POLYCYCLIC POLYAMINES: SYNTHESIS AND CONFORMATIONAL ANALYSIS

VAN BRUCE JOHNSON

Follow this and additional works at: https://scholars.unh.edu/dissertation

Recommended Citation
JOHNSON, VAN BRUCE, "POLYCYCLIC POLYAMINES: SYNTHESIS AND CONFORMATIONAL ANALYSIS" (1982).
Doctoral Dissertations. 1318.
https://scholars.unh.edu/dissertation/1318

This Dissertation is brought to you for free and open access by the Student Scholarship at University of New Hampshire Scholars' Repository. It has been accepted for inclusion in Doctoral Dissertations by an authorized administrator of University of New Hampshire Scholars' Repository. For more information, please contact nicole.hentz@unh.edu.
POLYCYCLIC POLYAMINES: SYNTHESIS AND CONFORMATIONAL ANALYSIS

Abstract
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.

Keywords
Chemistry, Organic

This dissertation is available at University of New Hampshire Scholars' Repository: https://scholars.unh.edu/dissertation/1318
INFORMATION TO USERS

This reproduction was made from a copy of a document sent to us for microfilming. While the most advanced technology has been used to photograph and reproduce this document, the quality of the reproduction is heavily dependent upon the quality of the material submitted.

The following explanation of techniques is provided to help clarify markings or notations which may appear on this reproduction.

1. The sign or “target” for pages apparently lacking from the document photographed is “Missing Page(s)”. If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting through an image and duplicating adjacent pages to assure complete continuity.

2. When an image on the film is obliterated with a round black mark, it is an indication of either blurred copy because of movement during exposure, duplicate copy, or copyrighted materials that should not have been filmed. For blurred pages, a good image of the page can be found in the adjacent frame. If copyrighted materials were deleted, a target note will appear listing the pages in the adjacent frame.

3. When a map, drawing or chart, etc., is part of the material being photographed, a definite method of “sectioning” the material has been followed. It is customary to begin filming at the upper left hand corner of a large sheet and to continue from left to right in equal sections with small overlaps. If necessary, sectioning is continued again—beginning below the first row and continuing on until complete.

4. For illustrations that cannot be satisfactorily reproduced by xerographic means, photographic prints can be purchased at additional cost and inserted into your xerographic copy. These prints are available upon request from the Dissertations Customer Services Department.

5. Some pages in any document may have indistinct print. In all cases the best available copy has been filmed.
Johnson, Van Bruce

POLYCYCLIC POLYAMINES: SYNTHESIS AND CONFORMATIONAL ANALYSIS

University of New Hampshire

Ph.D. 1982

University Microfilms International 300 N. Zeeb Road, Ann Arbor, MI 48106
PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy. Problems encountered with this document have been identified here with a check mark √.

1. Glossy photographs or pages _____
2. Colored illustrations, paper or print _____
3. Photographs with dark background _____
4. Illustrations are poor copy ✓
5. Pages with black marks, not original copy _____
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages ✓
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) _________ lacking when material received, and not available from school or author.
12. Page(s) _________ seem to be missing in numbering only as text follows.
13. Two pages numbered _________. Text follows.
14. Curling and wrinkled pages _____
15. Other _____________________________________________

University Microfilms International
POLYCYCLIC POLYAMINES: SYNTHESIS AND 
CONFORMATIONAL ANALYSIS

BY
Van E 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.

Dissertation Director, Gary R. Weisman
Assistant Professor of Chemistry

James D. Morrison
Professor of Chemistry

Kenneth K. Andersen
Professor of Chemistry

Charles W. Owens
Professor of Chemistry

Donald C. Sundburg
Assistant Professor of Chemical Engineering

Date: Jan 29, 1982
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, invaluable 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

DEDICATION .................................................................... iii

ACKNOWLEDGEMENTS .................................................... iv

LIST OF FIGURES............................................................ vii

LIST OF TABLES ............................................................. xiii

ABSTRACT ...................................................................... xiv

## CHAPTER ONE - INTRODUCTION

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

Synthesis ........................................................................... 6

Anticipated Properties ....................................................... 8

Complexation Properties .................................................. 9

Electrochemical Properties ................................................. 10

Discussion ........................................................................ 13

Synthesis ........................................................................... 13

Classical Approach ......................................................... 16

Modified Classical .......................................................... 20

Cleavage Routes-Cleavage of Tetracyclic Bis-aminals ....... 24

Cleavage of a Tricyclic Orthoamide ................................... 26

## CHAPTER TWO - TRICYCLIC ORTHOAMIDES

Discussion ........................................................................ 41

Synthesis ........................................................................... 41

Conformational Analysis of the Orthoamides ..................... 47

Introduction .................................................................... 47

Conformational Analysis of the Orthoformamides ............... 55

Stereochemical Variation in the Orthoformamides ............... 55

Conformational Analysis of H-222 ................................... 64

Conformational Analysis of H-322 ................................... 67

Conformational Analysis of H-332 ................................... 70

Conformational Analysis of H-333 ................................... 75

Conformational Analysis of the Orthoacetamides ............... 79

Introduction .................................................................... 79

Conformational Analysis of Me-222 ................................. 80

Conformational Analysis of Me-322 ................................. 83

Conformational Analysis of Me-332 ................................. 84

Conformational Analysis of Me-333 ................................. 89

Conformational Analysis of the Orthopropionamides .......... 101

Introduction .................................................................... 101

Conformational Analysis of Et-222 ................................. 102

Conformational Analysis of Et-322 ................................. 103

Conformational Analysis of Et-332 ................................. 108

Conformational Analysis of Et-333 ................................. 115
## List Of Figures

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Polycyclic Polyamines</td>
<td>3</td>
</tr>
<tr>
<td>1.2</td>
<td>Tetracyclic Tetraamines</td>
<td>6</td>
</tr>
<tr>
<td>1.3</td>
<td>General Synthetic Schemes</td>
<td>7</td>
</tr>
<tr>
<td>1.4</td>
<td>$1,5,9,13$-tetraazatricyclo[7.7.3.3$^{(5,13)}$]docosane</td>
<td>8</td>
</tr>
<tr>
<td>1.5</td>
<td>Electrochemically Active Polyamines</td>
<td>12</td>
</tr>
<tr>
<td>1.6</td>
<td>Classical Acylation-Reduction Sequence</td>
<td>14</td>
</tr>
<tr>
<td>1.7</td>
<td>Modified Classical Scheme</td>
<td>15</td>
</tr>
<tr>
<td>1.8</td>
<td>Cleavage Routes</td>
<td>15</td>
</tr>
<tr>
<td>1.9</td>
<td>Summary of Synthetic Efforts</td>
<td>16</td>
</tr>
<tr>
<td>1.10</td>
<td>Gel Permeation Chromatogram</td>
<td>17</td>
</tr>
<tr>
<td>1.11</td>
<td>Synthetic Steps Needed to Complete Synthesis</td>
<td>19</td>
</tr>
<tr>
<td>1.12</td>
<td>Proposed Alternate Synthesis</td>
<td>20</td>
</tr>
<tr>
<td>1.13</td>
<td>Richman-Atkins Synthesis of Macrocyclic Amines</td>
<td>21</td>
</tr>
<tr>
<td>1.14</td>
<td>Modified Richman-Atkins Approach to Triamines</td>
<td>22</td>
</tr>
<tr>
<td>1.15</td>
<td>Modified Richman-Atkins Approach to Tetraines</td>
<td>23</td>
</tr>
<tr>
<td>1.16</td>
<td>Cleavage of Tetracyclic bis-Aminals</td>
<td>24</td>
</tr>
<tr>
<td>1.17</td>
<td>Cleavage of a bis-Aminal</td>
<td>26</td>
</tr>
<tr>
<td>1.18</td>
<td>Preparation of Monoprotected Intermediate</td>
<td>27</td>
</tr>
<tr>
<td>2.1</td>
<td>Tetraazapolycyclics Prepared by Insertion Reactions</td>
<td>29</td>
</tr>
<tr>
<td>2.2</td>
<td>Triazapolycyclics Prepared by Insertion Reactions</td>
<td>30</td>
</tr>
</tbody>
</table>
2.3 General Structure of Tricyclic Orthoamides ............ 30
2.4 Acyclic Orthoacid Derivatives ......................... 31
2.5 Synthesis of Acyclic Amide Acetals .................. 32
2.6 Synthesis of Acyclic Amide Acetals .................. 32
2.7 Synthesis of Acyclic Orthoamides .................... 33
2.8 Synthesis of Acyclic Orthoamides .................... 33
2.9 Synthesis of Acyclic Orthoamides .................... 34
2.10 Dismutation of Acyclic Ester Aminals ................ 34
2.11 Transamination of Acyclic Amide Acetals ............. 34
2.12 Electrolytic Dissociation of Acyclic Amide Acetals ....................................... 34
2.13 Mechanism of Transamination of Acyclic Amide Acetals ....................................... 35
2.14 Synthesis of Ketene Aminals .......................... 36
2.15 Synthesis of a Tricycloorthoacetamide ............... 37
2.16 Synthesis of hexamethylorthobenzamide ............... 37
2.17 Synthesis of a Tricycloorthoacetamide ............... 37
2.18 Relative Hydrolytic Stability of Acyclic Orthoacid Derivatives ....................................... 38
2.19 Mechanisms for Synthesis of Acyclic Orthoamides ....................................... 38
2.20 Alkylation of Acyclic Orthoamides .................. 39
2.21 Acylation of Acyclic Orthoamides .................. 39
2.22 Generalized Structure of the Tricyclic Orthoamide Series ....................................... 40
2.23 Tricyclic Orthoamide Series .......................... 41
2.24 Original Synthesis of Tricyclic Orthoformamides ....................................... 41
2.25 Improved Synthesis of Tricyclic Orthoformamides ....................................... 42
2.26 Wuest's Synthesis of H-222 and H-333 ................. 43
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.27</td>
<td>Synthesis of Amide Acetals</td>
<td>44</td>
</tr>
<tr>
<td>2.28</td>
<td>Richman-Atkins Synthesis of Triamines</td>
<td>45</td>
</tr>
<tr>
<td>2.29</td>
<td>Mechanism for the Formation of Tricyclo Orthoamides</td>
<td>46</td>
</tr>
<tr>
<td>2.30</td>
<td>Conformations of the Tricycloorthoamides</td>
<td>51</td>
</tr>
<tr>
<td>2.31</td>
<td>Anomeric Effect</td>
<td>53</td>
</tr>
<tr>
<td>2.31.5</td>
<td>Conformations and Spectral Data of the Tricycloorthoformamides</td>
<td>56</td>
</tr>
<tr>
<td>2.32</td>
<td>Angular Dependence of MO Overlap</td>
<td>57</td>
</tr>
<tr>
<td>2.33</td>
<td>$^1J_{CH}$ Data for Model Compounds</td>
<td>58</td>
</tr>
<tr>
<td>2.34</td>
<td>Resonance Argument</td>
<td>61</td>
</tr>
<tr>
<td>2.35</td>
<td>Oxidation of H-333</td>
<td>62</td>
</tr>
<tr>
<td>2.36</td>
<td>$^{13}C$ Shift Correlations for H-222</td>
<td>65</td>
</tr>
<tr>
<td>2.36.5</td>
<td>H-222cct</td>
<td>66</td>
</tr>
<tr>
<td>2.37</td>
<td>Torsion Angle Diagram of H-222</td>
<td>66</td>
</tr>
<tr>
<td>2.38</td>
<td>Reasonable Conformations of H-322</td>
<td>68</td>
</tr>
<tr>
<td>2.39</td>
<td>Torsion Angle Diagram of H-322</td>
<td>69</td>
</tr>
<tr>
<td>2.40</td>
<td>All possible Conformations of H-322</td>
<td>70</td>
</tr>
<tr>
<td>2.40.5</td>
<td>Reasonable Conformations of H-332</td>
<td>71</td>
</tr>
<tr>
<td>2.41</td>
<td>Torsion Angle Diagrams of H-332</td>
<td>72-73</td>
</tr>
<tr>
<td>2.41.5</td>
<td>Solvent Dependent NMR Data for H-332</td>
<td>75</td>
</tr>
<tr>
<td>2.42</td>
<td>Reasonable Conformations of H-333</td>
<td>76</td>
</tr>
<tr>
<td>2.43</td>
<td>$^{13}C$ Shift Correlations for H-333</td>
<td>77</td>
</tr>
<tr>
<td>2.44</td>
<td>Torsion Angle Diagram for H-333</td>
<td>78</td>
</tr>
<tr>
<td>2.46</td>
<td>Conformations and $^{13}C$ Methyl Shifts of the Tricyclic Orthoacetamides</td>
<td>79</td>
</tr>
<tr>
<td>2.47</td>
<td>Me-222cct</td>
<td>81</td>
</tr>
<tr>
<td>2.48</td>
<td>Torsion Angle Diagram of Me-222</td>
<td>82</td>
</tr>
<tr>
<td>2.49</td>
<td>$^{13}C$ Shift Correlations for Me-222</td>
<td>83</td>
</tr>
</tbody>
</table>
2.50 Reasonable Conformations of Me-322 .................83
2.50.5 Torsion Angle Diagrams for Me-322 ..................85
2.51 Reasonable Conformations of Me-332 ..................86
2.51.5 Torsion Angle Diagrams for Me-332 ..................87-88
2.52 Reasonable Conformations of Me-333 .................89
2.53-s 13C Spectra of Me-333 at 25°C .......................91
2.54-s 13C Spectra of Me-333 at -26.7°C ....................92
2.55-s 13C Spectra of Me-333 at -44.8°C ....................93
2.56-s 13C Spectra of Me-333 at -67.1°C ....................94
2.53 Torsion Angle Diagrams of Me-333 and of Hydrocarbon Analogs ..................99-100
2.54 Conformations of the Tricyclic Ortho-
propionamides .........................................101
2.55 Et-222ct ...........................................102
2.56 Torsion Angle Diagram of Et-222 .....................103
2.57 Rotomers of the Reasonable Conformations of Et-322 ..................104
2.58 Torsion Angle Diagrams of Et-322 .....................105-107
2.59 Reasonable Conformations of Et-332 ..................109
2.60 Torsion Angle Diagrams of Et-332 .....................110-113
2.61 Reasonable Conformations of Et-333 ..................115
2.61.5 Torsion Angle Diagrams for Et-333 ..................116-117
2.62 13C Spectrum of Et-333 at -14°C .......................119
2.63 13C Spectrum of Et-333 at -40°C .......................120
2.64 13C Spectrum of Et-333 at -80°C .......................121
2.66 Degenerate Conformational Process for Et-333 ..........122
2.67 Experimental and Simulated DNM R Spectra of Et-333 ..................124
2.69 Schematic of the Degenerate Conformational Process of Et-333..............................126
2.70 Schematic of Proposed Intermediates in the Degenerate Conformational Process of Et-333...127
2.71 Reactions of Acyclic Orthoamides.......................................................128
2.72 Hydrolysis of Acyclic Orthoamides..................................................129
2.73 Alkylation of H-222........................................................................129
2.74 Alkylation of Cyclic Amide Acetals....................................................130
2.75 Stereochemistry of Alkylation of H-222............................................130
2.76 Alkylation of H-333, Me-333, and Et-333.........................................131
2.77 Stereochemistry of Alkylation of H-333 and Me-333.............................132
2.78 Stereochemistry of Alkylation of Et-333.............................................133
2.79 Dialkylated Products of the 333 series..............................................134
2.80 Monofluoroborate Salt of H-333.........................................................134
2.81 Alkylation-Hydrolysis sequence for H-333........................................137
2.82 Classical Protection Scheme for 1,4,7-triazaclyclododecane.....................138
2.83-a Proposed Synthetic Application of the Alkylation-Hydrolysis sequence for H-333......139
2.83-b Alkylation of H-333 by chloromethylated resins............................139
2.84 Mechanism of Hydrolysis of Acyclic Orthoamides................................140
2.85 Mechanism of Hydrolysis of Acyclic Orthoesters..................................141
2.86 Inductive Withdrawal Model...............................................................142
2.87 Alternating-Attenuating Inductive Withdrawal Model............................144
2.88 Angular Dependence of Inductive Withdrawal........................................144
2.89 Protonated H-222 and H-333..............................................................146
2.90 Protonated Tetraazatetracyclic..........................................................148
# List of Tables

