Spring 1982

POLYCYCLIC POLYAMINES: SYNTHESIS AND CONFORMATIONAL ANALYSIS

VAN BRUCE JOHNSON

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University of New Hampshire PH.D. 1982

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POLYCYCLIC POLYAMINES: SYNTHESIS AND CONFORMATIONAL ANALYSIS

BY

Van B Johnson

B. S. (Chemistry), Southern Connecticut State College, 1977

A DISSERTATION

Submitted to the University of New Hampshire

in Partial Fulfillment of

the Requirements for the Degree of

Doctor of Philosophy

in

Chemistry

May, 1982

This dissertation has been examined and approved.

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Assistant Professor of Chemical Engineering

Jan 29, 1982

Date

DEDICATION

This dissertation is dedicated to my family. They are the reason.

ACKNOWLEDGEMENTS

Gary R Weisman has been throughout my graduate work a tireless teacher, enthusiastic researcher, invaluble resource, and a friend. I am grateful for his efforts on my behalf. I am, of course, grateful to the chemistry department for its financial and morale support. There are a number of individuals who deserve my special thanks including: Mike Coolidge - for setting up the computer programs and training me in their use, Rudy Seitz - for the use of the syringe pump, Kathy Gallagher - for training me on the FX90Q, Bill Dotchin and Dee Cardin for same day service on the mass spec. and CHN analyses.

TABLE OF CONTENTS

List Of Figures

List of Tables

ABSTRACT

POLYCYCLIC POLYAMINES: SYNTHESIS AND CONFORMATIONAL ANALYSIS

by

Van B Johnson

University of New Hampshire, May, 1982

The synthesis, conformational analysis, and reactivity of a homologous series of tricyclic orthoamides is discussed. The tricyclic orthoformamides, orthoacetamides, orthopropionamides, and orthobenzamides were synthesized by the uncatalyzed condensation of macrocyclic triamines with amide acetals. The conformations were studied spectrally (IR, ^{1}H NMR, ^{13}C NMR, DNMR) and by the application of empirical force field calculations(MM2). In most (but not all) cases the minimized conformations as generated by MM2 were found to be in agreement with the experimentally determined conformations. The alkylation, acylation, and hydrolysis of these compounds is also discussed.

Efforts towards the synthesis of the spherically shaped host molecule 1,5,9,13-tetraazatricyclo[7.7.3.$3^{5,13}$]-docosane are described. A classical acylation-reduction sequence was employed in this synthesis. Cyclizations were carried out under high dilution conditions. The design and construction of a new high dilution apparatus is described.

High yields of monomeric cyclic intermediates were obtained. Monomeric cyclic intermediates were purified by preparative gel permeation chromatography (GPC). The modification of a Waters 200 analytical GPC unit are described as are the column packing procedures for preparative GPC columns.

CHAPTER I

INTRODUCTION

Efforts Towards the Synthesis of 1,5,9,13-tetraazatricyclo[7.7.3.3$^{(5,13)}$]docosane

The use of macrocyclic tetraamines as ligands for the complexation of transition metals has been extensively investigated by a number of groups and several reviews are available on the subject[1-12]. These studies have demonstrated the utility of tertiary macrocyclic amines as ligands for the complexation of transition metal cations. Comparison of the stabilities of the complexes of macrocyclic ligands with analogous acyclic ligands led to the observation that the macrocyclic complexes evidenced significantly higher stability constants. This enhanced stability was first observed by Busch[13] and Cabbiness and Margerum[14-17] and was termed the macrocyclic effect by the latter authors.

The enhanced stability of the macrocyclic complexes is commonly attributed to a number of factors[18]. A major contributing factor is that the donor atoms in the macrocyclic ligands are shielded from solvation while in the acyclic ligands they are highly solvated. Since the solvation energy of the ligand must be overcome during

complexation it follows that the macrocyclic complexes will be more stable[19]. Another important factor contributing to the enhanced stabilities is that during complexation the acyclic ligands must undergo extensive ordering which is entropically unfavorable. The prearranged macrocyclic ligand does not suffer this entropy loss upon complexation and hence yields more stable complexes. It should be remembered that even though the macrocyclic ligands enjoy an entropic advantage during complexation this advantage must be earned during the synthesis of the ligand. Other factors which contribute to the enhanced stability are the following: 1) the relative steric and conformational energies of the free and complexed ligand, 2) lattice topologies of the donor atoms and the coordination preferences of the metal ion, 3) relationship between the ionic radius of the guest(metal ion) and the cavity size of the host(ligand) and, 4) ligand "thickness"[39].

The reported stabilities of the macrocyclic ligands led to the inevitable extension to the use of bicyclic ligands. The anticipated increase in stability was realized through the use of bicyclic ligands. The stabilities of the bicyclic complexes are explainable in the same terms as the macrocyclic ligands. A series of bicyclic ligands which have been extensively investigated are Lehn's compounds(e.g. compound 2,fig.1.1) which have come to be known as

cryptands[21-24].

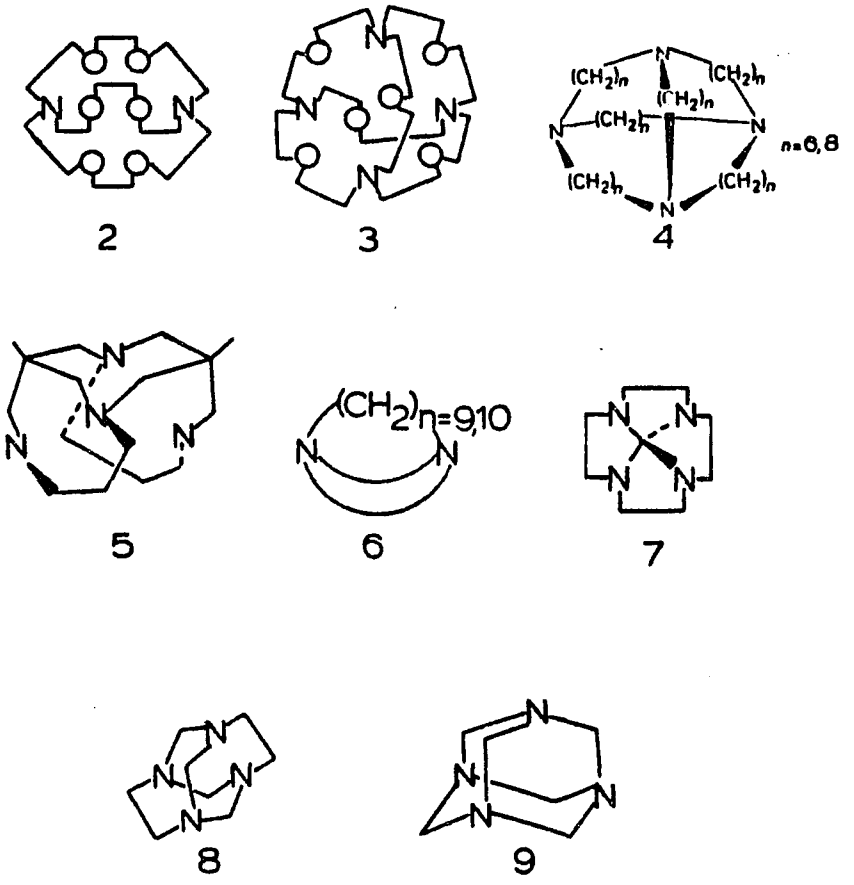


fig. 1.1

Ultimately the extension of these results led to the use of the most highly ordered ligands(due to the trivalency of the nitrogen bridgeheads), the tricyclic tetraamine ligands such as compound 3(fig.1.1). Complexes of these ligands have yielded even higher stability constants. The stabilities of the tricyclic complexes are explainable in the same terms as the macrocyclic and bicyclic complexes.

The use of macrotricyclic ligands has allowed better definition of the donor atom topologies and in particular the enforcement of tetrahedral coordination geometry. The attainment of tetrahedral coordination has been attempted through the use of sterically congested acyclic[26-27] and macrocyclic[28] ligands but these attempts have yielded only highly distorted tetrahedral geometries at best. Tetrahedral coordination geometries in the tetraaza tricyclics have been reported by Lehn[25], Schmidtchen[29], and Kemp[30] for compounds 3, 4, and 5 respectively (fig. 1.1). In addition, these ligands have yielded stable complexes with alkali metal.cations. The neutral tricyclic hosts possess very well defined cavity sizes and showed selectivity towards alkali and alkaline earth metal ion guests on the basis of size(ionic radius). The quaternized cationic hosts[31,32] have also evidenced selectivity towards anionic guests, such as the halides, on the basis of size. The diprotonated form of the bicyclic diamine prepared by Simmons and Park[33] (compound 6, fig.1.1) also exhibited selectivity towards the halides on the basis of size. Richman[34] has reported the synthesis and unique properties of tetraazatetracyclic 7(fig.1.1). Tetrahedral disposition of the nitrogens in 7 is enforced by the central carbon atom. Host-guest complexation is of course impossible in tetracycle 7.

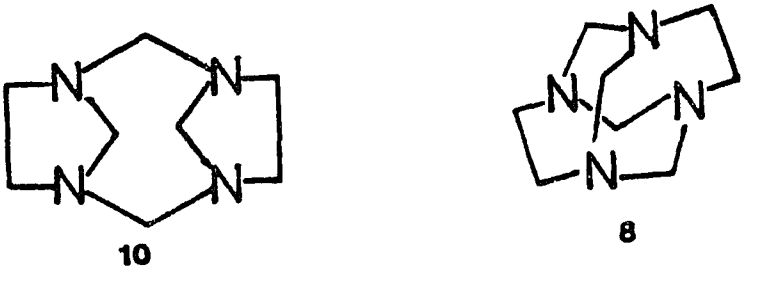
Another interesting property of the smaller members of the tricyclic ligands(e.g. 8.fig.1.1) arrises from the close proximity of the nitrogens in these species. The forcing together of the lone pairs results in strong non-bonded interactions. The destabilization resulting from these interactions facilitates their stepwise oxidation. The radical cations of tetraaza cage compounds, resulting from their one electron oxidation, are stabilized by three electron σ bonding between the nitrogens[35-38]. The dications, resulting from their two electron oxidation, are stabilized by σ bonding between the nitrogens[35-38].

Two excellent reviews that treat the structure and properties of these organic complexation agents and their design[39] and synthesis[40] are available. Several other reviews covering macrocyclic chemistry[41,42] and synthesis[43,44] have recently become available.

Synthesis

The synthesis of tetraaza polycyclic cage compounds began in 1859 when Butlerow[45] condensed ammonia with formaldehyde and obtained hexamethylenetetraamine (9,fig.1.1). This compound is the parent of a homologous series but it bears little resemblance to the higher homologs in its chemical and physical properties or in its synthesis. Being composed entirely of aminal linkages makes this parent hydrolytically unstable in acid solution. Also, the size of the cavity is far too small to accomadate any guests and futhermore the nitrogen lone pairs are directed towards the exterior of this diamond lattice molecule, so host guest complexation is impossible.

A higher homolog in this series was prepared by the condensation of ethylenediamine and formaldehyde[45a]. The crystalline product obtained from this reaction was initially assigned structure 10 (fig.1.2). This compound was later shown by proton NMR[45b,c] and X-ray crystal structure determination[45d] to be 8.



10 8

fig. 1.2

The syntheses of all other higher homologs have involved one of two basic strategies. The first route is an acylation-reduction sequence first developed by Stetter[46] for macrocyclcic synthesis(fig.1.3a) and extended by Park and Simmons[47] to the synthesis of bicyclics (fig.1.1 and

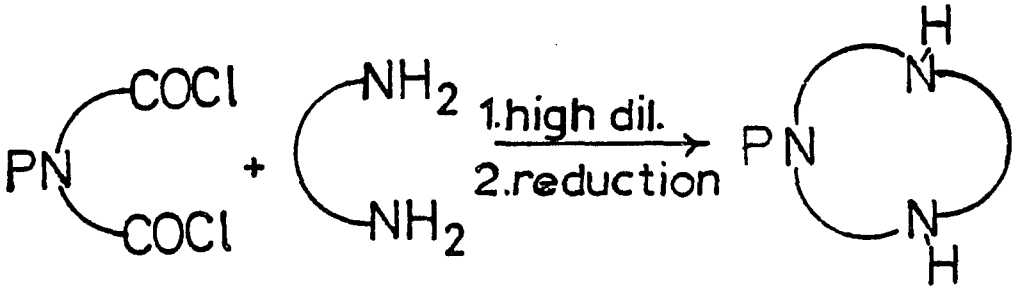


fig. 1.3a

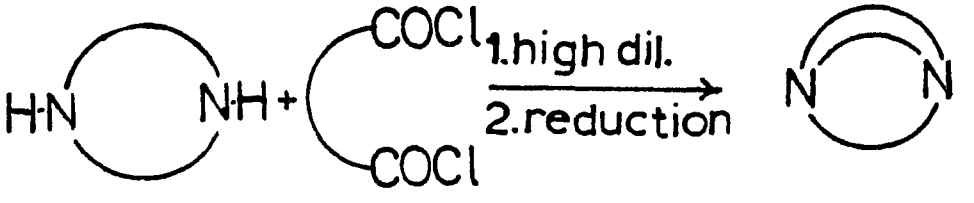


fig. 1.3b

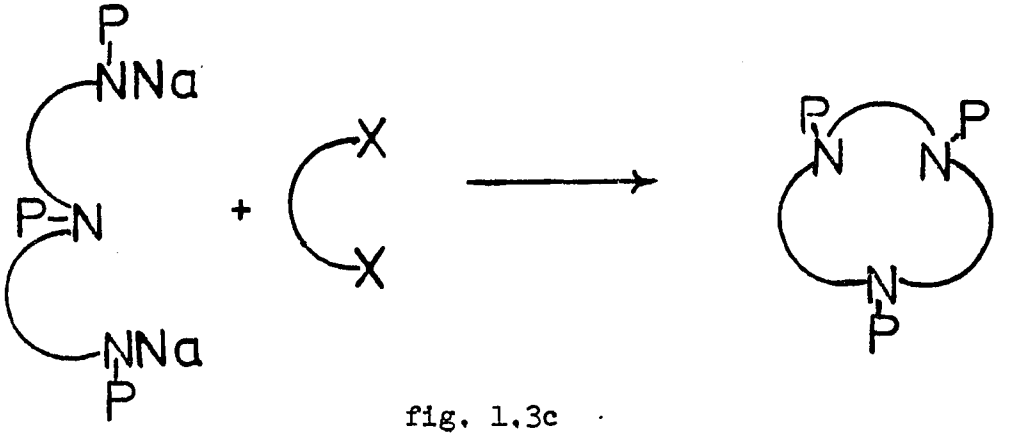


fig. 1.3c

by Lehn to the synthesis of tricyclics[51] (e.g.3, fig.1.1). The Stetter approach and the Simmons extension both employ the principle of high dilution with all the experimental difficulties inherent to this technique. The second route is a nucleophilic substitution scheme first employed by Stetter[48] under high dilution conditions and later extended by Richman and Atkins[52] to the synthesis of macrocycles without the need for high dilution(fig.1.3c).

Anticipated Properties

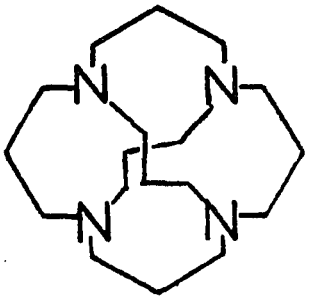


fig. 1.4

The highly symmetrical title compound 1(fig.1.4) promises to possess many interesting physical properties in addition to its aesthetic appeal. C-P-K (Corey-Pauling-Koltun) space filling models indicate that this molecule should possess a roughly spherically shaped cavity with tetrahedrally arrayed nitrogen lone-pairs directed towards the center of the cavity. The geometrical constraints of

the carbon bridging, between the nitrogens, enforces the tetrahedral array of nitrogen lone pairs. These structural features should result in several interesting physical properties.

Complexation Properties

Corey-Pauling-Koltun (C-P-K) models indicate that 1 should possess a cavity large enough to accomodate lithium cation, a proton, or some transition metal cations such as copper(II). The complexes of the metal cations and 1 should provide the limiting examples of tetrahedral coordination of these cations. These complexes should prove to be interesting subjects for multinuclear NMR(e.g. $^{7}Li^{\oplus}$). Characterization of the metal NMR parameters in these complexes should provide a yardstick by which other investigators might measure the degree of tetrahedral coordination in complexes less structurally constrained than these complexes.

Protonation of 1 could conceivably occur on its interior. This should result in an unusually slow intermolecular proton transfer rate several orders of magnitude slower than the normal diffusion controlled rate of proton transfer between heteroatoms. Futhermore, once protonation has occurred and the proton is in the interior of 1 it should rapidly exchange among all four nitrogens and

be strongly intramolecularly hydrogen bonded. This condition should make its deprotonation essentially impossible perhaps redendering 1 the ultimate Bronsted base.

Electrochemical Properties

McKinney and Geske[49] were the first to observe and the first to report the unusual stability of the radical cation of DABCO(11,fig.1.5). Following this report several studies appeared which attempted to elucidate the mode of stabilization of the DABCO radical cation. Theoretical studies of this system[49b,c,d] have shown that this radical cation could be stabilized by overlap of the nitrogen lone pairs and the σ^*orbitals of the ethylene carbon bridges. Experimental evidence has been reported which supports the theoretical model. In particular, Nelsen[49e] has studied the stabilities of the radical cations of 12, 13, and 14(fig. 1.5). In this series the ethylene bridges, which allow the DABCO-like overlap, were successively removed and a trend of destabilization was observed. Nelsen[36] also reported that tetrazaadamantane(9,fig.1) does not have a stable radical cation. This was attributed to the fact that the only orbitals alligned for interaction with the nitrogen lone pairs are C-N orbitals which are too low in energy to allow efficient overlap. Also, the radical cation of 9 would be inductively destabilized by the 1-3 nitrogen arrangement. The relative importance of these two factors

could not be determined from the study[49e].

The radical cations of amines of this general structure have also been shown to be stabilized by through space interactions. Nelsen[37] reported the stable radical cation of 8(fig.1.5). This radical cation is only slightly less stable than the DABCO radical cation. Nelsen observed that all four nitrogens were equivalent and that the charge was delocalized over all four nitrogens via a combination of 1-3(through space) and 1-4(through bond) interactions of the lone pairs, the relative importance of which could not be ascertained. In a later report by Nelsen[49f] it was shown that the stability and the equivalence of the nitrogens was due entirely to a rapidly equilibrating three electron bond between two sets of paired nitrogens. The term "three electron σ-bond" was first advanced by Alder[49g] to explain the stability and spectral properties of the radical cation of 15(fig.1.5). Alder later reported three electron σ-bonding in the radical cation of 16 (fig.1.5)[49h] and most recently in the radical cations of 17 and 18 (fig.1.5)[49l].

Alder has recently reviewed the special properties of di- and polyamines including their electrochemical benavior[49h]. Nelsen has reviewed the electrochemical properties of nitrogen compounds[49i].

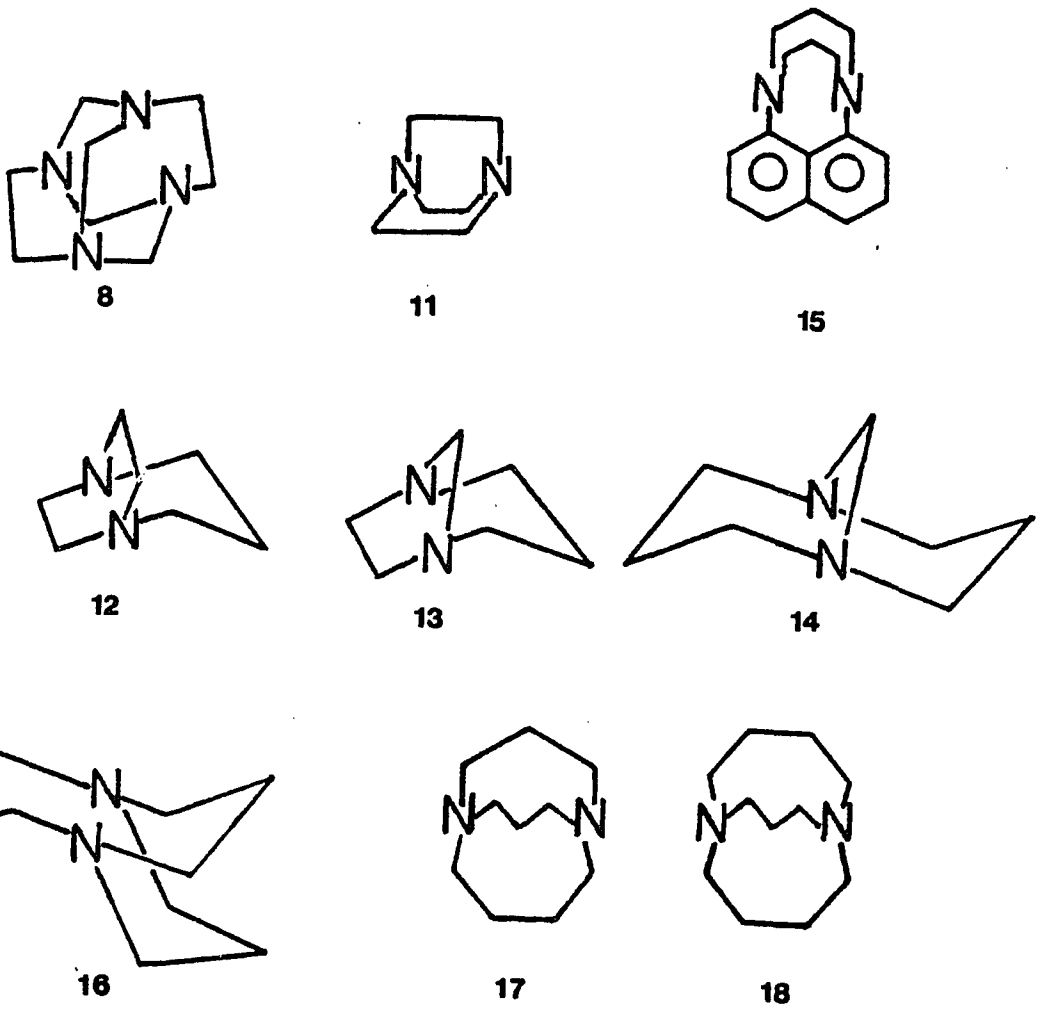


fig. 1.5

In summary, a number of interrelated factors are responsible for the observed stabilities of these radical cations. The stabilizing factors appear to be the through bond interactions in 1-4 nitrogen arrays and the through space interactions of 1-3 arrays. Destabilization is principally inductive in the 1-3 arrays. The relative importance of these factors has not been ascertained.

The title compound has structural features which may result in interesting electrochemical properties. It will be noted that all nitrogen arrays are 1-5 thereby eliminating all through bond interactions and essentially all inductive destabilization. The major interaction in 1 should be through space due to the close proximity of the nitrogen lone pairs in the cavity. The interaction of four nitrogen lone pairs in a tetrahedral array results in one bonding and three degenerate antibonding orbitals[49k]. Therefore a one electron oxidation should be facilitated since the electron will be removed from a high energy antibonding orbital. The resulting radical cation would be delocalized simultaneously over all four nitrogens. This would be an interesting contrast to the two nitrogen systems 15-18 and the equilibrating pairs of nitrogens in 8. Presumably the simultaneous participation of four nitrogen lone pairs, instead of two, would result in enhanced stability for the radical cation of 1.

Discussion

A. Synthesis

The efforts towards the synthesis of 1 have employed three general approaches. The first and most actively pursued was the classical acylation-reduction sequence. The

second approach employed the Richman and Atkins nucleophilic substitution scheme without the need for high dilution and some attempts at variations of this technique. The third approach considered is a totally new procedure which involved the cleavage of aminal linkages in an intermediate tetracyclic compound. Also included in this third approach is a cleavage of a tricyclic orthoamide to yield the first intermediate in the classical sequence but without the need for high dilution. These three schemes are presented in figures 1.6, 1.7, and 1.8 respectively.

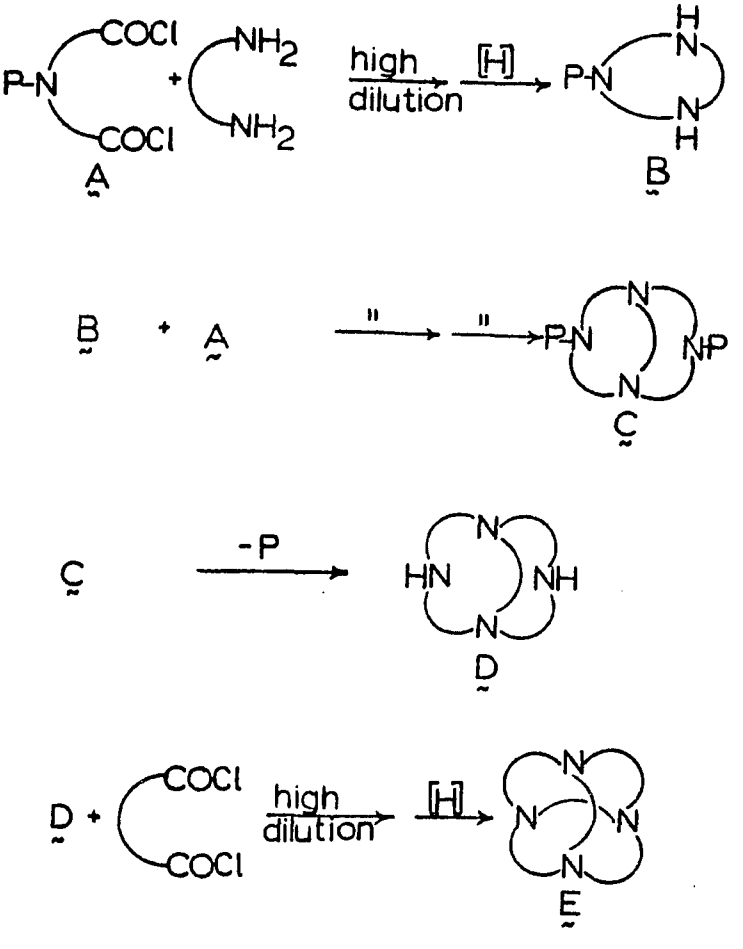


fig. 1.6

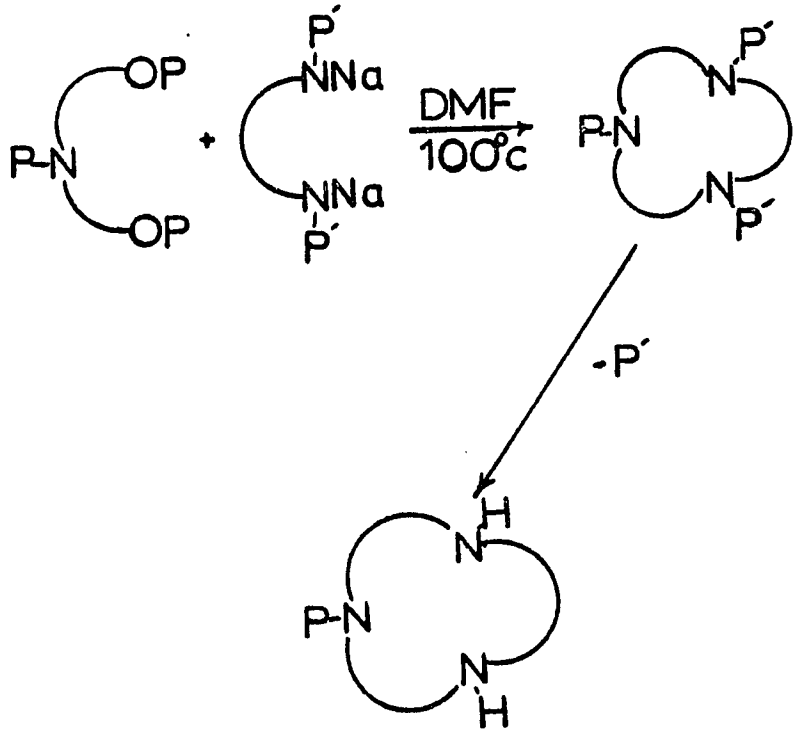

OP
P-N
OP
P'
NNa
NNa
P'
DMF
100°c
P-N
N
P'
N
P'
-P'
N
H
P-N
N
H

fig. 1.7

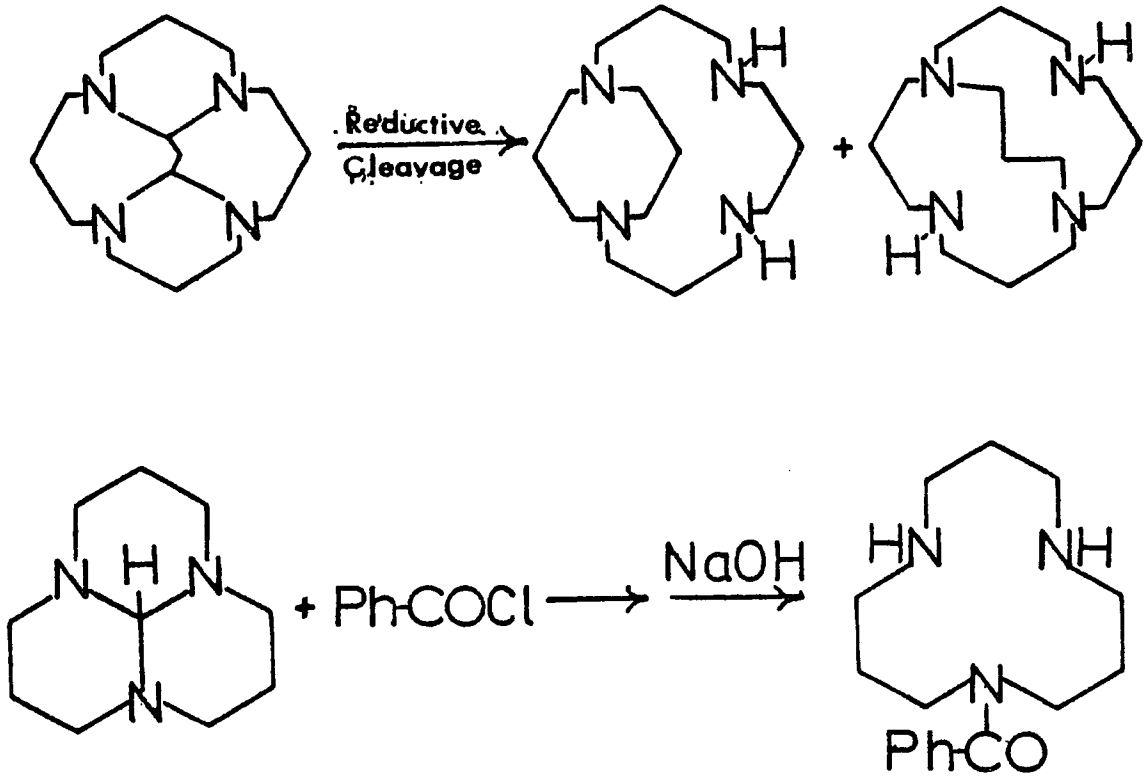

Reductive
Cleavage
N
H
+ PhCOCl
NaOH
HN
NH
PhCO

fig. 1.8

Classical Approach. As stated, this approach has been the most actively pursued of the three. The work performed on this synthesis to date is summarized in figure 1.9. The

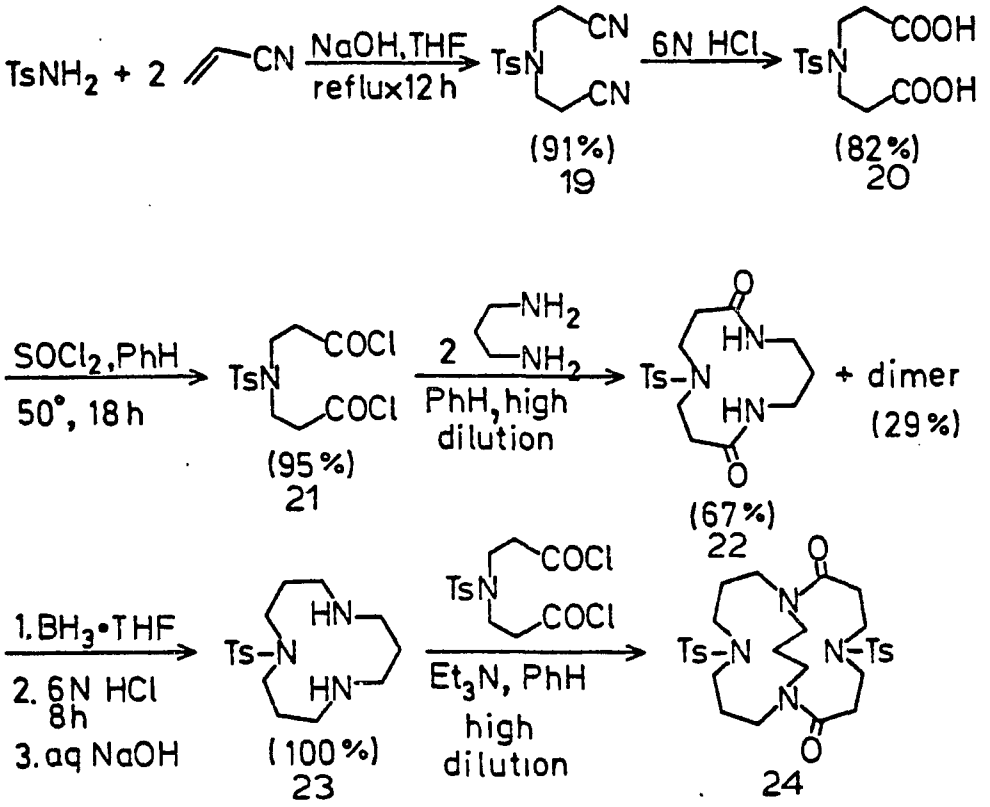


fig. 1.9

synthesis began with the double conjugate addition of bis-toluenesulfonamide and two equivalents of acrylonitrile to yield the bis-nitrile 19 in 91% yield. 19 was then hydrolyzed to yield the bis-carboxylic acid 20 in 82% yield. The bis-acid chloride 21 was prepared in 95% yield by the reaction of 20 with excess thionyl chloride. Bis-acid chloride 21 was of central importance to this synthesis in that four of the six carbon bridges in 1 are

introduced using 21. The monoprotected intermediate 22 was prepared in 67% yield by the reaction of 21 with two equivalents of 1,3-diaminopropane under high dilution conditions employing the high dilution apparatus described in the experimental section. The bis-amide contained

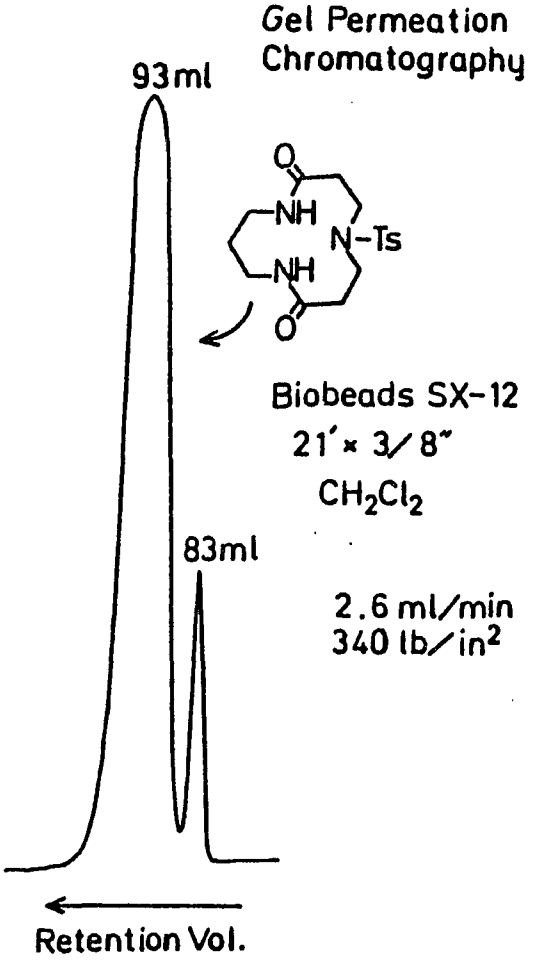


fig. 1.10

a minor aromatic impurity but was used in subsequent steps without further purification. The second equivalent of 1,3 diaminopropane acts as a base to react with the HCl which is a byproduct of the formation of the amide bonds. The HCl must be neutralized to preserve the reactivity of the amine.

The major side reaction of entropically unfavorable cyclization reactions is the formation of linear and cyclic oligomers. The isolation of the monomeric bis-amide 22 was accomplished through the use of preparative scale gel permeation chromatography(GPC). GPC is capable of separating compounds on the basis of size. The preparative scale GPC unit used in this study was constructed by modification of an analytical GPC unit as described in the experimental section. A nearly baseline separation was accomplished for the purification of 22 as can be seen in fig.1.10. Bis-amide 22 was reduced by diborane/THF to yield 23 in impure form. The material was used in subsequent reactions without further purification. The bicyclic intermediate 24 was prepared from the reaction of 23 with 1 equivalent of 21 under high dilution conditions employing triethylamine as the base. The purification and analysis of 24 awaits the packing of a suitable GPC column since the material would be excluded on the existing SX-12 column. The steps needed to complete the synthesis are presented in fig. 1.11.

Two major problems are present in this synthesis. The first is its linearity. Linearity is particularly troublesome in this sequence because it contains three high dilution steps which must necessarily be run on a small scale and generally do not give high yields of monomeric

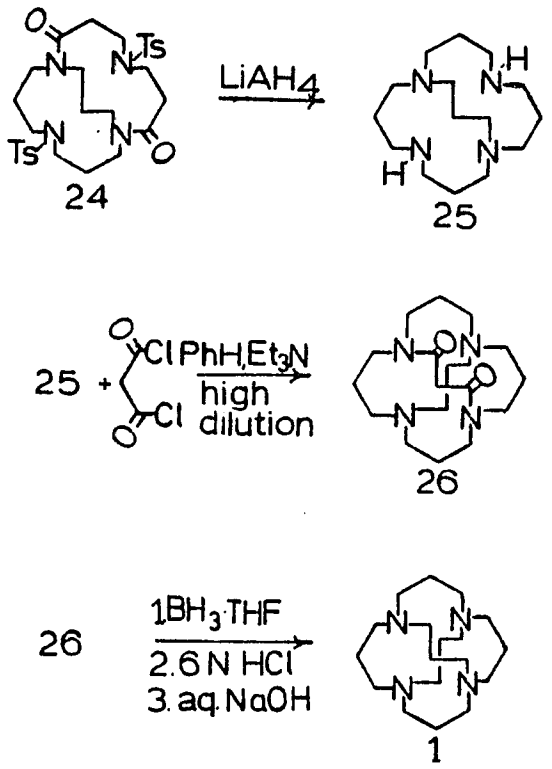


fig. 1.11

compounds. This drawback is amplified in this sequence since the last of these bottleneck reactions occurs at the end of this linear sequence. The other problem involves the diborane reduction of the last intermediate bis-amide 26 to yield the product. 26 is an anti-Bredt amide in that the nitrogen lone pairs are twisted relative to the carbonyl π systems. Under the appropriate reaction conditions(amide in excess)[50] amides having this structure can yield aldehydes(or alcohols) resulting from the cleavage of the C-N bond. However, Schmidtchen[31] and Lehn[51] have successfully reduced relatively strained bicyclic bis-amides with diborane. These considerations make it impossible to predict if the amide linkages will be cleaved or if the reduction to the amine will occur. If the cleavage does

occur then the general scheme presented in fig. 1.12 will have to be explored.

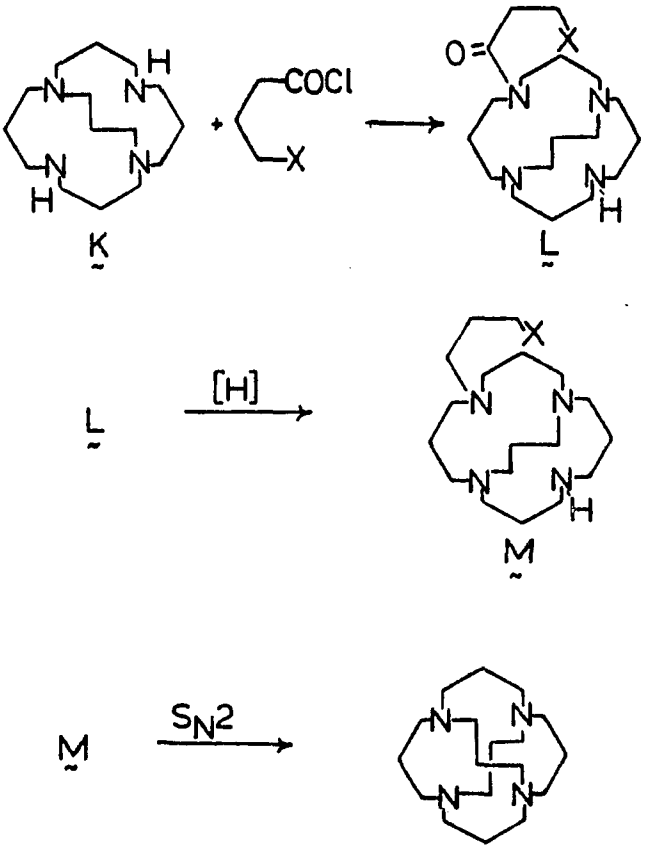


fig. 1.12

The problem of linearity in this synthesis can be partially circumvented through the use of the cleavage reactions (fig. 1.8). Detailed experimental for the synthesis of these compounds are presented in the experimental section.

Modified Classical. The goal of this approach was the synthesis of a monoprotected cyclic triamine without the need for high dilution conditions. Richman and Atkins[52] have reported high yield cyclizations to yield triamines and tetraamines employing di-sodium salts of bis-p-toluene-sulfonamides (bis-tosylamides) and di-p-toluene- sulfonates (tosylates) in DMF (fig. 1.13).

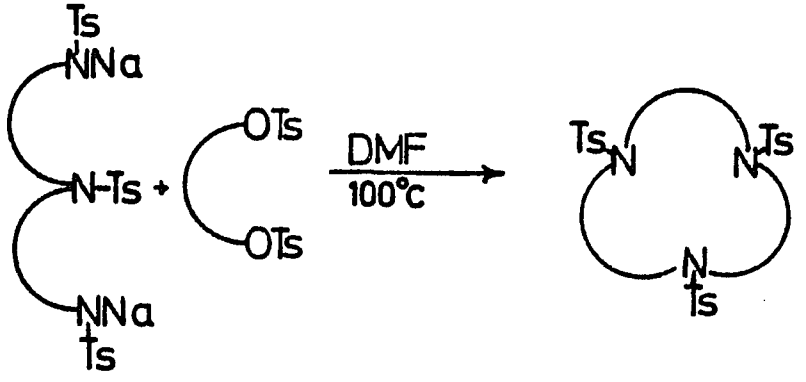
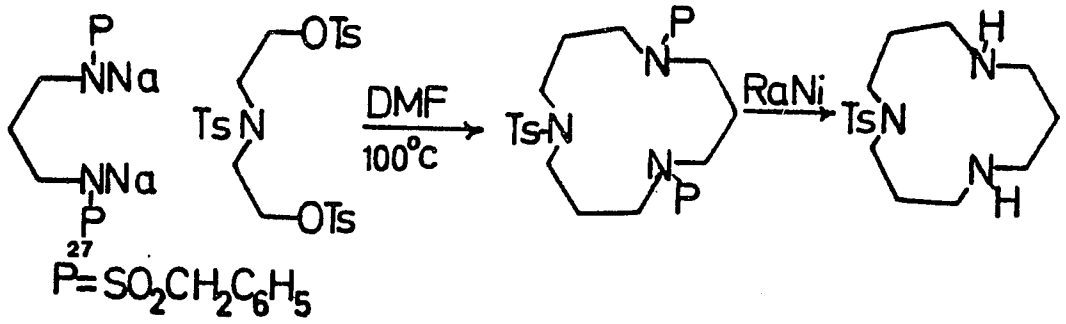


fig. 1.13

Koyama has also reported a similar procedure employing dibromides instead of ditosylates[53]. It has been suggested[54] that the bulky tosyl groups reduce the internal entropy(rotational entropy) of the starting materials thereby promoting the cyclization reaction. Thus it was proposed that if a bulky protecting group could be found which also promoted cyclizations, but was easier to cleave than bis-tosylamides, then a mixed cyclization followed by a selective deprotection would yield the desired monoprotected intermediate 23 (fig. 1.14).

Phenylmethanesulfonyl was selected because of its similarity to tosyl in its bulkiness and its ease of cleavage by Raney Nickel hydrogenation towards which tosylamides are inert[55,56] (fig. 1.14). A review of the methods for tosylamide cleavages is available.[57]



Unfortunately, this approach has been plagued by low yields of the phenylmethanesulfonamides and sulfonates. Some reasonable yields of the sulfonamides were obtained when the reactions were run at -77°C(see experimental section) and further exploration of this approach might be warranted. The intermediate in these reactions has been shown to be a highly reactive sulfene[58]. The low yields in these reactions are probably due to the myriad of side reactions that sulfenes are known to undergo[59].

To test the effectiveness of the phenylmethane-sulfonamides and sulfonates in promoting cyclizations the reaction depicted in fig. 1.15 was attempted. This particular reaction was selected because it allows direct comparison with the Richman and Atkins procedure. The smalll quantities of starting materials made the product separation and identification impossible.

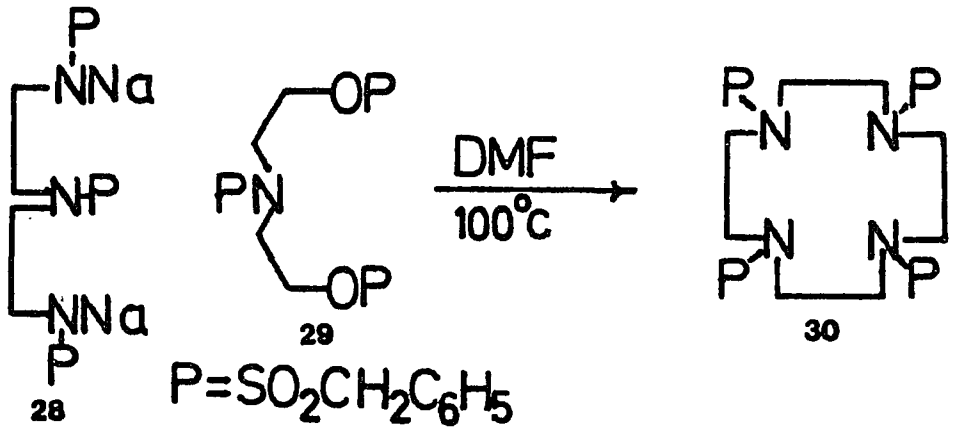


fig. 1.15

It must be concluded that this approach was not successful. It is included in this report since it was abandoned before it was conclusively shown to be unworkable. In particular, the encouraging yields of the starting materials, when the reactions were run at -77°C, may make this a viable approach. It will be noted that there now exist reactions that allow the preparation of the monoportected triamines (see orthoamide cleavage section)

for some rings sizes. But the approach outlined above is much more general and, if successful, would be applicable to the synthesis of many different ring systems. In addition there is always a need for selective protection methods for polyamines.

Cleavage Routes-Cleavage of Tetracyclic Bis-aminals. As previously stated one of the major problems with the synthesis of 1 is its linearity. One possible method

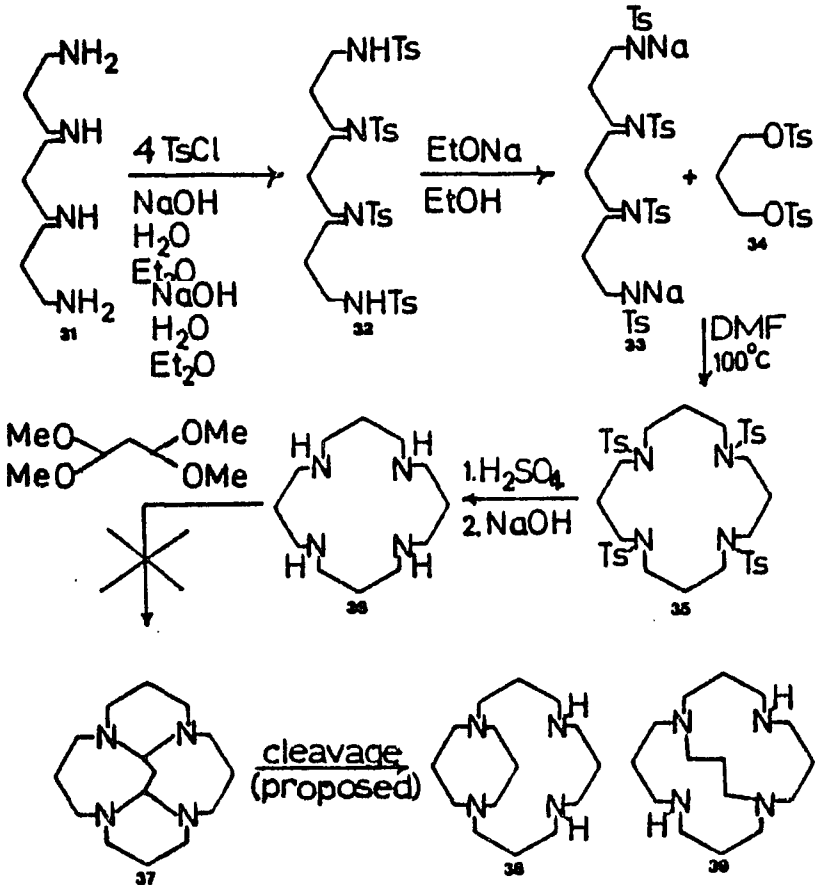


fig. 1.16

of circumventing the need for high dilution reactions might be to synthesize a tetracyclic intermediate and then cleave bonds to yield a bicyclic material. This approach is potentially the most powerful in terms of ease of synthesis. Unfortunately this approach also turned out to be the least successful.

Efforts towards the utilization of this approach are outlined in fig. 1.16. The tetraamine 36 was synthesized in good yields by published procedures[60a]. Conversion to 37 was attempted via an acid catalyzed procedure. Several acid catalyst and solvent combinations were attempted as outlined in the experimental section. All attempts at the synthesis of 37 failed.

Cleavage reactions which might be employed to produce compounds 38 and 39 from 37 have been the subject of another study[60]. The aminal cleavage reactions which were examined (BH_3/THF, $NaBH_3CN$) were not successful on model tetracyclic systems. It was hoped that if a cleavage reaction had been developed then the cleavage of 37 would yield some of the desired symmetrical compound 39, containing two twelve membered rings, in addition to the unsymmetrical isomer 38, containing one eight membered ring and one sixteen membered ring.

It has been reported recently that di-isobutyl-aluminumhydride (DIBALH) cleaves aminals incorporated in macrocyclic rings[61]. This reagent was used to effect the conversion presented in fig.1.17. Note that the cleavage yielded the undesired unsymmetrical product exclusively. The preparation of 42 was also reported by these investigators.

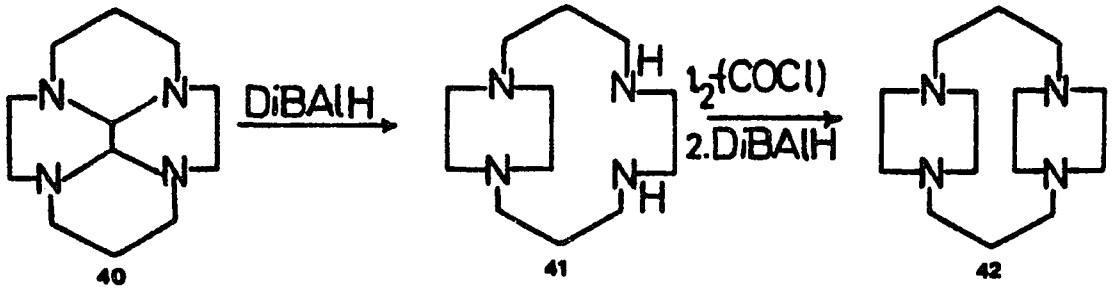
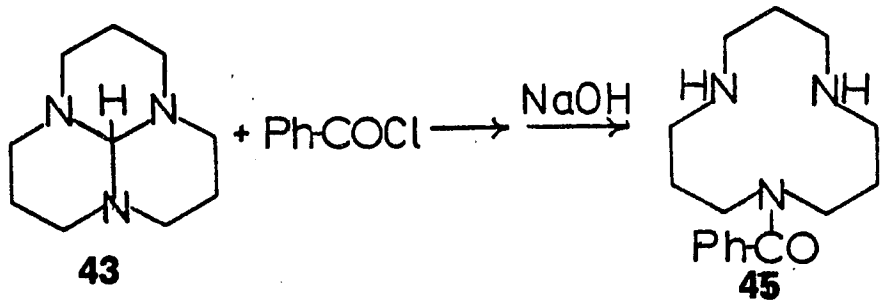


fig. 1.17

Cleavage of a Tricyclic Orthoamide to Yield Monoprotected Triamines. In connection with another study compound 43 (fig. 1.18) was synthesized. (The full details of the synthesis of 43 are contained in chapter 2. It was found that compound 43 underwent an acylation with benzoyl chloride to yield 44 which was subsequently hydrolyzed to the desired monoprotected intermediate 45(fig. 1.18). This

reaction eases the problem of linearity in the synthesis of 1 in that it allows the synthesis of the first monoprotected intermediate without the need for high dilution conditions.



43 45

fig. 1.18

CHAPTER 2

TRICYCLIC ORTHOAMIDES

Reports by Richman and Atkins[52] concerning the preparation of macrocyclic triamines and tetraamines in high yields without the need for high dilution have made these hitherto synthetically challenging amines readily available in large quantities. The ease of preparation of these amines has produced a flurry of activity concerning the reexamination of the classical reactions of secondary amines employing these macrocyclic amines as starting materials.

The reactions of secondary amines with aldehydes have been the subjects of study for many years[62] and have produced many compounds of industrial and academic interest. It was only logical that the first reactions to be examined employing these macrocyclic amines were condensations with aldehydes. Turner and coworkers[63] were the first to examine the reaction of glyoxal with a substituted 1,4,8,11-tetraazatetradecane to produce 47(fig. 2.1). A later report from these laboratories[64] described the syntheses and conformational analyses of 48-52(fig. 2.1). Subsequently another group reported the synthesis of several members of this previously reported series (48-52, fig. 2.1)[65,66]. A report from these laboratories also described the syntheses and conformational analyses of 53 and 54(fig.2.1) prepared by the reaction of the appropriate

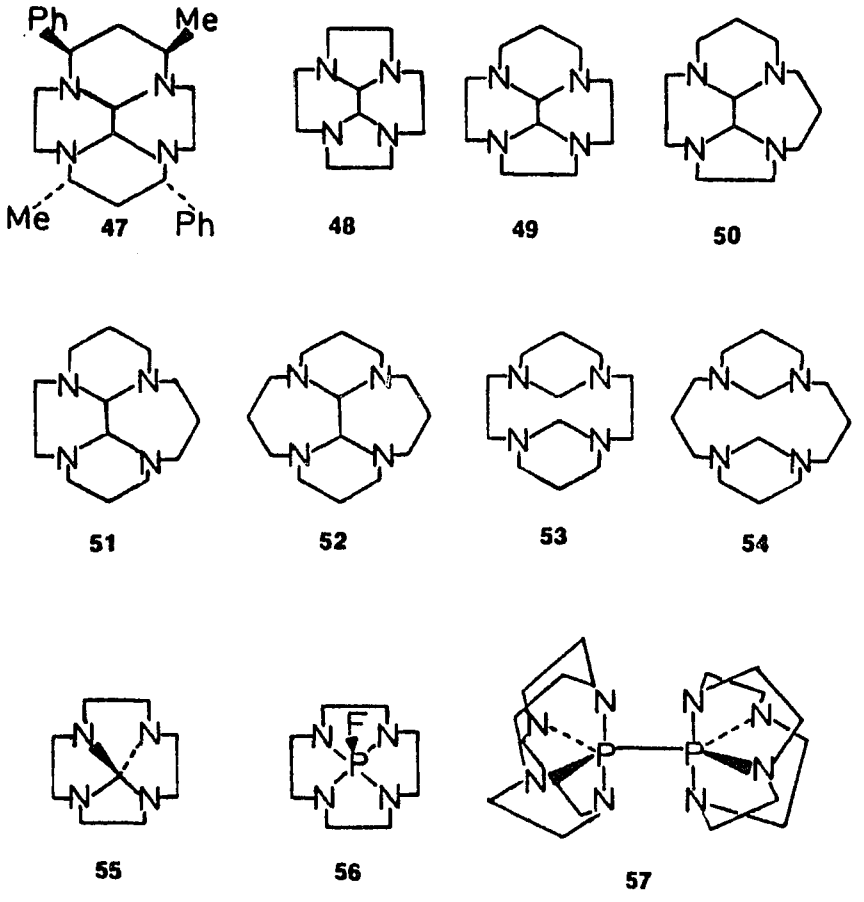


fig 2.1

macrocyclic tetraamines with formaldehyde[67]. Richman[34] has incorporated a single carbon into the center of a macrocyclic tetraamine to yield tetracycle 55(fig. 2.1). Richman has also incorporated phosphorous into the center of macrocyclic tetraamines to yield compounds 56[68] and 57[69](fig. 2.1).

Similar work has been undertaken employing macrocyclic triamines. Richman[70] has incorporated a boron into the center of a series of macrocyclic triamines to produce compounds 58-61(fig. 2.2). Verkade[71] and coworkers have introduced phosphorous into the center of a macrocyclic triamine to yield compound 62(fig.2.2). These workers also

prepared various oxidized derivatives of 62.

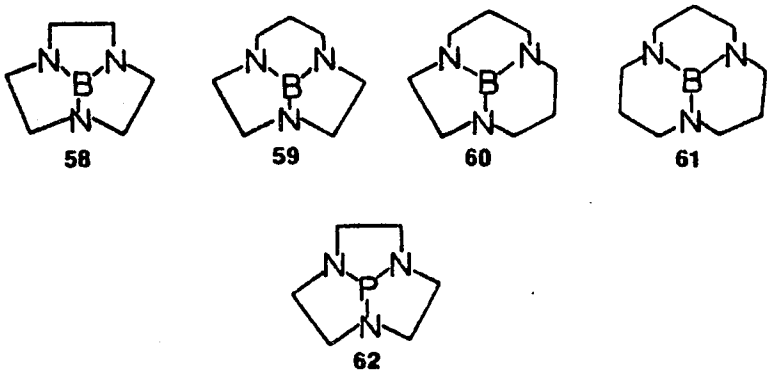


fig 2.2

Recently several groups have reported the reaction of orthoacid derivatives with macrocyclic triamines. The products of these reactions have the general tricyclic structure 63(fig.2.3).

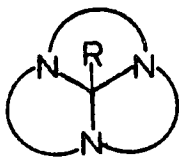


fig 2.3

Orthoamides are one of several stable derivatives of orthoacids. Orthoacids are hydrates of ordinary carboxylic acids having the general formula 64(fig.2.4). While orthoacids have never been isolated or even observed as intermediates, several derivatives of orthoacids are stable, isolable, and even common organic compounds. Probably the most common derivatives are the orthoesters 65(fig.2.4), such as triethylorthoformate. Other common derivatives are the amide acetals 66 (fig. 2.4), such as N,N,-dimethylformamide

dimethylacetal 67 (fig. 2.4). Ester aminals 68 (fig. 2.4) are also stable orthoacid derivatives but less

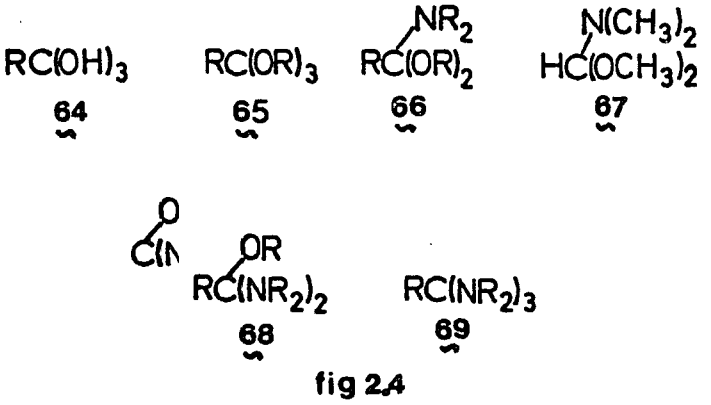


fig 2.4

commonly encountered than the esters and acetals. The perazaderivatives of orthoacids are the orthoamides 69 (fig.2.4).

Several nomenclatures for orthoacid derivatives are currently in use. Some authors refer to all orthoacid derivatives which contain an aminoalkyl residue as orthomides while others reserve the name orthoamides only for the peraza derivatives. In the following discussions the nomenclature used in conjunction with fig. 2.4 will be adhered to. Another common designation for the orthoamides is 1,1,1-tris-dialkyl(or diaryl)aminoalkanes. This nomenclature will also be employed in these discussions.

The first mention of orthoamides in the literature was in 1887 when Busz and Kekule[72] reported the preparation of tris-dialkylaminoalkanes through the reaction of 1,1,1-trichloroethane with secondary amines. This report

was later shown to be incorrect[73]. The first authentic preparation of an orthoacid derivative was reported in 1907 when Lander[74] prepared amide acetals through the rection of amide chlorides with alkoxides (fig.2.5). The field then lay dormant until 1956 when the systematic study of

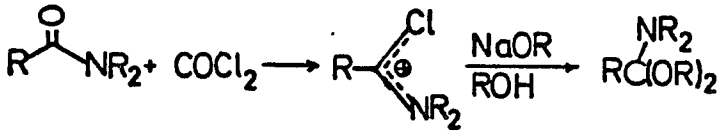


fig 2.5

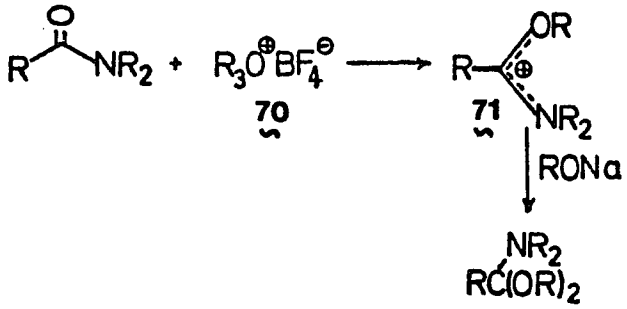
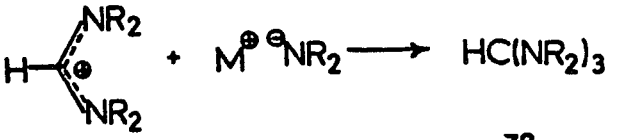


fig 2.6

orthoacid derivatives was reopened by Meerwein[74a], who reported the reaction of tertiary amides with oxonium salts 70 (fig.2.6). The resulting oxo-iminium salts 71 (fig.2.6) were then reacted with alkoxides to yield the amide acetals. Immediately after the Meerwein report Bredereck reported a more convenient procedure for the preparation of amide acetals[75]. Bredereck used the reaction of tertiary amides with dialkylsulfates to generate the intermediate iminium ions which were then reacted with alkoxides to yield the amide acetals in good yield. Following these reports a flurry of activity in orthoacid derivative chemistry was reported by Meerwein, Bredereck, Eilingsfeld, and Arnold.

This work has been extensively reviewed[76-80].

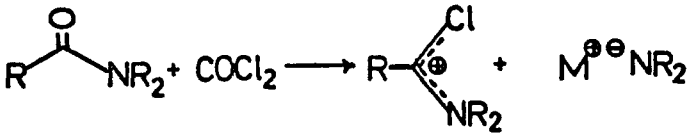
During the 1960's a number of methods for the preparation of orthoamides were reported. One of the best methods reported was the reaction of N,N,N',N'-tetrasubstituted formamidinium salts (72,fig.2.7) with alkalai metal amides to yield the tris-dimethylaminomethanes 73(fig.2.7)[81-84].



72 73

fig 2.7

The reaction of iminium chlorides 74(fig2.8) with alkalai metal amides also yields orthoamides[73].



74

73

fig 2.8

Orthoamides may also be prepared from 1,1,1-haloalkanes and secondary amines in the presence of a base such as alkalai alkoxides or sodium hydride[82,85-88].

The various orthoacid derivatives may be interconverted In particular, orthoamides may be prepared from orthoformates and lithium dimethylamide[87,89] (fig.2.9). Aminal esters will dismutate to yield a mixture of orthoamides and amide acetals in the presence of traces of alcohol[82,90-92] (fig.2.10).

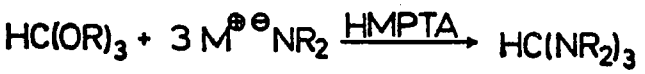


fig 2.9

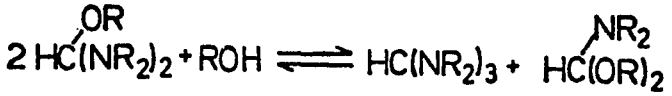


fig 2.10

Transamination of amide acetals has been used to prepare tris-dialkylaminomethanes[87] (fig.2.11).

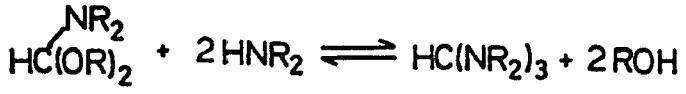


fig 2.11

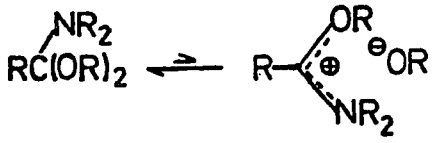


fig 2.12

Meerwein has demonstrated the electrolytic dissociation of amide acetals (fig.2.12). The position of the equilibrium was found to be dependent upon the solvating

power of the solvent and also upon the stability of the carbonium ions and the anions which were formed[93].

Since the transamination of amide acetals does not require acid catalysis the mechanism of this reaction, in neutral media, probably invovles the initial generation of intermediate 75(fig.2.13). This intermediate then reacts with secondary amines to yield an ester aminal 76 (fig.2.13). Meerwein[93] has also shown that ester aminals undergo the same type of electrolytic dissociation as the amide acetals. Therefore a second ionic intermediate 77(fig.2.13) is probably formed in this manner. This intermediate can then react with another secondary amine to yield the orthoamide. The equilibria can be driven by the high reaction temperatures which remove the lower boiling alcohol residues from the solution.

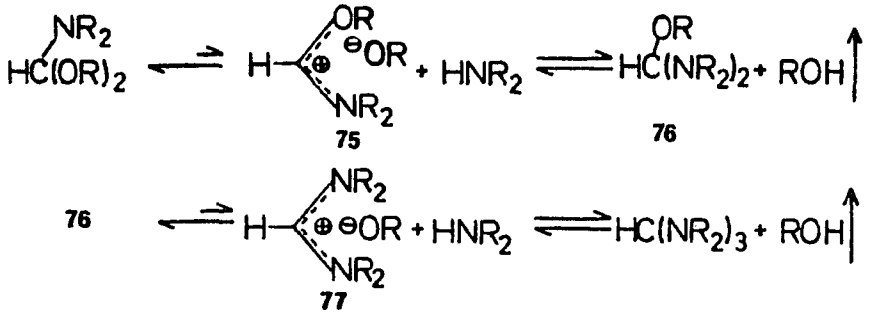


fig 2.13

Prior to this work the transamination reaction has only been run successfully on formamide acetals or on acetals bearing no α-hydrogens. When acetals bearing α-hydrogens have been employed in this reaction then the only isolable

products have been ketene aminals 78 (fig.2.14). These products result from the elimination of an alcohol residue from the intermediate ester aminal 79 (fig.2.14).

