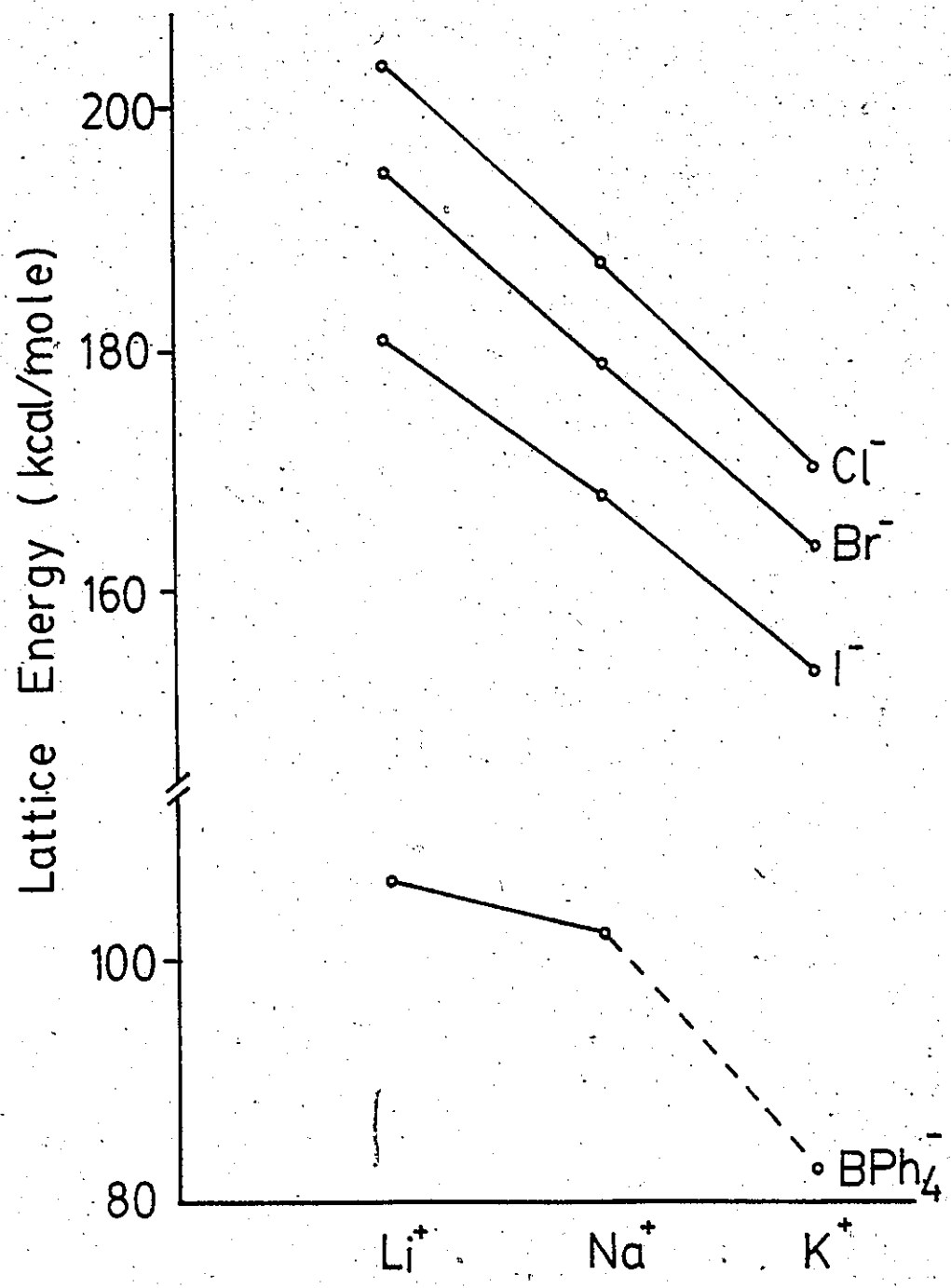
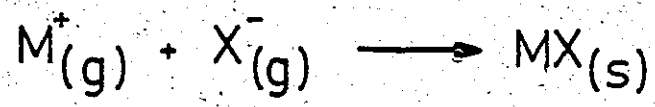
the spectra of chlorides and bromides give strong evidence for an operative anion effect. As a revised approximation to the FD condition, the cation released from the molecular cavity of the ligand, instead of entering the gas phase, may be viewed as joining the waiting external anion on the emitter surface:



From this approximation, one anticipates a negative correlation on the stability of the cryptate in FD to the ionic lattice energies of alkali metal salts. As shown in Figure 3, the recombination energies of chlorides are 9 kcal/mol higher than those of bromides which in turn are 11 kcal/mol higher than iodides. Although the thermodynamic information for tetraphenylborates is not complete, experimental and theoretical results allow one to estimate that the lattice energy of alkali metal tetraphenylborates are ca 65 kcal/mol lower than the corresponding iodides.^{54,55} Thus a reasonable origin for the anion effect on the cryptate stability in FD has been located. The larger the recombination energy of the cation and anion, the larger the driving force to push the complex to decompose, and thus the less stable the complex. It is thus concluded that the stability of the cryptates under FD is at least partly an inverse function of the ionic lattice energy of the salt.

Figure 3.

Lattice Energies of Some Alkali Metal Salts.



CHAPTER V
CONCLUSION

In solution, a cryptand displays high selectivity toward the cation that fits well into its molecular cavity. However, under FD conditions, the ligand loses its selectivity and complexes with "misfit" cations as well as the "best fit" one, whenever it can include the cation completely. Most of the alkali metal cryptates give intense spectra with the cryptate cation, $(L+C)^+$, as the base peak. The desorption process is relatively smooth and occurs at relatively low anode heating current. These characteristics may make the ligand useful in the analysis of trace amounts of alkali metal ions.⁵⁶ Addition of a cryptand large enough to hold up the biggest cation in question may result in a smoother desorption process and more intense peaks related to the cations.

A final remark has to be made on the anion effect, which is negligible in solution. A marked anion effect is observed in the stability of the cryptates under FD conditions. The larger anion, which has a smaller recombination energy with the cation, stabilizes the cryptates. This anion effect is correlated with the lattice energy of the salt used. The higher the lattice energy of the salt, the less stable the complex formed. In a study of Li^+ attachment to organic molecules in FD, $LiBPh_4$ was used as the cationiz-

ing reagent. The results were successful, but the choice of this big anion was not explained. From the above results, it is suggested that for a given cation, the use of an anion that gives a small salt lattice energy may facilitate the cationization process (i.e. stabilize the complex) under FD conditions. Thus for cationizing nucleosides, a big anion, e.g. BPh_4^- , may be the first choice. However, as described previously, a significant structural effect was observed in the cationization process for nucleosides, suggesting that substituted naphthoates may well be worth trying. Effects from slight structural changes of the anion may help in understanding the role of the anion on the cationization process (i.e. stability of the complex).

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PART II

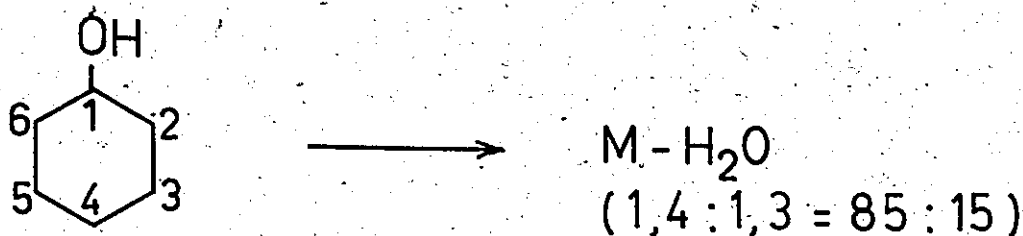
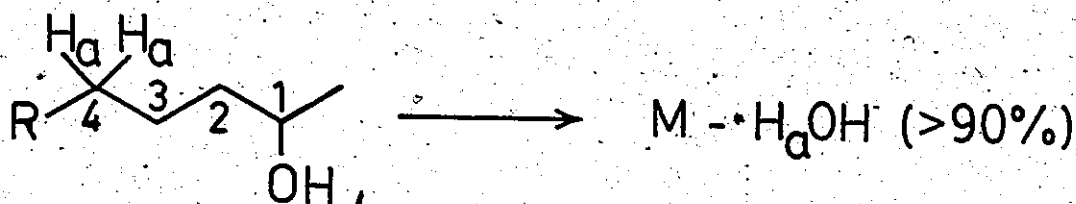
STEREOCHEMICAL DIFFERENTIATION OF ALCOHOL DERIVATIVES

