

Electrostatic Forces in Aqueous Media and the Nature of the Cation- π Interaction

Thesis by
Sandro Mecozzi

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

California Institute of Technology
Pasadena, California

1997
(Submitted June 20, 1996)

© 1997

Sandro Mecozzi

All Rights Reserved

A Silvia con amore infinito

Acknowledgments

My graduate career at Caltech has been enriched in many different ways by the assistance, the suggestions and the advice provided by many people.

Six years ago, I was lucky enough to be accepted in the Dougherty group. In this group I found many friends and an extremely stimulating scientific environment. I will always remember our group meetings where theoretical physics could easily mix with the last techniques of molecular biology and where any question, I would say any thought, as weird it could be, always found a prompt answer. However, above all, in this group I found Dennis Dougherty. He has not only been a superb research advisor, but I would say, in many instances he has been a friend. When the times were difficult he was always there to help, and it is especially because of his constant encouragement, advice and tolerance that I have been able to grow during my permanence at Caltech. He always left me free to try new experiments, and I cannot remember of just one time when he did not answer my persistent and at times, I now realize, annoying questions. I could not have hoped for a better mentor.

I also enjoyed very much the large number of scientific seminars I have been exposed to. The theoretical series seminars gave me some moments to relax and between a superstring and an Hamiltonian, I was enormously

stimulated by the organic chemistry, the physical chemistry, and the biochemistry seminars. I greatly appreciated to be able to learn science directly from the people that made it.

I need to thank the members of my committee, Dr. Barbara Imperiali, Dr. Harry Gray and Dr. Erik Carreira for their support and suggestions during these years. I especially thank Harry Gray for cheering me up on many occasions with his contagious optimism and enthusiasm. During our conversations he always surprised me with Italian words pronounced in perfect Italian accent.

Many people deserve a mention for having helped me. I know that this list cannot be exhaustive and I apologize to anyone I could have unintentionally left out. Anthony West, Jr. has been my computational buddy. His enthusiasm for calculations is contagious. His patience with my endless questions is greatly appreciated. I consider myself very lucky to be his friend. Pat Kearney and Laura Mizoue introduced me to the chemistry of cyclophanes and helped me very much when I joined the group. They also deserve a special mention together with Wenge Zhong and Jennifer Ma for having made room 249 an oasis of peace. Dave Schultz, Leslie Jimenez, and Joshua Jacobs were always prodigal of suggestions for my chemistry.

Michael Murray always brought a note of enthusiasm in the lab and the nights shared with him in the computer room, writing our theses, were full of fun. Rich Barrans and Jon Forman deserve credit for having developed the statistical treatment used in the calculation of binding constants from NMR and CD data. I have to say that any other past or present member of the Dougherty group left an impression on me. Many thanks also go to Silvia Cavagnero, Dennis Dougherty, Justin Gallivan, Jennifer Ma, Anthony West, Jr., Seth Miller and Jeff Clites for proofreading the initial draft or parts of this thesis. All remaining errors are solely the responsibility of the author.

I leave the molecular recognition project in the increasingly able hands of Jennifer Ma and Sarah Ngola and I know that they will keep the torch high. Finally, I thank Silvia Cavagnero for her love and for sharing her life with me. I cannot possibly imagine life without her. My last thought is for little Cecilia. During the writing of this thesis she found many shortcuts on the keyboard to erase a whole paragraph or a whole chapter with only one strike. I am glad she never used her power against me. Instead, she gave me the most precious of all gifts: her smile.

Abstract

The forces responsible for the molecular recognition of organic compounds in aqueous media are mainly hydrophobic and electrostatic forces. It has been known for some time that water-solvated positively charged organic compounds, such as *N*-methylquinolinium and adamantyl trimethylammonium, are bound by cyclophane receptors, in aqueous media, more strongly than neutral organic molecules. The origin of this interaction can be found in the attraction between the cation and the electron-rich face of the aromatics in the host. This intermolecular force has been called the cation- π interaction. We report our findings on the nature of this interaction. We performed a series of high level *ab initio* computational studies on the binding of the sodium cation to the π face of eleven aromatic molecules. Binding energies were evaluated at the 6-31G**//6-31G** level. We then replaced the sodium cation in the optimized complex with a dummy probe atom and evaluated the electrostatic potential at that point. This procedure allowed us to calculate the electrostatic contribution to the binding. A plot of the electrostatic potentials vs. the binding energies showed that the electrostatic component of the cation- π interaction is highly variable. However, across the series of examined molecules, essentially 100% of the variation in binding energy is reflected in the electrostatic term. All other factors, including induced dipole interactions, charge transfer, and dispersion

forces, are absorbed in a constant term worth ca. 12 kcal/mol in the prototype aromatics considered in this study. These results prompted us to use electrostatic potential surfaces of aromatics as a qualitative and semi-quantitative guide for cation- π interactions. We report the electrostatic potential surfaces for seventeen different π systems. We found that the trend found in the binding of sodium cation to the π surface of the aromatic can be easily reproduced by simple visual inspection of these surfaces. We evaluated the electrostatic potential surfaces with *ab initio* and semi-empirical calculations and we found that AM1 surfaces can reproduce the trends found in the *ab initio* surfaces. We then report a series of AM1 electrostatic potential surfaces for a larger series of aromatic systems, and show their relevance to medicinal and biological issues.

The synthesis of a neutral water-soluble cyclophane receptor is then reported. This molecule originated from previous studies on a similar receptor bearing four peripheral carboxylates. The uncertain importance of these carboxylates on the binding of cations inspired us to make its neutral water-soluble analog. We report the binding affinities of this host for some neutral and positively charged guests. The absence of the external negative charges results in a decrease of approximately 1.5 kcal/mol in selected guests.

Finally, synthetic approaches to the synthesis of two new cyclophane receptors are reported. In one case we added four more peripheral negative charges to the host, and in the other case we made a water-soluble cyclophane with only one carboxylate adjacent to the binding cavity. The former receptor was designed to study long-range electrostatic interactions in aqueous media, while the latter host was designed to study short-range electrostatic interactions.

Table of Contents

Acknowledgments.....	iv
Abstract.....	vii
List of Figures.....	xiv
List of Tables.....	xxii
Chapter 1: Supramolecular Aspects of Cyclophane Chemistry.....	1
1.1 Introduction.....	2
1.2 Molecular Recognition by Cyclophane Receptors.	
1. General Issues.....	4
1.3 Molecular Recognition by Cyclophane Receptors.	
2. The Dougherty Approach.....	10
1.4 References.....	26
Chapter 2: The Nature of the Cation- π Interaction.....	32
2.1 Introduction.....	33
2.2 Molecular Quadrupole Moments.....	34
2.3 Long-Range and Short Range Intermolecular Forces.....	41
2.4 Electrostatics as a Predictive Quantitative Tool for Cation- π Interactions in Aromatics.....	42
2.5 Appendix A.	