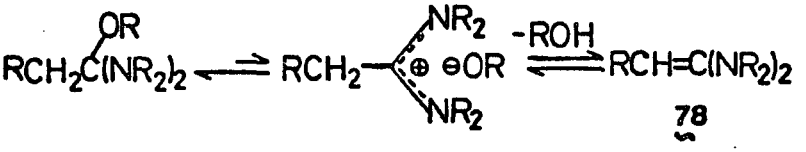
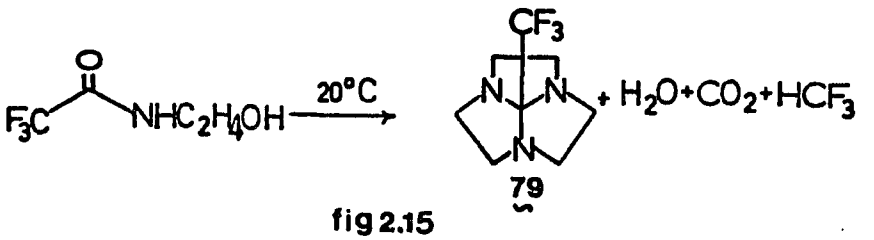


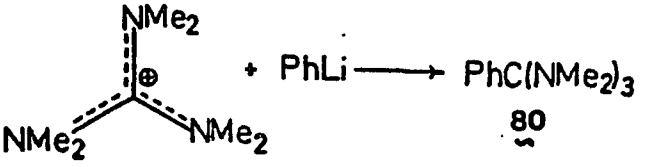
fig 2.14

The preparations outlined in fig.2.5-2.11 and fig.2.13 all pass through an ester aminal intermediates. These schemes are therefore subject to the ketene aminal side reaction discussed above. The majority of the known orthoamides were prepared by one of these methods. It comes as no surprise then that the majority of the known orthoamides are orthoformamides. Only three examples of orthoamides of higher orthoacids have been reported and in these isolated cases they have been prepared by very different routes. There is one report of a trifluoro-acetamide 79[94] (fig.2.15) but in this case the tricyclic orthoacetamide was prepared quite by accident in the pyrolysis reaction shown in fig. 2.15. Another reported example is the orthobenzamide 80 prepared by the reaction of phenyllithium with hexamethylguanidium chloride 81[95] (fig.2.16). The third reported example is the difluorochloroorthoacetamide 82 which was prepared by the reaction sequence outlined in fig.2.17[96].



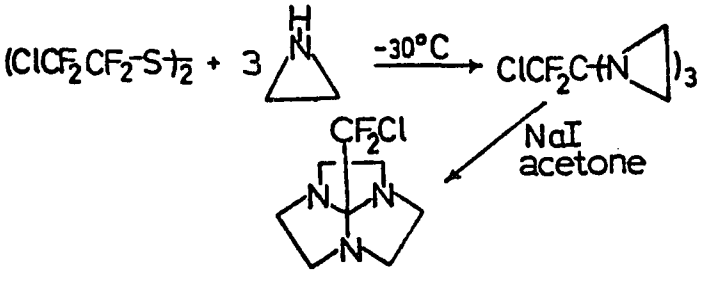
79

fig 2.15



80

fig 2.16



82

fig 2.17

The application of the above mentioned synthetic procedures have resulted in the preparation of a vast array of acyclic[76-80] and bicyclic[97] orthoamides. Most of the resulting orthoamides are stable, colorless liquids with an amine-like smell. They are generally stable at elevated temperatures and are medium to strong bases with pK_b's of approximately 9.5(hydrogen bonding method)[80].

The synthetic utility of the orthoacid derivatives stems from their high reactivity. They react with a variety of acidic compounds (both carbon and X-H acids), organometallics, and various electrophiles. Hydrolysis in acid, base, or neutral media occurs very readily in most cases. The susceptibility towards hydrolysis of orthoacid derivatives increases as more dialkylamino residues are

substituted onto the orthoacid parent(fig.2.18). Amidinium ions 83(fig.2.19) have been shown to be intermediates during the hydrolysis of orthoamides[95,98]. Cyclic and sterically hindered amide acetals are more resistant towards hydrolysis.

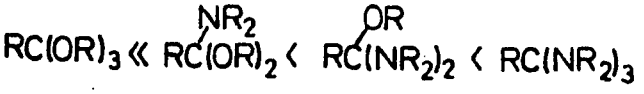
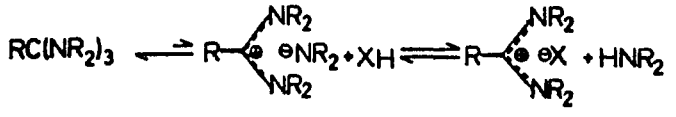
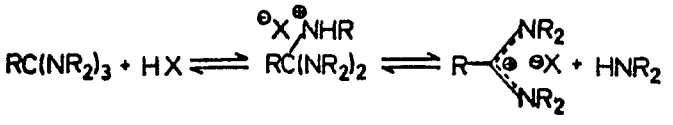


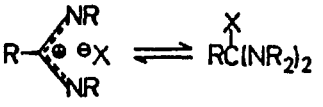
fig 2.18

It is generally accepted that the reaction of orthoamides with X-H acidic compounds proceeds via one of two pathways depending on the reaction conditions and the structure of the starting materials. The two possible pathways are presented in fig. 2.19.



path a





path b

fig 2.19

Path a is favored by very stable intermediate amidinium ions, low kinetic and thermodynamic acidity of X-H(e.g. R_2NH), as well as high solvent polarity. Conversely, path b is favored if relatively unstable amidinium ion intermediates are generated, if X-H is very acidic, and in solvents with low dielectric constants. If the intermediate amidinium ions are very stable then the reaction will end at the amidinium salt.

Orthoacid derivatives react with alkylating agents preferentially at the nitrogen(if one is present). The tris-(N-alkyl-N-aryl)aminomethanes react with methyl iodide to yield formamidinium salts(fig.2.20)[82,85].

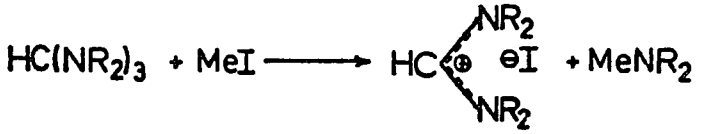
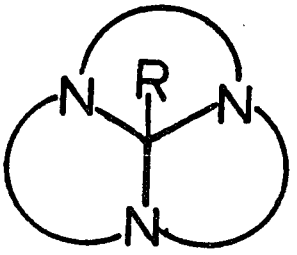


fig 2.20

fig 2.21

Formamidinium salts are also formed through the reaction of tris-(N-alkyl-N-aryl)aminomethanes with carboxylic acid chlorides(fig.2.20)[82]. If alkylation would result in very unstable cationic intermediates, as is the case for some cyclic amide acetals, then salts of the form 84 are isolated(fig.2.21)[99].

The synthesis, physical properties, reactivities, and synthetic applications of orthoacid derivatives have been extensively reviewed by several authors[76-80]. A complete review of the entire area of orthoacid derivative chemistry is beyond the scope of this report. The reader is directed to one of the comprehensive and excellent reviews of the subject.



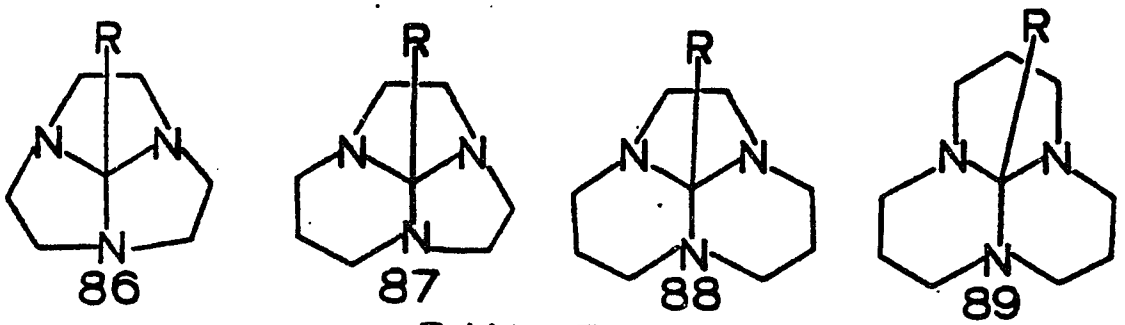
85
fig 2.22

The subjects of this report are the tricyclic orthoamides of general structure 85(fig.2.22). The two initial reports concerning the parent orthoformamides(R=H) were made by Atkins[94,95] but did not appear in the primary literature. Before these initial reports appeared there were three groups(including Atkins) working independently in this field. Reports from these groups appeared simultaneously in the primary literature[96-99]. The initial approaches of these groups were slightly different but all three were based on the reaction of orthoacid derivatives with macrocyclic triamines.

Discussion

Synthesis

As part of a general program of research into the stereochemistry, conformational analysis, and reactivities of polycyclic polyamines, the series of tricyclic orthoamides presented in fig.2.23 were prepared.



R=H,Me,Et

fig 223

Our initial synthetic approaches to these interesting compounds involved the acid catalyzed condensations of triethylorthoformate with macrocyclic triamines(fig.2.24). This approach yielded the desired products in the two cases which were examined, 86 and 88 (fig.2.23, R=H), but in low yield(9% and 38% respectively). Later syntheses employed

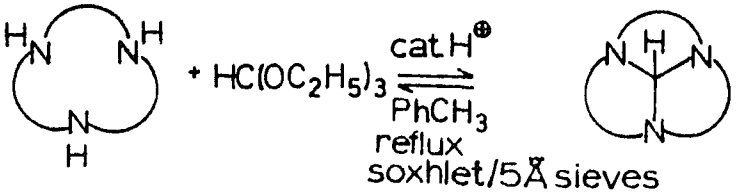


fig 2.24

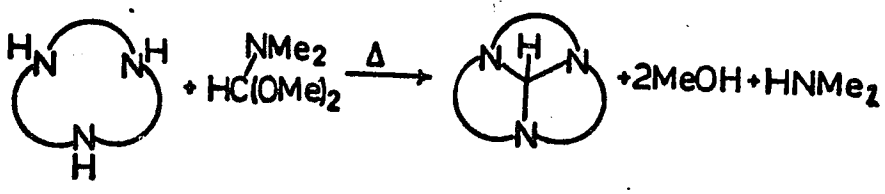


fig 2.25

the more reactive amide acetals. While these initial investigations were underway two other groups were also synthesizing the parent orthoformamides (R=H) of this series. Atkins was the first to report the synthesis of two members of the parent series[100,101] (These reports did not appear in the primary literature.) Atkins also reacted an orthoacid derivative with macrocyclic triamines except he used the more reactive reagent N,N-dimethylformamide dimethylacetal (fig.2.25). He obtained good yields of 86-89

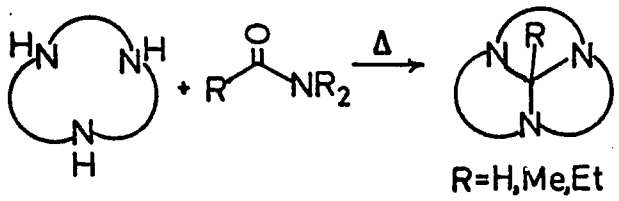
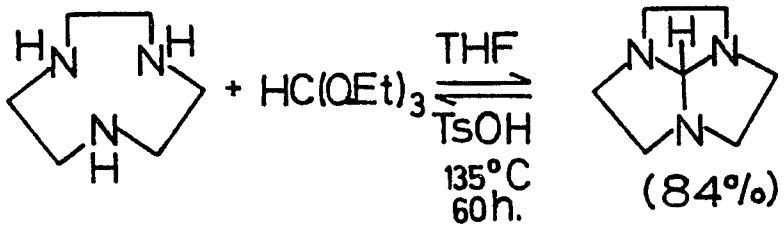


fig 2.265

(R=H,fig.2.23). His later reports in the primary literature detailed the synthesis and some of the interesting properties of the tricyclic orthoformamides[102]. During this time another group of investigators headed by

Wuest[104,105] was also investigating these compounds. Wuest prepared two members of the series according to the synthetic procedures outlined in fig.2.26.



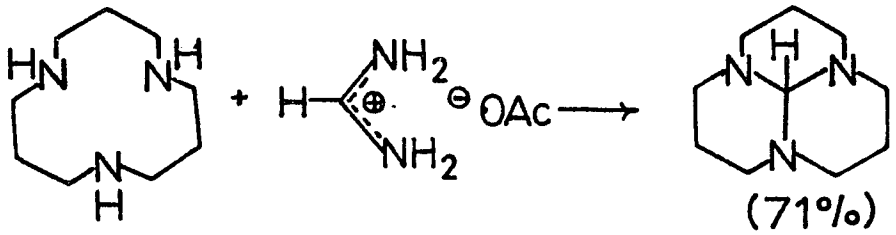


fig 2.26

It will be noted that all of these approaches are based upon the synthetic methods previously developed for orthoamide synthesis and are not novel approaches. The novelty of these syntheses is the use of the macrocyclic triamines and the tricyclic structure of the products. Our report[103], Atkin's report[102], and Wuest's report[104,105] on the parent orthoformamides appeared in the primary literature simultaneously.

A more recent report from these laboratories describes the syntheses and conformational analyses of the higher homologs of the series(R=Me, Et) [106] (fig.2.265). These

materials were prepared by the uncatalyzed condensation of N,N-dimethylacetamide dimethylacetal or N,N-dimethylpropionamide dimethylacetal with macrocyclic triamines to yield the tricyclic orthoacetamides and orthopropionamides respectively. These are the first examples of orthoamides of higher acids to be synthesized by this route and are a significant addition to this previously limited class of orthoamides. The amide acetals used in these preparations were synthesized by the method of Bredereck[107] (fig.2.27).

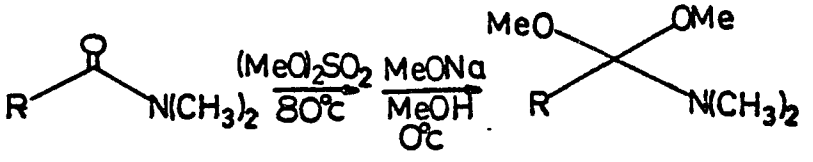


fig 2.27

The macrocyclic triamine precursers were prepared by the method of Richman and Atkins[52] (fig.2.28). In this method the appropriate acyclic triamine was reacted with 3 equivalents of p-toluenesulfonyl chloride followed by reaction of the resulting tris-tosylamide with 2 equivalents of sodium ethoxide to yield the corresponding di-sodium salt. This di-sodium salt was then reacted with the ditosylate of an appropriate diol in DMF at 100 C to yield the macrocyclic tris-tosylamide. Hydrolysis of the macrocyclic tosylamide was accomplished by the general

method of Raymond[60a] whereby the tosylamides were cleaved in concentrated sulfuric acid at 100°C. Typically a base workup yielded the triamines in good yields.

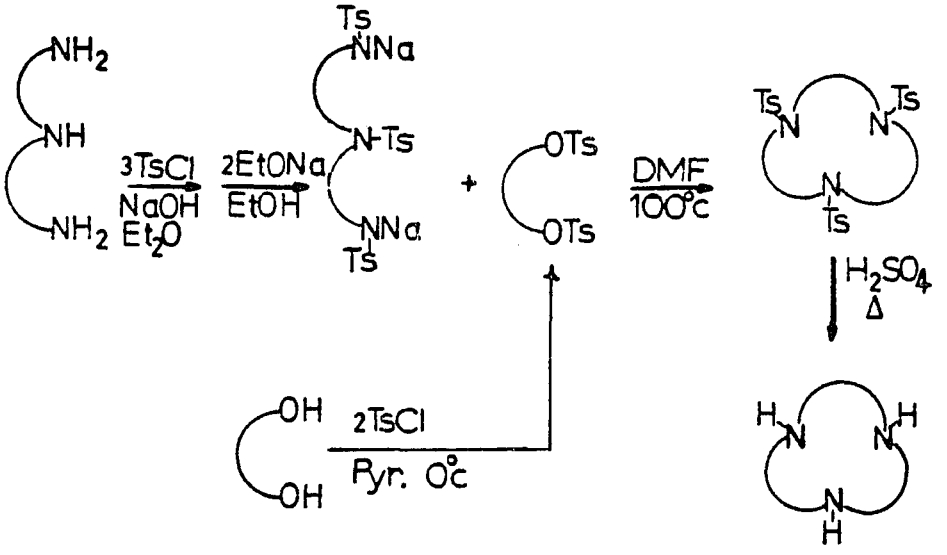


fig 2.28

As was pointed out in the introduction, all previous attempts at the synthesis of orthoamides of higher acids employing amide acetals and secondary amines had resulted in ketene aminals instead of the desired orthoamides. The mechanism for formation of the tricyclic orthoamides is presented in fig. 2.29. The yields of the orthoamides are high by this procedure and so the pathway that leads to the ketene aminals (the exclusive pathway for acyclic systems) must not be operative to any great extent. Presumably the orthoacetamides and orthopropionamides are formed instead of the ketene aminals because the intramolecular reaction to yield the tricyclic products must be faster than the intermolecular proton abstraction that would yield the ketene aminals. It is presumed that the proton abstraction must be intermolecular because the steric requirements of 90

are such that intramolecular proton abstraction is geometrically impossible. Examination of models also

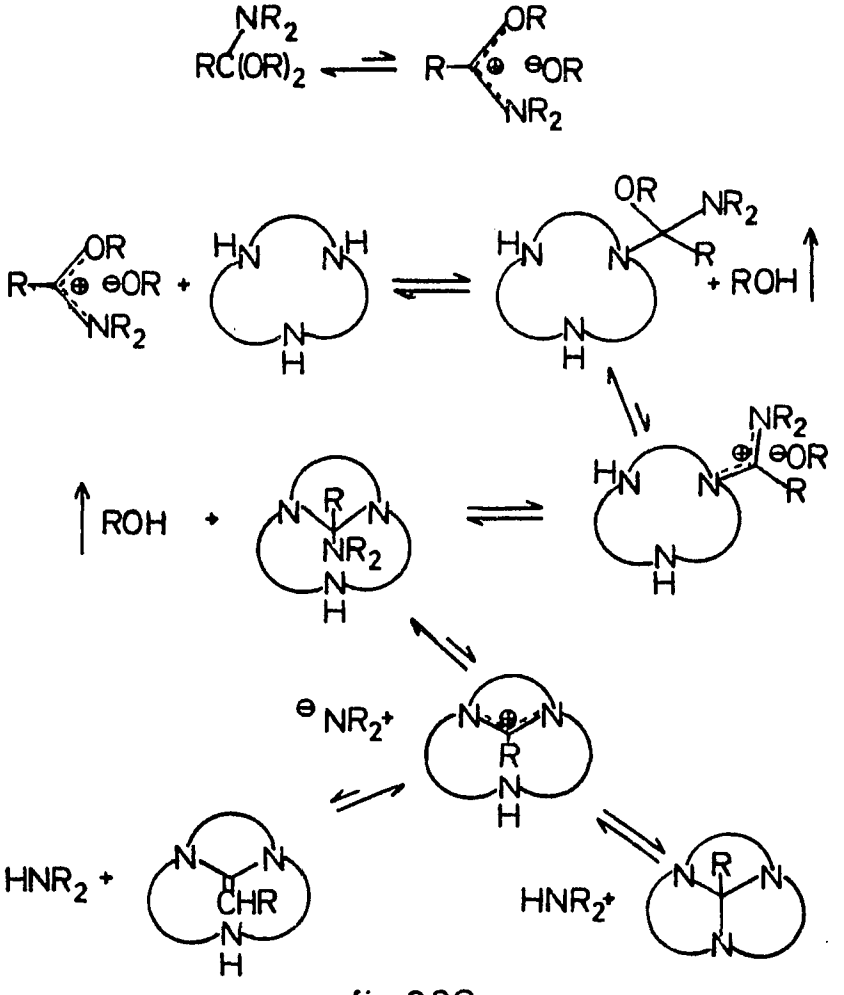


fig 229

indicates that 91 would be very high in energy due to unfavorable steric interactions between the ketene aminal portion of the molecule and the adjacent ring system. These two factors are most likely responsible for the observed course of the reaction in the cyclic cases.

The following sections discuss the novel spectroscopic properties, chemical properties, and reactivities of the tricyclic orthoamides.

Conformational Analysis of the Orthoamides

Introduction

The stereochemistry and conformational analysis of polycyclic polyamines with bridgehead nitrogens continues to be an area of active research[64,108,109]. An excellent review is available concerning the spectral methods used to determine the stereochemistry of the bridgehead nitrogen[110]. The more general area of heterocyclic conformational analysis continues to be actively studied by many groups and excellent reviews[111,112] and books[113] are available on the subject.

The application of ^{1}H and ^{13}C NMR to the study of conformational analysis in general and to heterocycles[114] in particular has advanced these areas of study dramatically. The application of variable temperature techniques to NMR[115-125] (Dynamic NMR) has produced a wealth of information concerning both the determination of conformation and the energy barriers associated with conformational processes[126]. These techniques have been used to advantage in the study of the conformational

analysis of the orthoamides.

Infrared spectroscopy was also used to determine the stereochemistry at the nitrogen bridgeheads. In particular, the appearence of Bohlmann bands[110,127] in the 2700-2800cm^{-1} region of the IR spectra of amines is indicative of an antiperiplanar(ap) relationship between the nitrogen lone pairs and the adjacent C-H bonds.

Empirical force field calculations were also applied in this study of the orthoamides. Allinger's MM2[128,129] force field was used in these calculations. MM2 has been proven reliable in the calculations of the geometries and energies(steric energies and heats of formation) for hydrocarbons. The force field has been parameterized for a number of functional groups[130] including amines[131-133]. Allinger has reviewed the force field method[134,135]. Generally amine geometries have been shown to be quite reliable. The relative energies of conformations calculated by MM2 are also generally reliable. Polar compounds are particularly troublesome for MM2 since the program does not adequately account for electrostatic contributions. The calculated total energies for polar molecules have a strong dependence on DIELC(a constant which is input into the calculations that is essentially the effective dielectric constant of the solvent;we used 1.5) and for this reason this constant must be specified when quoting calculated energies of polar compounds. The reliability of the total

energies (which includes electrostatic term) is particularly suspect for polyfunctional molecules[136,111]. Since the orthoamides are polar trifunctional molecules we have taken the approach of elucidating the conformations of the orthoamides spectroscopically and then comparing the experimentally determined conformations with those calculated by MM2.

Through the application of the techniques described above the conformations of the orthoamides, as presented in fig. 2.30 have been assigned. Included in this figure are the point groups to which each conformation belongs. One striking feature of the parent orthoformamides is the variation of the orientation of the nitrogen lone pairs relative to the central methine C-H bond. The lone pairs are approximately syn to this C-H bond in the smallest member of the orthoformamides and are ap in the largest member. This variation in lone pair orientation gives rise to many interesting spectroscopic and chemical properties in these compounds. Similar variations in lone pair orientation are present in the orthoacetamides and orthopropionamides giving rise to interesting spectroscopic and chemical properties in these compounds also. A detailed discussion of these properties is included in the discussion section.

To facilitate the discussion of these compounds a simplified nomenclature will be employed. The names of the compounds will have the general form R-lmn where R is the substituent bonded to the central carbon and l,m,n are the numbers of methylenes in the carbon bridges of the tricyclic ring system. Thus the smallest member of the orthoformamides(fig.2.30) 91 is called H-222 and the largest member 94 H-333. When more then one conformation is possible, as is the case for Me-333, then the conformation will be specified by indicating the stereochemistry of the bridgeheads. As an example, 98 would be called trans,trans,trans-Me-333 or simply 98-ttt. In some cases there may exist more than one cis,cis,trans conformation. In these cases the conformations will be differentiated by reference to the point group to which they belong.

For the purposes of conformational analysis this is really a two dimensional series. The first dimension is varying ring size with constant R size and the second is varying R size with constant ring size. We see conformational and reactivity dependences in both of these dimensions. Some of these dependences can be easily assigned to variation in a single dimension and some surely result from an interplay of both. For this reason this series is both a bountiful subject and a challenge.

In general, the variation in the R group size can be expected to exert its effect due to steric interactions. The variation in ring size manifests itself in a greater conformational freedom in the larger rings. Thus it can be seen in fig.2.30 that in the 333 series a gradual change

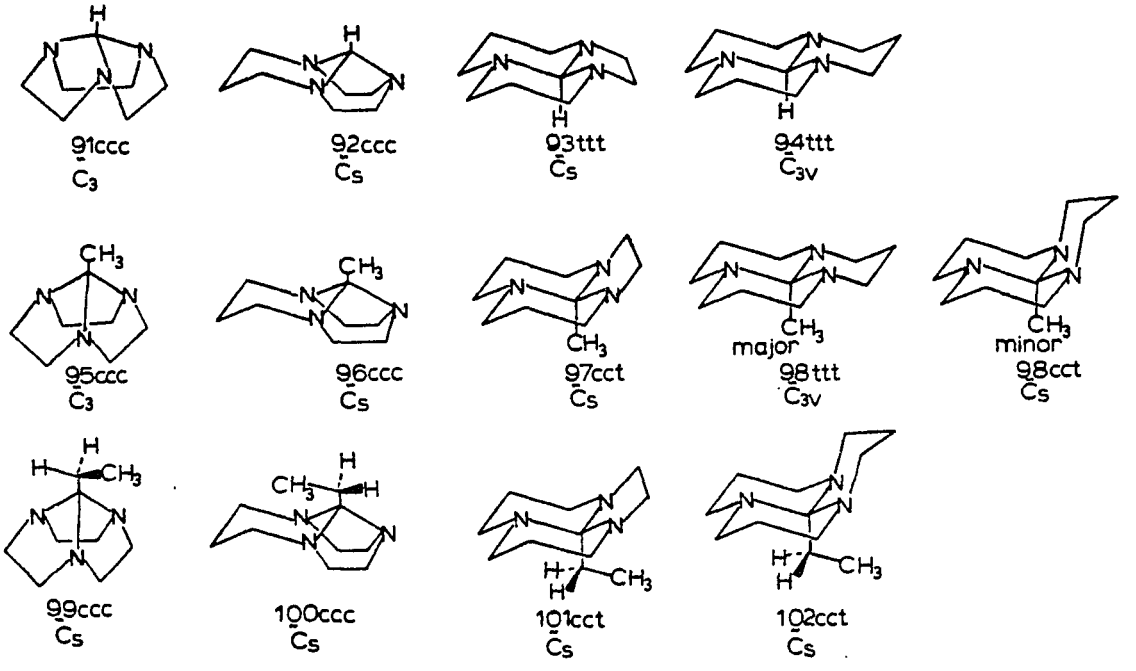


fig 2.30

occurs from an all-trans ring system in the formamide , to a mixture of cis,cis,trans and all-trans in the acetamide , and finally to a cis,cis,trans conformation in the propionamide. The ability of the 333 series to adopt conformations which minimize the steric strain introduced by the increasingly larger R groups is attributed to the conformational freedom allowed them by the larger ring system. These changes can be contrasted with the constancy of conformation in the 222 series. In this latter series only slight conformational changes are possible due to the

restrictively small ring system.

It should be noted that in addition to the variation in R and ring size another conformational effect is operative in these systems. The term "anomeric effect" was coined by Lemieux in 1958 to describe the axial preference of an electronegative substituent in the C-1 position in pyranoid rings. It was quickly recognized that this effect was not restricted to carbohydrates. The term "generalized anomeric effect"[137] grew out of this realization. The generalized anomeric effect states that there is a preference for an antiperiplanar relationship between the lone pair of a heteroatom and an electronegative substituent in the α-position(fig.2.31). The effect was first explained in terms of dipolar interactions. Edward[138] reasoned that an antiperiplanar disposition of dipoles should be lower in energy than a gauche disposition. The more recent, and now generally accepted, explaination is based on MO considerations. According to MO theory the overlap of the lone pair orbital of the heteroatom with the σ^* orbital of the C-X bond results in net stabilization. This overlap is maximized when the lone pair is antiperiplanar to the C-X bond. Upon examination of the assigned conformations of the orthoamides in fig. 2.30 it becomes immediately obvious that the all-cis and the all-trans configurations are disfavored by the anomeric effect. In the cis,cis,trans conformations some (although not all) of the unfavorable interactions are relieved. Thus the anomeric effect favors

the cis,cis,trans conformations. The anomeric effect has recently been comprehensively reviewed[139].

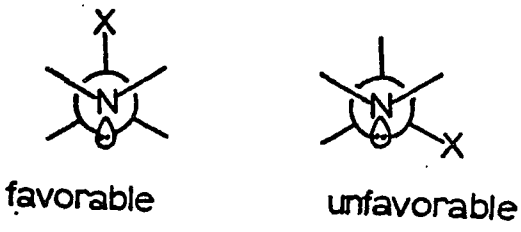


fig 2.31

The detailed conformational analysis of the orthoamides is contained in the discussion section. The discussion is broken down into three sections according to the R group. Each section contains an initial discussion of general spectroscopic trends followed by a compound by compound survey of the conformational analysis including all relevant spectroscopic data and MM2 results.

A final note concerning terminology is necessary. There is some disagreement among conformational analysts as to the precise definition of conformation. The original definition specified that stereoisomers that are interconvertable by rotations about single bonds are conformers. Clearly this definition is inadequate in systems containing heteroatoms capable of pyramidal inversions. For the purposes of the following discussion we will adhere to the definition advanced by Riddell. Riddell states that, conformations are stereoisomers that, "can be interconverted either by rotation about bonds of order

approximately one, with any concomitant small distortions of bond lengths and angles, or by inversion at a three coordinate center in the molecule, or by pseudorotation at phosphorous"[113].

Conformational Analysis of the Orthoformamides

This section deals with the conformational analysis of the orthoformamides(R=H). All relevant spectral data is presented in tabular form. The actual spectra of these compounds are included in appendix 1. The interpretation of these spectra is discussed in terms of the conformational analyses. EFF calculation (see MM2 calculations section for a complete discussion) results are quoted in support of the spectral data if the two methods agree. Discussions of the failings of MM2 to predict minimum energy conformations in cases where spectral data clearly contradicts the MM2 results are also included.

The NMR data (^{1}H and ^{13}C) are presented in table 2.1. The relevant IR data, $^{1}J_{CH}$ coupling constants, and the assigned conformations for the orthoformamides are presented in fig. 2.31.

Stereochemical Variation in the Orthoformamides

Fig. 2.31 shows the stereochemical variation of the nitrogen lone pairs relative to the central C-H methine bond. According to EFF calculations the lone pairs are approximately syn to the methine C-H (12.5^{o} from syn) in

H-222. In H-322 one lone pair is approximately syn (0.15°) and the other two are approaching gauche (32.2° and 32.4°). In H-332 the lone pairs are antiperiplanar (176.1°, 179.9°, 176.6°) and in H-333 they are also antiperiplanar (180°). This variation of the lone pair-central methine dihedral angle gives rise to a systematic variation in the ^{1}H chemical shifts and the $^{1}J_{CH}$ through the series.

Table 2.1

Product	60MHz ^{1}H NMR (δ, $CDCl_3$)	^{13}C NMR (δ_C, $CDCl_3$) N-CH-N	$-CH_2-N$	$-CH_2-CH_2-CH_2-$	$^{1}J_{CH}$ (methine) (Hz)
91	2.5-3.35(AA'BB',12H) 5.03 (s,1H,methine)	104.1	52.0	----------	184 ± 1
92	1.05 (d of quintets, J=13;3Hz,1H) ca. 1.5-2.3(m,1H) ca. 2.2-3.7(m,12H) 4.32 (s, 1H, methine)	93.3	45.9, 49.0 56.2	16.5	169 ± 1
93	1.1-3.37 (m)‡	96.6	47.7, 48.9 51.8	23.6	140 ± 3
94	1.22-1.49 (m,3H)* 1.58-2.22 (m,9H) 2.25 (s,1H,methine) 2.61-2.90 (m,6H)	100.0	53.9	24.2	141 ± 3

‡Neither 60 MHz nor 90 MHz spectra permitted assignment of the methine
*90 MHz, acetone-d_6; δ(methine) in $CDCl_3$ = 2.32

δ	5.03	4.32	2.56	2.25
$^{1}J_{CH}$	184	169	140	140
IR		2700-2800 cm^{-1}	2700-2800 cm^{-1}	2700-2800, 2400 cm^{-1}

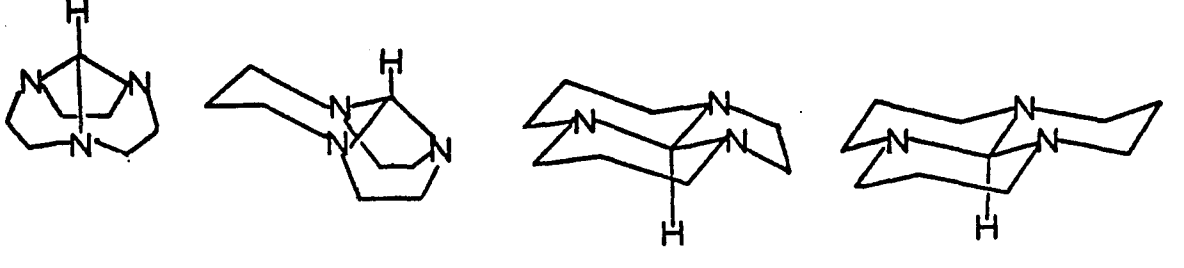


fig. 2.31

It has been observed that the $^1J_{CH}$ associated with a C-H bond which is antiperiplanar to a nitrogen lone pair is smaller than the coupling constant associated with C-H bonds which are syn or gauche to the lone pairs[140a-k]. Theoretical studies indicate that the orbital overlap of the lone pairs with the σ^* orbital of the C-H bond is responsible for the variation in the coupling constant[141-143]. The angular dependence of the orbital overlap and the magnitude of $^1J_{CH}$ are qualitatively illustrated in fig.2.32.

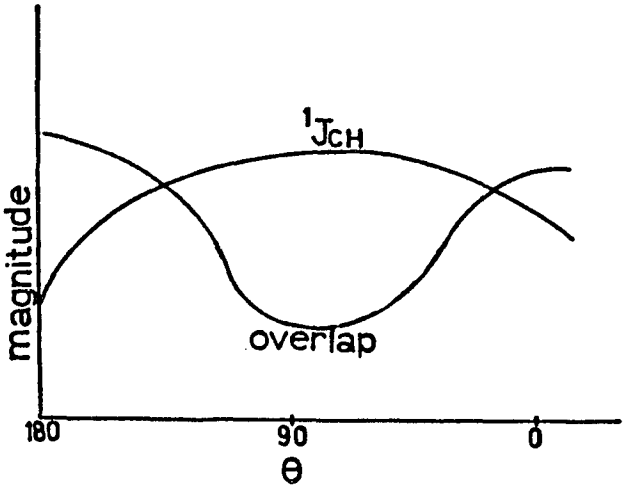


fig.2.32

Note that $^1J_{CH}$ decreases as the orbital overlap increases which leads to the conclusion that $^1J_{CH}$ should approach a maximum value as the dihedral angle approaches 90.

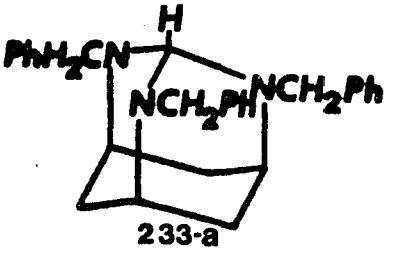
Examination of the coupling constants for the series and a number of model compounds (fig.2.33) reveals that the

variation in $^{1}J_{CH}$ cannot be attributed solely to lone pair orientational effects. When the magnitude of the overlap is considered it becomes obvious that the coupling constants for H-222 and H-322 seem too large. If lone pair effects were the sole cause of the observed variation in the series then $^{1}J_{CH}$ should be smaller than the $^{1}J_{CH}$ of model compound 2.33-a where the dihedral angles are each 60°.

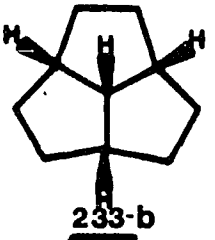
Orthoamides : $^{1}J_{CH}$

Compound	methine $^{1}J_{CH}$ (Hz)
$(Me_2N)_3CH$	147.5
222	184
322	169
332	141
333	141

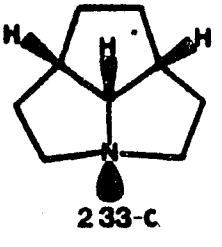
$\Delta J = 43$



233-a — 159



233-b — 137



233-c — 156

fig 2.33

Clearly factors other then just lone pair orientational effects are involved here. A major contributing factor must be the strain present in the smaller members of the series. The large $^{1}J_{CH}$ for 2.33-b clearly shows that angle strain is present in the H-222 hydrocarbon analog. the angle strain caused by the constraints of the ring system are probably worse in H-222 due to the shorter C-N bonds. In particular, the constraints of the rings in H-222 and H-322 should result in flattening of the nitrogens and compression of the N - C - N bond angles of the methine carbon. The increased s character of the C-H bond due to this angle strain would result in an increase in $^{1}J_{CH}$. The relationship between $^{1}J_{CH}$ and the hybridization of the carbon is well documented[144,145]. Equation 2.1, relating the %s character to the coupling constant, has received much use (and abuse[146,147]). It has been reported that equation 2.1 does not hold in the presence of electronegative substituents[148] (even though the

$$^{1}J_{CH} = 5.7 \times (\%s) - 18.4(Hz) \qquad \text{eq. 2.1}$$

qualitative relationship still holds) and so attempts at factoring out the relative contributions of the lone pair effects and the hybridization effects cannot be undertaken. The fact that the coupling constants for H-332 and H-333 are smaller than $^{1}J_{CH}$ for tris-dimethylaminomethane

indicates that the lone pair orientational effects observed in other systems are also present in the orthoformamides.

Examination of the coupling constants for 2.33-b, 2.33-c and H-222 leads to the conclusion that the effects of the added nitrogens on $^1J_{CH}$ are not additive. The coupling constant increases by 18.6 Hz from 2.33-b to 2.33-c due to the introduction of a single nitrogen. If the effect were purely additive then the $^1J_{CH}$ for H-222 would be expected to be 192.8 Hz (137 + 3(18.6) = 192.8). Since the observed coupling constant is considerably less than 192.8 Hz it must be concluded that the effects of the nitrogen on $^1J_{CH}$ are in fact not additive.

In summary it can be stated that the variation in the $^1J_{CH}$ coupling constant results from an interplay of lone pair orientational effects and strain effects and that the relative contribution of the two effects cannot be ascertained. It should be noted that the assumption has been made here that the increase in $^1J_{CH}$ methine resulting from the electronegative nitrogen substituents is constant throughout the series. This assumption seems reasonable since the methine carbon is bonded to three nitrogens in all four members of the series.

A variation in the chemical shift of the methine hydrogen was also observed in this series. Hydrogens which

are antiperiplanar to lone pairs generally resonate upfield of those which are syn or gauche to a lone pair[149-153]. The use of this spectral parameter to assign the stereochemistry of fused ring systems with nitrogen bridgeheads is generally accepted and has been reviewed[110]. The shifts are attributed to a combination of n- σ^* interactions (lone pair effect) and C-C and C-H magnetic anisotropies (alkyl effect). The relative importance of these two factors has been the subject of much conjecture and is still a matter of controversy[149-153]. The effect of the lone pairs on the NMR spectrum is conveniently illustrated by the resonance argument presented

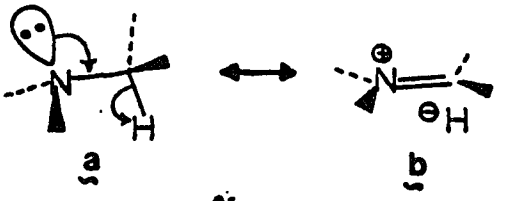


fig 234

in fig.2.34. Resonance structure 2.34-b, which should be maximized when the lone pairs are antiperiplanar to the C-H bond, will cause upfield shifts of the methine hydrogen. This hyperconjugative argument is in agreement with Deslongchamps' principle[154-157]. The chemical reactivity of H-333 also reflects the contribution from resonance form 2.34-b. Wuest[104] has reported that the pyrolysis of the conjugate acid of H-333 (tetrafluoroborate salt) yielded the corresponding guanidinium tetrafluoroborate and molecular hydrogen (fig. 2.35). Wuest has also reported the clean

reaction of H-333 with various oxidizing agents to yield the guanidinium cations[104].

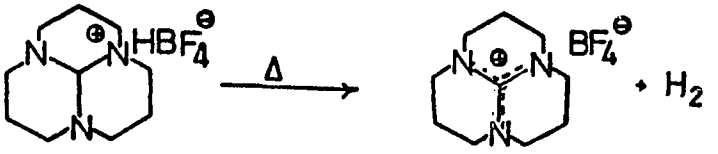


fig 2.35

In summary the upfield shift of the methine hydrogen in the orthoformamide series results from a combination of lone pair and alkyl shifts. The relative importance of the two effects has not been be determined. The lone pair effect is clearly operative in these systems and is probably the most dramatic example of this effect ever reported.

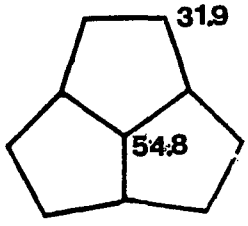
The orientation of the lone pairs relative to the methine C-H also manifests itself in the infrared spectra of these compounds. As was mentioned in the introduction, Bohlmann bands in the 2700-2800cm^{-1} region of the IR spectrum have been attributed to C-H stretching frequencies of C-H bonds which are antiperiplanar to a nitrogen lone pair. The low frequency of the absorbance results from the lengthening and weakening of the C-H bond as predicted by the resonance argument presented in fig. 2.34. Bohlmann bands are observed in the 2700-2800cm^{-1} region for H-322, H-332, and H-333. We have assigned these absorbances to C-H

bonds in the rings that are antiperiplanar to a single nitrogen lone pair. Bohlmann bands are also observed at 2400cm^{-1} in the IR spectra of H-332 and H-333. We have assigned these very low frequency absorbances to the central methine C-H bond which is antiperiplanar to three nitrogen lone pairs. The assignment of these absorbances to the central methine is possible because this absorbance is absent in the IR spectrum of Me-333. Bohlmann bands were originaly thought to be observable only when two C-H bonds were antiperiplanar to a nitrogen lone pair. Subsequent studies[110a] determined that Bohlmann bands are also observed in cases were only a single C-H bond is antiperiplaner to a nitrogen lone pair (see reference 110 for a disscussion of this point).

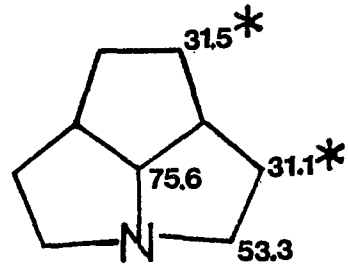
All of these spectral trends were used in making the assignments of the conformations of the orthoformamides. These trends are in agreement with the assigned conformations although they are larger in magnitude than previously reported examples. The magnitude of the spectral changes observed in these compounds is of course due to the participation of three nitrogen lone pairs. The literature precedents for these spectral characteristics, in most cases, involved only a single nitrogen and would be expected to be of a lesser magnitude.

Conformational Analysis of H-222(91). Models indicate that the only reasonable conformation for this compound is the all-cis slightly twisted C_3 conformation presented in fig. 2.31. Strong evidence for the all-cis conformation is the complete absence of Bohlmann bands in the 2700-2800cm^{-1} region of the IR. In the all-cis conformation neither the central methine C-H nor the ring C-H bonds are antiperiplanar to nitrogen lone pairs. The downfield ^1H chemical shift of the methine proton is also in agreement with the assigned conformation as is the large $^1J_{CH}$ for the methine C-H. ^{13}C empirical shift correlations employing model compounds 2.33b[158] and 2.33-c[159a] (fig. 2.36) also support the assigned conformation.

If the alternate cis, trans, trans conformation (the other most likely conformation for H-222) were also present (as a minor form or as the sole conformation) then some dynamic line broadening might be observed. The complete lack of dynamic line broadening in the ^{13}C spectrum of H-222 down to -100 C might be an indication that H-222ctt (fig.2.365) is in fact not present. The lack of dynamic line broadening in the NMR does not conclusively rule out H-222ctt since the conformational processes in five membered rings are known to have low barriers and usually cannot be observed in the NMR at accessible temperatures. Conformation H-222ctt can be ruled out by the absence of

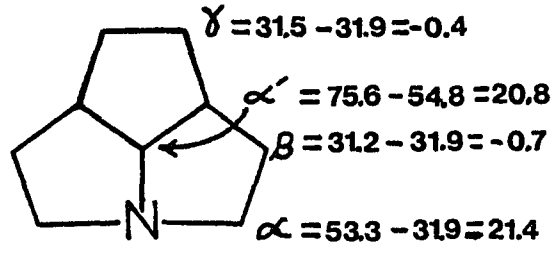


b

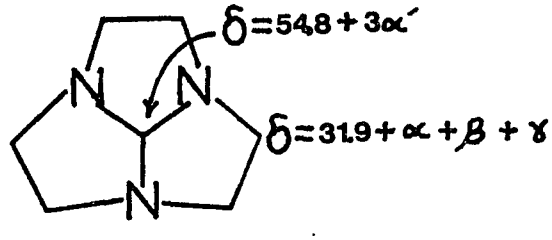


c

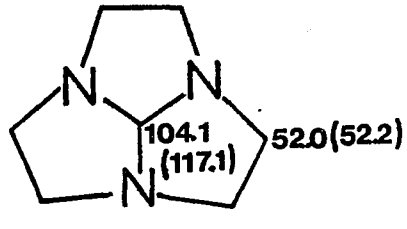
$\Delta\delta_{c-b}$ upon introduction of one N



calculated shifts for H-222



Agreement: actual (calcd.) shifts



*tentative assignments

fig 2.36

Bohlmann bands in the IR since conformation H-222ctt would be expected to exhibit Bohlmann bands.

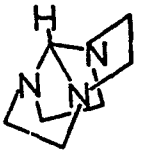
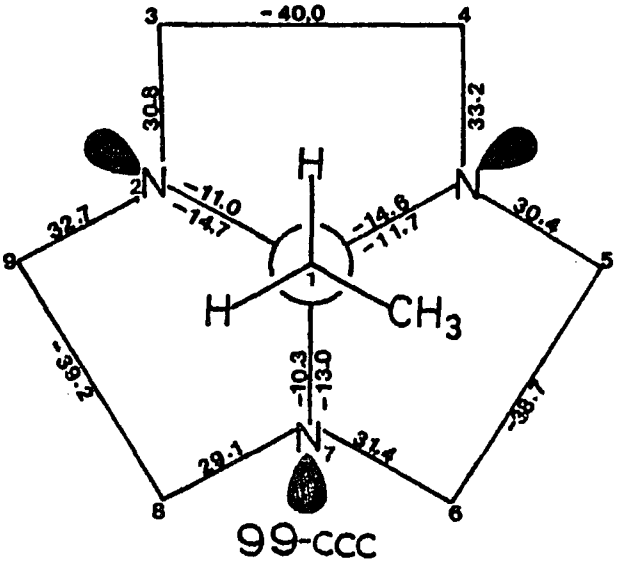


fig2365

Osawa[159a] has recently reported a detailed empirical force field study of the hydrocarbon analog of H-222. Osawa concluded that the hydrocarbon has the slightly twisted C_3 symmetry that we have assigned to H-222. His study indicated that the hydrocarbon rapidly interconverts between two enantiomeric C_3 conformers resulting in apparent C_{3V} symmetry.

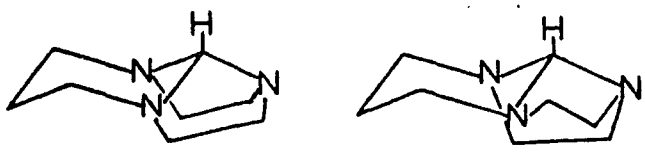


99-ccc
E=44.2
fig 256

The minimized ground state conformation as generated by MM2 is shown in fig. 2.37 along with the calculated energy. The minimized conformation has C_3 symmetry (in agreement with the hydrocarbon analysis). The torsion angles indicate that the three five membered rings each adopt the half chair form as opposed to the envelope conformation. Although we have not performed the calculations, it is assumed that H-222 undergoes a conformational process similar to that of the hydrocarbon whereby two enantiomeric C_3 conformations are interconverted by a low energy pathway resulting in the apparent C_{3V} symmetry. The energy barrier for this process should be so low that it should not be observable by dynamic NMR techniques..

The spectal data, the MM2 results, and the reported calculations for the hydrocarbon analog all support the assigned conformation.

Conformational Analysis of H-322 (92). Models indicate that the most reasonable conformation for H-322 is the all-cis conformation H-322ccc (fig.2.38). The results of the MM2 calculations support this assignment over H-322cct (fig.2.38). The presence of Bohlmann bands in the IR for this compound are due to C-H bonds in the six membered ring.

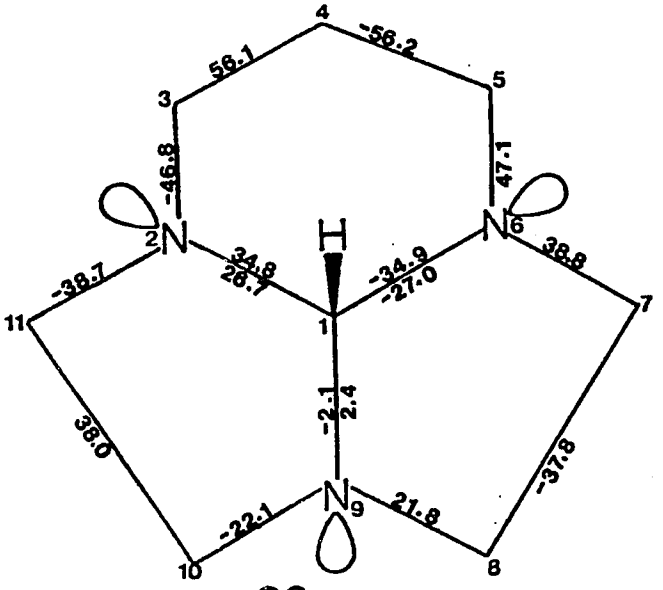


92ccc 92cct

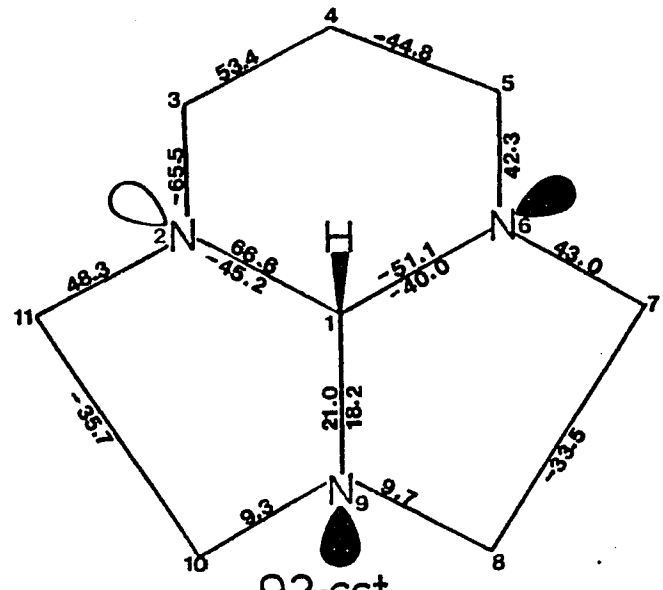
fig 2.38

The methine proton chemical shift and the methine $^{1}J_{CH}$ are both supportive of the assigned conformation. The absence of dynamic line broadening in the ^{13}C spectrum down to -100°C is consistent with the assigned conformation but does not conclusively rule out the possibility of other conformations (conformational processes in five membered rings would probably not be observable in the NMR at accessible temperatures). The upfield resonance of C-4 (16.5 ppm) (see figure 2.39 for numbering system) points toward sterically compressed H-322ccc (where C-4 is gauche to C-7 and C-11) as opposed to H-322cct (where C-4 is gauche to C-7 and antiperiplanar to C-11)[160,161].

MM2 calculations have been performed on H-322ccc and H-322cct and their minimized geometries and energies are shown in fig. 2.39. The torsion angles in H-322ccc indicate that the two five membered rings are distorted envelopes and that the six membered ring adopts a flattened chair conformation. As can be seen in fig. 2.39 the distortions in H-322cct are more severe resulting in the higher energy content.



92-ccc
E=39.4



92-cct
E=40.8

fig 239

It should be noted that we have not calculated the energies of all the possible conformations of H-322. All six of the possible conformations of H-322 are shown in fig. 2.40. The other four conformations were not calculated because they seemed to us to be too strained to be considered as reasonably populated minima.

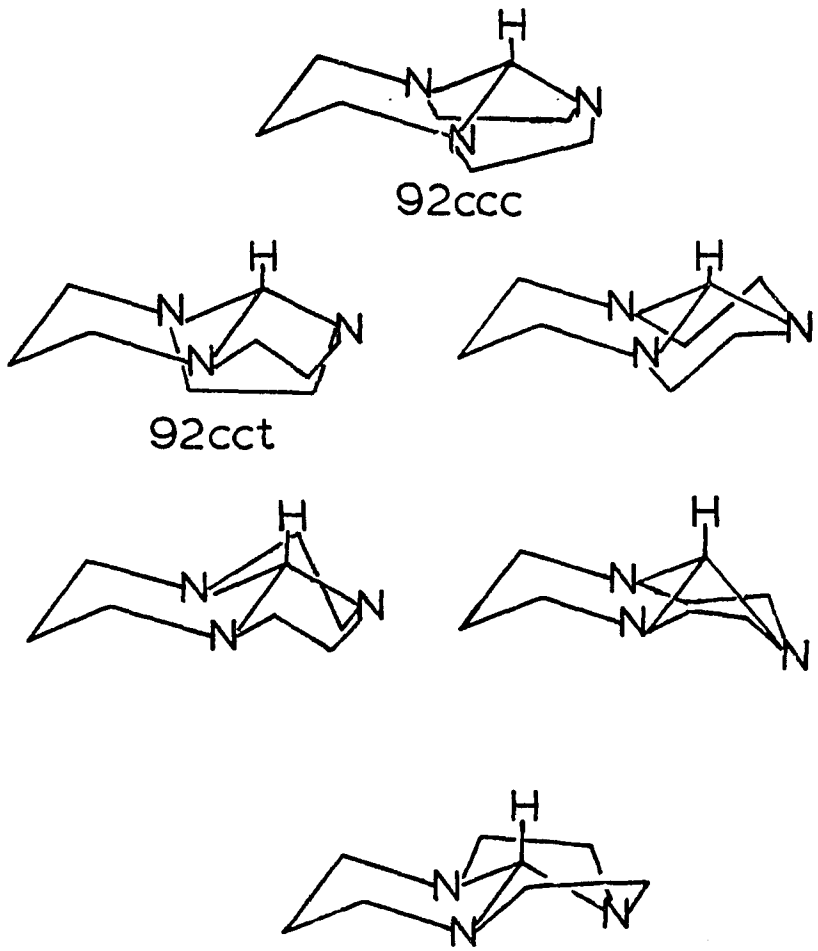


fig 2.40

Conformational Analysis of H-332 (93). The conformational analysis of H-332 is not as straightforward as for the H-222 and H-322. EFF calculations indicate that there are three ground state conformations all within 1.5 kcal/mol of one another (fig.2.405). Fortunately the

spectral data allows the assignment of H-332ttt as the major conformation in $CDCl_3$. The most important spectral data used in this assignment are the $^1J_{CH}$ coupling constant for the methine carbon, the unusually low frequency Bohlmann bands in the IR, and the chemical shift of the methine proton. The $^1J_{CH}$ was found to be 140 Hz which is the same as the $^1J_{CH}$ in H-333 (where the MM2 results are unambiguous and the assignment of the all-trans conformation is well defined spectrally). Also there is an unusually low frequency Bohlmann band in the IR indicating a C-H bond antiperiplanar to three nitrogen lone pairs (assignment of the observed absorbance to the central methine C-H was made in analogy to H-333). The chemical shift of the methine proton also supports the assignment of the all-trans conformation since it is so similar to that of H-333.

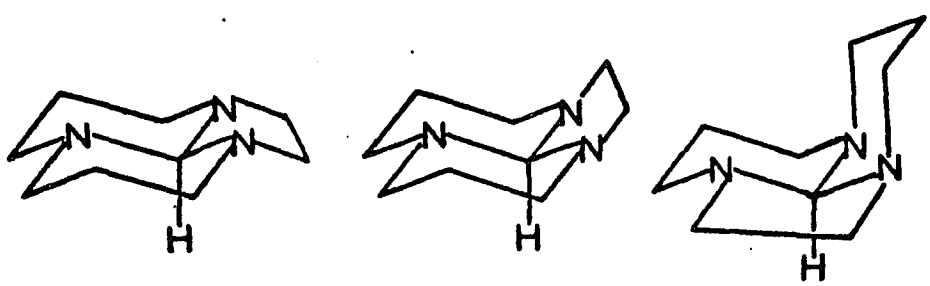
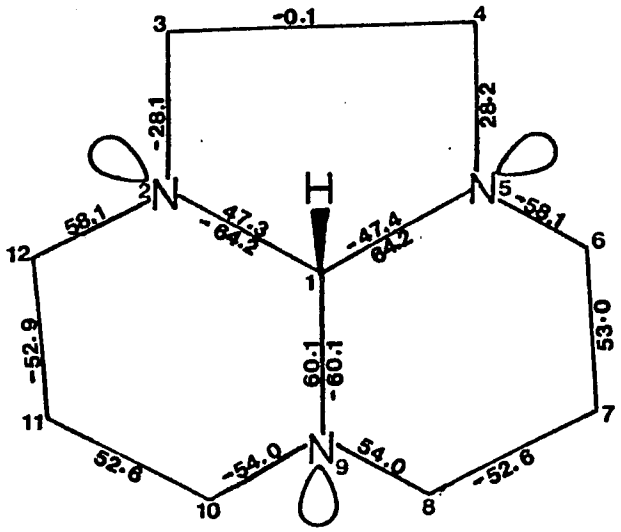
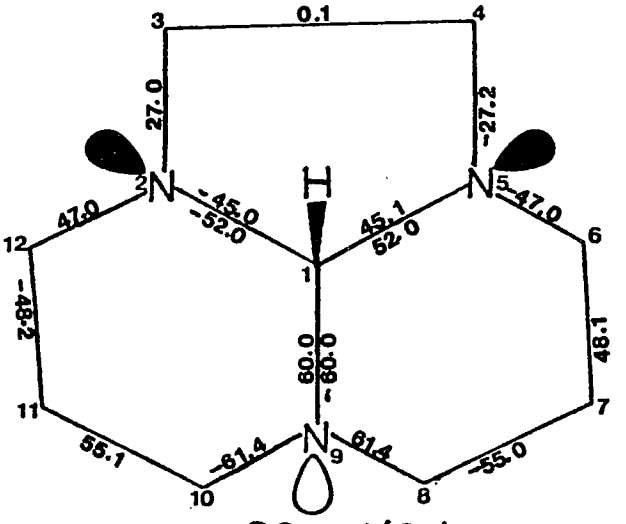


fig 2.405

As can be seen from the MM2 results in fig.2.41 the three lowest energy ground state conformations of H-332 are all within 1.5 kcal/mol of one another making the assignment of the minimum energy conformation on the basis of MM2 tenuous. Spectral data, in particular the solvent

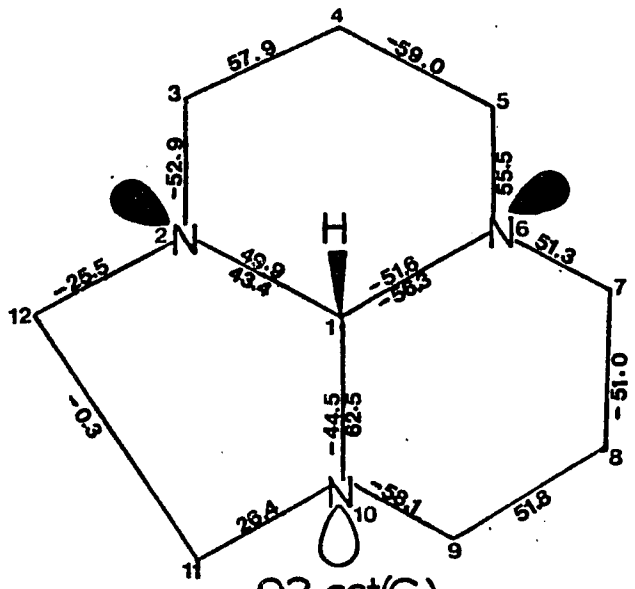


93-ttt
E=33.9



93-cct(Cs)
E=34.5

fig 241

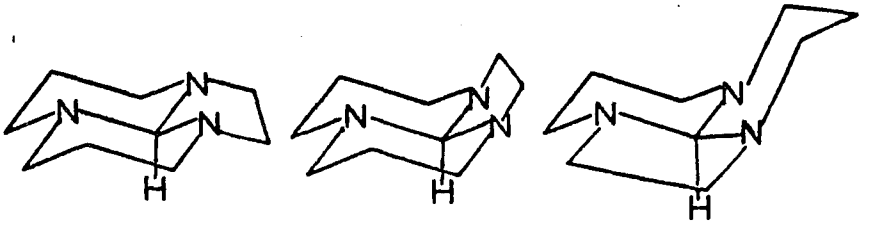


93-cct(C_1)
E=34.6
fig 2.41

dependency of the ^{1}H NMR spectra, indicated that MM2 was correct in assigning several conformations which are very close in energy. The solvent dependent ^{1}H NMR data is presented in fig.2.415. This data and the DNMR behavior of this compound indicate that H-332ttt dominates in $CDCl_3$ and that in acetone a mixture of conformations were present. The ^{13}C spectra of H-332 in $CDCL_3$ showed no dynamic line broadening down to -60°C but in acetone the spectra began to broaden at -66°C and continued to broaden down to -100°C. However the peaks never resharpened so it was impossible to discern which of the cis, cis, trans conformations (or indeed if both) were present in addition to the all-trans in acetone. At first glance it may seem surprising that the more polar H-332ttt is favored in the solvent of lower dielectric constant ($CDCl_3$; 2.56 D) while in the more polar solvent (acetone; 2.80D) the presence of the less polar conformations are evidenced. This point might seem to mitigate against the assignment of the all-trans conformation in chloroform. However, others have commented in the literature on the unusual solvent properties of chloroform[112,162,163]. In particular, Lemieux[163] has reported that chloroform seems to favor conformations disfavored by the anomeric effect (as in this case) and Eliel[112] has pointed out the well known ability of chloroform to dissolve very polar compounds. These two observations indicate that one should not interpret the solvent properties of chloroform simply on the basis of its

dielectric constant. Certainly the results presented here are another example supporting this contention.

Examination of the MM2 minimized geometries for the three ground state conformations (that we considered) shows that the five membered rings in all three conformations adopt envelope conformations (fig. 2.41). The two six membered rings in H-332ttt adopt distorted chairs. The six membered rings in H-332cct(C_s) and H-332cct(C_1) adopt distorted flattened chairs. As was the case for H-322 there are many more possible conformations of H-332 but these were not calculated because they seemed to us to be higher energy conformations.



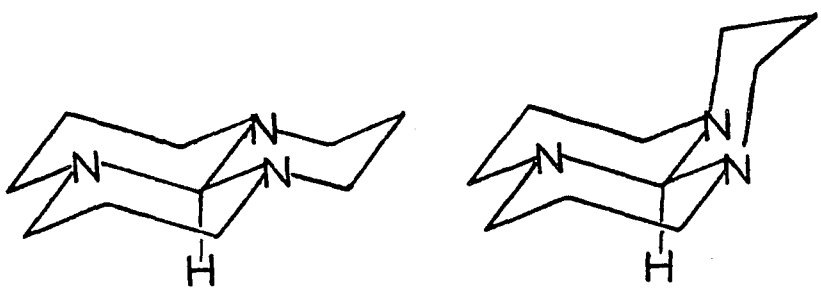
D=2.165 D=1.294 D=1.248

Solvent	δ_H(methine)	$^1J_{CH}$(methine)
$CDCl_3$	2.56	141.0
Acetone$_{d6}$	2.80	147.1

fig 2.415

Conformational Analysis of H-333 (94). The MM2 calculations allow assignment of the minimum energy conformation to the all-trans C_{3V} conformation shown in fig. 2.42. This assignment is also strongly supported by

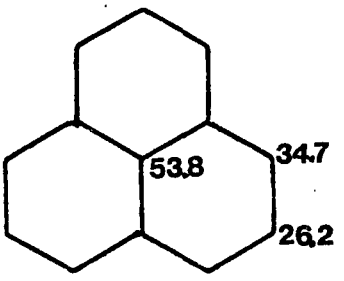
spectral evidence. The IR exhibits strong Bohlmann bands in the 2700-2800 cm^{-1} region characteristic of C-H bonds which are antiperiplanar to nitrogen lone pairs. These absorbances were assigned to C-H bonds in the rings which are antiperiplanar to a single nitrogen lone pair. There are also Bohlmann bands at 2400 cm^{-1} which we have assigned to the central C-H bond. ^{13}C empirical shift correlations employing model compounds 2.43-a[164] and 2.43-b[165] (fig.2.43) also support the assigned structure[167]. In addition to the evidence presented above the complete lack of dynamic line broadening in the ^{13}C NMR spectra of H-333 down to -100°C supports the assigned structure over the alternative H-333cct (fig.2.42) (see conformational analysis of Et-333). The chemical shift of the methine proton and the $^{1}J_{CH}$ coupling constant for the methine carbon also support the assigned structure.



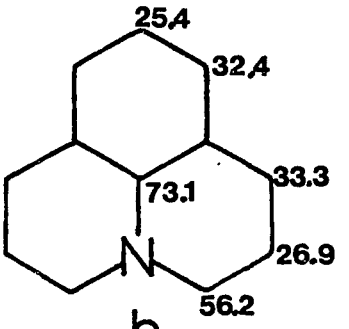
94-ttt 94-cct

fig 2.42

Examination of the torsion angle diagram of the minimized geometry of H-333ttt (fig. 2.42) indicate that this conformation has three nearly perfect chairs. The higher energy H-333cct (all chair) conformation has one

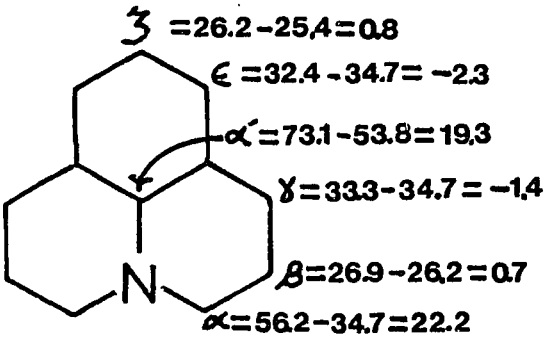


a

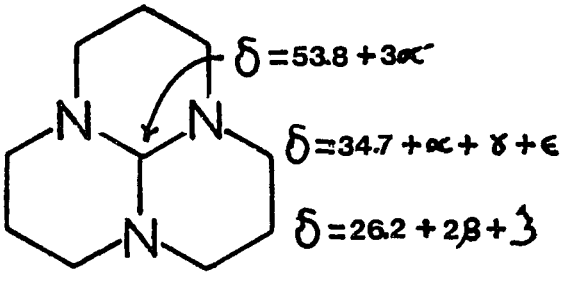


b

$\Delta\delta_{b-a}$ upon introduction of one Nitrogen



Calculated shifts for H-333



Agreement: actual(calcd.) shifts

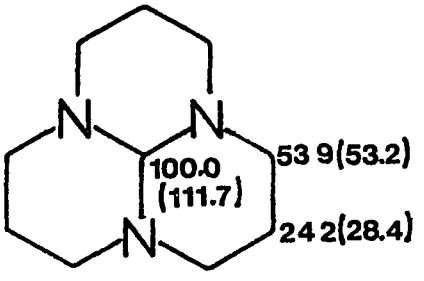
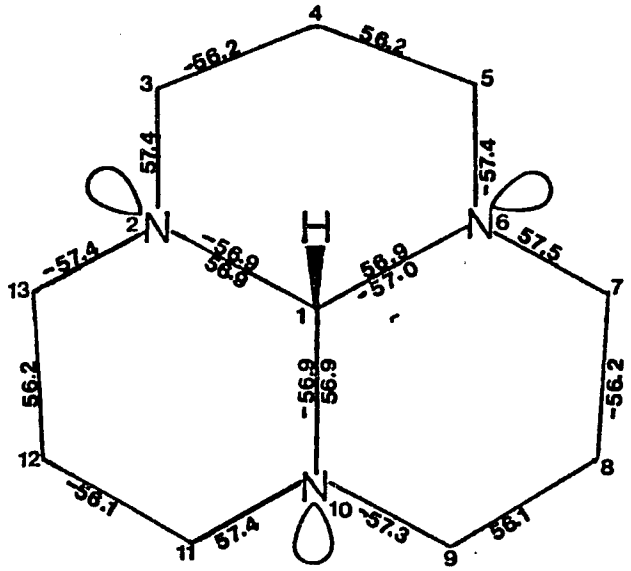
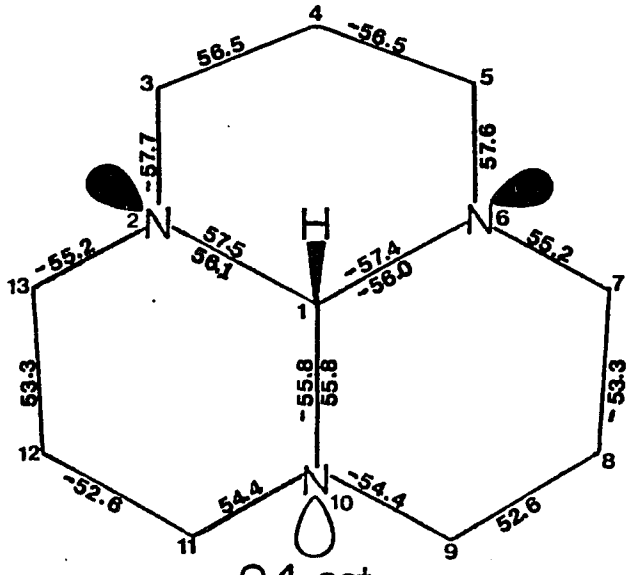


fig 2.43

nearly perfect chair and two slightly flattened chairs.