BY VARIOUS MASS SPECTROMETRIC TECHNIQUES

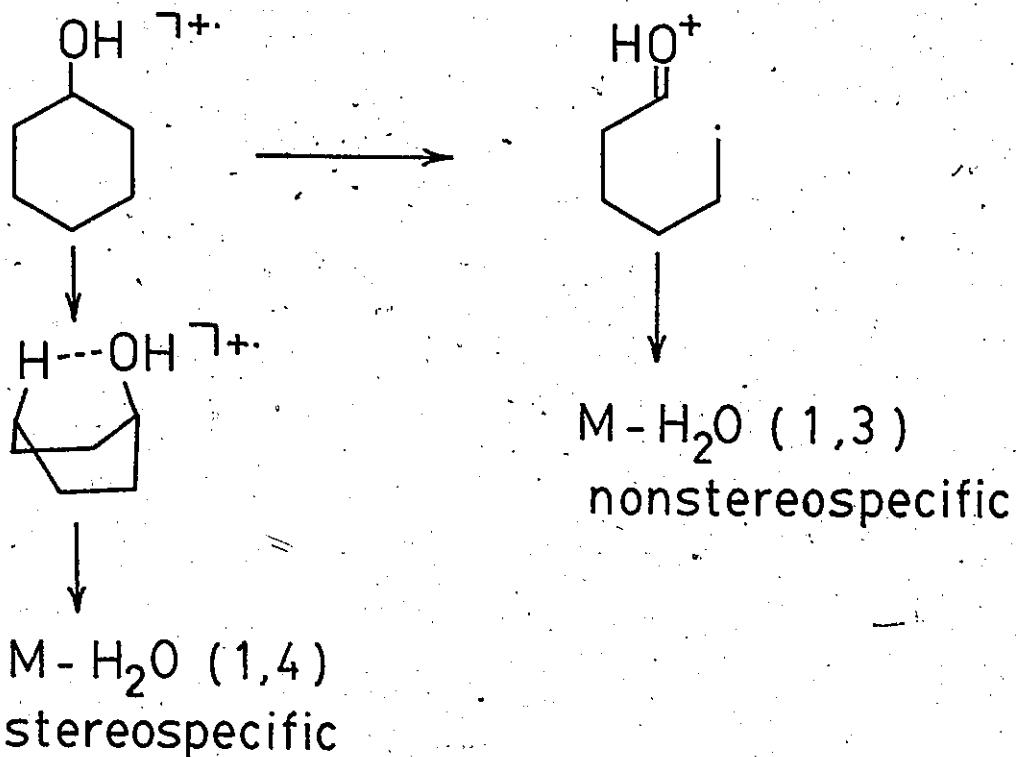
CHAPTER I
INTRODUCTION

A. Stereochemical Studies in Mass Spectrometry

The differences in the fragmentation pattern of electron impact (EI)-mass spectra of stereoisomers was first recognized in the fifties.¹⁻³ The stereoisomeric effects may arise from the difference in energy contents between isomers and/or rearrangement reactions of the molecular ions that are affected by the accessibility of the two groups participating in the reaction. The unimolecular rearrangement reaction is especially useful for structural problems due to its high dependence on spatial relationships in the molecular ion during the bond making stage. Such reactions, e.g. elimination of a small molecule from the molecular ion, provide important information about the configuration of the molecule and has been used for structural assignments. Specificity of a rearrangement reaction can be seen from the elimination of a water molecule from the acyclic alcohols.⁴ The C-4 hydrogen atoms are preferentially eliminated (>90%). In contrast, the stereospecificity is lower in the loss of water from cyclic alcohols.^{5,6}

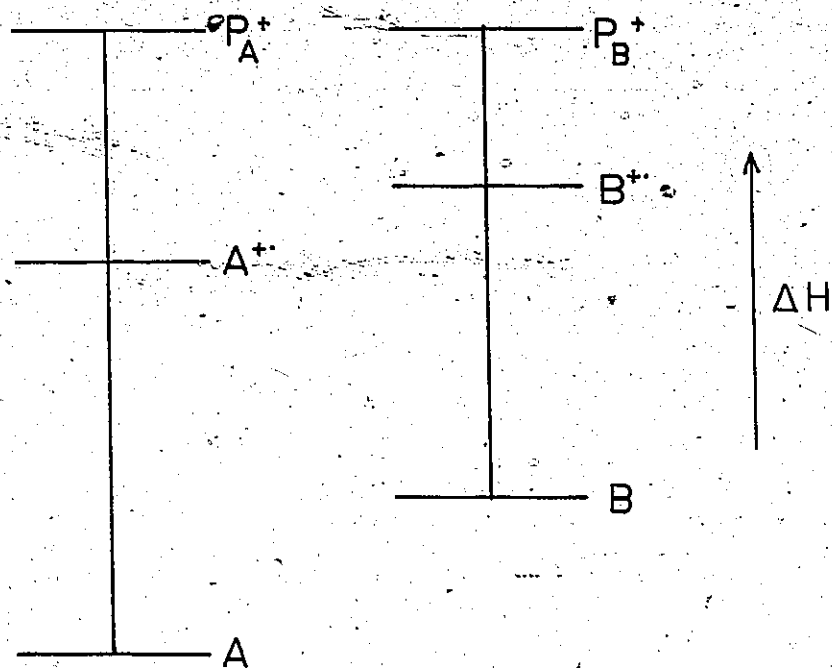


In 1,4 elimination of water from cyclohexanol, the cis-4-hydrogen is transferred to the hydroxyl group via a ring-intact boat conformation, and thus is highly stereospecific. In the 1,3-elimination, a prior α -cleavage scrambles the diastereotopic hydrogens on C-3 and C-5 and thus is non-stereospecific.⁶



In FD, stereochemically dependent elimination reactions have also been observed. The cis- and trans-aldrin-4, 5-diol have been studied by FD and have shown different intensities for the $M - H_2O$ peak. The ion is more intense in the trans-isomer than in the cis one.⁷ The reason for the difference was not explained. However, it could be because of the availability of an activated hydrogen in the adjacent carbon in the trans isomer.

It is not the purpose here to outline every stereochemically dependent mass spectral reaction. There are a few review articles that discuss this matter in more detail.⁸⁻¹³ Besides the highly stereochemically sensitive rearrangement reactions, there is another type of reaction that has perhaps small but real effects on the appearance of the mass spectra of stereoisomers. Under EI, the simple cleavage reaction of diastereomers that leads each of the isomers to a common product ion, the difference of the appearance potentials (AP) of the product ions reflects the difference between the heats of formation ($-\Delta H_f$) of the isomers (Figure 1).^{14,15} P_A^+ and P_B^+ are structurally identical species. If the isomers incorporate similar amounts of energy in the ionization process, the decomposed ion from the less stable isomer, P_B^+ , should undergo faster further decompositions. As a consequence, diminished ion intensity of P_B^+ results. Figure 2 shows support for this idea.



Simple model predicts:

- (1) $\% \Sigma P_A^+ > \% \Sigma P_B^+$
- (2) $AP, (P_A^+) > (P_B^+)$

where A & B are diastereomers and
 P_A^+ & P_B^+ are structurally identical

Figure 1. Scheme for Relating Appearance Potential Differences And Product Ion Intensities to The Relative Heats of Formation of Diastereomers And Constitutional Isomers