	Theory of Long-Range Intermolecular Forces.....	58
2.6	Appendix B.	
	Sample of Input Files for the Calculation of Binding Energies and Electrostatic Potentials.....	63
2.7	Appendix C.	
	The Binding of the Hydronium Ion to Benzene.....	71
2.8	Appendix D.	
	Multipole Moments for Compounds 1-11.....	73
2.9	References.....	79
 Chapter 3: Electrostatic Potential Surfaces as a Qualitative Guide for Cation-π Interactions.....		
3.1	Introduction.....	83
3.2	<i>Ab Initio</i> Calculation of Binding Energies.....	84
3.3	Electrostatic Potential Surfaces in the Evaluation of Cation- π Interactions.....	91
3.4	Biological Considerations.....	110
3.5	Final Remarks.....	113
3.6	References.....	117
 Chapter 4: A Neutral Water-Soluble Cyclophane Receptor.....		
4.1	Introduction.....	120

4.2	Design and Synthesis of a Neutral Water-Soluble Cyclophane Host.....	124
4.3	Binding Studies of Host NSP.....	133
4.4	Attempts to Improve the Water-Solubility of Host NSP.....	152
4.5	Theoretical Studies.....	160
4.6	Final Remarks.....	166
4.7	Experimental Section.....	167
4.8	Appendix. Energies in Hartrees for the Complexes $\text{Na}^+\text{-C}_6\text{H}_6\text{-Cl}^-$ and $\text{Na}^+\text{-C}_6\text{H}_{14}\text{-Cl}^-$ Discussed in Section 4.4.....	178
4.9	References.....	182

Chapter 5: Synthesis of Model Cyclophane Receptors for the Study of Long-Range and Short-Range Electrostatic Interactions in Aqueous Media

		184
5.1	Introduction.....	185
5.2	Binding Properties of the PentaCarboxy Host.....	186
5.3	Increasing the Number of Peripheral Negative Charges.....	189
5.4	A Cyclophane Receptor for the Study of Short-Range Electrostatic Forces.....	198
5.5	Final Remarks.....	204
5.6	Experimental Section.....	209
5.7	References.....	220

Appendix A: A Catalyst for Enantioselective Radical Reactions.....	222
Experimental Section.....	232
References.....	235
Appendix B: The Interaction Between Benzene and Hexafluorobenzene	
.....	237
References.....	246

List of Figures

Figure 1.1. Geometrical and energetic complementarity of two different systems.....	5
Figure 1.2. General structure of the Dougherty cyclophane hosts and their main characteristics.....	10
Figure 1.3. Some of the host structures that have been studied in the Dougherty group.....	12
Figure 1.4. General synthesis of the ethenoanthracene unity.....	14
Figure 1.5. Final steps in the synthesis of host P.....	16
Figure 1.6. $-\Delta G^{\circ}_{298}$ (kcal/mol) in aqueous borate buffer for binding to host P.....	17
Figure 1.7. Different cases of π - π interactions.....	19
Figure 1.8. CPK representations of host P in the rhomboid and toroid conformations.....	20
Figure 1.9. Calculated maximum upfield shifts (in ppm) for the protons of guest 30 upon binding to host P.....	22
Figure 2.1. A pictorial representation of the cation- π interaction.....	33

Figure 2.2. Generation of dipole and quadrupole moments from a separation of charges, and dipole moments respectively.....	36
Figure 2.3. Laboratory Reference Frame for a point charge A and a molecule B.....	38
Figure 2.4. Electrostatic potential surface of benzene (HF/6-31G**).....	40
Figure 2.5. Aromatic structures evaluated in the present study.....	43
Figure 2.6. Geometry of the complex benzene- Na^+	44
Figure 2.7. Hammett plot for the binding constants of 1-11 to Na^+ and the substituent constant σ_m	48
Figure 2.8. Hammett plot for the binding constants of 1-11 to Na^+ and the substituent constant σ_m^+	49
Figure 2.9. Correlation between binding energy and electrostatic potential ($E_{p_{\text{opt}}}$) for molecules 1-11 in their complexes with sodium cation.....	50
Figure 2.10. Correlation between binding energy and electrostatic potential ($E_{p_{\text{unopt}}}$) for molecules 1-11 in their complexes with sodium cation.....	52
Figure 2.11. Binding energy/electrostatic potential plots for two classes of compounds.....	56
Figure 2.12. Definition of the relative positions of the charges e_i and e_j of the molecules a and b respectively.....	59

Figure 2.13. Geometry of the optimized complex between benzene and the hydronium ion.....	71
Figure 3.1. Structures of compounds 1-17.....	85
Figure 3.2. Structures of the optimized complexes between aromatics 1-17 and Na ⁺	87
Figure 3.3. Structures of the optimized complexes between heteroatom and Na ⁺ in compounds 2, 3,4,6,8, and 14.....	90
Figure 3.4. <i>Ab initio</i> 6-31G** electrostatic potential surfaces for compounds 1-6.....	93
Figure 3.5. <i>Ab initio</i> 6-31G** electrostatic potential surfaces for compounds 7-12.....	94
Figure 3.6. <i>Ab initio</i> 6-31G** electrostatic potential surfaces for compounds 13-17.....	95
Figure 3.7. The electrostatic potential surface of benzene calculated by <i>ab initio</i> and PM3, AM1, and MNDO methods.....	98
Figure 3.8. AM1 electrostatic potential surfaces for compounds 1-6.....	100
Figure 3.9. AM1 electrostatic potential surfaces for compounds 7-12.....	101
Figure 3.10. AM1 electrostatic potential surfaces for compounds 13-17.....	102

Figure 3.11. representative structures for which AM1 electrostatic potential surfaces have been calculated.....	104
Figure 3.12. AM1 electrostatic potential surfaces for compounds 18-23.....	105
Figure 3.13. AM1 electrostatic potential surfaces for compounds 24-29.....	106
Figure 3.14. AM1 electrostatic potential surfaces for compounds 30-32.....	107
Figure 3.15. AM1 electrostatic potential surfaces for compounds 33-37.....	108
Figure 3.16. The complex between phenol and formamide.....	111
Figure 3.17. Electrostatic potential surface for the system depicted in figure 3.16.....	111
Figure 3.18. The complex phenol-formamide- Na^+	112
Figure 3.19. The four nucleic bases A, G, T, C.....	114
Figure 3.20. <i>Ab initio</i> HF/6-31G//6-31G** electrostatic potential surfaces for A, T, G, C.....	115
Figure 4.1. Host P owes its water-solubility to the four external negatively charged groups.....	120
Figure 4.2. The tetramethylester P_E	127
Figure 4.3. Attempted aminolysis by classical methods.....	128

Figure 4.4. Mechanism for the reaction between a methyl ester and Tris in DMSO using K_2CO_3 as a base.....	130
Figure 4.5. Synthesis of hosts 13 and 14	131
Figure 4.6. D values for the binding of nitro guests to anti-NSP.....	138
Figure 4.7. Molecular graph for guests 22 and 26	139
Figure 4.8. Host SP.....	142
Figure 4.9. X-ray structure of 8 . Unit cell is visible.....	145
Figure 4.10. Another view of the structure of 8	146
Figure 4.11. Structure of 8 . 45° rotation from view in Figure 4.9.....	147
Figure 4.12. Structure of 8 . 90° rotation from view in Figure 4.9.....	148
Figure 4.13. Hosts P and syn-NSP optimized by molecular mechanics calculations using the force field CFF91.....	149
Figure 4.14. Hosts P and syn-NSP optimized by molecular mechanics calculations using the force field CVFF.....	150
Figure 4.15. Retrosynthetic analysis for the introduction of two Tris groups starting from one methyl ester.....	153
Figure 4.16. Steric hindrance affected the alkylation of diethylmalonate by 22 , while diazomalonate proved to be an extremely stable compound.....	155