94-ttt
E=26.6



94-cct
E=28.8
fig. 2.44

Conformational Analysis of the Orthoacetamides

Introduction

The spectral data for the orthoacetamides is presented in table 2.2 and our assigned conformations in fig.2.46. Attention is called to the large range of chemical shifts of the methyl carbon resonances ($\Delta\delta$=31.7ppm, ambient T). The range of shifts is attributable to a combination of steric

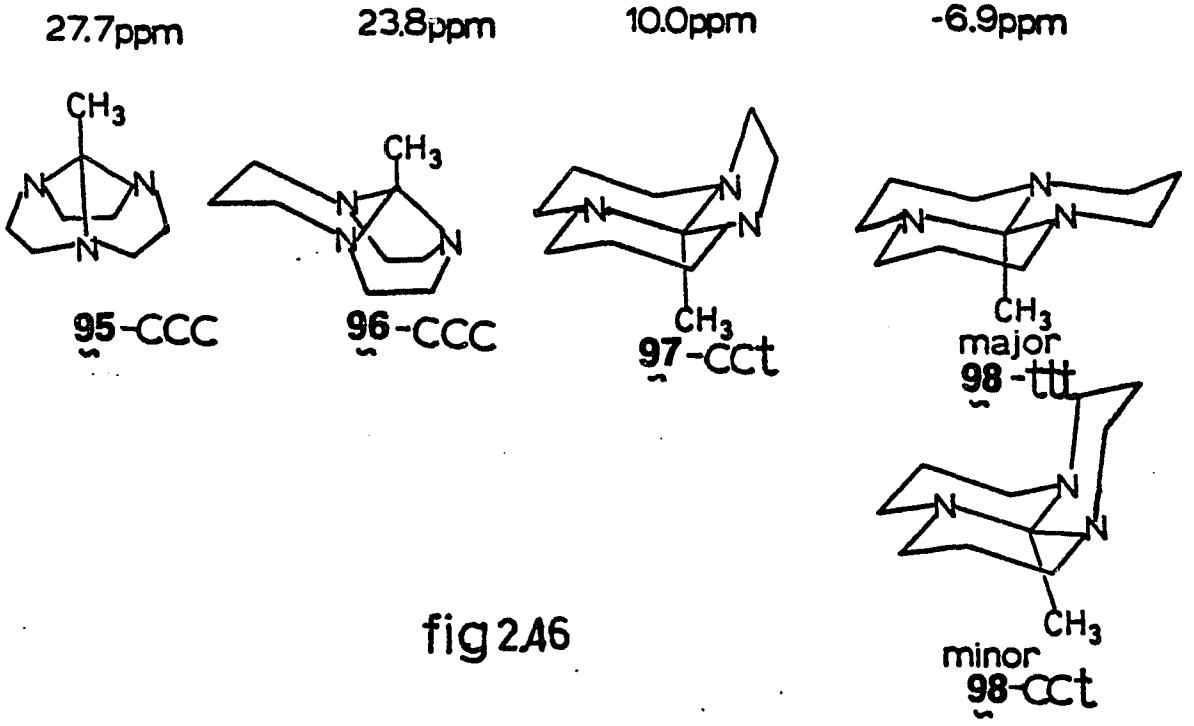


fig 2.46

Table 2.2

Compound	$N-\underline{C}(CH_3)-N$	$\underline{CH_2}$-N	$CH_2-\underline{CH_2}-CH_2$	C-$\underline{CH_3}$
95	111.4	51.8	---	27.7
96	94.7	54.9, 51.9 44.6	13.1	23.8
97	86.9	49.4, 45.6 43.7	20.1	10.0
98[a]	86.0	49.0	24.6	-4.0
98[b]	85.9	48.7(br)	24.7(br)	-6.6(br)

a. T = 302°K; b. T = 206°K

Orthopropionamides: ^{13}C NMR (δ_c, $CDCl_3$).

compression and lone pair orientational effects. The δ_c(methyl) of Me-222 is in good agreement with the methyl chemical shift of its carbon analog[168] which has been reported to be 28.4 ppm. The δ C (methyl) of the hypothetical hydrocarbon analog of Me-333ttt is calculated to be +6.8ppm[167,169], however, so lone pair orientational effects or increased steric compression, due to the shorter C-N bonds, must be invoked to explain the additional upfield shift of the methyl resonance in Me-333. Several reports have documented that carbons which are antiperiplanar to a nitrogen lone pair in amines[170-172], aziridines[173], oxaziridines[174], and oximes[175] resonate upfield of carbons which are syn or gauche to nitrogen lone pairs. The origin of this effect is presumably the net stabilizing (hyperconjugative) overlap between the nitrogen lone pair orbital and the σ^* orbital of the adjacent C-C bond. The observed range of methyl shifts for the orthoacetamides support the assigned conformations.

Conformational Analysis of Me-222 (95). As was the case with H-222, molecular models indicate that the most reasonable conformation for Me-222 is the all-cis slightly twisted C_3 conformation shown in fig. 2.46. The absence of Bohlmann bands in the IR of 95 indicates that this compound is in fact the all-cis conformation. The cis,trans,trans (95ctt, fig.2.47, the only other reasonably

possible conformation, albeit exceedingly unlikely) should exhibit Bohlmann bands.

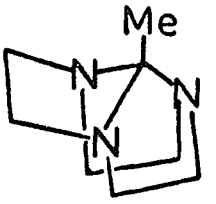
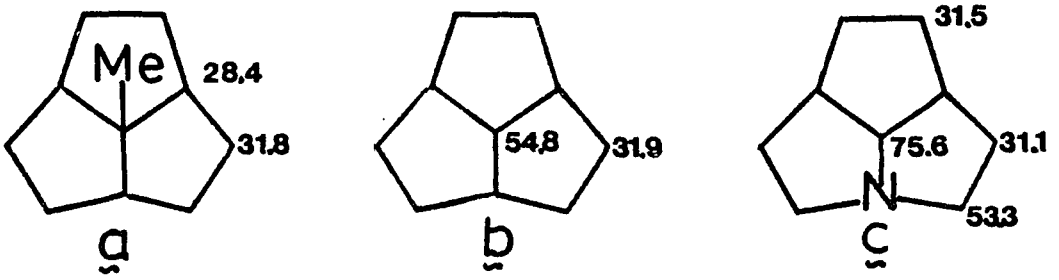


fig 2.47

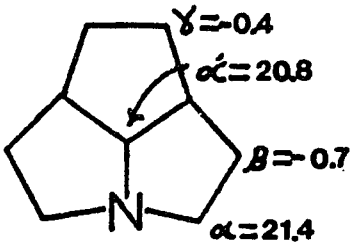
Empirical ^{13}C chemical shift correlations employing suitable tricyclic model compounds, 2.49-a[168], 2.49-b[158], 2.49-c[159] of known conformation provide additional support for the assigned structure (fig.2.49). The ^{1}H NMR of Me-222 and H-222 have AA'BB' patterns which are almost identical providing some support for the hypothesis that these two compounds possess the same conformation.

The minimized geometry calculated for Me-222 is shown in fig. 2.48. Examination of the torsion angles indicate that this compound adopts the slightly twisted C_3 conformation as was the case with the parent H-222 and the hydrocarbon analog. The torsion angles also indicate that the three five membered rings each adopt half chair conformations with angles very similar to those which were calculated for the parent. As was the case with the parent, it is assumed that this compound undergoes a low energy conformational process which interconverts two enantiomeric C_3 conformers resulting in apparent C_{3V} symmetry (see

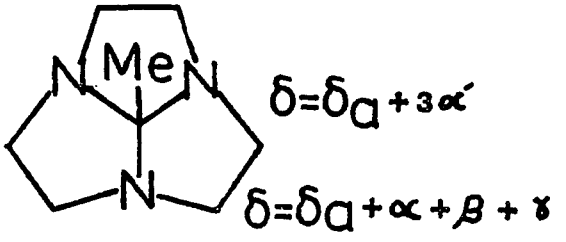
conformational analysis of H-222).



$\Delta\delta_{c-b}$ upon introduction of one N (see H-222)



calculated shifts for Me-222 ($\delta=\delta_a+\Delta\delta_{c-b}$)



Agreement: actual(calcd.) shifts

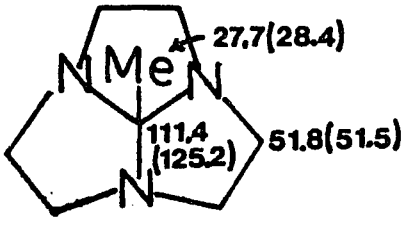
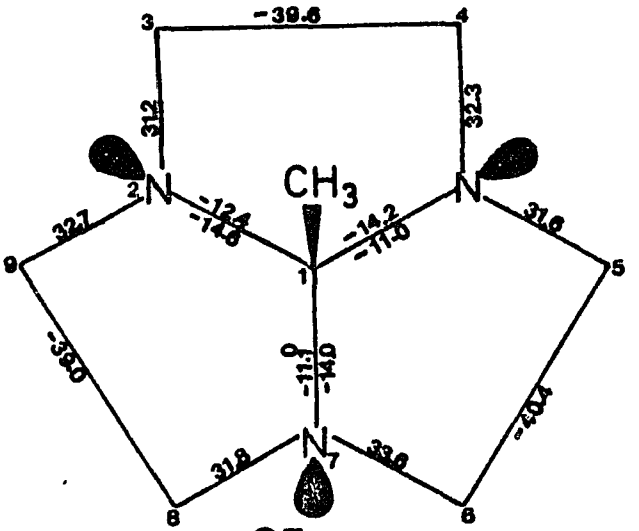
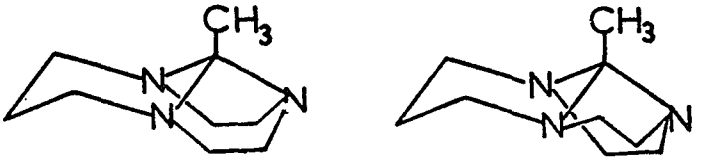


fig 249



95-ccc
E=42.3
fig 2.48

Conformational Analysis of Me-322(96). Models indicate that the all-cis conformation (96cct) and the cis, cis, trans conformation (96cct) sould be the lowest energy ground states for this compound. MM2 calculations were performed on these two conformations only because models indicated that the other possible conformations should be too high in energy to be significantly populated (see conformational analysis of H-322). MM2 calculations found 96ccc to be 3 kcal/mol lower in energy than 96cct (fig.2.50). The spectral data is consistent with the assignment of 96ccc



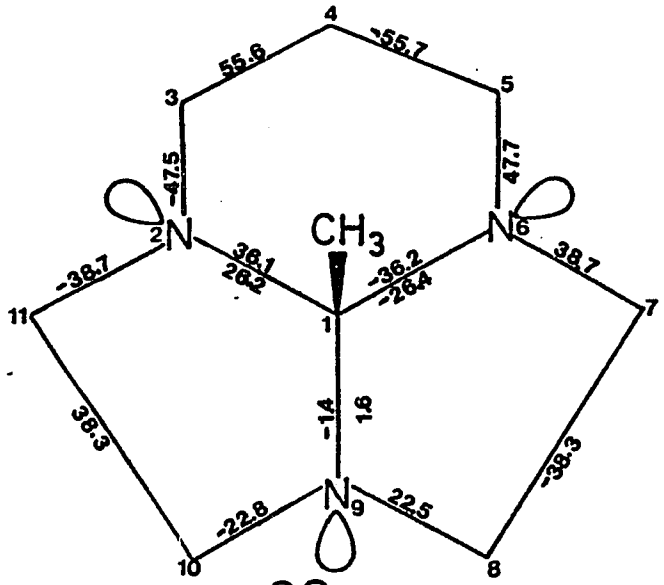
96ccc
E=43.2

96cct
E=46.2

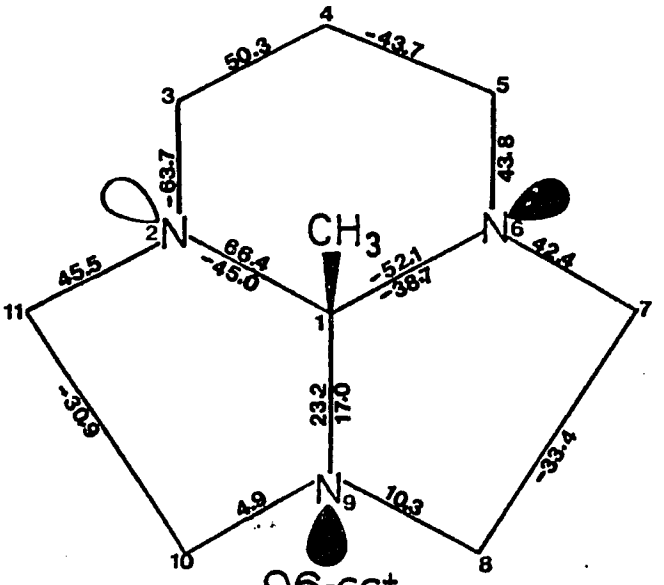
fig.2 50

as the major conformation. In particular, the ^{13}C shifts, especially the upfield resonance of C-4 (13.1 ppm) points toward sterically compressed 96ccc over 96cct. The similarity of the ^{1}H spectra of H-322 and Me-322 also suggested that Me-322 exists predominantly in the all-cis conformation as did the parent orthoformamide. Examination of the torsion angle diagrams of the minimized geometries of 96ccc and 96cct (fig.2.505) indicate that the two five membered rings in 96ccc are distorted envelopes and that the six membered ring is a flattened chair. In 96cct one of the five membered rings adopts a distorted envelope, the other is a distorted half chair, and the six membered ring is a severely distorted chair. 96cct is particularly strained about the trans ring juncture.

Conformational Analysis of Me-332 (97). MM2 assigned two ground state conformations for Me-332 within 2 kcal/mol of one another. These are the two cis,cis,trans conformations 97cct(C_s) and 97cct(C_1) which are shown in fig. 2.51. MM2 assigned 97cct(C_s) as the lowest energy conformation. The ^{13}C spectrum of Me-332 at room temperature contained six sharp resonances. These resonances showed no dynamic line broadening in either $CDCl_3$ (down to -65°C) or in acetone-d_6 (down to -100°C). The lack of broadening and the number of lines demands that the conformation possess a mirror plane which bisects the



96-ccc
E=43.2



96-cct
E=46.2
fig2.505

ethylene bridge of the five membered ring and contains the quaternary carbon, methyl carbon, and the bridgehead nitrogen common to the six membered rings. These symmetry considerations are consistent only with 97cct(C_s) and 97ttt. Since 97ttt was calculated to be almost 5 kcal/mol higher in energy we conclude that the Me-332 global minimum is 97cct(C_s).

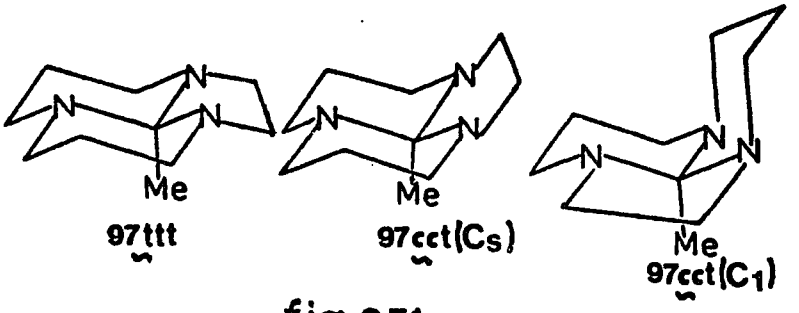
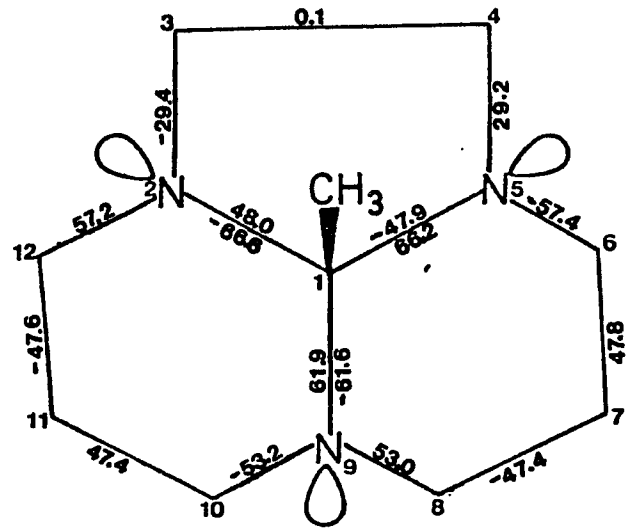
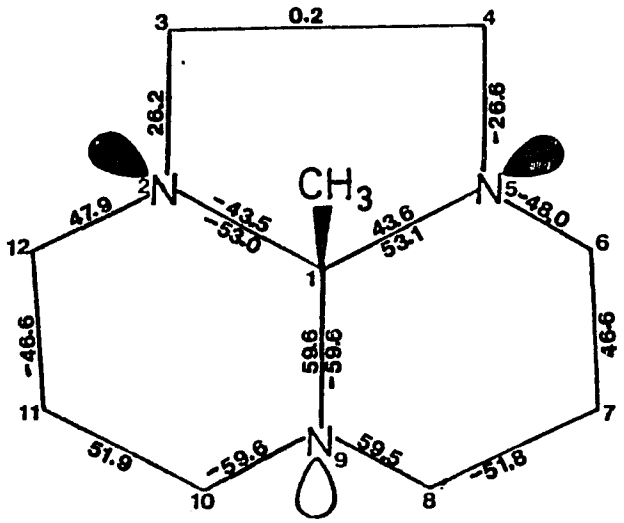


fig 2.51

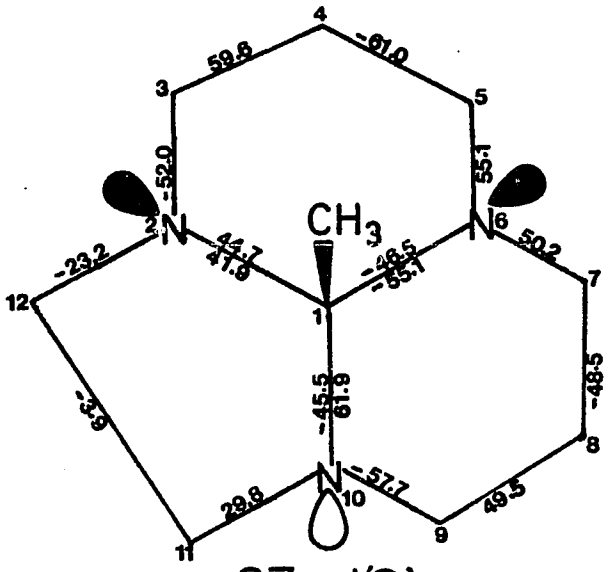
The torsion angle diagrams of the minimized geometries of the three ground state conformations discussed above are shown in fig. 2.515 along with their calculated energies. Energies of the other possible conformations of Me-332 were not calculated because these conformations were considered to be of higher energy. Examination of the torsion angle diagrams of the conformations shown in fig. 2.515 reveals that the five membered rings in all three adopt envelope conformations. The six membered rings in all three are flattened chairs.



97-ttt
E=44.3



97-cct(Cs)
E=39.5
fig 2.515



97-cct(C_1)
E=41.7
fig 2.515

Conformational Analysis of Me-333 (98). MM2 calculated that the all-trans conformation 98ttt was 0.2 kcal/mol lower in energy than the cis,cis,trans conformation (98cct, fig.2.52). Calculations were also performed on the

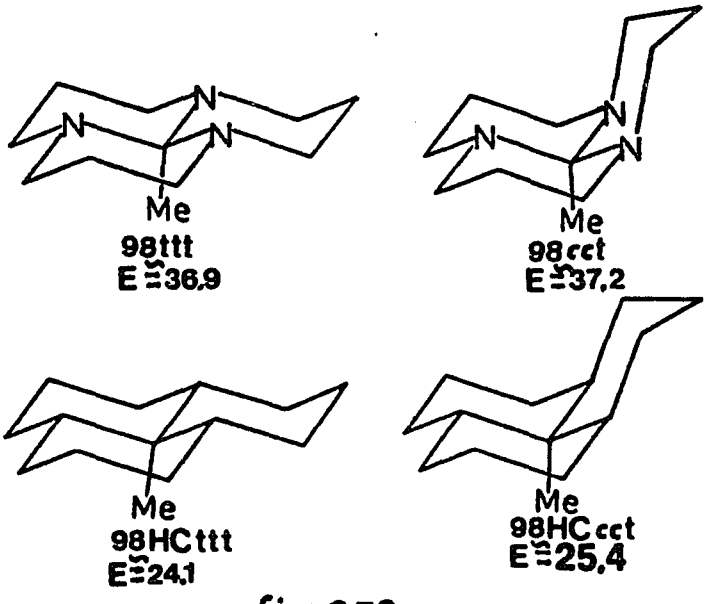


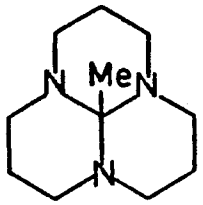
fig 252

hypothetical hydrocarbon analogs 98HCttt and 98HCcct (fig.2.52). According to our calculations 98HCttt is approximately 1.2 kcal/mol lower in energy than 98HCcct. A recent report[176] calculated the energy difference between the hydrocarbons to be 15 kcal/mol, a value which we consider to be in error. But since the calculated energies in the orthoacetamide case are not greatly different it is imprudent to rely too heavily upon these numbers when assigning conformation. Fortunately the spectral data allows unambiguous determination of the major conformation of this compound. The remarkably high field (-4.0 ppm)

methyl resonance of Me-333 indicates the predominance of sterically compressed (C_{3V}) 98ttt in which the methyl resonance is gauche to six methylene carbons and antiperiplanar to all three nitrogen lone pairs (see introduction for a discussion of the lone pair effect).

The dynamic ^{13}C NMR behavior of Me-333 in $CDCl_3$ (see spectra:fig.2.53-2.56) is also consistent with the predominance of 98ttt over 98cct. At temperatures below ambient, as exchange was slowed, the methyl signal (as well as the other resonances) broadened and then began to resharpen at lower temperatures, the methyl shift changing from -4.0 ppm to -6.9 ppm during the process. This latter value represents the methyl chemical shift of 98ttt. No peaks attributable to 98cct were observed at the lowest attainable temperatures (in $CDCl_3$). However, the slow exchange limit had not been achieved so peaks due to the minor conformation may still have been broadened into the baseline. Chemical shift interpolation based on an estimated chemical shift of 12.4 ppm for 98cct yields 14% of the minor conformation at 302 K[106]. Since ΔS_n (98cct-98ttt), the trivial entropy difference due to the symmetry number differences, is 2.18 cal/mol-deg, it is expected that 98cct should amount to only 4% of the equilibrium mixture at 206 K in $CDCl_3$. The preceeding analysis has been published in communication form[106].

fig 2.53-s



Temp= 25°c
see Appendix 2 for δ values

fig 2.54-s

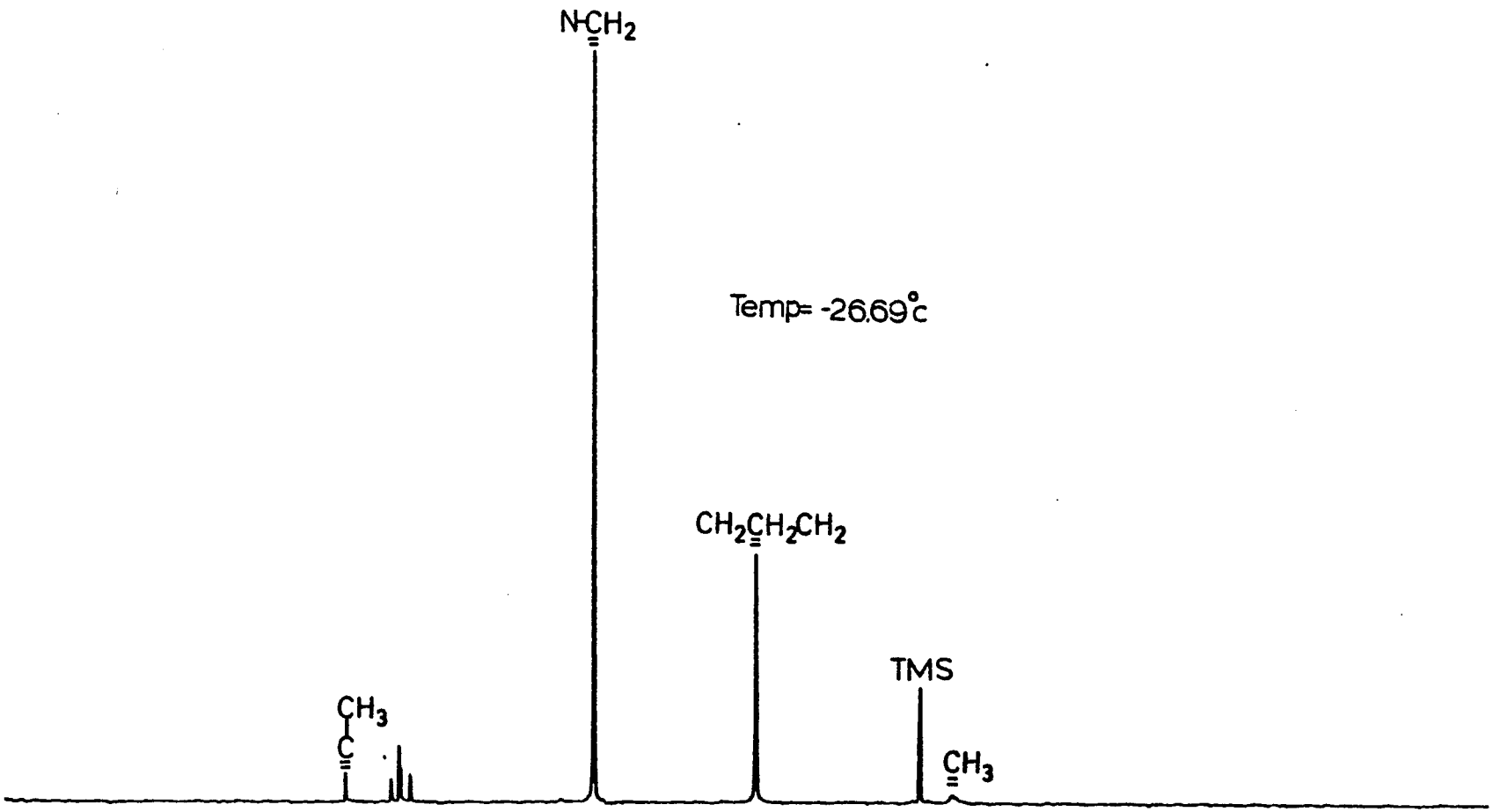


fig 2.55-s

Temp=-44.82°C

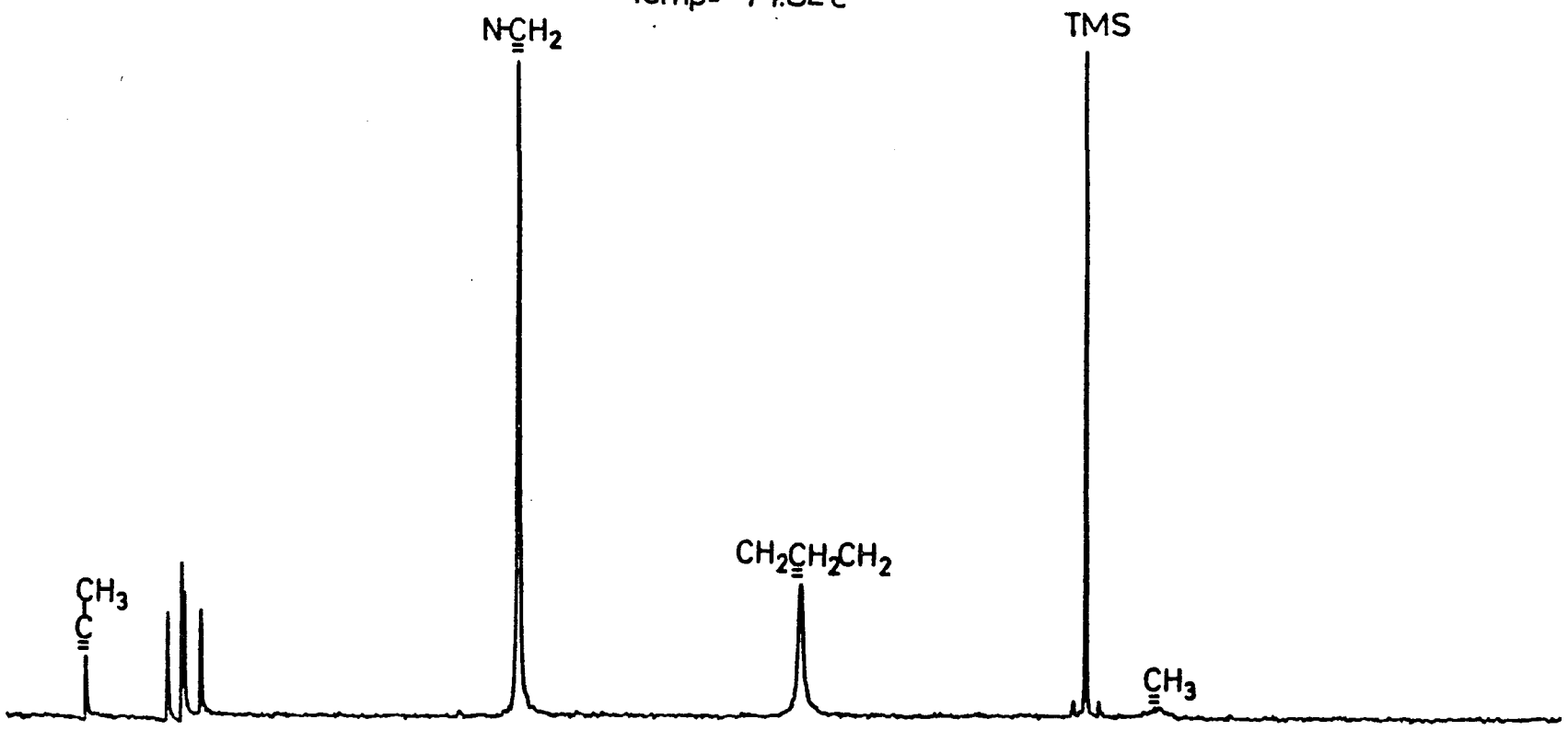
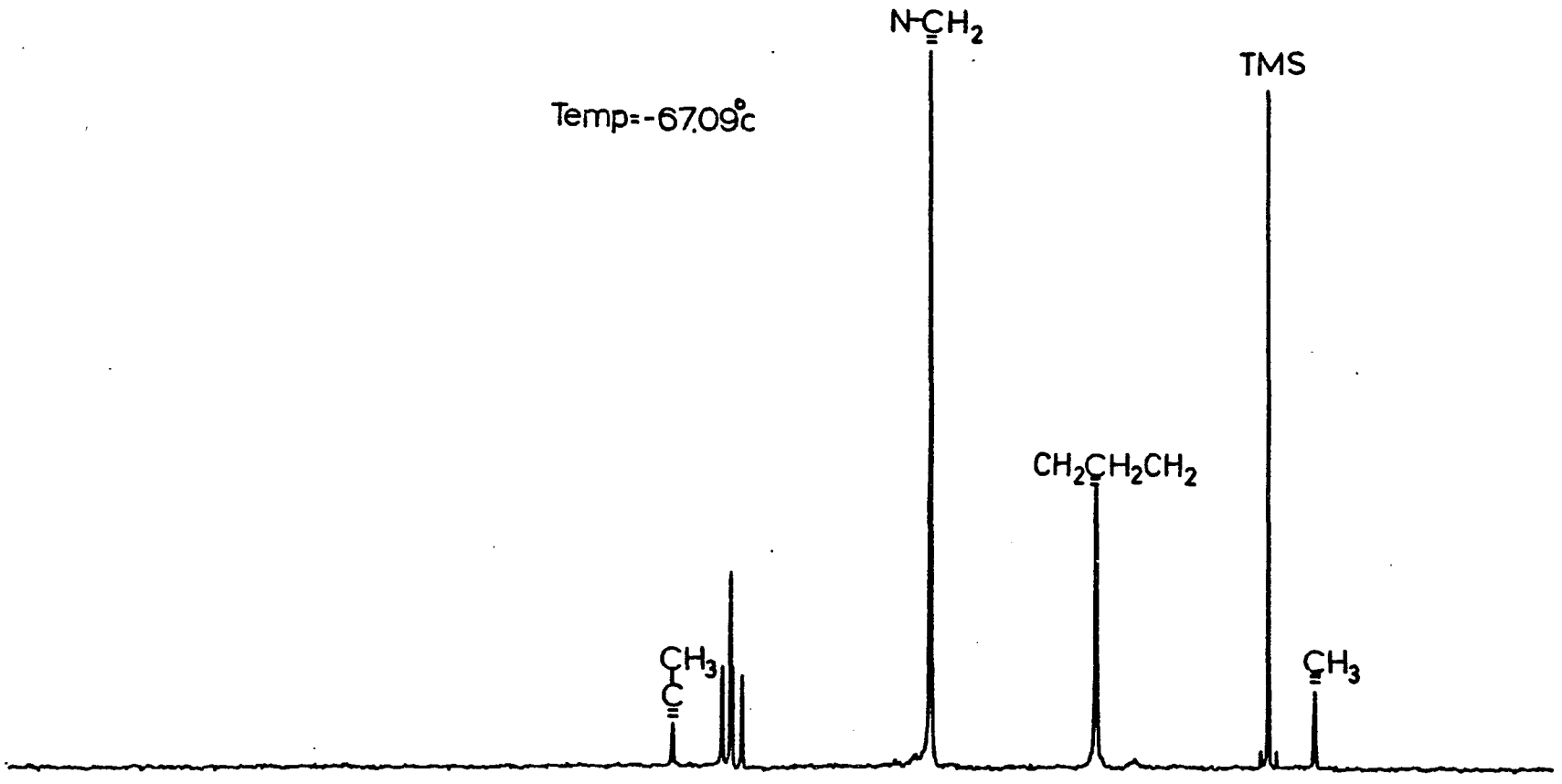


fig 2.56-s



The same low temperature experiment was also performed in acetone-d_6 . The same phenomenon was also observed but the chemical shift of the methyl resonance of 98ttt at low temperature was -6.2 ppm and a broad resonance was observed at 12.4 ppm. This latter peak was assigned to the methyl carbon resonance of 98cct because of its chemical shift value. Application of Eliel's[177] chemical shift interpolation method yields a value of 33% of 98cct at 302K. It is expected that 98cct should account for approximately 12% of the mixture at 173 K (assuming ΔS° is equal to the trivial entropy due to the symmetry number). Comparison of the heights of the methyl resonances of the two conformations at 173 K yields a value of approximately 4% of 98cct. The fact that the methyl resonance of 98cct was still very broad at this temperature makes this latter estimate questionable.

The experimentally determined ΔH of 1.1(acetone) and 1.8($CDCl_3$) kcal/mol are significantly different than the 0.2 kcal/mol difference obtained from MM2 calculations. This discrepency points out again the unreliability of the energies as calculated by MM2 for polar compounds.

The ^{13}C spectrum of Me-333 exhibits solvent dependency. The solvent dependency of the methyl resonance is of particular interest since it is an indicator of the relative amounts of 98ttt and 98cct present in the

equilibrium mixture. The relevant data on this point are shown in table 2.3.

Table 2.3

SOLVENT	DIELECTRIC CONSTANT	E_T	δ_c(methyl) at Amb. Probe T
n-hexane	1.88	30.9	-1.63
$CDCl_3$	4.73	39.1	-4.01
$Acetone_{d6}$	20.7	42.2	0.00
CD_3CN	38.8	46.0	-1.35

It had been expected that an increase in the dominance of 98ttt (which has the higher dipole moment) would be observed as the solvent polarity was increased. Clearly the position of the 98cct-98ttt equilibrium is solvent dependent but the dependence does not seem to correlate with the dielectric constant of the solvent or the E_T [178]. The increased dominance of 98ttt in $CDCl_3$ was not surprising since several workers in this field have commented on the ability of chloroform to favor conformations disfavored by the anomeric effect. The result that seems most surprising is that the methyl chemical shift has a more negative value in n-hexane than in the much more polar acetonitrile. This result may be due to aggregation of the polar solute in the very non-polar medium or some other form of specific solvation. A recently reported study suggests that the anomeric effect "disappears with increasing solvent polarity" due to solute-solvent interactions in $(CH_3\text{-}O)_2CH_2$[179]. Our results are not consistent with

this interpretation. It must be concluded that the position of the equilibrium may correlate with solvent polarity but because of special effects in some of the solvents utilized in this study this correlation was not definitively established.

The dynamics of Me-333 were also examined as a function of solvent. The temperature at which the maximum broadening of the methyl resonance occured was determined in $CDCl_3$ and in acetone-d_6. The results of this experiment are shown in table2.4.

Table 2.4

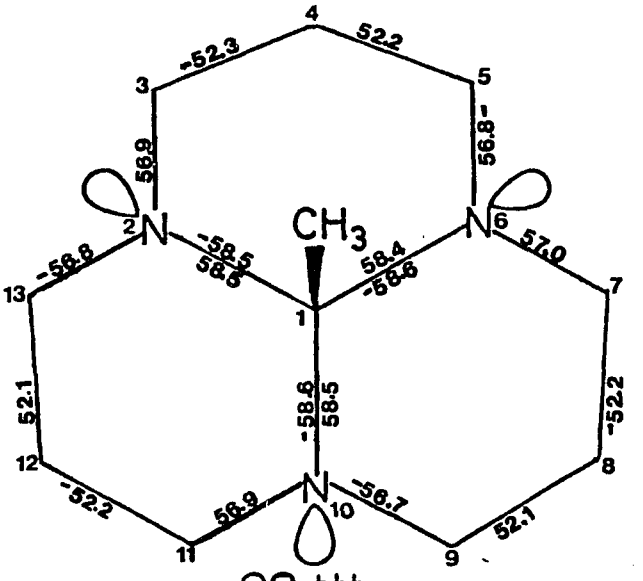
SOLVENT	E_T	T. of max. broadening	δ_c	$\nu_{\frac{1}{2}}$ max	$\Delta\nu$	k^{180}
$CDCl_3$	39.1	$-44.8 \pm 3^{\circ}C$	-6.27	47.7 Hz	420.0Hz	2643 sec^{-1}
Acetone$_{d6}$	42.2	$-40.0 \pm 3^{\circ}C$	-5.40	55.7 Hz	401.0Hz	2520 sec^{-1}

It will be noted that the rates of this process in the two solvents are not significantly different. This result indicates that the transition states leading to the intermediates for the interconversion of 98cct-98ttt do not have ionic character. It is well known that reactions with ionic transition states preceeding ionic intermediates have rates which are directly proportional to the ionizing power of the solvent. Winstein[178] has reported a 500 fold increase in the rates of solvolysis of p-methoxyneophyl toluenesulfonate on going from $CHCl_3$ to acetone. Since

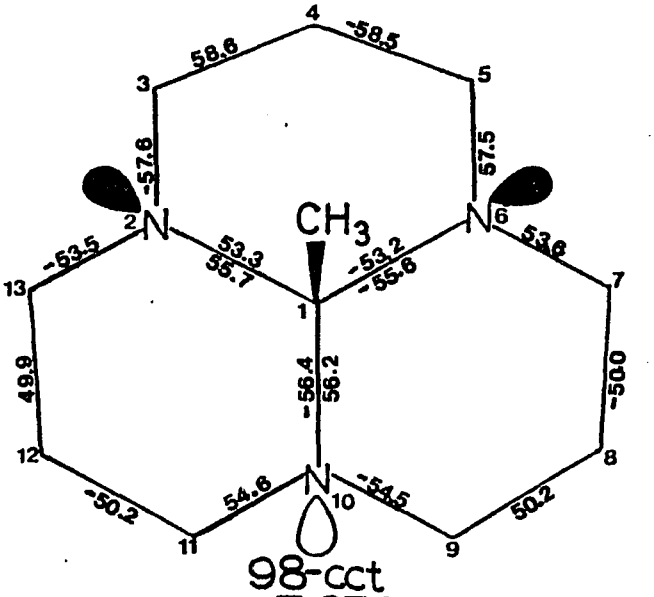
our observed rate is essentially unaffected by the solvent change it must be concluded that the transition states leading to intermediates involved in this process do not have ionic character. Therefore the interconversion of 98ttt and 98cct is a conformational process.

The torsion angle diagrams of 98ttt, 98cct, 98HCttt, and 98HCcct are shown in fig. 2.53 along with their calculated energies. Inspection of the torsion angles for 98HCttt reveals that this hypothetical hydrocarbon would consist of three nearly perfect chairs. On the other hand the torsion angles of 98ttt indicate three slightly flattened chairs. The distortions of the orthoacetamide relative to the hydrocarbon are due to the shorter C-N bonds. The same analysis applies to 98cct relative to 98HCcct.

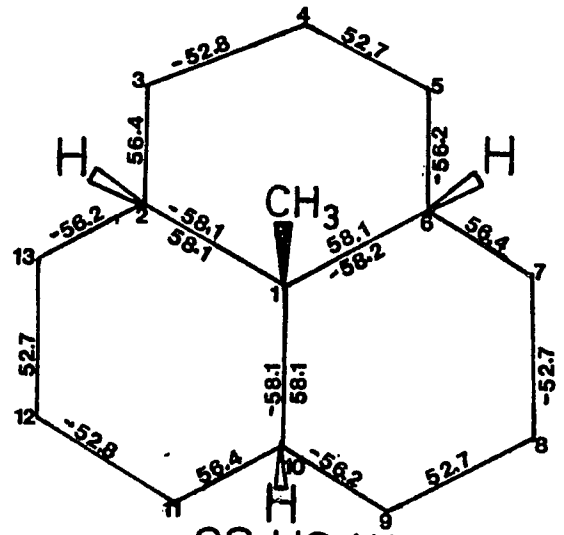
A comparison of the torsion angles of 98cct relative to 98ttt reveals that there is a greater degree of flattening of the chairs in 98cct. The increased flattening in 98cct is probably a major factor in the energy difference between these two conformations.



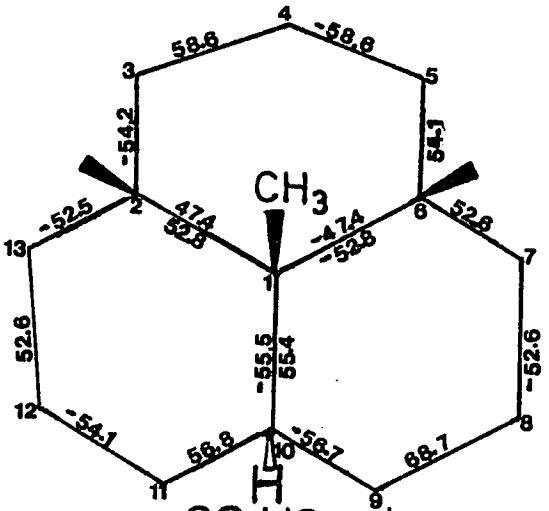
98-ttt
E=36.9



98-cct
E=37.2
fig2.53



98-HC-ttt
E=24.1



98-HC-cct
E=25.4

fig 253

Conformational Analysis of the Orthopropionamides

Introduction

The spectral data for the orthopropionamides is presented in table 2.5 and the assigned conformations in fig. 2.54. The actual spectra of these compounds are contained in Appendix 1.

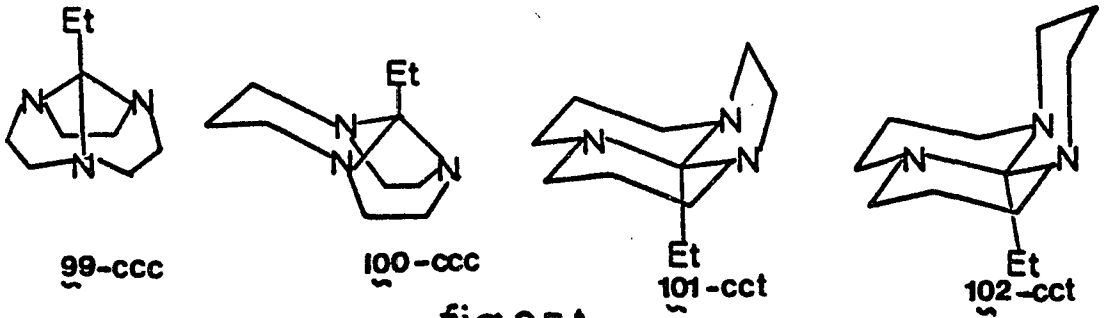


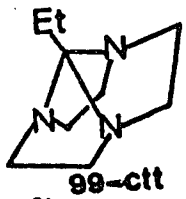
fig 2.54

Table 2.5

Compound	N-C-N (CH2)	CH2-N	CH2-CH2-CH2	CH2-CH3	CH2CH3
99	113.8	51.9	--------	33.6	9.6
100	97.0	55.8, 52.1 44.7	12.5	28.2	9.8
101	88.8	48.9, 45.6 43.3	19.8	11.4	7.4
102[a]	87.1	49.1	22.3	13.0	7.9
102[b]	86.5	51.0, 48.4 46.5	26.3, 19.6	12.9	8.2

a. T = 302°K (acetone-d_6); b. T = 193°K(acetone-d_6)

Conformational Analysis of Et-222 (99). As was the case with the two lower homologs of the 222 ring system, models indicate that the only reasonable conformation is the all-cis slightly twisted local C_3 (ring system) conformation shown in fig.2.54. The absence of Bohlmann bands in the IR indicates that this compound is, in fact 99ccc, since 99ctt (fig.2.55, the other most reasonable conformation) should exhibit Bohlmann bands.

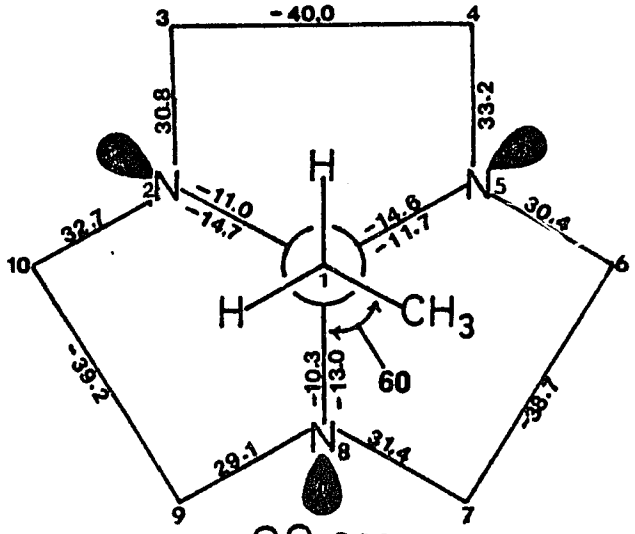


99-ctt
fig 2.55

This compound and the two lower homologs all have remarkably similar AA'BB' patterns in their ^{1}H NMR spectra suggesting that all three compounds exist in the same conformation.

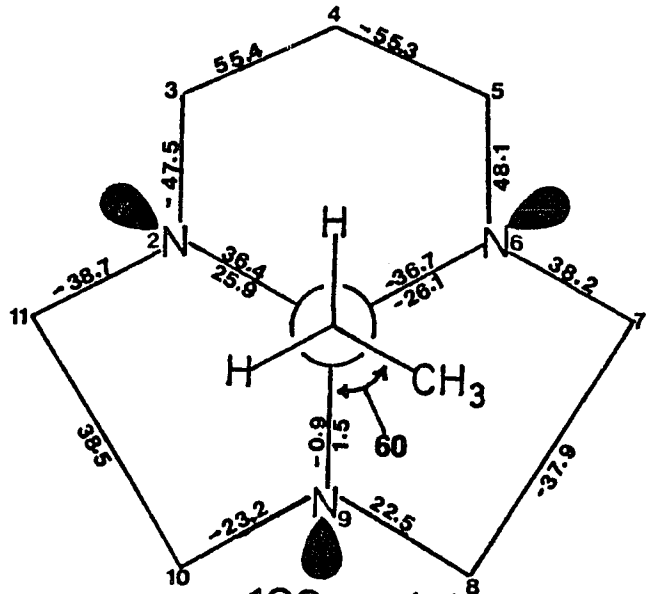
The minimized geometry of 99ccc is shown in fig. 2.56 along with its calculated energy. The torsion angle diagram indicates that Et-222 has the same slightly twisted (local) C_3 conformation as the two lower homologs. The torsion angles also indicate that the three five membered rings each adopt half chair conformations. This compound no doubt also undergoes the same low energy conformational process as the

two lower homologs and the hydrocarbon analog(see analyses of H-222 and Me-222) in addition to ethyl rotation.

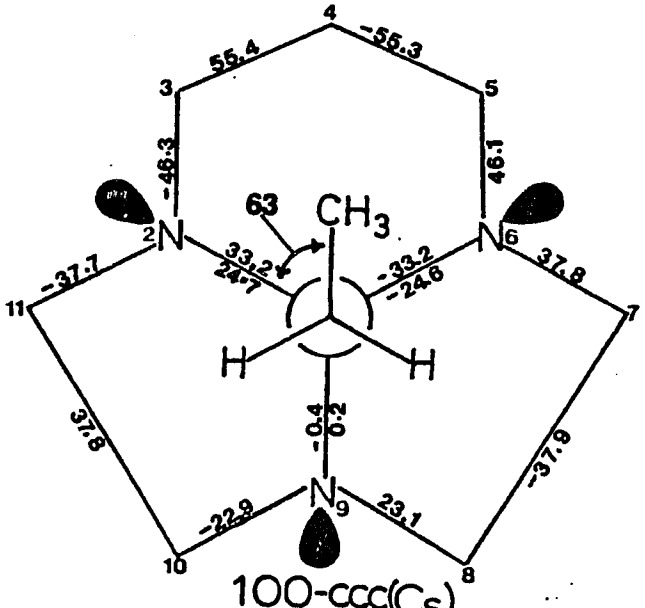


99-ccc
E=44.2
fig 2.56

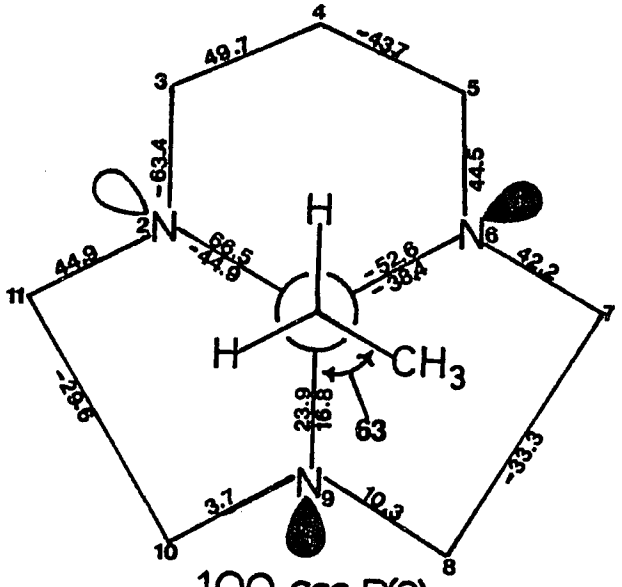
Conformational Analysis of Et-322 (100). MM2 calculations indicate that the lowest energy conformation of this compound are 100ccc rotomers (fig.2.54). The rotomers of the alternative cis,cis,trans ring conformation, 100cct-(R1-3), (fig.2.57) are between 3.2-9.0 kcal/mol higher in energy. The fact that the parent H-322 has been shown to adopt the all-cis conformation coupled with the fact that the large ethyl group would tend to further favor the all-cis ring conformation (where the steric interactions between the large ethyl group and the rings are minimized) would seem to support the assignment. The upfield resonance of C-4 (12.5 ppm, see fig.2.58 for numbering scheme)



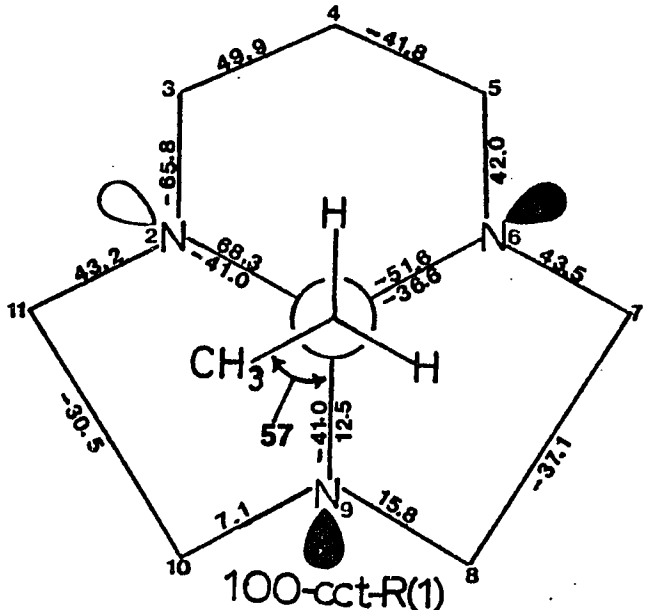
100-ccc(C_1)
E=44.9



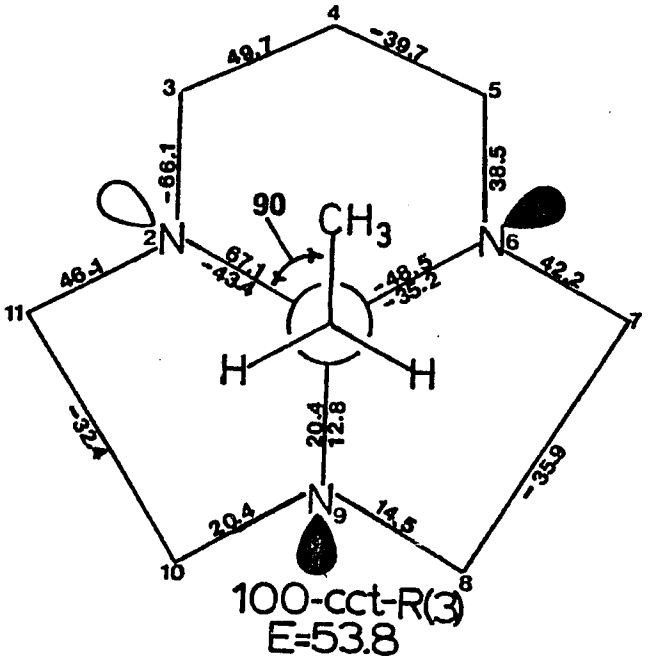
100-ccc(C_s)
E=48.1
fig 2.58



100-ccc-R(2)
E=48.1
fig 2.58



100-cct-R(1)
E=51.3
fig 2.58



100-cct-R(3)
E=53.8

supports the assignment of the sterically compressed all-cis conformation as opposed to the cis,cis,trans. Although no low temperature NMR was performed on this compound it is doubtful that any conformational changes in the five membered rings would be observable at accessible temperatures. Consequently the assignment of the all-cis conformation can only be considered tentative.

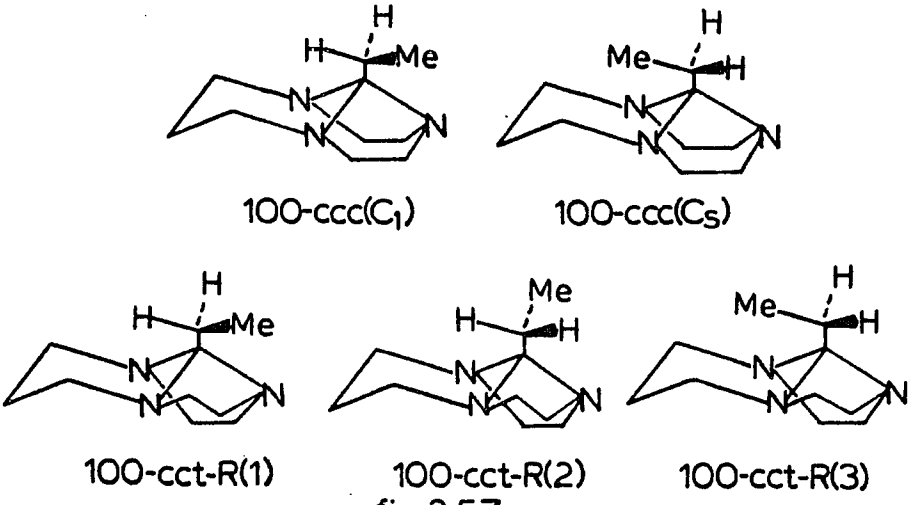


fig 2.57

EFF calculations have been performed on several of the possible ground state conformations of Et-322. We have not calculated all the possible conformations (see H-322 analysis) because we considered the remaining conformations to be higher in energy. The minimized geometries of the conformations which we calculated are presented in fig.2.58 along with their energies. The torsion angle diagrams for the two rotomeric all-cis conformations indicate that the

two five membered rings each adopt distorted half chairs and that the six membered ring adopts a flattened chair. The six membered ring in 100ccc(C_s) shows more severe flattening than the six membered ring in 100ccc(C_1) due to the position of the ethyl group in 100ccc(C_s). Examination of the torsion angle diagrams for the cis,cis,trans conformations reveals the strain present in these conformations at the trans ring junctures. In 100cct(R3) the six membered ring is a flattened chair, one of the five membered rings is a distorted half chair, and the other five membered ring is intermediate between half chair and envelope conformations. In each 100cct-(R1) and 100cct-(R2) the six membered ring is a flattened chair, one of the five membered rings is a half chair, and the other five membered ring is a distorted envelope.

Conformational Analysis of Et-332 (101). MM2 calculations rule out the possibility of the dominance of the all-trans conformations of Et-332. The cis,cis,trans conformations and their calculated energies are presented in fig.2.59. The ambient temperature ^{13}C NMR spectrum of Et-332 contains seven sharp lines which show no evidence of dynamic line broadening in either $CDCl_3$ (down to -60°C) or in acetone-d_6 (down to -100°C). The number of lines and the lack of dynamic broadening rules out conformations 101cct-6(R1-3) on the basis of symmetry (see analysis of Me-332). Since the all-trans conformations (which also

satisfy the symmetry considerations) were calculated to be between 6-15 kcal/mol higher in energy it must be concluded that this compound exists as a mixture of 101ccc-5(R1) and 101cct-5(R2).

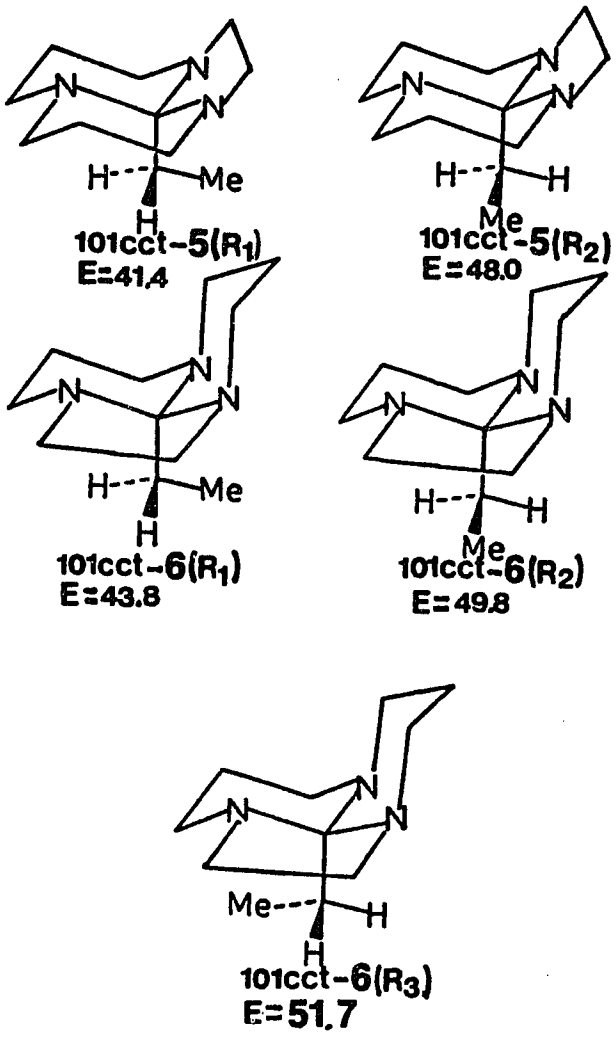


fig 2.59

The minimized geometries of the conformations which we calculated are shown in fig. 2.60 along with their energies. Conformations which we considered to be high in energy (e.g. all-cis) were not calculated. Examination of

satisfy the symmetry considerations) were calculated to be between 6-15 kcal/mol higher in energy it must be concluded that this compound exists as a mixture of 101ccc-5(R1) and 101cct-5(R2).

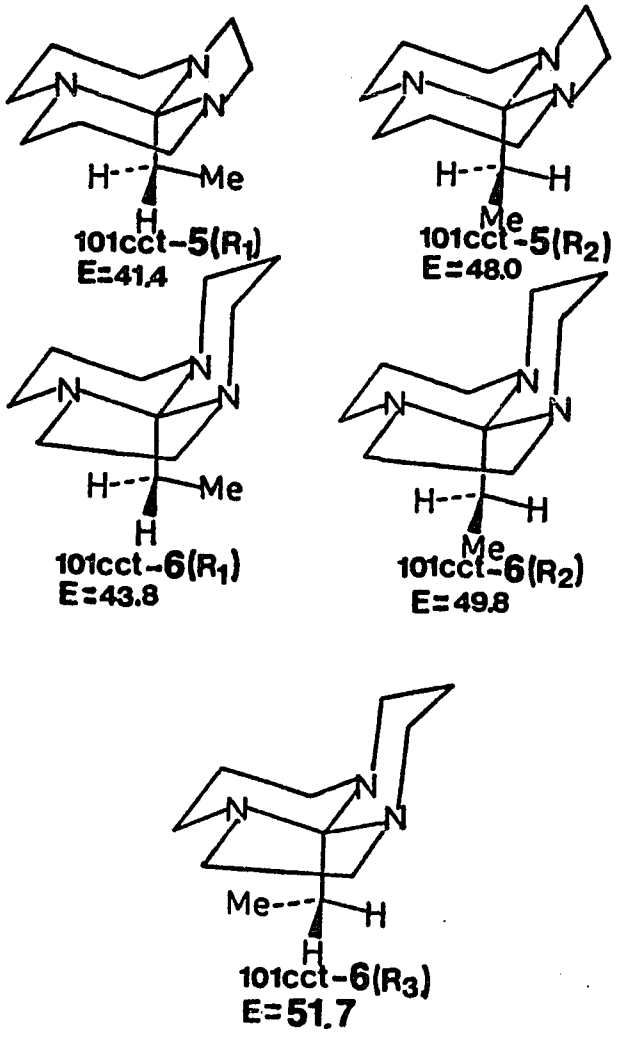
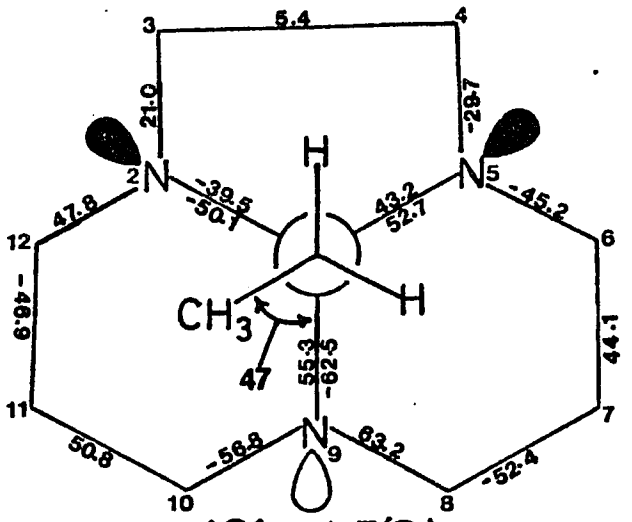
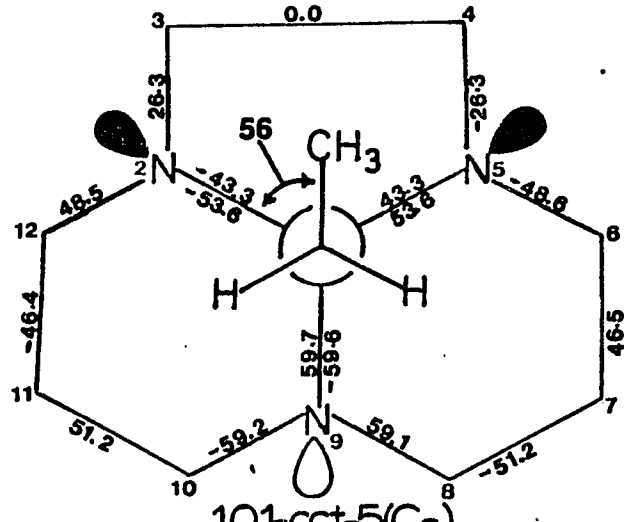


fig 2.59

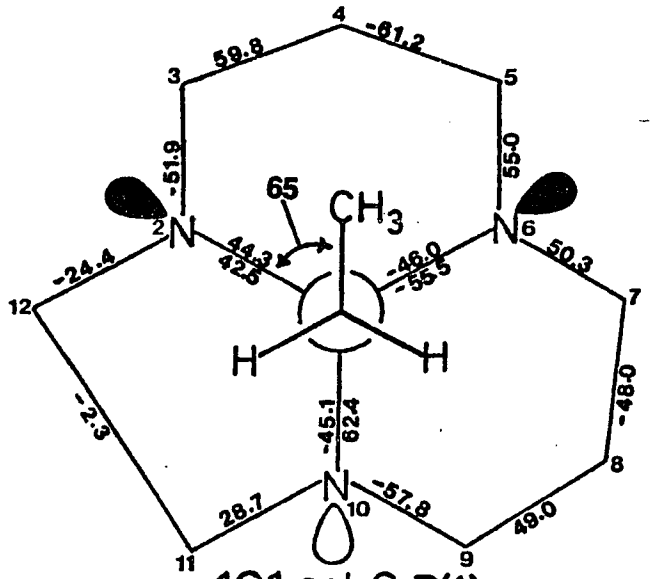
The minimized geometries of the conformations which we calculated are shown in fig. 2.60 along with their energies. Conformations which we considered to be high in energy (e.g. all-cis) were not calculated. Examination of



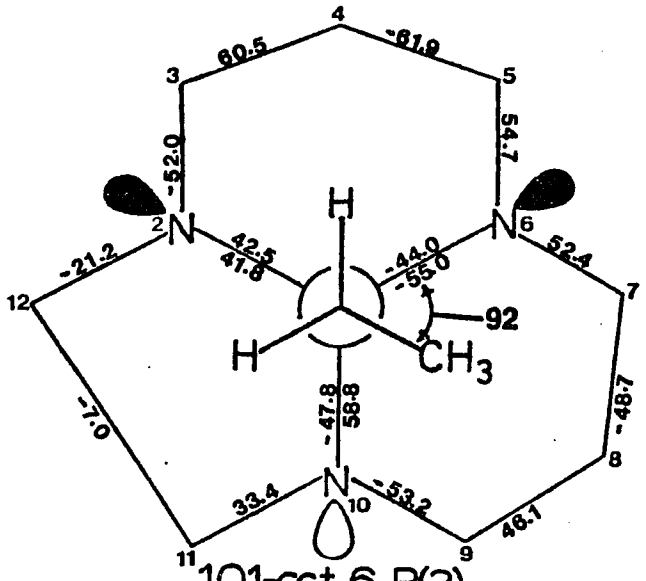
101-cct-5(C_1)
E=48.0



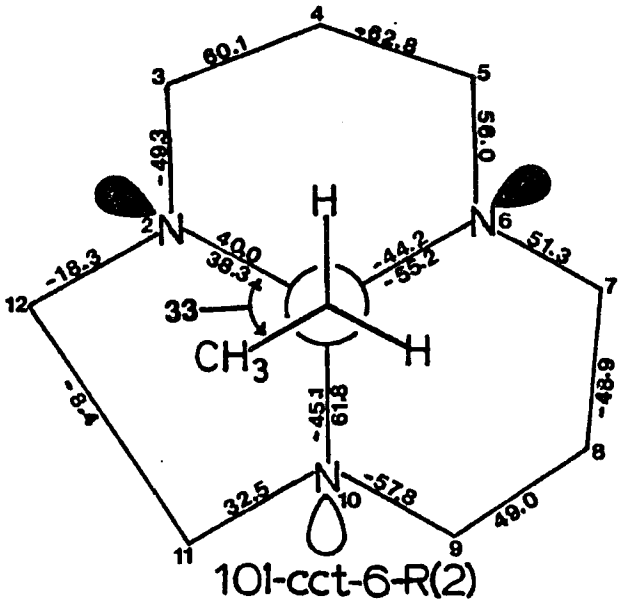
101-cct-5(C_s)
E=41.4
fig 2.60



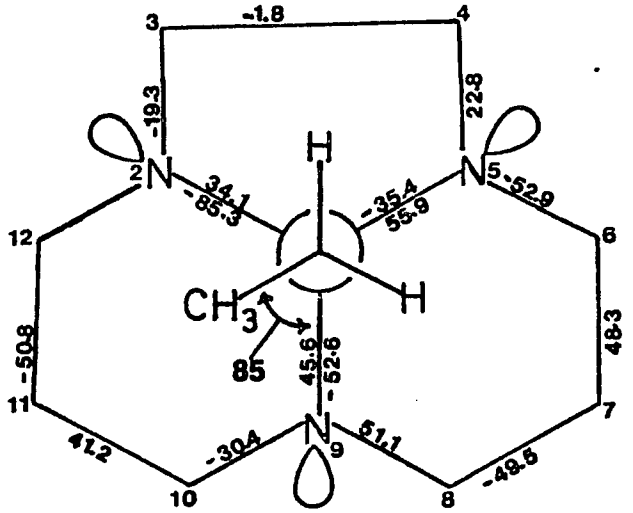
101-cct-6-R(1)
E=43.8



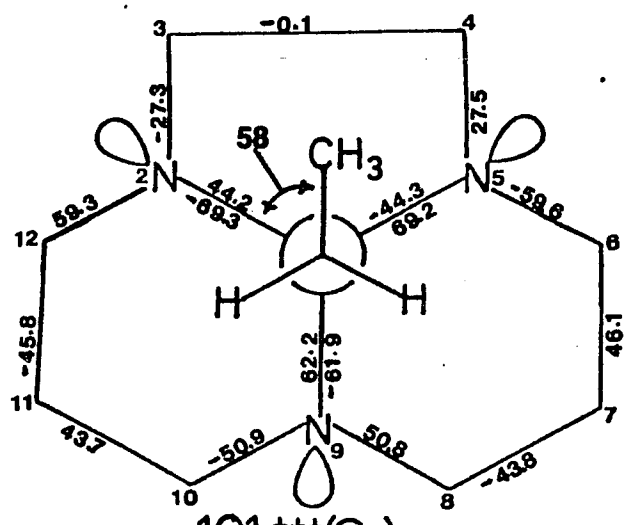
101-cct-6-R(3)
E=51.7
fig260



101-cct-6-R(2)
E=50.0
fig 260



101-ttt(C_1)
E=55.0



101-ttt(C_s)
E=53.4

fig 2.60

the torsion angle diagrams in fig. 2.60 reveals that the five membered rings in all of these conformers adopt envelope or distorted envelope conformations. The six membered rings in 10lttt(C_1) and 10lttt(C_s) are severely distorted chairs which accounts for their higher energy content. 10lcct-5(C_1) and 10lcct-5(C_s) have six membered rings which are flattened at the cis ring juncture. The avoidance of steric interactions between the ethyl group and the six membered ring in 10lcct-5(C_1) makes the distortions of the six membered ring more severe than in 10lcct-5(C_s) and accounts for its higher energy content. 10lcct-6(R3) and 10lcct-6(R2) have flattened chairs in the six membered rings at the cis ring juncture which accounts for a large part of their higher energy content. The remainder of the high energy content of 10lcct-6(R3) and 10lcct-6(R2) must be due to unfavorable steric interactions between the ethyl group and the six and five membered rings respectively. 10lcct-6(R1) is a relatively low energy conformation because the positioning of the ethyl group under the cis fused six membered ring reduces the unfavorable steric interactions between the ethyl group and the ring. The six membered rings are also flattened in 10lcct-6(R1) but not as severely as in 10lcct-6(R2) and 10lcct-6(R3) which further accounts for the lower energy content of 10lcct-6(R1).