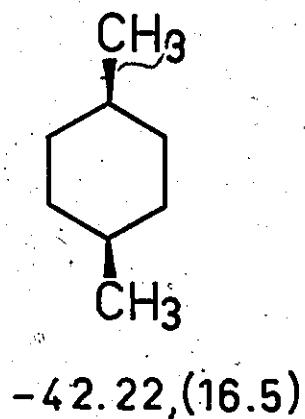
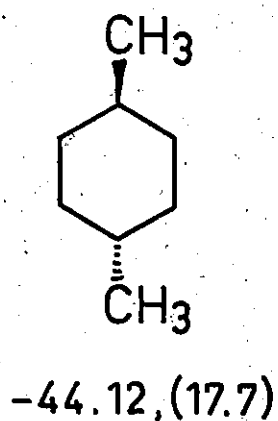
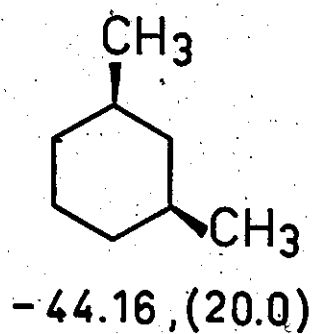
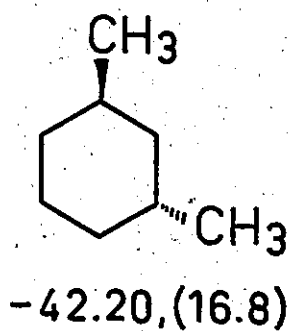
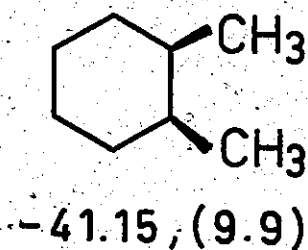
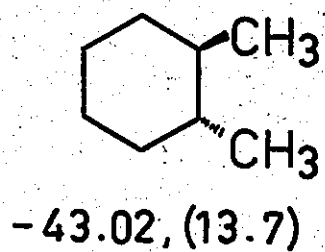
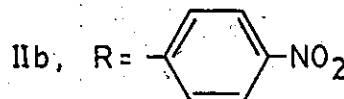
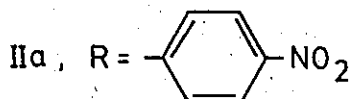
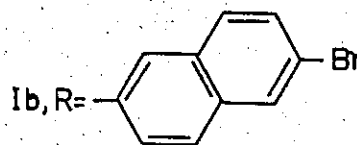
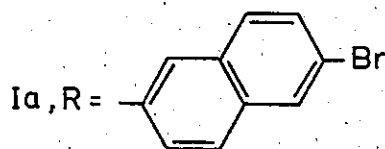
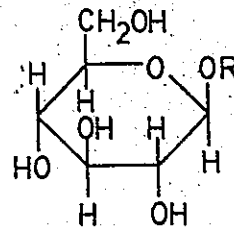
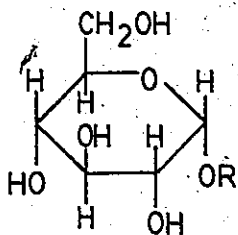


Figure 2. Relationship between Thermochemical Stability and Ion Intensity for Loss of Methyl Radical. Data Presented as ΔH_f (in kcal/mol), ($\% \Sigma [M - CH_3]^+$)

In 1973, Beckey and Schulten showed that the isomeric glycosides (Ia, Ib, IIa and IIb) give distinguishable FD spectra.¹⁶ The cleavage of the glycosidic bond of the α -isomers was enhanced by a factor of 2 to 5 over the β -isomers.



The difference was explained by the fact that less stable α -glycosides were more subject to cleavage to release the steric hindrance in the molecular ion.

B. EI Studies of Dialkyl Phthalates

Homologous dialkyl phthalic acid esters have been studied by EIMS and a fragmentation pattern has been proposed.¹⁷⁻¹⁹ The fragmentation pattern was divided into two

main steps: (1) from molecular ion to m/z 167 and then m/z 149 (Scheme 1); (2) from m/z 167 to m/z 76 (Scheme 2). Most of the esters studied gave weak but observable peaks for the molecular ions. The molecular ion lost one of the two hydrocarbon chains by a double McLafferty rearrangement²⁰ involving a transfer of two hydrogen atoms to give $[A]^+$ (Scheme 1). A McLafferty rearrangement of $[A]^+$ gave rise to m/z 167 which then lost a water molecule to give m/z 149. Loss of a water molecule from $[A]^+$ gave $[B]^+$ which underwent further decomposition to give m/z 149 (Scheme 1).

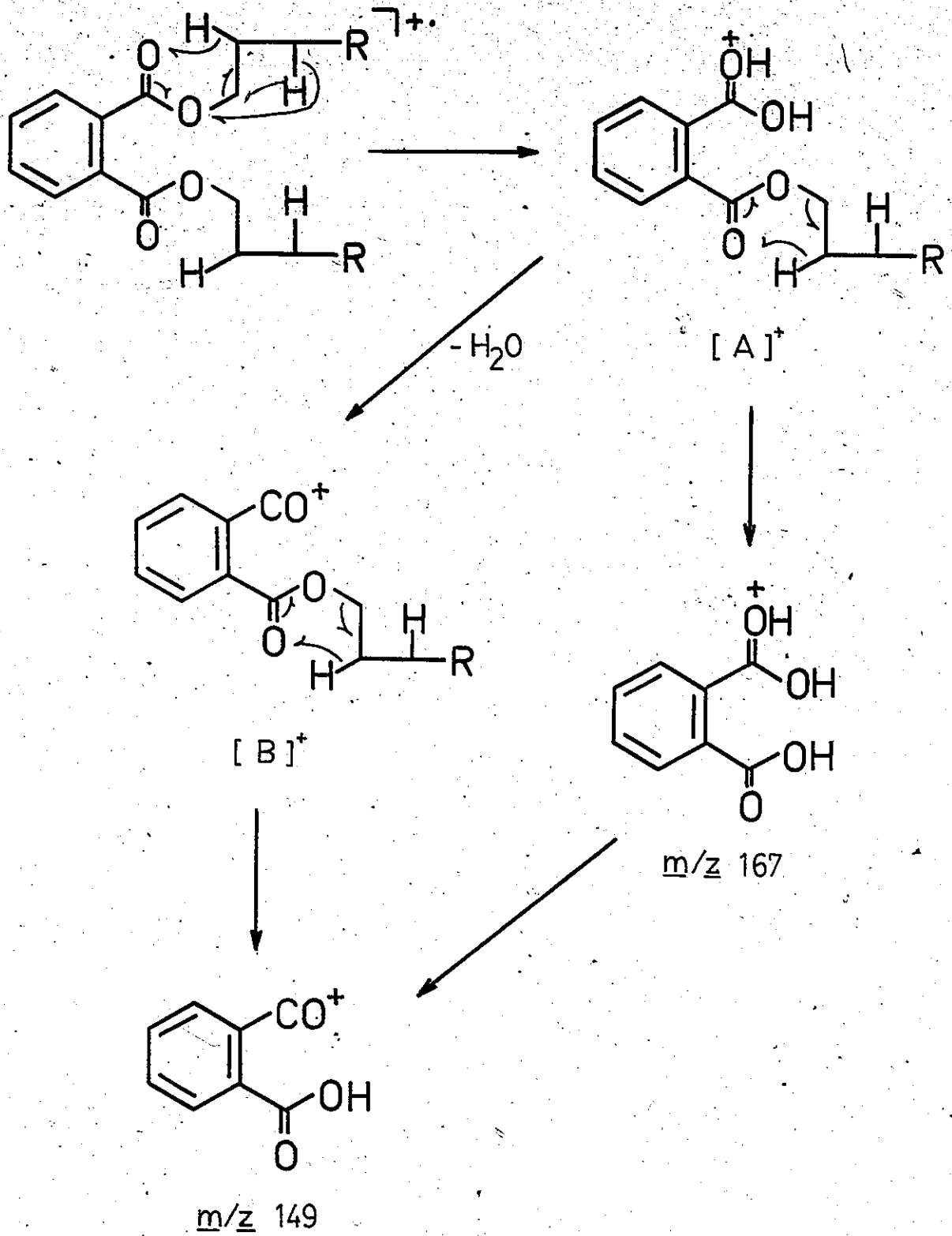
Loss of carbon monoxide from m/z 149 furnished m/z 121 which decomposed to m/z 93. Loss of a COOH radical from m/z 149 led to m/z 104 which decomposed to CO and $[C_6H_4]^+$ (m/z 76) (Scheme 2).

Loss of a COOH radical from m/z 167 gave $[C_7H_6O_2]^+$ (m/z 122) which followed the decomposition pathway as benzoic acid (Scheme 2).