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>NMR Data for the Orthoformamides</td>
<td>56</td>
</tr>
<tr>
<td>2.2</td>
<td>$^{13}$C NMR Data for the Orthoacetamides</td>
<td>79</td>
</tr>
<tr>
<td>2.3</td>
<td>Solvent Dependent $^{13}$C of Me-333</td>
<td>96</td>
</tr>
<tr>
<td>2.4</td>
<td>Solvent Dependent $^{13}$C of Me-333</td>
<td>97</td>
</tr>
<tr>
<td>2.5</td>
<td>$^{13}$C NMR Data for the Orthopropionamides</td>
<td>101</td>
</tr>
<tr>
<td>2.5-5</td>
<td>IR and UV Data for Acyclic and Cyclic Amidinium Ions</td>
<td>135</td>
</tr>
<tr>
<td>2.6</td>
<td>Chemical Shift and $^{1}J_{CH}$ Changes in H-222 and H-333 Upon Protonation</td>
<td>146</td>
</tr>
</tbody>
</table>
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. 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".

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
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 and macrocyclic 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, Schmidtchen, and Kemp 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 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 (compound 6, fig. 1.1) also exhibited selectivity towards the halides on the basis of size. Richman has reported the synthesis and unique properties of tetraazatetracyclic (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. Fig. 1.1) arises 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 \( \sigma \) bonding between the nitrogens\(^{35-38} \). The dications, resulting from their two electron oxidation, are stabilized by \( \sigma \) 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\textsuperscript{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 accommodate any guests and furthermore 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\textsuperscript{45a}. The crystalline product obtained from this reaction was initially assigned structure 10 (fig.1.2). This compound was later shown by proton NMR\textsuperscript{45b,c} and X-ray crystal structure determination\textsuperscript{45d} to be 8.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig1.2.png}
\caption{fig. 1.2}
\end{figure}
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 for macrocyclic synthesis (fig. 1.3a) and extended by Park and Simmons to the synthesis of bicyclics (fig. 1.1 and 1.3a).

**Fig. 1.3a**

\[
\begin{align*}
\text{COCl} & \quad \text{COCl} \\
\text{H-N} & \quad \text{NH}_2 \\
\end{align*}
\]

1. High dil.  
2. Reduction

**Fig. 1.3b**

\[
\begin{align*}
\text{HN} & \quad \text{NH}^+ \\
\text{COCl} & \quad \text{COCl} \\
\end{align*}
\]

1. High dil.  
2. Reduction

**Fig. 1.3c**

\[
\begin{align*}
\text{P-N} & \quad \text{X} \\
\text{X} & \quad \text{X} \\
\end{align*}
\]
by Lehn to the synthesis of tricyclics\textsuperscript{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\textsuperscript{48} under high dilution conditions and later extended by Richman and Atkins\textsuperscript{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 \textsuperscript{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 \( \text{1} \) should possess a cavity large enough to accommodate lithium cation, a proton, or some transition metal cations such as copper(II). The complexes of the metal cations and \( \text{1} \) should provide the limiting examples of tetrahedral coordination of these cations. These complexes should prove to be interesting subjects for multinuclear NMR (e.g. \( \text{7Li} \)). 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 \( \text{1} \) 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. Furthermore, once protonation has occurred and the proton is in the interior of \( \text{1} \) it should rapidly exchange among all four nitrogens and
be strongly intramolecularly hydrogen bonded. This condition should make its deprotonation essentially impossible perhaps rendering 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 \(\sigma^*\) 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 aligned 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\textsuperscript{49e}.

The radical cations of amines of this general structure have also been shown to be stabilized by through space interactions. Nelsen\textsuperscript{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\textsuperscript{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 \( \sigma \)-bond" was first advanced by Alder\textsuperscript{49g} to explain the stability and spectral properties of the radical cation of \( 15 \) (fig.1.5). Alder later reported three electron \( \sigma \)-bonding in the radical cation of \( 16 \) (fig.1.5)\textsuperscript{49h} and most recently in the radical cations of \( 17 \) and \( 18 \) (fig.1.5)\textsuperscript{49i}.

Alder has recently reviewed the special properties of di- and polyamines including their electrochemical behavior\textsuperscript{49h}. Nelsen has reviewed the electrochemical properties of nitrogen compounds\textsuperscript{49i}. 
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. 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. 1.7

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

\[
\text{TsNH}_2 + 2 \overset{\text{CN}}{\xrightarrow{\text{NaOH,THF, reflux 12h}}} \text{TsN} \overset{\text{CN}}{\xrightarrow{\text{6N HCl}}} \text{TsN} \overset{\text{COOH}}{\xrightarrow{}} \text{TsN} \overset{\text{COOH}}{\xrightarrow{}} \]

(91%) (82%)

\[
\text{SOCl}_2, \text{PhH} \rightarrow \overset{\text{50\(^\circ\), 18h}}{\xrightarrow{}} \text{TsN} \overset{\text{COCl}}{\xrightarrow{}} \overset{\text{2 NH}_2}{\xrightarrow{\text{PhH, high dilution}}} \text{TsN} \overset{\text{NH}}{\xrightarrow{}} \overset{\text{O}}{\xrightarrow{}} \text{dimer} \overset{\text{95\%}}{\xrightarrow{}} (29\%)
\]

\[
\overset{\text{1BH}_3 \text{THF}}{\xrightarrow{2.6 \text{N HCl, 8h}}} \overset{\text{3aq NaOH}}{\xrightarrow{3.0 \text{aq NaOH}}} \overset{\text{Et}_3 \text{N, PhH, high dilution}}{\xrightarrow{23}} \text{TsN} \overset{\text{COCl}}{\rightarrow} \overset{\text{Et}_3 \text{N, PhH, high dilution}}{\xrightarrow{24}} \]

(67%) (100%) (100%)

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

\[
\text{Gel Permeation Chromatography}
\]

\[
\begin{align*}
\text{Biobeads SX-12} \\
21' \times 3/8'' \\
\text{CH}_2\text{Cl}_2 \\
2.6 \text{ ml/min} \\
340 \text{ lb/in}^2
\end{align*}
\]

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
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 \( \text{26} \) to yield the product. \( \text{26} \) is an anti-Bredt amide in that the nitrogen lone pairs are twisted relative to the carbonyl \( \pi \) 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.

\[
\begin{align*}
K + COCl & \rightarrow L \\
L & \stackrel{[H]}{\rightarrow} M \\
M & \stackrel{S_N^2}{\rightarrow} M'
\end{align*}
\]

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 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).

Koyama has also reported a similar procedure employing dibromides instead of ditosylates. It has been suggested 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 (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\textsuperscript{55,56} (fig. 1.14). A review of the methods for tosylamide cleavages is available.\textsuperscript{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 \(-77^\circ C\) (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\textsuperscript{58}. The low yields in these reactions are probably due to the myriad of side reactions that sulfenes are known to undergo\textsuperscript{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
small quantities of starting materials made the product
separation and identification impossible.

![Diagram of chemical reactions](image)

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

![Chemical Reaction Diagram]

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. 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. The aminal cleavage reactions which were examined (EH_3/THF, NaEH_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\(^6\). 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.

\[ \text{fig. 1.17} \]

**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.

\[
\begin{align*}
    \text{43} + \text{PhCOCl} & \rightarrow \text{NaOH} \\
    \rightarrow & \text{45}
\end{align*}
\]

fig. 1.18
CHAPTER 2

TRICYCLIC ORTHOCAMIDES

Reports by Richman and Atkins\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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)\textsuperscript{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
macrocyclic tetraamines with formaldehyde. Richman has incorporated a single carbon into the center of a macrocyclic tetraamine to yield tetracycle $(\text{fig. 2.1})$. Richman has also incorporated phosphorous into the center of macrocyclic tetraamines to yield compounds $(\text{fig. 2.1})$.

Similar work has been undertaken employing macrocyclic triamines. Richman has incorporated a boron into the center of a series of macrocyclic triamines to produce compounds $(\text{fig. 2.2})$. Verkade and coworkers have introduced phosphorous into the center of a macrocyclic triamine to yield compound $(\text{fig. 2.2})$. These workers also
prepared various oxidized derivatives of 62.

![Chemical structures](image)

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).

![Chemical structure](image)

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 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\textsuperscript{73}. The first authentic preparation of an orthoacid derivative was reported in 1907 when Lander\textsuperscript{74} prepared amide acetals through the reaction of amide chlorides with alkoxides (fig.2.5). The field then lay dormant until 1956 when the systematic study of orthoacid derivatives was reopened by Meerwein\textsuperscript{74a}, who reported the reaction of tertiary amides with oxonium salts \textsuperscript{70}(fig.2.6). The resulting oxo-iminium salts \textsuperscript{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\textsuperscript{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\textsuperscript{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'-tetrastituted formamidinium salts (72, fig. 2.7) with alkalai metal amides to yield the tris-dimethylaminomethanes 73(fig. 2.7)\textsuperscript{81–84}.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) \text{NR}_2; \node (b) at (2,0) \text{M}^{\ominus} \text{NR}_2; \node (c) at (4,0) \text{HC(NR}_2\text{)}_3; \draw (a) -- (b) -- (c);
\end{tikzpicture}
\end{center}

The reaction of iminium chlorides 74(fig 2.8) with alkalai metal amides also yields orthoamides\textsuperscript{73}.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) \text{R} \text{NR}_2 + \text{COCl}_2 \rightarrow \text{R} \text{Cl} + \text{M}^{\ominus} \text{NR}_2; \node (b) at (2,0) \text{RC(NR}_2\text{)}_3; \draw (a) -- (b);
\end{tikzpicture}
\end{center}

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\textsuperscript{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).

\[
\text{HC(OR)}_3 + 3 \text{M}^\Theta \text{NR}_2 \xrightarrow{\text{HMPTA}} \text{HC(NR}_2)_3
\]

fig 2.9

\[
\begin{align*}
\text{OR} \\
2 \text{HC(NR}_2)_2 + \text{ROH} &\rightleftharpoons \text{HC(NR}_2)_3 + \text{HC(OR)}_2 \\
\end{align*}
\]

fig 2.10

Transamiration of amide acetals has been used to prepare tris-dialkylaminomethanes\(^{87}\) (fig. 2.11).

\[
\text{HC(OR)}_2 + 2 \text{HNR}_2 \rightleftharpoons \text{HC(NR}_2)_3 + 2 \text{ROH}
\]

fig 2.11

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.

Since the transamination of amide acetals does not
require acid catalysis the mechanism of this reaction, in
neutral media, probably involves 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 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.

Prior to this work the transamination reaction has only
been run successfully on formamide acetals or on acetals
bearing no \(\alpha\)-hydrogens. When acetals bearing \(\alpha\)-hydrogens
have been employed in this reaction then the only isolable
products have been ketene aminals\textsuperscript{78}(fig.2.14). These products result from the elimination of an alcohol residue from the intermediate ester aminal\textsuperscript{79}(fig.2.14).

\[
\begin{array}{c}
\text{RCH}_2\text{CINR}_2\text{OR} \\
\leftrightarrow \text{RCH}_2\text{CINR}_2\text{NR}_2 \quad \text{NR}_2 \quad \text{RCH}_2\text{CINR}_2\text{OR} \\
\leftrightarrow \text{RCH} = \text{CINR}_2\text{NR}_2
\end{array}
\]

\textsuperscript{78}

\textbf{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 trifluoroacetamide \textsuperscript{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 \textsuperscript{80} prepared by the reaction of phenyllithium with hexamethylyguanidium chloride \textsuperscript{81,95}(fig.2.16). The third reported example is the difluorochloroorthoacetamide \textsuperscript{82} which was prepared by the reaction sequence outlined in fig.2.17\textsuperscript{56}. 