Conformational Analysis of Et-333 (102). The analysis of Et-333 is in essence the choice between assignment of 102ttt or 102cct (fig.2.61) or a mixture of the two

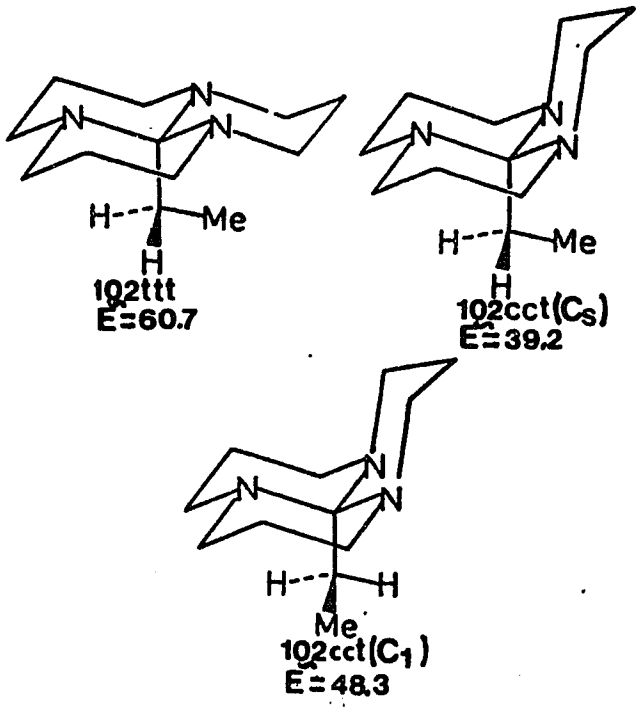
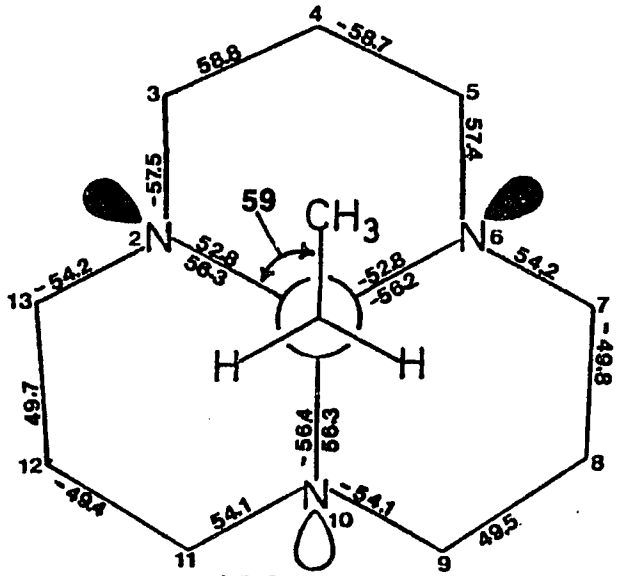
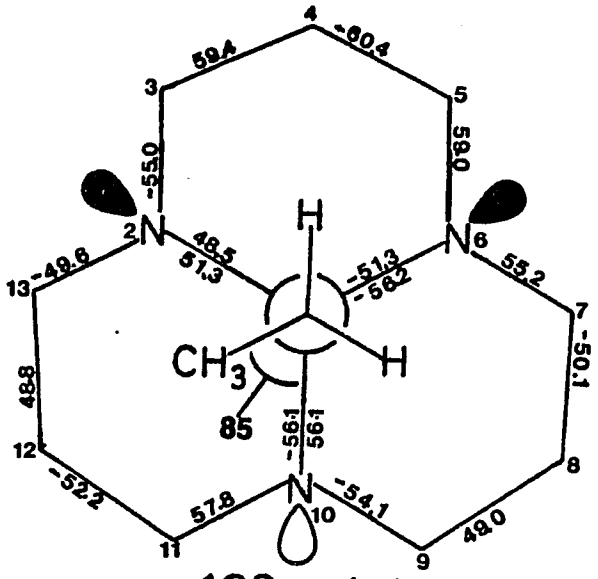


fig 2.61

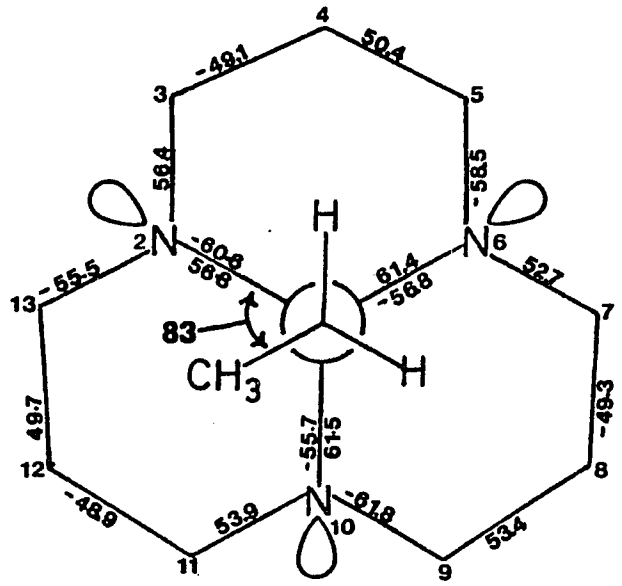
conformers. The possible conformations that we considered and their calculated energies are shown in fig.2.61. MM2 calculations indicate a dominance of 102cct(C_s). The fact that 102cct(C_1) is 9 kcal/mol higher in energy than 102cct(C_s) indicates that the steric interactions between the ethyl group and the ring force this material to adopt the cis,cis,trans conformation. The minimized geometries and energies of the three possible all chair conformations of Et-333 are shown in fig.2.615. In 102cct(C_s) (the minimum energy conformation) the two cis-trans fused rings are slightly flattened and the cis,cis fused ring is a



102-cct(Cs)
E=39.2
fig 2.615



102-cct(C_1)
E=48.4
fig 2.615


4
-49.1
50.4
3
5
58.4
-58.5
H
2
N
-60.6
56.8
61.4
-56.8
N
6
-55.5
52.7
13
7
83
CH3
H
49.7
-49.3
-55.7
61.5
12
8
-48.9
53.9
N
-61.8
53.4
10
11
9

102-ttt
E=60.7

nearly perfect chair. The high energy content of 102ttt is accounted for by the unfavorable steric interactions between the ethyl group and the ring and by distortions of the chair conformations of the rings. 102cct(C_1) is higher in energy than 102cct(C_s) because of unfavorable steric interactions between the ethyl group and the ring and because of more extensive flattening of the three chairs.

The fact that the ring system of this compound does have the cis,cis,trans conformation was proven by ^{13}C DNMR. As can be seen in fig.2.61, 102ttt should have only three types of ring carbons if ethyl rotation is fast on the NMR time scale. On the other hand, the cis,cis,trans conformations should have six different types of ring carbons. Clearly the ^{13}C NMR of this compound should allow unambiguous assignment of conformation. The ambient temperature ^{13}C NMR spectrum of Et-333 exhibited only three types of ring carbon resonances (see spectra 2.62-2.64). But upon lowering the temperature dynamic behavior was evidenced. The spectrum in the slow exchange region has six ring carbon resonances making the assignment of conformation 102cct unambiguous. Note that the three resonances assignable to the methylenes to the nitrogen are in the intensity ratio of 1:1:1 as expected for 102cct. Note also that the carbon resonances assignable to the ring carbons α to the nitrogens are in the intensity ratio of 2:1 as predicted for 102cct (with the assumption of either

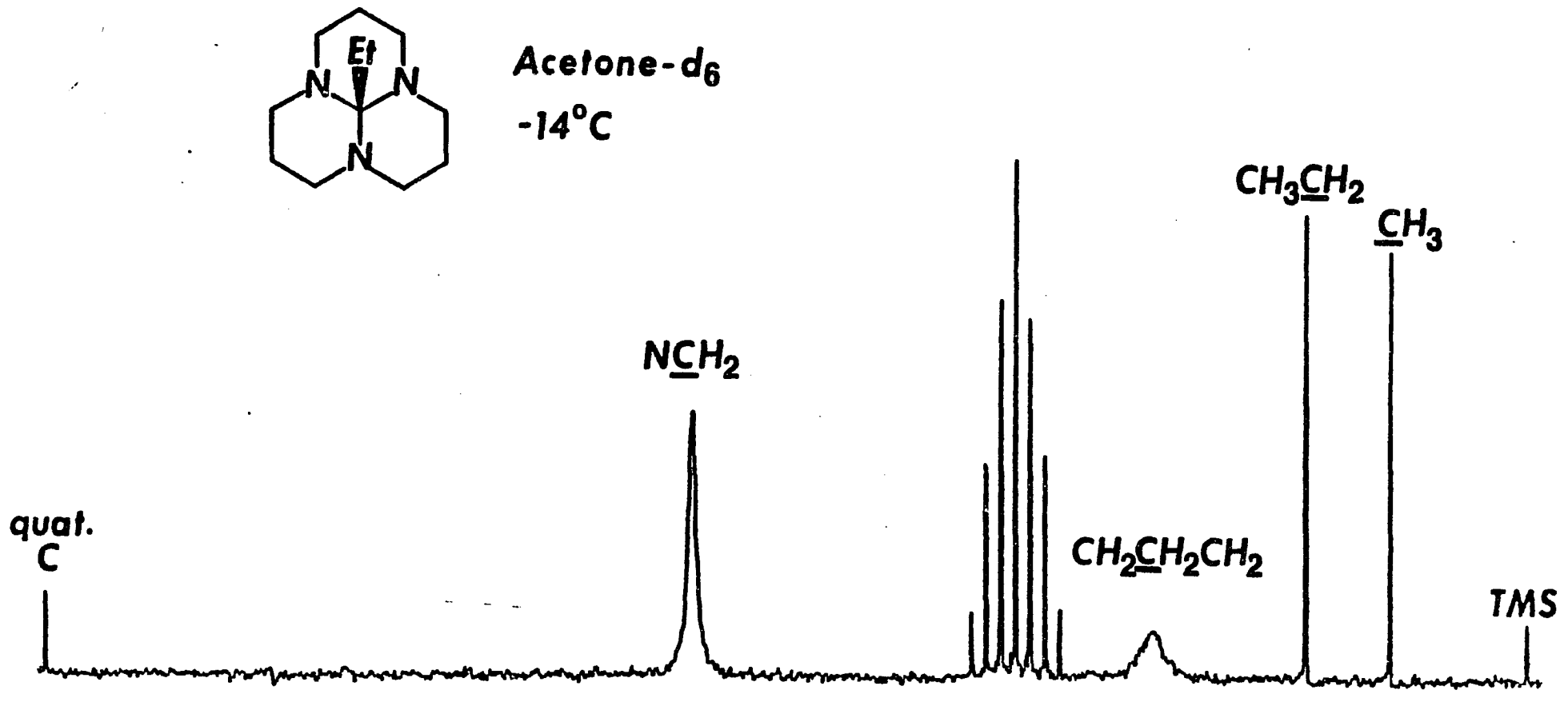

Et
N
N
N
Acetone-d_6
-14°C
$CH_3\underline{C}H_2$
$\underline{C}H_3$
$N\underline{C}H_2$
quat.
C
$CH_2\underline{C}H_2CH_2$
TMS

fig 2.62

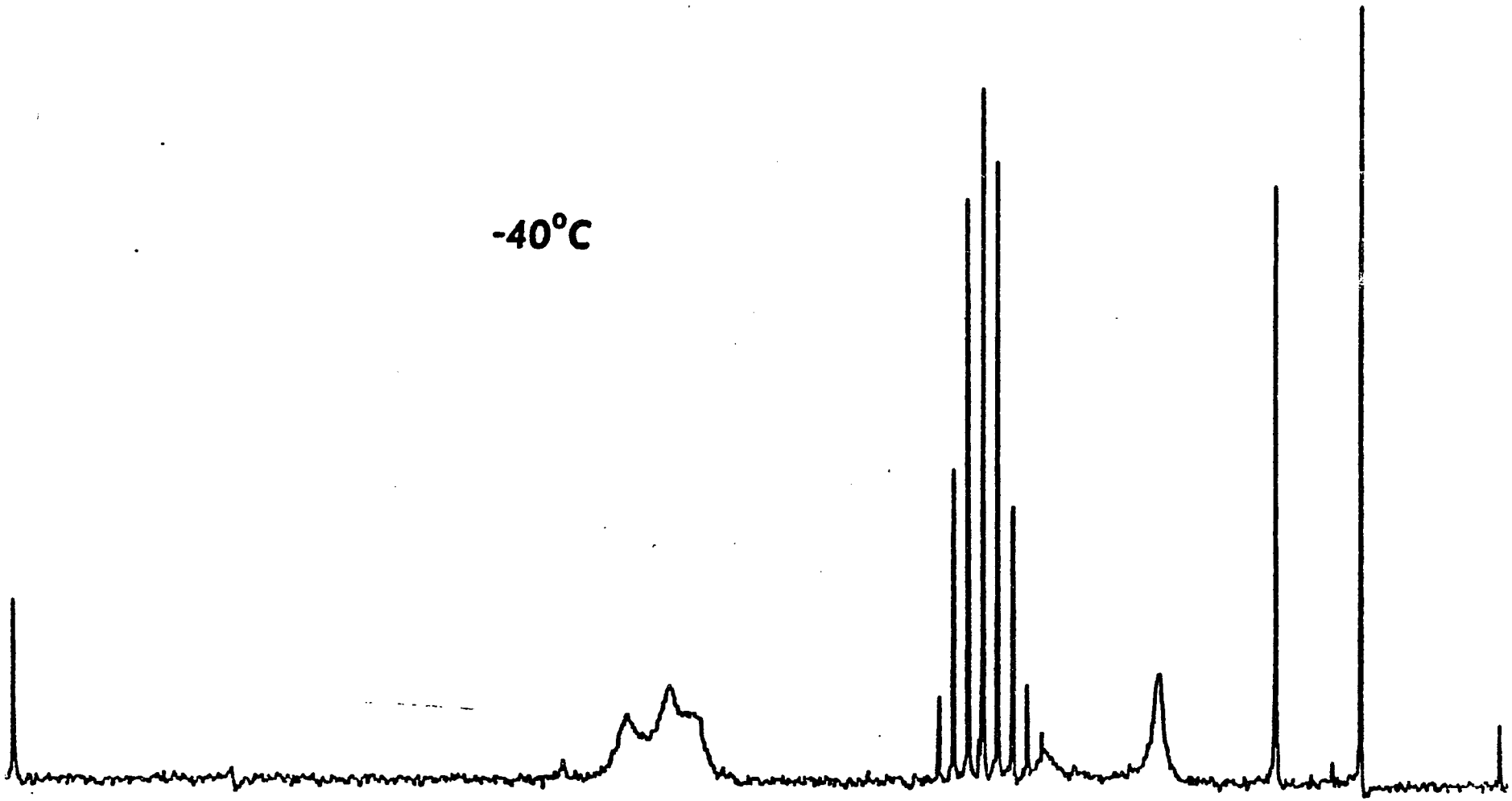


fig2.63

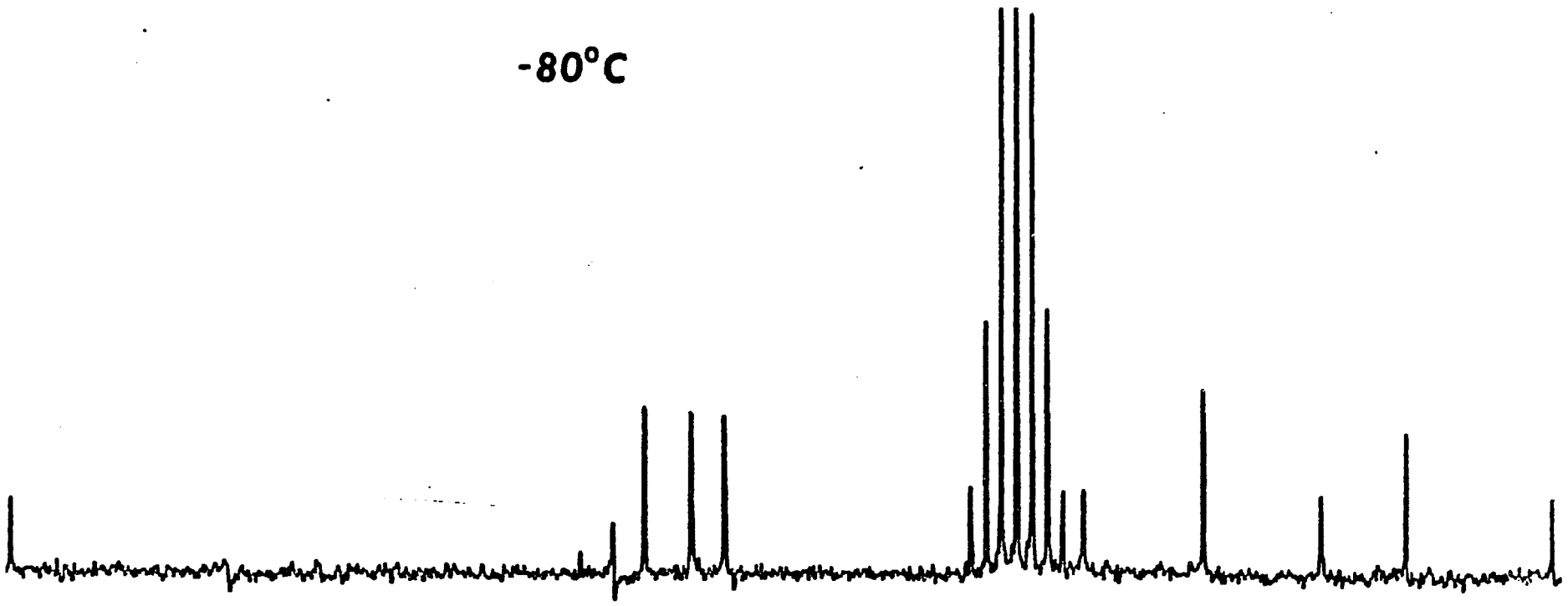


fig2.64

102cct(C_s) dominance or fast ethyl rotation). The only other process that could account for the number of observed resonances for the ring system is one that calls for slow rotation of the ethyl group in the all-trans conformation. The possibility of slow rotation in this conformation is not unreasonable. But consideration of the minimized energy (60 kcal/mol) and examination of models leads one to the conclusion that the all-trans conformation is too high in energy to be significantly populated.

The fact that the ambient temperature spectrum of Et-333 has only two perimeter ring carbon resonances indicates that these are averaged resonances. Averaging occurs by a degenerate conformational process which is fast on the NMR time scale at ambient temperatures resulting in average C_{3V} symmetry. This degenerate process is shown in

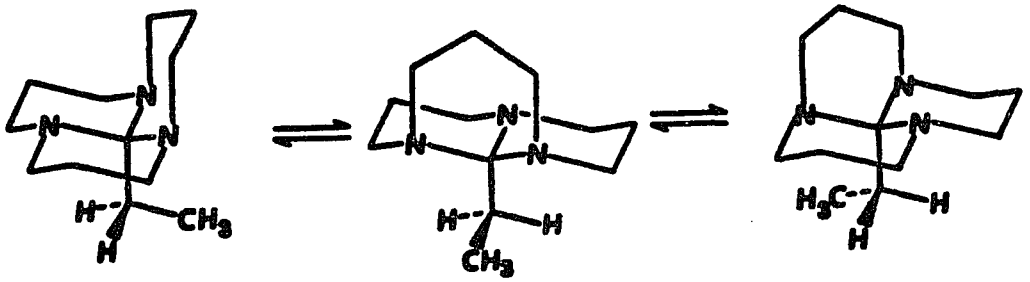


fig 2.66

fig.2.66. Total line shape analysis of the resonances assigned to the perimeter carbons α to the nitrogens, near the coalescence temperature, yielded a value of 11.72 kcal/mol as the Δg_{-37} for this process. Total line shape analysis was performed at a number of temperatures in

the intermediate exchange region. The experimental and simulated spectra are shown in fig. 2.67. The free energies of activation($\Delta G^{\ddagger}$) were calculated by application of equation 2.2[126]. The energies obtained from equation 2.2 were calculated in Joules/mol and were then converted to the more generally used units of kcal/mol. Incorporation of $\Delta G^{\ddagger}$ in terms of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ in equation 2.2 yields equation

$$\Delta G^{\ddagger} = 8.31T(23.76 + \ln T/k + \ln K) \quad \text{eq. 2.2}$$

$T = {}^{\circ}K$
k=rate constant
K=transmission coefficient(=1)

$$\ln T/k = 23.76 + \ln K - \Delta H^{\ddagger}/8.31T + \Delta S^{\ddagger}/8.31 \quad \text{eq 2.3}$$

2.3. A plot of lnk/T vs. 1/T was prepared. A straight line was obtained which indicates that if errors are present in this data then they must be systematic. Linear regression analysis of the data used to prepared this plot yielded a slope of -6.66×10^{-3} and a y-intercept of 26.89 with a correlation of -0.99. The use of this slope and the y-intercept with equation 2.3 yields values of 13.2 kcal/mol and 26.0 + 1.0 e.u. for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ respectively. (The preceeding method of analysis can be found in reference 126.) 102ttt is probably not an intermediate on the energy surface since the calculated difference of 27.5 kcal/mol between 102cct(C_s) and 102ttt is much larger than the

experimentally determined barrier.

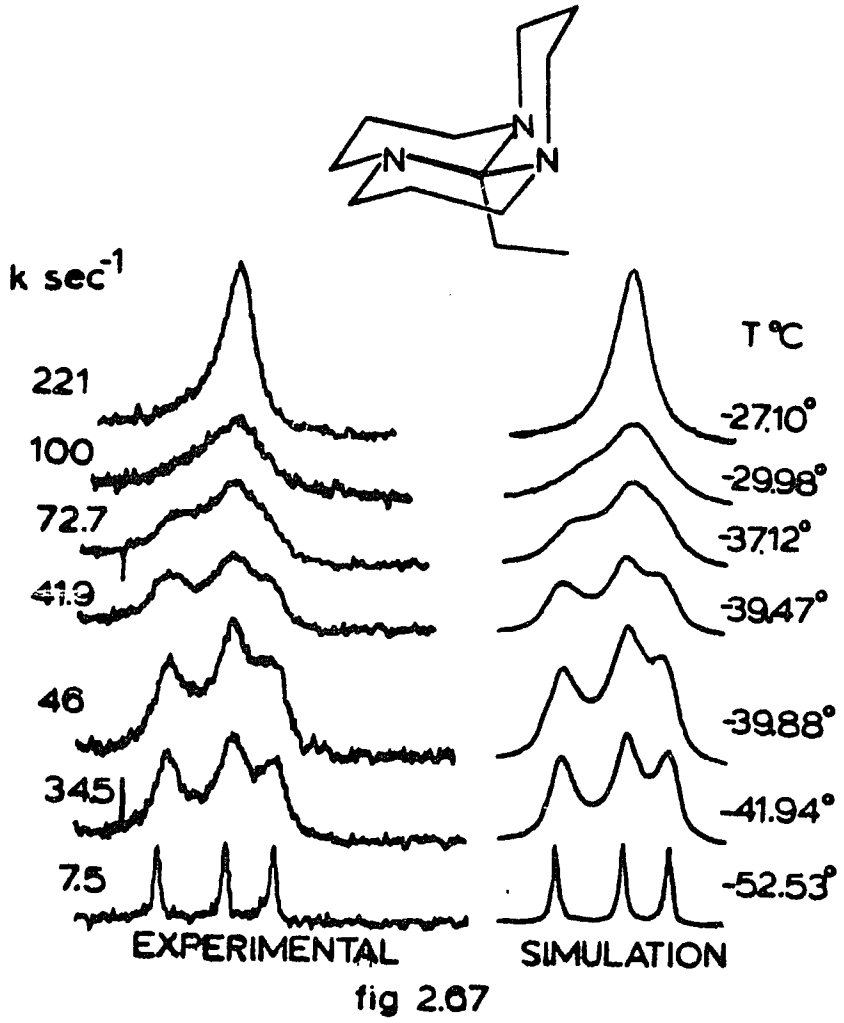


fig 2.67

The process requires two nitrogen inversions, two ring reversals, and concomitant rotation of the ethyl group. A reasonable mechanism for this process can be proposed employing the chair-chair (C-C) to chair-twist (C-T) to twist-twist (T-T) conformational process in cis-decalin as a model. An in-depth molecular mechanics treatment of the cis-decalin interconversion has recently been reported[181]. A schematic of the proposed mechanism for Et-333 is shown in

fig. 2.69 and fig. 2.70. Inversion of N-6 converts 102A to 102B which can be converted to 102C by a ring torsion. 102C has a pseudorotation circuit open to it which allows it to assume conformations which allow generation of 102B or 102B' via ring torsions. The only difference between the ring torsions that yield 102B from 102C and those that yield 102B' from 102C is that they occur in different rings. Inversion of N-10 in 102B' generates 102A' which completes the cycle (note that 102A and 102A' are distinguishable only through the artificial labeling of the three rings). The conformations of 102B and 102B' have been minimized by MM2[182]. The minimized geometries and the energies of these proposed intermediates are shown in fig. 2.70. Inspection of the torsion angle diagram of 102B indicates that it is composed of two slightly distorted chairs and one slightly distorted twist boat. In 102C one of the rings adopts a near perfect chair, one adopts an almost pure boat, and the third adopts a conformation intermediate between a boat and a twist boat. The energy difference between 102A and 102C (10.7 kcal/mol) is of a magnitude that is compatible with the experimentally determined barrier for this process (13.2 kcal/mol). Although we have not carried out detailed EFF calculations for this process we feel that the proposed mechanism accounts for the experimentally observed process in a reasonable manner.

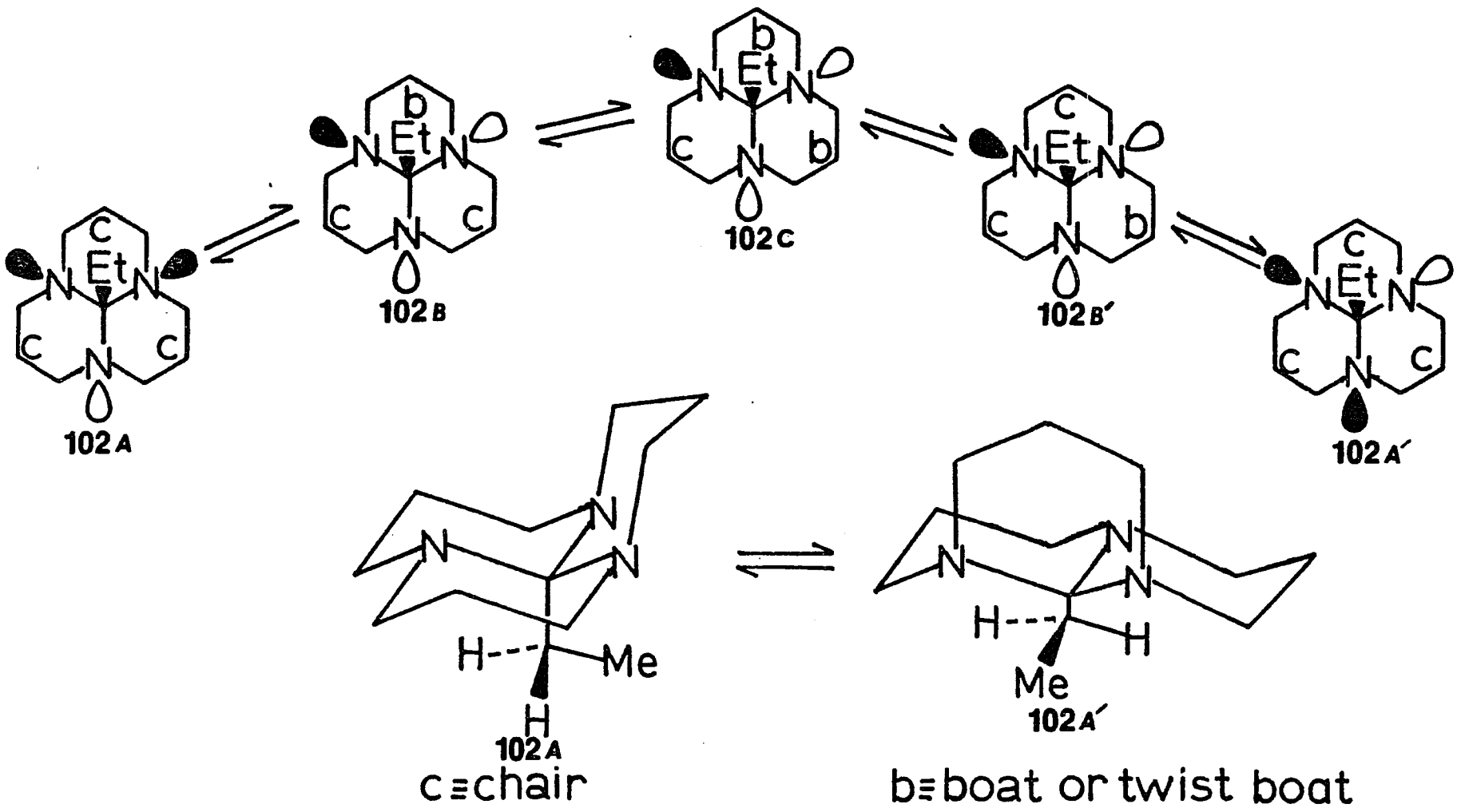
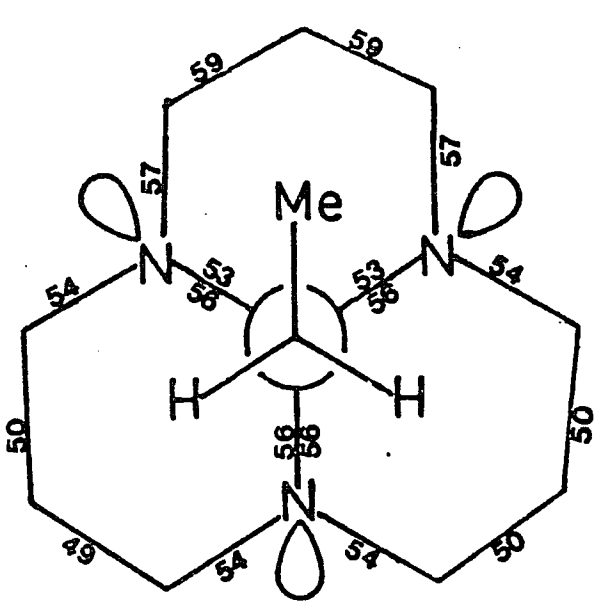
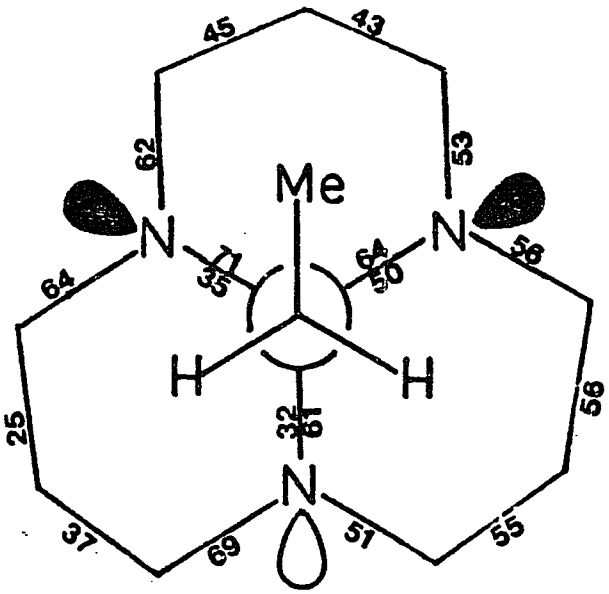
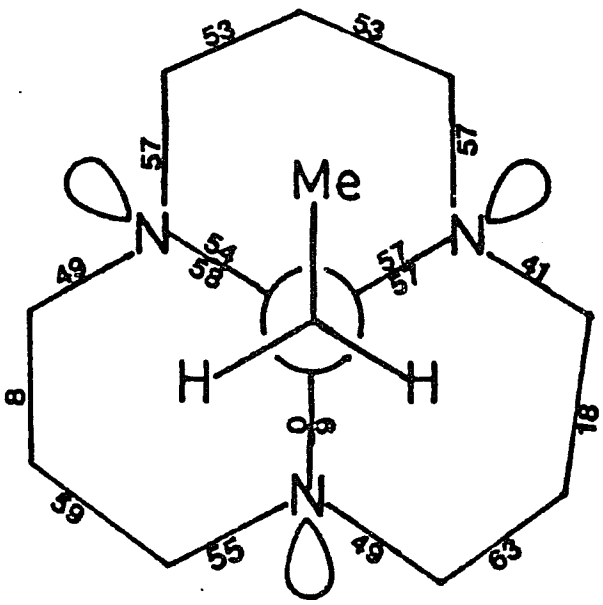
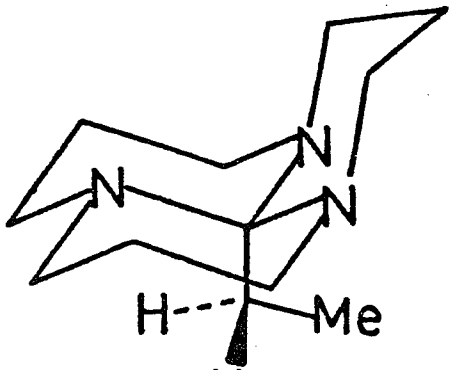

102A
102B
102C
102B'
102A'
H---
Me
H
102A
c≡chair
b≡boat or twist boat

fig. 2.69

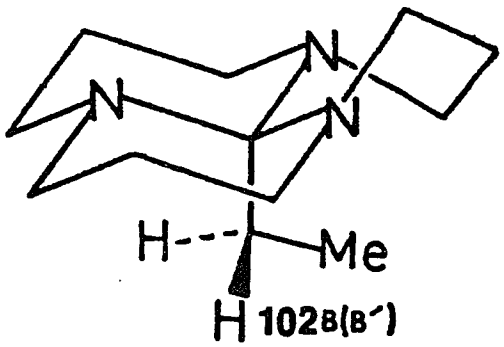




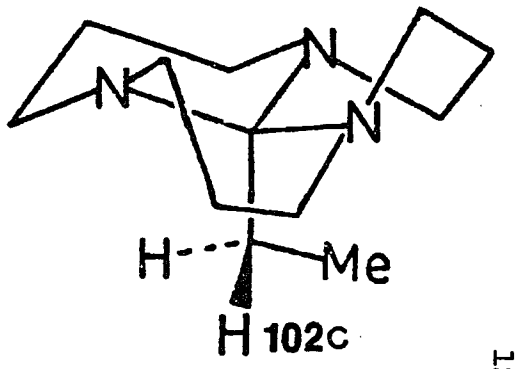




102 A(A′)



102 B(B′)



102 C

fig. 2.70

Structure Reactivity Relationships Of The Orthoamides

Introduction

Clemens and Emmons have stated that the most characteristic reaction of orthoamides is their conversion to formamidinium salts[82]. The most commonly employed methods of effecting this conversion have been alkylation, acylation, and treatment with concentrated mineral acids[80,82,183] (fig.2.71).

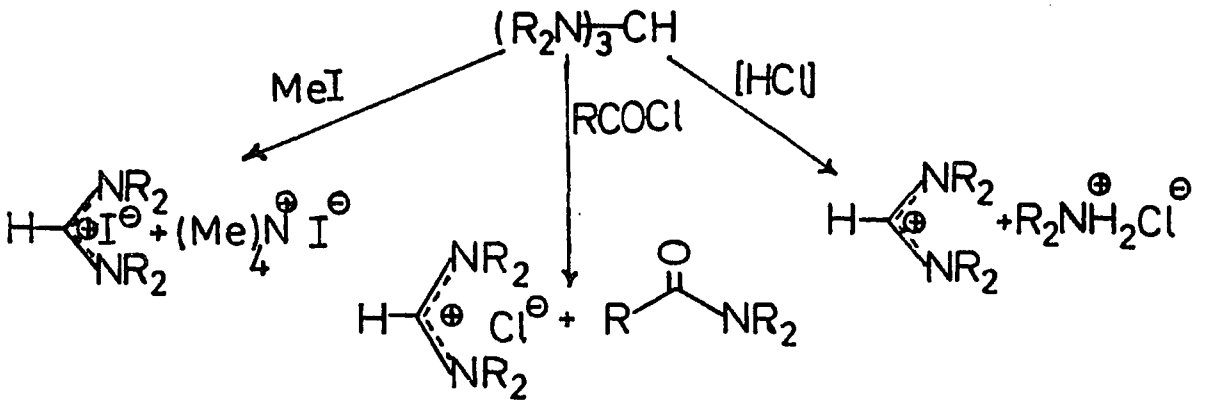


fig 2.71

Another characteristic reaction of acyclic orthoamides is their hydrolysis in aqueous acidic, neutral, and basic media. The hydrolysis of acyclic orthoamides yields amides plus amines (fig. 2.72).

We have undertaken a limited survey of these reactions on members of the tricyclic orthoamide series. The goals of this study were the elucidation of structure reactivity

relationships in the series and the development of useful synthetic sequences.

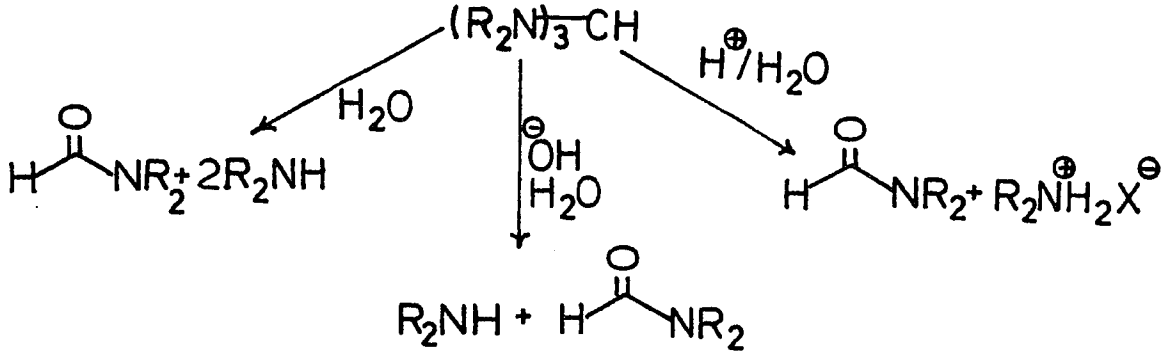


fig 2.72

Alkylation of Orthoamides. Atkins has reported the reaction of H-222 with excess methyl iodide (fig.2.73)[102].

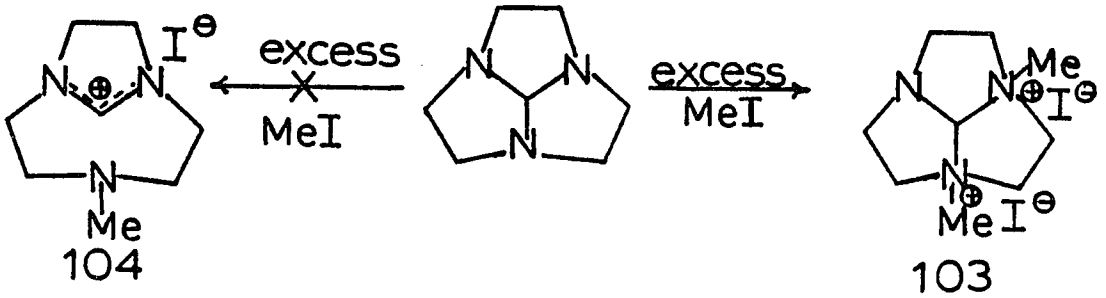


fig 2.73

The product of this reaction was salt 103 in which the tricyclic integrity of the starting material was preserved. Atkins stated that 103 was obtained instead of the bicyclic amidinium ion 104 presumably because of the instability of 104 (fig.2.73). The generation of salts such as 105 (fig.2.74) from some cyclic amide acetals has been previously explained in terms of the instability of the alternate carboxonium product 106.

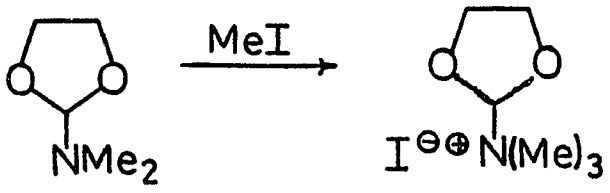


fig 2.74

A kinetic argument can be advanced which also accounts for the observed reactivity of H-222. The generation of the bicyclic amidinium ion 104 from cation 107 (fig. 2.75) is under stereoelectronic control. The lone pairs in

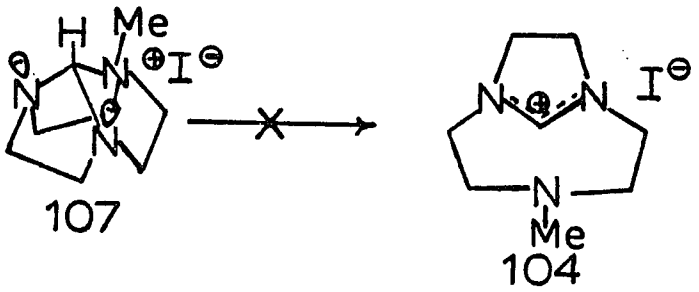
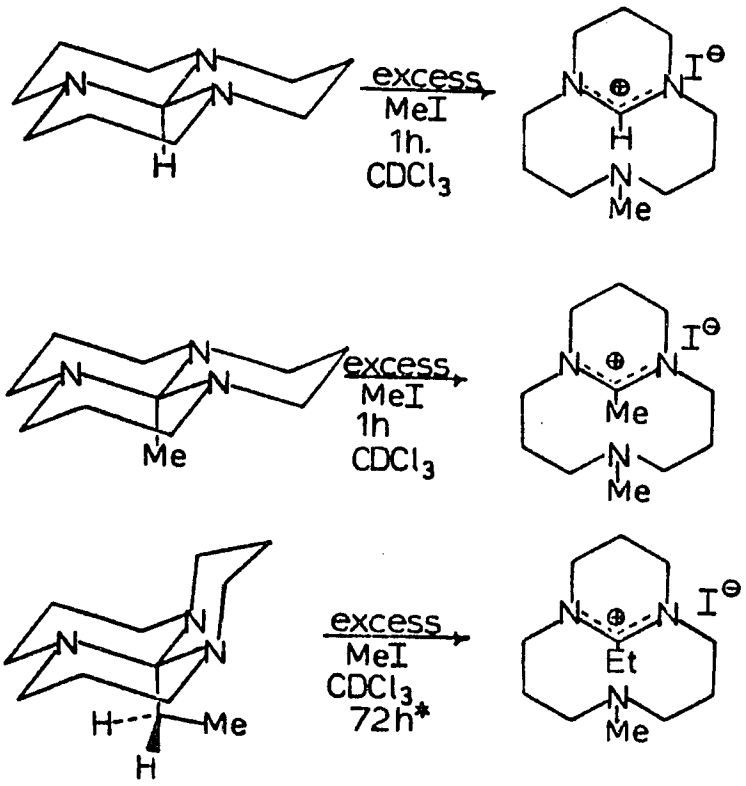


fig 2.75

107 are approximately anticlinal to the C-N bond which must be broken to generate 104. According to Delongchamps' principle[154-157] this stereochemical relationship of the lone pairs to the breaking C-N bond should make the bond breaking slow in 107. Furthermore, conformations of 107 which result in the preferred antiperiplanar (ap) arrangement of lone pairs relative to the C-N bond should be very high in energy. The net result of these considerations is that before the slow reaction to yield 104 can take place the second alkylation occurs to yield salt 103. Since it is impossible to obtain 104 from 103 the tricyclic structure is preserved. The argument presented above is in agreement

with results of alkylations of the 333 series. The results obtained in these laboratories are presented in fig.2.76.



* The reaction mixture contained only starting material after 1 h. and a mixture of starting material and product after 24 h.

fig 2.76

Because of stereoelectronic considerations the alkylation of H-333 and Me-333 most likely occurs as presented in fig.2.77 although alkylation might also occur in in the cis,cis,trans conformation to yield intermediates analogous to 2.78-b (fig.2.78). Et-333 exists in the cis,cis,trans conformation which contains two different types of nitrogens, therefore alkylation must occur by one or both of the pathways shown in fig.2.78.

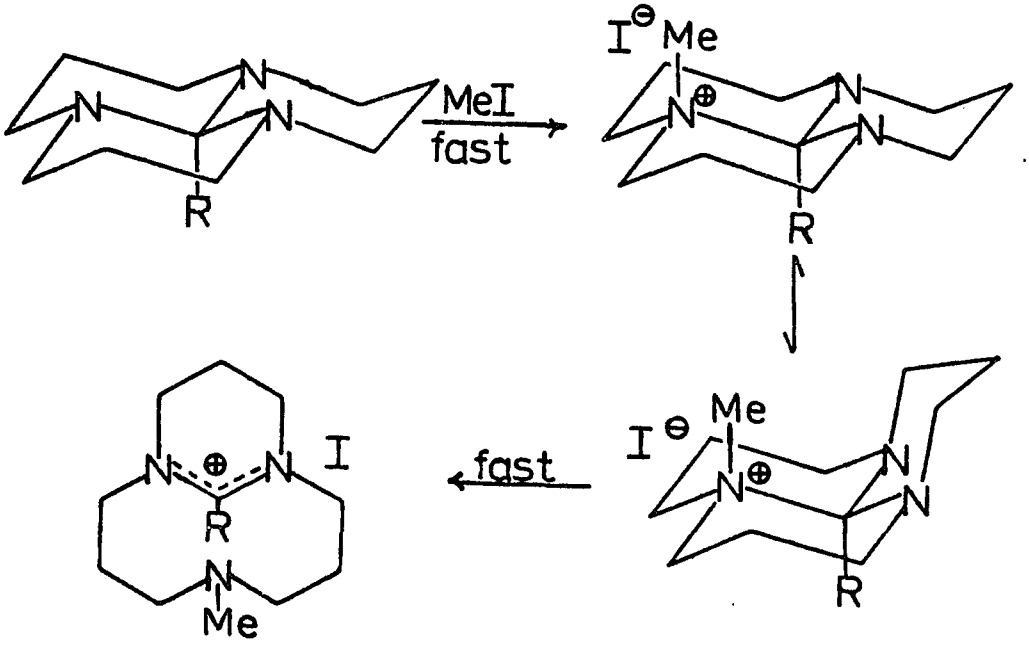


fig 2.77

The fact that the H-333 and the Me-333 reactions are fast implies that the rate of the alkylation step is responsible for the slow overall reaction rate for Et-333. Inspection of models reveals that N_B is sterically shielded by the two axially situated methylene carbons bonded to N_A. The N_A nitrogens are sterically shielded by the ethyl group. The steric shielding of the nitrogens must contribute to the slow alkylation rates. Alkylation at N_B yields intermediate 2.78-a which is destabilized by two 1-3 diaxial interactions. The steric strain present in triaxially substituted 2.78-a could be relieved somewhat by partial bond breaking of the quaternary carbon - quaternary nitrogen bond. Alkylation at N_A generates the high energy intermediate 2.78-b. The gauche arrangements of lone pairs relative to the C-N bond which must be broken in 2.78-b

necessitates a conformational process to yield 2.78-c. The high energy double boat 2.78-c is probably not an intermediate. 2.78-c has the preferred (ap) arrangement of lone pairs for the stereoelectronically controlled opening

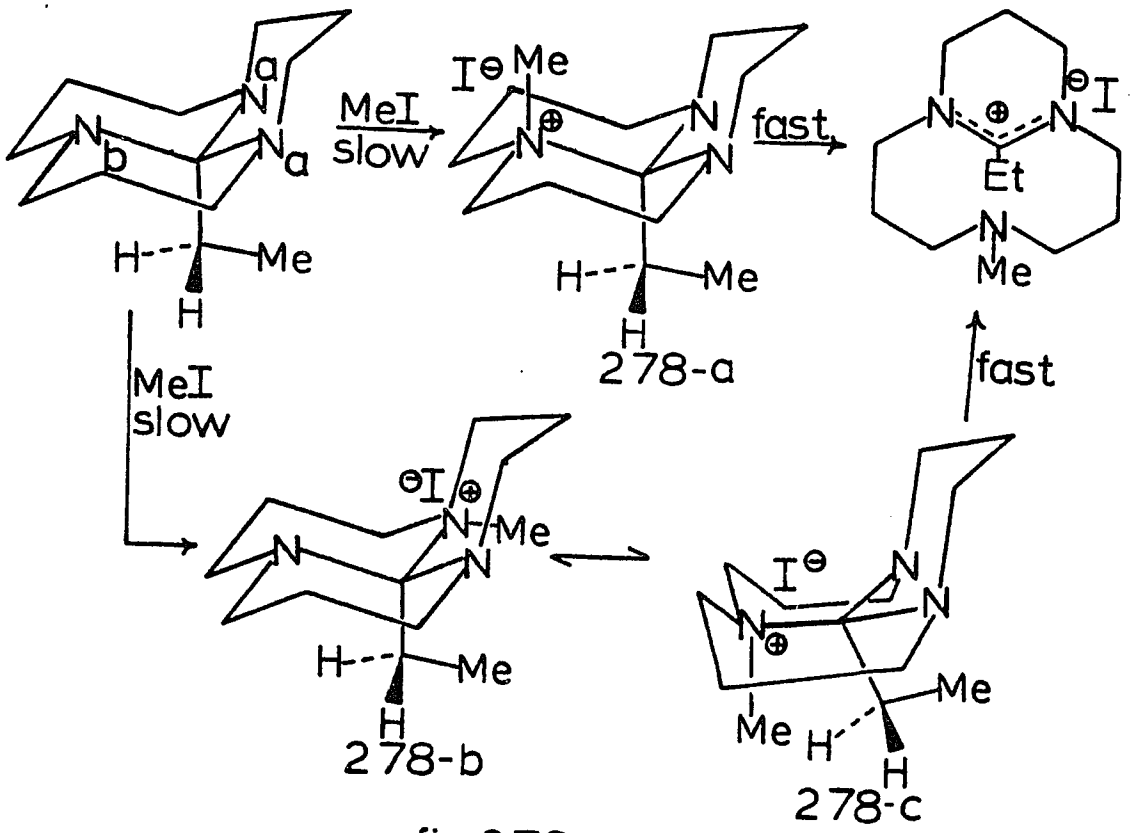
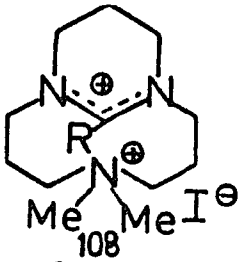


fig 2.78

to product. The strain present in 2.78-c is probably relieved somewhat by partial bond breaking of the quaternary carbon - quaternary nitrogen bond. It will be noted that H-333 and Me-333 (fig.2.77) must also pass through an intermediate analogous to 2.78-a. It must therefore be concluded that the rates of alkylation of the 333 series are kinetically controlled by the accessibility of the nitrogens in the starting materials. The observed alkylation rates lend further support to the assigned conformations of the 333 series.

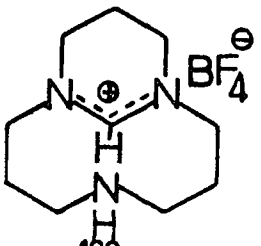
It is interesting that no dialkylated products such as 108 (fig.2.79) are produced in these reactions. This result



108

fig 2.79

must mean that the dialkylated products would be too sterically congested and/or that the amine nitrogen lone pairs are unavailable for reaction. Wuest[104] has reported that the IR spectrum of 109 (fig.2.80) contained absorbances characteristic of both the open bicyclic structure (1660 cm^{-1}) and also for the closed tricyclic structure (near 2900 cm^{-1}, Bohlmann bands). He interpreted these results as an indication of a transannular interaction between the amine nitrogen and the amidinium system in 109. The alkylation products of the 333 orthoamides exhibited similar IR absorbances.



109

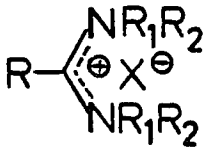
fig 2.80

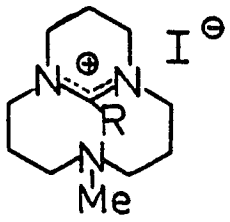
A transannular interaction of this type in the products of the alkylation of H-333, Me-333, and Et-333 might help explain the observed monoalkylation. The C=N stretching frequency in the IR and the UV spectra of these compounds are in close agreement with the published spectral data of

acyclic model amidinium systems[184] (table 2.5-5). The similarity of the spectral parameters of the acyclic amidinium ions (where no transannular interactions are present) and these bicyclic amidinium systems seemed to indicate either the absence of interaction or a weak interaction.

A crystal structure determination of 110 [185] was undertaken (in collaboration with E. Gabe, NRC, Canada) to determine whether a transannular interaction was in fact present in 111 (in the solid state). This compound crystallized from CH_2Cl_2/hexane in the monoclinic $P_{21/m}$ space group and contained two molecules per unit cell. The positions of all of the atoms were accurately determined by collecting data at 115 K.

Table 2.5-5





R	$\nu_{C=N}(cm^{-1})^a$	$\lambda_{max}(nm)$	$\nu_{C=N}(cm^{-1})$	$\lambda_{max}(nm)$
H	1652	224[b]	1672.4	221
Me	1607		1608.8	226
Et	1605		1602.3	

a: $R_1 = R_2 = Me, X = ClO_4$ b: $R_1 = R_2 = Me, X = PF_6$

The structure contained several features which indicated that a transannular interaction was in fact present in 110. First, the tertiary amine was found to be pyramidalized with the lone pair towards the amidinium carbon. Secondly, the distance between the amidinium carbon and the tertiary nitrogen was found to be 2.585 Å. Transannular interactions have been observed between the nitrogen and the carbonyl in ten membered macrocyclic aminoketones at comparable distances[186]. Thirdly, the hydrogen on the amidinium carbon was found to be 0.1881 Å above the plane containing the carbon and nitrogen atoms of the amidinium system. The deviation from planarity of the carbonyl group in macrocyclic aminoketones has been used as a measure of transannular interactions in these compounds[186]. The interaction of the sp^3 orbital of the nitrogen with the p-orbital of the amidinium carbon should impart more s character to the p-orbital. This interaction should lower the energy of this p-orbital thereby inducing hybridization changes in the amidinium carbon (i.e. more sp^3 character) resulting in a loss of planarity. This interaction is analogous to transannular interactions in macrocyclic aminoketones. Delocalization of the positive charge onto a third nitrogen must favor this interaction. This interaction should be favored conformationally because the transannular strain (generally found in ten membered rings[186b]) is replaced in 110 by a favorable interaction. Torsional strain and large angle strain (the two other major

contributors to the conformational energies of medium rings) also seem to be minimized in conformations of 110 in which a transannular interaction is present. The interaction is disfavored by the loss of overlap in the amidinium system resulting from the hybridization changes of the amidinium carbon. The magnitude of this interaction in 110 must be determined by the interplay of these factors.

It is concluded that the observed monoalkylation results from both steric congestion of the dialkylated products and from the reduced nucleophilicity of the tertiary nitrogen (due to the transannular interaction) in 110. Although we have no direct evidence, it can be reasonably assumed that the monoalkylation of Me-333 and Et-333 are also determined by these two factors.

Synthetic Applications of the Alkylation of H-333. Compound 135 was prepared by the base catalyzed hydrolysis of 134 (fig.2.81). The initial product 111, which was

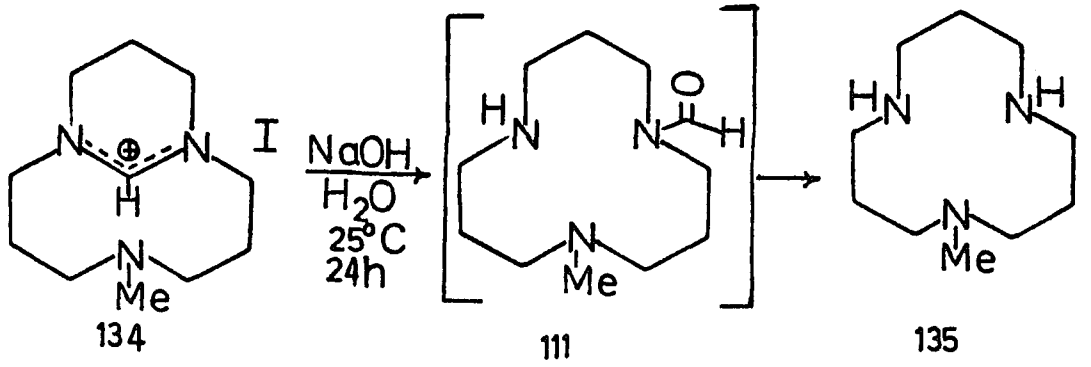


fig 2.81

detected by ^{13}C NMR, was easily hydrolyzed in the basic medium at 25°C to yield the monomethyl macrocycle.

The preparation of 135 by alkylation, reductive alkylation or by an acylation-reduction sequence would inevitably lead to a mixture of products (fig.2.82).

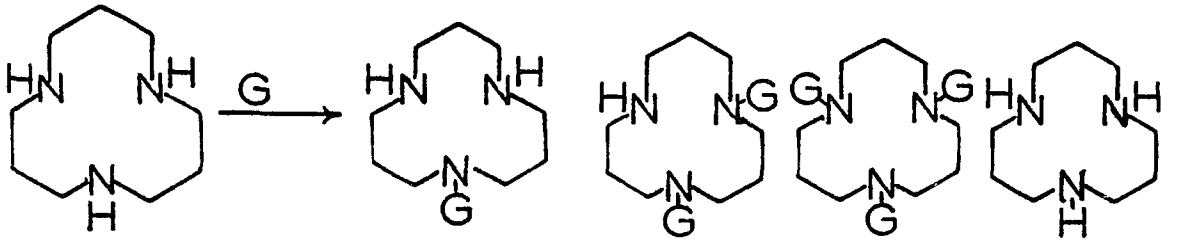


fig 2.82

The alkylation of H-333 followed by base hydrolysis allows the facile high yield synthesis of 135 in analytically pure form. Through the variation of the alkylating agent a number of interesting and useful products might be prepared. Several of these proposed syntheses are presented in fig.2.83-a and 2.83-b.

A series of compounds of the general formulas 113-116 should be accessible via sequence 283-a. The lipophilicity, steric requirements, and the number of donor atoms in the complexation cavity of 116 could be systematically varied through the use of appropriate alkyl halides and aldehydes. 116 could be immobilized on glass beads through the use of an appropriate alkylating agent (R= $-(CH_2)_n-OH$). The

use of chloromethylated organic resins, as in fig.2.83-b, would allow immobilization of 117. The resins prepared by these sequences might be useful for ion selective chromatography. These particular resins would probably evidence selectivity for ions having ionic radii of approximately 0.6 Å in the presence of larger ions. Many other sequences can be envisaged making the alkylation - hydrolysis sequence of H-333 a powerful synthetic method for the functionalization of the 1,5,9-triazacyclododecane macrocycle.

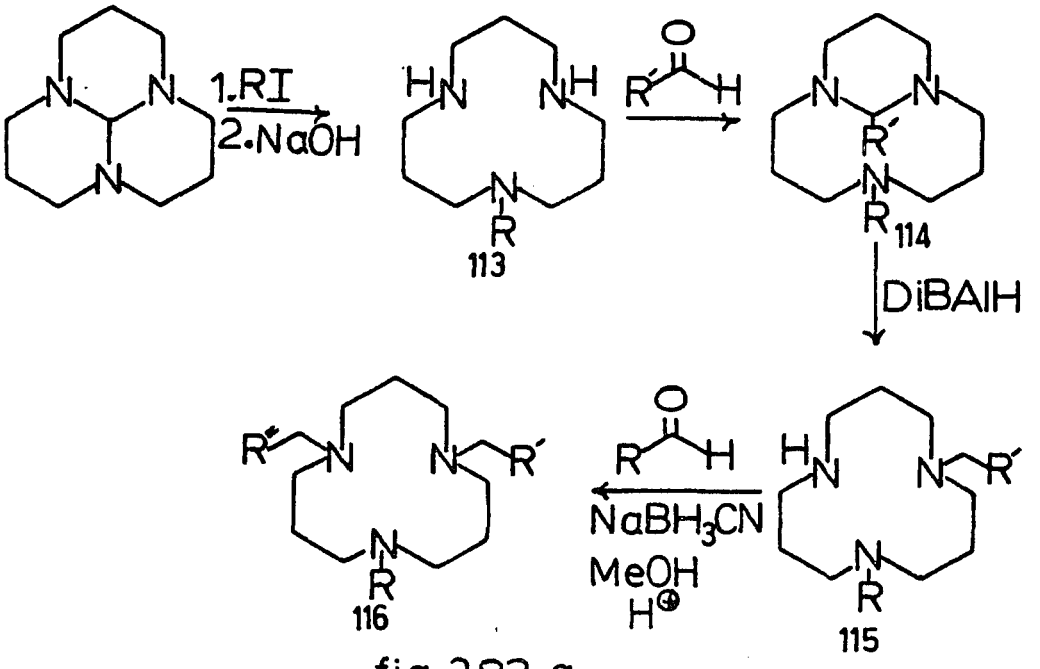


fig 283-a

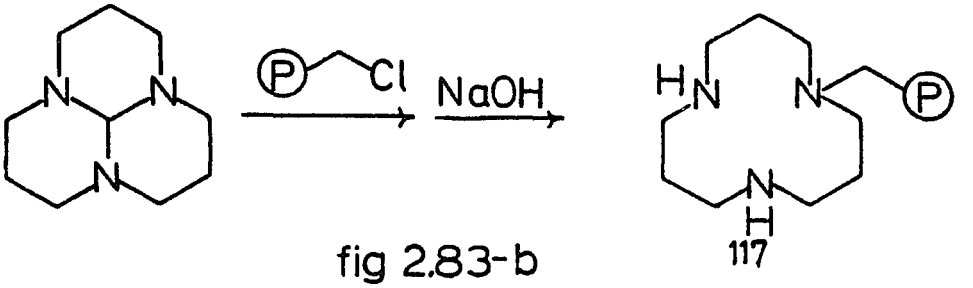


fig 2.83-b

HYDROLYSIS

The hydrolysis of acyclic orthoamides proceeds readily in neutral, acidic, and basic media to yield carboxamides and amines[80]. Amidinium ions have been shown to be intermediates in these reactions[98,295]. Cyclic and sterically hindered amide acetals are more resistant to hydrolysis[187]. The mechanism shown in figure 2.84 has been found to hold under acidic, neutral, and weakly alkaline conditions.