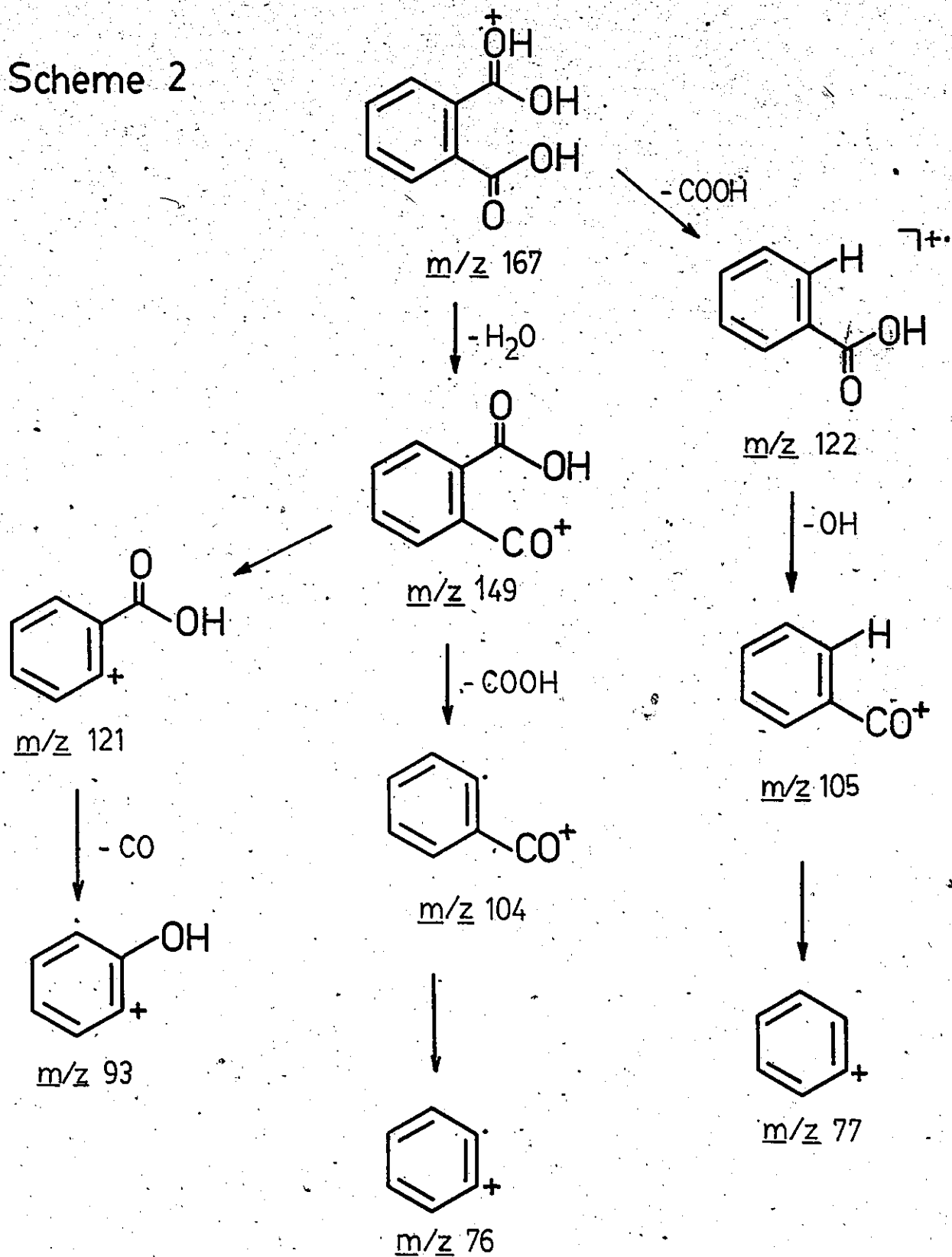
C. EI Studies of Dialkyl Carbonates

Dialkyl carbonates have been studied by Djerassi *et al.*²¹ The spectra obtained were simple. The molecular peaks were small but noticeable. Fragmentation of these compounds was simple. The molecular ions lost both of the alkyl groups in steps. A fragmentation pathway for these compounds is given in Scheme 3.

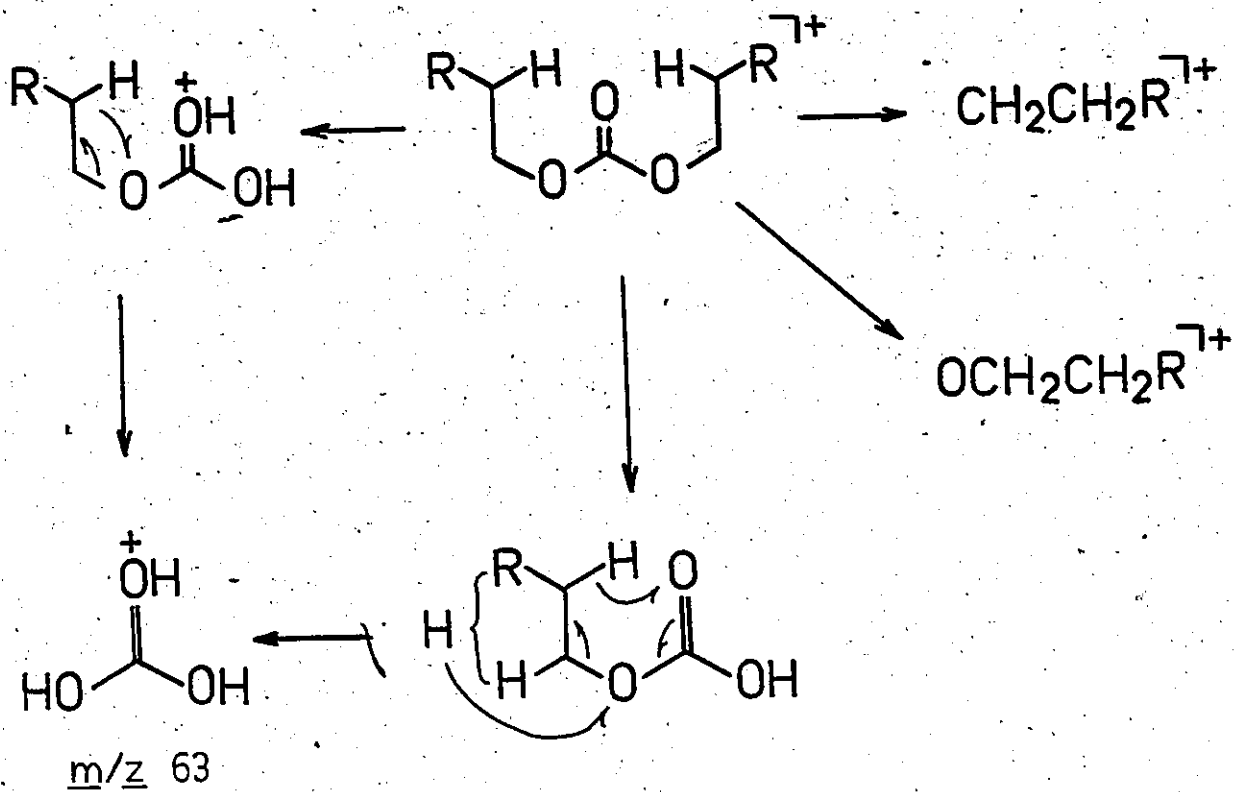
Scheme 1



Scheme 2



Scheme 3



D. Statement of Problem

Reactions with steric dependence under mass spectrometric conditions have received intensive study, especially under electron impact ionization. However, reactions under FD conditions have so far received sparse attention. The primary requirement for samples being done by field desorption is that they must be nonvolatile under working conditions. In addition, structural features favoring fragmentation must be built in so that any differences due to stereochemistry will be clearly expressed. With these two criteria in mind, acid phthalates and high molecular weight carbonates have been prepared from isomeric cyclohexyl alcohols, and have been studied under FD, FI and EI conditions.

CHAPTER II

EXPERIMENTAL

A. Instrumental

The FD spectra were recorded as described in the experimental section in Part I of this dissertation. The FD spectra are an average of at least 15 scans at an anode heating current of 12 to 15 mA.

The FI and EI spectra were recorded with the same mass spectrometer and data system as described in Part I. The samples were introduced into the ionization chamber from a direct insertion probe. In both cases, the ion source temperature was kept at ca 150° and the probe temperature was kept at 100-120°. For the FI spectra, no heating current was passed through the anode. For the EI spectra, energy for the bombarding electrons was 70 eV.

Melting points, determined with a Fisher-Johns melting apparatus, and boiling points were uncorrected.

The NMR spectra were recorded on a Jeol 60 instrument with tetramethylsilane as internal standard. The IR spectra were recorded with a Beckmann IR 12.

B. Chemicals

The trans-1-decalone, cis-1-decalol, 2-decalol (mixture of cis and trans isomers), triphenylmethyl chloride,

lithium aluminum hydride (LAH), tri-sec-butylborohydride (as a 1 M solution in tetrahydrofuran (THF)) and 4-tert-butylcyclohexanol (mixture of cis and trans isomers) were purchased from Aldrich Chemical Co., The triphenylmethyl chloride was recrystallized from acetyl chloride/petroleum ether (1/10) before use. The 9-fluorenylmethyl chloroformate was purchased from Pierce Chemical Co. Phthalic anhydride was purchased from Fisher Scientific Co. and recrystallized from benzene before use.