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 $\text{3}\text{3}$ (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.

$$RC(OR)_{3} < RC(OR)_{2} < RC(NR_{2})_{2} < RC(NR_{2})_{3}$$

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

$$RC(NR_{2})_{3} + XH \rightarrow RC(NR_{2})_{2} + HNR_{2}$$

Path b

$$RC(NR_{2})_{3} + HX \rightarrow RC(NR_{2})_{2} + RNX + HNR_{2}$$

Fig 2.19
Path a is favored by very stable intermediate amidinium ions, low kinetic and thermodynamic acidity of X-H (e.g. \(R_2\text{NH}\)), 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)aminoethanes react with methyl iodide to yield formamidinium salts (fig. 2.20)\(^{82,85}\).

\[
\text{HC(NR}_2\rangle_3 + \text{MeI} \rightarrow \text{HC} \overset{\text{I}}{\overset{\text{NR}_2}{\text{Me}}} + \text{MeNR}_2
\]

**fig 2.20**

\[
\text{HC(NPh}_3\rangle + \text{RCl} \rightarrow \text{MeN} \overset{\text{Ph}}{\overset{\text{N}}{\overset{\text{Ph}}{\text{Cl}}} + \text{MeN}_\text{Ph} \overset{\text{R}}{\overset{\text{N}}{\text{Ph}}}
\]

**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 \(\text{64}\) are isolated (fig. 2.21)\(^{99}\).
The synthesis, physical properties, reactivities, and synthetic applications of orthoacid derivatives have been extensively reviewed by several authors\textsuperscript{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.

![Diagram of tricyclic orthoamide](85)

The subjects of this report are the tricyclic orthoamides of general structure \textsuperscript{85}(fig.2.22). The two initial reports concerning the parent orthoformamides (R=H) were made by Atkins\textsuperscript{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\textsuperscript{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.
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.

Our initial synthetic approaches to these interesting compounds involved the acid catalyzed condensations of triethyl orthoformate 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
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\textsuperscript{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%

\begin{equation}
\text{HN} \quad \text{HN} \quad \text{HN} + \text{HCl(OMe)}_2 \xrightarrow{\Delta} \text{HN} \quad \text{HN} + 2\text{MeOH} + \text{HNMe}_2
\end{equation}

\textit{fig 2.25}

(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\textsuperscript{102}. During this time another group of investigators headed by
Wuest\textsuperscript{104,105} was also investigating these compounds. Wuest prepared two members of the series according to the synthetic procedures outlined in fig.2.26.

\[
\begin{align*}
\text{HNN} & \quad + \quad \text{HC(OEt)}_3 \\ & \quad \xrightarrow{\text{THF, TsOH}} \\ & \quad 135^\circ C \\ & \quad 60\text{h.} \\ & \quad (84\%)
\end{align*}
\]

\[
\begin{align*}
\text{NN} & \quad + \quad \text{NH}_2 \text{OAc} \\ & \quad \rightarrow \\ & \quad (71\%)
\end{align*}
\]

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\textsuperscript{103}, Atkin's report\textsuperscript{102}, and Wuest's report\textsuperscript{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)\textsuperscript{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\textsuperscript{107} (fig.2.27).

\[
\begin{align*}
\text{fig 2.27}
\end{align*}
\]

The macrocyclic triamine precursors were prepared by the method of Richman and Atkins\textsuperscript{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\textsuperscript{60a} whereby the tosylamides were cleaved in concentrated sulfuric acid at 100°C. Typically a base workup yielded the triamines in good yields.

\begin{align*}
\text{fig 2.28}
\end{align*}

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

\[
\begin{align*}
NR_2 & \rightarrow R(\text{OR})_2 \\
R(\text{OR})_2 & \rightarrow R + \text{OR} \quad \text{OR} \quad \text{NR}_2 \\
\text{NR}_2 & \rightarrow \text{OH} \\
\text{ NR}_2 & \rightarrow \text{OH} \\
\text{NR}_2^+ & \rightarrow \text{HNR}_2^+ \\
\text{HNR}_2^+ & \rightarrow \text{NR}_2^+ \\
\text{fig 229}
\end{align*}
\]

indicates that $S_1$ 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. An excellent review is available concerning the spectral methods used to determine the stereochemistry of the bridgehead nitrogen. The more general area of heterocyclic conformational analysis continues to be actively studied by many groups and excellent reviews and books 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 in particular has advanced these areas of study dramatically. The application of variable temperature techniques to NMR (Dynamic NMR) has produced a wealth of information concerning both the determination of conformation and the energy barriers associated with conformational processes. 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 appearance of Bohlmann bands in the 2700-2800 cm\(^{-1}\) 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 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 including amines. Allinger has reviewed the force field method.

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\textsuperscript{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 than 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 $\text{trans,trans,trans-Me-333}$ or simply $98$-$\text{ttt}$. In some cases there may exist more than one $\text{cis,cis,trans}$ 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 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" 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 \( \alpha \)-position (fig. 2.31). The effect was first explained in terms of dipolar interactions. Edward reasoned that an antiperiplanar disposition of dipoles should be lower in energy than a gauche disposition. The more recent, and now generally accepted, explanation is based on MO considerations. According to MO theory the overlap of the lone pair orbital of the heteroatom with the \( \sigma^* \) 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 \(^{139}\).

\[
\begin{array}{c}
\text{favorable} \\
\text{unfavorable}
\end{array}
\]

**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 interconvertible 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\textsuperscript{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, $^1J_{CH}$ 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° 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°, 179.5°, 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 1H chemical shifts and the 1J\textsubscript{CH} through the series.

**Table 2.1**

<table>
<thead>
<tr>
<th>Product</th>
<th>60MHz 1H NMR (δ, CDCl\textsubscript{3})</th>
<th>13C NMR (δ, CDCl\textsubscript{3})</th>
<th>1J\textsubscript{CH} (methine) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>2.5-3.35 (AA'BB', 12H) 5.03 (s, 1H, methine)</td>
<td>N-CH=CH- 104.1 52.0 184 ± 1</td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>1.05 (d of quintets, J=13 Hz, 1H) ca. 1.5-2.3 (m, 1H) ca. 2.2-3.7 (m, 12H) 4.32 (s, 1H, methine)</td>
<td>93.3 45.9, 49.0 56.2 169 ± 1</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>1.1-3.37 (m)</td>
<td>96.6 47.7, 48.9 23.6 140 ± 3</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>1.22-1.49 (m, 3H) 1.58-2.22 (m, 9H) 2.25 (s, 1H, methine) 2.61-2.90 (m, 6H)</td>
<td>100.0 53.9 24.2 141 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

*Neither 60 MHz nor 90 MHz spectra permitted assignment of the methine 90 MHz, acetone-d\textsubscript{6}; δ(methylene) in CDCl\textsubscript{3} = 2.32

δ 5.03 4.32 2.56 2.25

1J\textsubscript{CH} 184 169 140 140

IR 2700-2800 cm\textsuperscript{-1} 2700-2800 cm\textsuperscript{-1} 2700-2800 cm\textsuperscript{-1} 2400 cm\textsuperscript{-1}

fig. 231
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 $^{14}$.$^{c-e-k}$. Theoretical studies indicate that the orbital overlap of the lone pairs with the $\sigma^*$ 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.

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°.

<table>
<thead>
<tr>
<th>Orthoamides: $^{1}J_{CH}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound</strong></td>
</tr>
<tr>
<td>$(Me_2N)_3CH$</td>
</tr>
<tr>
<td>222</td>
</tr>
<tr>
<td>322</td>
</tr>
<tr>
<td>332</td>
</tr>
<tr>
<td>333</td>
</tr>
<tr>
<td>233-a</td>
</tr>
<tr>
<td>233-b</td>
</tr>
<tr>
<td>233-c</td>
</tr>
</tbody>
</table>

fig 2.33
Clearly factors other than 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

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

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 $\text{J}_{\text{CH}}$ 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 $\text{J}_{\text{CH}}$ 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 $\text{J}_{\text{CH}}$ are in fact not additive.

In summary it can be stated that the variation in the $\text{J}_{\text{CH}}$ 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 $\text{J}_{\text{CH}}$ 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\textsuperscript{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\textsuperscript{110}. The shifts are attributed to a combination of \(n-\sigma^*\) 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\textsuperscript{149-153}. The effect of the lone pairs on the NMR spectrum is conveniently illustrated by the resonance argument presented 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\textsuperscript{154-157}. The chemical reactivity of H-333 also reflects the contribution from resonance form 2.34-b. Wuest\textsuperscript{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.$^{104}$

![Reaction diagram](fig 235)

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 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 2400 cm$^{-1}$ 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 originally thought to be observable only when two C-H bonds were antiperiplanar to a nitrogen lone pair. Subsequent studies determined that Bohlmann bands are also observed in cases were only a single C-H bond is antiperiplanar to a nitrogen lone pair (see reference 110 for a discussion 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 C₃ conformation presented in fig. 2.31. Strong evidence for the all-cis conformation is the complete absence of Bohlmann bands in the 2700-2800 cm⁻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 ¹JCH for the methine C-H. ¹³C empirical shift correlations employing model compounds 2.33b¹⁵₈ and 2.33-c¹⁵₉a (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 ¹³C 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
Δδ_{c-b} upon introduction of one N

γ = 31.5 - 31.9 = -0.4

α' = 75.6 - 54.8 = 20.8

β = 31.2 - 31.9 = -0.7

α = 53.3 - 31.9 = 21.4

calculated shifts for H-222

δ = 54.8 + 3α'

δ = 31.9 + α + β + γ

Agreement: actual (calcd.) shifts

* tentative assignments

fig 2.36
Bohllmann bands in the IR since conformation H-222ctt would be expected to exhibit Bohllmann bands.

fig 2365

Osa wa$^{55}$ has recently reported a detailed empirical force field study of the hydrocarbon analog of H-222. Osa wa concluded that the hydrocarbon has the slightly twisted C₃ symmetry that we have assigned to H-222. His study indicated that the hydrocarbon rapidly interconverts between two enantiomeric C₃ conformers resulting in apparent C₃ᵥ symmetry.

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 spectral 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.
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 $-100^\circ C$ 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.

![Conformational Analysis of H-332](image)

**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 CDCl₃. The most important spectral data used in this assignment are the $^{1}J_{CH}$ coupling constant for the methine carbon, the unusually low frequency Bohlmann bands in the IR, and the chemical shift of the methine proton. The $^{1}J_{CH}$ was found to be 140 Hz which is the same as the $^{1}J_{CH}$ 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.

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(C₄)

E=34.6

fig 241
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$^\circ$C but in acetone the spectra began to broaden at -66$^\circ$C and continued to broaden down to -100$^\circ$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(C5) and H-332cct(C4) 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.

Conformational Analysis of H-333 (94). The MM2 calculations allow assignment of the minimum energy conformation to the all-trans C3v 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 \(^{2.43-a}\) and \(^{2.43-b}\) (fig. 2.43) also support the assigned structure. 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\(^\circ\)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.

![diagram](image)

**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
Δδ 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.
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 ($\Delta \delta = 31.7$ ppm, ambient $T$). The range of shifts is attributable to a combination of steric

\[ \begin{array}{cccc}
5^c & 27.7 \text{ ppm} & 23.8 \text{ ppm} & 10.0 \text{ ppm} & -6.9 \text{ ppm} \\
\end{array} \]

![Fig 2.46](image)

Table 2.2

<table>
<thead>
<tr>
<th>Compound</th>
<th>$N \cdot CH_3$</th>
<th>CH_2-N</th>
<th>CH_2-CH_2-CH_2</th>
<th>C-CH_3</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>111.4</td>
<td>51.8</td>
<td>13.1</td>
<td>27.7</td>
</tr>
<tr>
<td>96</td>
<td>94.7</td>
<td>54.9, 51.9</td>
<td>44.6</td>
<td>23.8</td>
</tr>
<tr>
<td>97</td>
<td>86.9</td>
<td>49.4, 45.6</td>
<td>43.7</td>
<td>10.0</td>
</tr>
<tr>
<td>98\textsuperscript{a}</td>
<td>86.0</td>
<td>49.0</td>
<td>24.16</td>
<td>-4.0</td>
</tr>
<tr>
<td>98\textsuperscript{b}</td>
<td>85.9</td>
<td>48.7(br)</td>
<td>24.7(br)</td>
<td>-6.6(br)</td>
</tr>
</tbody>
</table>

a. $T = 302^\circ K$; b. $T = 206^\circ K$

Orthopropionamides: $^{13}$C NMR ($\delta_c$, CDCl\_3).
compression and lone pair orientational effects. The \( \delta_C \) (methyl) of \textit{Me-222} is in good agreement with the methyl chemical shift of its carbon analog\(^\text{168}\) which has been reported to be 28.4 ppm. The \( \delta_C \) (methyl) of the hypothetical hydrocarbon analog of \textit{Me-333ttt} is calculated to be +6.8 ppm\(^\text{167,169}\), 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 \textit{Me-333}. Several reports have documented that carbons which are antiperiplanar to a nitrogen lone pair in amines\(^\text{170-172}\), aziridines\(^\text{173}\), oxaziridines\(^\text{174}\), and oximes\(^\text{175}\) 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 \( \sigma^* \) 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 \textit{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 \textit{cis,trans,trans} (95ttt, fig. 2.47, the only other reasonably
possible conformation, albeit exceedingly unlikely) should exhibit Bohlmann bands.

![Diagram](image)

**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).

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

\[ \delta = \delta_a + \Delta \delta_{c-b} \]

Agreement: actual (calcd.) shifts

fig 249
Conformational Analysis of Me-322(96). Models indicate that the all-cis conformation (96cct) and the cis, cis, trans conformation (96cct) should 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.
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 $-65^\circ$C) or in acetone-d$_6$ (down to $-100^\circ$C). The lack of broadening and the number of lines demands that the conformation possess a mirror plane which bisects the
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 \(97\text{cct}(C\text{s})\) and \(97\text{ttt}\). Since \(97\text{ttt}\) was calculated to be almost 5 kcal/mol higher in energy we conclude that the \(\text{Me-332}\) global minimum is \(97\text{cct}(C\text{s})\).