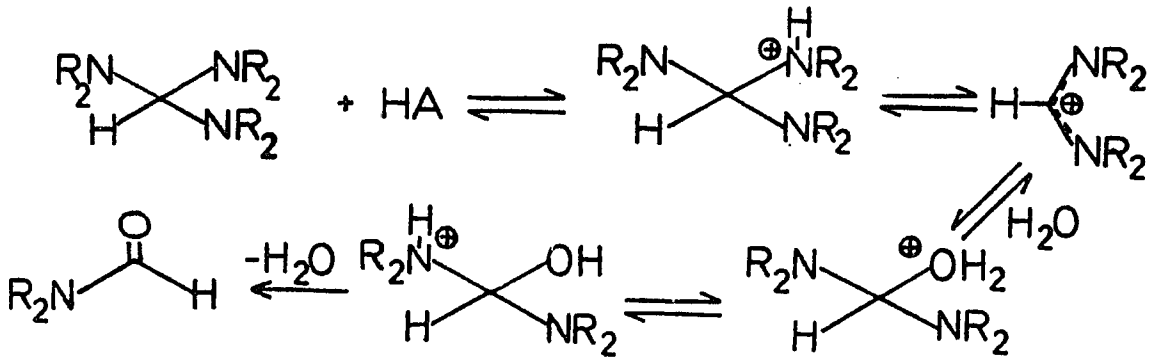


fig 2.84

Mcclelland[188-189] has reported the kinetics of hydrolysis of orthoesters and amide acetals as a function of pH. The kinetic evidence supports the mechanism shown in fig.2.85. Under most conditions the rate determining step was found to be (1) (fig.2.85), dissociation of the orthoester to yield the intermediate 2.85-a. This is true for all acyclic orthoesters. Steps (2) and (3) have been reported to be rate determining in the hydrolysis of some cyclic orthoesters[190-192] possessing one or more of the

following features: 1) cationic intermediate 2.85-a is very stable, 2) the lone pairs of the orthoester are aligned favorably for the stereoelectronically controlled dissociation step (1), and or 3) 2.85-a is sterically hindered towards nucleophilic attack.

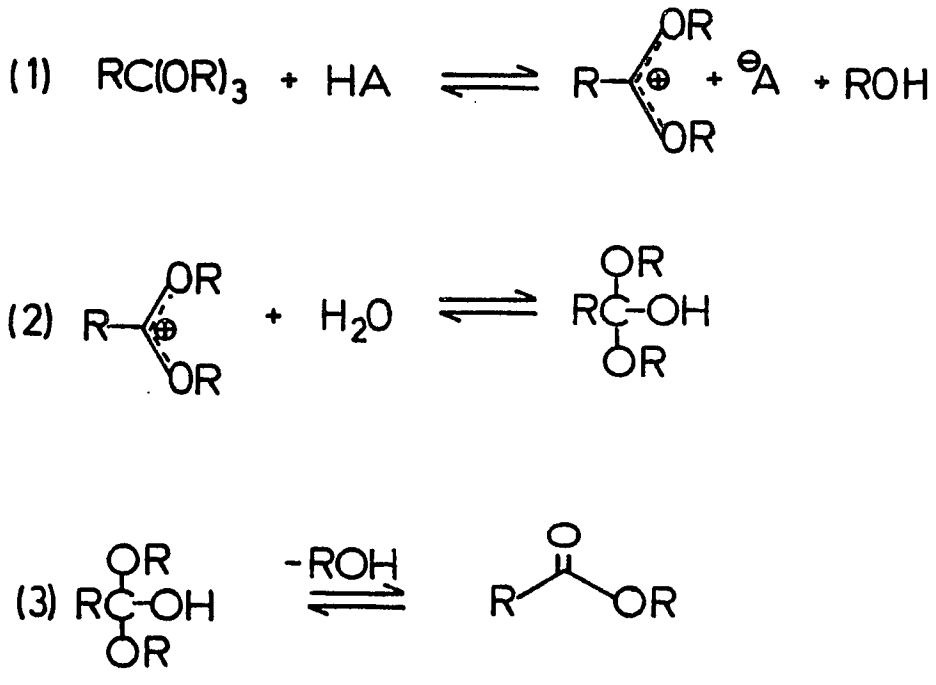


fig 2.85

Initial investigations in this area were directed at determining the effect of protonation upon $^{1}J_{CH}$ (methine) in the orthoformamides. It was originally thought that since $^{1}J_{CH}$ evidenced a dependence on lone pair orientation that this parameter should exhibit a dependence upon protonation. In particular, it was anticipated that $^{1}J_{CH}$ should increase if one or more of the lone pairs of electrons on the nitrogens were protonated. Because of the

angular dependence of the lone pair-σ^* C-H overlap (see conformational analysis of the orthoformamides) one would expect H-333 to show a greater increase in $^1J_{CH}$ than that of H-222.

Likewise, δC(methyl) of the orthoacetamides exhibited a dependence upon the lone pair orientation relative to the central C-methyl bond. (See conformational analysis of the orthoacetamides.) It was anticipated that the tying up of one or more of the lone pairs by protonation would produce downfield shifts of the methyl resonances. Due to the angular dependence of the nitrogen lone pair-σ^*C-methyl overlap it was anticipated that the $\Delta\delta_C$ (methyl) upon protonation would be larger for Me-333 than for Me-222.

Our experimental design assumed that the $\Delta\delta_c$ (methyl) and the Δ^1J_{CH} due to the inductive contribution (of the positively charged nitrogen) would be the same in the 222 and the 333 compounds. This assumption is based upon the attenuating inductive withdrawal model (fig.2.86[193a]). According to this model the effect that an electronegative substituent will exert upon any given carbon is only related to the distance between the two.

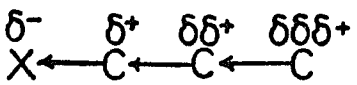


fig 2.86

Morishima[193b] has discussed the effect of protonation upon the chemical shifts of amines in terms of the inductive withdrawal of electron density from the adjacent framework onto the positively charged nitrogen. His results were interpreted in terms of Pople's[193c] alternating attenuating model arrived at by CNDO-SCF molecular orbital calculations (fig.2.87). According to this model alpha carbons will have decreased electron density (deshielded- downfield shifts) and beta carbons will have increased electron density (shielded- upfield shifts). Morishima's results supported this model. He also reported a conformational dependence of the magnitude of the beta carbon shifts. The experimentally determined variation of the upfield shifts of the beta carbon atoms as a function of the dihedral angle between the nitrogen lone pair and the C_{alpha}- C_{beta} bond is qualitatvely illustrated in fig.2.88. Morishima demonstrated the same angular dependence of the " inductive effect" upon the beta carbon's charge density employing CNDO/2 MO calculations. A recent report[193d] has stated that the "induced charge alteration predicted by CNDO/2 theory may be an artifact of the calculations rather than a molecular property". Eliel[193e] has reported alternating attenuating shifts upon protonation of trans - decahydroquinolines. But in the same report Eliel questioned Morishima's prediction of a conformational dependence of this effect since Morishima's conclusions were based in part on conformations that have

been subsequently shown to be incorrect.

If Morishima's theory is correct one must conclude that the methyl carbon shifts upon protonation of the orthoacetamides might have to be interpreted in terms of the "σ inductive effect" and the "lone pair overlap effect". The relative importance of these two effects would be difficult to determine.

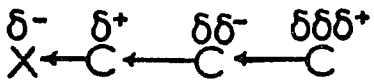


fig 2.87

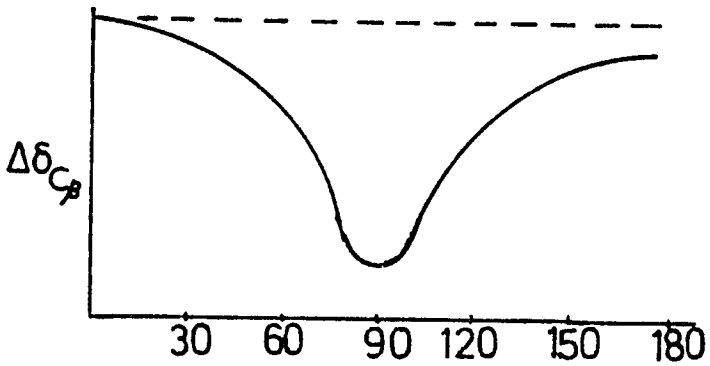


fig 2.88

A similar problem exists with the interpretation of the observed changes in the $^1J_{CH}$ upon protonation. Protonation increases the electronegativity of the nitrogen which causes an increase in $^1J_{CH}$. If Pople's alternating attenuating model holds, then the relative contributions of the σ inductive effect and the lone pair

overlap effect would have to be determined.

Morishima's results call into question our assumption that the effect of the positively charged nitrogen will be the same in the 222 and the 333 compounds. This assumption might also be questioned on the basis of field effects. The positive charge of the protonated forms of these compounds is carried not only by the nitrogen but also by the hydrogen. Clearly this hydrogen is closer to the carbon (or carbon bond) of interest in the 222 compounds than in the 333 compounds (fig.2.89). The contribution of this field effect (if any) cannot be quantitatively determined. The pK_as of H-222 and H-333 were determined by potentiometric titration to be 6.55 and 7.31 (see appendix 3 for experimental data) respectively. (The second and third pK_as could not be determined.) The difference in basicity might be partially due to the decreased importance of destabilization by inductive withdrawal in H-333 (i.e. bridges which contain three methylene carbons in H-333 vs two methylene carbons in the H-222 bridges). This difference in basicity would also have to be taken into account to quantitatively treat the effect that the tying up of lone pairs has upon the spectral parameters of these compounds. This consideration is more important in the cases where more than one equivalent of acid was added. The pK_a difference might also be due to the presence of a small amount of a bicyclic amidinium system in protonated

H-333. Clearly the interpretation of the observed spectral changes in these compounds upon protonation is complex.

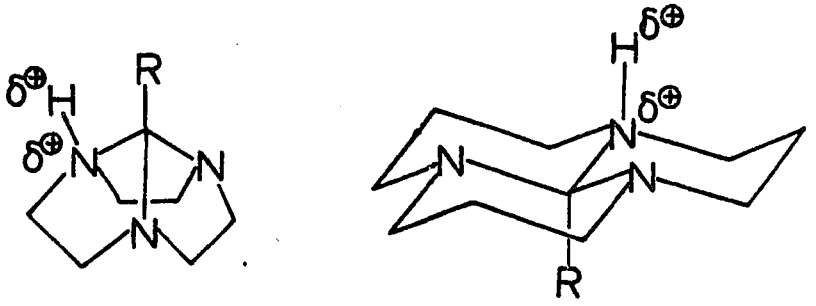


fig 2.89

The effect of protonation upon the ^{13}C spectra of H-222, H-333, Me-222, and Me-333 are shown in table 2.6.

Table 2.6

COMP.	SOLVENT	PROTON SOURCE	METHOD	No. Eq.	FREE AMINE δ_c	FREE AMINE J^1_{CH}	PROTONATED δ_c	PROTONATED J^1_{CH}	$\Delta\delta_c$	ΔJ^1_{CH}
H-222	D_2O	DCl	PT	1	101.8	183.1	106.8	193.9	5.0	10.8
H-222	D_2O	DCL	V	2	101.8	183.1	-	-	-	-
H-222	$CDCl_3$	CF_3CO_2H	W	1	104.1	184.0	108.4	193.9	4.3	9.8
H-222	$CDCl_3$	CF_3CO_2H	W	2	104.1	184.0	108.6	198.7	4.5	14.7
H-333	$CDCl_3$	CF_3CO_2H	V	1	100.0	140.1	98.3	157.5	-1.7	17.4

COMP.	SOLVENT	PROTON SOURCE	METHOD	No. Eq.	FREE AMINE δ_c(4°)	FREE AMINE δ_c(Me)	PROTONATED δ_c(4°)	PROTONATED δ_c(Me)	$\Delta\delta_c$(4°)	$\Delta\delta_c$(Me)
Me-222	$CDCl_3$	$TsOH\cdot H_2O$	W	1	111.4	27.7	119.2	23.6	7.8	-4.1
Me-333	$CDCl_3$	CF_3CO_2H	V	1	86.0	-4.0	89.9	1.2	3.9	5.2

METHOD: PT; Potentiometric Titration
W; Weighed
V; Volume

$\Delta\delta_C = \delta_C$(protonated) $- \delta_C$(free amine)

$\Delta J^1_{CH} = J^1_{CH}$(protonated) $- J^1_{CH}$(free amine)

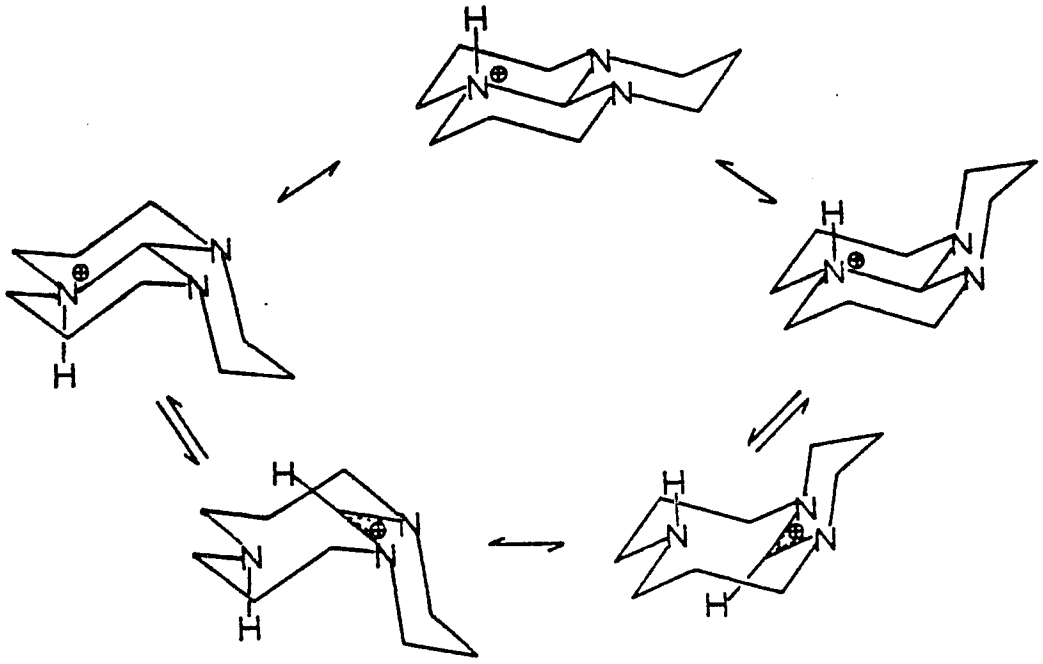
$\Delta\delta$:Positive Numbers; downfield shifts
Negative Numbers; upfield shifts

These results are not totally consistent with a lone pair overlap effect or with the inductive effect of the positively charged nitrogen. Subsequent studies revealed a fundamental difference in the behavior of the 222 and the 333 systems in acidic media. The results of these studies (which will be discussed shortly) made the question of inductive withdrawal vs. lone pair effects on the ^{13}C spectra of these systems a moot point. Fortunately some rather interesting and unexpected results were observed in this study even though the original questions were never answered.

The observed Δ^1J_{CH} and $\Delta\delta_C$ upon addition of 1 equivalent of acid to the 222 compounds were unsurprising. The downfield shift of the quaternary carbon (H-222 and Me-222) ,the increased $^1J_{CH}$ (H-222), and the upfield shift of the methyl resonance (Me-222) are readily explainable in terms of the inductive effect of the positively charged nitrogen. The addition of a second equivalent of acid to H-222 in D_2O resulted in a hydrolysis reaction. This reaction is discussed in a later section (see hydrolysis of H-222).

The addition of 1 equivalent of acid to H-333 in $CDCl_3$ produced the surprising result that the quaternary carbon was shifted upfield slightly. The ^1H DNMR spectrum of H-333 in the presence of 1 equivalent of acid evidenced

significant broadening. Wuest[104] has also reported the temperature dependence of this ^1H DNMR spectrum. He reported that the broadened resonances of H-333 in the presence of 1 equivalent of acid in D_2O sharpened at 70°C to a spectrum requiring average D_{3h} symmetry[2.26 (quin.,6H), 3.39 (t,12H), 4.65 (s,1H)]. These observations are consistent with the process depictd in scheme 1. Our results are in agreement with Wuest's proposed process.



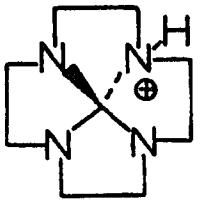
scheme 1

Wuest could not tell whether the open or the closed form of H-333 was the dominant form from his ^1H experiment[104]. We endeavored to answer this question by a variable temperature ^{13}C DNMR experiment. The carbon DNMR of H-333 plus 1 equivalent of DCl in methanol - d_4 had only two sharp resonances at ambient probe temperature. The

resonance assigned to the central carbon was broadened into the baseline. As the temperature was lowered the ring carbon resonances broadened and continued to broaden down to -65°C. At -15°C the methine carbon resonance began to grow out of the baseline at 99.8 ppm. (The DNMR data is contained in Appendix 2.) This resonance continued to sharpen down to -65°C and was gradually shifted upfield to 96.8 ppm. The resonance was assigned to the methine carbon of the protonated closed form of H-333 (because the shift of the amidinium carbon would be considerably further downfield). The upfield shift ($\delta_{amb.}$(MeOH) = 100.0 ppm for neutral H-333) must be due to the effect of the positively charged nitrogen although this observation is not consistent with Morishima's[193b] results. The slow exchange region could not be reached because of severe anisotropic line broadening due to high solvent viscosity at temperatures below -65°C.

This temperature dependent DNMR behavior is consistent with a predominance of the protonated tricyclic with a small amount of the bicyclic amidinium ion. At ambient temperature the process depicted in Scheme 1 must be fast on the DNMR time scale resulting in averaged resonances for the ring carbons. The methine carbon resonance was broadened into the baseline because of the large chemical shift difference between the open and closed forms for this carbon. As the temperature was lowered (and exchange was

slowed) only the peaks assignable to the protonated tricyclic H-333 were observable indicating a predominance of this form. Richman[34] has reported a similar degenerate rearrangement with the monoprotonated tetracyclic tetraamine 7 (fig.2.90).



7

fig 2.90

It is concluded, on the basis of the ^{13}C chemical shifts and the lack of broadening of these resonances at ambient probe temperature and the lack of change in the ^{1}H spectra at elevated temperatures (see hydrolysis of H-222) that H-222 exists solely as the closed tricyclic structure in the presence of 1 equivalent of acid. The same conclusion must be drawn concerning Me-222. H-333 exists predominantly as the closed tricyclic in equilibrium with a small amount of open form in the presence of 1 equivalent of acid. The fact that the quaternary carbon of Me-333 was shifted downfield in the presence of 1 equivalent of acid suggests that a higher proportion of the open form is present when this compound is protonated than is present when H-333 is protonated.

Hydrolysis of H-222. H-222 was stable in neutral media.

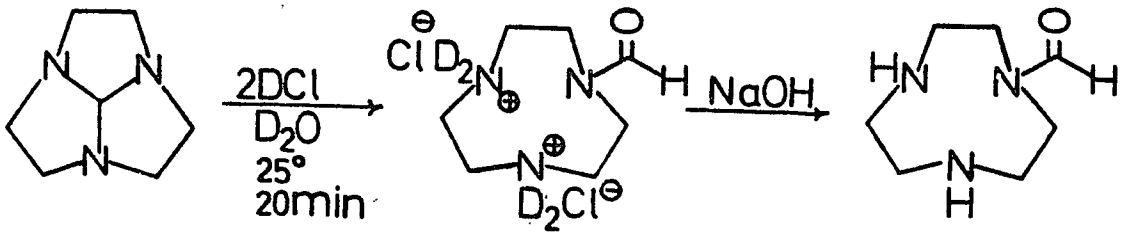


fig 2.92

The ^1H NMR (d_2O) of H-222 in the presence of one equivalent of DCl remained unchanged up to 102°C. In the presence of two equivalents of acid it was rapidly hydrolyzed to the monoformamide macrocycle 118 (fig.2.92). After a base workup compound 138 was isolated in good yield.

The progress of this reaction was followed by the growth of the formamide proton resonance at 8.17 ppm indicating that the reaction was complete in 20 minutes. When the reaction was followed by ^{13}C DNMR, only peaks assignable to the starting material and product were observable. No peaks assignable to bicyclic intermediates were observed. The UV spectrum of the reaction mixture showed no absorbances assignable to the amidinium chromophore. Since the reaction must pass through a bicyclic amidinium ion one must conclude that this intermediate was present in very low concentrations. These observations are consistent with the mechanism presented in fig.2.93.

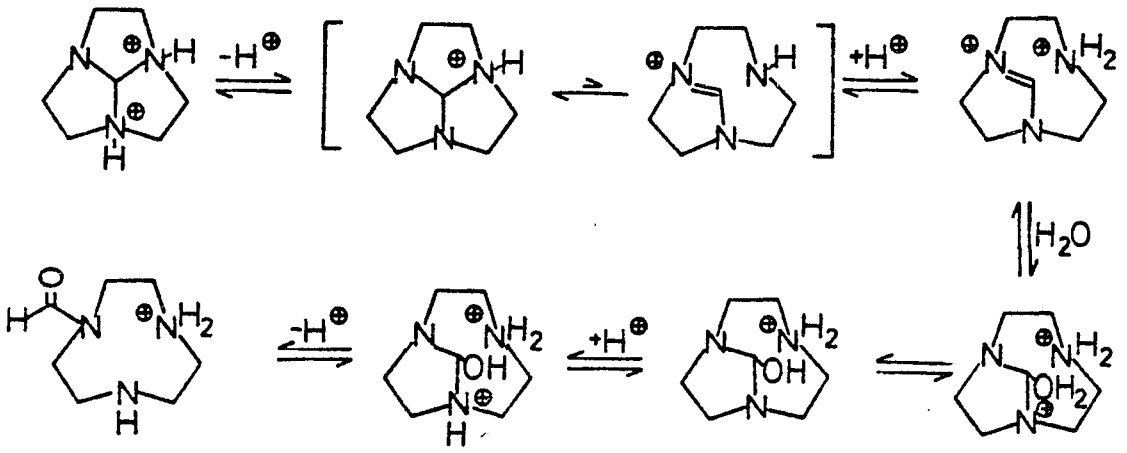


fig 2.93

This reaction provides a very good method of monoprotecting 1,4,7-triazacyclononane. This reaction

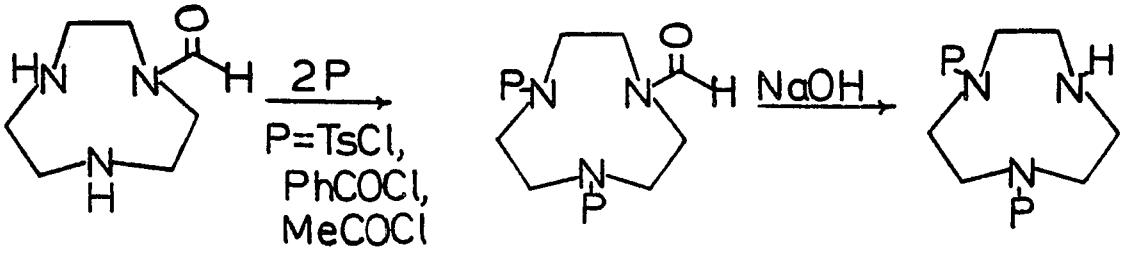
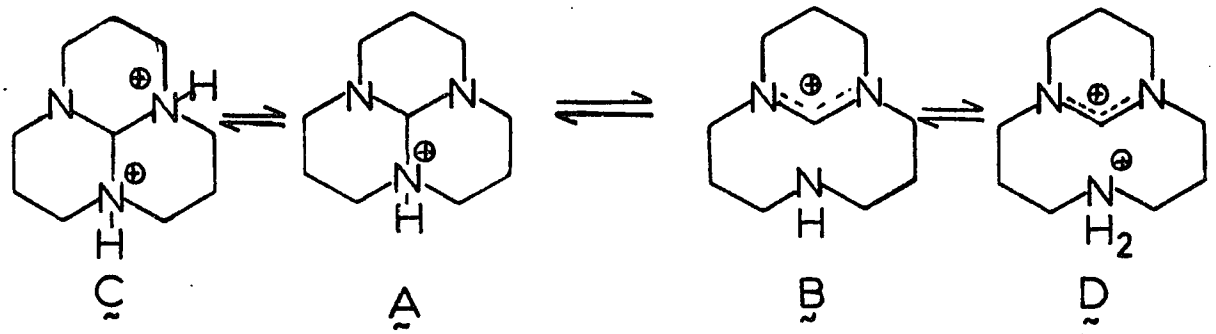


fig 2.94

allows the facile introduction of a removable protecting group without the problems associated with the preparation of monoprotected macrocyclic triamines by classical methods. (See alkylation section for a discussion of the problems associated with classical protection schemes.) The sequence presented in figure 2.92 could easily be extended to the preparation of the diprotected macrocycle (fig.2.94).

Hydrolysis of H-333. The addition of a second equivalent of aqueous acid to H-333 produces a very different result than in the H-222 case. It will be recalled that the addition of the first equivalent of acid to H-333 resulted in an equilibrium mixture of 2.95A and 2.95B (fig.2.95). The addition of the second



C A B D

fig 2.95

equivalent of acid shifted the equilibrium presented in fig.2.95 to the right so that 2.95D became the predominant species. 2.95D was found to be exceedingly resistant towards acid hydrolysis since the heating of the reaction mixture for 30 days at 90°C followed by a base workup resulted in nearly quantitative recovery of H-333.

The remarkable difference in susceptability towards acid hydrolysis of H-222 and H-333 must be attributed to the effect of the ring size on the stabilities of the intermediate amidinium ions (fig.2.96). Evidently intermediate 2.96-2 has more iminium ion character than 2.96-1. The eight membered ring in 2.96-2 must not allow the necessary coplanarity of the nitrogens and the central carbon for efficient overlap of the nitrogen lone pairs with

the vacant p-orbital on the carbon. An increase in the iminium ion character would impart hydrolytic instability (ie iminium ions are more susceptible to nucleophilic attack than are amidinium ions). The resistance of the ten membered amidinium ion 2.96-1 towards hydrolysis must be attributed to efficient overlap in the amidinium system and to the resistance of the amidinium carbon towards nucleophilic attack.

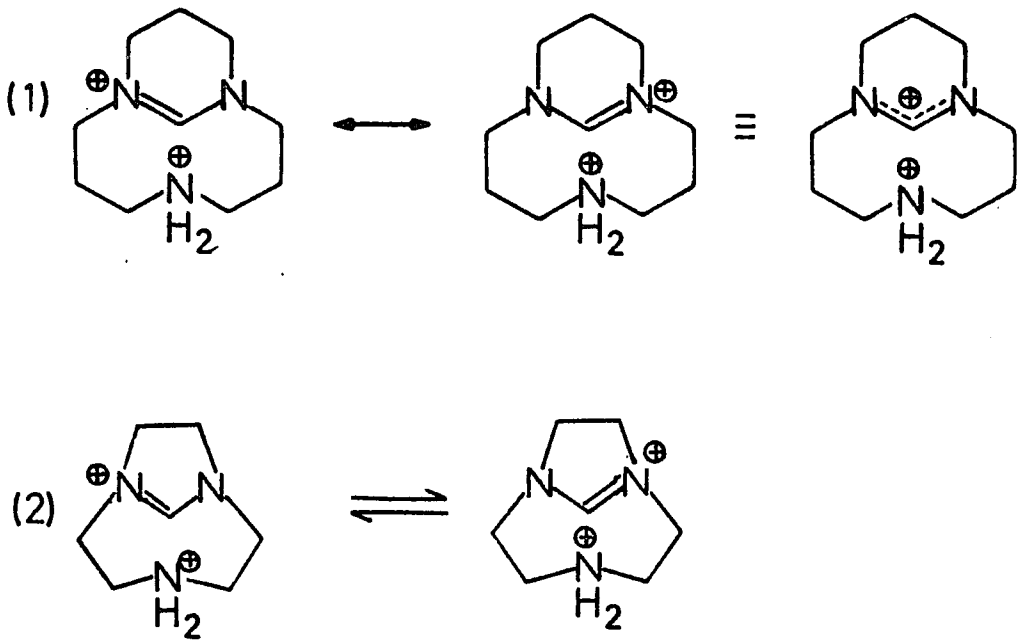


fig 2.96

The predominance of B (fig.2.95) was proven by following the changes in the ^{13}C spectrum as a function of pH and by a variable temperature ^{13}C experiment with H-333 plus 2 equivalents of DCl in aqueous(D_2O) methanol-d_4. The ^{13}C spectrum of H-333 plus 2 equivalents of acid at 65° C consisted of one broad line at 147.5 ppm and two sharp lines at 50.5 and 25.0 ppm. The downfield peak was assigned to the central carbon. The two other resonances were

assigned to the ring carbons. At ambient probe temperature the central carbon resonance was broadened into the baseline and the ring carbon resonances were broadened slightly.

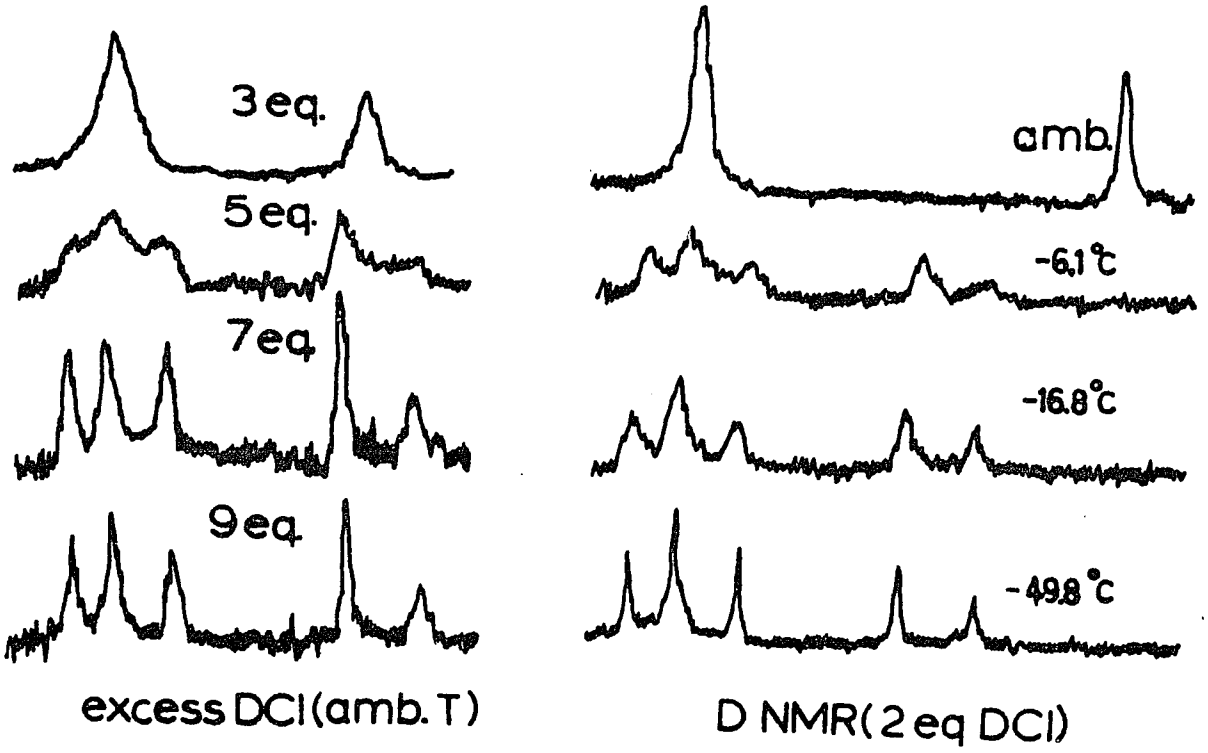


fig 2.97

As the temperature was lowered the resonances broadened further and then began to resharpen. The spectrum at -50°C consisted of six slightly broadened lines: 155.2, a group of three at 55.4, 50.0, and 44.3 (intensity ratio ca. 1:1:1), and a second group at 28.2 and 20.4 (intensity ratio ca. 2:1). This same type of spectral behavior was also observed at ambient probe temperature when successive aliquots of excess of acid were added to H-333 in methanol-d_4. Traces of the ^{13}C spectra which were recorded for these experiments are presented in fig.2.97. (DNMR data is contained in Appendix 2.)

At the lowest attainable temperatures only peaks assignable to the bicyclic amidinium system were observed indicating a predominance of the open form. The ^{13}C behavior is consistent with the generalized scheme presented in fig.2.98.

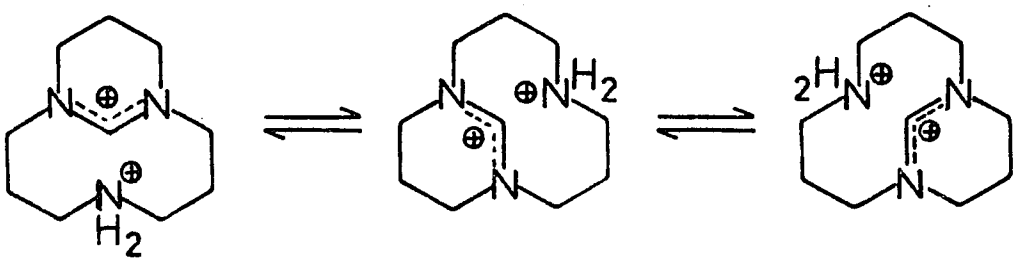


fig 2.98

This process is fast on the DNMR time scale at 65°C resulting in the observed averaged resonances. The intermediates on this pathway are closed mono- and diprotonated H-333. The central carbon resonance was not observable at ambient temperature because of the large chemical shift difference between this resonance in the bicyclic structure and in the corresponding tricyclic form of H-333. Therefore, a small equilibrium concentration of tricyclic form (either monoprotonated or diprotonated) exists at ambient temperature.

The explaination of the pH dependent ^{13}C DNMR requires consideration of the equilibrium constants for the proton transfers required for this process. The scheme presented in fig.2.985 contains all of the possible proton

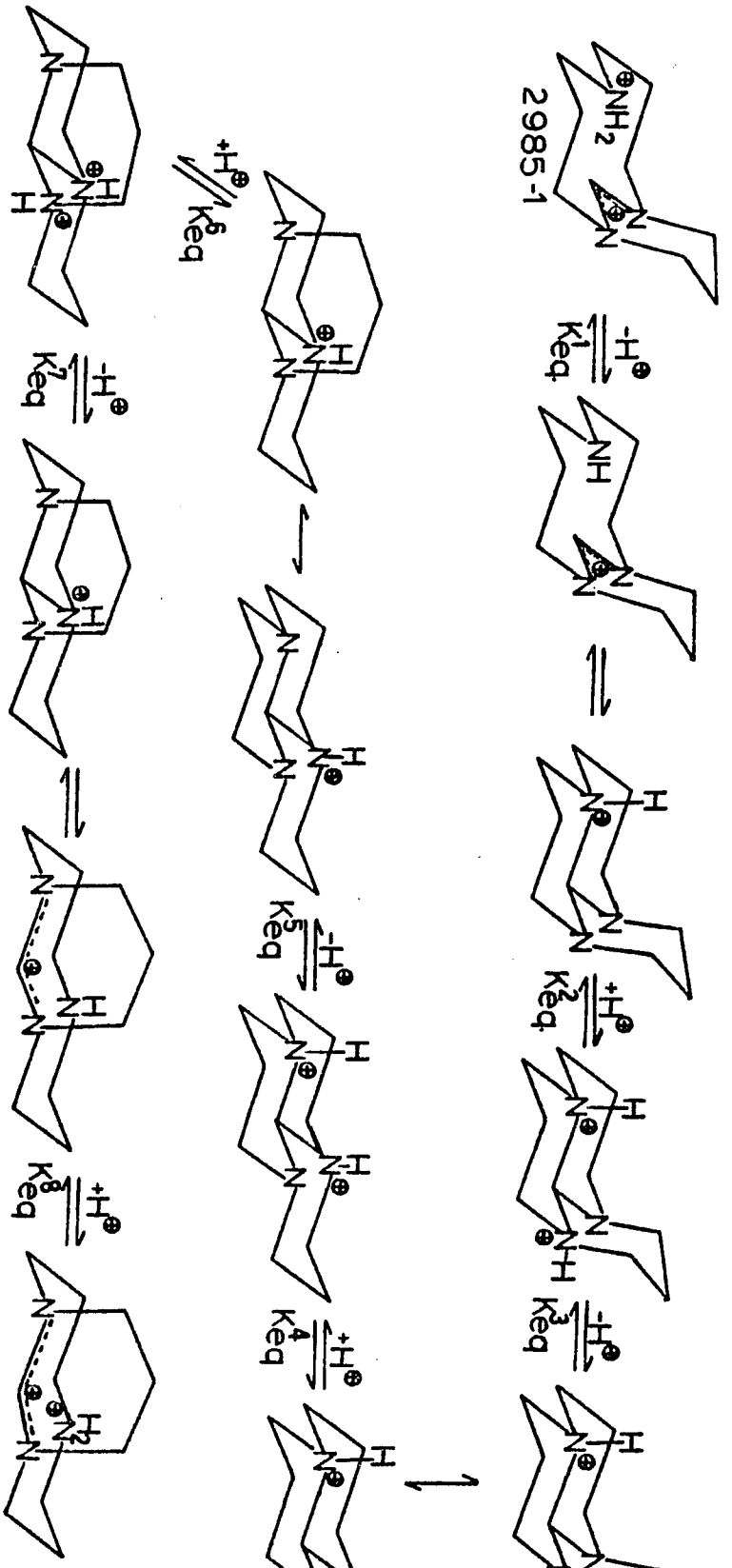


fig 2.985

transfers and conformational processes that could possibly occur on the pathway of this degenerate rearrangement. To explain the data it is first necessary to make the reasonable assumption that the pK_a of the amine nitrogen in 2.985-1 (or 2.985-1') is much larger than the pK_as of the protonated closed forms of H-333. Once this assumption is made then it follows that the interconversion of 2.985-1 to 2.985-1' (or 2.985-1' to 2.985-1) is dependent only on the magnitudes of $K_{eq}1$ (and$K_{eq}8$ respectively) and pH. Since additional acid would shift these equilibria towards 2.985-1 and 2.985-1' the rate of interconversion of these two species would be impeded.

An estimate of the percentage of the open form of H-333 in the presence of 2 equivalents of acid can be made employing Eliel's chemical shift interpolation method[106]. A value of 95% of the open form at -50°C is obtained when the following assumptions are made; 1) δC(methine) of closed protonated H-333 = 96.9 ppm = δC (methine) of H-333 plus 1 equivalent of acid at 65°C and 2) δC (methine) of open H-333 = 158.4 ppm = δC (methine) of 5-methyl-5,9-diaza-1-azonibicyclo[7.3.1]tridec-1(13)-ene (134).

The hydrolyses of the unsymmetrical orthoamides were also examined. The possible products resulting from the hydrolyses of H-322 and H-332 are presented in fig.2.99.

The ^{1}H and ^{13}C DNMR of the products of these reactions indicated the presence of all possible products in addition to recovered starting materials. Separations of the mixtures of isomers were not attempted and no further studies of these reaction were undertaken.

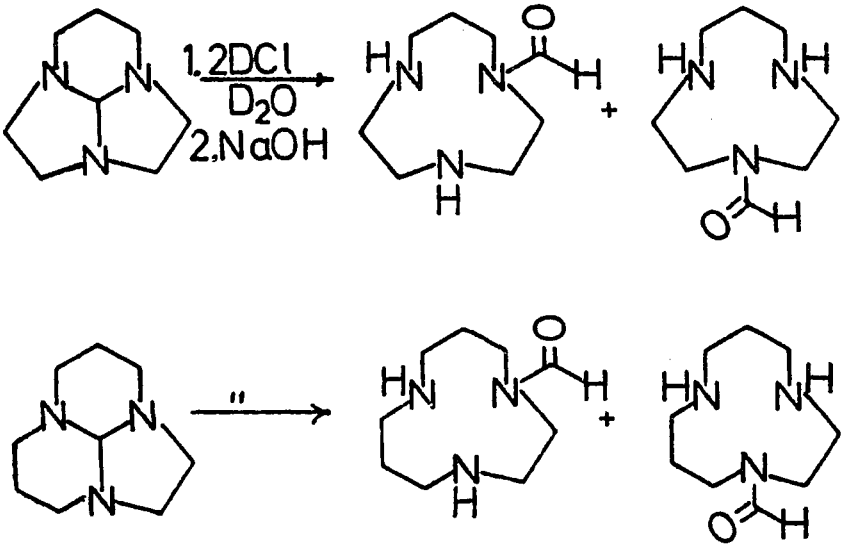
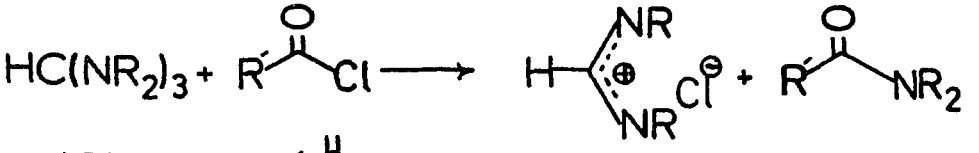


fig 299

Acylation of H-333

The reaction of acyclic orthoamides with carboxylic acid chlorides yields carboxamides and formamidinium chlorides (fig.2.100).



$HC(NR_2)_3 + R'COCl$

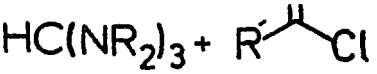


fig 2.100

The known reactivity of acyclic orthoamides coupled with our desire to develope protection - deprotection schemes for macrocyclic polyamines led us to examine the reaction of H-333 with acylating agents. H-322 and H-332 were not acylated because we anticipated mixtures of products. H-222 was not acylated because alkylation resulted in preservation of its tricyclic integrity and because a protection scheme based on the hydrolysis of H-222 had already been developed.

The reaction of H-333 with benzoyl chloride in refluxing benzene (fig.2.101) yielded a hygroscopic crystalline product 120.

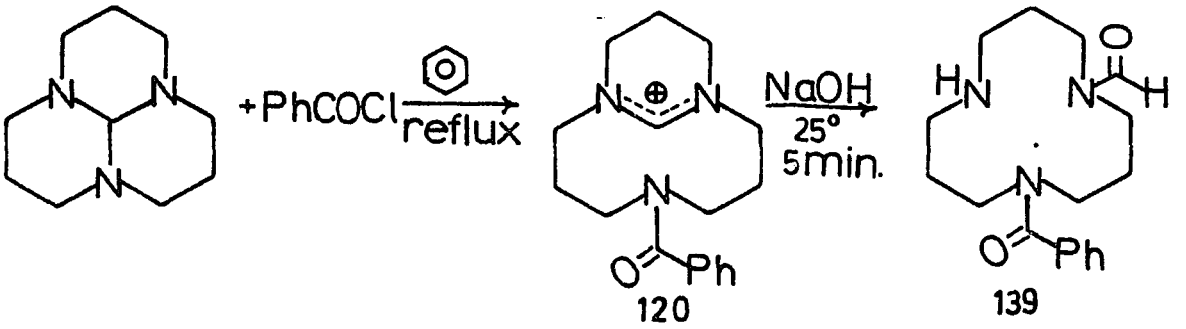


fig 2.101

The IR of 120 exhibited both the carbonyl and the amidinium stretching frequencies in the 1600 - 1700 cm^{-1} region. The ^{1}H NMR was consistent with the assigned structure. The ^{13}C NMR contained eleven lines with chemical shifts which were compatible with the assigned structure. Rotation about the C - N amide bond was fast on the NMR time scale as indicated by the number of lines (in the ^{13}C spectrum) and by the narrow line widths of the ring carbon resonances. The double bond character of the C - N amide bond is probably reduced by steric inhibition of resonance and by participation of the nitrogen lone pair in a transannular interaction with the amidinium carbon. The rotational barrier of dimethylbenzamide has been estimated to be 15.5 kcal/mol[211] indicating that rotation could be slow on the NMR time scale. 120 was stable in neutral aqueous media but was rapidly hydrolyzed in dilute NaOH. The hydrolysis of 120 in dilute NaOH to yield 139 was followed by proton NMR. The disappearence of the amidinium proton resonance indicated that the hydrolysis was completed within minutes. The hydrolysis of formamide 121 (fig.2.102) under very mild

conditions indicates the ease with which these formamides can be hydrolyzed. Therefore long reaction times in the hydrolysis of 120 must be avoided to preserve the formamide.

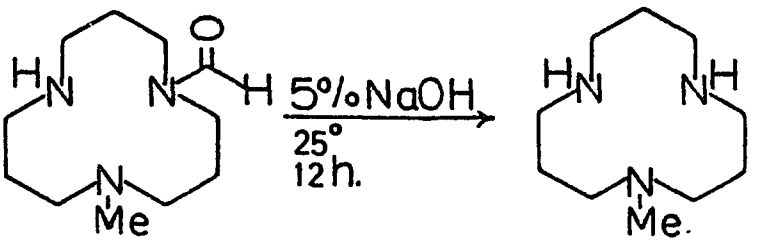


fig 2.102

group in 139. It might even be worthwhile examining the hydrolysis of 120 at lower temperatures. The ^{13}C NMR spectrum of 139 exhibited two resonances (of unequal intensity) which were assigned to the formamide carbon indicating slow rotation about the C -N amide bond. There are 17 ring carbon resonances (out of a possible 18, indicating one degeneracy) resulting from the slow rotation about the C - N formamide bond. ^{1}H NMR was also consistent with the assigned structure but some minor impurities were observable. The presence of some minor impurities was confirmed by TLC (neutral alumina, 5% ethanol/CH_2Cl_2). Although 139 was not purified (due to time contraints) it is expected that it should be possible to obtain 139 in pure form.

The reaction sequence shown in fig.2.101 is the basis of a powerful protection - deprotection scheme for the 1,4,7 - triazacyclododecane macrocycle. The entire proposed sequence is shown in fig.2.103.

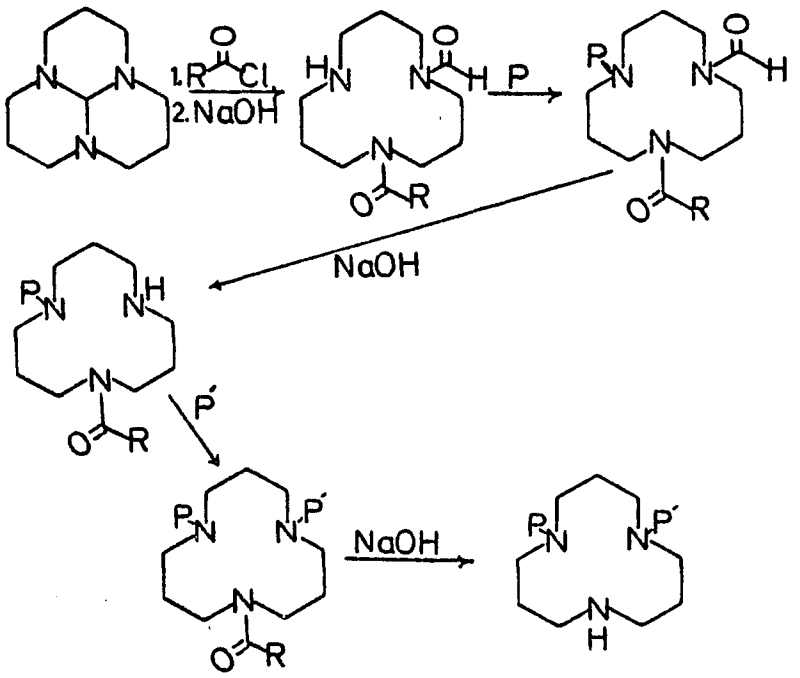


fig 2.103

This sequence allows the differentiation of all three nitrogens in the macrocycle. The two pieces of work needed to completely develop this sequence are purification of 139 and finding reaction conditions which would allow the selective hydrolysis of the formamide in the presence of the benzamide. Considering the ease with which formamide 121 was hydrolyzed the latter detail should pose no problem.

The orthoamides have been studied by empirical force field calculations (Allinger's MM2[128,129]) to determine the relative energies of the reasonable ground state conformations. The force field is very well parameterized for hydrocarbons[195] and has been shown to yield reliable energies and geometries for paraffins. The force field has also been parameterized for a number of other functionalities with varying degrees of success. Recently it has been parameterized for amines and has been shown to yield reliable geometries in many cases for simple aliphatic amines[131,132]. The energies for polyamines as calculated by MM2 are less reliable than the geometries. We have several cases where the X-ray crystal structures of some polycyclic aminals have been determined and excellent agreement was found between the calculated and experimentally determined geometries have been found[196]. There are, however, several structural features present in the orthoamides for which MM2 has not been parameterized. Therefore when examining the energies as computed by MM2 for this series these shortcomings should be kept in mind.

An important point to consider when interpreting MM2 results is that the total energy term which is generated is best compared to the enthalpy and as such does not include

entropy differences between conformations. The trivial entropy difference can be an important factor in the total free energy difference between conformations which have markedly different symmetries. For example, the trivial entropy difference between H-333cct and H-333ttt amounts to 2.18 eu (in favor of the less symmetrical H-333cct) and is recognized as an important factor in the relative energies of the ground state conformations of the 333 orthoformamides (and acetamides).

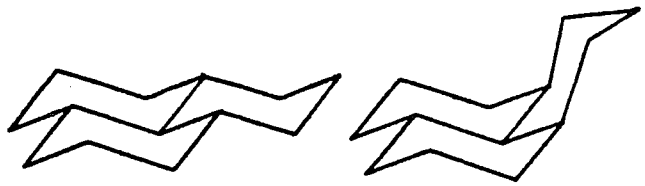
The first major structural feature of the orthoamides for which MM2 has not been parameterized is the ability of nitrogen to flatten. This feature should be especially important in the 222 and the 322 ring systems. Nitrogen flattening would reduce bending strain in these systems. Rather than try to factor out this contribution it was treated as a systematic error which should be constant for a given ring system. this error probably results in calculated energies on the high side.

Another problem with the MM2 force field arises in the treatment of the electrostatic term (dipole contribution) in trifunctional molecules. Allinger has stated that preliminary calculations of trifunctional molecules give "erratic" results and "it seems that further investigations - experimental and theoretical - are required before the road clears for molecular mechanical studies of more

complicated structures" [136]. Since the orthoamides are trifunctional molecules, with the added complication of having all three dipoles bonded to a single carbon, it seems wise to heed Allinger's warning and view the dipole term with some suspicion. For this reason the steric energies (excludes the electrostatic term) and the total energies (includes the electrostatic term) are tabulated. Fortunately, for all but one of the cases, the electrostatic contribution does not change the relative energies of the conformations.

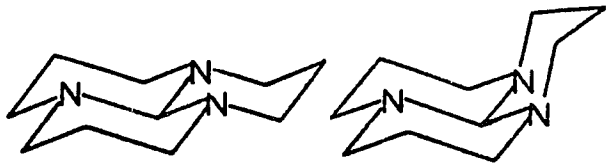
A third unparameterized structural feature present in the orthoamides (which is related to the dipole contribution) is the anomeric effect[139]. Examination of models indicates that the anomeric effect should favor *cis, cis, trans* conformations over *trans, trans, trans* conformations in the tricyclic orthoamides. MM2 may take this effect into account somewhat in the dipole term in that anti dipoles are generally considered more stable than syn or gauche dipoles. The uncertainty of the dipole term in trifunctional molecules makes a discussion on the treatment of the anomeric effect, by MM2, in the orthoamides difficult, but some insight into this effect may be gained by the following treatment. To determine if MM2 was accounting for the anomeric efect the results of the MM2 calculations for the hydrocarbons *94-HC-cct* and *94-HC-ttt* were compared with those for *94-cct* and *94-ttt*. The results

of this comparison are presented in fig.2.104.



94-HC-ttt 94-HC-ctt ΔE

15.51 18.58 3.07



94-ttt 94-cct

26.58 28.11 1.53

ΔΔE =1.54 kcal/mol.

fig.2.104

The smaller difference in energy between 94-cct and 94-ttt must be attributed to the substitution of N for C and the anomeric effect. A similar comparison of the experimentally determined data for the known model systems 2.105a- 2.105d yields a similar result but of smaller magnitude (fig.2.105) [197]. The Δ-Δ E of the tricyclics would be expected to be larger than the model system because of the additional nitrogen in the orthoamides.

MM2 calculations were performed on model compounds 2.105c and 2.105d. Δ H was calculated to be 0.83 kcal/mol.

When ΔS_{mix} is taken into account then a value of 0.66 kcal/mol (T= -150°C) is obtained for ΔG. This value agrees quite well with the reported ΔG of 0.65 kcal/mol which has been determined by ^{13}C DNMR at -150°C[197b].

Similar calculations were performed on the cis, cis, trans and the trans, trans, trans conformations of Me-333 and the analogous hydrocarbons. The results of this comparison are shown in fig.2.106.

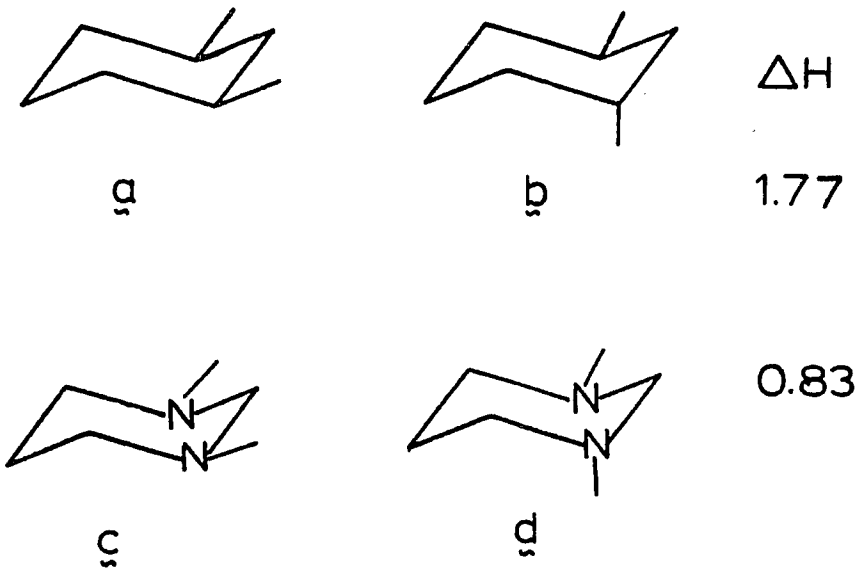
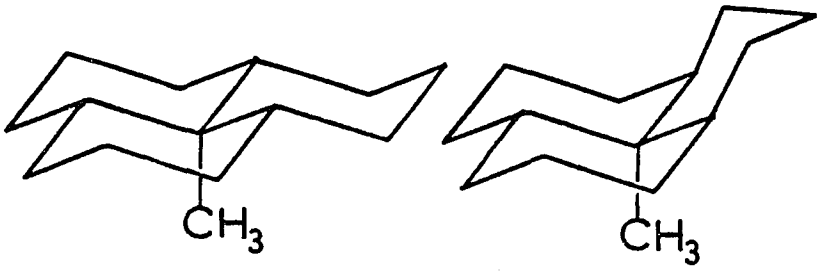


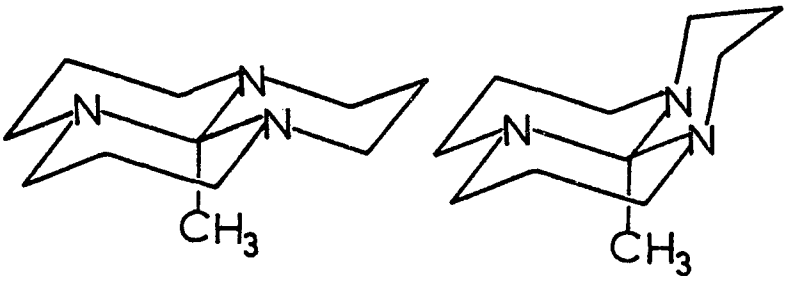
fig.2.105

The anomeric effect is presently formulated in terms of MO theory (see conformational analysis of the orthoamides) and as such cannot possibly be accounted for by MM2. But it appears that MM2 is artificially compensating for the anomeric effect in the dipole term. The presence and

magnitude of this compensation can be seen by comparing the $\Delta-\Delta E_{steric}$ (excludes the dipole term) and



98-HC-ttt	98-HC-cct	ΔE
24.13	25.37	1.24



98-ttt	98-cct	
36.95	37.18	0.23

$\Delta\Delta E = 1.01$ kcal/mol.

fig. 2.106

$\Delta-\Delta E_{total}$ (includes the dipole term) for relavent conformations. As an illustrative example, consider the differences in the calculated energies between the cis,cis,trans (favorable anomeric effect) and the all-trans conformations of Me-333 (fig.2.106). In this case the $\Delta-\Delta E_{steric}$ = 1.06 kcal/mol and the $\Delta-\Delta E_{total}$ = 0.23

kcal/mol, where $\Delta\text{-}\Delta E_i = E_{i\ c,c,t} - E_{i\ t,t,t}$. The more favorable disposition of the dipoles in the cis,cis,trans conformation is the reason that the dipole term favors this conformation over the all-trans. Edward was the first to report the observation that compounds exhibiting favorable anomeric effects always possessed the lower energy disposition of dipoles[138]. He attributed the anomeric effect to this more favorable disposition of dipoles. The magnitude of the observed anomeric effects could not be adequately accounted for in terms of the electrostatic model and this led to the now generally accepted MO formulation. It must be concluded that MM2 is (in an artificial way) compensating for the anomeric effect, for the orthoamides, in the dipole term. The magnitude of the calculated effect is probably on the low side because it is calculated purely from electrostatic terms.

The following discussion of the MM2 results is divided into two sections. In the first section the ground state conformations which have been analyzed with MM2 are presented on a compound by compound basis. In this first section the major interactions which contributed to the assignment of the conformation of lowest energy are presented. Also included in this section are tabulations of the energy factors (e.g. torsional, bending, etc.) which the program has calculated for minimized conformations. The specific interactions which make contributions to the total

energies of the ground states are not abstracted by the program and can only be ascertained by a systematic search of the raw computer output. This search has been undertaken and specific interactions have been determined.ined. The presentation of the quantitative aspects of these interactions has not been attempted here due to the enormity of that endeavor. The qualitative aspects of these interactions, however, are presented. The reader is directed to the raw computer output for these compounds for quantitative data.

The second section addresses the energy trends present in the ground states of lowest energy as calculated by MM2. Graphical analysis of the energy trends as a function of ring size (with constant R size) and as a function of R size (with constant ring size) are presented. This analysis gives a good overview of the contributing energy factors governing the minimum energy conformations of the orthoamides and allows identification of trends in these factors as a function of R and ring sizes. These trends allow one to make valuable generalizations concerning the preferred conformations and the energy factors which govern these preferences.

It is obvious from the preceeding discussion that the absolute energies of the orthoamides (as calculated by MM2) cannot be relied upon. But even with admittedly important

structural features unaccounted for by MM2, the relative energies of ground state conformations can probably be relied upon if they are not very close in energy. The geometries which were computed are probably fairly accurate.

The tabulated energy factors for the orthoamides are contained in figures 2.1065 - 2.114. These figures are located at the end of this section.

222 Ring System

The ground state conformations which were considered for the 222 series are presented in fig.2.1065. Conformations other than the all-cis were excluded due to the obvious strain that nitrogen inversion would impart to this ring system (i.e. Fieser models of the trans conformations cannot be constructed without breakage). Since the all-cis slightly twisted C_3 structures (see conformational analysis of H-222) are the only reasonable conformations they were assigned as ground states of minimum energy for the series.

322 Ring System

322 Orthoformamides. The results of the calculations for the most reasonable ground states for this series are presented in fig.2.109. There are several more possible ground states (see conformational analysis of H-322) which we did not calculate because we considered these to be higher energy conformations. The major energy factor which destabilizes 92-cct results from distortions of the central C-N-C bond angles. One of these central angles is compressed 6.8 degrees and the other angles are distorted to accommodate this compression. Distortions in the central C-N-C angles cause further distortions of the adjacent C-C-N angles.

322 Orthoacetamides. The two calculated conformations of Me-322 are presented in fig.2.705. The factors which destablize 96-cct are the same C-N-C angle distortions which destablized the cis,cis,trans conformation in H-322. The distortions are slightly more severe in Me-322 because avoidance of steric interactions between the methyl and the ring system causes further flattening of the ring system.

322 Orthopropionamides. The calculated conformations for Et-322 are presented in fig.2.108. These conformations can be broken down into two subgroups on the basis of the ring conformations. Members of the cis,cis,trans subgroup are higher in energy than the all-cis subgroup. Again the cis,cis,trans conformations are destabilized by distortions

of the central C-N-C bond angles. This effect is compounded by 1-4 interactions between the methyl of the ethyl group and the rings (particularly in 100cct-(R2) and 100cct-(R3)). Of the all-cis rotomers, 100ccc(C_1) is favored because unfavorable 1-4 interactions between the methyl of the ethyl group and the ring are minimized.

332 Ring System

332 Orthoformamides. The most reasonable conformations for H-332 are presented in fig.2.109. Note that all three conformations are within 0.7 kcal/mol of one another. The analysis is complicated further because MM2 has assigned higher energies to conformations which should be favored by the anomeric effect. It must be concluded that the relative energies of the conformations as assigned by MM2 are suspect.

Having acknowledged the problems with the assigned energies, a discussion of how MM2 arrived at these energies is presented below because these arguments are pertinent to the discussion of the energies of the orthoacetamides and orthopropionamdes. 93ttt was assigned as the minimum energy ground state conformation. Cis,cis,trans conformations are destabilized by distortions of the central C-N-C bond angles. Also in 93cct(C_1) there is increased torsional

energy in the cis-trans fused six membered ring due to flattening of the chair conformation.

332 Orthoacetamide. The reasonable conformations for Me-332 are presented in fig.2.110. Note that there is a wider range of energies in these ground states than was present in the corresponding orthoformamides. The anomeric effect should favor 97cct(C_s) (the conformation which was assigned the lowest energy). 97ttt is destabilized by stretching of the C-N bonds and by interactions between the methyl hydrogens and the hydrogens in the five membered ring and the axial hydrogens in the six membered rings. 97cct(C_1) is destabilized primarily by two interactions. The first involves hydrogens on the carbons alpha to the nitrogen in the cis,trans fused six membered ring and the hydrogens in the five membered ring. The second is between the methyl hydrogens and hydrogens on the carbons alpha to the nitrogen in the cis,trans fused ring.

332 Orthopropionamides. The calculated ground state conformations are presented in fig.2.111. These are separated into three families on the basis of ring conformations. 101cct-6(R1) is destabilized by C-N bond stretching, torsional strain due to the envelope conformation of hydrogens in the five membered ring, and interactions between hydrogens in the five membered ring and hydrogens on the carbon alpha to the nitrogen in the cis,cis

fused six membered ring. Additional 1-4 interactions between the ethyl group and the five membered ring further destabilize 101cct-6(R1). All of the other conformations are between 6.5 and 15 kcal/mol higher in energy. The very high energies of these conformations result primarily from 1-4 interactions between the ethyl group and the rings and because of flattening of the ring system.

As was the case with the corresponding orthoacetamides, the anomeric effect would tend to stabilize further the conformations of lowest energy. It must be concluded that the relative energies of the ground state conformations, as assigned by MM2, are reliable.

333 Ring System

333 Orthoformamides. The calculated conformations of the orthoformamides are presented in fig.2.112. The entire difference in energy between these conformations is principaly due to the different number of gauche and anti interactions and to the bending strain in the C-N-C bond angles in 94cct. The symmetries of 94cct and 94ttt require the consideration of the trivial entropy difference between these two conformations. The more symmetrical all-trans conformation has C_{3V} symmetry whereas the cis,cis,trans conformation belongs to the C_S point group. Therefore

94cct should have an entropic advantage over 94ttt. The trivial entropy difference between these two conformations (as calculated by equation 2.4 [198]) amounts to 2.18 eu. At room temperature this amounts to a 0.65 kcal/mol entropic advantage for 94cct. Note that in this case the additional energy difference does not change the assignment of 94ttt as the minimum energy conformation. Another consideration is that the anomeric effect should also favor 94cct. But since ΔH = 2.2 kcal/mol it is concluded that the assignment of 94ttt as the lowest energy ground state conformation is reasonable.

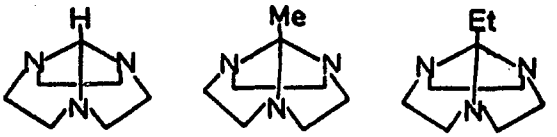
333 Orthoacetamides. The calculated (all-chair) conformations of Me-333 are presented in fig.2.113. Note that the energies of the calculated conformations are very close together. Several points need to be made concerning the relative energies of 98cct and 98ttt. First, if the trivial entropy advantage, in favor of the less symmetrical 98cct, is added to the calculated enthalpy then 98cct is assigned as the minimum energy conformation at room temperature. Secondly, the anomeric effect (which should also favor 98cct) might further favor 98cct to the point of predominance. The spectral evidence clearly indicates that 98ttt is the major conformation. It must therefore be concluded that the calculated energy difference between 98ttt and 98cct is too small.

The calculations indicate that 98cct is destabilized by stretching of C-N bonds and by the introduction of two gauche interactions involving the C-N bonds of the cis,cis fused ring with the C-C bonds in the two cis,trans fused rings (see fig.2.114).

333 Orthopropionamides. The calculated conformations for Et-333 are presented in fig.2.115. In this case the energies of the ground states are not close together and the anomeric effect would further favor 101cct(C_s) (the minimum energy conformation). The assignment of 101cct(C_s) is no doubt correct. 101ttt and 101cct(C_1) are destabilized by interactions between the ethyl group and the axial hydrogens on the rings. The additional energy of 101ttt results from distortions of the C-N-C bond angles.

Conclusion. Due to the unparameterized structural features present in the orthoamides, the calculated enthalpies of the ground state conformations must be used only in a qualitative manner. One extremely useful qualitative treatment is the assignment of the minimum energy ground states. The anomeric effect in model systems was found to be worth approximately 0.30 kcal/mol (ignoring the shorter C-N bonds). This suggests that if the calculated enthalpies differ by at least 0.7 kcal/mol (which is a conservative estimate) then the conformation of minimum enthalpy can be reliably assigned solely on the basis of the

calculated enthalpies. If, on the other hand, the calculated H between ground states is very small (i.e. H-332 and Me-333) then the assignment of the minimum enthalpy ground state conformation must be done only after giving due consideration to the unparameterized structural features applicable to the particular case.