Triphenylmethyl sodium

In a crucible containing 10 ml. of mineral oil was placed 0.25 g (11 mmol) of freshly cut sodium. Heat was applied until the sodium had melted, and 8.5 g of mercury was added slowly. The amalgam was broken into small pieces while it was still soft. The solution was then allowed to cool to room temperature. The amalgam was washed twice with petroleum ether, once with diethyl ether and then transferred to a 125 ml Erlenmyer flask. To this flask was added 1.4 g (5 mmol) of triphenylmethyl chloride and 50 ml of dry diethyl ether. The flask was then fitted with a rubber stopper and was shaken for at least 8 hr., during which period the solution slowly became deep red in colour. The flask was refrigerated for one hour to allow the solids (sodium chloride and mercury) formed in the reaction to settle.

Preparation of Acid Phthalates

The acid phthalates were prepared from phthalic anhydride and the corresponding alcohols according to the method described by Prokipcak.²¹ A general procedure is given as follows:

To an ethereal solution of 1.25 mmol of an alcohol was added the triphenylmethyl sodium solution with stirring under nitrogen until a persisting red solution was obtained (ca 25 ml). To this solution, 1.3 mmol of phthalic anhydride was added in one portion and the mixture was stirred at room temperature for 3 hr., after which period 10 ml of water was added. The aqueous layer was separated and added into a crushed ice and concentrated hydrochloric acid mixture. The aqueous solution was then extracted three times with diethyl ether. The ethereal extracts were combined, washed with water and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded a solid which was then recrystallized from petroleum ether (90-110).

For individual acid phthalates, only a brief description for the separation of isomers, if necessary, and melting point of the compound will be given. Each acid phthalate was recrystallized 3 times from petroleum ether (90-110) before mass spectral analysis.

cis- and trans-4-tert-Butylcyclohexyl Acid Phthalates (1 and 2)

4-tert-Butylcyclohexanol was purchased as a mixture of isomers. The mixed acid phthalates were prepared as described above. The isomeric acid phthalates were separated by fractional crystallization from petroleum ether (90-110). Individual isomers were then recrystallized from the same solvent at least 3 times.

cis-4-tert-butylcyclohexyl acid phthalate (1):

m.p. 140 - 141

lit²² 141 - 142trans-4-tert-butylcyclohexyl acid phthalate (2):

m.p. 146 - 147

lit²² 146.2 - 146.72-Decalyl Acid Phthalates

The 2-decalol was purchased as a mixture of isomers. The mixture separated into two fractions--the solid and liquid fractions. The two fractions were then separated and acid phthalates of both fractions were prepared.

Two acid phthalates were separated from the solid fraction reaction product by fractional crystallization from petroleum ether (90-110).

cis-trans-2-decalyl acid phthalate (7):

m.p. 153-155

lit²³ 153

trans-trans-2-decalyl acid phthalate (8):

m.p. 176-178°

lit²³ 180°

Only one acid phthalate was obtained from the liquid fraction.

cis-cis-2-decalyl acid phthalate (6):

m.p. 115-117°

lit²³ 116°cis-cis-1-Decalyl Acid Phthalate (5)

This acid phthalate was prepared from cis-cis-1-decalol and phthalic anhydride by the general procedure.

m.p. 181-182°, lit²³ 176°trans-cis-1-Decalyl Acid Phthalate (4)

To 5 ml of 1 M tri-sec-butylborohydride in THF solution was added a solution of 1.25 mmol of trans-1-decalone in 2 ml of THF at -78° with stirring under nitrogen. The solution was stirred for an additional hour and 1 ml of water was added. During the addition, the mixture was allowed to warm to ambient temperature. One ml of 3 N NaOH solution was added followed by cautious addition of 1 ml of 30% H₂O₂. To the mixture was then added 2 g of K₂CO₃ and the aqueous layer was separated and extracted twice with THF. The organic layer and extracts were combined and dried over anhydrous MgSO₄. Evaporation of solvent gave white

crystals, m.p. 44-45°. The acid phthalate was then prepared from the general procedure, m.p. 120-122, lit²³ 121.

trans-trans-1-Decalyl Acid Phthalate (3)

A solution of 30 mmol of trans-1-decalone in 5 ml of dry ether was added slowly to a suspension of 10 mmol of LAH in 10 ml of dry ether at a rate to maintain gentle reflux. The mixture was refluxed for 3 hr. after the addition, and 2 ml of ice cold water was added cautiously to destroy excess hydride. Dilute hydrochloric acid was added until all solids dissolved. The aqueous layer was separated and extracted 3 times with ether. The ethereal layer and extracts were then combined, washed with water and dried over anhydrous MgSO₄. Evaporation of solvent afforded white crystals which melted at 40-55°. The crude product was then used for the preparation of acid phthalate without purification, following the general procedure. The trans-trans-1-decalyl acid phthalate was then separated by fractional crystallization from petroleum ether (90-110). The crystals were recrystallized 3 times with the same solvent, m.p. 166-168, lit²³ 168.

Separation of cis- and trans-4-tert-butylcyclohexanol

A mixture of 1 g of the isomers was chromatographed over 15 g of silica gel (35-70 mesh). The column was eluted with pentane/CH₂Cl₂ (9/1), 50 ml portions being taken. Fractions 5-8 gave ca 0.3 g of the cis-isomer while fractions

12-15 gave 0.4 g of the trans-isomer. Intermediate fractions gave mixtures of both isomers.

cis-4-tert-Butylcyclohexyl 9-fluorenylmethyl carbonate (9)

To a solution of 0.286 g of 9-fluorenylmethyl chloroformate in 2 ml of chloroform was added a solution of 0.214 g of cis-4-tert-butylcyclohexanol with stirring at -20° . The solution was then stirred for 15 min. A solution of 0.166 g pyridine in 4 ml of chloroform was added dropwise, during which period the solution was allowed to rise to ambient temperature. The solution was then stirred for another 2 hr. followed by the addition of 10 ml chloroform. The solution was washed with water until washings were neutral, and then dried over $MgSO_4$. Evaporation of solvent gave a white solid which was then run through a column of 15 g silica gel (35-70 mesh). The column was eluted with petroleum ether (35-60)/ CH_2Cl_2 (4/1). The carbonate obtained was then recrystallized with petroleum ether (90-110), m.p. 118-119 $^{\circ}$.

IR : 3060, 3040 (m), C-H stretching, aromatic

2950 (s), 2860 (m), C-H stretching, saturated.

1730 (s), C=O stretching.

1270 (s), C=O stretching.

NMR: δ 6.5-7.1 (multiplet, 8H)

δ 4.1 (multiplet, 3H)

δ 0.95-2.15 (envelope, 10H)

δ 0.85 (singlet, 9H).

The identity of this compound was further confirmed by the mass spectral results to follow: m/z 378 (3%), m/z 178 (100%), m/z 165 (8%).

trans-4-tert-Butylcyclohexyl 9-fluorenylmethyl carbonate (10)

The trans-4-tert-butylcyclohexyl 9-fluorenylmethyl carbonate was prepared by the method described above by using trans-4-t-butylcyclohexanol instead of cis-4-t-butylcyclohexanol. After chromatography, trans-4-t-butylcyclohexyl 9-fluorenylmethyl carbonate was obtained as a viscous oil which refused to give solids upon crystallization.

IR : 3080, 3050 (m), C - H stretching aromatic
2960, 2860 (s), C - H stretching, saturated.
1738 (s), C = O stretching
1275 (s), C = O stretching
NMR: δ 6.6-7.2 (multiplet, 8H)
 δ 4.14 (multiplet, 3H)
 δ 0.95-2.2 (envelope, 10H)
 δ 0.85 (singlet, 9H).

The identity of this compound was further confirmed by the mass spectral results to follow: m/z 378 (3%), m/z 178 (100%), m/z 165 (8%).

CHAPTER III
RESULTS AND DISCUSSION

A. Mass Spectra of Isomeric 4-t-Butylcyclohexyl Acid Phthalates

The cis- and trans-4-t-butylcyclohexyl acid phthalates (1 and 2 respectively) were studied under FD and EI conditions. Under FD, both isomers give simple and similar spectra with $[M+H]^+$ as the base peak. The FD spectra of 1 and 2 are presented in Table 1. Fragmentation of the isomers is simple. Cleavage of the butyl group gives an ion at m/z 57, $[C_4H_9]^+$. Elimination of a butane molecule from the protonated molecular ion gives m/z 247, $[M+H-C_4H_{10}]^+$. Cleavage of the single bond at either side of the ester oxygen gives m/z 149, $[C_8H_5O_3]^+$, and m/z 139, $[C_{10}H_{19}]^+$. Elimination of a water molecule from $[M+H]^+$ furnishes m/z 287, $[C_{18}H_{23}O_3]^+$. The fragmentation pathway of these isomers under FD is presented in Scheme 4. There is no information on position for the attached proton in the molecular ion. However, for mechanistic rational, this proton is placed wherever convenient.