Figure 4.17. Condensation of aminodiethylmalonate with 35 yielded the tetraester 36.....	155
Figure 4.18. Synthesis of amine 39.....	157
Figure 4.19. Attempted synthesis of host 41.....	158
Figure 4.20. Two interesting molecules could be made starting from host 41.....	159
Figure 4.21. The system used to model the interaction of remote carboxylates and positively charged guests.....	161
Figure 4.22. Energies in Hartrees for the system sodium cation-benzene-chloride anion.....	162
Figure 4.23. Pictorial representation of the hypothesized transmission of electrostatic interactions by the aromatic ring.....	163
Figure 4.24. Orientation of cyclohexane and benzene in the two model systems studied.....	164
Figure 5.1. Structures of hosts NSP, P, and CP.....	186
Figure 5.2. Macrocyclization to yield 4 was not successful.....	190
Figure 5.3. Introduction of phosphate groups in a molecule containing a primary alcohol.....	191

Figure 5.4. Synthesis of phosphoramidite 6	192
Figure 5.5. A cyclophane with four phosphate groups.....	192
Figure 5.6. Synthetic scheme for the synthesis of host 14	193
Figure 5.7. Deprotection of the phosphate groups.....	194
Figure 5.8. Synthetic scheme for the synthesis of host 10	195
Figure 5.9. ^1H NMR spectrum of 10 in pure D_2O and in borate buffer.....	197
Figure 5.10. Synthesis of the 3/4 molecule 19	200
Figure 5.11. Synthesis of linker 23	201
Figure 5.12. Final steps in the synthesis of host 17	202
Figure 5.13. Schematic representation of the interaction between a point charge and a dipole moment.....	206
Figure 5.14. Approximations in the definition of the classical dipole moment.....	208
Figure A1. The initial design of a catalyst for enantioselective radical reactions.....	225
Figure A2. Reaction of diazonium salts with copper(I) complexes generates radicals that will cyclize if the aliphatic chain is long enough.....	226

Figure A3. Attempted synthesis of receptor 1.....	227
Figure A4. tautomerism of 4-hydroxyphenanthroline 3.....	228
Figure A5. Synthesis of 4-substituted phenanthrolines.....	229
Figure A6. Proposed synthetic scheme for molecule 11.....	231
Figure B1. Electrostatic potential surfaces of benzene and hexafluorobenzene.....	239
Figure B2. Approximated solid state interactions in solid benzene, solid hexafluorobenzene, and a cocrystallized mixture of benzene- hexafluorobenzene.....	240
Figure B3. Geometries at which the complex benzene-hexafluorobenzene has been studied.....	242
Figure B4. Energy-distance curve for the complex benzene- hexafluorobenzene estimated through HF/6-31G** calculations.....	243
Figure B5. Fit of the energy/distance curve for the attractive region of the plot.....	244

List of Tables

Table 2.1. HF energies (in Hartree) for compounds 1-11 and the complexes 1•••Na⁺-11•••Na⁺	46
Table 2.2. HF binding energies in kcal/mol and electrostatic contribution in kcal/mol to the binding energies for 1:1 complexes of compounds 1-11 with Na ⁺	47
Table 3.1. Calculated HF/6-31G**//6-31G** binding energies for compounds 1-17 with sodium cation.	
Table 3.2. Calculated HF/6-31G**//6-31G** binding energies for heteroatom complexes of compounds 2, 3, 4, 6, 8, and 14 with sodium cation.....	89
Table 4.1. - ΔG°_{298} for binding to hosts anti-NSP and syn-NSP in 10% MeCN/10 mM aqueous NaCl and for binding to host P in 10% MeCN/borate buffer.....	135
Table 4.2. - ΔG°_{298} for binding of selected guests to hosts P and SP in borate buffer.....	143
Table 4.3. Summary of results for the MP2/6-31G** calculations on the two systems of Figure 4.24.....	165

Table 5.1. $-\Delta G^\circ_{298}$ in borate buffer for binding to hosts CP and P.....	187
Table B1. HF/6-31G** and MP2/6-31G** energies for the complex benzene-hexafluorobenzene at the geometries shown in Figure B2.....	242
Table B2. MP2/6-31G** calculation of the interaction energy in the complex benzene/hexafluorobenzene.....	245

Chapter 1

Supramolecular Aspects of Cyclophane Chemistry

1.1 Introduction

The synthesis of urea by Friedrich Wöhler¹ in 1828 signaled the birth of the scientific discipline called organic chemistry. Chemistry is, by definition, the science of interactions, of changing properties. Its goal is the understanding of the nature of mutations and transformations of matter. It is therefore no surprise that, since the synthesis of urea, organic chemists have synthesized ever more complex structures and, in so doing, they have developed a vast array of tools and methodologies for the manipulation of the covalent bond. Highly sophisticated total syntheses of natural products and their derivatives marked the progress of organic chemistry in the last fifty years. In many of these syntheses, the goal of making a tremendously complex molecule is associated with the development of methodologies for increasing stereochemical control and selectivity in the process of breaking and forming the covalent bond.² However, progress in understanding the physical basis of the chemical bond³ and the application of these concepts to other scientific disciplines, lead to the recognition that the most relevant structures and processes found in Nature, such as enzymatic catalysis, substrate binding to a receptor, the wide field of gene regulation and expression, and the formation of multiprotein complexes⁴, are based on noncovalent intermolecular interactions. From this point of view, the chemistry of the covalent bond is only the first step to enter the much wider and more

biologically relevant chemistry of the non-covalent bond, often referred to as supramolecular chemistry.

Supramolecular chemistry is eminently an interdisciplinary science, whose research objects are the wide fields of:

- 1) Chemical biology, an emerging discipline that includes bioorganic chemistry, biochemistry, molecular biology and molecular medicine.
- 2) The general study of intermolecular interactions, whose increasingly deeper understanding will lead to evolutions and revolutions in many fields of science.
- 3) Organic synthesis, through the evaluation and synthesis of unusual and topologically relevant molecules, and the development of catalysts based on non-covalent interactions.
- 4) Materials science, especially through the understanding of the intermolecular interactions and arrays that lead to the prediction of specific and collective properties such as magnetism or conductivity, or even superconductivity. Crystal engineering and the predicted nanotechnologies find their place here.

The previous list is all but complete; in general, supramolecular chemistry consists of the study of any chemical species more complex than molecules themselves. Any molecular complex, *self-assembled or not*, has therefore to be regarded as an example of supramolecular chemistry.

Supramolecular chemistry is the chemistry of the future and the present work wants to be a modest contribution to this discipline.

1.2 Molecular Recognition by Cyclophane Receptors. 1. General Issues

The term molecular recognition has been used in many instances as synonymous of supramolecular chemistry. However, it is the opinion of the author that the expression molecular recognition is more properly defined as the *recognition* event between two molecular (one of which can be atomic in the case of recognition of ions) species, the host, or receptor, and the guest. The host must be as large as necessary in order to incorporate the guest molecule. Therefore, without exceptions, the host is always bigger than the guest. Recognition between a host and a guest implies geometrical and energetic (interactional) complementarity, as shown in Figure 1.1. In addition to size and shape, a receptor is also characterized by its conformation, chirality and dynamics, as well as, by the dimensionality, connectivity and cyclic order of its molecular graph.