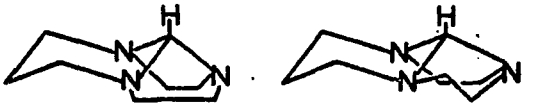


91-ccc 95-ccc 99-ccc

222 RING SYSTEM

ENERGY FACTOR(kcal/mol)	91-ccc	92-ccc	99-ccc
Compression	1.0426	1.2333	1.4062
Bending	8.1777	8.1777	8.4071
Stretch-bend	-0.1743	-0.1902	-0.1440
VanderWaals			
1,4	6.3447	7.1661	7.9255
other	-1.4499	-2.6531	-3.1386
Torsional	17.5776	22.0196	23.2139
Dipole	6.5316	6.5280	6.5277
Total Energy	38.0500	42.2809	44.1977
Steric Energy	31.4968	35.7529	37.6700
Dipole Moment(D)	1.607	1.596	1.590

fig 2.1065

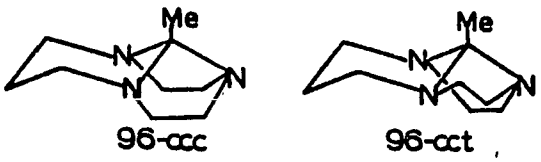


92-ccc 92-cct

322 Orthoformamides

Energy Factor(kcal/mol)	92-ccc	92-cct
Compression	1.2183	1.2849
Bending	10.8896	13.1406
Stretch-bend	0.1416	0.0272
VanderWaals		
1,4	8.2072	9.4110
other	-1.8911	-2.3841
Torsional	14.2862	13.5108
Dipole	6.5139	5.8050
Total Energy	39.4287	40.7953
Steric Energy	32.9148	34.9903
Dipole Moment(D)	1.728	1.105

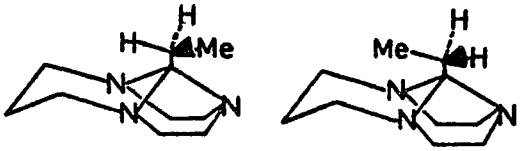
fig 2.107



322 Orthoacetamides

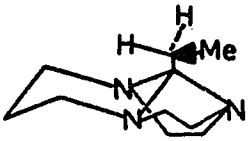
Energy Factor(kcal/mol)	96-ccc	96-cct
Compression	1.5433	1.5740
Bending	10.9567	14.0062
Stretch-bend	0.1507	0.1164
VanderWaals		
1,4	9.1181	9.7697
other	-2.9453	-2.1896
Torsional	17.8711	17.1702
Dipole	6.5053	5.7647
Total Energy	43.1999	46.2143
Steric Energy	36.6946	40.4496
Dipole Moment(D)	1.717	1.149

fig 2.1075

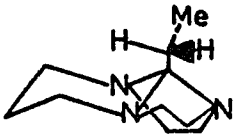


100-ccc(C_1)

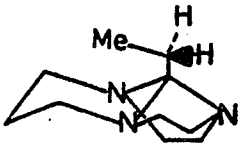
100-ccc(C_s)



100-cct-R(1)



100-cct-R(2)

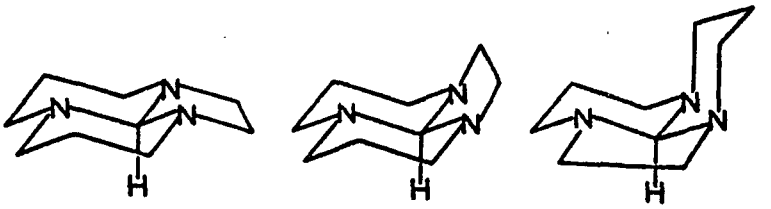


100-cct-R(3)

322 Orthopropionamides

Energy Factor(kcal/mol)	100-ccc(C_1)	100ccc(C_s)	100cct(R_1)	100cct(R_2)	100cct(R_3)
Compression	1.7240	1.9907	1.7434	1.8151	1.9984
Bending	11.2777	11.9578	14.1910	16.4971	16.8559
Stretch-bend	0.2025	0.2552	0.1786	0.2115	0.2451
VanderWaals					
1,4	9.8716	10.0033	10.5202	10.7090	11.0712
other	-3.5243	-2.8690	-2.5839	-2.5942	-1.9689
Torsional	18.7986	20.2417	18.2509	18.9025	19.8653
Dipole	6.5077	6.4949	5.7613	5.7242	5.7195
Total Energy	44.8578	48.0746	48.0617	51.2652	53.7864
Steric Energy	38.3501	41.5797	42.3004	45.5401	48.0669
Dipole Moment(D)	1.712	1.710	1.160	1.125	1.123

fig 2.108

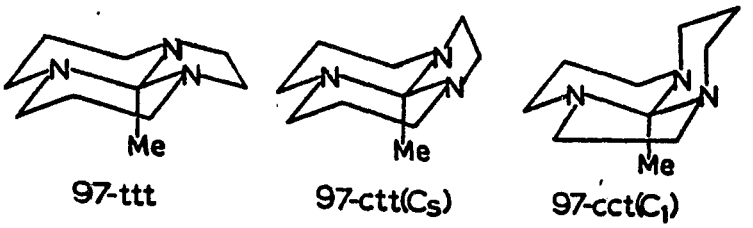


93-ttt 93-ctt(C_s) 93-ctt(C_1)

332 Orthoformamides

Energy Factor(kcal/mol)	93-ttt	93-cct(C_s)	93-cct(C_1)
Compression	1.4153	1.1797	1.4218
Bending	7.7841	8.0498	6.7591
Stretch-bend	0.2349	0.2939	0.2602
VanderWaals			
1,4	12.1329	11.5266	12.3893
other	-3.2657	-3.3256	-3.0287
Torsional	8.8545	10.8429	10.9071
Dipole	6.7385	5.9589	5.8730
Total Energy	33.8945	34.5262	34.5819
Steric Energy	27.1560	28.5673	28.7089
Dipole Moment(D)	2.165	1.294	1.248

fig 2.109

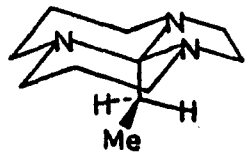


97-ttt 97-ctt(C_s) 97-cct(C_1)

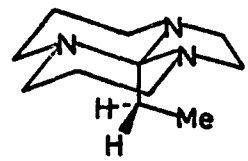
332 Orthoacetamides

Energy Factor(kcal/mol)	97-ttt	97-cct(C_s)	97-cct(C_1)
Compression	2.0448	1.6300	2.2838
Bending	13.0013	9.0558	8.8657
Stretch-bend	0.5234	0.4521	0.3770
VanderWaals			
1,4	11.7388	12.0356	12.8801
other	-0.8163	-2.7176	-1.6148
Torsional	10.9900	13.1122	13.1027
Dipole	6.8639	5.9046	5.7899
Total Energy	44.3459	39.4726	41.6846
Steric Energy	37.4820	33.5680	35.8947
Dipole Moment(D)	2.166	1.334	1.262

fig 2.110



101-ttt(C_1)

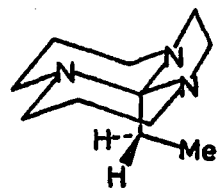


101-ttt(C_s)

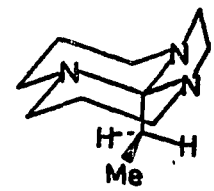
332 (all-trans) Orthopropionamides

Energy Factor(kcal/mol)	101-ttt(C_1)	101-ttt(C_s)
Compression	2.5278	2.4382
Bending	19.4152	17.9919
Stretch-bend	0.7983	0.8377
VanderWaals		
1,4	12.7938	12.4074
other	-0.4295	-0.4019
Torsional	12.9881	13.1989
Dipole	6.9325	6.9237
Total Energy	55.0262	53.3960
Steric Energy	48.0937	46.4723
Dipole Moment(D)	2.164	2.160

fig 2.111



101-cct-5(C_s)

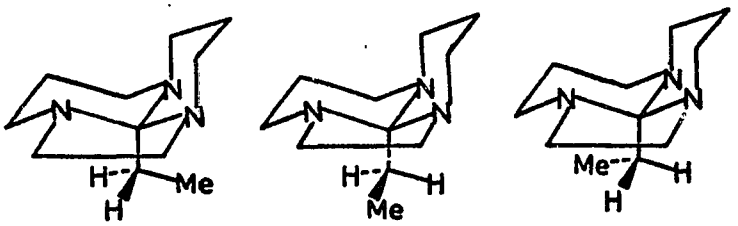


101-cct-5(C_1)

332 (cis,cis,trans) Orthopropionamides

Energy Factor(kcal/mol)	101-ccc-5(C_s)	101-cct-5(C_1)
Compression	1.8555	2.1014
Bending	9.4056	12.6487
Stretch-bend	0.5307	0.6505
VanderWaals		
1,4	12.7797	13.1169
other	-3.0626	-2.2133
Torsional	14.0200	15.8264
Dipole	5.9006	5.8458
Total Energy	41.4295	47.9855
Steric Energy	35.5289	42.1307
Dipole Moment(D)	1.346	1.340

fig2111

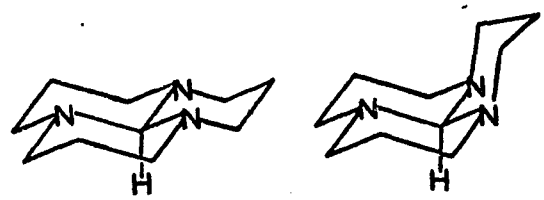


101-cct-6R(1) 101-cct-6R(2) 101-cct-6R(3)

332 (cis,cis,trans) Orthopropionamides

Energy Factor(kcal/mol)	101-cct-6R(1)	101-cct-6R(2)	101-cct-6R(3)
Compression	2.5295	2.8807	2.9255
Bending	9.1678	12.2577	14.1487
Stretch-bend	0.4453	0.5974	0.5792
VanderWaals			
1,4	13.5828	14.0044	14.2872
other	-2.0257	-1.2727	-1.6640
Torsional	14.1016	15.6131	15.6448
Dipole	5.7862	5.7473	5.7536
Total Energy	43.5875	49.8278	51.6750
Steric Energy	37.8013	44.0805	45.9214
Dipole Moment(D)	1.271	1.249	1.282

fig 2.111

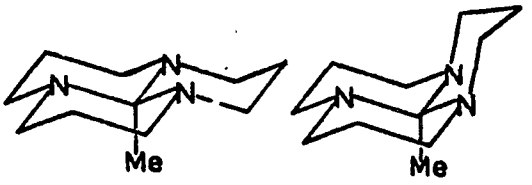


94-ttt 94-cct

333 Orthoformamides

Energy Factor(kcal/mol)	94-ttt	94cct
Compression	1.8627	1.7658
Bending	2.4327	3.5830
Stretch-bend	0.5284	0.6225
VanderWaals		
1,4	14.8250	14.3576
other	-3.4388	-2.7881
Torsional	3.8047	5.3200
Dipole	6.5621	5.9010
Total Energy	26.5768	28.7618
Steric Energy	20.0147	22.8608
Dipole Moment(D)	2.170	1.299

fig 2.112

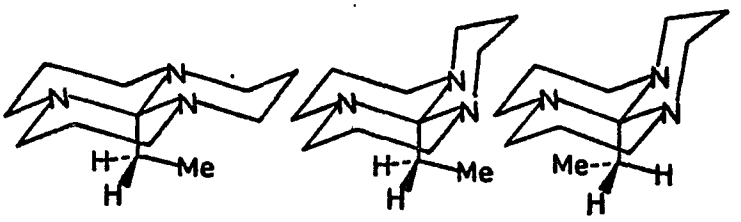


98-ttt 98-cct

333 Orthoacetamides

Energy Factor(kcal/mol)	98-ttt	98-cct
Compression	2.9044	3.1238
Bending	6.4623	5.6914
Stretch-bend	0.8392	0.8499
VanderWaals		
1,4	14.5314	14.8750
other	-0.8634	-0.5218
Torsional	6.4371	7.3563
Dipole	6.6383	5.8041
Total Energy	36.9495	37.1760
Steric Energy	30.3112	31.3746
Dipole Moment(D)	2.172	1.332

fig 2.113



102-ttt 102-cct(C_s) 102-cct(C_1)

333 Orthopropionamides

Energy Factor(kcal/mol)	102-ttt	102-cct(C_s)	102-cct(C_1)
Compression	15.8171	3.4286	4.2315
Bending	12.6498	6.0355	10.5837
Stretch-bend	1.1836	0.9348	1.1649
VanderWaals			
1,4	15.0693	15.5672	16.4475
other	0.1008	-0.9270	0.2782
Torsional	9.1809	8.3476	9.9458
Dipole	6.6992	5.7975	5.7410
Total Energy	60.7007	39.1842	48.3924
Steric Energy	54.0015	33.3867	42.6514
Dipole Moment(D)	2.169	1.343	1.332

fig 2.114

Evaluation Of The Energy Trends In The Minimum Energy Ground States Of The Orthoamides By MM2

The following section is an analysis of the energy trends present in the minimum energy ground states of the orthoamides. The analysis was undertaken to identify energy trends in the two dimensions of the series, namely as a function of varying R size with constant ring size and as a function of varying ring size with constant R size. This analysis was performed graphically because the trends are more easily identified from the inspection of plots of energy parameters than by the inspection of the same data in tabular form.

It should be stressed here that this is an analysis of the energy trends as calculated by MM2. This is an attempt to examine the systematics of the program and to identify the importance which MM2 has placed on the various energy factors in the ground states of minimum energy of the orthoamides.

Graphs 1 and 1a are plots of the total energy as a function of the two dimensions of the series. At a glance it becomes obvious that the series passes through an energy maximum at the 322 ring system regardless of the size of the

R group or the number of carbons in the rings. The reason for this maximum is easily ascertained by an inspection of graphs 2,3,and 4. Note that on these graphs the energy of bending also passes through a maximum at the 322 ring system and that the general shapes of the bending curves and the total energy curves are very similar. It is obvious that the energy of bending is a major contributing factor for the high calculated energies of the 322 ring system. Intuitively one might have expected that the 222 ring system would be the highest in energy. Evidently the fusion of a six membered ring and two five membered rings was considered worse than the fusion of three five membered rings.

One may ask the question as to whether it is a valid analysis to compare the total energies of compounds that differ in the number of atoms since some quantities are a function of the number of atoms in the molecule. It would be inappropriate to compare the calculated energies between completely dissimilar compounds (dissimialr in the sense that these materials had no structural similarities). But the comparisons being made here are between compounds which are structurally very similar. In fact, the energy relationships in these compounds are heavily dependent on the central C-N bonds which are common to all the orthoamides. As an example, examination of the raw data for the bending energies of Et-222 and Et-322 shows that the additional methylene carbon in Et-322 makes an insignificant

contribution itself to the bending energy. The overwhelming contribution to the bending energies of these two compounds come from distortions of the central C-N-C bond angles. The bending energies of these central angles is determined in turn from the constraints of the ring system which determine their geometry. Therefore it is a valid exercise to compare the bending energies between homologs in this series. Similar arguements can be made for contributions from compression, stretch-bend, torsional, and dipole energies. The comparison of the energy contributions from the van der Waals' 1-4 interactions are an exception in that it is clear that the energy associated with the 1-4 interactions are dependent upon the total number of carbons in the molecule which are disposed 1-4 to one another.

Examination of the curve for the torsional energy in graphs 2-8 indicate that this energy factor has a strong dependence on ring size and almost no dependence on R size. The reason for this dependence is the larger number of eclipsed bonds in the smaller ring systems and the favorable chair conformations in the larger rings. Note that the torsional energy is a function of the total number of carbons but obviously the number of carbons in this series is not the determining factor since the torsional energy actually goes down as more carbons are added to the rings. This fact points out again the validity of examining energy trends within the series and not just between conformations.

Examination of the torsional energy curves in plots 5-8 indicates that there is a small dependence on R size which is in the direction expected for the addition of carbon - carbon bonds.

A general trend which becomes obvious upon examination of the curves in plots 5-8 is that the energy differences resulting from substitution of Me for H are much larger than the energy changes resulting from the substitution of Et for Me. This is reasonable since in the smaller ring systems, where the ring carbons are turned down away from the R group, the largest interactions are between the methylene hydrogens of the ethyl group and the rings. These interactions should be essentially the same for the methyl and the ethyl group. In the larger ring systems the same energy trends are observed but in this case the interactions between the rings and the R groups should be more substantial and would be expected to be highly dependent on R size. But in the larger ring systems the compounds adopt conformations which minimize these steric interactions.

Van der Waals' 1-4 interactions show a strong dependence on ring size and little or no dependence on R size. As was previously mentioned this observation is readily explainable in that as the number of atoms which are disposed 1-4 to one another increases so will the contribution of this factor to the total energy. The

rotational freedom of the R group allows it to adopt a conformation in which these interactions are minimized. The ring carbons are more restricted in the possible positions that they may occupy and therefore make a larger contribution to this energy term.

Examination of plots 2-4 indicates that the two major energy factors of the minimum energy ground states are the torsional energy and the van der Waals' 1-4 interactions. All other interactions are constant in relation to the variation in these parameters. It will be noted that the intersection of these two curves always occurs at the 332 ring system indicating that the determination of the minimum energy ground state conformation in this ring system will result from a more subtle interplay of the energy parameters rather than a predominance of a single parameter as in the other ring systems.

The preceeding examples serve as illustrative examples of the reasoning used in identifying these trends. Similar analyses of these graphs yield a number of generalizations which are abstracted and listed below without the lengthy discussion which accompanied the previous examples. The reader is directed to the plots for verification of the conclusions listed below.

1) COMPRESSION: Bond compression is a relatively minor and

constant energy factor.

2) BENDING: a)Bending is least severe in the larger ring systems, b)Bending passes through a maximum at the 322 ring system, c) and within a particular ring system the bending energy increases with increasing R size.

STRETCH-BEND: a)Stretch-bend is a relatively minor and constant energy factor.

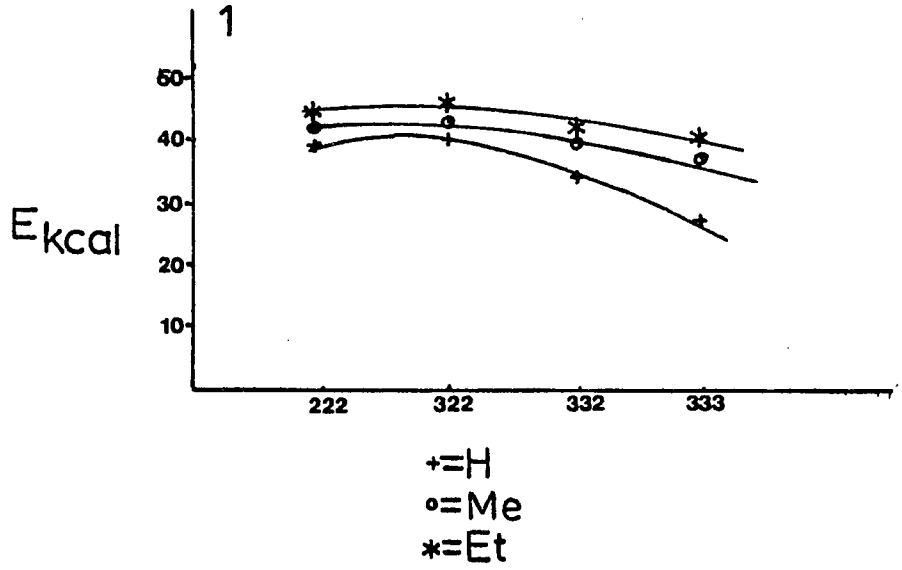
VAN DER WAAL'S 1-4: a)These are most unfavorable in the cis,cis,trans conformations, b)increase linearly and gradually in the all trans (or all-cis) conformations with increasing R size, c)and are the major energy factor in the 333 ring system.

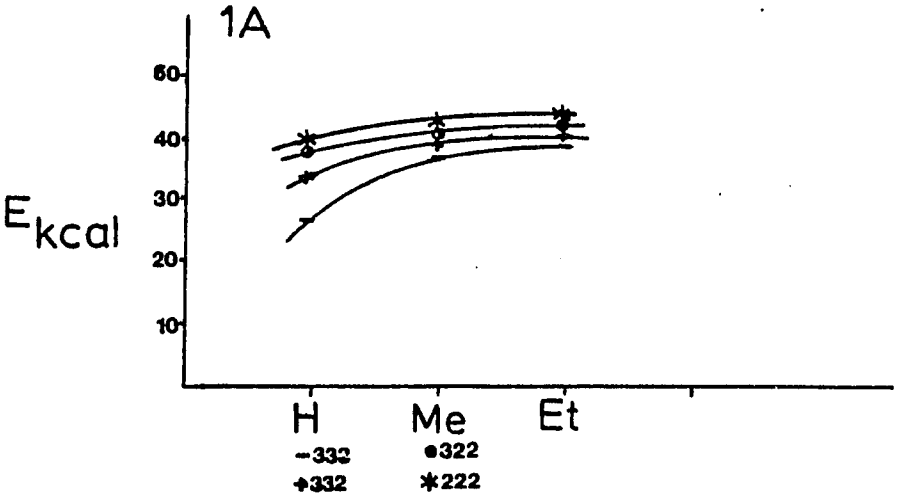
VAN DER WAAL'S OTHER: a)These interactions make a maximum negative (stabilizing) contribution in the all-trans (or all-cis) conformations. b)In the all-trans conformation these interactions become increasingly negative with increasing R size.

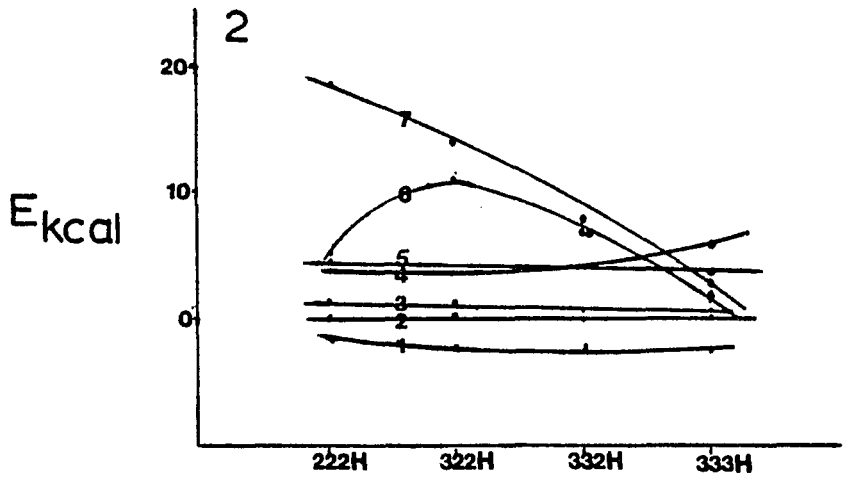
TORSIONAL: a) The torsional term is most severe in the small ring systems, b)increases most dramatically for all ring systems upon substitution of Me for H and remains essentially constant upon substitution of Et for Me.

DIPOLE: a)This interaction is minimized in the cis,cis,trans conformations.

GENERAL OBSERVATIONS: 1)Torsional energy is the major contributor to the total energy of all the orthoamides except the 333 systems where van der Waals' 1-4 interactions are the dominant energy factor. 2)The high torsional energies of the small ring systems are due primarily to eclipsing of hydrogens and eclipsing of the central C-N bonds with C-C bonds of the rings and with other C-N bonds. 3)Bending energies are due to distortions of the central C-N-C bond angles. 4) Van der Waals' 1-4 interactions increase as the rings become larger simply because of the larger number of atoms disposed 1-4 to one another. 5)Stretch-bend, compression, bending, and dipole energy factors show no dependence upon the size of the R group. 6)The orthoamides adopt conformations which minimize the steric interactions between the R groups and the rings.


1
50
40
30
20
10
E_{kcal}
222
322
332
333
+=H
o=Me
*=Et


1A
60
40
30
20
10
E_{kcal}
H
Me
Et
-332
+332
•322
*222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3
2
1
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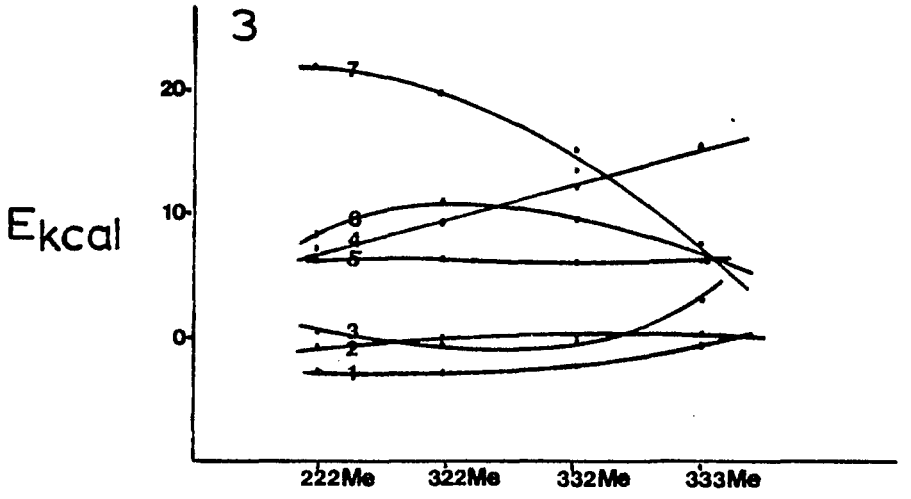
322H
332H
333H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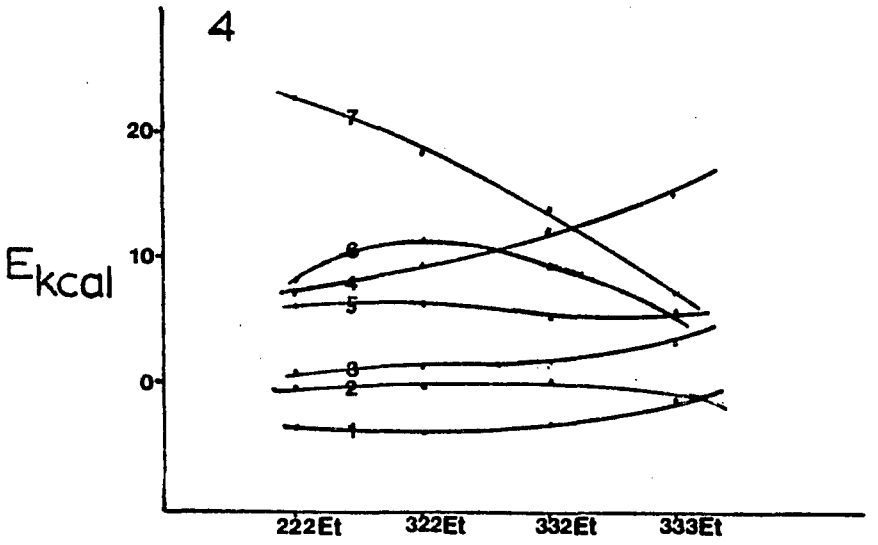
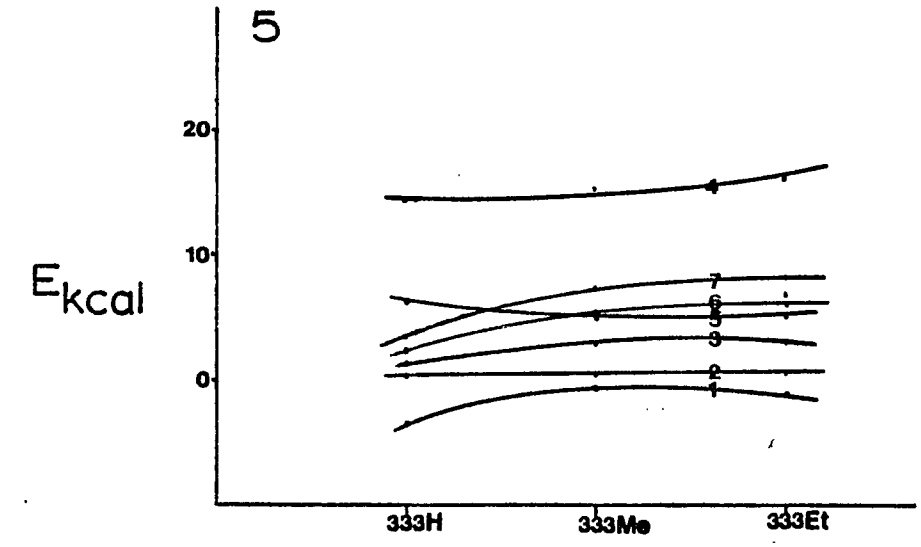


1= VanderWaal's other
2= Stretch-Bend
3= Compression
4= VanderWaal's 1-4
5= Dipole
6= Bending
7= Torsional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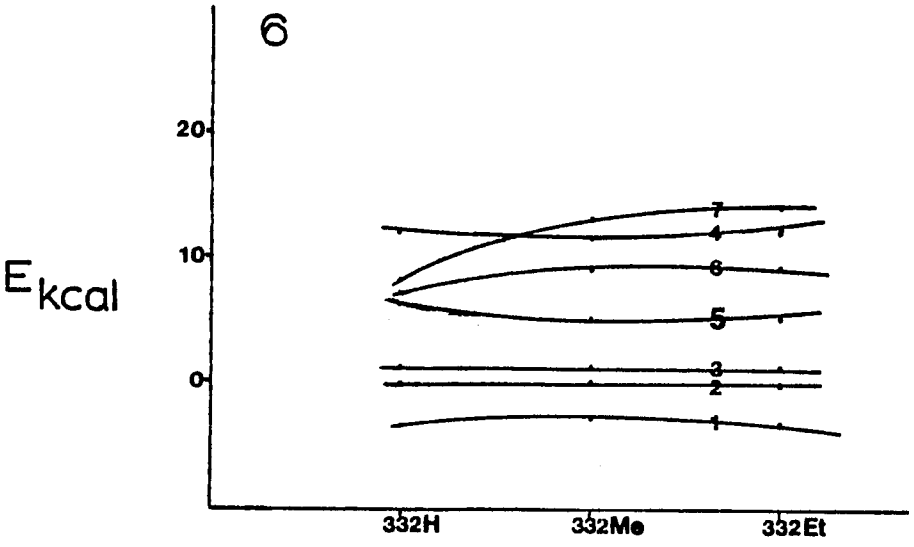
E_{kcal}
7
6
5
4
3
2
1
333H
333Me
333Et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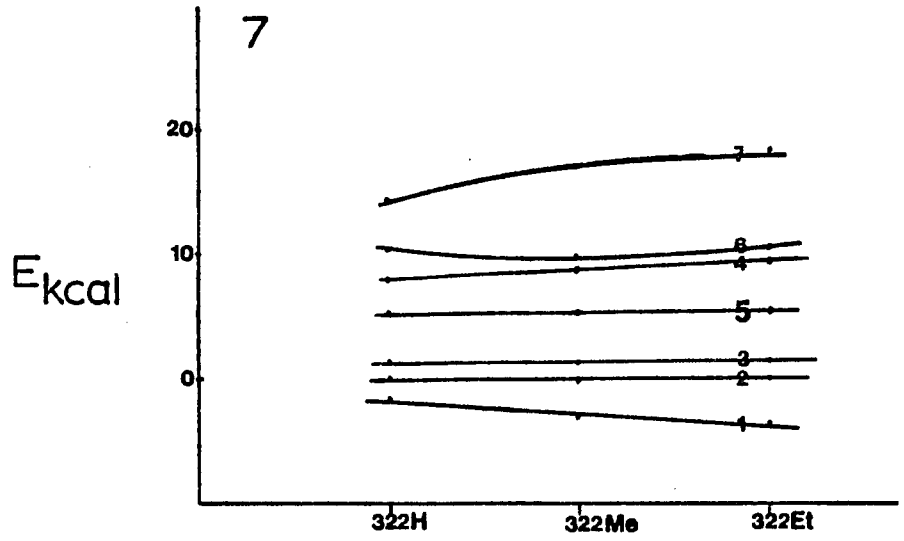
332Me
332Et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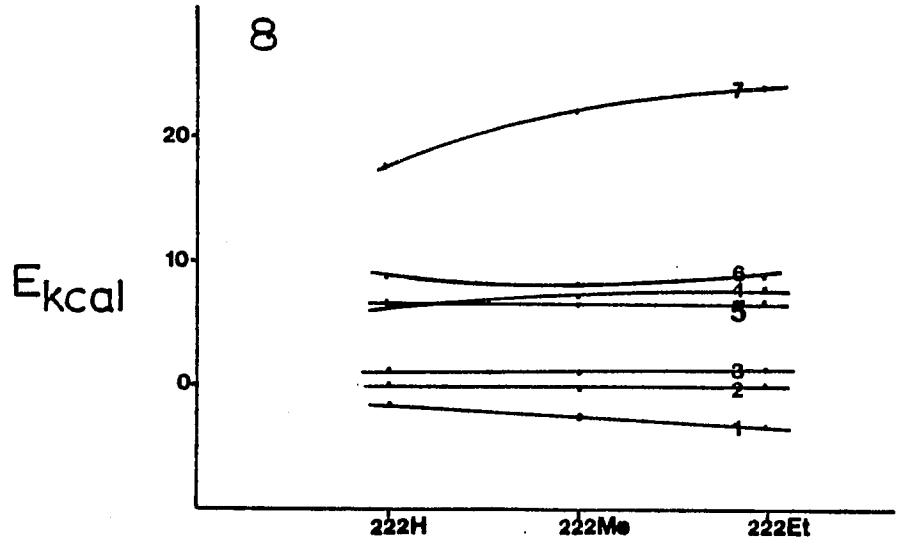
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222H
222Me
222Et

CHAPTER 3

EXPERIMENTAL

General

Melting points were recorded on a Thomas-Hoover Unimelt and are uncorrected.

Routine ^{1}H NMR spectra were recorded on a Varian EM-360A continuous wave spectrometer or a JEOL-FX-90Q FT instrument. When higher fields were required then the Bruker WH-270 spectrometer located at the Bitter National Magnet Laboratory in Cambridge,Ma was utilized. All chemical shifts(^{1}H,^{13}C) are referenced to internal tetramethylsilane unless otherwise indicated. $CDCl_3$ was employed as the NMR solvent unless otherwise stated. Infrared spectra were recorded on either Perkin-Elmer 283B or Perkin-Elmer 337 grating infrared spectrophotometers employing carbon tetrachloride as the solvent unless otherwise noted. Ultraviolet spectra were recorded on a Varian-Cary 219 double beam programable spectrophotometer. Routine mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6Em mass spectrometer by department personnel. High resolution mass spectra were obtained at the Massachusetts Institute of Technology mass spectral facility. CHN analyses were determined with a F and M model 185 or a

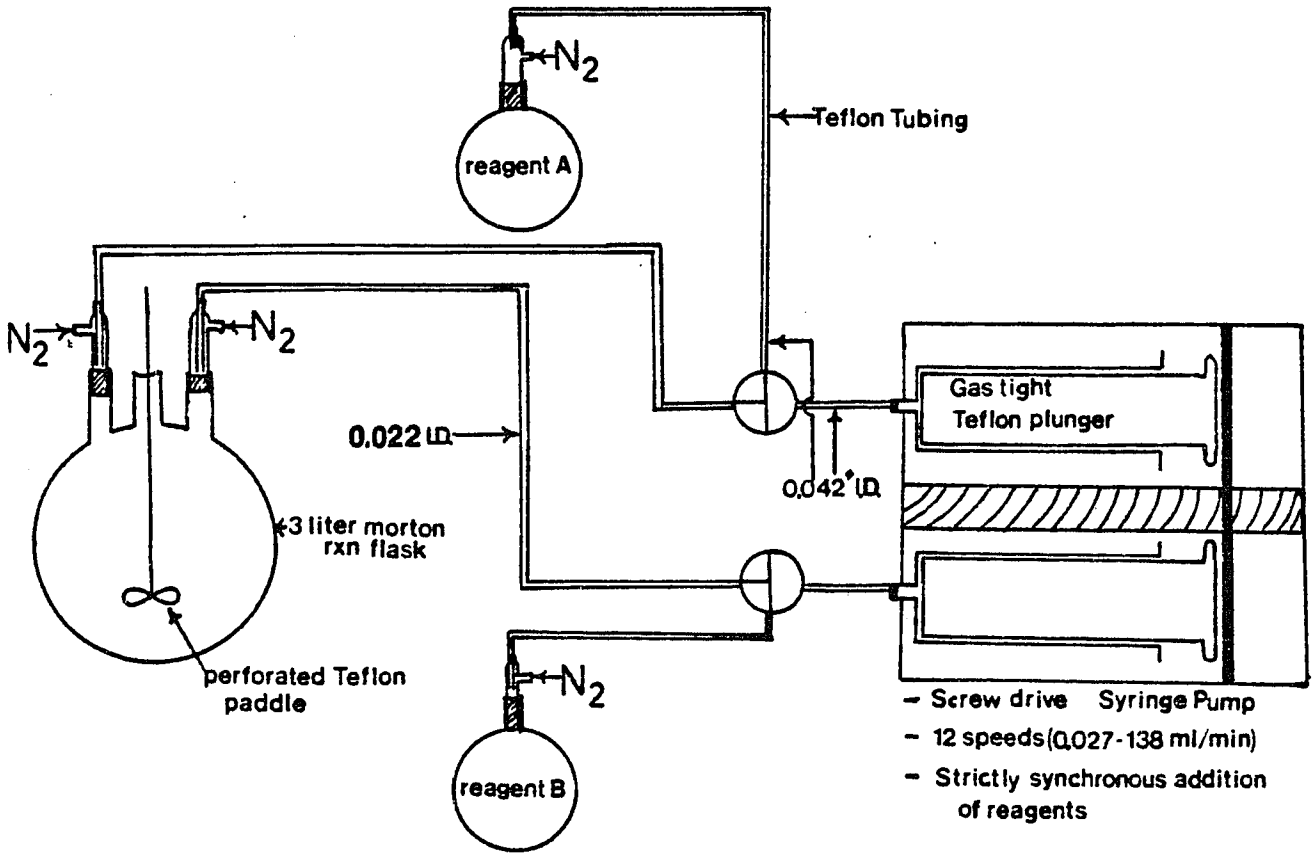
Perkin-Elmer 240B elemental analyzer by departmental personnel.

All reactions were run under an atmosphere of anhydrous nitrogen. CH_2Cl_2 and hydrocarbon solvents were fractionally distilled from calcium hydride and stored over 3 Å molecular sieves. Benzene was distilled from sodium wire. Tetrahydrofuran was distilled from benzophenone ketyl immediately before use. Reagent grade chloroform was used without further purification. Reagent grade anhydrous ether was stored over sodium wire. Reagent grade anhydrous MeOH and absolute EtOH were stored over 3 Å molecular sieves. Dimethylformamide was distilled from calcium hydride under reduced pressure and stored over 3 Å molecular sieves prior to use. All NMR solvents were stored over 3 Å molecular sieves. Unless otherwise stated all reagents were obtained commercially and were used without further purification.

Instrumental Aspects

High Dilution Apparatus

The apparatus shown in figure 3.1 was used for all cyclizations requiring application of the principle of high dilution. With the exception of the syringe pump, the entire apparatus was constructed from inexpensive and



High Dilution Apparatus

fig 3.1

readily available components. The syringe pump allows the controlled, strictly synchronous, and reproducible addition rates necessary for consistently successful high dilution reactions. One other investigator has mentioned the use of a syringe pump for this purpose[200]. The apparatus was designed so that reactions could be run under an anhydrous inert atmosphere allowing the use of moisture and oxygen

sensitive reagents. All surfaces exposed to reagents are inert(glass or teflon) with the exception of the stainless steel luer lock fittings on the syringes. The 0.022 in. I.D. teflon tubing leading to the reaction flask produces uniformly small droplets during addition. The gas tight teflon syringe plungers were machined to the dimensions of a Multifit^{TM}(Becton-Dickinson) glass plunger. By warming the syringes with a heating pad the high coefficient of expansion of the Teflon can be taken advantage of to insure a tight fit.

In summary, the advantages of this system over previously reported systems[201] are: 1) the entire apparatus is inexpensive, 2) addition rates are strictly synchronous and reproducible, 3) all breakable components are easily and cheaply replaced, and 4) the system is inert and its genrally applicable to various chemical systems.

Improvements which are recommended are: 1) prediluters and, 2) modifications to automate the operation including solenoids to operate the valves and syringe pump.

Gel Permeation Chromatography

Preparative scale gel permeation chromatography[212] (GPC) was performed on a modified Waters 200 analytical GPC unit. A schematic of the preparative unit is found in

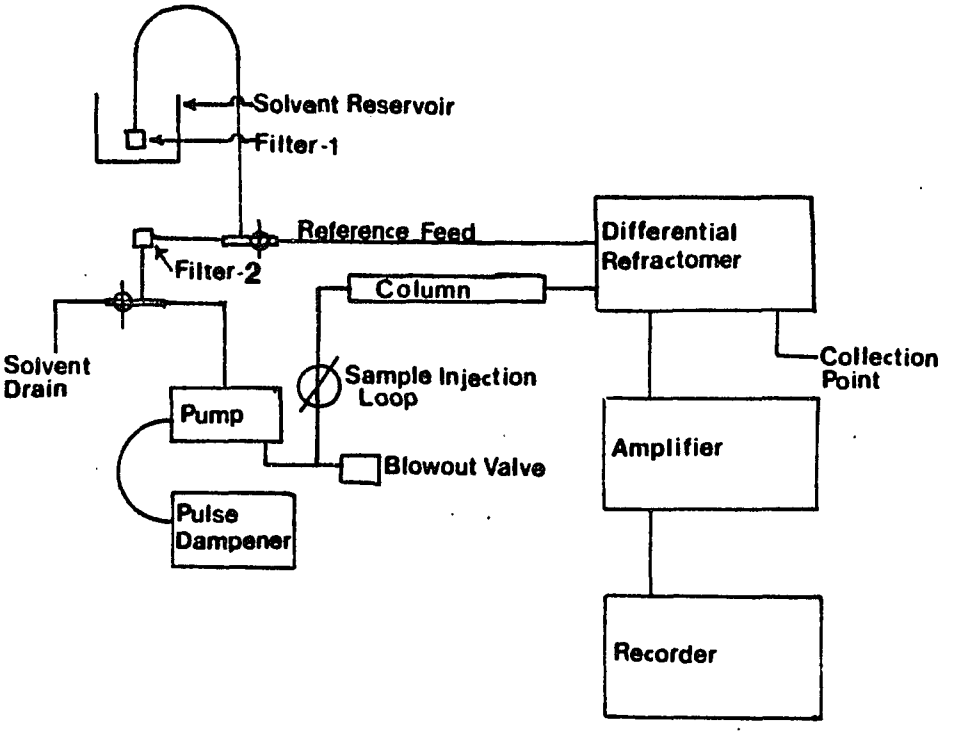
figure 3.2 The major modifications of the Waters 200 were the following; 1) elimination of the thermostated column environment, 2) use of preparative columns with appropriate packings, 3) reduction of the detection sensitivity necessitated by the larger sample sizes, 4) inclusion of a LDC Model 709 pulse dampener, and 5) use of higher operating pressures.

Separations were performed at ambient temperatures employing dichloromethane as the eluent. Typical flow rates were 2.61 mL/min. with 340 psi of backpressure.

Experimental. Solvent: Dichloromethane useed was freshly distilled from calcium hydride. The eluent was freshly distilled or boiled and cooled immediately prior to use to insure that the solvent was degassed. (If the solvent was not degassed prior to use it degassed at the pressure gradient exiting the column causing column damage and detection problems in the differential refractometer due to bubbles.)

Sample Preparation: Samples were recrystallized and scrupulously dried prior to injection. Weighed samples were dissolved in a minimum of solvent and filtered through a fine glass frit and then diluted up to 10 mL in a volumetric flask. Sample injection sizes were determined by the injection loop size and the molarity of the solution.

Prepararative GPC Unit



PUMP: Milton-Roy Model No. 196-29 (pressure;1000psi,capacity;160ml/min)

PULSE DAMPENER: LDC Model No.709

DIFFERENTIAL REFRACTOMETER: Optical bench assembly from Waters GPC-200

RECORDER: Leeds & Northrup Co., Speeodomax W(response time;5 sec. full travel, chart speed; 6 in/h)

SOLVENT and REFERENCE LINES: Teflon 1/8" I.D. (all other lines were stainless steel LC 1/8" tubing)

BLOW-OUT VALVE: Hoke Co. No. 6528L-4B(brass) (pressure range;350-1500psi adjustable to any pressure within that range)

AMPLIFIER: electronics from Waters GPC-200

SAMPLE INJECTION LOOP: 1.6 ml loop and injector from Waters GPC-200

fig. 3.2

Column Packing Procedure: The packing technology was essentially that developed by Stephen Peacock in the laboratories of D. J. Cram at the University of California at Los Angeles[167]: 1) 150 g of Biorad SX-12 Biobeads were allowed to swell in dichloromethane overnight. 2) The packing slurry was poured into a 4 foot stainless steel precolumn which was capped at the bottom after air and some

solvent had drained. The precolumn was then attached to an HPLC pump. The packing was never allowed to go dry and care was taken not to overfill the precolumn to avoid sealing problems when it was attached to the column. 3) The precolumn was then attached to a 21 ft x 3/8 in O.D. aluminum column(standard GC tubing) which was capped at the top with a 10 micron frit and a teflon return line. 4) The HPLC pump was set at its maximum flow rate(10 mL/min) and the column was packed at this flow rate until a backpressure of 1000psi was attained. The flow rate was then adjusted to maintain this backpressure and the column was packed at this pressure for 24 h. The first several hundred mL of solvent that exited the column were clouded with monomer and were discarded. 5) The flow rate was increased to attain a backpressure of 1300psi and the column was packed at this pressure for 3-4 h. 6) the column was then capped and inverted. Excess column was then cut off and the end was capped with a 10 micron frit and designated "in". 7) One smooth bend was put into the previously straight column by wrapping it around a 55 gal. barrel.

The preceeding packing procedure produced a 21ft column with the following characteristics: 1) flow rate of 2.61 mL/min with 340 psi of backprsessure and, 2) exclusion volume of 84 mL(Carbowax M as standard).

Immediately upon installation of the column its characteristics and effeciency were recorded by injecting various mixtures and single compounds. The retention volumes of these standards were noted as a reference to check for column deterioration at a later date.

pKa Determinations

The following procedure was employed to determine the pKa's of H-222 and H-333. Ca. 90 mg of amine was weighed into an Erlenmyer flask and diluted with 50 mL of 0.5M aq NaCl. An Orion 701 digital pH meter was calibrated with pH4 and pH7 buffers. The amine was then titrated with 0.1024 M aq HCl. The HCl was standardized by titrating weighed samples of anhyd Na_2CO_3.

DNMR

All variable temperature work was carried out in 5 mm tubes on the JEOL FX90Q equipped with a JEOL Temperature Controller NM-VTS. Temperatures were measured by the chemical shift thermometer reported by Led and Petersen[213]. The probe was allowed to equilibrate ca. 15-20 minutes at each temperature before running spectra and before measuring temperature. Temperatures are believed to

be accurate to within ±1 C.

Internal heteronuclear field-frequency pulse lock has been employed in all cases with utilization of the dueterium signal of the solvent as the lock signal.

In all cases a room temperature spectra was recorded prior to the low temperature runs. A second room temperature spectra was also recorded after the completion of the low temperature runs. In practice it was found more convenient to record the spectrum in the slow exchange region first and then record additional spectra at appropriate higher temperatures. The probe was tuned frequently during temperature changes and then again after equilibration at desired temperatures.

Sample solutions were prepared by dissolving a wieghed sample into a measured volume of dueterated solvent. The solution was then cooled to -77°C in a dry ice acetone bath to check the solubility of the sample at low temperatures. Concentrations were maximized in this fashion to reduce run times. Typically samples were ca. 1 M.

Synthesis

Phenylmethanesulfonyl chloride. The crude solid prepared in 40% yield by the method of Sprague and Johnson[202] was recrystallized from CH_2Cl_2/hexane.mp 91-91.5°C (lit. mp 91-92°C).

1,3-N,N'-di-(phenylmethanesulfonyl)-diaminopropane(27). Phenylmethanesulfonyl chloride (3.1821 g,16.748 mmol) was dissolved in 35 mL of anhyd CH_2Cl_2 under a nitrogen atmosphere. A solution of 1,3-diaminopropane (0.6187 g, 8.361 mmol) and triethylamine (2.50 mL,16.75 mmol) in anhyd methylene chloride was added in a single aliquot with vigorous stirring. After 0.25 h the reaction solution was washed with H_2O(60 mL) and the solvent was evaporated to yield 3.3714 g of crude reaction solids which were recrystallized three times from MeOH to yield 0.5583 g (17.5%) of product as shiny floculent platlettes. mp 167.5° C; IR (KBr) 3250, 1305, 1070 cm^{-1}; ^1H NMR 1.15(quintet, 2H), 2.92(br q, 4H), 4.29(s, 4H), 7.1 (br t, 2H), 7.4(s, 10H);Anal.Calcd for $C_{17}H_{22}N_2O_4S_2$:C, 53.45; H, 5.82;N, 7.34. Found:C, 53.31;H, 6.36;N, 7.31. Note;a)ca.33 % loss was due to spillage; b) Reversed addition of reagents produced lower yields.

Attempted Synthesis of N,N',N'''-tri-(phenylmethane sulfonyl)-1,3,7-triazaheptane(28). Diethylenetriamine

(0.3115 g, 3.02 mmol) and triethylamine (0.6132 g, 6.04 mmol) were dissolved in 30 mLanhyd methylene chloride and cooled to 0°C. Phenylmethanesulfonyl chloride(2.2878 g, 12.04 mmol) was dissolved in 30 mL anhyd CH_2Cl_2 and cooled to 0°C. The sulfonyl chloride was added to the amine solution in two aliquots at 0°C. The resulting solution was stirred for 0.4 h at 0°C. The reaction solution was then washed three times each with H_2O(25 mL) and 5% sodium bicarbonate(25 mL), dried over Na_2SO_4, filtered, and the solvent evaporated at reduced pressure to yield 12.19 g of crude product. This was recrystallized from MeOH three times to yield 0.2446 g (14.3%) of product as an impure microcrystalline solid:mp 174.5-175.5°C; IR (KBr) 3270, 1390 cm^{-1};^1H NMR (Me_2SO-d_6 3.02(m, 8H), 3.28(s, 2H), 4.29(s, 4H), 4.39(s, 4H), 7.32(s, 15H). This material was used in subsequent reactions without further purification.

Attempted Synthesis of N-phenylmethanesulfonyl-2,2'-imino-diethanol-1,5-di-(phenylmethanesulfonate)(29).

phenylmethanesulfonyl chloride (1.1415 g, 6.01 mmol) was dissolved in 30 mL anhyd CH_2Cl_2 and cooled to -77°C. Diethanolamine (0.2142 g, 2.0 mmol) and triethylamine(0.6087 g, 6.0 mmol) were dissolved in 10 mL anhyd CH_2Cl_2 and cooled to -77°C. The amine solution was added to the sulfonyl chloride solution and stirred for 5 min. at -77°C. The reaction solution was washed three times with H_2O(25 mL), dried over Na_2SO_4, filtered, and the solvent was

evaporated at reduced pressure to yield 1.1497 g of crude reaction solid. This was recrystallized from abs EtOH to yield 0.5111 g (51%) of impure white crytalline product. mp 144-146°C(softens at 139°C); IR (KBr) 3020, 2980, 1590, 1550, 1170, 990, 785, 705 cm^{-1} ^1H NMR 3.12(t, 4H), 3.92(t, 4H), 4.15(s, 2H), 4.30(s, 4H), 7.28(s, 5H) , 7.30(s, 10H). The impure material was used in subsequent reactions without further purification.

1-N-p-toluenesulfonyl-3,3'-iminodipropanonitrile(19). 19 was prepared in improved yield by a modification of a reported procedure[203]. A solution of 10 mL of 4.52N NaOH, p-toluenesulfonamide(45.89 g, 0.2684 mol) and acrylonitrile (28.9 g, 0.5368 mol) in 350 mL of freshly distilled THF was refluxed for 37 h. Evaporation of the solvent at reduced pressure yielded a white crystalline material which was recrystallized from H_2O to yield 67.55 g (91%) of 19 as white needles:mp 103-105°C (lit. mp 104.5°C, yield 43%); IR (KBr)2240 cm^{-1};^1H NMR 2.45 (s, 3H), 2.75(t, 3H), 3.47(t, 4H), 7.63(AA'BB', 4H).

1-N-p-toluenesulfonyl-3,3'-iminodipropanoic acid(20). 20 was prepared in improved yield by a modification of a reported procedure[203]. A mixture of 19(52.0464 g, 0.1951 mol) in 500 mL of 6N HCl was refluxed with stirring until a homogeneous yellow solution was formed(ca.2 h). Longer reaction times resulted in dramatically lower yields due to

cleavage of the tosylamide. The yellow solution was cooled to 5 C and the resulting white crystalline product was collected by suction filtration. The product was washed with H_2O until the wash H_2O no longer contained chloride($AgNO_3$ test). Recrystallization from H_2O yielded 50.44 g (82%) of the product as a white microcrystalline solid: mp 168-170°C (lit. mp 168-170°C, yield 57%);IR (KBr) 3000(br), 1670 cm^{-1};^1H NMR 2.45(s, 3H), 2.52(t, 4H), 3.38(t, 4H), 7.52(AA'BB', 4H).

1-N-p-toluenesulfonyl-3,3'-iminodipropanoyl chloride(21). A mixture of 20(10.81 g, 3.43 mmol), thionyl chloride(20 mL), and 100 mL of anhyd benzene was heated to 50°C under a nitrogen atmosphere for 18 h at which time a clear homogeneous solution indicated that the reaction was complete. Anhyd heptane was cannulated into the warm solution until a slight turbidity resulted. The solution was then cooled to 0°C resulting in two crops of white microplatlette product which were collected by filtration under nitrogen to yield 11.53 g (96%): mp 71.5-72.5°C; IR (KBr)1770 cm^{-1};^1H NMR 2.41 (s, 3H), 3.32(AA'BB', 8H), 7.50(AA'BB', 4H);Anal. Calcd for $C_{13}H_{15}NCl_2O_4S$:C, 44.36;H4.30; N, 3.98. Found:C, 44.85;H4.33;N, 4.23.

N-p-toluenesulfonyl-1,5,9-triazacyclododec-4,10-dione(22) . 1, 3-diaminopropane(0.4091 g, 5.529 mmol) was dissolved in 500 mL of anhyd benzene in a 1000 mL reservoir flask A(see

diagram 3.1). 21 (0.9713 g, 2.765 mmol) was dissolved in 500 mL of anhyd benzene in reservoir flask B. The two reagents were then added simultaneously via a syringe pump apparatus (at a rate of 0.689 mL/min.) into a 2 L Morton reaction flask containing 1 L of anhyd benzene which was stirred at a rate of 1300 R.P.M.. All reagents and the reaction were handled under a nitrogen atmosphere. After the addition was complete the reaction was stirred for 12 h. The solvent was then evaporated under reduced pressure to yield crude reaction solids which were washed with 50 mL of H_2O, 50 mL of 5% aq HCl, and then with H_2O to remove 1, 3-diaminopropane dihydrochloride. The resulting material was dried in vacuo to yield 0.9333 g of crude product. Recrystallization from CH_2Cl_2 removed some polymeric materials. Pure monomer was obtained by gel permeation chromatography(column 20 ft, 3/8 in;Bio-Beads SX-12; backpressure 350 psi; temp 25°C ;retention volume 93 mL) to yield 0.65 g (67%):mp 300°C(decomp); IR (KBr) 3240, 1680 cm^{-1};^1H NMR 1.75(quintet, 2H), 2.35(s, 3H), 2.40(t, 3H), 2.40(t, 4H) 2.9-3.9(m, 8H), 7.00(br t, 2H), 7.55(AA'BB', 4H); Anal. Calcd for $C_{16}H_{23}N_3[DO_4S$: C, 54.44; H, 6.56; N, 11.91. Found:C, 54.43; H, 6.72; N 11.60.

N-p-toluenesulfonyl-1,5,9-triazacyclododecane(23). 22(0.5590 g, 1.583 mmol) was dissolved in 75 mL of freshly distilled THF under a nitrogen atmosphere. 40 mL of 0.9 M BH_3/THF(Ventron) was syringed into the reaction flask

through a septum capped stopcock. The resulting solution was refluxed for 24 h. H_2O was then added to the cooled solution(Caution:H_2 evolution). The solvent was then evaporated under reduced pressure and the resulting white solid was dissolved in 25 mL of 5% aq HCl and stirred for 12 h at 25°C. Evaporation of the solvent at reduced pressure yielded a white solid which was dissolved in 25 mL of 5% aq NaOH and extracted with $CHCl_3$(10X15 mL). The combined extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated at reduced pressure to yield 0.5276 g of hygroscopic product as an impure soft crystal mass.:mp 57-59°C; IR (CCl_4) 2900, 1320, 750 cm^{-1}; ^1H NMR 0.85(quintet, 2H), 1.80(quintet, 2H), 2.05(br s, 2H), 2.40 (s, 3H), 2.68, 2.70(overlapping t, 8H), 3.23(t, 4H), 7.50(AA'BB', 4H).

5,13-N,N'-di-p-toluenesulfonyl-1,5,9,13-tetraaza-bicyclo[7.7.3]-nonadec-2,8-dione(24). 23(0.5276 g, 1.623 mmol) and triethylamine (0.3286 g, 3.247 mmol) were dissolved in 500 mL of anhyd benzene in reservoir flask A. 21 (0.5714 g, 1.623 mmol) was dissolved in 500 mL of anhyd benzene in reservoir flask B. The reagents were added simultaneously at a rate of 0.689 mL/min. to a 2 L Morton reaction flask containing 1 L of anhyd benzene being stirred a rate of 1300 R.P.M.. The reaction was stirred for 12 h after the addition was complete and then the solvent was evaporated at reduced pressure to yield 1.3457 g of crude reaction solids

which were washed with H_2O, 5% aq HCl, and then with H_2O until the wash H_2O no longer contained chloride($AgNO_3$ test). The residue was then dried in vacuo to yield 0.9593 g of crude product. The purification and analysis of this product awaits the packing of an appropriate GPC column (e.g. SX-8).

N,N',N''-tri-p-toluenesulfonyl-1,5,9-triazanonane(141). 141 was prepared by the method of Koyama[204] whereby 1,5,9-triazanonane(99.09 g, 0.7551 mol) and NaOH (90.62 g, 2.26 mol) were dissolved in 560 mL of H_2O with cooling under a reflux condenser. p-Toluenesulfonylchloride (451.93 g, 2.3707 mol) dissolved in 1050 mL of anhyd ether was added dropwise to the stirred aq solution over a nine hour period(CAUTION: Exothermic reaction). The resulting mixture was stirred for 92 h and the clear ether and H_2O layers were decanted from the heavy yellow oil. The oil was dissolved in 1 L of CH_2Cl_2 and washed with H_2O (4x250 mL) followed by saturated NaCl(2x300 mL). The CH_2Cl_2 phase was dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure(Foaming may occur) to yield 432.75 g (95%) of 141 as a golden yellow oil. NMR ($CDCl_3$)1.67(t, 4H), 2.35(s, 9H), 2.35-3.32(brm, 8H), 5.61 (t, 2H), 7.00-7.90(m, 12H).

N,N',N''-tri-p-toluenesulfonyl-1,5,9-triazanonane-1,9-disodium salt(142). 142 was prepared by the method of

Richman and Atkins[205]. 141 (210.15 g, 0.3540 mol) in 500 mL of abs EtOH was heated to reflux and the heat was removed. 500 mL of 1.416 M sodium ethoxide solution(freshly prepared by reaction of sodium metal(16.28 g, 0.7081 mol) with 500 mL of abs EtOH) was added immediately in a single aliquot with vigorous stirring. The product, which precipitated within minutes, was collected by suction filtration under nitrogen, washed with abs EtOH, and dried in vacuo at 75°C (12 mm) for 72 h to yield 202.82 g (90%) of white hygroscopic product which was used in subsequent steps without further purification: NMR (Me_2SO-d_6) 1.46(brm, 4H), 2.32(s, 3H), 3.11 (brm, 8H), 6.95-7.81 (m, 12H).

N,N',N''-tri-p-toluenesulfonyl-1,5,9-triazacyclododecane (149). 149 was prepared in 21% yield by the method of Richman and Atkins[205] from 142 and 34. Recrystallization of the crude product from CH_2Cl_2/hexane yielded crystalline product:mp 173-175°C (lit.[205] 173°C).

1,5,9-triazacyclododecane(153). 153 was prepared after the method of Raymond[60a] . 149(5.5356 g, 8.7347 mmol) and 30 mL of 98% H_2SO_4 were heated to 100°C with stirring for 56 h under a nitrogen atmosphere. The dark reaction mixture was then cooled to 0°C and 40 mL of abs EtOH were added dropwise(CAUTION: Exothermic). The sulfate salt of 153 was precipitated by addition of 100 mL of anhyd ether and collected by suction filtration under nitrogen. The salt

was dissolved in a minimum of H_2O(directly on the filter frit). The resulting aq solution was adjusted to pH 10(concd NaOH, 0°C) and extracted with $CHCl_3$(6X20 mL). The combined extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to yield a yellow oil which was purified by kugelrohr distillation(bp 90-95°C (0.1 mm)) to yield 1.2304 g (82%) of 153 as a white semisolid. NMR ($CDCl_3$) 1.62(quintet, 6H), 1.68(s, 6H), 2.75(t, 12H); mass spectrum, m/z(rel intensity) 171 (100). The trihydrobromide of 153 has been previously reported[204].

N,N-dimethylpropionamide dimethylacetal(127). 127 was prepared in 19.6% yield by the method of Bredereck[206]. The crude material which was synthesized by the method of Bredereck was purifed by filtering off the white salt bi-product(which forms during the reaction) under nitrogen. The salt was then washed with anhyd ether to remove any residual product which might be adsorbed on the salt. The ether washings and the crude product were combined and the ether was evaporated under reduced pressure. Fractional distillation yielded pure 127: bp 215-23°(11 mm) lit.[207] bp 30°C (1 mm); All spectral data was consistent with published data[207].

N,N',N''-tri-p-toluenesulfonyl-1,4,7-triazacyclononane(146). 146 was prepared in 82% yield from 143 and 145 by the method

of Richman and Atkins[205]. Recrystallization from CH_2Cl_2/ hexane yielded crystalline material which was used in subsequent reactions without further purification. mp 205-209°C (lit.[205] mp 222-223°C).

1,4,7-triazacyclononane(150). 150 was prepared in 82% yield from 146 by a procedure modeled after Raymond's[60a, 208] procedure (see 153 for detailed experimental) for the preparation of tetraamines: bp ca.85°C (12 mm); ^1H NMR ($CDCl_3$) 2.14 (s, 3H), 2.78(s, 12H). The material was used in subsequent reactions without further purification. The trihydobromide of 150 has been previously reported[204].

N,N',N''-tri-p-toluenesulfonyl-1,4,7-triazacyclodecane(147). 147 was prepared in 57% yield from 142 and 34 by the method of Richman and Atkins[205]. Recrystallization from CH_2Cl_2/hexane yielded pure material: mp 233-235°C (lit.[205] mp 234-236°C).

1,4,7-triazacyclodecane(151). 151 was prepared in 66% yield from 147 by a procedure modeled after Raymond's[60a, 208] procedure (see 153 for detailed experimental) for the preparation of tetraamines: bpca.88°(12 mm) ^1H NMR ($CDCl_3$) 1.60(quintet, 2^iH), 2.48-3.13(m, 15^iH). The material was used in subsequent reactions without further purification. The trihydrobromides of 151 has been previously reported[204].

N,N',N''-tri-p-toluenesulfonyl-1,4,8-triazacycloundecane (148). 148 was prepared in 82% yield from 142 and 34 by the method of Richman and Atkins[205]. Recrystallization of the crude product from CH_2Cl_2/hexane yielded crystalline material which was used in subsequent reactions without further purification: mp 209-213°C (lit.[205] mp 213°C).

1,4,8-triazacycloundecane(152). 152 was prepared from 148 in 75% yield by a procedure modeled after Raymond's[60a,208] procedure (see 153 for a detailed experimental) for the preparation of tetraamines. bpca.90°C (12 mm); ^{1}H NMR ($CDCl_3$) 1.55(quintet, 4H), 2.42-3.02(m, 15H). The material was used in subsequent reactions without further purification. The trihydrobromide of 152 has been previously reported[204].

N,N',N''-tri-p-toluenesulfonyl-1,4,7-triazaheptane(140): was prepared in 97% yield by a published procedure[205] mp 162-167°C (lit.[205] mp 173°C); ^{1}H NMR ($CDCl_3$) 2.31 (brs, 9H), 2.99(brm, 8H), 7.00-7.90(m, 12H).

N,N',N''-tri-p-toluenesulfonyl-1,4,7,-triazaheptane-1,7-disodium salt(143). was prepared in 82% yield by the general method of Richman and Atkins[205](See 142 for detailed procedure.): mp 260°C(decomp); ^{1}H NMR (Me_2SO-d_6) 2.28(brs, 9H), 2.68(brm, 8H), 6.90-7.60(m, 12H). The material was used in subsequent reactions without

further purification.

1,2-propanediol-di-p-toluenesulfonate(145). 145 was prepared in 86% yield by a published procedure[209]. mp 126-128°C (lit.[210]. mp 126°C); ^{1}H NMR ($CDCl_3$) 2.43(s, 6H), 4.18(s, 4H), 7.16-7.90(AA'BB', 8H).

1,5,9,13-tetraazatricyclo[11.3.1.1^{5,9}]octadecane(54). 1,5,9,13- Tetraazacyclohexadecane(36) (173.3 mg, 0.7587 mmol) was suspended in 150 mL of CH_3CN. 200 mL of 37% formalin solution was added via syringe. The resulting solution was stirred overnight. The solvent was evaporated under reduced pressure to yield white crystalline material which was sublimed at 52°C (0.1 mm) to yield 184.7 mg (97%) of white crystaline 54. mp 78-80°C ; IR (CCl_4) 2970, 2930, 2870, 2850, 2750, 2730, 2690, 1225, 1125, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.26(brm, 2H), 1.55(quintet, 8H), 2.29-3.60(2 brm, 16H), 3.83(brm, 2H); ^{13}C NMR ($CDCl_3$) 21.56(t), 24.49(t), 49.46(t), 55.04(t), 67.88(t); Anal. Calcd for $C_{14}H_{28}N_4$: C, 66.62;H, 11.18;N, 22.20: Found:C, 66.63;H, 11.42;N, 22.14.

cis-1,5,9,13-tetrazatetracyclo[7.7.2.0^{5,13}.0^{13,18}]octadecane(52). 1,5,9,13-tetraazacyclohexadecane (36) (98.6 mg, 0.4317 mmol) was suspended in 30 mL of CH_3CN. Sufficient H_2O was added to dissolve the amine. 0.10 mL of 40% aq glyoxal(ca.0.686 mmol) was dissolved in 20 mL of CH_3CN and

was added to the amine solution in a single aliquot. The resulting solution was heated to 50°C for 1 h. The solvent was evaporated under reduced pressure to yield a yellow crystal mass which was sublimed at 55°C (0.1 mm) to yield 66.8 mg (62%) of white crystalline 36: mp 99.5-101.5°C; IR (CCl_4) 2910, 2830, 2750, 1130, 1125, 1105, cm^{-1}; ^{13}C NMR ($CDCl_3$) 20.05(d), 22.05(t), 51.8(t), 55.48(t), 84.57(d); Anal. Calcd for C_{14}, H_{26}, N_4: C, 67.15; H, 10.47; N, 22.37: Found: C, 66.95; H, 10.73; N, 22.38.

1,5,9,13-tetraazatridecane(31). 31 was prepared in 46% yield by a published procedure for the preparation of 1,5,8,12-tetraazadecane[60a] the only modification being the substitution of 1,3-dibromopropane for 1,2-dibromoethane (see 153 for workup procedures). bp 144-146°C (0.3 mm) (lit.[60a,208]. bp 135-136°C (0.1 mm). The ^1H spectrum was identical to the published spectrum (Sadtler Spectrum 21974).

N,N',N''N'''-tetra-p-toluenesulfonyl-1,5,9,13-tetraazatridecane(32). 32 was prepared. 31 in 89% yield by a published procedure[208]. All physical and spectral data agreed with published data[60a, 208].

N,N',N''N'''-tetra-p-toluenesulfonyl-1,5,9,13-tetraazatridecane-1,13-di-sodium salt(33). 32(81.84 g, 0.1017 mmol) was dissolved in 200 mL of abs EtOH and heated to reflux

with mechanical stirring under a nitrogen atmosphere. The heat was removed and 135 mL of 1.51 M sodium ethoxide (prepared fresh by the reaction of sodium metal (4.67 g, 0.2034 mmol) with 135 mL of abs EtOH) was added in a single aliquot to the vigorously stirred solution. The resulting solution was stirred for 3 h and then allowed to stand for 12 h during which time the product precipitated. The white solid was collected by suction filtration under nitrogen and dried in vacuo at 80°C for 48 h to yield 48.17 g (56%) of white crystalline solid. mp 240°C (decomp). ^{1}H NMR (Me_2SO-d_6) 1.50 (brm, 6H), 2.28 (s, 6H), 2.38 (s, 6H), 2.93 (brm, 12H), 6.90-7.80 (m, 16H). The material was used in subsequent reactions with out further purification.

1,3-propanediol-di-p-toulenesulfonate(34). 34 was prepared in 73% yield by a published procedure[209]. mp 91.5-93°(lit.[210]. mp 91-92°).