![Diagram](image)

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 \(\text{Me-332}\) 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-cct(C4)
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 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 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\textsubscript{3v}) 98\text{ttt} 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\textsubscript{3} (see spectra: fig. 2.53-2.56) is also consistent with the predominance of 98\text{ttt} over 98\text{cct}. 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 98\text{ttt}. No peaks attributable to 98\text{cct} were observed at the lowest attainable temperatures (in CDCl\textsubscript{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 98\text{cct} yields 14\% of the minor conformation at 302 K\textsuperscript{106}. Since $\Delta S_n$ (98\text{cct}-98\text{ttt}), the trivial entropy difference due to the symmetry number differences, is 2.18 cal/mol-deg, it is expected that 98\text{cct} should amount to only 4\% of the equilibrium mixture at 206 K in CDCl\textsubscript{3}. The preceding analysis has been published in communication forrn\textsuperscript{106}. 
fig 2.53-s

Temp = 25°C
see Appendix 2 for δ values

N-CH₂

CH₂CH₂CH₂

CH₃

TMS

CH₃
fig 2.55-s

Temp = -44.82°C
fig 2.56-s

Temp=-67.09°C

N-CH₂

TMS

CH₂CH₂CH₂

CH₃
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 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 $\Delta S$ 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 $\Delta H$ 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 discrepancy 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

<table>
<thead>
<tr>
<th>SOLVENT</th>
<th>DIELECTRIC CONSTANT</th>
<th>E_T</th>
<th>δ_c(methyl) at Amb. Probe T</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-hexane</td>
<td>1.88</td>
<td>30.9</td>
<td>-1.63</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>4.73</td>
<td>39.1</td>
<td>-4.01</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>20.7</td>
<td>42.2</td>
<td>0.00</td>
</tr>
<tr>
<td>CD₃CN</td>
<td>38.8</td>
<td>46.0</td>
<td>-1.35</td>
</tr>
</tbody>
</table>

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 Eₜ. The increased dominance of 98ttt in CDCl₃ 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 (CH₃-O)₂CH₂. 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 occurred was determined in CDC$_3$ and in acetone-$d_6$. The results of this experiment are shown in table 2.4.

**Table 2.4**

<table>
<thead>
<tr>
<th>SOLVENT</th>
<th>$R_T$</th>
<th>$T_{max}$</th>
<th>$\delta_c$</th>
<th>$V_{max}$</th>
<th>$\Delta V$</th>
<th>$k^{180}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC$_3$</td>
<td>39.1</td>
<td>$-44.8 \pm 3^\circ C$</td>
<td>$-6.27$</td>
<td>47.7 Hz</td>
<td>420.0 Hz</td>
<td>2643 sec$^{-1}$</td>
</tr>
<tr>
<td>Acetone$_{d6}$</td>
<td>42.2</td>
<td>$-40.0 \pm 3^\circ C$</td>
<td>$-5.40$</td>
<td>55.7 Hz</td>
<td>401.0 Hz</td>
<td>2520 sec$^{-1}$</td>
</tr>
</tbody>
</table>

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 88cct-98ttt do not have ionic character. It is well known that reactions with ionic transition states preceding ionic intermediates have rates which are directly proportional to the ionizing power of the solvent. Winsten$^{178}$ 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 \texttt{98ttt} and \texttt{98cct} is a conformational process.

The torsion angle diagrams of \texttt{98ttt}, \texttt{98cct}, \texttt{98HCttt}, and \texttt{98HCcct} are shown in fig. 2.53 along with their calculated energies. Inspection of the torsion angles for \texttt{98HCttt} reveals that this hypothetical hydrocarbon would consist of three nearly perfect chairs. On the other hand the torsion angles of \texttt{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 \texttt{98cct} relative to \texttt{98HCcct}.

A comparison of the torsion angles of \texttt{98cct} relative to \texttt{98ttt} reveals that there is a greater degree of flattening of the chairs in \texttt{98cct}. The increased flattening in \texttt{98cct} is probably a major factor in the energy difference between these two conformations.
98-HC-qtt
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](image)

**Table 2.5**

<table>
<thead>
<tr>
<th>Compound</th>
<th>N(CH₂)₂</th>
<th>CH₂-N</th>
<th>CH₂-CH₂-CH₂</th>
<th>CH₂-CH₃</th>
<th>CH₂CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>113.8</td>
<td>51.9</td>
<td>---</td>
<td>33.6</td>
<td>9.6</td>
</tr>
<tr>
<td>100</td>
<td>97.0</td>
<td>55.8</td>
<td>52.1</td>
<td>12.5</td>
<td>28.2</td>
</tr>
<tr>
<td>101</td>
<td>88.8</td>
<td>48.9</td>
<td>45.6</td>
<td>19.8</td>
<td>11.4</td>
</tr>
<tr>
<td>102ᵃ</td>
<td>87.1</td>
<td>49.1</td>
<td>22.3</td>
<td>13.0</td>
<td>7.9</td>
</tr>
<tr>
<td>102ᵇ</td>
<td>86.5</td>
<td>51.0</td>
<td>48.4</td>
<td>26.3</td>
<td>19.6</td>
</tr>
</tbody>
</table>

* a. T = 302°C (acetone-d₆); b. T = 193°C (acetone-d₆)
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 Eohlmann bands in the IR indicates that this compound is, in fact 99ccc, since 99ctt (fig. 2.55, the other most reasonable conformation) should exhibit Eohlmann bands.

![fig 2.55](image)

This compound and the two lower homologs all have remarkably similar AA'BB' patterns in their $^1H$ 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.

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)
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.

\[
\begin{align*}
100-ccc(C_1) & & \\
100-ccc(C_5) & & \\
100-cct-R(1) & & 100-cct-R(2) & & 100-cct-R(3) \\
\end{align*}
\]

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 \textit{100ccc}(C_s) shows more severe flattening than the six membered ring in \textit{100ccc}(C_1) due to the position of the ethyl group in \textit{100ccc}(C_s).

Examination of the torsion angle diagrams for the \textit{cis,cis,trans} conformations reveals the strain present in these conformations at the trans ring junctures. In \textit{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 \textit{100cct-(R1)} and \textit{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.

\textbf{Conformational Analysis of Et-332 (101).} \textit{MM2} calculations rule out the possibility of the dominance of the all-trans conformations of Et-332. The \textit{cis,cis,trans} conformations and their calculated energies are presented in fig.2.59. The ambient temperature $^{13}\text{C}$ NMR spectrum of Et-332 contains seven sharp lines which show no evidence of dynamic line broadening in either CDCl$_3$ (down to $-60^\circ\text{C}$) or in acetone-$d_6$ (down to $-100^\circ\text{C}$). The number of lines and the lack of dynamic broadening rules out conformations \textit{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).

![Diagrams](image1)

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 \textit{101ccc-5(R1)} and \textit{101cct-5(R2)}.

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. \textit{all-cis}) were not calculated. Examination of
101-cct-5(C₁)
E=48.0

101-cct-5(C₅)
E=41.4
fig 260
101-<sub>ttt</sub>(C<sub>1</sub>)

\[ E = 55.0 \]

101-<sub>ttt</sub>(C<sub>s</sub>)

\[ E = 53.4 \]

fig 260
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 \(10\text{lctt}(C_1)\) and \(10\text{lctt}(C_6)\) are severely distorted chairs which accounts for their higher energy content. \(10\text{lctt-5}(C_1)\) and \(10\text{lctt-5}(C_6)\) 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 \(10\text{lctt-5}(C_1)\) makes the distortions of the six membered ring more severe than in \(10\text{lctt-5}(C_6)\) and accounts for its higher energy content. \(10\text{lctt-6}(R3)\) and \(10\text{lctt-6}(R2)\) 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 \(10\text{lctt-6}(R3)\) and \(10\text{lctt-6}(R2)\) must be due to unfavorable steric interactions between the ethyl group and the six and five membered rings respectively. \(10\text{lctt-6}(R1)\) 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 \(10\text{lctt-6}(R1)\) but not as severely as in \(10\text{lctt-6}(R2)\) and \(10\text{lctt-6}(R3)\) which further accounts for the lower energy content of \(10\text{lctt-6}(R1)\).
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 conformers. The possible conformations that we considered and their calculated energies are shown in fig. 2.61. MM2 calculations indicate a dominance of 102cct(C₅). The fact that 102cct(C₁) is 9 kcal/mol higher in energy than 102cct(C₅) 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. 2.61. In 102cct(C₅) (the minimum energy conformation) the two cis-trans fused rings are slightly flattened and the cis,cis fused ring is a
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(C1) is higher in energy than 102cct(Cs) 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 13C 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 13C NMR of this compound should allow unambiguous assignment of conformation. The ambient temperature 13C 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
102cct(C₆) 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 C₃ᵥ symmetry. This degenerate process is shown in

![Diagram](image)

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⁻ 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. 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 $\ln k/T$ 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 $-6.66 \times 10^{-3}$ 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 $\pm$ 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.

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. 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 102E 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. 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.
Fig. 2.69

c = chair

b = boat or twist boat
fig. 2.70
Introduction

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

\[
\begin{align*}
\text{HCONR}_2 + 2\text{R}_2\text{NH} & \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{HCONR}_2^+ \text{R}_2\text{NH}_2^+ \\
\text{(R}_2\text{N})_3\text{CH} & \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{HCONR}_2^+ \text{R}_2\text{NH}_2^+ \\
\end{align*}
\]

fig 2.72

Alkylation of Orthoamides. Atkins has reported the reaction of H-222 with excess methyl iodide (fig. 2.73)\textsuperscript{102}. The product of this reaction was salt \text{103} in which the tricyclic integrity of the starting material was preserved. Atkins stated that \text{103} was obtained instead of the bicyclic amidinium ion \text{104} presumably because of the instability of \text{104} (fig. 2.73). The generation of salts such as \text{105} (fig. 2.74) from some cyclic amide acetals has been previously explained in terms of the instability of the alternate carboxonium product \text{106}. 

\[
\begin{align*}
\text{N}^+\text{I}^- & \quad \xrightarrow{\text{excess MeI}} \quad \text{N}^+\text{I}^- \\
\text{Me} \quad \text{104} & \quad \xrightarrow{\text{excess MeI}} \quad \text{Me} \quad \text{105} \\
& \quad \text{103} \\
\end{align*}
\]
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 107 are approximately anticlinal to the C-N bond which must be broken to generate 104. According to Delongchamps' principle they 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 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.
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_E 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 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 must mean that the dialkylated products would be too sterically congested and/or that the amine nitrogen lone pairs are unavailable for reaction. Wuest\textsuperscript{104} has reported that the IR spectrum of 109 (fig. 2.80) contained absorbances characteristic of both the open bicyclic structure (1660 cm\textsuperscript{-1}) and also for the closed tricyclic structure (near 2900 cm\textsuperscript{-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.

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\(_2\)Cl\(_2\)/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**

<table>
<thead>
<tr>
<th>R</th>
<th>(v_{C=N}(\text{cm}^{-1}))</th>
<th>(\lambda_{\text{max}}(\text{nm}))</th>
<th>(v_{C=N}(\text{cm}^{-1}))</th>
<th>(\lambda_{\text{max}}(\text{nm}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1652</td>
<td>224(^{b})</td>
<td>1672.4</td>
<td>221</td>
</tr>
<tr>
<td>Me</td>
<td>1607</td>
<td></td>
<td>1608.8</td>
<td>226</td>
</tr>
<tr>
<td>Et</td>
<td>1605</td>
<td></td>
<td>1602.3</td>
<td></td>
</tr>
</tbody>
</table>

\(a: R_1=R_2=\text{Me}, X=\text{ClO}_4\) \(b: R_1=R_2=\text{Me}, X=\text{PF}_6\)
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. Thirdly, the hydrogen on the amidinium carbon was found to be 0.188 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. 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) is replaced in 110 by a favorable interaction. Torsional strain and large angle strain (the two other major
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
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).

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 alkylation 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 alkylation 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.
HYDROLYSIS

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

![Chemical structure of hydrolysis reaction]

\textbf{fig 2.84}

McClelland\textsuperscript{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\textsuperscript{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.

\[
\text{(1) } RC(OR)_3 + HA \leftrightarrow R\overset{\ominus}{\text{O}} + \Theta A + ROH
\]

\[
\text{(2) } R\overset{\ominus}{\text{O}} + H_2O \leftrightarrow R\overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}}
\]

\[
\text{(3) } R\overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}}\overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}} \overset{\ominus}{\text{O}}
\]

Initial investigations in this area were directed at determining the effect of protonation upon $^{1}J_{\text{CH}}$ (methine) in the orthoformamides. It was originally thought that since $^{1}J_{\text{CH}}$ evidenced a dependence on lone pair orientation that this parameter should exhibit a dependence upon protonation. In particular, it was anticipated that $^{1}J_{\text{CH}}$ 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-$\sigma^* C-H$ overlap (see conformational analysis of the orthoformamides) one would expect $H-333$ to show a greater increase in $^1J_{\text{CH}}$ than that of $H-222$.

Likewise, $\delta C(\text{methyl})$ 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-$\sigma^* C$-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 $\Delta ^1J_{\text{CH}}$ 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\textsuperscript{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.

\[
\begin{align*}
\delta^- & \quad \delta^+ & \delta^+ & \delta^+
\end{align*}
\]

$X \leftarrow C \leftarrow C \leftarrow C$

\text{fig 2.86}
Morishima\textsuperscript{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\textsuperscript{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\textsubscript{alpha}—C\textsubscript{beta} bond is qualitatively 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\textsuperscript{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\textsuperscript{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 "\( \sigma \) inductive effect" and the "lone pair overlap effect". The relative importance of these two effects would be difficult to determine.

![Diagram of molecular structure](image)

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 \( \sigma \) 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 $pK_a$s 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 $pK_a$s 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.