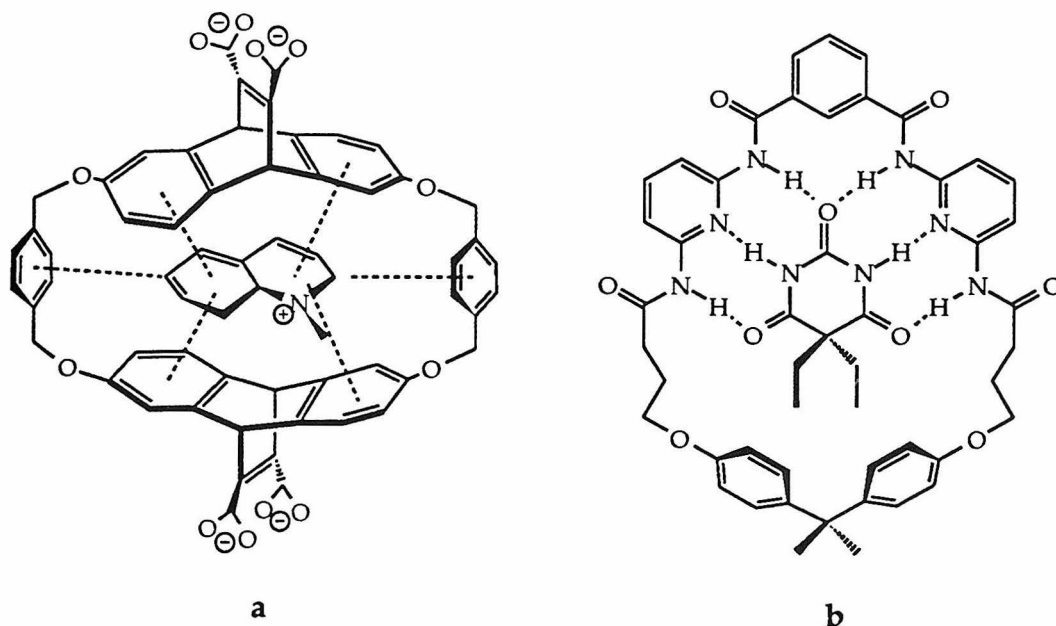


Figure 1.1. Geometrical and energetic complementarity of two different systems. (a) a positively charged guest is trapped in a cavity of just the right size and is surrounded by six interacting aromatic rings. (b) a geometrically shaped rigid cavity contains the functional groups, capable of hydrogen bonding, complementary to those in the guest.

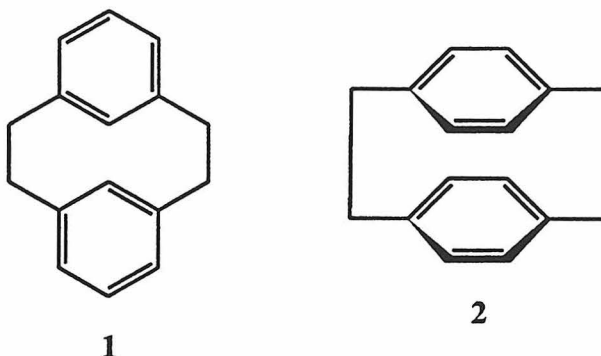
The portion of the host that directly interacts with the guest through an array of intermolecular interactions is called the binding site of the receptor. In order to have large differences in the free energies of binding, the binding site must be characterized by multiple interaction sites and by large contact areas between the host and the guest. This is necessary because non-covalent interactions are relatively weak when compared to covalent bonds. Solvent effects are also of paramount importance. Solvent molecules can interact with the host and the guest in such a way that they can minimize or maximize some specific interactions. For example, hydrogen bonding interactions have been mainly used in selected aprotic solvents. Also, in order to maximize their

mutual interaction, the host and the guest should have complementary hydrophobic and hydrophilic domains.

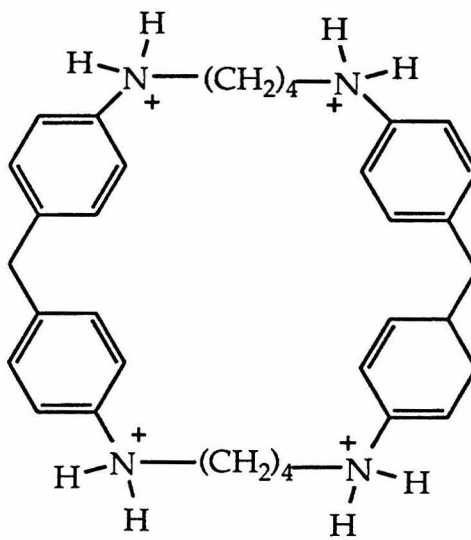
The first reported examples of synthetic receptors are some crown ethers discovered by Pedersen as the side products in the preparation of polyethers by polymerization.⁵ Since the discovery of Pedersen, the design and development of receptors, catalysts and carriers that use non-covalent forces to associate two or more species has witnessed outstanding developments.⁶ An enormous variety of receptors now exists that can bind charged or neutral molecules using different driving forces such as electrostatic interactions, hydrogen bonding, hydrophobic forces, dispersion forces, cation- π interactions, charge-transfer interactions, and polarizability related forces.⁷ It is important to emphasize at this point, that the binding interactions between a host and a guest are never due to *only* one force. It is a combination of intermolecular interactions that cause the receptor to bind the guest molecule, although, in some cases, one force can be clearly dominant over the others.

Cyclophanes, i.e., bridged aromatic compounds, are the most important class of artificial receptors.⁸ Any kind of guest, from inorganic and organic cations and anions to neutral molecules, have been complexed by cyclophane hosts, exploiting every known intermolecular force.

The first known cyclophane is [2,2]-metacyclophane **1** synthesized by Pellegrin in 1899.⁹



Since then, a vast array of cyclophane structures have been synthesized.^{6f,8} Many different cyclophanes were synthesized fairly early, most notably the efforts by Cram on the [2,2]-paracyclophane **2** and derivatives in the 1950's.¹⁰ However, it was only in 1980 that Koga reported the first unambiguous evidence for the stoichiometric inclusion of an apolar guest into the cavity of a synthetic cyclophane host, both in aqueous solution and in the solid state.¹¹ In fact, Koga showed the formation of a 1:1 complex between the tetraprotonated host **3** and 2,7-naphthalendiols in dilute hydrochloric acid at pH<2.