The isomers display similar EI spectra. The molecular ion is missing in both cases. The dominant ion in both spectra is m/z 149, $[C_8H_5O_3]^+$. The peak corresponding to the elimination of a phthalic acid from the molecular ion at m/z 138 is small. The isomers follow a similar pattern to known fragmentation pathway for the dialkyl phthalates.¹⁸

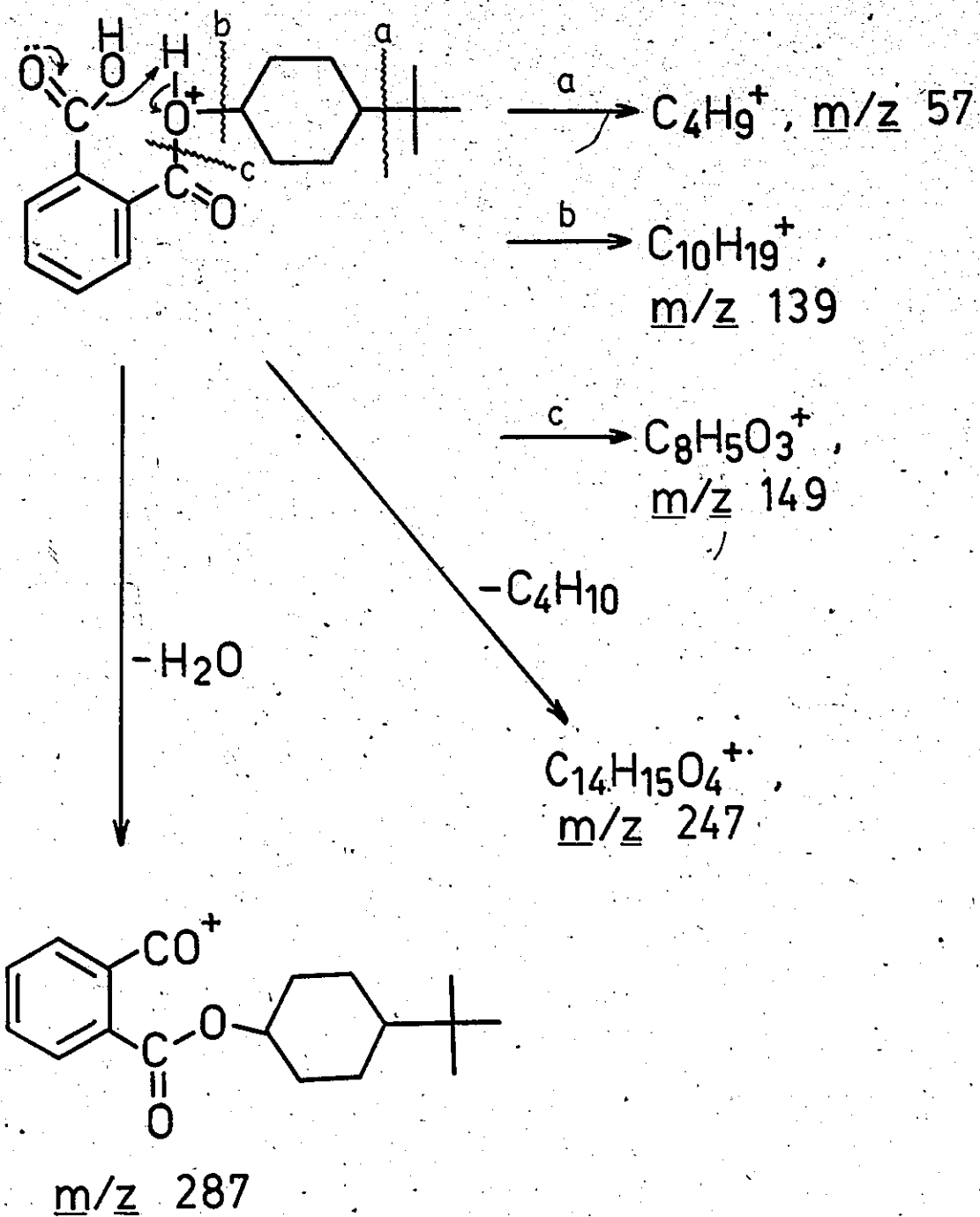
Table 1

FD Spectra of cis- and trans-4-t-Butylcyclohexyl
Acid Phthalates (1 and 2)^a

<u>m/z</u>	ions	<u>1</u>	<u>2</u>
57	$[C_4H_9]^+$	34	34
139	$[C_{10}H_{19}]^+$	22	40
140		2	3
149	$[C_8H_5O_3]^+$	27	34
150		2	2
247	$[C_{14}H_{15}O_4]^+$	4	6
287	$[C_{18}H_{23}O_0]^+$	3	4
305	$[M + H]^+$	100	100
306		17	17

a. Spectra are presented in % relative abundance.

Scheme 4



The EI spectra of 1 and 2 are listed in Table 2 and a fragmentation pathway is presented in Scheme 5. In the spectrum of 1, there exists a small but noticeable peak at m/z 248, which corresponds to the loss of C_4H_8 from the molecular ion. However, this peak is missing in the spectrum of 2. This can be explained by the possible close contact between the ester oxygen and the 4-*t*-butyl group in the cis isomer. Such an arrangement is impossible for the trans isomer.

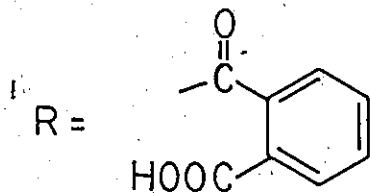
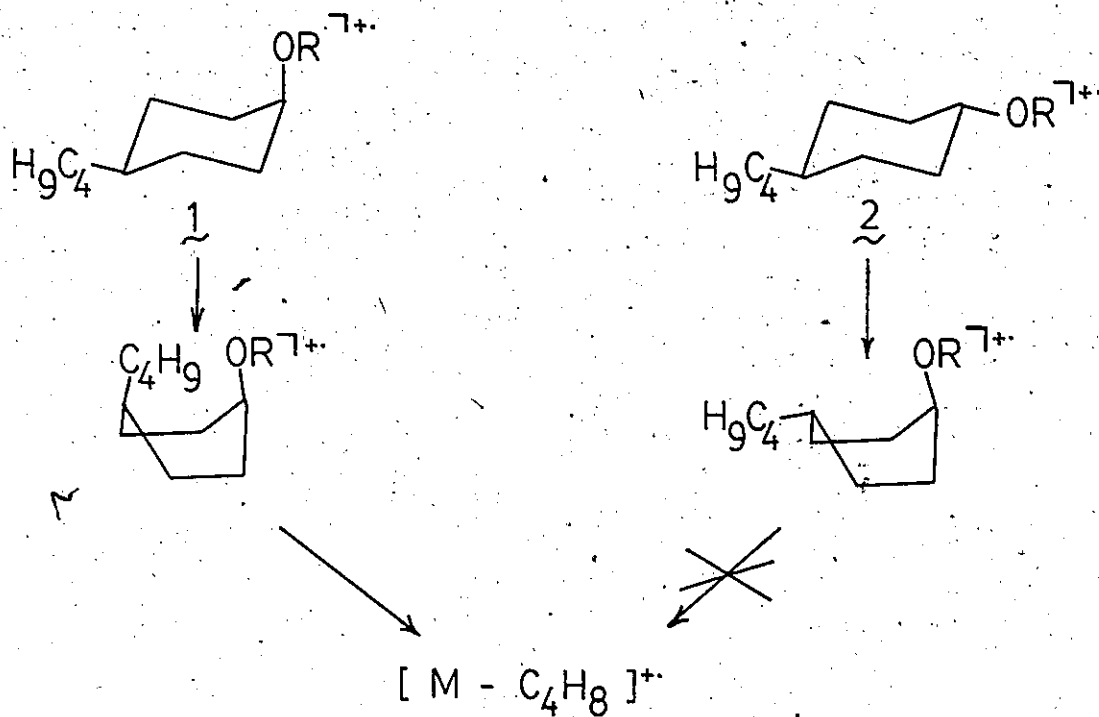