N,N',N''N'''-tetra-p-toluenesulfonyl-1,5,9,13-tetraazacyclohexadecane(35). 35 was prepared in 35% yield from 33 and 34 by a published procedure[60a, 208]. mp 250-255°C (decomp) (lit.[60a, 208]. mp 252-255°C (decomp), lit.. yield 59%). All physical and spectral data were in agreement with published data.

1,5,9,13-tetraazacyclohexadecane(36). 36 was prepared in 53% yield by a published procedure[208]. mp 83-85°C

(lit.[208]. mp 84°C).

Attempted Syntheses of 1,5,9,13-tetraazatetracyclo[7.7.3.$0^{5,19}$.$0^{13,17}$]nonadecane (37). Method A: 1,5,9,13-tetraazacyclohexadecane(51.1 mg, 0.2237 mmol) was dissolved in 25 mL of CH_3CN. Malonaldehyde bisdimethylacetal(0.0391 mL, 0.3353 mmol) was added followed by one drop of 12 M HCl(delivered via a drawn capillary). The resulting mixture was heated to 50°C for 1 h under a nitrogen atmosphere. The solvent was evaporated and the resulting white solid was dissolved in 10 mL of 5% aq NaOH and extracted with $CHCl_3$(15X10 mL). The combined extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated to yield 50.4 mg of starting material.

Method B: 1,5,9,13-tetraazacyclohexadecane(50.4 mg, 0.2206 mmol) was dissolved in 35 mL of anhyd MeOH. This solution was adjusted to pH4 with 12 M HCl. Malonaldehyde bisdimethylacetal(0.0391 mL, 0.3353 mol) was added via syringe and the resulting solution was heated to reflux for 17 h. The workup procedure as described for method A again yielded 50 mg of starting material.

Method C: 1,5,9,13-tetraazacyclohexadecane(53.0 mg, 0.2320 mmol) was dissolved in 50 mL of anhyd MeOH. Glacial acetic acid(two drops) was added followed by malonaldehyde

bisdimethylacetal(0.0391 mL, 0.3353 mmol). The resulting solution was heated to reflux for 24 h. The work up procedure as described in method A again yielded 52.5 mg of starting material.

Method D: 1,5,9,13-tetraazacyclohexadecane(42.2 mg, 0.185 mmol) was dissolved in 25 mL of anhyd MeOH. 10 mL of 5% aq HCl was added followed by malonaldehyde bisdimethylacetal(0.080 mL, 0.6706 mmol) and the resulting solution was heated to reflux for 2 h. The work up procedure as described in method A yielded 35.3 mg of starting material.

Method E: 1,5,9,13-tetraazacyclohexadecane(35.3 mg, 0.155 mmol) was dissolved in 75 mL of anhyd MeOH. p-Toluenesulfonic acid dihydrate(2 crystals) was added followed by malonaldehyde bisdimethylacetal (0.0391 mL, 0.335 mmol). The resulting solution was heated to reflux for 92 h. The workup as described in method A yielded 36.4 mg of white crystals. ^{1}H NMR indicated mostly starting material but also contained some new minor resonances. This material was sublimed at 55°C (0.2 mm) to yield 24 mg of white crytalline material. The ^{1}H NMR remained unchanged. TLC on neutral alumina(EtOH) indicatded two spots.

<u>N-p-toluenesulfonyl-2,2'-iminodiethanol-1,5-di-p-toluenesulfonate(144)</u>. Diethanolamine(20.00 g, 0.190 mol) was

dissolved in 160 mL of anhyd pyridine and cooled to -6°C. p-Toluenesulfonylchloride(108.78 g, 0.5706 mmol) was dissolved in 180 mL of anhyd pyridine and cooled to -6°C. The tosylchloride solution was added to the amine solution over a 1 h period at 0°C. The resultant burgundy solution was allowed to stand at -6°C for 24 h. The resultant slushy burgundy solution was poured over a slush consisting of 500 mL of 6 N aq HCl and 1000 g of crushed ice and then extracted with CH_2Cl_2 (3x250 mL). The combined extracts were washed with ice cold 10% aq HCl(5X100 mL)(CAUTION:Exothermic. Vent separatory funnel frequently.), then with ice H_2O until the smell of pyridine could no longer be detected in the wash H_2O, and then with brine (250 mL). The CH_2Cl_2 solution was then dried over Na_2SO_4, filtered, and the solvent was evaporated at reduced pressure at <u>room temperature</u> to yield a viscous burgundy oil. Trituration with 95% EtOH yielded a yellow solid which was collected by suction filtration and washed with cold 95% EtOH until all of the yellow coloration was removed. Recrystallization from 95% EtOH at 60°C yielded three crops of white crystalline material: yield 71.22 (66%) g;mp 83-85°C;^{1}H NMR ($CDCl_3$) 2.40(s, 3H), 2.42(s, 6H), 3.32(t, 4H), 4.10(t, 4H), 7.00-7.90(m, 12H). The material was used in subsequent reactions without further purification.

<u>N,N',N''N'''-tetra-p-toluenesulfonyl-1,4,7,11-tetraazacyclo-</u>

tetradecane(154). 154 was prepared in 30% yield(lit.[205] yield 58%) by the method of Richman and Atkins[205] from 144 and 143. The following modifications of the reported procedure simplified the work up. The crude reaction solids were dissolved in CH_2Cl_2 and filtered to remove sodium tosylate. The solution was then dried over Na_2SO_4, filtered, and the solvent was evaporated at reduced pressure to yield solid crystalline product which was recrystallized from $CHCl_3$/ EtOH: mp 228-232°C (lit.[205]. mp 234-236° C); ^1H NMR ($CDCl_3$) 1.88(brm, 4H), 2.41 (brm, 12H), 2.63-3.86(brm, 16H), 7.00-7.90(m, 16H).

Orthoformamides(91-94). 91-94 were synthesized by method A and or method B as indicated.

Method A: Macrocyclic triamine(0.5 mmol), triethylorthoformate (0.75 mmol), and macrocyclic triamine trihydrochloride (0.07 mmol) were dissolved in 75 mL of anhyd toluene and refluxed in a flask equipped with a Soxhlet extractor containing 5 Å molecular sieves. The solvent was then distilled off to yield a yellow oil which was dissolved in 7 mL of 5% aq NaOH The basic solution was extracted with $CHCl_3$(10x10 mL). The combined extracts were then dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to yield the orthoformamide as a clear oil.

Method B: Macrocyclic triamine(0.5 mmol) and N, N-dimethylformamide dimethylacetal(0.50 mmol) were heated to 85°C for 3 h in a 5 mL round bottom flask fitted with a short path distillation head. Residual MeOH and dimethylamine were evaporated in vacuo to yield the product. (Purification techniques varied from compound to compound and are included in the individual experimental sections).

1,4,7-triazatricyclo[5.2.1.$0^{4,10}$]decane(91). 91 was prepared in 9% yield by method A and in 25% yield by method B from 91 by Robert E. Fiala. 91 was purified by kugelrohr distillation: bp ca.80°C (2.5 mm); IR (CCl_4) 2960, 2930, 2910, 2870, 2830, 1235, 1150, 1105, 1060, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) 2.50-3.35(AA'BB', 12H), 5.03(s, 1H); ^{13}C NMR ($CDCl_3$) 52.0(t), 104.1 (d); mass spectrum, m/z(rel intensity) 139(60).

1,4,7-triazatricyclo[5.3.1.$0^{4,11}$]undecane(92). 92 was prepared in 85% yield by method B from 151 and was purified by kugelrohr distillation: bpca.82°C (2.5 mm); IR (CCl_4) 2938, 2879, 2860, 2800, 1270, 1255, 1175, 1155ch $^{-1}$; ^1H NMR ($CDCl_3$) 1.05(d of t of t, J=13;3;3 Hz, 1H), 2.35-3.35(m, 12H), 4.32(s, 1H); ^{13}C NMR ($CDCl_3$) 16.5(t), 45.9(t), 49.0(t), 56.2(t), 93.3(d); mass spectrum, m/z(rel intensity) 153(10), 152(100).

1,4,8-triazatricyclo[6.3.1.$0^{4,12}$]dodecane(93). 93 was

prepared in 38% yield by method A and in 68% by method B and was purified by kugelrohr distillation: bpca.85°C (2.5 mm); IR (CCl_4) 2930, 2850, 2770, 2730, 1260, 1145, 915 cm^{-1}; ^1H NMR ($CDCl_3$) 1.10-3.40(m); ^{13}C NMR ($CDCl_3$) 23.6(t), 47.7(t), 48.9(t), 56.2(t), 93.3(d); mass spectrum, m/z(rel intensity) 167(10), 166(100).

1,5,9-triazatricyclo[7.3.1.$0^{5,13}$]tridecane(94). 94 was prepared in 74% yield by method B from 153 and was purified by sublimation at 40°C (0.1 mm): mp 39-41°C; IR (CCl_4) 2939, 2919, 2840, 2800, 2795, 2740, 2700, 2670, 2600, 2580, 2495, 2430, 2400, 1290, 1165, 1135, 1125, 1100, 1035, 915 cm^{-1}; ^1H NMR (Me_2CO-d_6) 1.22-1.49(m, 3H), 1.58-2.22(m, 9H), 2.25(s, 1H, methine), 2.61-2.90(m, 16H); ^{13}C NMR (Me_2CO-d_6) 24.2(t), 53.9(t), 100.0(d); mass spectrum, m/z(rel intensity) 181 (10), 180(100).

Orthoacetamides(95-98). 95-98 were synthesized according to the following general scheme: Macrocyclic triamine (0.5 mmol) and 90% methanolic solution of N,N-dimethylacetamide dimethylacetal(0.5 mmol) were heated to 85°C for 3 h with stirring in a 5 mL round bottom flask fitted with a short path distillation head. Residual MeOH and dimethylamine were evaporated in vacuo to yield the crude products. (Purification procedures varied from compound to compound and are included in the individual experimental sections.)

10-methyl-1,4,7-triazatricyclo[5.2.1.$0^{4,10}$]decane(95). 95 was prepared in 82% yield from 150 according to the general procedure described above and was purified by kugelrohr distillation followed by gas chromatography(15% Carbowax 20M, 5% KOH on Chrom. W): bpca.80°C (2.5 mm) IR (CCl_4) 2970, 2930, 2880, 2840, 1490, 1470, 1440, 1410, 1330, 1279, 1210, 1170, 1125, 1095, 1050, 1000, 885 cm^{-1}; ^1H NMR ($CDCl_3$) 1.34 (s, 3H), 2.50-3.32(AA'BB', 12H); ^{13}($CDCl_3$) 27.7(q), 51.8(t), 111.4(s); mass spectral peak match calcd for $C_8H_{12}N_3$ 153.12659; found 153.12734(error=-4.9ppm); calcd for $C_7H_{12}N_3$ 138.10312; found 138.10219(error=-6.1ppm).

11-methyl-1,4,7-triazatricyclo[5.3.1.$0^{4,11}$]undecane(96). 96 was prepared in 85% yield according to the general procedure described above from 152 and was purified by kugelrohr distillation followed by gas chromatography(15% Carbowax 20M, 5% KOH on Chrom. W): bpca.83°C (2.5 mm); IR (CCl_4) 2979, 2939, 2905, 2880, 2860, 2820, 1370, 1360, 1345, 1332, 1320, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) 0.915(d of t of t, J=13.7$^+$ 0.10 Hz;3;2.8 Hz$^+$0.10 Hz, 1H), 1.514(s, 3H), 1.62-2.52(m, 1H), 2.55-3.55(m, 12H); ^{13}C NMR ($CDCl_3$) 13.06(t), 23.8(q), 44.6(t), 51.7(t), 54.9(t), 94.7(s); mass spectral peak match calcd for $C_9H_{17}N_3$ 167.14224; found 167.14115(error=6.5ppm); Calcd for $C_8H_{14}N_3$ 152.11877; found 152.12001 (error=-8.2ppm).

12-methyl-1,4,8-triazatricyclo[6.3.1.$0^{4,12}$]dodecane(97). 97 was prepared according to the procedure described above from 152 and was purified by kugelrohr distillation followed by gas chromatography(15% Carbowax 20M, 5% KOH on Chrom. W): bpca.87°C (2.5 mm) IR (CCl_4) 2940, 2860, 2800, 2750, 2730, 1425, 1270, 1255, 1215, 1205, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) 1.10(d of t of t, 2H), 1.32(s, 3H), 1.89-3.39(m, 12H); ^{13}C NMR ($CDCl_3$)10.0(q), 20.1 (t), 43.7(t), 45.6(t), 49.4(t), 86.9(s); mass spectral peak match calcd for $C_{10}H_{19}N_3$ 181.1579; found 181.1560 (error=1.04ppm).

13-methyl-1,5,9-triazatricyclo[7.3.1.$0^{5,13}$]tridecane(98). 98 was prepared from 153 according to the above described procedure and was purified by column chromatography(basic alumina, 5% EtOH/CH_2Cl_2, v/v) to yield 98 as a clear oil:IR (CCl_4) 2905, 2880, 2840, 2760, 2740, 2700, 2640, 2620, 1405, 1370, 1275, 1255, 1185, 1115, 1095, 1085, 1065, 1050, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) 1.01 (3, 3H), 1.41 (d of t of t, 3H), 1.80-2.72(m, 15H); ^{13}C($CDCl_3$) -4.01(q), 24.6(t), 49.0(t), 86.0(s) ;mass spectral peak match calcd for $C_{10}H_{18}N_3$ 180.15007; found 180.152355 (error=-1.26ppm).

Orthopropionamides(99-102). 99-102 were prepared according to the following procedure: Macrocyclic triamine(0.5 mmol) and N,N-dimethylpropionamide dimethylacetal(0.5 mmol) were heated to 85°C for 3 h with stirring in a 5 mL round bottom

flask fitted with a short-path distillation head. Residual MeOH and dimethylamine were evaporated *in vacuo* to yield the crude products.(Purification procedures varied from compound to compound and are included in the individual experimental sections).

10-ethyl-1,4,7-triazatricyclo[5.2.1.$0^{4,10}$]decane(99). 99 was prepared in 53% yield from 150 by the above described procedure and was purified by kugelrohr distillation followed by column chromatography(basic alumina, 5% EtOH/CH_2Cl_2, v/v) to yield 130 as a clear oil:bpca.75° (2.5 mm); IR (CCl_4) 2962, 2936, 2878, 2835, 1450, 1269, 1250, 1000 cm^{-1}; ^1H NMR ($CDCl_3$)1.01 (t, 3H), 1.67(q, 2H), 2.75-3.20(AA'BB', 12H); ^{13}C NMR ($CDCl_3$) 9.6(q), 33.6(t), 51.9(t), 113.8(s); mass spectral peak match calcd for $C_9H_{17}N_3$ 167.14224; found 167.14336(error=-6.7ppm): Calcd for $C_7H_{12}N_3$ 138.10312; found 138.10238(error=5.4ppm).

11-ethyl-1,4,7-triazatricyclo[5.3.1.$0^{4,11}$undecane(100). 100 was prepared in 43% yield from 103 by the above described procedure and was purified by kugelrohr distillation:bpca.75°C (0.5 mm); I.R. (CCl_4) 2965, 2930, 2878, 2950, 2810, 1355, 1345, 1280, 1160, 735 cm^{-1}; ^1H NMR ($CDCl_3$)0.89(t, 3H), 1.79(q, 2H), 2.02-2.62(m, 2H), 2.70-3.50(m, 13H); ^{13}C NMR ($CDCl_3$)9.8(q), 12.5(t), 28.2(t), 44.7(t), 52.1 (t), 55.8(t), 97.0(s); mass spectral

peak match calcd for $C_{10}H_{19}N_3$ 181.15789; found 181.15978 (error=-1.0ppm); Calcd for $C_8H_{14}N_3$ 152.11877; found 152.11851 (error=1.7ppm).

12-ethyl-1,5,9-triazatricyclo[6.3.1.$0^{9,12}$]tetradecane(101). 101 was prepared in 82% yield from 152 by the above described procedure and was purified by kugelrohr distillation:bpca.80°C (0.5 mm); IR (CCl_4) 2950, 2870, 2810, 2760, 2740, 2680, 2650, 1498, 1472, 1440, 1380, 1365, 1355, 1340, 1305, 1290, 1272, 1200, 1100 cm^{-1}; ^1H NMR ($CDCl_3$)0.80(t, 3H), 0.90-3.39(m, 18H); ^{13}C NMR ($CDCl_3$)7.4(q), 11.4(t), 19.8(t), 43.3(t), 45.6(t), 48.9(t), 88.8(s); mass spectral peak match calcd for $C_{11}H_{21}N_3$ 195.17354; found 195.17219 (error=6.9ppm); Calcd for $C_9H_{16}N_3$ 166.13442; found 166.13482(error=-2.4ppm).

13-ethyl-1,5,9-triazatricyclo[7.3.1.$0^{5,13}$]tridecane(102). 102 was prepared in 65% yield from 153 by the above described procedure and was purified by kugelrohr distillation followed by column chromatography(basic alumina, 5% EtOH/CH_2Cl_2, v/v) to yield 102 as a white crystalline solid: mp 41-43°C; IR (CCl_4) 2950, 2939, 2930, 2910, 1350, 1285, 1065 cm^{-1}; ^1H NMR (Me_2CO-d_6) 0.80(t, 3H), 1.11-2.13(m, 8H), 2.70-2.83(AA'BB', 12H); ^{13}C NMR (Me_2CO-d_6) 7.9(q), 13.0(t), 22.3(t), 49.1 (t), 87.1 (s); mass spectral peak match calcd for $C_{12}H_{22}N_3$

208.18137; found 208.18083(error=2.6ppm); Calcd for $C_{10}H_{18}N_3$ 180.15007; found 180.15155(error=-8.2ppm).

5-methyl-5,9-diaza-1-azonibicyclo[7.3.1]tridec-1(13)-ene (134). 94 (53.1 mg, 0.293 mmol) was dissolved in 5 mL of $CHCl_3$ in a stoppered 10 mL round bottom flask. 0.1 mL (1.61 mmol) of methyl iodide was added via syringe. The resulting solution was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure to yield 85.9 mg (91%) of white crystalline product: mp 230-234° C(decomp); IR (KBr) 2957, 2937, 2817, 2777, 1672, 1425, 1330, 1220, 1199, 1120, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) 1.15-3.80(m, 19H), 4.00-4.75(d of t, 2H), 9.28(s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) 19.8(t), 22.8(t), 41.7(q), 42.7(t), 54.3(t), 58.2(t), 158.4(d); Anal. calcd for $C_{11}H_{22}N_3I$: C, 40.88;H, 6.86;N, 13.00. Found: C, 40.67;H, 6.95;N, 12.72.

1-methyl-1,5,9-triazacyclododecane(135). 134 (100.6 mg, 0.3112 mmol) was dissolved in 20 mL of 5% aq NaOH and was stirred at room temperature for 12 h under N_2. The reaction mixture was extracted with $CHCl_3$ (10 X 10 mL). The combined extracts were then dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to yield a yellow oil. Kugelrohr distillation (80°(2.5 mm)) followed by sublimation (45°(0.1 mm)) yielded 52.3 mg (91%) of the product as hygroscopic white crystals:

mp 46.5-49.5°C; IR (KBr)3318, 3280, 2930, 2800, 1460, 1295, 1255, 1128, 1048; ^{1}H NMR ($CDCl_3$, 90 MHz) 1.73-1.50(m, 6H), 2.13(s, 3H), 2.48(t, 4H), 2.71-2.77(m, 10H); ^{13}C NMR ($CDCl_3$) 26.11(t), 40.41(q), 47.62(t), 49.84(t), 57.32(t); mass spectrum, m/z(rel intensity) 185(100); Anal. calcd for $C_{10}H_{23}N_3$: C, 64.81;H, 12.51;N, 22.67. Found: C, 64.56;H, 12.62;N, 22.54.

5,13-dimethyl-5,9-diaza-1-azoniabicyclo[7.3.1]tridec-1(13)-ene(136). 98 (53.4 mg, 0.273 mmol) was dissolved in 5 mL of $CHCl_3$ in a stoppered round bottom flask. 0.2 mL (3.21 mmol) of methyl iodide was added via syringe and the resulting solution was stirred at room temperature for 1 h under N_2. The solvent and the excess methyl iodide were evaporated under reduced pressure to yield 57.7 mg (63%) of white crystalline product: mp 230-240°C(decomp); IR (KBr) 2970, 2950, 2850, 2800, 1608.8, 1510, 1475, 1395, 1325, 1225, 1212, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) 1.30-3.90(m, 22H), 4.10-4.82(d of t, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) 20.0(t), 22.8(q), 24.4(t), 43.3(t), 46.2(t), 54.1 (t), 58.7(t), 169.1 (s); Anal calcd for $C_{12}H_{24}N_3I$: C, 42.74;H, 7.17;N, 12.46. Found: C, 42.70;H, 7.38;N, 12.52.

13-ethyl-5-methyl-5,9-diaza-1-azoniabicyclo[7.3.1]tridec-1(13)-ene(137). 102 (28.6 mg, 0.137 mmol) was dissolved in 5 mL of $CHCl_3$ in a stoppred 10 mL round bottom flask. 0.2

mL (3.21 mmol) of methyl iodide was added via syringe and the resulting solution was stirred at room temperature for 72 h under N_2. The solvent and the excess methyl iodide were evaporated under reduced pressure to yield 41.1 mg (85%) of white crystalline product: mp 230-240° (decomp); IR (KBr) 2950, 2940, 2930, 2800, 1602.3, 1350, 1270, 1260, 1187, 1065, cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) 0.95(t, 2H), 1.18-3.85(m, 22H), 4.20-4.85(d of t, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) 14.4, 20.0, 23.9, 25.8, 42.8, 46.7, 50.8, 54.3, 175.5; Anal. calcd for $C_{13}H_{26}N_3I$: C, 44.45;H, 7.46;N, 11.96. Found: C, 44.50;H, 7.67;N, 11.69.

<u>1-formyl-1,4,7-triazacyclononane(138)</u>. <u>91</u> (83.8 mg, 0.6029 mmol) was dissolved in 0.5 mL of D_2O. 0.22 mL of 5.5657 N DCl/D_2O was added via syringe and the resulting solution was stirred at room temperature for 0.5 h. The reaction mixture was made basic with 5% NaOH and extracted with $CHCl_3$ (10 x 15 mL). The combined extracts were dried over Na_2SO_4, filtered, and the $CHCl_3$ evaporated at reduced pressure to yield 82.3 mg (87) of product as a white crystalline solid. The solid was sublimed at 55°C (0.1 mm) to yield pure product: mp 68-72°C; IR (CCl_4) 2920, 2850, 1678; ^1H NMR ($CDCl_3$, 90 MHz) 1.80(s, 2H), 2.75(s, 4H), 2.99-3.51 (m, 8H), 8.15(s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) 163.9(d), 52.9(t), 50.3(t), 49.7(t), 48.9(t), 48.7(t), 47.0(t); mass spectral peak match calcd for $C_7H_{15}N_3O$ 157.12151 found 157.12149 (error=0.13 ppm). [note: the high

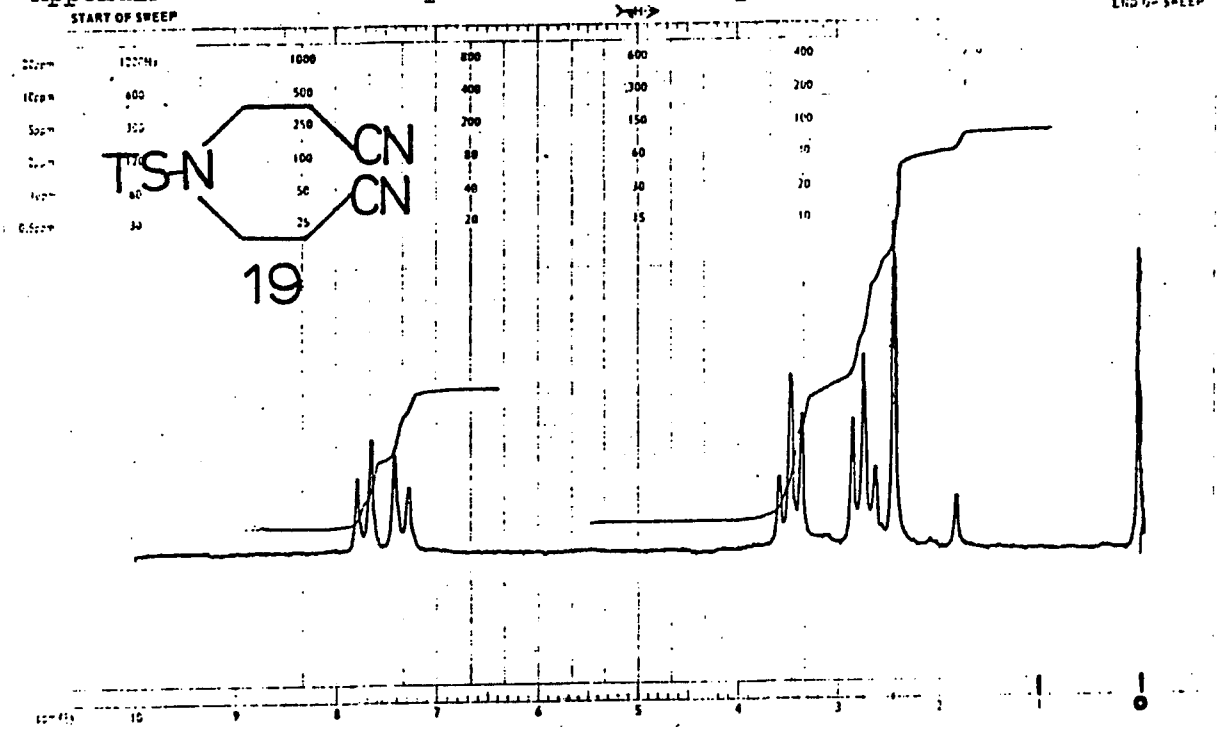
resolution mass spectrum indicated the presence of a small amount of higher molecular weight impurities].

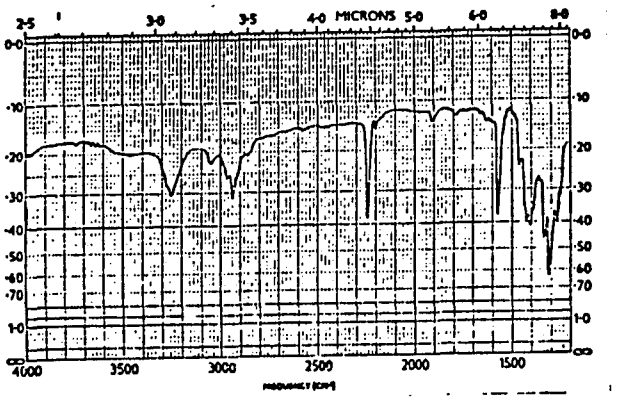
Attempted Sythesis of 1-formyl-4-benzoyl-1,4,7-triazacyclododecane(139). 94 (119.3 mg, 0.659 mmol) was dissolved in 10 mL of anhyd benzene in a round bottom flask fitted with reflux condenser, nitrogen inlet, and a magnetic stirrer. Benzoyl chloride (92.6 mg, 0.659 mmol) was dissolved in 2 mL of anhyd benzene and was then added in a single aliquot to the amine solution with stirring. The resulting solution was heated to reflux with stirring for 12 h under N_2. The solvent was then evaporated under reduced pressure to yield a white hygroscopic crystalline solid. The intermediate product was dissolved in 5 mL of D_2O. 0.2 mL of 40% NaOD in D_2O was added via syringe and the resulting solution was shaken for 5 min (^1H NMR indicated that the hydrolysis was complete). The basic solution was extracted with $CHCl_3$ (10 X 10 mL), the combimed extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to yield 179.1 mg of a yellow oil. Column chromatography (basic alumina, 5% EtOH/CH_2Cl_2, v/v) yielded 147.7 mg of a clear oil. ^1H NMR indicated the presence of impurities. The product would not sublime or distill at 100°C (0.1 mm). Heating the product at 95 C (0.1 mm) for 3 days reduced the amount of impurities but did not remove them completely. Recrystallization was attempted in

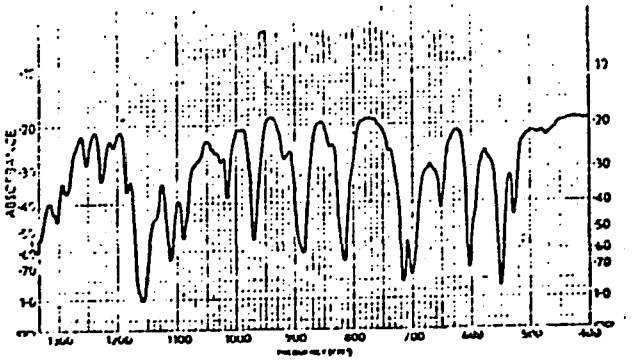
CH_2Cl_2/hexane without success. ^1H NMR ($CDCl_3$, 60 MHz) 0.85(m, impurity), 1.95(m, 6H), 1.68(m, 4H), 3.45(m, 8H), 7.42(s, 5H), 8.09(s, 1H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz)172.6, 172.5, 163.8, 162.9, 137.2, 129.3, 128.5, 126.4, 47.2, 46.2, 45.6, 44.4, 43.9, 43.5, 43.1, 42.0, 41.8, 41.2, 40.7, 28.1, 27.6, 27.3, 26.9, 24.9, 24.0.

APPENDICES

Appendix 1: ^{1}H and IR Spectra for New Compounds







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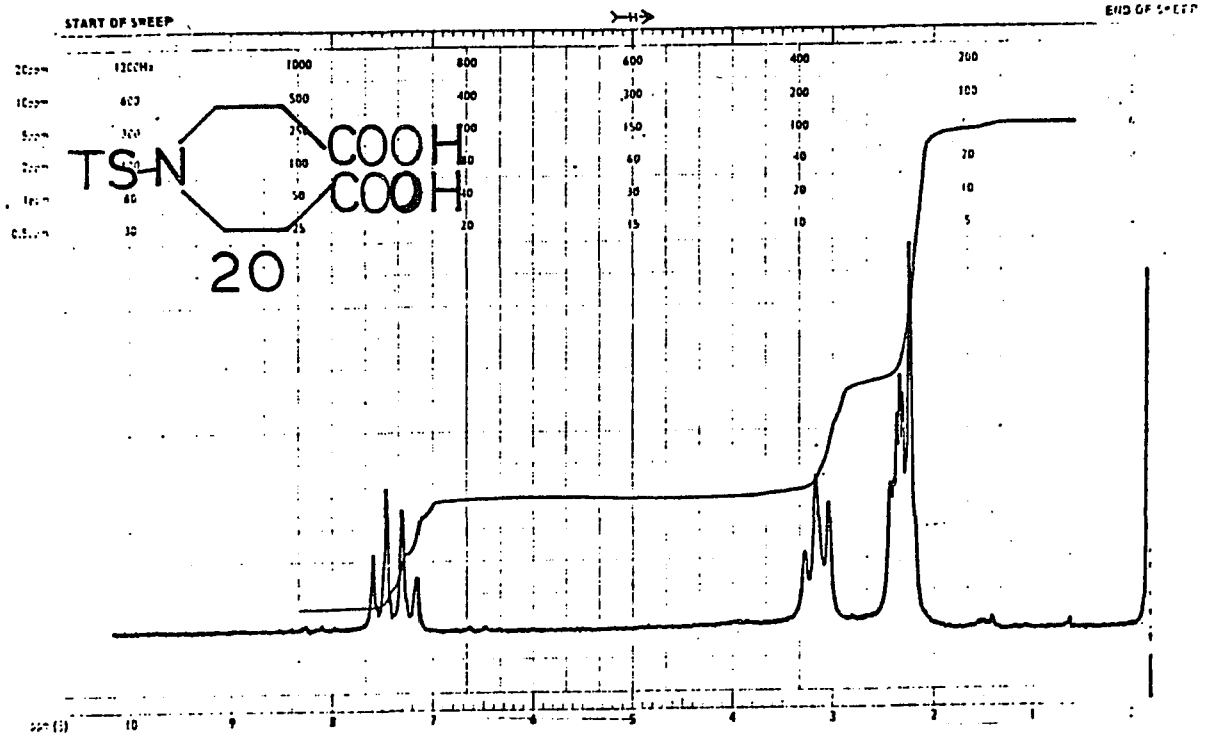
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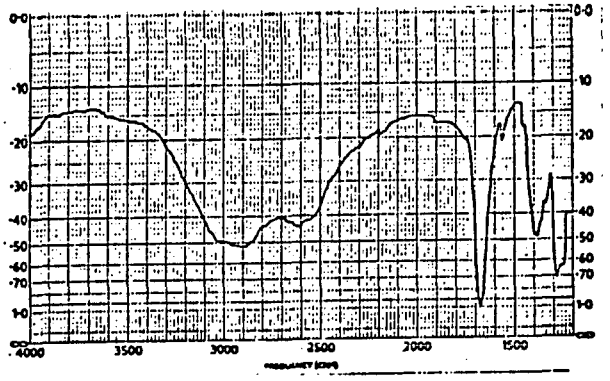
COOH
20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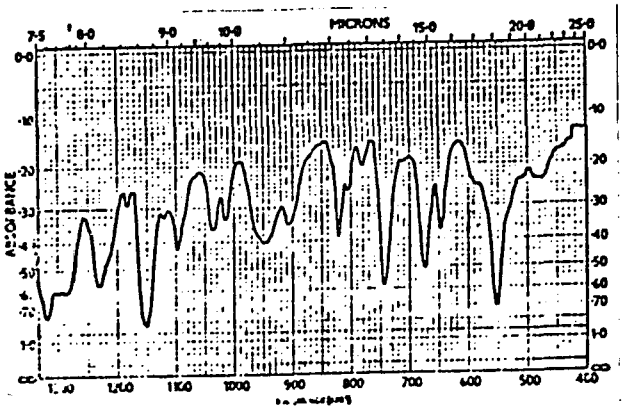
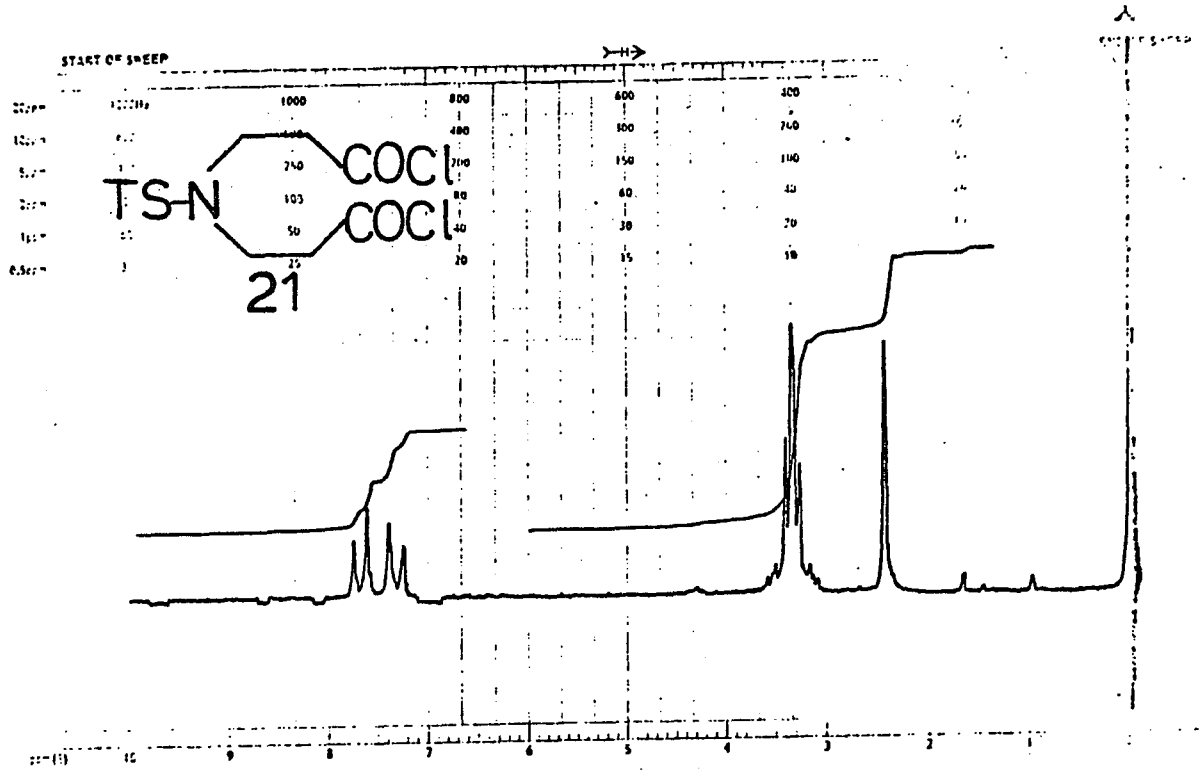

MICRONS
ABSORBANCE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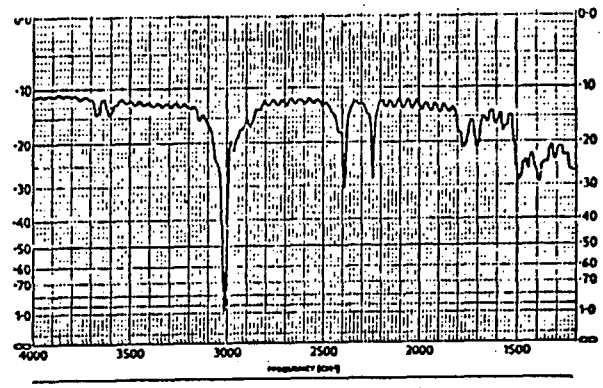

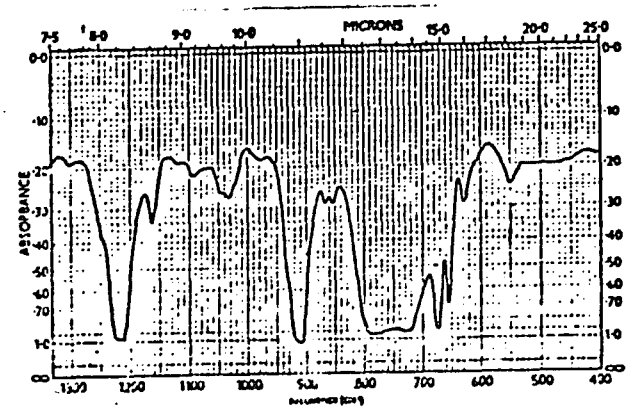
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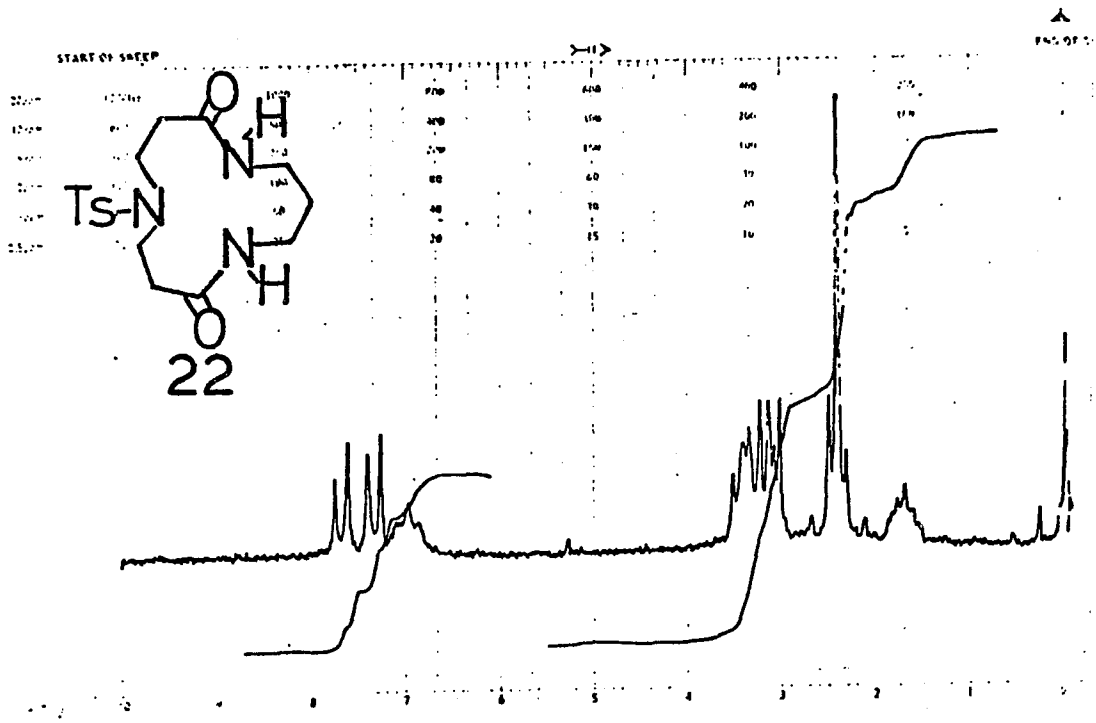
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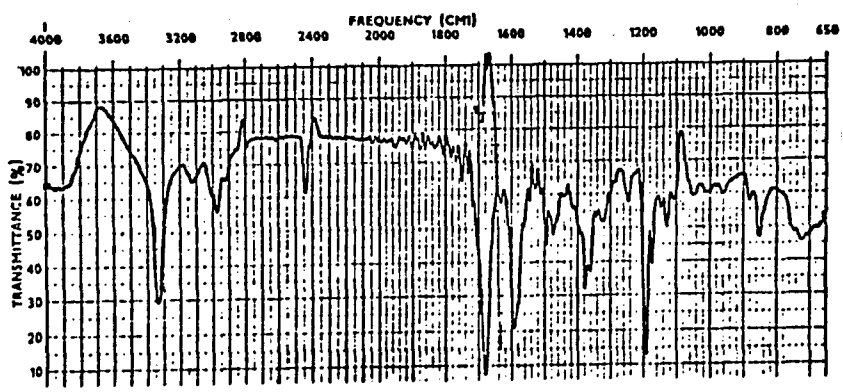
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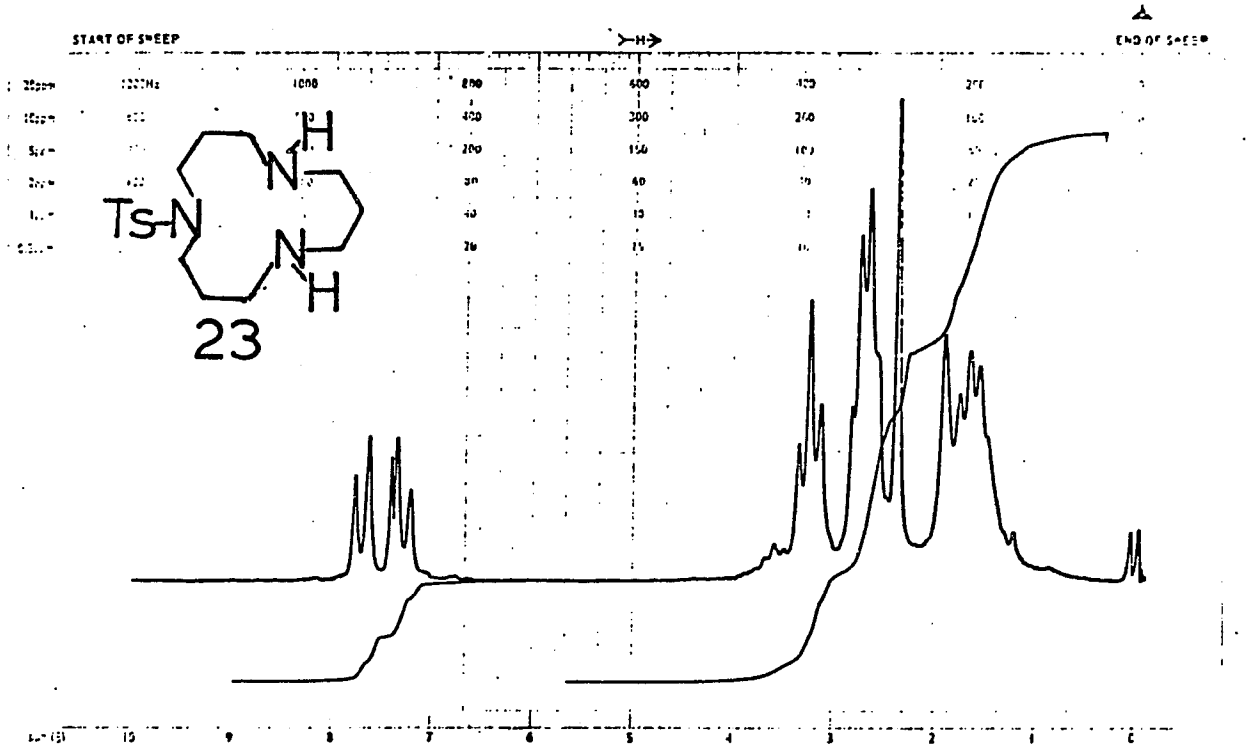

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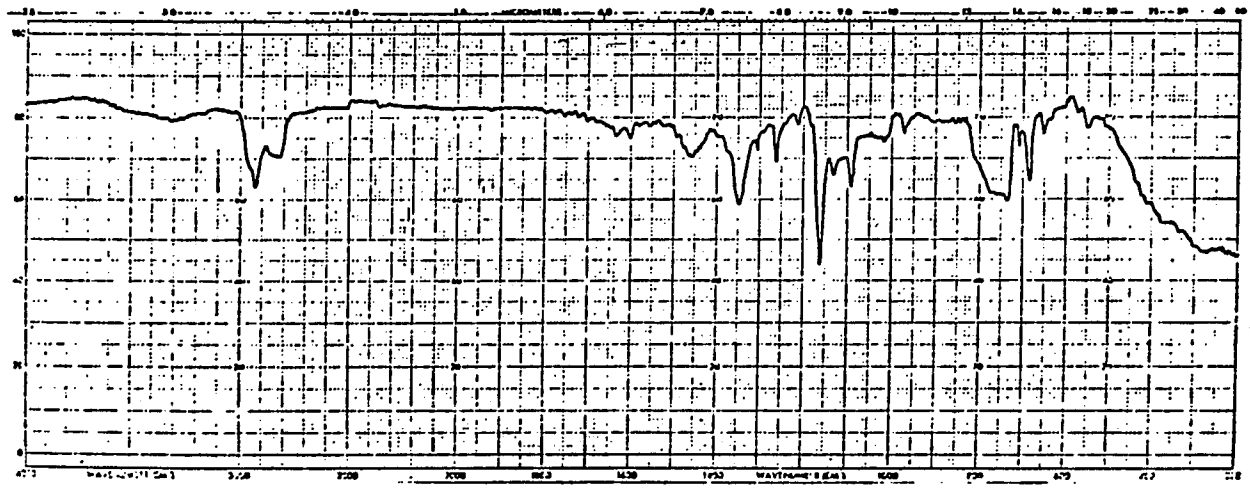

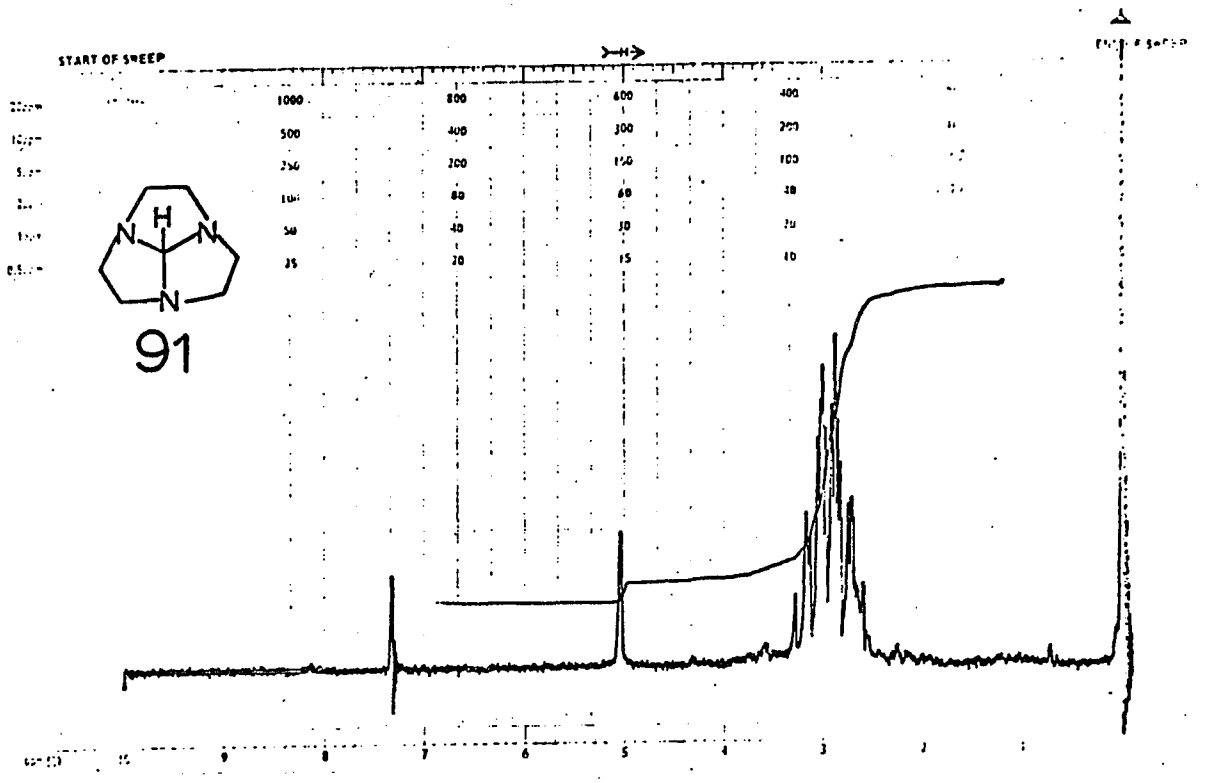
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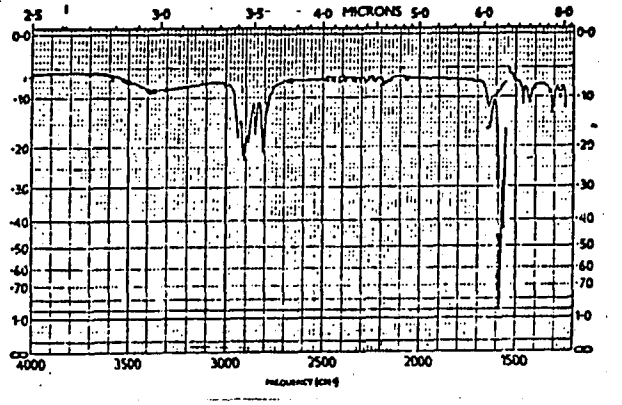
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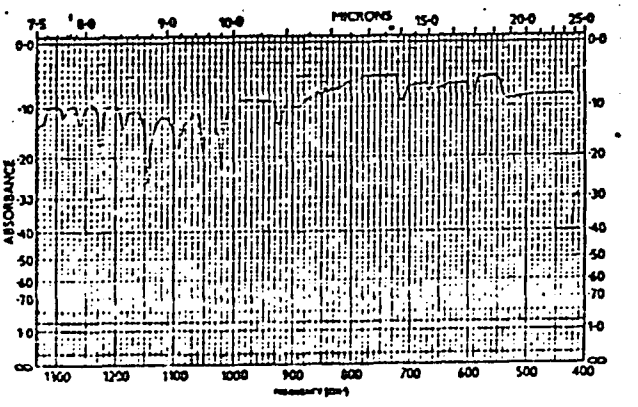
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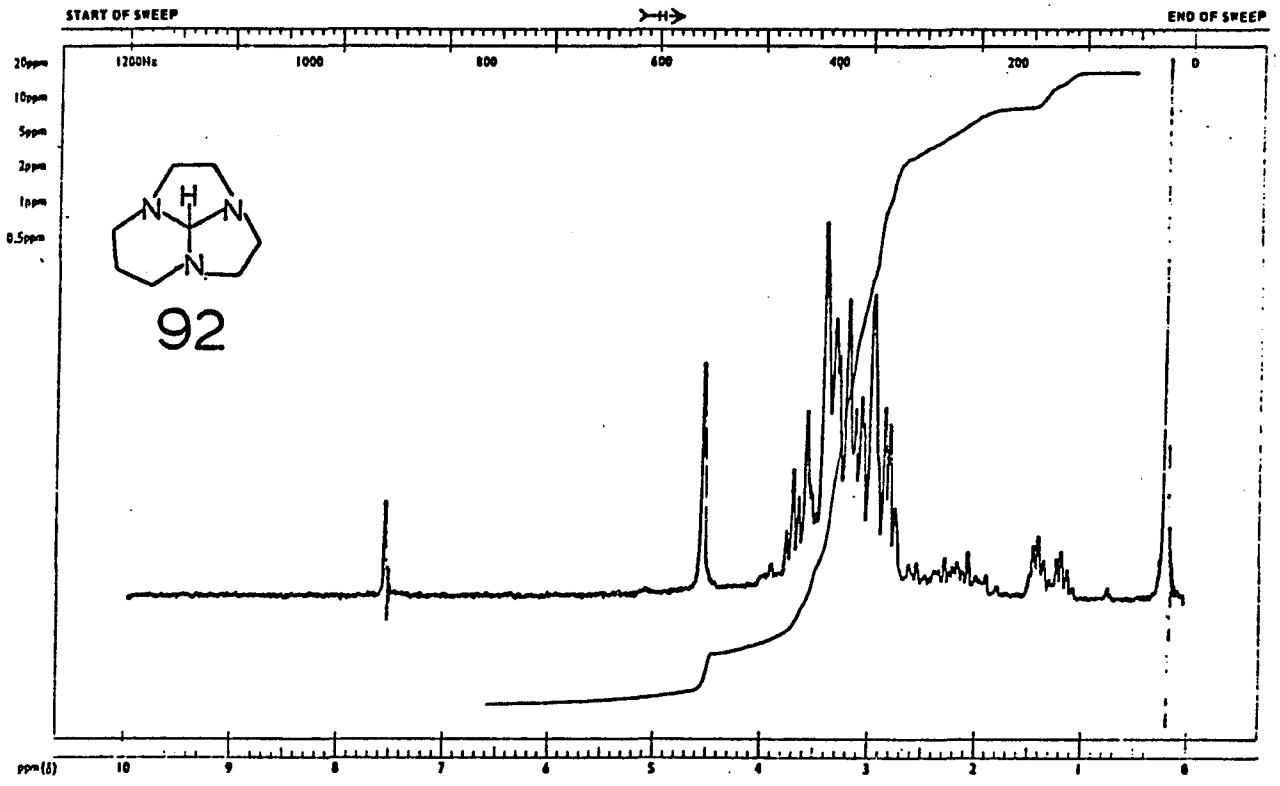
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N
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ppm (δ)
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7
6
5
4
3
2
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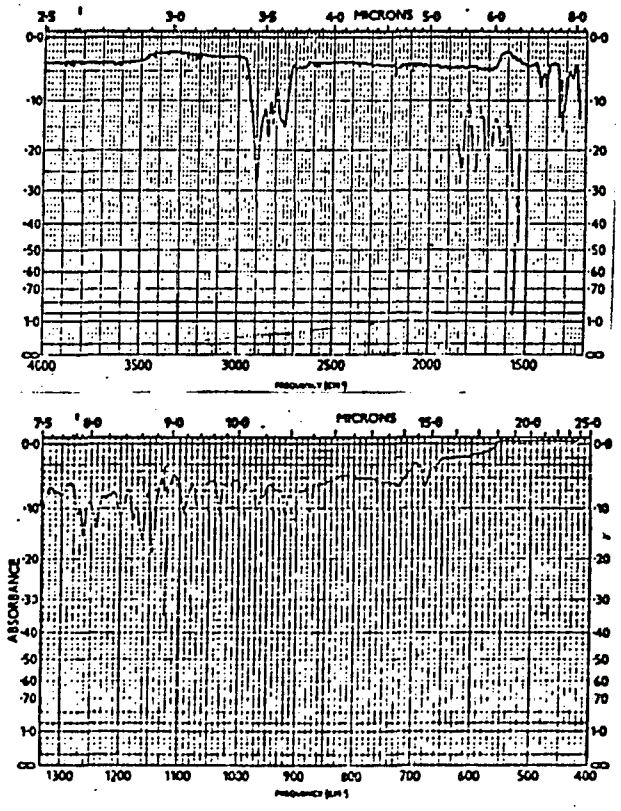
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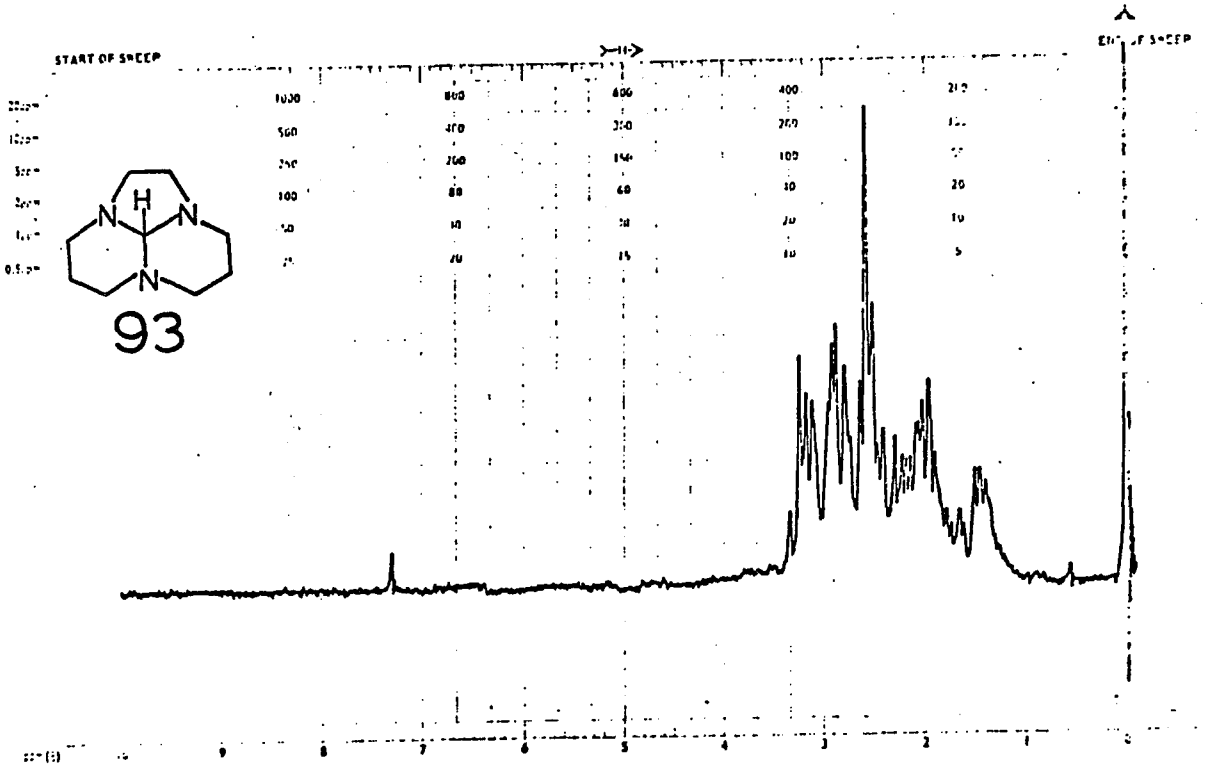
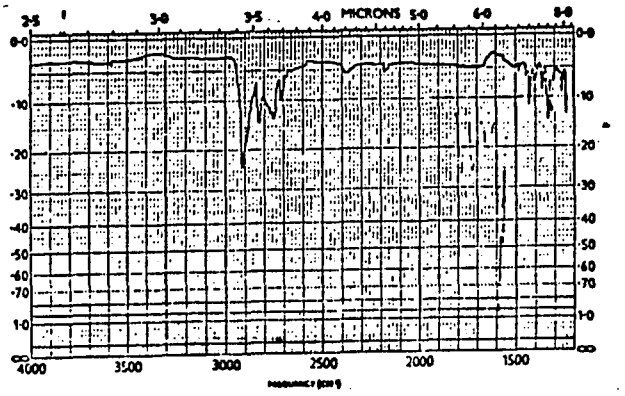
3500
3000
2500
2000
1500
MICRONS
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400


START OF SWEEP
END OF SWEEP

93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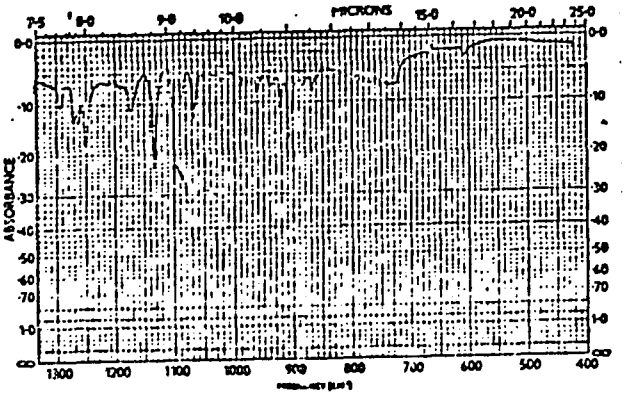
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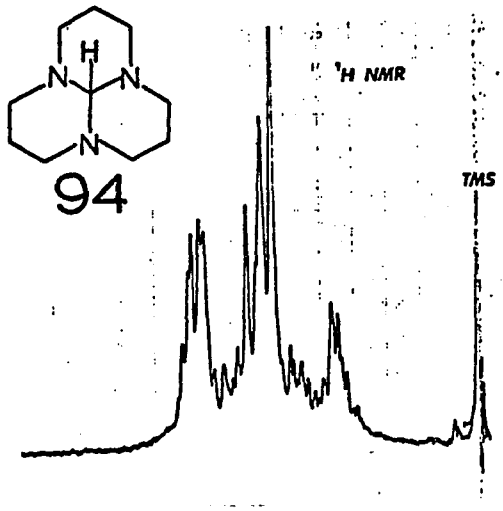
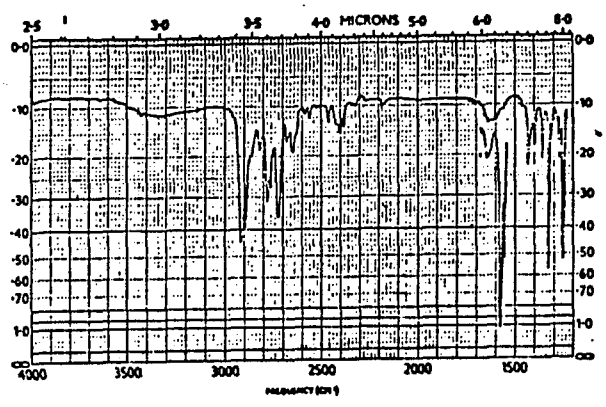
500
400


H
N
N
N
94
^1H NMR
TMS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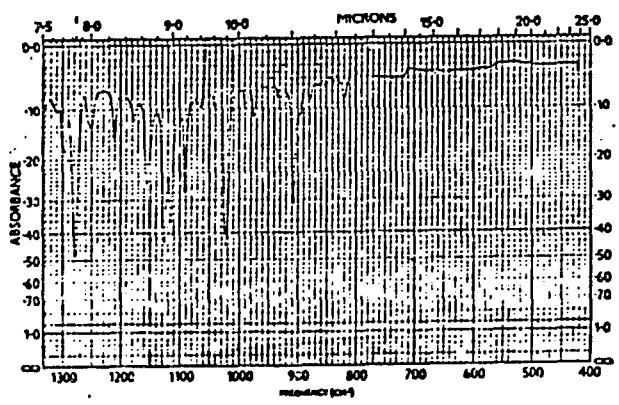
MICRONS
ABSORBANCE
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1200
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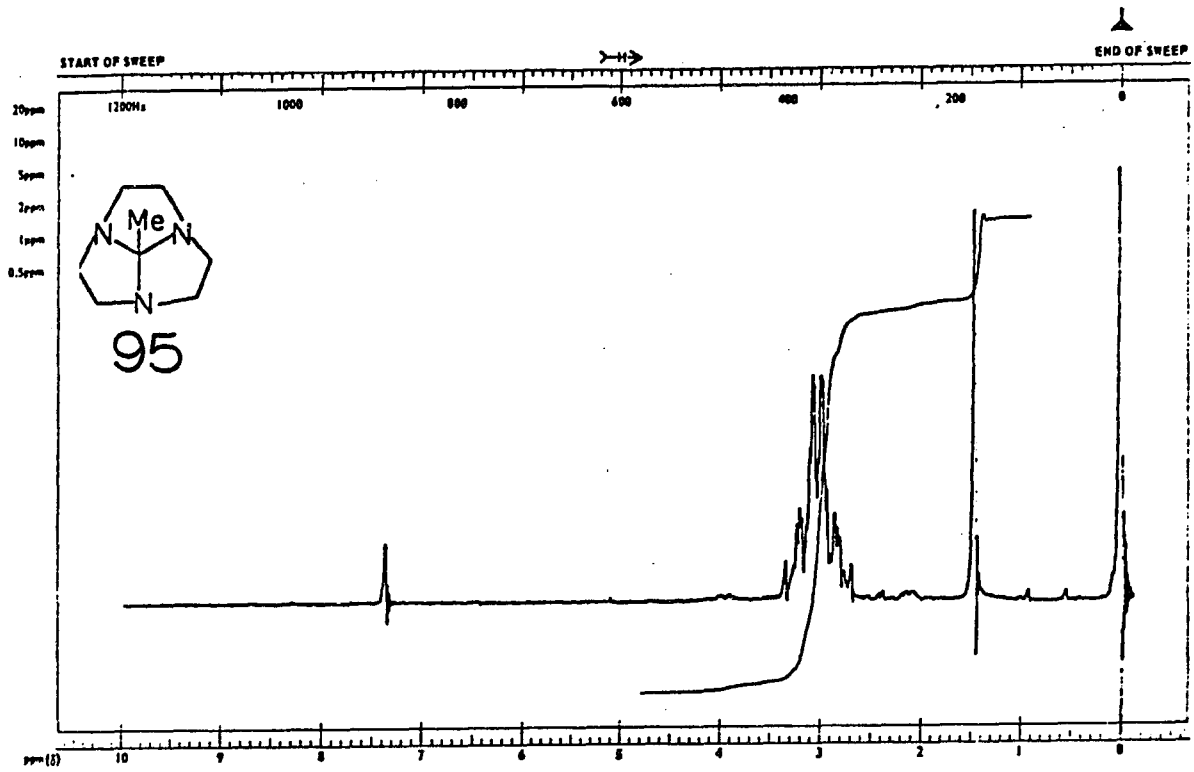
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20ppm
10ppm
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2ppm
1ppm
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Me
N
N
N
95
ppm (δ)
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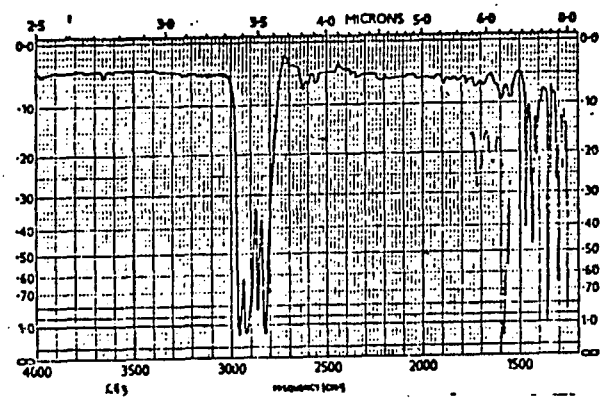
9
8
7
6
5
4
3
2
1
0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3·0
3·5
4·0 MICRONS 5·0
6·0
8·0
0·0
·10
·20
·30
·40
·50
·60
·70
1·0
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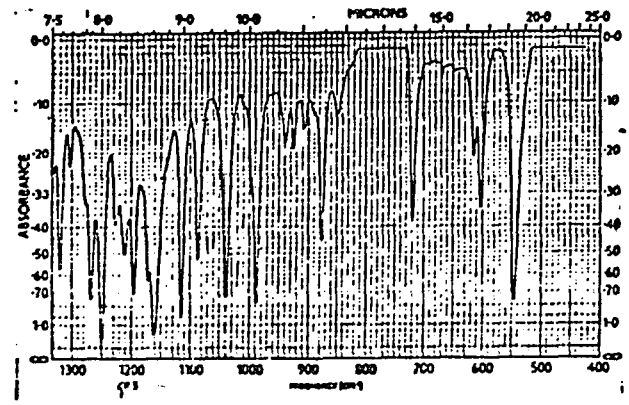
3500
3000
2500
2000
1500