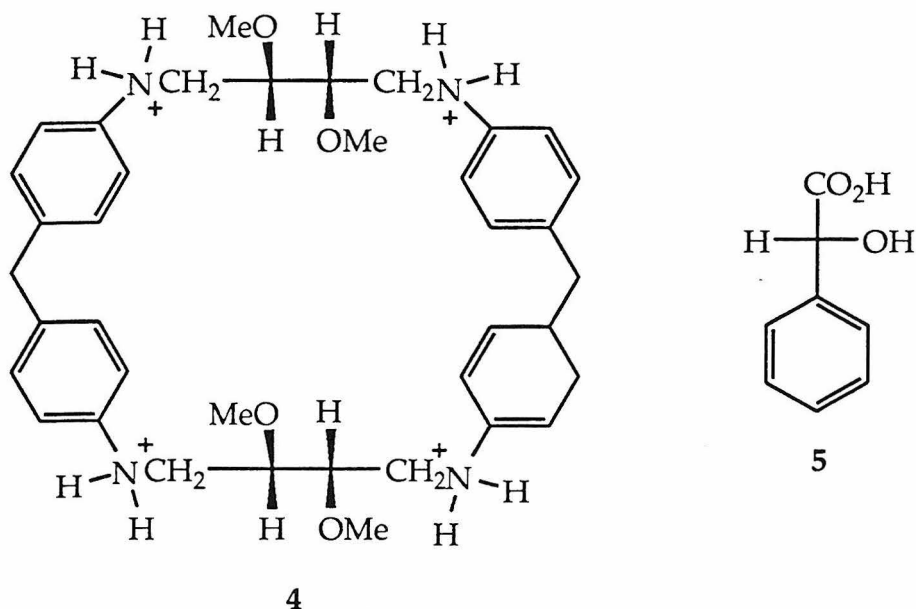
3

Another important aspect of Koga's cyclophane chemistry was that the conclusive proof of formation of the complex was done by ^1H -NMR studies of the chemical shifts of the host and the guest upon complexation. This actually established ^1H -NMR as the best method for studying cyclophane inclusion complexes in solution.

Molecular recognition in aqueous systems, compared to that in organic solvents, is attractive especially for the uniqueness and importance of water. Water is the solvent upon which life, as we know it, is based. Any improvement in our comprehension of host-guest complexes and intermolecular interactions in water is therefore related to possible advances in the understanding of the processes of life.

Another property of a receptor that was immediately recognized for its applications, is the potential for forming diastereomeric complexes of

differential stability with the enantiomers of a guest. This would open the way to simple and effective resolution of racemates. To make this possible, the host must, of course, be chiral. The first syntheses of chiral polyethers to resolve racemic cationic guests were reported by Gaeta¹² and by Cram¹³. Koga was, once again, the first to report the synthesis of the first optically active cyclophane **4** with an apolar cavity, capable of forming diastereoisomeric complexes in water with the enantiomers of chiral aromatic compounds such as mandelic acid **5**.¹⁴



Since the pioneering studies by Koga, some other groups have been involved in molecular recognition by cyclophane receptors in water, most notably, those of Diederich¹⁵, Lehn¹⁶, Vögtle^{6b, 17} and Wilcox¹⁸. All these groups have developed cyclophane hosts with various symmetry elements. They are water-soluble by virtue of polyether chains or positively charged groups.

A different approach by the Dougherty group will be presented in the next section. It forms the starting point for the present work, and it will be therefore reviewed in some detail.

1.3 Molecular Recognition by Cyclophane Receptors. 2. The Dougherty Approach.

The Dougherty group has been active in the field of molecular recognition for about ten years.¹⁹ Our work revolves around a family of water-soluble macrocyclic cyclophane hosts based on the 9,10-ethenoanthracene (common name: dibenzobarrelene) system. The general structure of the receptor is shown in Figure 1.2.

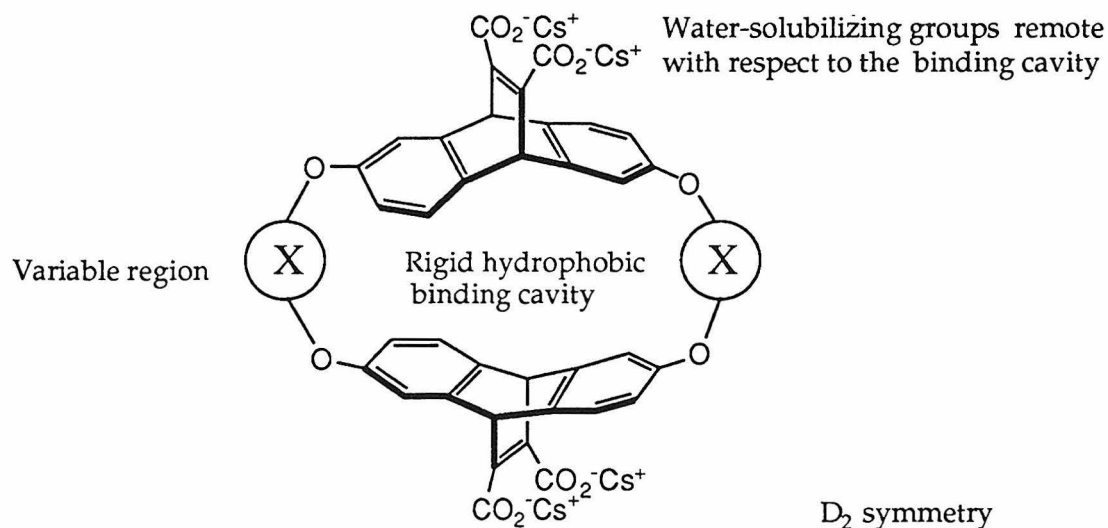
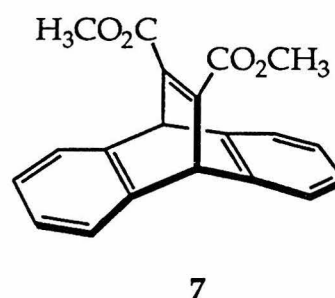
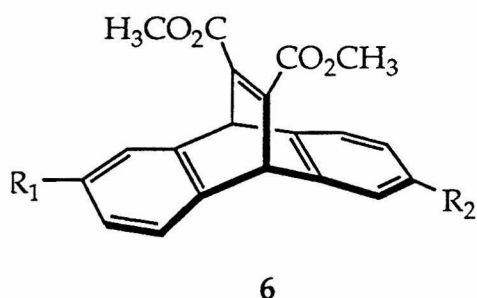


Figure 1.2. The general structure of the ethenoanthracene-based Dougherty cyclophane hosts and their main characteristics.

In these receptors, two 9,10-ethenoanthracene units are connected to various aromatic or aliphatic linkers via ether bonds. The

ethenoanthracene unit provides a rigid, concave hydrophobic surface that gives the structure a high degree of preorganization. Furthermore, the ethenoanthracenes are synthesized as diesters **6**; basic hydrolysis of the ester groups yields a total of four carboxylate groups in the final receptor that make the hosts water-soluble at moderate pH's (a borate buffer solution at pH=9 solubilizes these receptors up to millimolar concentrations).



The position of the carboxylates is also of paramount importance. Due to the rigid structure of the 9,10-ethenoanthracene unit, the carboxylates are far from the hydrophobic cavity and cannot move closer to strongly interact with a bound guest. This separation clearly increases the hydrophobicity of the binding cavity, compared for example to Koga's host **3**. Finally, it can be noticed, that the ethenoanthracene unit is chiral when substituted at the 2- and 6-positions. When the two substituents are the same ($R_1=R_2$), one symmetry element, the C_2 axis of the parent ethenoanthracene **7** is preserved. A cyclophane made up of two of these chiral units will therefore have a D_2 symmetry if both the subunits have the same absolute configuration or it will have C_{2h} symmetry if they have

opposite configurations. These symmetry elements make these hosts particularly simple to be studied by NMR techniques. Furthermore, it is clear that the intrinsic chirality of the twisted structure of the cycle (not a simple chiral influence on a grossly achiral framework as in Koga's host **4**) makes this class of cyclophanes particularly suitable for enantioselective complexation.