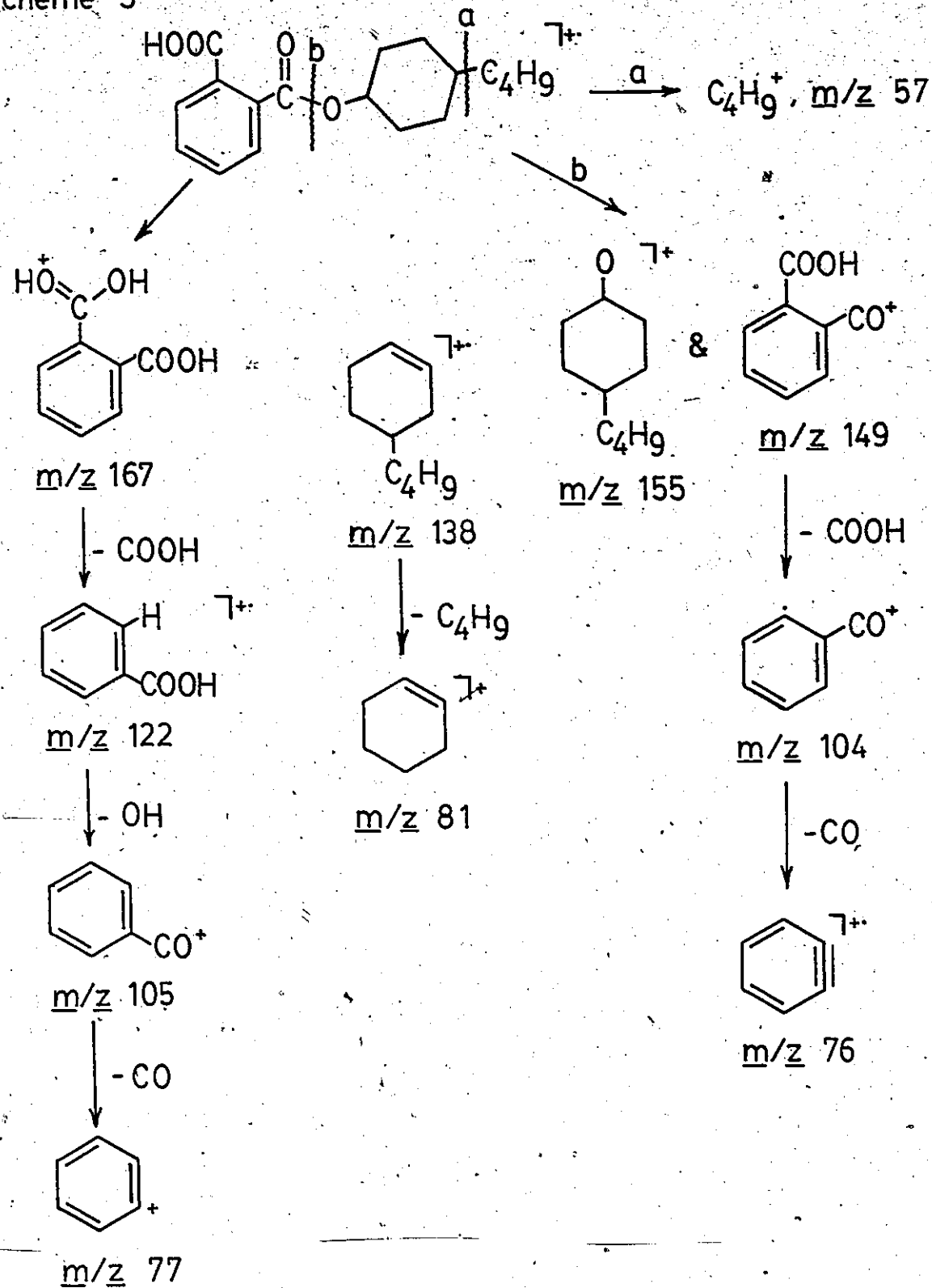
Table 2

EI Spectra of cis- and trans-4-t-Butylcyclohexyl
Acid Phthalates (1 and 2)^a

<u>m/z</u>	ions	<u>1</u>	<u>2</u>
57	$[C_4H_9]^+$	19	30
76	$[C_6H_4]^+$	2	3
77	$[C_6H_5]^+$	1	1
81	$[C_6H_9]^+$	10	12
93	$[C_6H_5O]^+$	4	4
104	$[C_7H_4O]^+$	1	2
105	$[C_7H_5O]^+$	2	1
121	$[C_7H_5O_2]^+$	3	3
122	$[C_7H_6O_2]^+$	2	2
123	$[C_7H_7O_2]^+$	8	8
138	$[C_{10}H_{18}]^+$	1	2
149	$[C_8H_5O_3]^+$	100	100
155	$[C_{10}H_{19}O]^+$	2	1
167	$[C_8H_7O_4]^+$	78	55
248	$[C_{14}H_{16}O_4]^+$	2	--

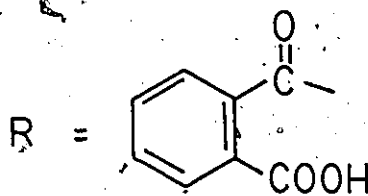
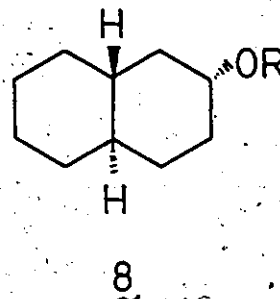
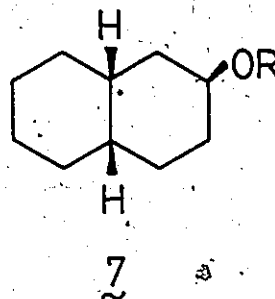
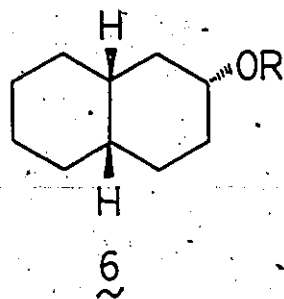
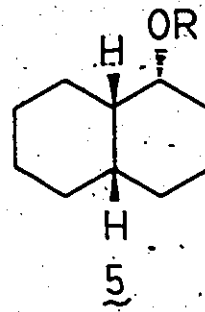
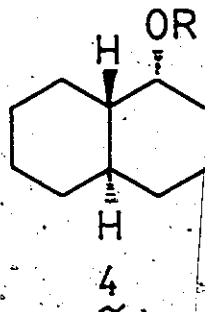
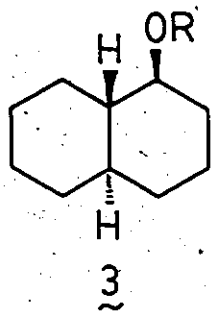
a. Spectra are presented in % relative abundance.

Scheme 5



B. Mass Spectra of Decalyl Acid Phthalates

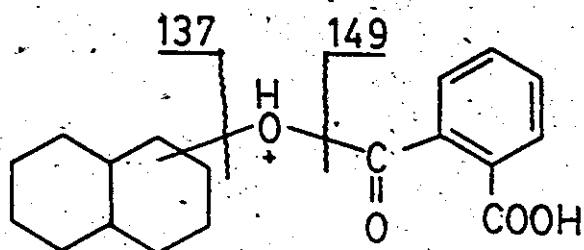
Six isomeric decalyl acid phthalates were prepared and their FD and EI spectra were obtained. The six isomers are trans-trans-1-decalyl acid phthalate (3), trans-cis-1-decalyl acid phthalate (4), cis-cis-1-decalyl acid phthalate (5), cis-cis-2-decalyl acid phthalate (6), cis-trans-2-decalyl acid phthalate (7), and trans-cis-2-decalyl acid phthalate (8).



All of the six isomers display similar FD spectra and follow a similar fragmentation pathway as for 1 and 2. The FD spectra of these isomers are listed in Table 3. The protonated molecular ion, $[M+H]^+$, appears as the dominant ion in all of the spectra. Cleavage of the ester linkage at either side of the oxygen gives m/z 137, $[C_{10}H_{17}]^+$, or m/z 149, $[C_8H_5O_3]^+$. A small peak is formed at m/z 285, $[C_{18}H_{21}O_3]^+$, from the elimination of a water molecule from $[M+H]^+$ ion. In the spectra of trans-1-decalyl acid phthalates, 3 and 4, a relatively intense molecular peak at m/z 302 is observed. The M^+ peak is either small or missing from the spectra of other isomers.