7·5
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10·0
MICRONS
15·0
20·0
25·0
0·0
·10
·20
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·50
·60
·70
1·0
ABSORBANCE
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1100
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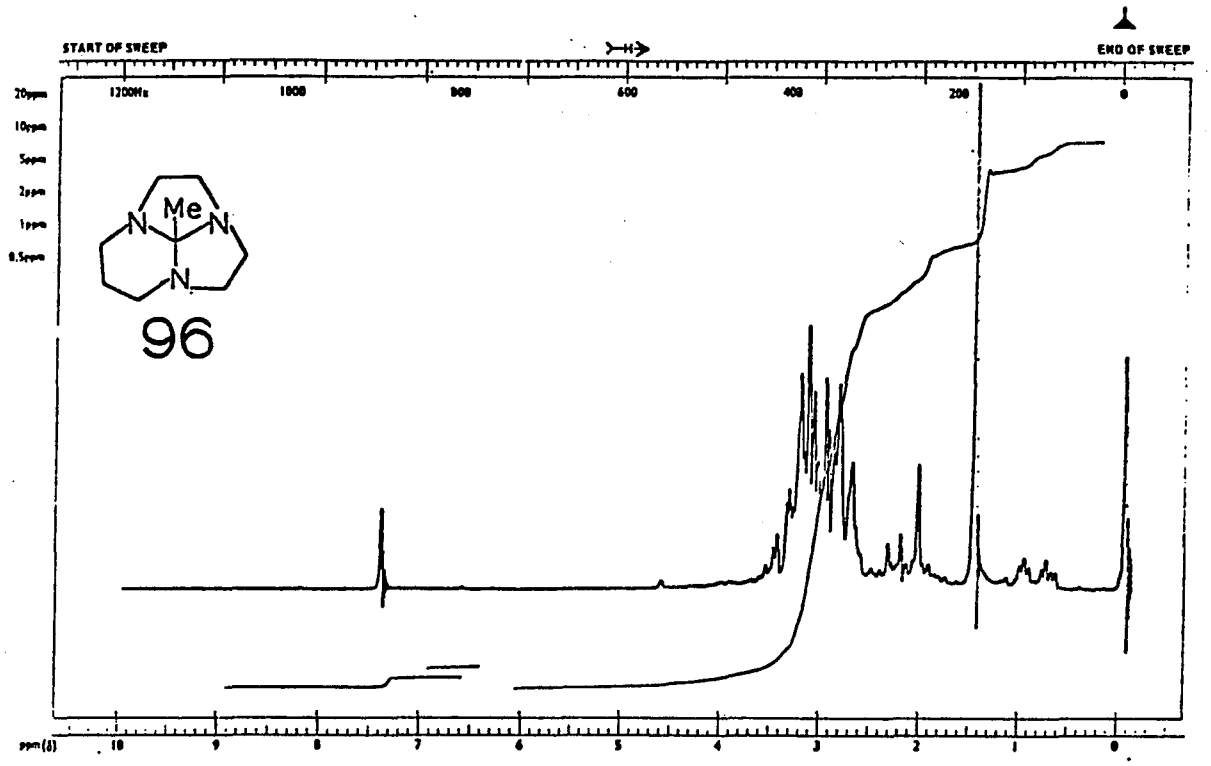
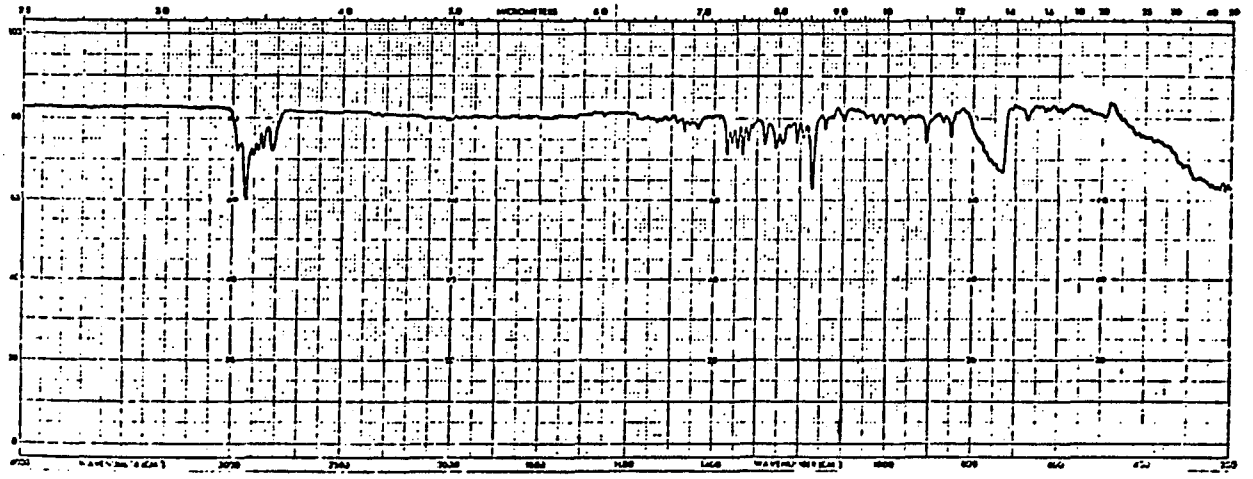
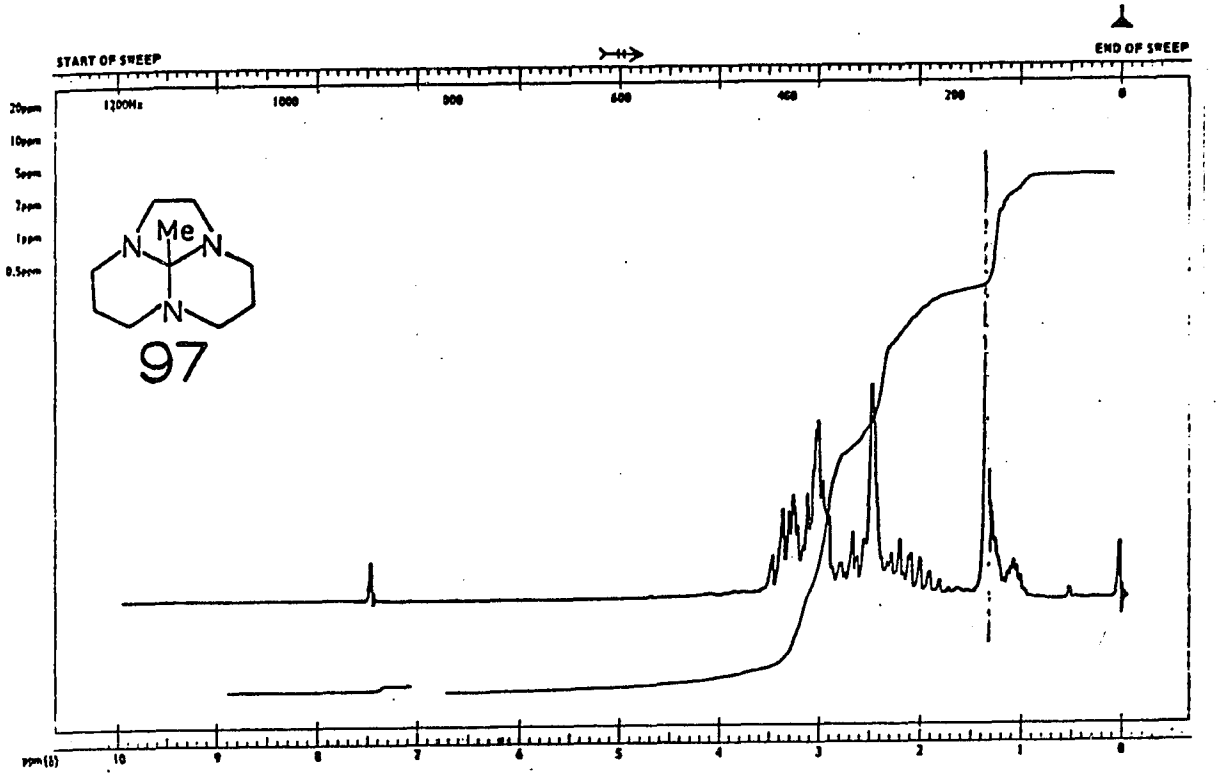
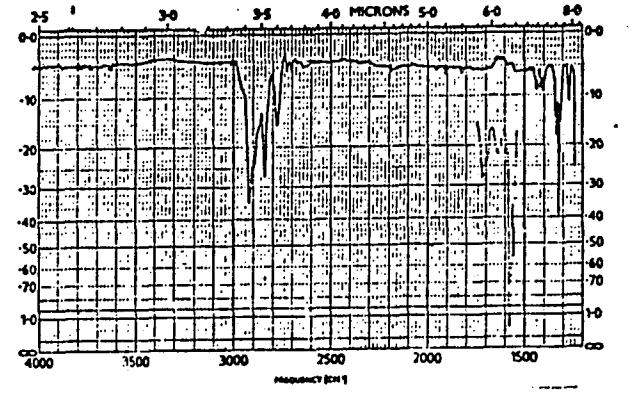

START OF SWEEP
END OF SWEEP
Me
N
N
N
96
ppm(δ)




START OF SWEEP
END OF SWEEP
Me
N
N
N
97
ppm(δ)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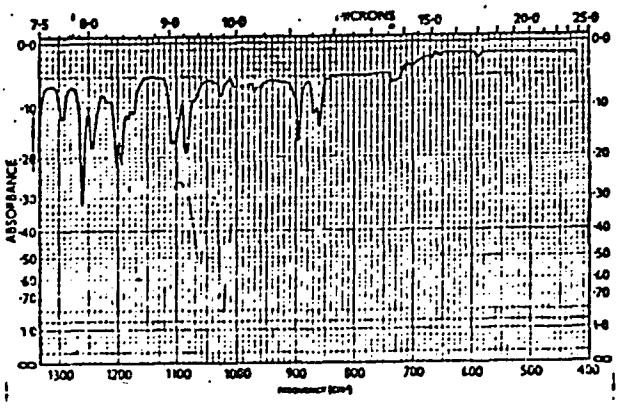
MICRONS
ABSORBANCE
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1200
1100
1000
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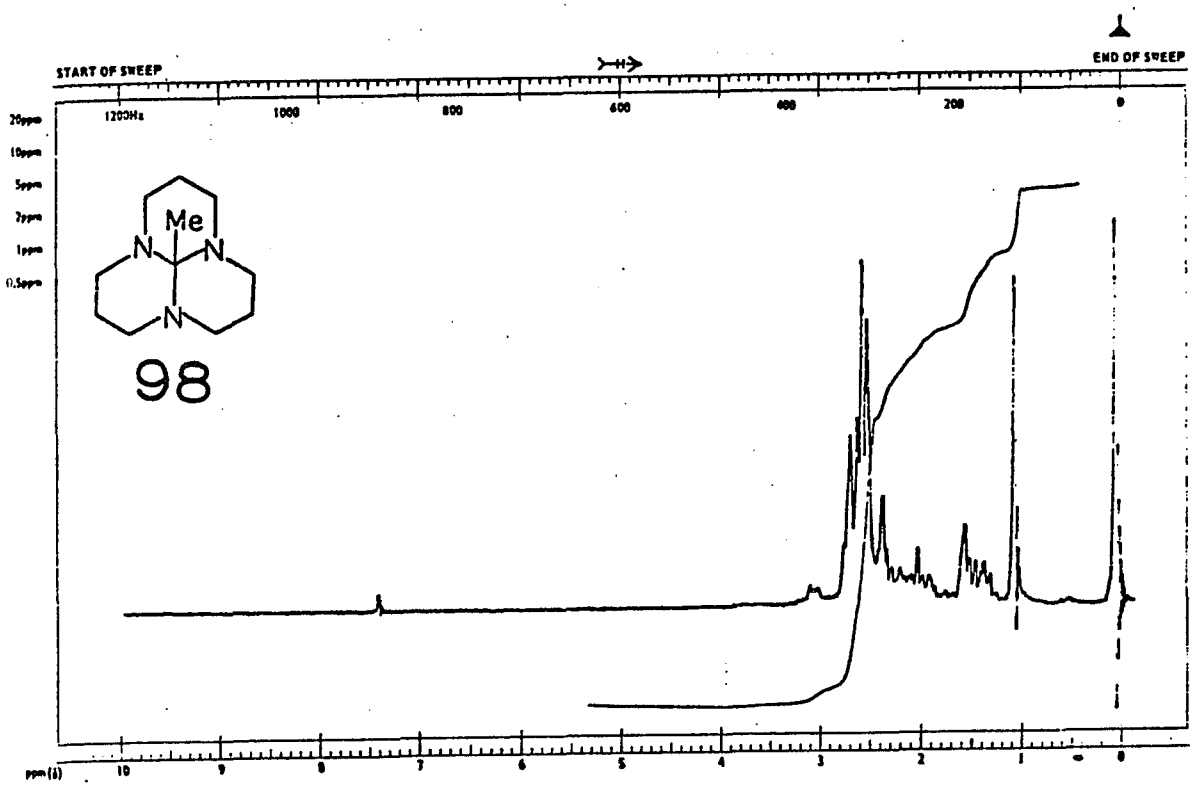
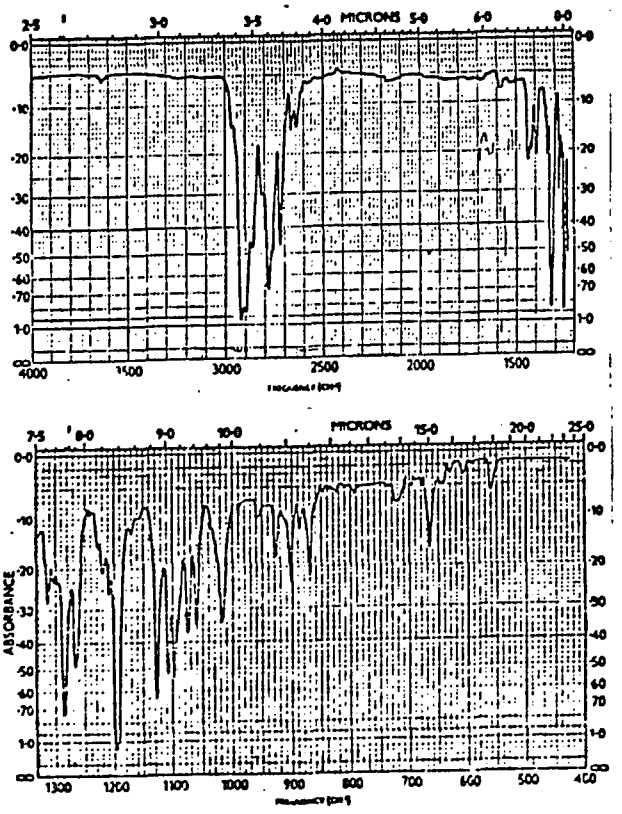
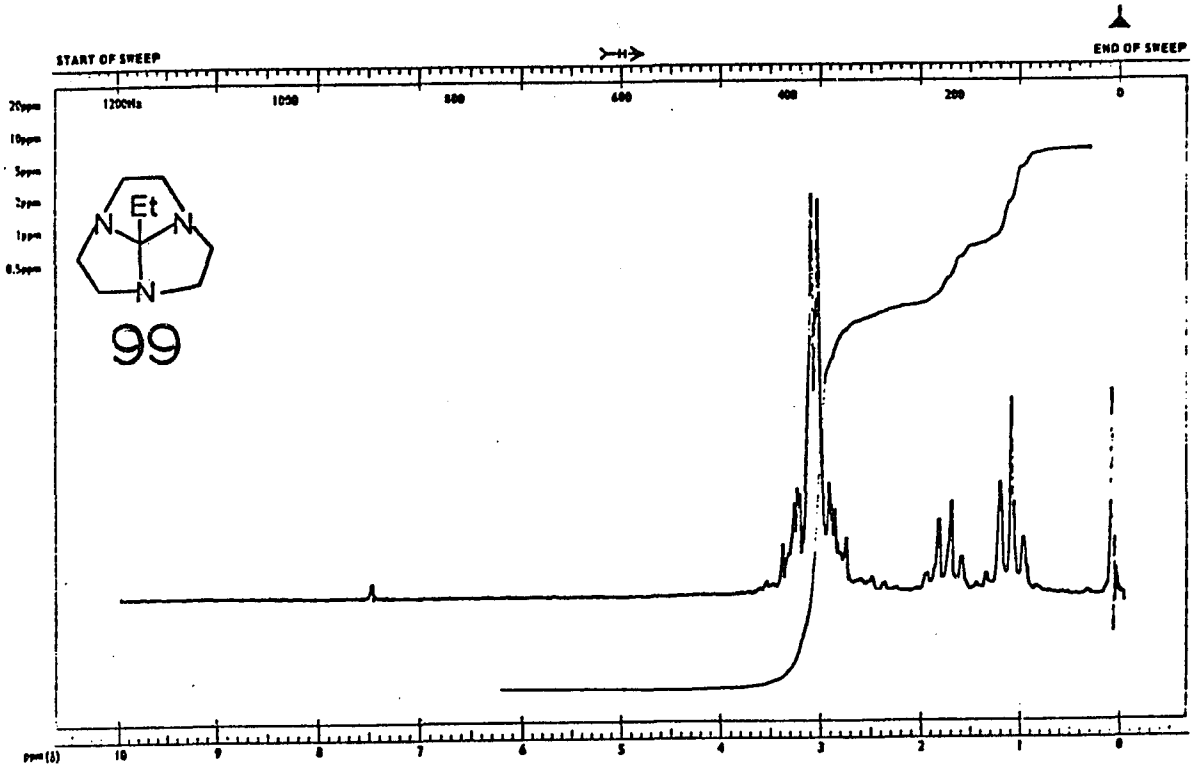
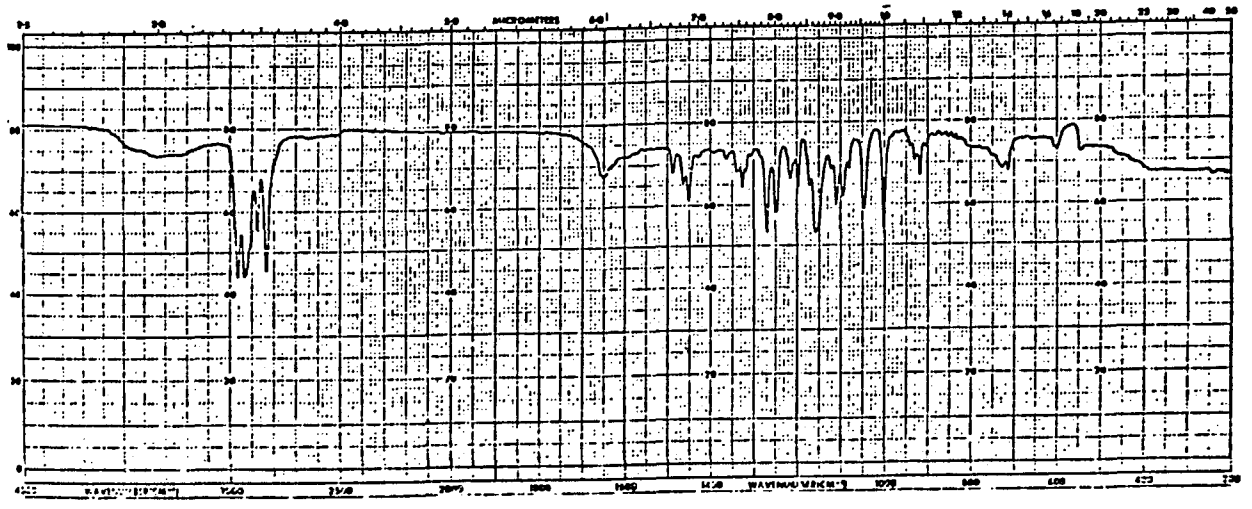
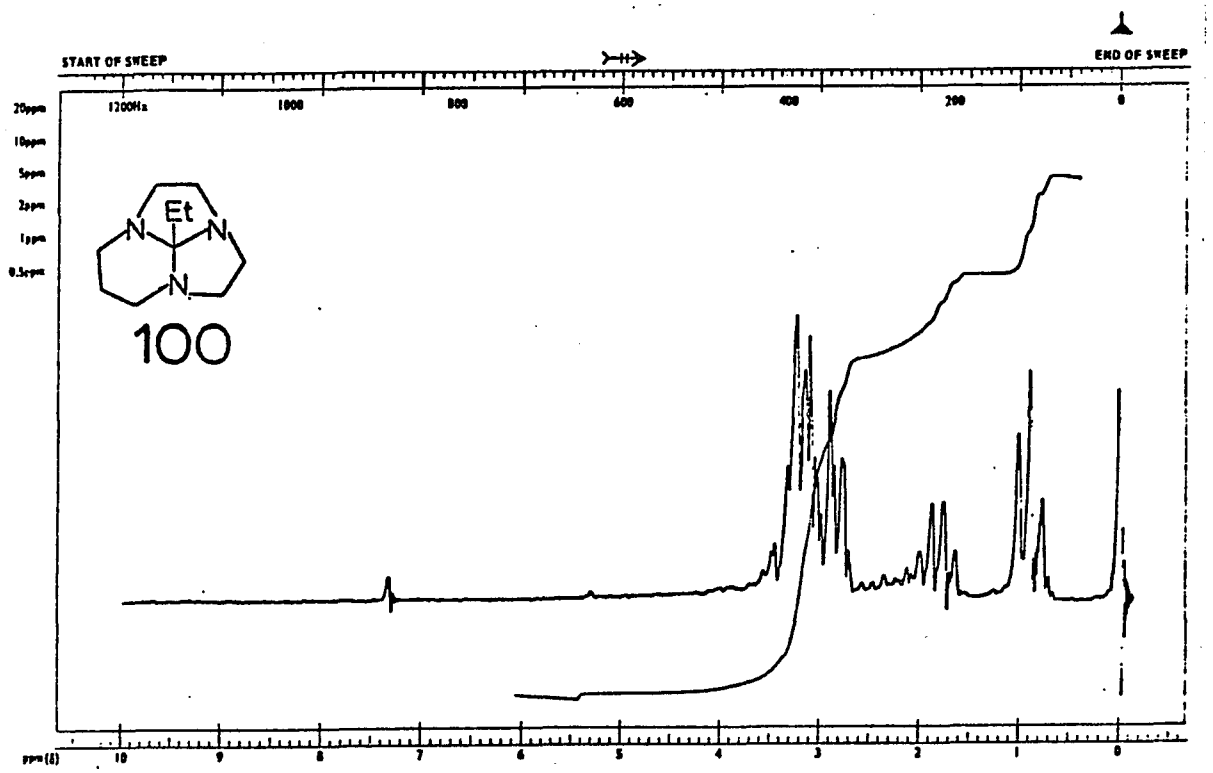
600
500
400

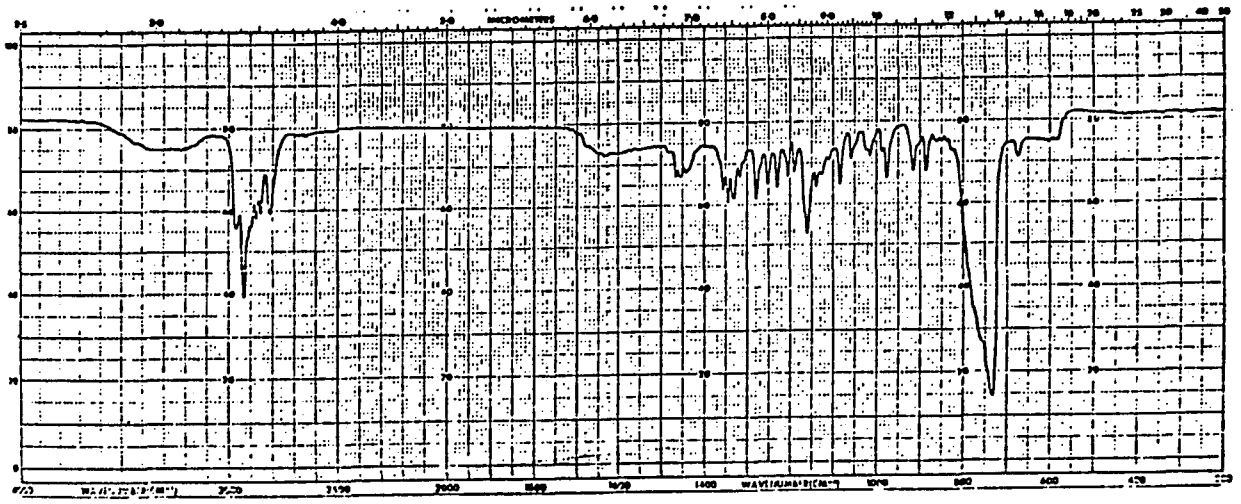

START OF SWEEP
END OF SWEEP
Me
N
N
N
98

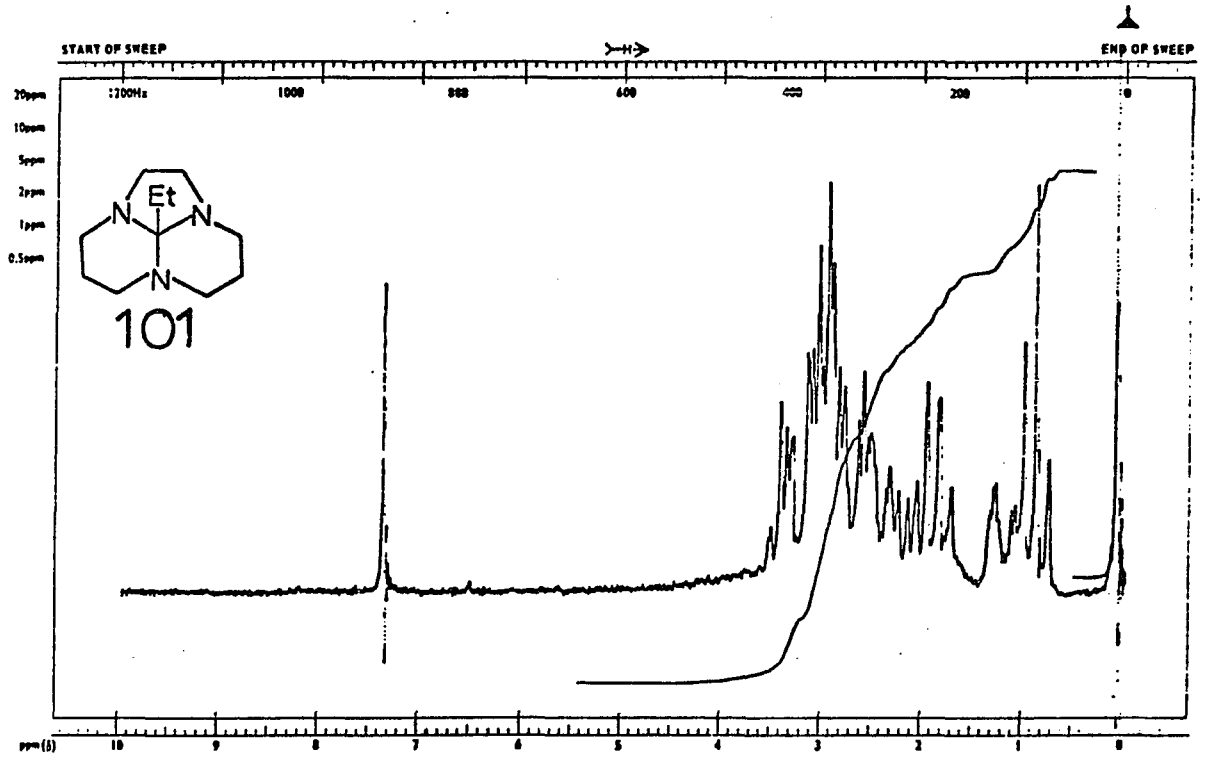

MICRONS
ABSORBANCE

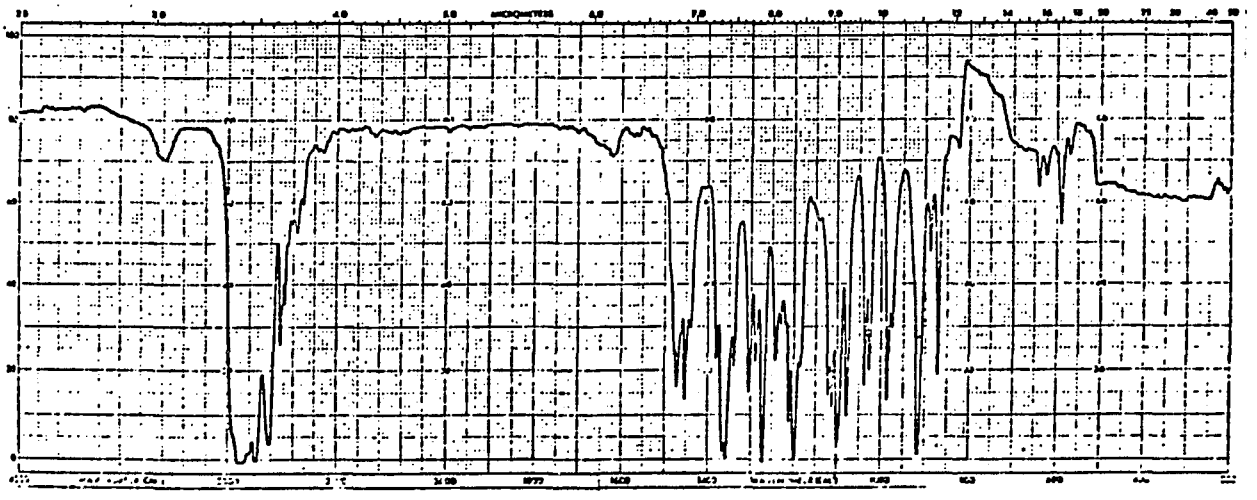

START OF SWEEP
END OF SWEEP
Et
N
N
N
99
ppm (δ)

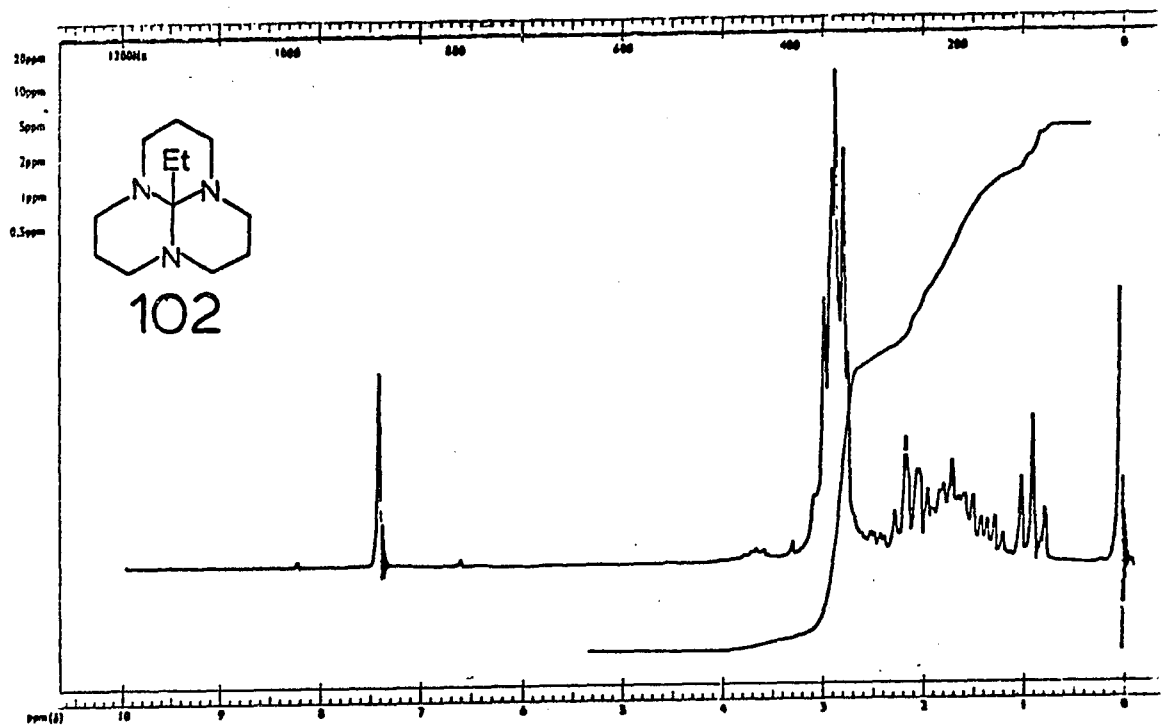


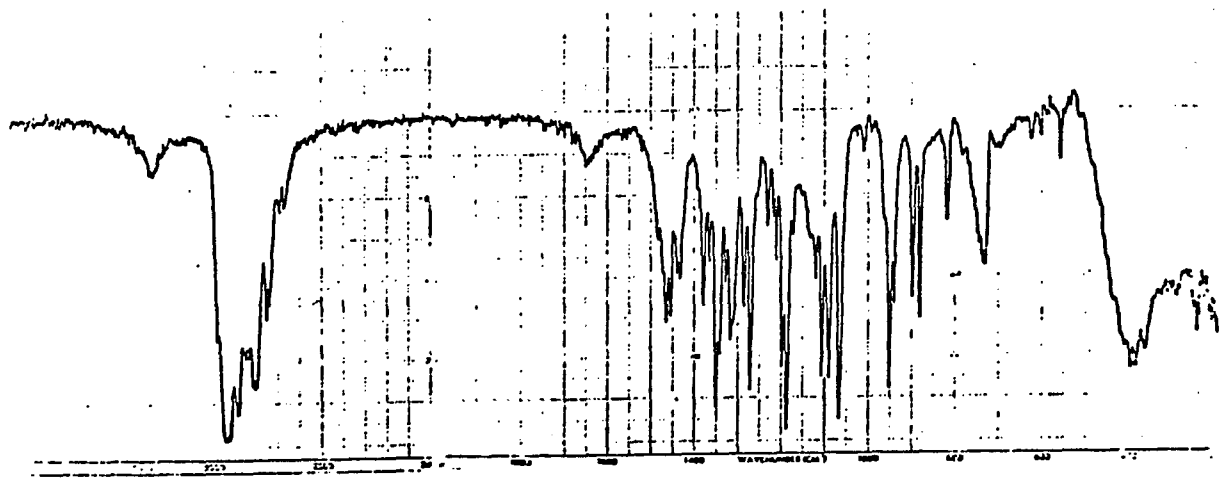

START OF SWEEP
END OF SWEEP
1200Hz
1000
800
600
400
200
0
20ppm
10ppm
5ppm
2ppm
1ppm
0.5ppm
Et
N
N
N
100
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0

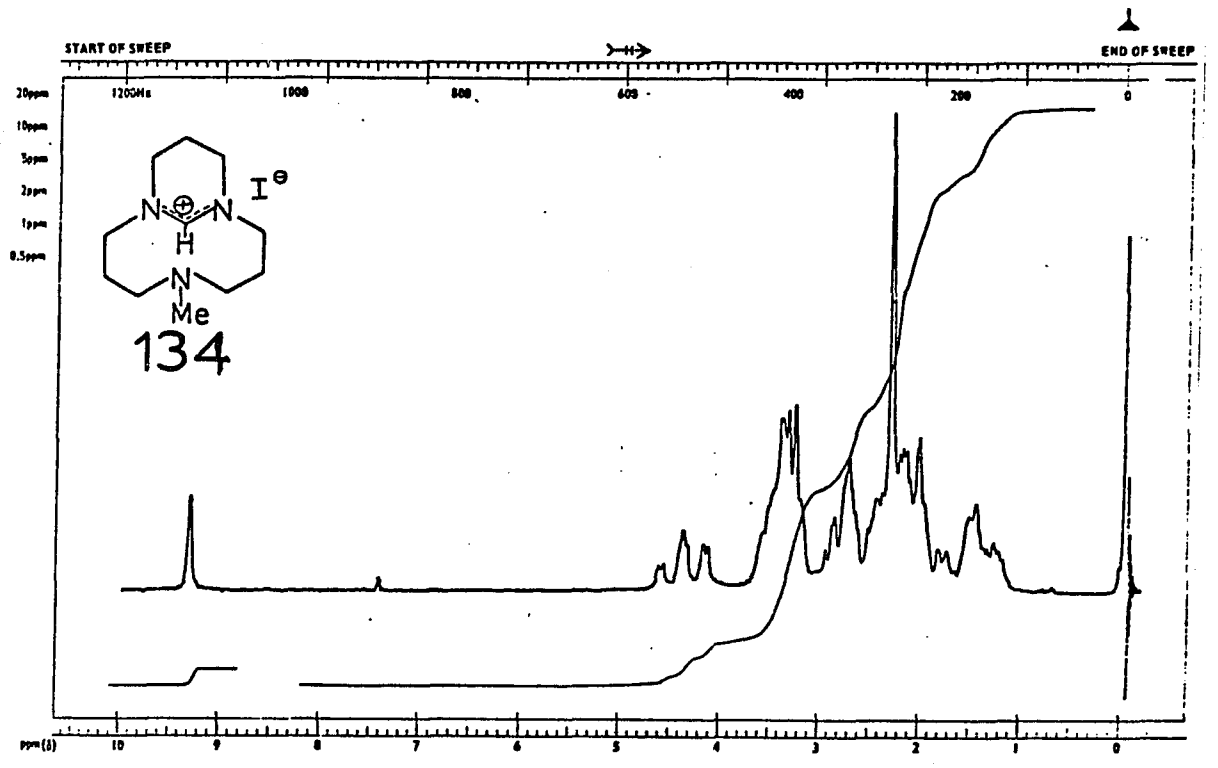


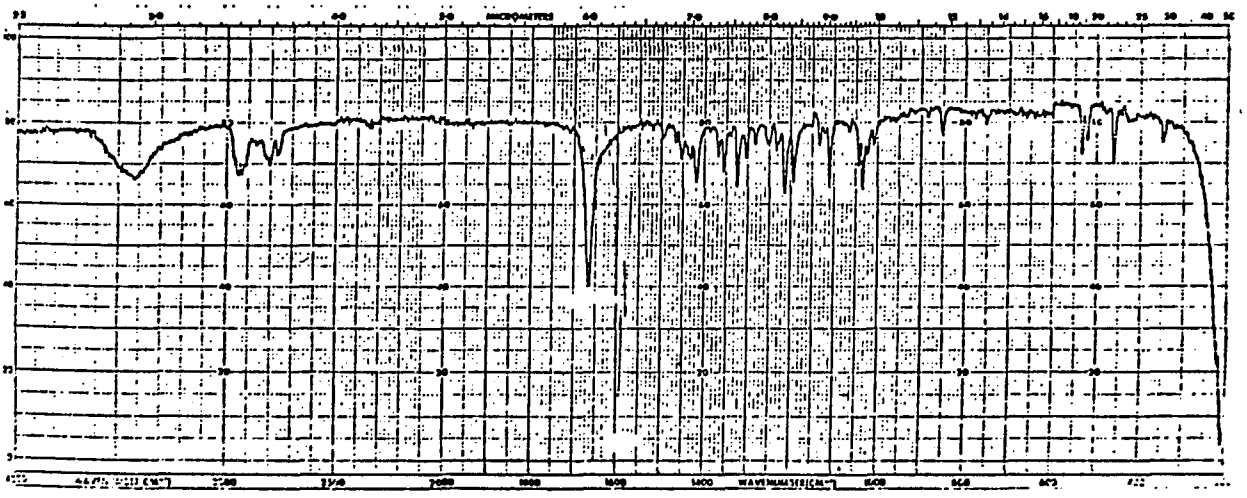

START OF SWEEP
END OF SWEEP
Et
N
N
N
101
ppm (δ)

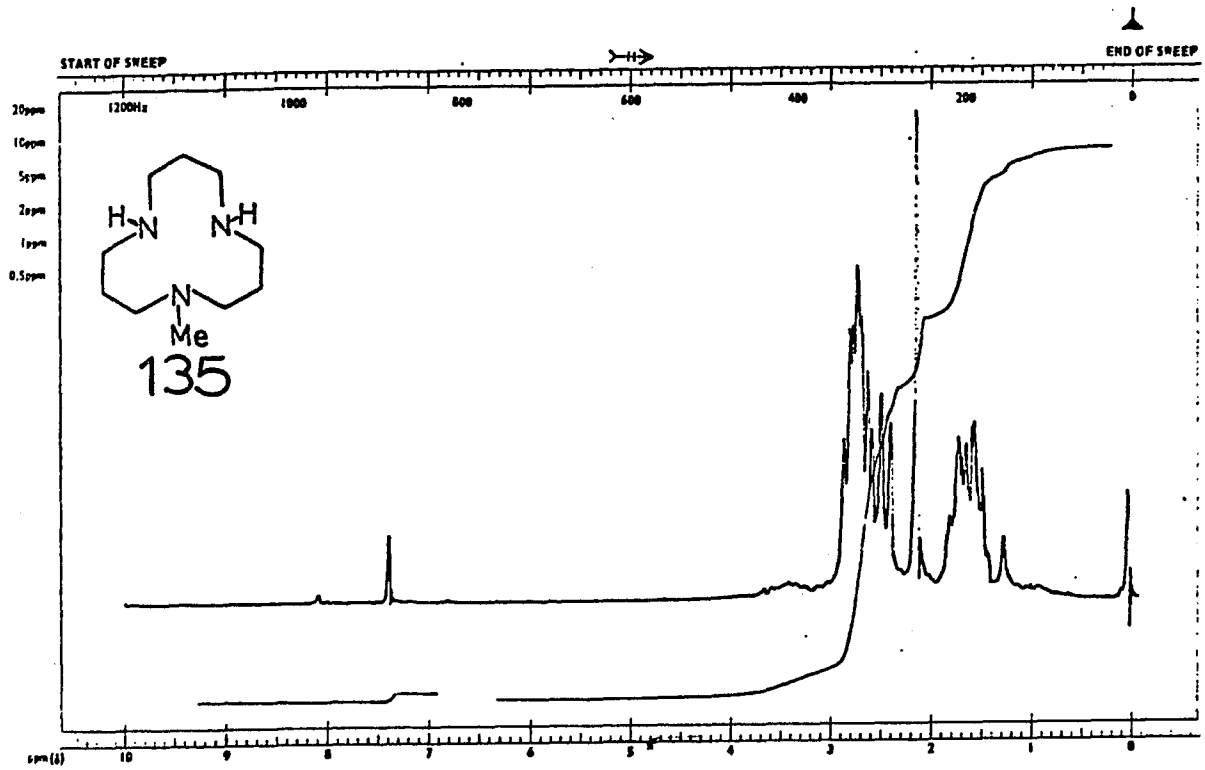



Et
N
N
N
102




START OF SWEEP
END OF SWEEP
1200Hz
1000
800
600
400
200
0
20ppm
10ppm
5ppm
2ppm
1ppm
0.5ppm
I⊖
N
H
N
Me
134
ppm(δ)
10
9
8
7
6
5
4
3
2
1
0




START OF SWEEP
END OF SWEEP
1200Hz
1000
800
600
400
200
0
20ppm
10ppm
5ppm
2ppm
1ppm
0.5ppm
H
N
N
H
N
Me
135
10
9
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7
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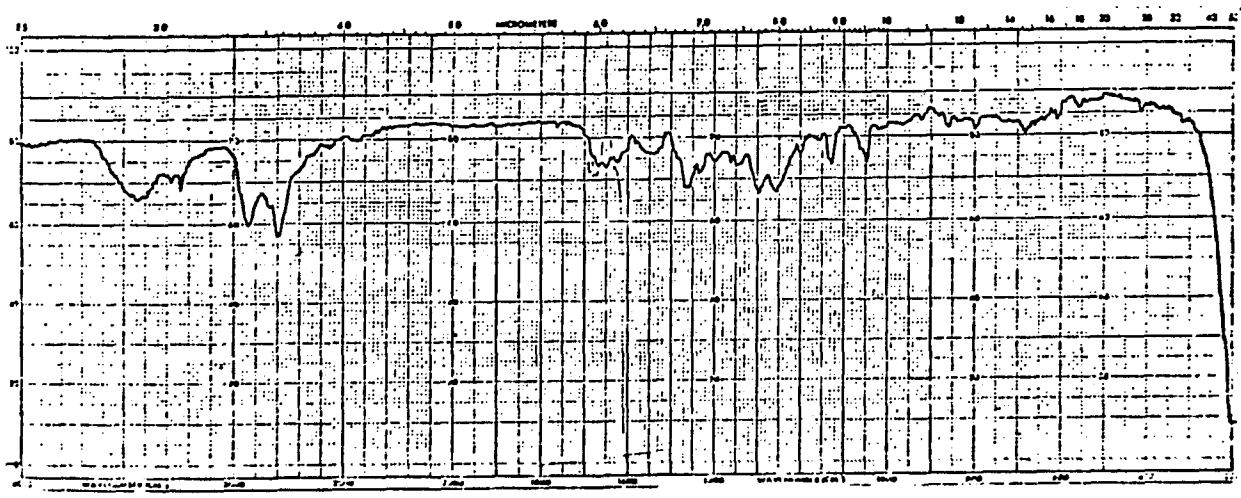
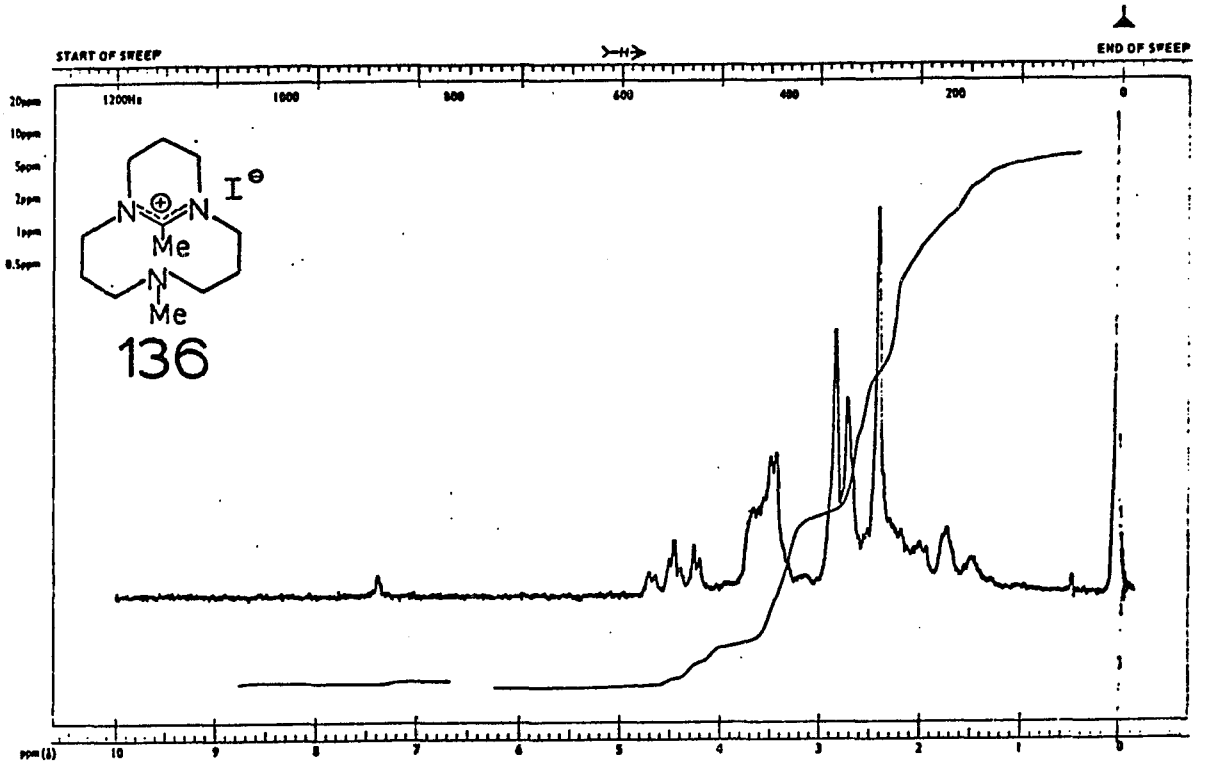
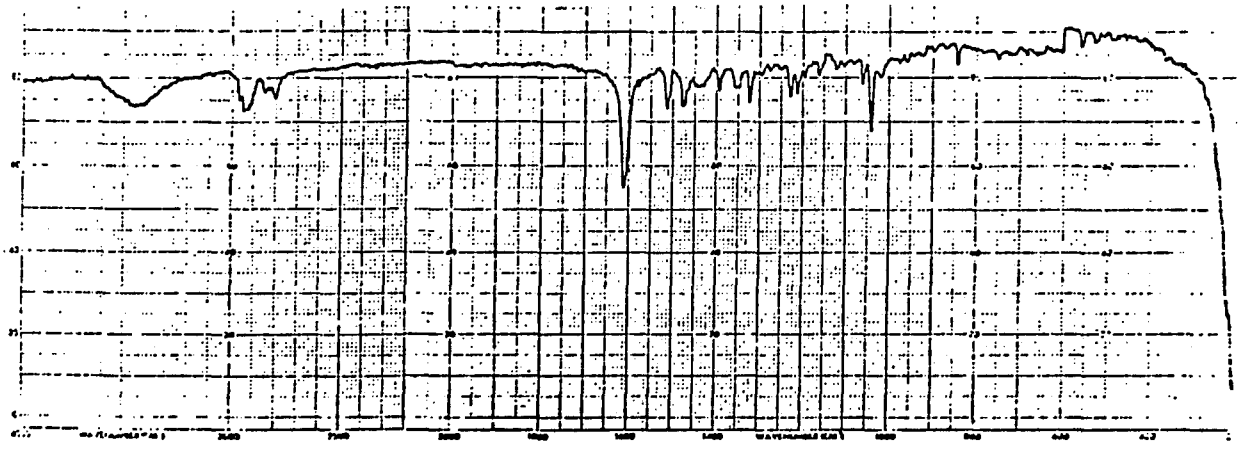
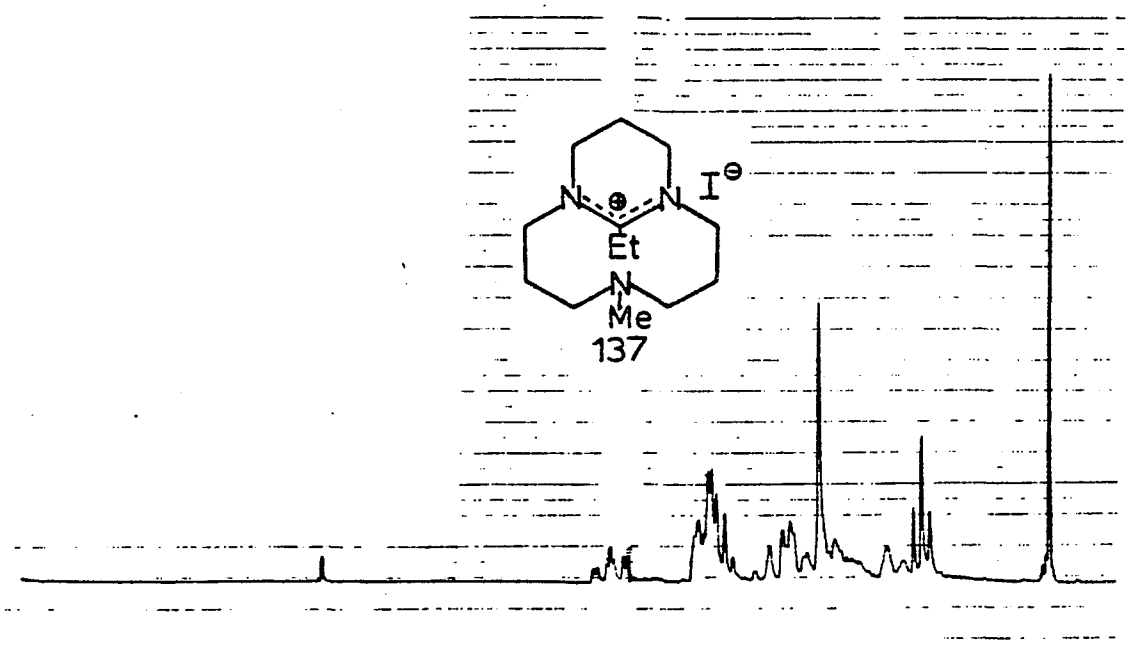
4
3
2
1
0




START OF SWEEP
END OF SWEEP
1200Hz
1000
800
600
400
200
0
20ppm
10ppm
5ppm
2ppm
1ppm
0.5ppm
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
I⊖
Me
Me
136





137

APPENDIX 2: ^{13}C Chemical Shifts of the Orthoamides

DNMR: ORTHOFORMAMIDES

Compound	Solvent	Temp(°C)	N-CH-N	CH_2N	$CH_2-CH_2-CH_2$
91	$CDCl_3$	29	104.1	52.0	-----
	$Acetone_{d6}$	-100	103.6	51.0	-----
92	$Acetone_{d6}$	29	94.1	56.7,49.5 46.4	17.2
	$Acetone_{d6}$	-66.3	92.5	56.6,49.6 46.0	15.2
	$Acetone_{d6}$	-100	91.9	56.6,49.7 46.0	14.6
93	$Acetone_{d6}$	29	96.2	52.4,48.9 48.1	23.3
	$Acetone_{d6}$	-39.1	96.2	52.3,48.6 47.7	23.0
	$Acetone_{d6}$	-66.3	96.2(sbr)	52.3(sbr) 48.5(sbr) 47.6(sbr)	22.9(sbr)
	$Acetone_{d6}$	-87.0	96.2(br)	52.4(br) 48.4(br) 47.4(br)	22.8(br)

(sbr): slightly broad
(br): broad
(vbr): very broad

DNMR: ORTHOFORMAMIDES cont.

Compound	Solvent	Temp(°C)	N N-CH-N	CH_2-N	CH_2-CH_2-CH_2
93	$Acetone_{d6}$	-100	96.4(vbr)	52.4(vbr) 48.4(vbr) 47.3(vbr)	22.8(vbr)
	$Acetone_{d6}$	-104	broadened into baseline	52.3(vbr) 48.1(vbr) 47.2(vbr)	22.2(vbr)
94	$CDCl_3$	29	100.0	53.9	24.2
	$CDCl_3$	-64	100.4	53.9	23.9
	$Acetone_{d6}$	29	101.3	54.6	24.9
	$Acetone_{d6}$	-100	101.0	54.1	24.2

DNMR: ORTHOACETAMIDES

Compound	Solvent	Temp(°C)	N-C(Me)-N	CH_2-N	$CH_2CH_2CH_2$	C-CH_3	CH_3 width at hieght(Hz)
97	$CDCl_3$	29	86.9	49.4,45.6 43.7	20.1	10.0	-----
	Acetone$_{d6}$	-100	87.3	49.6,45.6 43.7	20.2	9.6	-----
98	$CDCl_3$	29	86.0	49.0	24.6	-4.0	small but sharp
	$CDCl_3$	3.82	85.9	48.9	24.5	-4.3	small but sharp
	$CDCl_3$	-29.2	85.9	48.8	24.4	-5.0	30.52
	$CDCl_3$	-44.8	85.9	48.9(br)	24.5(vbr)	-6.3(vbr)	32.23
	$CDCl_3$	-55.5	85.8	48.8(br)	24.7(vbr)	-6.4(vbr)	beginning to resharpen
	$CDCl_3$	-67.1	85.9	48.7(sbr)	24.7(sbr)	-6.6(sbr)	
	$CDCl_3$	-29.9					32.96
	$CDCl_3$	-39.1					52.50
	$CDCl_3$	-44.0					20.80
	CD_3CN	29	87.1	49.7	25.1	-1.4	
	CD_3CN	3.82	87.0	49.5	25.1	-2.5(sbr)	
	CD_3CN	-13.5	87.0	49.5	25.1	-3.0(vbr)	
	CD_3CN	-29.2	vbr	49.4(sbr)	25.0(sbr)	broadened into baseline	

DNMR: ORTHOACETAMIDES cont.

Compound	Solvent	Temp(°C)	N N-C(CH$_3$)-N	CH$_2$-N	CH$_2$-CH$_2$-CH$_2$	C-CH$_3$
98	Acetone$_{d6}$	50.0	86.4	48.7	24.5	1.7
	Acetone$_{d6}$	29	86.4	49.5	24.5	0.0
	Acetone$_{d6}$	9.6	86.4	49.5	24.5	-0.4(sbr)
	Acetone$_{d6}$	2.2	86.4	49.4	24.5	-0.7(sbr)
	Acetone$_{d6}$	-9.3	86.5	49.4	24.5	-1.1(sbr)
	Acetone$_{d6}$	-11.0	86.5	49.4	24.5	-1.4(br)
	Acetone$_{d6}$	-35.8	86.6	49.2(sbr)	24.5(sbr)	slight lump in baseline
	Acetone$_{d6}$	-43.9	86.6	49.2(sbr)	24.6(sbr)	slight lump in baseline
	Acetone$_{d6}$	-49.8	86.6	49.2(br)	24.8(vbr)	beginning to resharpen
	Acetone$_{d6}$	-56.4	86.7(sbr)	49.4(vbr)	24.9(vbr)	-6.0(vbr)
	Acetone$_{d6}$	-63.0	86.8(sbr)	49.1(vbr)	24.9(vbr)	-6.1(vbr)
	Acetone$_{d6}$	-67.9	86.9(sbr)	49.1(vbr)	24.9(vbr)	-?(sbr)
	Acetone$_{d6}$	-82.0	86.9	49.1(vbr)	24.8(vbr)	-6.2
	Acetone$_{d6}$	-90.0	86.9	49.0(vbr)	24.7(vbr)	-6.2
	Acetone$_{d6}$	-100	86.9	49.0(vbr)	24.7(vbr)	-6.2

Note; Temp. of maximum broadening of the methyl resonance ca. -40, chemical shift- -5.4, width at half height- 55.7 Hz

DNMR: ORTHOPROPIONAMIDES

Compound	Solvent	Temp(°C)	N-C(CH$_2$)-N	CH$_2$-N	CH$_2$-CH$_2$-CH$_2$	CH$_2$-CH$_3$	CH$_2$CH$_3$
101	$CDCl_3$	29	88.8	48.9,45.6 43.4	19.8	11.4	7.4
	$CDCl_3$	-60	88.8	48.9,45.6 43.4	19.8	11.4	7.4
	$Acetone_{d6}$	29	89.2	49.6,46.3 43.9	20.6	11.8	8.0
	$Acetone_{d6}$	-50	88.9	49.2,45.8 43.6	20.2	11.5	8.2
	$Acetone_{d6}$	-70	88.8	49.1,45.7 43.4	19.9	11.4	8.2
	$Acetone_{d6}$	-90	88.8	49.1,45.6 43.3	19.8	11.5	8.3
102	$Acetone_{d6}$	29	87.1	49.1	22.3	13.0	7.9
	$Acetone_{d6}$	-14.3	86.7	48.9(br)	22.2(br)	12.9	8.0
	$Acetone_{d6}$	-20.9	86.7	48.8(br)	21.5(br)	12.9	8.0
	$Acetone_{d6}$	-27.1	86.6	48.8(vbr)	ca. 20.3(vbr)	12.9	8.0
	$Acetone_{d6}$	-30.0	86.7	48.7(vbr)	ca. 24.7(vbr) ca. 20.1(vbr)	12.9	8.0
	$Acetone_{d6}$	-37.1	86.6	48.7(vbr)[1]	ca. 26.3(vbr) ca. 20.3(vbr)	12.9	8.0

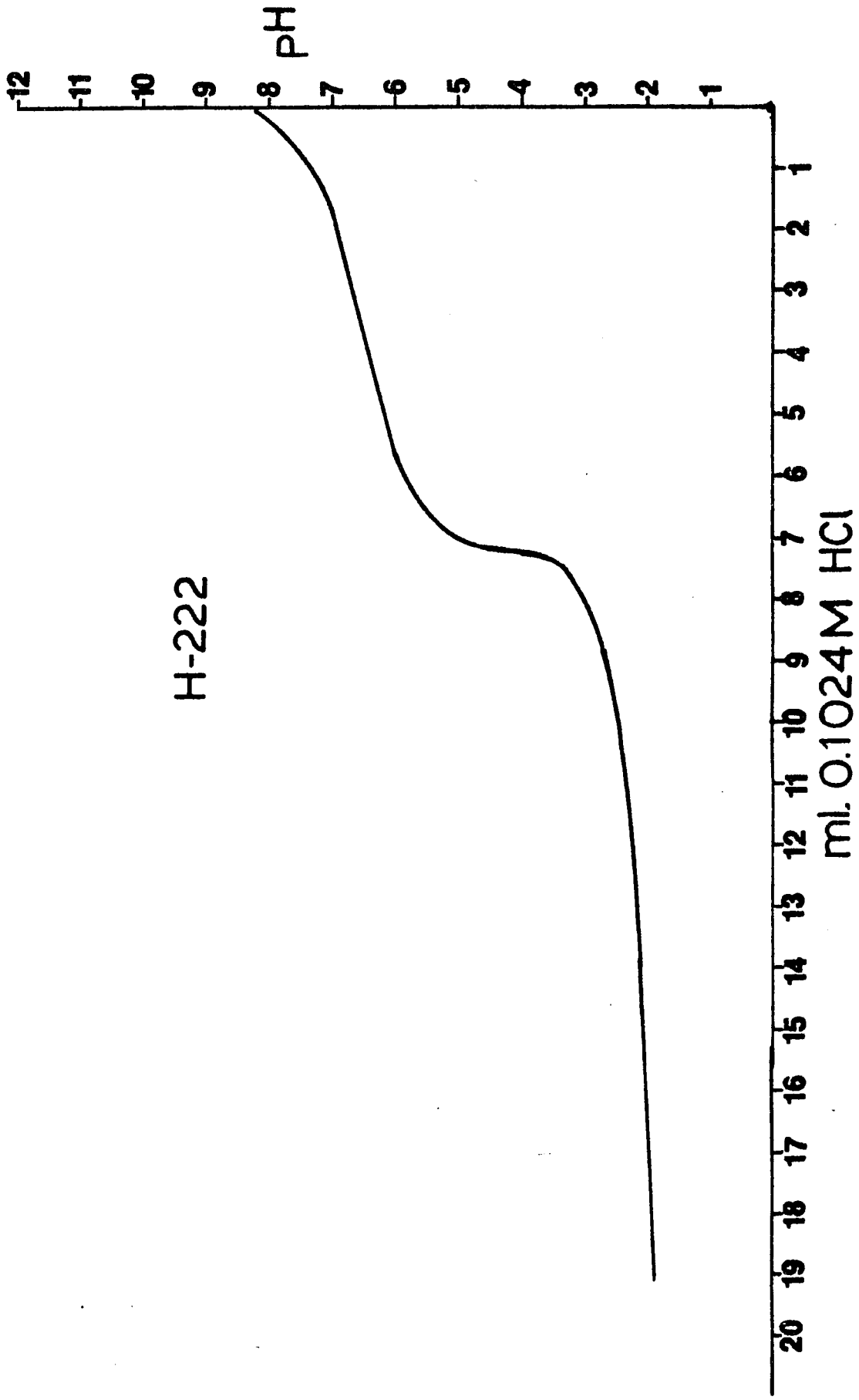
1;beginning to split into three peaks but still lumped together

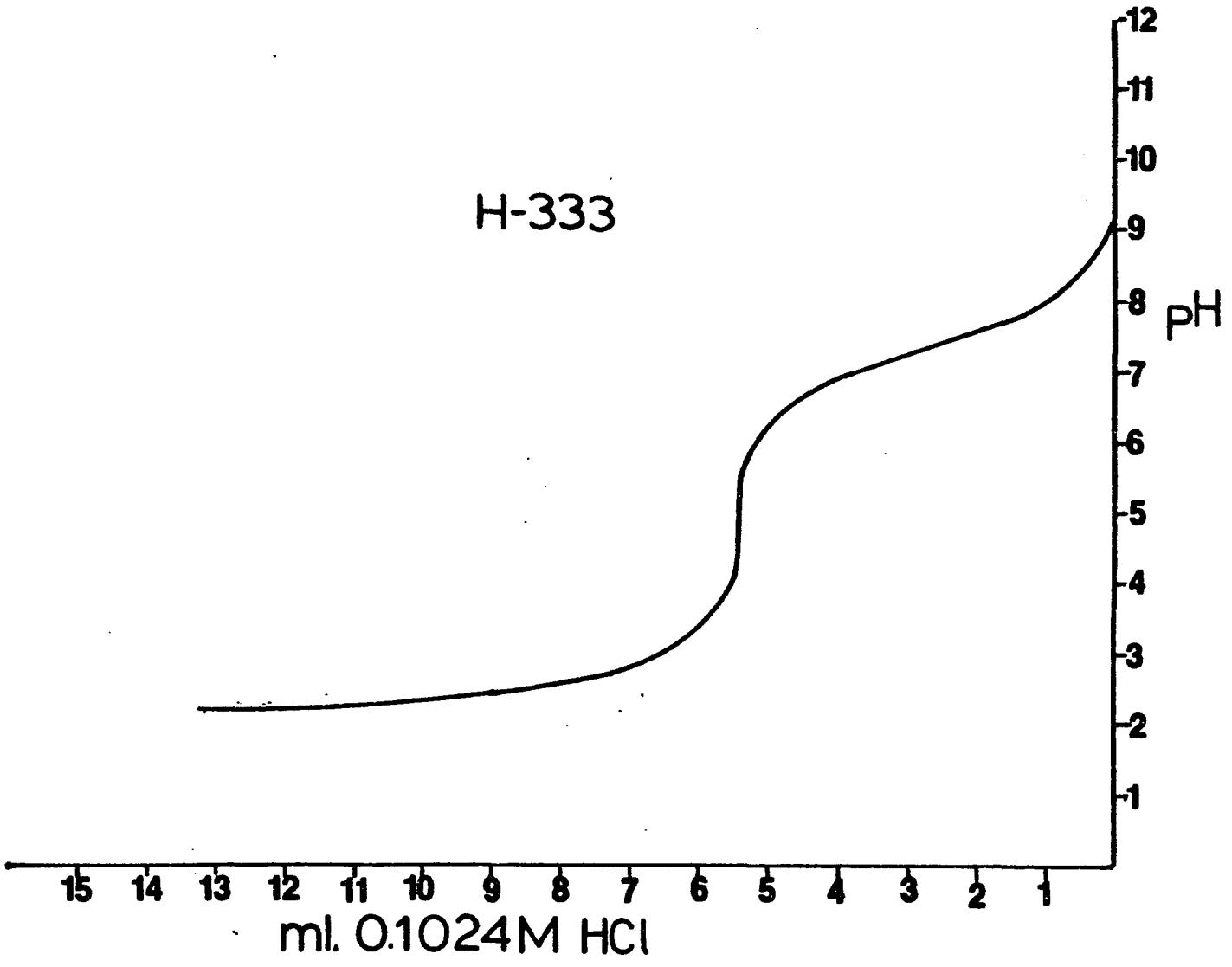
DNMR: ORTHOPROPIONAMIDES cont.

Compound	Solvent	Temp(°C)	N N-C(CH$_2$)-N	CH$_2$-N	CH$_2$-CH$_2$-CH$_2$	CH$_2$-CH$_3$	CH$_2$-CH$_3$
102	Acetone$_{d6}$	-39.5	86.6	ca. 50.8(vbr)[2] ca. 48.4(vbr)	ca. 26.2(vbr) ca. 19.8(vbr)	12.9	8.0
	Acetone$_{d6}$	-39.9	86.6	broad lump	26.5(vbr) 19.7(vbr)	12.9	7.9
	Acetone$_{d6}$	-41.9	86.6	51.0(br) 48.3(br) 46.6(br)	26.3(vbr) 19.8(vbr)	12.9	8.1
	Acetone$_{d6}$	-52.2	86.5	51.0(br) 48.4(br) 46.6(br)	26.4(sbr) 19.6(sbr)	12.9	8.1
	Acetone$_{d6}$	-80.3	86.5	51.0,48.4 46.5	26.3,19.6	12.9	8.2

2; a third shoulder was visible

Appendix 3: Potentiometric Titrations




H-333
12
11
10
9
8
7
6
5
4
3
2
1
pH
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
ml. 0.1024M HCl

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