Figure 1.3 reports the principal classes of hosts synthesized by previous members of the group.

	L ₁	L ₂	R	Name
			H	P
			H	C
			H	O
			H	S
			H	CP
			H	TMP
			Br	TBP
			Br	TMTBP

Figure 1.3. Some of the host structures that have been studied in the Dougherty group.

The members of this series are conventionally identified by letters that refer to the linkers L_1 and L_2 . Host P takes its name from the *p*-xylyl groups that serve as linkers. Host C takes its name by the two cyclohexyls. Host TBP is for tetrabromo and so on.

The general synthesis of this class of cyclophanes has been accomplished by two previous group members: Michael Petty and Timothy Sheppard and it has been previously reported^{19e, h, l, 20}. The procedures for the synthesis of the chiral ethenoanthracene unit are diagrammed in Figure 1.4. The synthesis starts from the commercially available anthraflavic acid **8**. This is reduced by aluminum amalgam to the air- and light-sensitive 2,6-dihydroxyanthracene **9**. Protection of the dihydroxyanthracene as its bis-*t*-butyl-dimethylsilyl ether **10** removes sensitivity and solubility problems. This compound then undergoes a diastereoselective Diels-Alder reaction using the chiral dienophile dimethylfumarate **11** aided by Lewis acid catalysts. The products of this reaction are only two isomers **12** and **13** that can be called syn and anti according to the relative placement of the silyl and the carboxylate groups. These diastereomers can be easily separated by silica gel chromatography (low temperature crystallization is also an option). Reaction of the separated products with diphenyl diselenide and potassium *tert*-butoxide, followed by acidic hydrolysis yields the two ethenoanthracenes **14** and **15**. These compounds can then be transesterified with methanesulfonic acid

to yield the two enantiomers **16** and **17**. Absolute stereochemistries have been assigned by NMR and CD measurements.

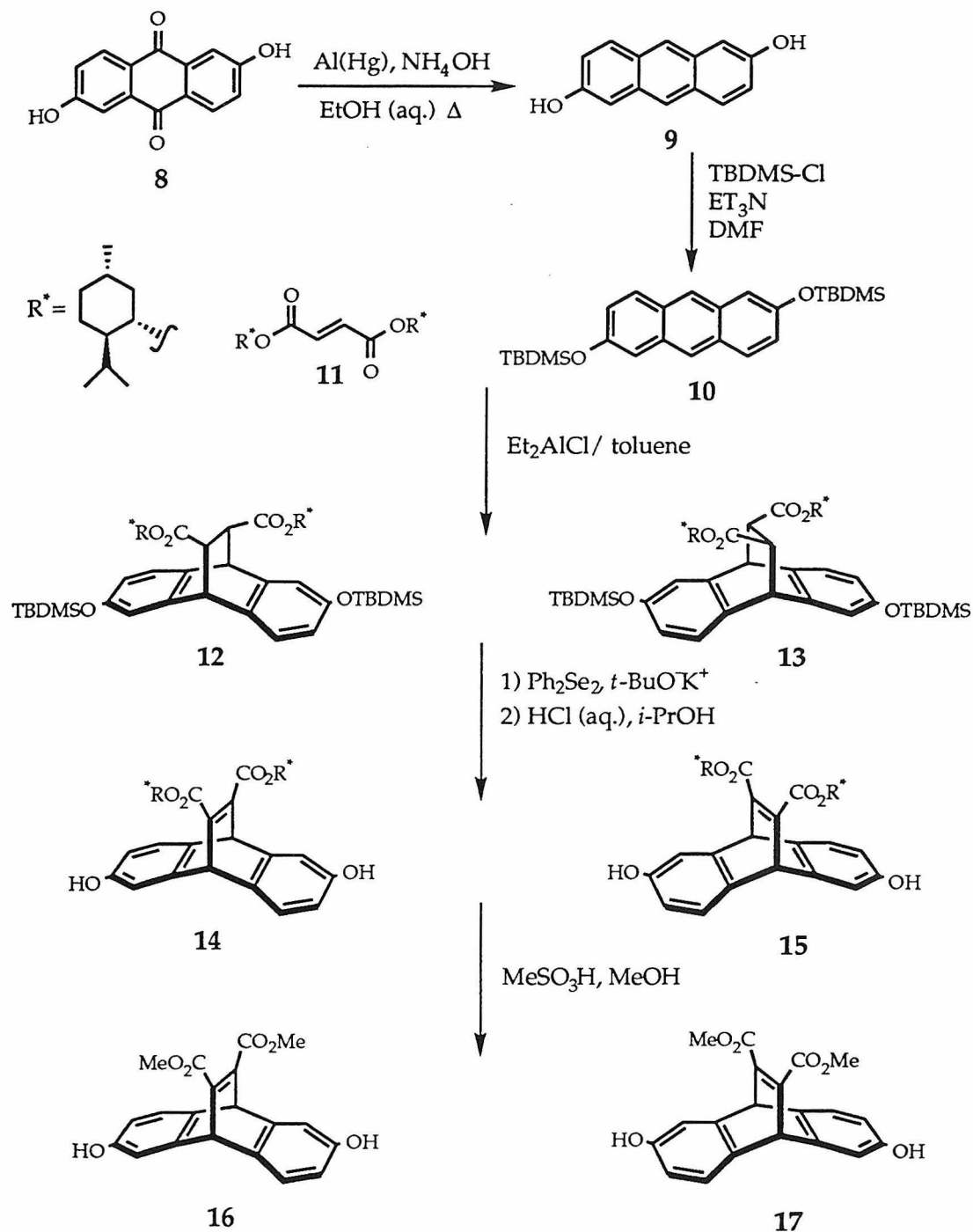


Figure 1.4. General synthesis of the ethenoanthracene unit.

The synthesis of the ethenoanthracene where the groups R (Figure 1.3) are not hydrogens are only slightly different from the general synthetic method described in Figure 1.4, and they will not be reported here.^{19a, 20} Similarly, the linker moieties L_1 and L_2 either have straightforward syntheses, or they are commercially available. Their synthesis will also not be described here.^{19a, 21}

Once the ethenoanthracene unities have been built, the host structures are synthesized by condensation with the appropriate linker dibromides in anhydrous dimethylformamide, using cesium carbonate as a base (Figure 1.5 shows the basic synthesis for the two enantiomers of host P). Symmetric macrocycles, such as P, are generated in a single step by delivering (via syringe pump) a solution of the chiral ethenoanthracene unit and the linker (1:1) in a flask containing cesium carbonate suspended in dimethylformamide during a period of at least 1 day, in order to insure the proper dilution for the macrocyclization reaction. The methyl esters of all the macrocycles are then hydrolyzed using cesium hydroxide in aqueous dimethylsulfoxide. After a quick purification with an ion-exchange column, the cesium salts are dissolved in deuterated aqueous buffer for NMR binding studies, or just aqueous borate buffer for circular dichroism binding studies.