![Chemical structure]

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

<table>
<thead>
<tr>
<th>COMP.</th>
<th>SOLVENT</th>
<th>PROTON</th>
<th>SOURCE</th>
<th>METHOD</th>
<th>No.</th>
<th>Eq.</th>
<th>δC (free amine)</th>
<th>JCH (free amine)</th>
<th>δC (protonated)</th>
<th>JCH (protonated)</th>
<th>ΔδC</th>
<th>ΔJCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-222</td>
<td>D2O</td>
<td>PT</td>
<td>DCl</td>
<td></td>
<td>1</td>
<td></td>
<td>101.8</td>
<td>183.1</td>
<td>166.8</td>
<td>193.9</td>
<td>5.0</td>
<td>16.8</td>
</tr>
<tr>
<td>H-222</td>
<td>D2O</td>
<td>V</td>
<td>DCl</td>
<td>W</td>
<td>2</td>
<td></td>
<td>101.8</td>
<td>183.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-222</td>
<td>CF3CO2H</td>
<td>W</td>
<td></td>
<td>V</td>
<td>1</td>
<td></td>
<td>104.1</td>
<td>184.0</td>
<td>108.4</td>
<td>193.9</td>
<td>4.3</td>
<td>9.2</td>
</tr>
<tr>
<td>H-222</td>
<td>CF3CO2H</td>
<td>W</td>
<td></td>
<td>V</td>
<td>2</td>
<td></td>
<td>104.1</td>
<td>184.0</td>
<td>108.6</td>
<td>198.7</td>
<td>4.5</td>
<td>14.7</td>
</tr>
<tr>
<td>H-333</td>
<td>CF3CO2H</td>
<td>V</td>
<td></td>
<td>V</td>
<td>1</td>
<td></td>
<td>100.0</td>
<td>110.1</td>
<td>98.3</td>
<td>157.5</td>
<td>-1.7</td>
<td>17.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMP.</th>
<th>SOLVENT</th>
<th>SOURCE</th>
<th>METHOD</th>
<th>No.</th>
<th>Eq.</th>
<th>δC (Me)</th>
<th>δC (Me)</th>
<th>δC (protonated)</th>
<th>δC (protonated)</th>
<th>ΔδC</th>
<th>ΔJCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-222</td>
<td>CDCl3</td>
<td>TeOH-H2O</td>
<td>W</td>
<td>1</td>
<td></td>
<td>111.4</td>
<td>27.7</td>
<td>119.2</td>
<td>23.6</td>
<td>7.8</td>
<td>-4.1</td>
</tr>
<tr>
<td>Me-333</td>
<td>CDCl3</td>
<td>CF3CO2H</td>
<td>V</td>
<td>1</td>
<td></td>
<td>86.0</td>
<td>-4.0</td>
<td>89.9</td>
<td>1.2</td>
<td>3.9</td>
<td>5.2</td>
</tr>
</tbody>
</table>

METHOD: PT; Potentiometric Titration

W; Weighed

V; Volume

$\Delta \delta_C = \delta_C(\text{protonated}) - \delta_C(\text{free amine})$

$\Delta J_{CH}^1 = J_{CH}^1(\text{protonated}) - J_{CH}^1(\text{free amine})$

Δδ: 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 $^{13}\text{C}$ 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 $\Delta^1J_{\text{CH}}$ and $\Delta\delta_\text{C}$ upon addition of 1 equivalent of acid to the 222 compounds were unsurprising. The downfield shift of the quaternary carbon ($\text{H-}222$ and $\text{Me-}222$), the increased $^1J_{\text{CH}}$ ($\text{H-}222$), and the upfield shift of the methyl resonance ($\text{Me-}222$) are readily explainable in terms of the inductive effect of the positively charged nitrogen. The addition of a second equivalent of acid to $\text{H-}222$ in $\text{D}_2\text{O}$ resulted in a hydrolysis reaction. This reaction is discussed in a later section (see hydrolysis of $\text{H-}222$).

The addition of 1 equivalent of acid to $\text{H-}333$ in CDC$_3$ produced the surprising result that the quaternary carbon was shifted upfield slightly. The $^1\text{H}$ NMR spectrum of $\text{H-}333$ in the presence of 1 equivalent of acid evidenced
significant broadening. Wuest\textsuperscript{104} has also reported the temperature dependence of this \textsuperscript{1}H DNMR spectrum. He reported that the broadened resonances of H-333 in the presence of 1 equivalent of acid in D\textsubscript{2}O sharpened at 70°C to a spectrum requiring average D\textsubscript{3h} symmetry[2.26 (quin.,6H), 3.39 (t,12H), 4.65 (s,1H)]. These observations are consistent with the process depicted in scheme 1. Our results are in agreement with Wuest's proposed process.

![Scheme 1](image)

Wuest could not tell whether the open or the closed form of H-333 was the dominant form from his \textsuperscript{1}H experiment\textsuperscript{104}. We endeavored to answer this question by a variable temperature \textsuperscript{13}C DNMR experiment. The carbon DNMR of H-333 plus 1 equivalent of DCl in methanol - d\textsubscript{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
close to the baseline at 99.8 ppm. (The DNMR data is
contained in Appendix 2.) This resonance continued to
the baseline at -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 (δ_{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 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 has reported a similar degenerate rearrangement with the monoprotonated tetracyclic tetraamine 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.

\[ \begin{array}{c}
\text{Cl} \quad \text{D} \quad \text{N} \\
\text{D} \quad \text{D} \quad \text{N} \\
\text{D} \quad \text{Cl} \quad \text{O} \\
\end{array} \]

\[ \begin{array}{c}
\text{D} \quad \text{N} \\
\text{D} \quad \text{D} \\
\text{D} \quad \text{Cl} \\
\end{array} \]

fig 2.92

The \(^1\text{H} \text{NMR (d}_2\text{O}) \) of H-222 in the presence of one equivalent of DC1 remained unchanged up to 102\(^{\circ}\) 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 \(^1\text{C} \text{DNNMR}, \) 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.
This reaction provides a very good method of monoprotecting 1,4,7-triazacyclononane. This reaction 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 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 susceptibility 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.

![Diagram of molecular structures](image)

**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 DC1 in aqueous(D$_2$O) 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.

H-333

3eq. 5eq. 7eq. 9eq. excess DCl(amb.T)

amb. -6.1°C -16.8°C -49.8°C

D NMR (2 eq DCl)

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-d₄. 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 $^{13}\text{C}$ behavior is consistent with the generalized scheme presented in fig.2.98.

\[ \text{fig 2.98} \]

This process is fast on the DMR 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 explanation of the pH dependent $^{13}\text{C}$ DMR requires consideration of the equilibrium constants for the proton transfers required for this process. The scheme presented in fig.2.98 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 \( pK_a \)'s 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 \( K_{eq} \) (and \( K_{eq} \)' 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) \( \delta_C \) (methine) of closed protonated H-333 = 96.9 ppm = \( \delta_C \) (methine) of F-333 plus 1 equivalent of acid at 65°C and 2) \( \delta_C \) (methine) of open H-333 = 158.4 ppm = \( \delta_C \) (methine) of 5-methyl-5,6-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.

![Chemical formulas and structures](image-url)
Acylation of H-333

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

\[
HC(NR_2)_3 + R'\text{Cl} \rightarrow H\text{Cl} + R'\text{NR}_2
\]

The known reactivity of acyclic orthoamides coupled with our desire to develop 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.
The IR of 120 exhibited both the carbonyl and the amidinium stretching frequencies in the \(1600 - 1700 \text{ cm}^{-1}\) region. The \(^1\text{H} \text{NMR}\) was consistent with the assigned structure. The \(^{13}\text{C} \text{NMR}\) 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 \(^{13}\text{C}\) 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 disappearance 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.

![Reaction diagram](image)

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$_2$Cl$_2$). Although 139 was not purified (due to time constraints) 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.

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\textsuperscript{126,129}) to determine the relative energies of the reasonable ground state conformations. The force field is very well parameterized for hydrocarbons\textsuperscript{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\textsuperscript{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\textsuperscript{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 effect 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.

\[ \Delta E = 3.07 \]

\[ \Delta \Delta E = 1.54 \text{ kcal/mol.} \]

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). The \( \Delta - \Delta E \) of the tricyclics would be expected to be larger than the model system because of the additional nitrogen in the orthoamides.

\[ \Delta \Delta E = 1.54 \text{ kcal/mol.} \]

MM2 calculations were performed on model compounds 2.105c and 2.105d. \( \Delta H \) was calculated to be 0.83 kcal/mol.
When $\Delta S_{\text{mix}}$ is taken into account then a value of 0.66 kcal/mol ($T = -150^\circ C$) is obtained for $\Delta C$. This value agrees quite well with the reported $\Delta C$ of 0.65 kcal/mol which has been determined by $^{13}$C NMR at $-150^\circ C$.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.

\[ \Delta H = 0.94 \text{ kcal/mol.} \]

\[ \Delta \Delta H = 0.94 \text{ kcal/mol.} \]

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 \( \Delta-\Delta E_{\text{steric}} \) (excludes the dipole term) and

\[
\begin{align*}
\text{98-HC-ttt} & \quad 24.13 \\
\text{98-HC-cct} & \quad 25.37 \\
\text{98-ttt} & \quad 36.95 \\
\text{98-cct} & \quad 37.18
\end{align*}
\]

\( \Delta\Delta E = 1.01 \text{ kcal/mol.} \)

\( \Delta-\Delta E_{\text{total}} \) (includes the dipole term) for relevant 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 \( \Delta-\Delta E_{\text{steric}} = 1.06 \text{ kcal/mol} \) and the \( \Delta-\Delta E_{\text{total}} = 0.23 \).
kcal/mol, where $\Delta - \Delta E_i = E_{i \text{c,c,t}} - E_{i \text{t,t,t}}$. 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. 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 $\text{MO}$ 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. 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 preceding 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\textsubscript{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 destabilize 96-cct are the same C-N-C angle distortions which destabilized 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 100ccct-(R2) and 100ccct-(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.2.1C9. 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 orthopropionamides. 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 93ccct(C1) 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 Ne-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 $\bar{97}cct(C_5)$ (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 principally 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 C3v symmetry whereas the cis,cis,trans conformation belongs to the Cs point group. Therefore
\(94\text{cct}\) should have an entropic advantage over \(94\text{ttt}\). The trivial entropy difference between these two conformations (as calculated by equation 2.4) amounts to 2.18 eu. At room temperature this amounts to a 0.65 kcal/mol entropic advantage for \(94\text{cct}\). Note that in this case the additional energy difference does not change the assignment of \(94\text{ttt}\) as the minimum energy conformation. Another consideration is that the anomeric effect should also favor \(94\text{cct}\). But since \(\Delta H = 2.2\) kcal/mol it is concluded that the assignment of \(94\text{ttt}\) as the lowest energy ground state conformation is reasonable.

333 Orthoacetamides. The calculated (all-chair) conformations of \(\text{Me-333}\) 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 \(98\text{cct}\) and \(98\text{ttt}\). First, if the trivial entropy advantage, in favor of the less symmetrical \(98\text{cct}\), is added to the calculated enthalpy then \(98\text{cct}\) is assigned as the minimum energy conformation at room temperature. Secondly, the anomeric effect (which should also favor \(98\text{cct}\)) might further favor \(98\text{cct}\) to the point of predominance. The spectral evidence clearly indicates that \(98\text{ttt}\) is the major conformation. It must therefore be concluded that the calculated energy difference between \(98\text{ttt}\) and \(98\text{cct}\) 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(C₆) (the minimum energy conformation). The assignment of 101cct(C₆) is no doubt correct. 101lltt and 101cct(C₄) are destabilized by interactions between the ethyl group and the axial hydrogens on the rings. The additional energy of 101lltt 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 $He_{333}$) 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.
### 222 Ring System

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>91-ccc</th>
<th>92-ccc</th>
<th>99-ccc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>1.0426</td>
<td>1.2333</td>
<td>1.4062</td>
</tr>
<tr>
<td>Bending</td>
<td>8.1747</td>
<td>8.1777</td>
<td>8.4071</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>-0.1743</td>
<td>-0.1902</td>
<td>-0.1440</td>
</tr>
<tr>
<td>VanderWaals</td>
<td>1.4</td>
<td>6.3447</td>
<td>7.1661</td>
</tr>
<tr>
<td></td>
<td>other</td>
<td>-1.4499</td>
<td>-2.6531</td>
</tr>
<tr>
<td>Torsional</td>
<td>17.5776</td>
<td>22.0196</td>
<td>23.2139</td>
</tr>
<tr>
<td>Dipole</td>
<td>6.5136</td>
<td>6.5280</td>
<td>6.5277</td>
</tr>
<tr>
<td>Total Energy</td>
<td>38.0500</td>
<td>42.2809</td>
<td>44.1977</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>31.4968</td>
<td>35.7529</td>
<td>37.6700</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>1.607</td>
<td>1.596</td>
<td>1.590</td>
</tr>
</tbody>
</table>

fig 2.1065
### Orthoformamides

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>92-ccc</th>
<th>92-cct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>1.2183</td>
<td>1.2849</td>
</tr>
<tr>
<td>Bending</td>
<td>10.8896</td>
<td>13.1406</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>0.1416</td>
<td>0.0272</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4</td>
<td>8.2072</td>
<td>9.4110</td>
</tr>
<tr>
<td>other</td>
<td>-1.8911</td>
<td>-2.3841</td>
</tr>
<tr>
<td>Torsional</td>
<td>14.2862</td>
<td>13.5108</td>
</tr>
<tr>
<td>Dipole</td>
<td>6.5139</td>
<td>5.8050</td>
</tr>
<tr>
<td>Total Energy</td>
<td>39.4287</td>
<td>40.7953</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>32.9118</td>
<td>34.9903</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>1.728</td>
<td>1.105</td>
</tr>
</tbody>
</table>