The EI spectra of these compounds are listed in Table 4. The molecular ion appears only in spectra of 3 and 4 in observable intensities. Fragmentation of these isomers follows the same pattern as for 1 and 2. Cleavage of the ester linkage gives m/z 149, $[C_8H_5O_3]^+$, which is the base peak in the spectra of 4, 6, 7 and 8. Elimination of a phthalic acid molecule from the molecular ion furnishes the base peak in the spectra of 3 and 5 at m/z 136, $[C_{10}H_{16}]^+$, which is also a major ion in the spectra of other isomers. A double McLafferty rearrangement gives m/z 167, $[C_8H_7O_4]^+$, which then fragments under the same pathway as given in Scheme 2.

Table 3

FD Spectra of Isomeric Decalyl Acid Phthalates^a

<u>m/z</u>	ions	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>
136	$[C_{10}H_{16}]^+$	2	5	5	3	3	4
137	$[C_{10}H_{17}]^+$	63	62	91	54	71	66
138		4	5	6	3	4	4
149	$[C_8H_5O_3]^+$	28	33	42	30	34	31
150		2	2	2	1	1	1
285	$[C_{18}H_{21}O_3]^+$	2	3	2	2	2	3
302	M^+	21	11	2	--	--	--
303	$[M+H]^+$	100	100	100	100	100	100
304		14	14	13	14	11	16

a. Spectra are presented in % relative abundance.

Table 4

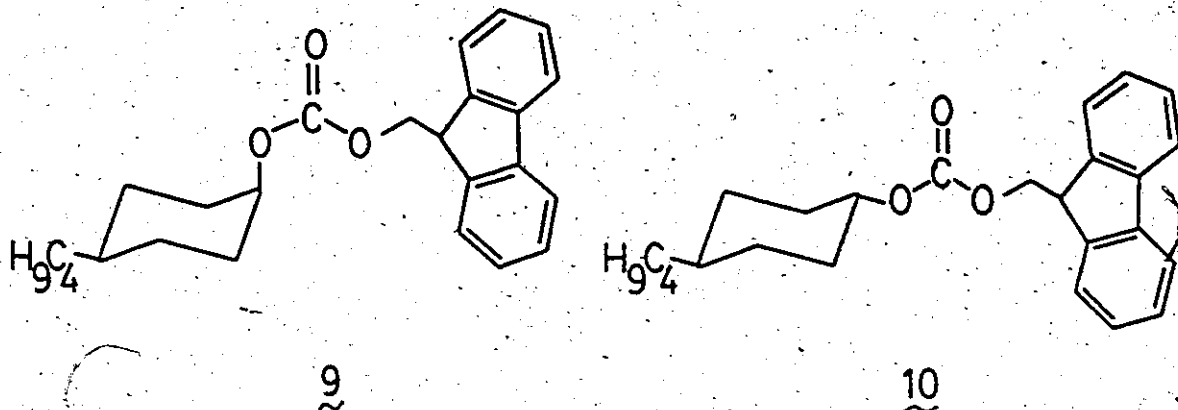
EI Spectra of Isomeric Decalyl Acid Phthalates^a

<u>m/z</u>	ions	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>
76	[C ₆ H ₄] ⁺	4	5	3	5	5	3
77	[C ₆ H ₅] ⁺	3	4	2	3	3	3
93	[C ₆ H ₅ O] ⁺	14	18	14	12	13	12
104	[C ₇ H ₄ O] ⁺	4	6	2	5	5	4
105	[C ₇ H ₅ O] ⁺	2	4	2	3	3	2
121	[C ₇ H ₅ O ₂] ⁺	13	12	11	12	11	10
122	[C ₇ H ₆ O ₂] ⁺	5	11	5	5	5	4
136	[C ₁₃ H ₁₆] ⁺	100	80	100	57	55	50
137		13	12	11	7	7	7
149	[C ₈ H ₅ O ₃] ⁺	91	100	57	100	100	100
150		12	40	9	15	13	13
153	[C ₁₀ H ₁₇ O] ⁺	5	48	3	6	4	3
167	[C ₈ H ₇ O ₄] ⁺	57	48	28	58	57	58
168		5	4	2	5	5	5
302	M ⁺	2	1	--	--	--	--

a. Spectra are presented in % relative abundance.

C. Mass Spectra of 4-t-Butylcyclohexyl 9-Fluorenylmethyl Carbonates

Isomeric 4-t-butylcyclohexyl 9-fluorenylmethyl carbonate (9 and 10) were prepared and studied by FI and EI.



The spectra are presented in Table 5. The FI spectrum of 9 shows elimination of 9-fluorenylmethyl hydrogen carbonate at m/z 138 (7%) which is missing in the FI spectrum of 10. Also intensity of m/z 196 is much higher in the spectrum of 9 (38%) than in the spectrum of 10 (8%). Both isomers fragment to give m/z 178 which is slightly more intense in the spectrum of 10 (69% ~~in~~ 10 compared to 47% in 9). In the trans isomer, 10, the 9-methylene hydrogen is transferred to the carbonyl oxygen preferentially which leads to the formation of m/z 178. However, in the cis isomer, 9, transfer of the α -hydrogen in the cyclohexyl ring is enhanced by the release of steric hindrance in the ring after fragmentation. Base peak for both spectra is the molecular ion at m/z 378. A fragmentation pathway is presented in Scheme 6.

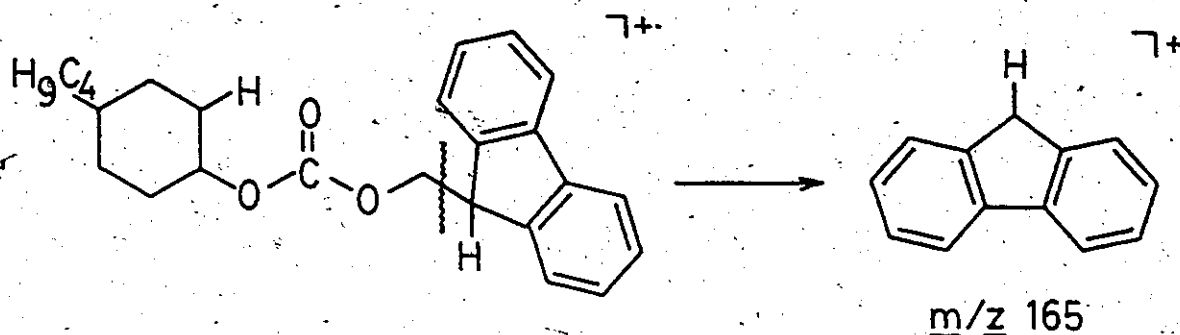
Table 5

Mass Spectra of cis- and trans-4-t-Butylcyclohexyl
9-Fluorenylmethyl Carbonate (9 and 10)^a

<u>m/z</u>	ions	FI		EI	
		<u>9</u>	<u>10</u>	<u>9</u>	<u>10</u>
57	$[C_4H_9]^+$	52	16	11	10
58	$[C_4H_{10}]^+$	15	19	--	--
138	$[C_{10}H_{18}]^+$	7	--	--	--
165	$[C_{13}H_9]^+$	--	--	--	--
178	$[C_{14}H_{10}]^+$	47	69	100	100
179		12	12	24	21
196	$[C_{14}H_{12}O]^+$	38	8	1	1
197		6	1	--	--
378	$[C_{25}H_{30}O_3]^+$	100	100	3	3
379		25	26	--	--

a. Spectra are presented in % relative abundance.

Isomers 9 and 10 give similar EI spectra. The base peak for both spectra is formed at m/z 178. The molecular ion and m/z 196 are small. The peak at m/z 138 is missing in both spectra. A peak at m/z 165 which corresponds to the cleavage of the benzylic bond is observed.



CHAPTER IV

CONCLUSION

The use of acid phthalate derivatives of cyclic alcohols for stereochemical differentiation in mass spectrometry has proved to be unsuccessful. Isomeric acid phthalates give similar FD spectra with protonated molecular ion as the base peak. Fragmentation mainly involves simple bond cleavages. The EI spectra of these compounds are also indistinguishable. The fragmentation follows closely to that proposed for dialkyl phthalates.¹⁷

The FI spectra of cis- and trans-4-t-butylcyclohexyl 9-fluorenylmethyl carbonate have a different appearance. The peak at m/z 138 appears in the spectrum of the cis-isomer but is absent in the spectrum of the trans-isomer. The intensity of m/z 196 is much higher in the cis- than in trans-isomer. These differences are mainly due to the sterically crowded environment in the cis-isomer. Both isomers give simple and indistinguishable EI spectra with m/z 178 as base peak. The molecular peak is small in both EI spectra. Therefore, it may be possible to use the acid chloride reagent to convert isomeric alcohols into carbonate derivatives and identify them.

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