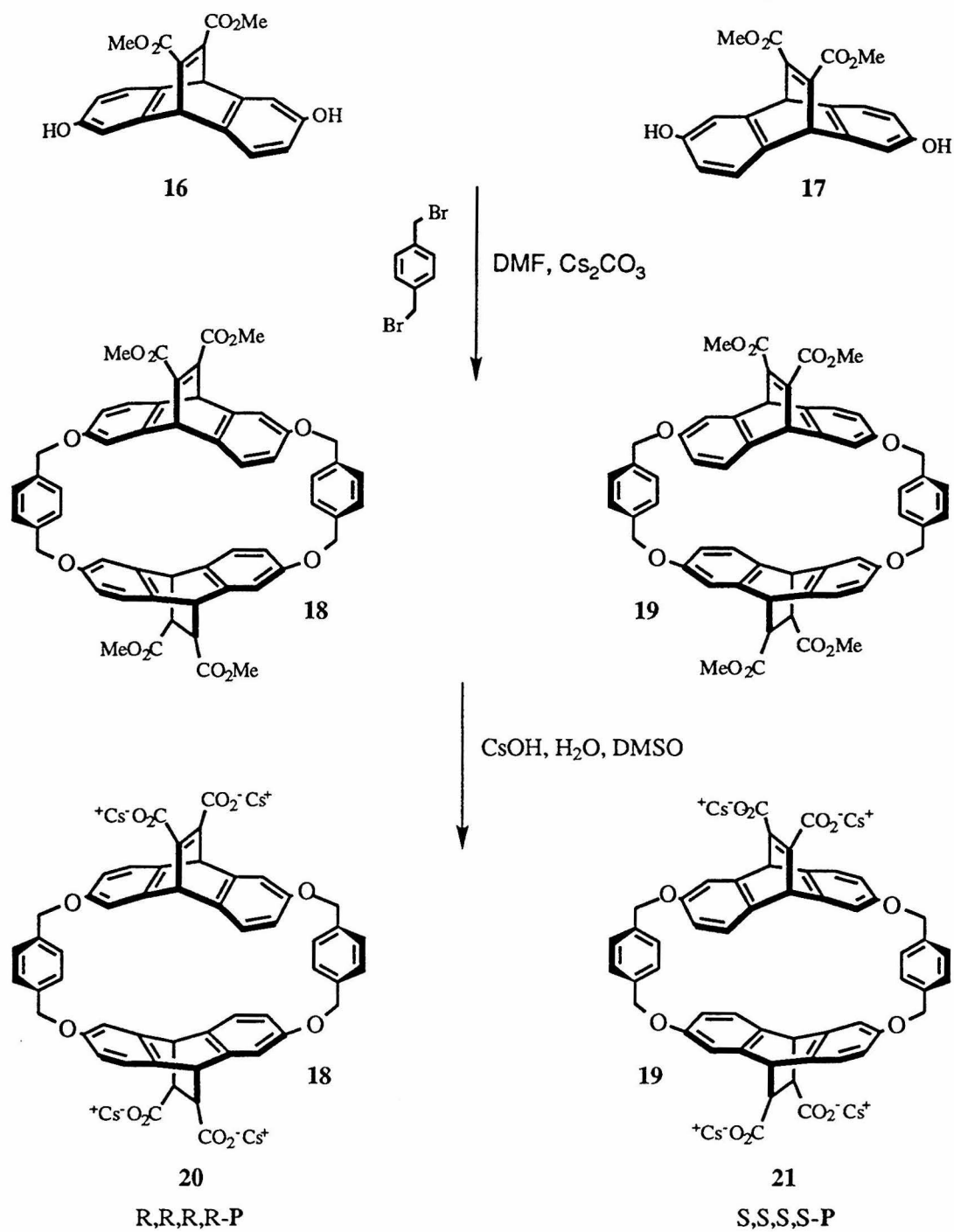


Figure 1.5. Final steps in the synthesis of host P.

Non-symmetric hosts such as CP need to be synthesized step by step and the overall synthesis is slightly longer. The synthesis of one of these hosts will be described in detail in chapter 5.

Out of this class of cyclophanes, host P is the most thoroughly studied. Typical binding free energies of guest molecules in aqueous borate buffer (pH=9), are shown in Figure 1.6.

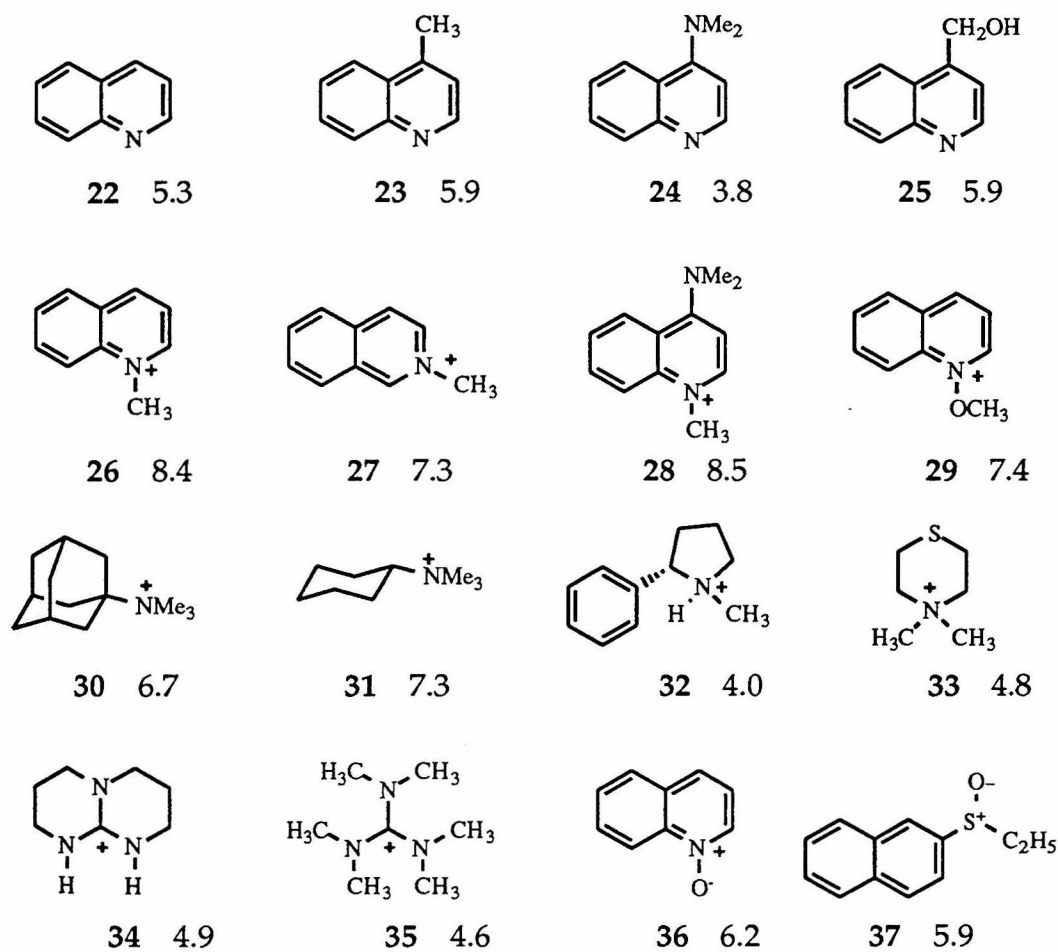


Figure 1.6. $-\Delta G^\circ$ (kcal/mol) in aqueous borate buffer for binding to host P.