*fig 2.107*
322 Orthoacetamides

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>96-occ</th>
<th>96-act</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>1.5433</td>
<td>1.5740</td>
</tr>
<tr>
<td>Bending</td>
<td>10.9567</td>
<td>14.0062</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>0.1507</td>
<td>0.1164</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4</td>
<td>9.1181</td>
<td>9.7697</td>
</tr>
<tr>
<td>other</td>
<td>-2.9453</td>
<td>-2.1896</td>
</tr>
<tr>
<td>Torsional</td>
<td>17.8711</td>
<td>17.1702</td>
</tr>
<tr>
<td>Dipole</td>
<td>6.5053</td>
<td>5.7647</td>
</tr>
<tr>
<td>Total Energy</td>
<td>43.1999</td>
<td>46.2143</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>36.6946</td>
<td>40.4496</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>1.717</td>
<td>1.149</td>
</tr>
</tbody>
</table>

fig 2.1075
322 Orthopropionamides

<table>
<thead>
<tr>
<th></th>
<th>$100$-ccc($C_1$)</th>
<th>$100$-ccc($C_2$)</th>
<th>$100$-cct($R_1$)</th>
<th>$100$-cct($R_2$)</th>
<th>$100$-cct($R_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy Factor</strong></td>
<td><strong>kcal/mol</strong></td>
<td><strong>kcal/mol</strong></td>
<td><strong>kcal/mol</strong></td>
<td><strong>kcal/mol</strong></td>
<td><strong>kcal/mol</strong></td>
</tr>
<tr>
<td>Compression</td>
<td>1.7240</td>
<td>1.9907</td>
<td>1.7434</td>
<td>1.8151</td>
<td>1.9984</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>0.2025</td>
<td>0.2552</td>
<td>0.1766</td>
<td>0.2115</td>
<td>0.2451</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1,4$</td>
<td>9.8716</td>
<td>10.0033</td>
<td>10.5202</td>
<td>10.7090</td>
<td>11.0712</td>
</tr>
<tr>
<td>other</td>
<td>-3.5243</td>
<td>-2.8690</td>
<td>-2.5839</td>
<td>-2.5942</td>
<td>-1.9689</td>
</tr>
<tr>
<td>Torsional</td>
<td>18.7986</td>
<td>20.2417</td>
<td>18.2509</td>
<td>18.9025</td>
<td>19.8653</td>
</tr>
<tr>
<td>Dipole</td>
<td>6.5077</td>
<td>6.4949</td>
<td>5.7613</td>
<td>5.7242</td>
<td>5.7195</td>
</tr>
<tr>
<td>Total Energy</td>
<td>44.8578</td>
<td>48.0746</td>
<td>48.0617</td>
<td>51.2652</td>
<td>53.7864</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>38.3501</td>
<td>41.5797</td>
<td>42.3004</td>
<td>45.5401</td>
<td>48.0669</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>1.712</td>
<td>1.710</td>
<td>1.160</td>
<td>1.125</td>
<td>1.123</td>
</tr>
</tbody>
</table>

*fig 2.108*
### 332 Orthoformamides

Energy Factor (kcal/mol) | 93-qtt | 93-ctt(C₆) | 23-ctt(C₃) |
--- | --- | --- | --- |
**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 |
### 332 Orthoacetamides

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>97-ghtt</th>
<th>97-ctt(C₅)</th>
<th>97-ctt(C₄)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>2.0448</td>
<td>1.6300</td>
<td>2.2838</td>
</tr>
<tr>
<td>Bending</td>
<td>13.0013</td>
<td>9.0558</td>
<td>8.8657</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>0.5234</td>
<td>0.4521</td>
<td>0.3770</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4</td>
<td>11.7388</td>
<td>12.0356</td>
<td>12.8801</td>
</tr>
<tr>
<td>other</td>
<td>-0.8163</td>
<td>-2.1716</td>
<td>-1.6148</td>
</tr>
<tr>
<td>Torsional</td>
<td>10.9900</td>
<td>13.1122</td>
<td>13.1027</td>
</tr>
<tr>
<td>Dipole</td>
<td>6.8639</td>
<td>5.9046</td>
<td>5.7899</td>
</tr>
<tr>
<td>Total Energy</td>
<td>44.3459</td>
<td>39.4726</td>
<td>41.6846</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>37.4820</td>
<td>33.5680</td>
<td>35.8947</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>2.166</td>
<td>1.334</td>
<td>1.262</td>
</tr>
</tbody>
</table>

**fig 2.110**
### 332 (all-trans) Orthopropionamides

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>101-ttt(C(_3))</th>
<th>101-ttt(C(_5))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>2.5278</td>
<td>2.4382</td>
</tr>
<tr>
<td>Bending</td>
<td>19.4152</td>
<td>17.9919</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>0.7983</td>
<td>0.8377</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4</td>
<td>12.7938</td>
<td>12.4074</td>
</tr>
<tr>
<td>other</td>
<td>-0.4295</td>
<td>-0.4019</td>
</tr>
<tr>
<td>Torsional</td>
<td>12.9881</td>
<td>13.1989</td>
</tr>
<tr>
<td>Dipole</td>
<td>6.9325</td>
<td>6.9237</td>
</tr>
<tr>
<td>Total Energy</td>
<td>55.0262</td>
<td>53.3960</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>48.0937</td>
<td>46.4723</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>2.164</td>
<td>2.160</td>
</tr>
</tbody>
</table>

**fig2.111**
332 (cis,cis,trans) Orthopropionamides

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>101-cct-5(C₅)</th>
<th>101-cct-5(C₆)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>1.8555</td>
<td>2.1014</td>
</tr>
<tr>
<td>Bending</td>
<td>9.4056</td>
<td>12.6487</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>0.5307</td>
<td>0.6505</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4</td>
<td>12.7797</td>
<td>13.1169</td>
</tr>
<tr>
<td>other</td>
<td>-3.0626</td>
<td>-2.2133</td>
</tr>
<tr>
<td>Torsional</td>
<td>14.0200</td>
<td>15.8264</td>
</tr>
<tr>
<td>Dipole</td>
<td>5.9006</td>
<td>5.8458</td>
</tr>
<tr>
<td>Total Energy</td>
<td>41.4295</td>
<td>47.9855</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>35.5289</td>
<td>42.1307</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>1.346</td>
<td>1.340</td>
</tr>
</tbody>
</table>
### 332 (cis,cis,trans) Orthopropionamides

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>101-cct-6R(1)</th>
<th>101-cct-6R(2)</th>
<th>101-cct-6R(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>2.5295</td>
<td>2.8807</td>
<td>2.9255</td>
</tr>
<tr>
<td>Bending</td>
<td>9.1678</td>
<td>12.2577</td>
<td>14.1487</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>0.4453</td>
<td>0.5974</td>
<td>0.5792</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4</td>
<td>13.5826</td>
<td>14.0044</td>
<td>14.2872</td>
</tr>
<tr>
<td>other</td>
<td>-2.0257</td>
<td>-1.2727</td>
<td>-1.6640</td>
</tr>
<tr>
<td>Torsional</td>
<td>14.1016</td>
<td>15.6131</td>
<td>15.6448</td>
</tr>
<tr>
<td>Dipole</td>
<td>5.7862</td>
<td>5.7473</td>
<td>5.7536</td>
</tr>
<tr>
<td>Total Energy</td>
<td>43.5875</td>
<td>49.8278</td>
<td>51.6750</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>37.8013</td>
<td>44.0805</td>
<td>45.9214</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>1.271</td>
<td>1.249</td>
<td>1.282</td>
</tr>
</tbody>
</table>

**fig 2.111**
### Orthoformamides

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

**fig 2.112**
333 Orthoacetamides

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>98-ttt</th>
<th>98-cct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>2.9044</td>
<td>3.1238</td>
</tr>
<tr>
<td>Bending</td>
<td>6.4623</td>
<td>5.6914</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>0.8392</td>
<td>0.8499</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4</td>
<td>14.5314</td>
<td>14.8750</td>
</tr>
<tr>
<td>other</td>
<td>-0.8634</td>
<td>-0.5218</td>
</tr>
<tr>
<td>Torsional</td>
<td>6.4371</td>
<td>7.3563</td>
</tr>
<tr>
<td>Dipole</td>
<td>6.6383</td>
<td>5.8041</td>
</tr>
<tr>
<td>Total Energy</td>
<td>36.9495</td>
<td>37.1760</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>30.3112</td>
<td>31.3746</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>2.172</td>
<td>1.332</td>
</tr>
</tbody>
</table>

fig 2.113
### 333 Orthopropionamides

<table>
<thead>
<tr>
<th>Energy Factor (kcal/mol)</th>
<th>102-ttt</th>
<th>102-cct(C&lt;sub&gt;3&lt;/sub&gt;)</th>
<th>102-cct(C&lt;sub&gt;5&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>15.8171</td>
<td>3.4286</td>
<td>4.2315</td>
</tr>
<tr>
<td>Bending</td>
<td>12.6498</td>
<td>6.0355</td>
<td>10.5837</td>
</tr>
<tr>
<td>Stretch-bend</td>
<td>1.1836</td>
<td>0.9348</td>
<td>1.1649</td>
</tr>
<tr>
<td>VanderWaals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4</td>
<td>15.0693</td>
<td>15.5672</td>
<td>16.4475</td>
</tr>
<tr>
<td>other</td>
<td>0.1008</td>
<td>-0.9270</td>
<td>0.2782</td>
</tr>
<tr>
<td>Torsional</td>
<td>9.1809</td>
<td>8.3476</td>
<td>9.9458</td>
</tr>
<tr>
<td>Dipole</td>
<td>6.6992</td>
<td>5.7975</td>
<td>5.7410</td>
</tr>
<tr>
<td>Total Energy</td>
<td>60.7007</td>
<td>39.1842</td>
<td>48.3924</td>
</tr>
<tr>
<td>Steric Energy</td>
<td>54.0015</td>
<td>33.3867</td>
<td>42.6514</td>
</tr>
<tr>
<td>Dipole Moment (D)</td>
<td>2.169</td>
<td>1.343</td>
<td>1.332</td>
</tr>
</tbody>
</table>

**fig 2.114**
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 la 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 (dissimilar 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 arguments 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 preceding 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.
$E_{kcal}$

1 = VanderWaal's other
2 = Stretch-Bend
3 = Compression
4 = VanderWaal's 1-4
5 = Dipole
6 = Bending
7 = Torsional
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 programmable 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$_2$Cl$_2$ 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
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\textsuperscript{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™ (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 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 generally 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 (GPC) was performed on a modified Waters 200 analytical GPC unit. A schematic of the preparative unit is found in
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 used 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.
**Preparative GPC Unit**

---

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

**PULSE DAMPENER:** LDC Model No. 709

**DIFFERENTIAL REFRACTOMETER:** Optical bench assembly from Waters GPC-200

**RECORDER:** Leeds & Northrup Co., Speedodam X (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: 350-1500 psi 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 1000 psi 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 1300 psi 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 preceding packing procedure produced a 21 ft column
with the following characteristics: 1) flow rate of 2.61
mL/min with 340 psi of backpressure and, 2) exclusion
volume of 84 mL (Carbowax M as standard).
Immediately upon installation of the column its characteristics and efficiency 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 Na₂CO₃.

**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. 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 weighed 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 \(\text{CH}_2\text{Cl}_2/\text{hexane}\). 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 \(\text{CH}_2\text{Cl}_2\) 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 \(\text{H}_2\text{O}\) (60 mL) and the solvent was evaporated to yield 3.3714 g of crude reaction solids which were recrystallized three times from \(\text{MeOH}\) to yield 0.5583 g (17.5%) of product as shiny floculent platlettes. mp 167.5°C; IR (KBr) 3250, 1305, 1070 cm\(^{-1}\); \(^1\)H 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 \(\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_4\text{S}_2\): 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 mL anhyd methylene chloride and cooled to 0°C. Phenylmethanesulfonyl chloride (2.2878 g, 12.04 mmol) was dissolved in 30 mL anhyd CH₂Cl₂ 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 H₂O (25 mL) and 5% sodium bicarbonate (25 mL), dried over Na₂SO₄, 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 (Me₂SO-ᵈ₆) 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 CH₂Cl₂ 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 CH₂Cl₂ 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 H₂O (25 mL), dried over Na₂SO₄, 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 crystalline product. mp 144-146°C (softens at 139°C); IR (KBr) 3020, 2980, 1590, 1550, 1170, 990, 785, 705 cm⁻¹. H 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. 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 H₂O 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. H 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. 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 H₂O until the wash H₂O no longer contained chloride (AgNO₃ test). Recrystallization from H₂O 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', 4H), 7.50 (AA'BB', 4H); Anal. Calcd for C₁₃H₁₅NCl₂O₄S: C, 44.36; H, 4.30; N, 3.98. Found: C, 44.85; H, 4.33; 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
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 H₂O, 50 mL of 5% aq HCl, and then with H₂O to remove 1,3-diaminopropane dihydrochloride. The resulting material was dried in vacuo to yield 0.9333 g of crude product. Recrystallization from CH₂Cl₂ 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; H 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 C₁₆H₂₃N₃[D₄S: 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 BH₃/THF (Ventron) was syringed into the reaction flask...
through a septum capped stopcock. The resulting solution was refluxed for 24 h. \( \text{H}_2\text{O} \) was then added to the cooled solution (Caution: \( \text{H}_2 \) 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 \( \text{Na}_2\text{SO}_4 \), 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\(^{-1}\); \(^1\text{H}\) 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 \( \text{H}_2\text{O}, 5\% \text{aq HCl} \), and then with \( \text{H}_2\text{O} \) until the wash \( \text{H}_2\text{O} \) no longer contained chloride (\( \text{AgNO}_3 \) 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-E).

\[ \text{N,N',N''-tri-p-toluenesulfonyl-1,5,9-triazanonane (141)} \]

\( 141 \) was prepared by the method of Koyama \( ^{204} \) whereby \( 1,5,9\)-triazanonane \( (99.09 \text{ g, 0.7551 mol}) \) and \( \text{NaOH} \) \( (90.62 \text{ g, 2.26 mol}) \) were dissolved in 560 mL of \( \text{H}_2\text{O} \) with cooling under a reflux condenser. \( \text{p-Toluenesulfonylchloride} \) \( (451.93 \text{ g, 2.3707 mol}) \) 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 \( \text{H}_2\text{O} \) layers were decanted from the heavy yellow oil. The oil was dissolved in 1 L of \( \text{CH}_2\text{Cl}_2 \) and washed with \( \text{H}_2\text{O} \) \( (4x250 \text{ mL}) \) followed by saturated \( \text{NaCl} \) \( (2x300 \text{ mL}) \). The \( \text{CH}_2\text{Cl}_2 \) phase was dried over \( \text{Na}_2\text{SO}_4 \), 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 \( \text{(CDC}_3\text{)} \) : 1.67 (t, 4H), 2.35 (s, 9H), 2.35-3.32 (brm, 6H), 5.61 (t, 2H), 7.00-7.90 (m, 12H).

\[ \text{N,N',N''-tri-p-toluenesulfonyl-1,5,9-triazanonane-1,9-disodium salt (142)} \]

\( 142 \) 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$_2$SO-δ$_6$) 1.46 (brm, 4H), 2.32 (s, 3H), 3.11 (brm, 8H), 6.95-7.81 (m, 12H).

$\text{N,NN',N''-tri-p-toluenesulfonyle-1,5,9-triazacyclododecane}$ (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$_2$Cl$_2$/hexane yielded crystalline product: mp 173-175°C (lit.$^{205}$ 173°C).

$\text{1,5,9-triazacyclododecane(153)}$. 153 was prepared after the method of Raymond$^{60a}$. 149 (5.5356 g, 8.7347 mmol) and 30 mL of 98% H$_2$SO$_4$ 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 H₂O (directly on the filter frit). The resulting aq solution was adjusted to pH 10 (concd NaOH, 0°C) and extracted with CHCl₃ (6X20 mL). The combined extracts were dried over Na₂SO₄, 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 (CDCl₃) 1.62 (quintet, 6H), 1.66 (s, 6H), 2.75 (t, 12H); mass spectrum, m/z (rel intensity) 171 (100). The trihydrobromide of 153 has been previously reported

N,N-dimethylpropionamide dimethylacetal (127). 127 was prepared in 19.6% yield by the method of Bredereck. The crude material which was synthesized by the method of Bredereck was purified 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°C (11 mm) lit., bp 30°C (1 mm); All spectral data was consistent with published data.

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. Recrystallization from CH₂Cl₂/hexane yielded crystalline material which was used in subsequent reactions without further purification. mp 205-209°C (lit. mp 222-223°C).

1,4,7-triazacyclononane (150). 150 was prepared in 82% yield from 146 by a procedure modeled after Raymond's procedure (see 153 for detailed experimental) for the preparation of tetraamines: bp ca.85°C (12 mm); ¹H NMR (CDCl₃) 2.14 (s, 3H), 2.78 (s, 12H). The material was used in subsequent reactions without further purification. The trihydrobromide of 150 has been previously reported.

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. Recrystallization from CH₂Cl₂/hexane yielded pure material: mp 233-235°C (lit. mp 234-236°C).

1,4,7-triazacyclodecane (151). 151 was prepared in 66% yield from 147 by a procedure modeled after Raymond's procedure (see 153 for detailed experimental) for the preparation of tetraamines: bp ca.88°C (12 mm); ¹H NMR (CDCl₃) 1.60 (quintet, 2¹H), 2.48-3.13 (m, 15¹H). The material was used in subsequent reactions without further purification. The trihydrobromides of 151 has been previously reported.
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. Recrystallization of the crude product from CH₂Cl₂/hexane yielded crystalline material which was used in subsequent reactions without further purification: mp 209-213°C (lit. mp 213°C).

1,4,8-triazacycloundecane (152). 152 was prepared from 148 in 75% yield by a procedure modeled after Raymond's procedure (see 153 for a detailed experimental) for the preparation of tetraamines. bp ca. 90°C (12 mm); ¹H NMR (CDCl₃) 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.

N,N',N''-tri-p-toluenesulfonyl-1,4,7-triazaheptane (140); was prepared in 97% yield by a published procedure mp 162-167°C (lit. mp 173°C); ¹H NMR (CDCl₃) 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 (See 142 for detailed procedure.): mp 260°C (decomp); ¹H NMR (Me₂SO-d₆) 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. mp 126-128°C (lit. 126°C; 1H NMR (CDCl₃) 2.43 (s, 6H), 4.18 (s, 4H), 7.16-7.90 (AA'BB', 8H).

1,5,9,13-tetraazatricyclo[11.3.1.1⁵,₉]octadecane (54).

1,5,9,13-tetraazacyclohexadecane (36) (173.3 mg, 0.7587 mmol) was suspended in 150 mL of CH₃CN. 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 crystalline 54. mp 78-80°C; IR (CCl₄) 2970, 2930, 2870, 2850, 2750, 2690, 1225, 1125, 1100 cm⁻¹; 1H NMR (CDCl₃) 1.26 (brm, 2H), 1.55 (quintet, 8H), 2.29-3.60 (2 brm, 16H), 3.83 (brm, 2H); 13C NMR (CDCl₃) 21.56 (t), 24.49 (t), 49.46 (t), 55.04 (t), 67.88 (t); Anal. Calcd for C₁₄H₂₈N₄: 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[7.7.2.0⁵,₁₃.0₁₃,₁₈]octadecane (52). 1,5,9,13-tetraazacyclohexadecane (36) (98.6 mg, 0.4317 mmol) was suspended in 30 mL of CH₃CN. Sufficient H₂O was added to dissolve the amine. 0.10 mL of 40% aq glyoxal (ca. 0.686 mmol) was dissolved in 20 mL of CH₃CN 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 (CCl₄) 2910, 2830, 2750, 1130, 1125, 1105, cm⁻¹;¹³C NMR (CDCl₃) 20.05(d), 22.05(t), 51.8(t), 55.48(t), 84.57(d); Anal. Calcd for C₁₄H₂₆N₄: 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 20°C for 48 h to yield 48.17 g (56%) of white crystalline solid. mp 240°C (decomp). 1H NMR (Me2SO-d6) 1.50 (brm, 6H), 2.28 (s, 6H), 2.38 (s, 6H), 2.23 (brm, 12H), 6.20-7.80 (m, 16H). The material was used in subsequent reactions without further purification.

1,3-propanediol-di-p-toulene sulfonate (34). 34 was prepared in 73% yield by a published procedure. mp 91.5-93°C (lit. mp 91-92°C).

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. mp 250-255°C (decomp) (lit. 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. mp 83-85°C.
Attempted Syntheses of 1,5,9,13-tetraazatetracyclo[7.7.3.0²,0².0¹,0¹]nonadecane (37). Method A: 1,5,9,13-tetraazacyclohexadecane (51.1 mg, 0.2237 mmol) was dissolved in 25 mL of CH₃CN. 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 CHCl₃ (15x10 mL). The combined extracts were dried over Na₂SO₄, 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 pH 4 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 crystalline material. The $^1$H NMR remained unchanged. TLC on neutral alumina (EtOH) indicated two spots.

N-p-toluenesulfonyl-2,2'-iminodiethanol-1,5-di-p-toluenesulfonate (144). Diethanolamine (20.00 g, 0.190 mol) was
dissolved in 180 mL of anhyd pyridine and cooled to -6°c.
P-toluenesulfonylchloride (103.78 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 CH₂Cl₂ (3x250 mL). The combined extracts
were washed with ice cold 10% aq HCl(5X100
mL)(CAUTION:Exothermic. Vent separatory funnel
frequently.), then with ice H₂O until the smell of
pyridine could no longer be detected in the wash H₂O, and
then with brine (250 mL). The CH₂Cl₂ solution was then
dried over Na₂SO₄, filtered, and the solvent was
evaporated at reduced pressure at room temperature 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; 1H NMR (CDCl₃) 2.40(s, 3H),
2.42(s, 6H), 3.32(t, 4H), 4.10(t, 4H), 7.00-7.50(m, 12H).
The material was used in subsequent reactions without
further purification.
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 CH₂Cl₂ and filtered to remove sodium tosylate. The solution was then dried over Na₂SO₄, filtered, and the solvent was evaporated at reduced pressure to yield solid crystalline product which was recrystallized from CHCl₃/ EtOH: mp 228-232°C (lit. 205. mp 234-236°C);¹H NMR (CDCl₃) 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 CHCl₃ (10x10 mL). The combined extracts were then dried over Na₂SO₄, 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 \textit{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\textsubscript{4}) 2960, 2930, 2910, 2870, 2830, 1235, 1150, 1105, 1060, 1030 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) 2.50-3.35 (AA'BB', 12H), 5.03 (s, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{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: bp ca. 82°C (2.5 mm); IR (CCl\textsubscript{4}) 2938, 2879, 2660, 2600, 1270, 1255, 1175, 1155 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) 1.05 (d of t of t, J=13, 3, 3 Hz, 1H), 2.35-3.35 (m, 12H), 4.32 (s, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{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 (CCl₄) 2930, 2850, 2770, 2730, 1260, 1145, 915 cm⁻¹; ¹H NMR (CDCl₃) 1.10-3.40(m); ¹³C NMR (CDCl₃) 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[7.3.1.0⁵,₁³]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 (CCl₄) 2939, 2919, 2840, 2800, 2795, 2740, 2700, 2670, 2600, 2580, 2495, 2430, 2400, 1290, 1165, 1135, 1125, 1100, 1035, 915 cm⁻¹; ¹H NMR (Me₂CO-d₆) 1.22-1.49(m, 3H), 1.58-2.22(m, 9H), 2.25(s, 1H, methine), 2.61-2.90(m, 16H); ¹³C NMR (Me₂CO-d₆) 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 (CCl₄) 2970, 2930, 2880, 2840, 1490, 1470, 1440, 1410, 1330, 1279, 1210, 1170, 1125, 1095, 1050, 1000, 885 cm⁻¹; ¹H NMR (CDCl₃) 1.34 (s, 3H), 2.50-3.32 (AA'BB*, 12H); ¹³(CDCl₃) 27.7(q), 51.8(t), 111.4(s); mass spectral peak match calcd for C₈H₁₂N₃ 153.12659; found 153.12734 (error = -0.9 ppm); calcd for C₇H₁₂N₃ 138.10312; found 138.10219 (error = -0.1 ppm).

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 (CCl₄) 2979, 2939, 2905, 2880, 2860, 2820, 1370, 1360, 1345, 1332, 1320, 1170 cm⁻¹; ¹H NMR (CDCl₃) 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(CDCl₃) 13.06 (t), 23.8 (q), 44.6 (t), 51.7 (t), 54.9 (t), 94.7 (s); mass spectral peak match calcd for C₉H₁₇N₃ 167.14224; found 167.14115 (error = 6.5 ppm); calcd for C₈H₁₄N₃ 152.11877; found 152.12001 (error = -8.2 ppm).
12-methyl-1,4,8-triazatricyclo[6.3.1.0^2^8]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): bp ca. 87°C (2.5 mm) IR (CCl₄) 2940, 2860, 2800, 2750, 2730, 1425, 1270, 1255, 1215, 1205, 1095 cm⁻¹; ¹H NMR (CDCl₃) 1.10 (d of t of t, 2H), 1.32 (s, 3H), 1.89-3.39 (m, 12H); ¹³C NMR (CDCl₃) 10.0 (q), 20.1 (t), 43.7 (t), 45.6 (t), 49.4 (t), 86.9 (s); mass spectral peak match calcd for C₁₀H₂⁹N₃ 181.1579; found 181.1560 (error = 1.04 ppm).

13-methyl-1,5,9-triazatricyclo[7.3.1.0^3^3]tridecane (98).

98 was prepared from 153 according to the above described procedure and was purified by column chromatography (basic alumina, 5% EtOH/CH₂Cl₂, v/v) to yield 98 as a clear oil: IR (CCl₄) 2905, 2880, 2840, 2760, 2740, 2700, 2640, 2620, 1405, 1370, 1275, 1255, 1185, 1115, 1095, 1085, 1065, 1050, 1005 cm⁻¹; ¹H NMR (CDCl₃) 1.01 (3, 3H), 1.41 (d of t of t, 3H), 1.80-2.72 (m, 15H); ¹³C(CDCl₃) -4.01 (g), 24.6 (t), 49.0 (t), 86.0 (s); mass spectral peak match calcd for C₁₀H₁⁸N₃ 180.15007; found 180.152355 (error = -1.26 ppm).

Orthopropionamides (99-102). 99-102 were prepared according to the following procedure: Macrocyclic triamine (0.5 mmol) and N,N-dimethylpropionamide dimethylacetel (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, 85 EtOH/CH$_2$Cl$_2$, v/v) to yield 130 as a clear oil: bp ca. 75° (2.5 mm); IR (CCl$_4$) 2962, 2936, 2878, 2835, 1450, 1269, 1250, 1000 cm$^{-1}$; $^1$H 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$_9$H$_{17}$N$_3$ 167.14224; found 167.14336 (error = -6.7 ppm); Calcd for C$_7$H$_{12}$N$_3$ 138.10312; found 138.10238 (error = 5.4 ppm).

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: bp ca. 75°C (0.5 mm); I.R. (CCl$_4$) 2965, 2930, 2878, 2950, 2810, 1355, 1345, 1280, 1160, 735 cm$^{-1}$; $^1$H 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=-1.0 ppm); Calcd for \( C_8H_{14}N_3 \) 152.11877; found 152.11851 (error=1.7 ppm).

12-ethyl-1,5,9-triazatricyclo[6.3.1.0^6,12]tetradecane (101).

101 was prepared in 82% yield from 152 by the above described procedure and was purified by kugelrohr distillation: bp ca. 80°C (0.5 mm); IR (CCl₄) 2950, 2870, 2810, 2760, 2740, 2680, 2650, 1498, 1472, 1440, 1380, 1365, 1355, 1340, 1305, 1290, 1272, 1200, 1100 cm⁻¹; \(^1\)H NMR (CDCl₃) 0.80 (t, 3H), 0.90-3.39 (m, 18H); \(^{13}\)C NMR (CDCl₃) 7.4 (q), 11.4 (t), 19.8 (t), 43.3 (t), 45.6 (t), 48.9 (t), 68.6 (s); mass spectral peak match calcd for \( C_{11}H_{21}N_3 \) 195.1754; found 195.17219 (error=6.9 ppm); Calcd for \( C_9H_{16}N_3 \) 166.13442; found 166.13482 (error=-2.4 ppm).

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/CH₂Cl₂, v/v) to yield 102 as a white crystalline solid: mp 41-43°C; IR (CCl₄) 2950, 2939, 2930, 2910, 1350, 1285, 1065 cm⁻¹; \(^1\)H NMR (Me₂CO-d₆) 0.80 (t, 3H), 1.11-2.13 (m, 8H), 2.70-2.83 (AA'BB', 12H); \(^{13}\)C NMR (Me₂CO-d₆) 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 = 2.6 ppm); Calcd for C_{10}H_{18}N_{3} 180.15007; found 180.15155 (error = -0.2 ppm).

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 CHCl₃ 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, 1189, 1120, 1040 cm⁻¹; ¹H NMR (CDCl₃, 60 MHz) 1.15-3.80 (m, 19H), 4.00-4.75 (d of t, 2H), 9.28 (s, 1H); ¹³C NMR (CDCl₃, 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_{3}I: 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 N₂. The reaction mixture was extracted with CHCl₃ (10 X 10 mL). The combined extracts were then dried over Na₂SO₄, filtered, and the solvent was evaporated under reduced pressure to yield a yellow oil. Kugelrohr distillation (80°C (2.5 mm)) followed by sublimation (45°C (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\(_3\)I: 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 stoppered 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 N₂. 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°C (decomp); IR (KBr) 2950, 2940, 2930, 2800, 1602.3, 1350, 1270, 1260, 1187, 1065, cm⁻¹; ¹H NMR (CDCl₃, 60 MHz) 0.95(t, 2H), 1.18-3.85(m, 22H), 4.20-4.85(d of t, 2H); ¹³C NMR (CDCl₃, 90 MHz) 14.4, 20.0, 23.9, 25.8, 42.8, 46.7, 50.8, 54.3, 175.5; Anal. calcd for C₁₃H₂₆N₃I: C, 44.45; H, 7.46; N, 11.96. Found: C, 44.50; H, 7.67; N, 11.69.

1-formyl-1,4,7-triazacyclononane(138). 91 (83.8 mg, 0.6029 mmol) was dissolved in 0.5 mL of D₂O. 0.22 mL of 5.5657 N DCl/D₂O 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 CHCl₃ (10 x 15 mL). The combined extracts were dried over Na₂SO₄, filtered, and the CHCl₃ 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 (CCl₄) 2920, 2850, 1676; ¹H NMR (CDCl₃, 90 MHz) 1.60(s, 2H), 2.75(s, 4H), 2.99-3.51 (m, 8H), 8.15(s, 1H); ¹³C NMR (CDCl₃, 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 C₇H₁₅N₃O 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 Synthesis 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 N₂. The solvent was then evaporated under reduced pressure to yield a white hygroscopic crystalline solid. The intermediate product was dissolved in 5 mL of D₂O. 0.2 mL of 40% NaOD in D₂O 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 CHCl₃ (10 X 10 mL), the combined extracts were dried over Na₂SO₄, filtered, and the solvent was evaporated under reduced pressure to yield 179.1 mg of a yellow oil. Column chromatography (basic alumina, 5% EtOH/CH₂Cl₂, 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
CH₂Cl₂/hexane without success. ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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
APPENDIX 2: $^{13}$C Chemical Shifts of the Orthoamides

DNMR: ORTHOFORMAMIDES

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Temp(°C)</th>
<th>N-C-H-N</th>
<th>CH$_2$N</th>
<th>CH$_2$-CH$_2$-CH$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>CDCl$_3$</td>
<td>29</td>
<td>104.1</td>
<td>52.0</td>
<td>60.0</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-100</td>
<td>103.6</td>
<td>51.0</td>
<td>60.0</td>
</tr>
<tr>
<td>92</td>
<td>Acetone$_d6$</td>
<td>29</td>
<td>94.1</td>
<td>56.7, 49.5</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-66.3</td>
<td>92.5</td>
<td>56.6, 49.6</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-100</td>
<td>91.9</td>
<td>56.6, 49.7</td>
<td>14.6</td>
</tr>
<tr>
<td>93</td>
<td>Acetone$_d6$</td>
<td>29</td>
<td>96.2</td>
<td>52.4, 48.9</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-39.1</td>
<td>96.2</td>
<td>52.3, 48.6</td>
<td>23.0</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-66.3</td>
<td>96.2(sbr)</td>
<td>52.3(sbr)</td>
<td>22.9(sbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-87.0</td>
<td>96.2(br)</td>
<td>52.4(br)</td>
<td>22.8(br)</td>
</tr>
</tbody>
</table>

(sbr): slightly broad
(br): broad
(vbr): very broad
<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>N-CH-N</th>
<th>CH$_2$-N</th>
<th>CH$_2$-CH$_2$-CH$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>93</td>
<td>Acetone$_d6$</td>
<td>-100</td>
<td>96.4(vbr)</td>
<td>52.4(vbr)</td>
<td>22.8(vbr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48.4(vbr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>47.3(vbr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-104</td>
<td></td>
<td>52.3(vbr)</td>
<td>22.2(vbr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48.1(vbr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>47.2(vbr)</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>CDCl$_3$</td>
<td>29</td>
<td>100.0</td>
<td>53.9</td>
<td>24.2</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-64</td>
<td>100.4</td>
<td>53.9</td>
<td>23.9</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>29</td>
<td>101.3</td>
<td>54.6</td>
<td>24.9</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-100</td>
<td>101.0</td>
<td>54.1</td>
<td>24.2</td>
</tr>
<tr>
<td>Compound</td>
<td>Solvent</td>
<td>Temp(°C)</td>
<td>N-C(Me)-N</td>
<td>CH$_2$-N</td>
<td>CH$_2$CH$_2$CH$_2$</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>----------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------------</td>
</tr>
<tr>
<td>97</td>
<td>CDC$_3$</td>
<td>29</td>
<td>86.9</td>
<td>49.4, 45.6</td>
<td>20.1</td>
</tr>
<tr>
<td></td>
<td>Acetone$_{d6}$</td>
<td>-100</td>
<td>87.3</td>
<td>49.6, 45.6</td>
<td>20.2</td>
</tr>
<tr>
<td>98</td>
<td>CDC$_3$</td>
<td>29</td>
<td>86.0</td>
<td>49.0</td>
<td>24.6</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>3.82</td>
<td>85.9</td>
<td>48.9</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-29.2</td>
<td>85.9</td>
<td>48.8</td>
<td>24.4</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-44.8</td>
<td>85.9</td>
<td>48.9(br)</td>
<td>24.5(vbr)</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-55.5</td>
<td>85.8</td>
<td>48.8(br)</td>
<td>24.7(vbr)</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-67.1</td>
<td>85.9</td>
<td>48.7(sbr)</td>
<td>24.7(sbr)</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-29.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-39.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-44.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD$_3$CN</td>
<td>29</td>
<td>87.1</td>
<td>49.7</td>
<td>25.1</td>
<td></td>
</tr>
<tr>
<td>CD$_3$CN</td>
<td>3.82</td>
<td>87.0</td>
<td>49.5</td>
<td>25.1</td>
<td></td>
</tr>
<tr>
<td>CD$_3$CN</td>
<td>-13.5</td>
<td>87.0</td>
<td>49.5</td>
<td>25.1</td>
<td></td>
</tr>
<tr>
<td>CD$_3$CN</td>
<td>-29.2</td>
<td>vbr</td>
<td>49.4(sbr)</td>
<td>25.0(sbr)</td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Solvent</td>
<td>Temp(°C)</td>
<td>N-CH(CH₃)-N</td>
<td>CH₂-N</td>
<td>CH₂-CH₂-CH₂</td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>-------------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>98</td>
<td>Acetone₆</td>
<td>50.0</td>
<td>86.4</td>
<td>48.7</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>29</td>
<td>86.4</td>
<td>49.5</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>9.6</td>
<td>86.4</td>
<td>49.5</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>2.2</td>
<td>86.4</td>
<td>49.4</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-9.3</td>
<td>86.5</td>
<td>49.4</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-11.0</td>
<td>86.5</td>
<td>49.4</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-35.8</td>
<td>86.6</td>
<td>49.2(sbr)</td>
<td>24.5(sbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-43.9</td>
<td>86.6</td>
<td>49.2(sbr)</td>
<td>24.6(sbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-49.8</td>
<td>86.6</td>
<td>49.2(br)</td>
<td>24.8(vbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-56.4</td>
<td>86.7(sbr)</td>
<td>49.4(vbr)</td>
<td>24.9(vbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-63.0</td>
<td>86.8(sbr)</td>
<td>49.1(vbr)</td>
<td>24.9(vbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-67.9</td>
<td>86.9(sbr)</td>
<td>49.1(vbr)</td>
<td>24.9(vbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-82.0</td>
<td>86.9</td>
<td>49.1(vbr)</td>
<td>24.8(vbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-90.0</td>
<td>86.9</td>
<td>49.0(vbr)</td>
<td>24.7(vbr)</td>
</tr>
<tr>
<td></td>
<td>Acetone₆</td>
<td>-100</td>
<td>86.9</td>
<td>49.0(vbr)</td>
<td>24.7(vbr)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>$^N\text{N-C(CH}_2\text{-N)}$</th>
<th>$\text{CH}_2\text{-N}$</th>
<th>$\text{CH}_2\text{-CH}_2\text{-CH}_2$</th>
<th>$\text{CH}_2\text{-CH}_3$</th>
<th>$\text{CH}_2\text{CH}_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>CDCl$_3$</td>
<td>29</td>
<td>88.8</td>
<td>48.9, 45.6</td>
<td>19.8</td>
<td>11.4</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>-60</td>
<td>88.8</td>
<td>48.9, 45.6</td>
<td>19.8</td>
<td>11.4</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>29</td>
<td>89.2</td>
<td>49.6, 46.3</td>
<td>20.6</td>
<td>11.8</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-50</td>
<td>88.9</td>
<td>49.2, 45.8</td>
<td>20.2</td>
<td>11.5</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-70</td>
<td>88.8</td>
<td>49.1, 45.7</td>
<td>19.9</td>
<td>11.4</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-90</td>
<td>88.8</td>
<td>49.1, 45.6</td>
<td>19.8</td>
<td>11.5</td>
<td>8.3</td>
</tr>
<tr>
<td>102</td>
<td>Acetone$_d6$</td>
<td>29</td>
<td>87.1</td>
<td>49.1</td>
<td>22.3</td>
<td>13.0</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-14.3</td>
<td>86.7</td>
<td>48.9 (br)</td>
<td>22.2 (br)</td>
<td>12.9</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-20.9</td>
<td>86.7</td>
<td>48.8 (br)</td>
<td>21.5 (br)</td>
<td>12.9</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-27.1</td>
<td>86.6</td>
<td>48.8 (vbr)</td>
<td>ca. 20.3 (vbr)</td>
<td>12.9</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-30.0</td>
<td>86.7</td>
<td>48.7 (vbr)</td>
<td>ca. 20.1 (vbr)</td>
<td>12.9</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Acetone$_d6$</td>
<td>-37.1</td>
<td>86.6</td>
<td>48.7 (vbr)</td>
<td>ca. 26.3 (vbr)</td>
<td>12.9</td>
<td>8.0</td>
</tr>
</tbody>
</table>

1: beginning to split into three peaks but still lumped together
DNMR: ORTHOPROPIONAMIDES cont.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Temp(°C)</th>
<th>N-C(CH₂)-N</th>
<th>CH₂-N</th>
<th>CH₂-CH₂-CH₂</th>
<th>CH₂-CH₃</th>
<th>CH₂-CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>Acetone d6</td>
<td>-39.5</td>
<td>86.6</td>
<td>ca. 50.8(vbr)²</td>
<td>ca. 26.2(vbr)</td>
<td>12.9</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Acetone d6</td>
<td>-39.9</td>
<td>86.6</td>
<td>broad lump</td>
<td>26.5(vbr)</td>
<td>12.9</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>Acetone d6</td>
<td>-41.9</td>
<td>86.6</td>
<td>51.0(br)</td>
<td>26.3(vbr)</td>
<td>12.9</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48.3(br)</td>
<td>19.8(vbr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46.6(br)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetone d6</td>
<td>-52.2</td>
<td>86.5</td>
<td>51.0(br)</td>
<td>26.4(sbr)</td>
<td>12.9</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48.4(br)</td>
<td>19.6(sbr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46.6(br)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetone d6</td>
<td>-80.3</td>
<td>86.5</td>
<td>51.0,48.4</td>
<td>26.3,19.6</td>
<td>12.9</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

² A third shoulder was visible
Appendix 3: Potentiometric Titrations

\[ \frac{H}{O} \]

ml. 0.1024 M HCl
H-333

ml. 0.1024M HCl

pH

211
REFERENCES


15. ibid, 1970, 92, 2151.

17. ibid, 1974, 96, 2941.


42. ibid, v.2, John Wiley and Sons, NY, 1981.


45a. C. A. Bischoff, Ber., 1898, 31, 3248.


49i. R. W. Alder, personal communication.


86. W. Stilz, German Patent, 1161285 (1964); Chem. Abstr., 1964, 60, 9156.


110a. M. Wiewiorowski, O. E. Edwards, and M. D. Pratek -


114. ibid, pp.34-39.


129. ibid, QCPE, 1981, 13, 395.


133. ibid, 1980, 181.


140a. V. M. S. Gil and A. C. P. Alives, Molecular Physics, 1969, 16, 527.

b. V. M. S. Gil and A. J. L. Pinto, ibid, 1970, 10, 573.


g. G. V. Binst and D. Tourwe, Heterocycles, 1973, 1, 257.


167. G. R. Weisman, private communication.


182. M. B. Coolidge, private communication.

183. see reference 77


189. ibid, 1978, 100, 7031.


196. G. R. Weisman and V. B. Johnson unpublished results