It may be noted that all the guests in Figure 1.6 are quite water-soluble. A large component of the driving force for complexation of all these guests is undoubtedly due to hydrophobic forces. This is especially true for the neutral guests (22-25). One can note the difference between 23 and 24. Intuitively, one can think that the sterical hindrance due to the dimethylamino group prevents a complete immersion of the aromatic portion in the receptor cavity. If this is true, as simple NMR chemical shift studies of the guests protons seem to show, part of the driving force for the binding of neutral guests is also due to donor-acceptor interactions between the aromatic walls of the host and the aromatic portion of the guest. This is an example of π - π stacking interactions as defined by Sanders and Hunter.²² In their model, offsettings between parallel aromatic rings allows favorable electrostatic interactions that overwhelm the expected face to face repulsion. When perturbative elements, such as heteroatoms, are introduced in the aromatic ring, the favorable electrostatic interactions can be even higher, Figure 1.7.

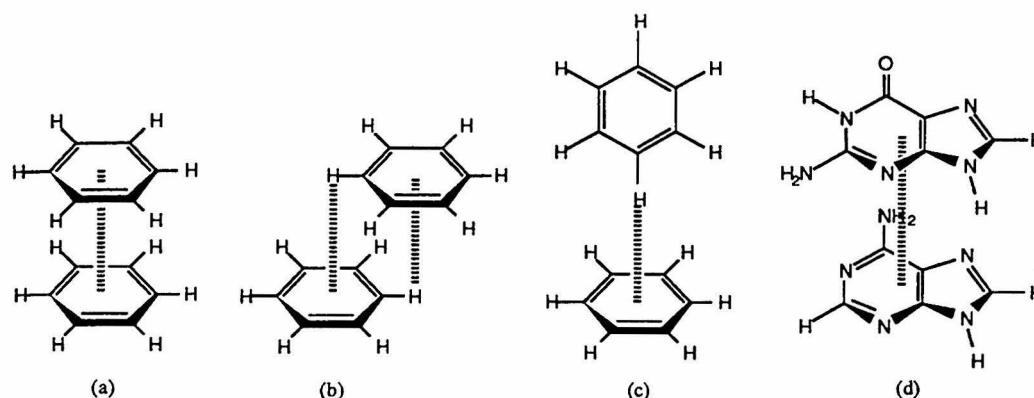


Figure 1.7. Different cases of π - π interactions. (a) Face to face repulsion between π -surfaces. (b) Offsetting of parallel π -surfaces allows attractive interactions. (c) "Classical" edge to face attractive interactions (d) Substituents in the aromatic rings can change the nature of the interaction. A general explanation for the effect of the substituents is reported in chapter 3 of this work.

However, the binding contribution due to this kind of π - π stacking interactions cannot be very high. Former group member Dave Stauffer showed that in chloroform the binding of neutral guests by host P is not detectable by NMR techniques.^{19g} This means that the contribution due to the π - π stacking between the host and a neutral guest is less than 2 kcal/mol and it is, in any case, difficult to quantify.

The data reported in Figure 1.6 also show that host P is able to bind two general classes of guests. One of these classes consists of flat aromatic guests such as N-methylquinolinium iodide **26** and analogous compounds. The other class is represented by bulkier guests such as adamantyltrimethylammonium iodide **30**. This difference in guest size and shape can be tolerated because, although host P has a rigid cavity, it can adopt two distinct conformations to accommodate different kind of

guests. A recent X-ray structure²³ of the tetramethylester of P shows that it can assume a C_2 symmetric rhomboid conformation (top of Figure 1.8) to bind flat aromatic guests. Molecular modeling of host P also showed that a more open, D_2 symmetric toroid conformation (bottom of Figure 1.8) can be adopted by this molecule. This is the preferred conformation to bind larger guests such as 30. The existence of these two alternative conformations in solution has been confirmed by NOE NMR experiments^{19e} as well as by circular dichroism data.²⁴

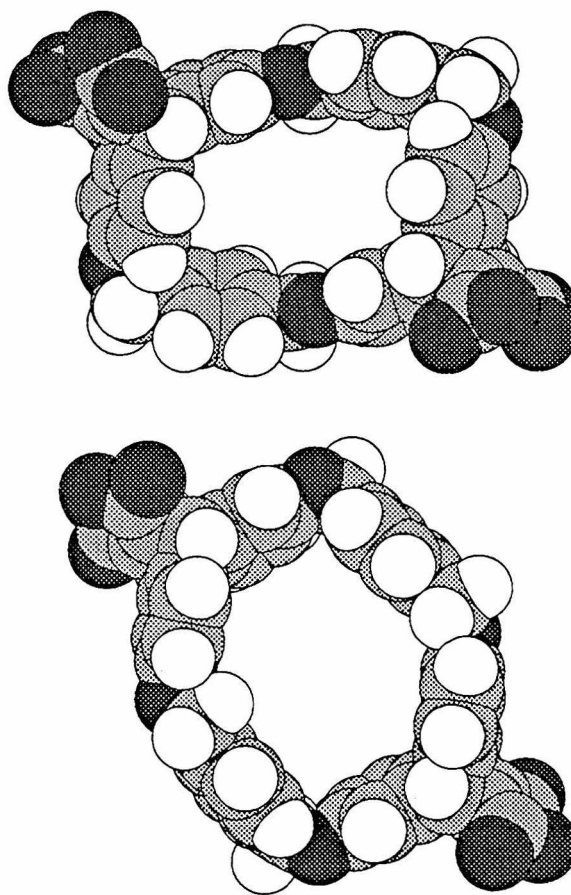


Figure 1.8. CPK representations of 21 in the rhomboid (top) and toroid (bottom) binding conformations.

One can see, from the data in Figure 1.6, that a highly hydrophobic receptor such as host P binds a wide variety of positively charged guests in water with high affinity. This effect can be quite dramatic. Let's consider guests 23 and 26. These two compounds are similar in size and shape, yet the charged guest 26 binds host P with a free energy of binding that is 2.5 kcal/mol higher than that for the neutral 23. This is an extremely surprising result, especially in consideration of the fact that the cation should be much more solvated than the neutral species in water. Calculations show that 26 is better solvated than 23 by 46.5 kcal/mol.^{19a} As such, the binding of these charged guests is more indicative of some kind of attraction between the host and the guest rather than of the action of repulsive forces between water and the guest molecule (hydrophobic forces). Even more surprisingly, study of the chemical shift changes in the binding of a guest such as 30 (which is composed of a large hydrophobic moiety and of charged group attached to it), showed that the signals of the quaternary ammonium group and of the protons close to this group move more than any other signal in the molecule (Figure 1.9)

This indicates that the ammonium group (charged) interacts with the hydrophobic binding cavity more than the hydrophobic moiety of the guest!

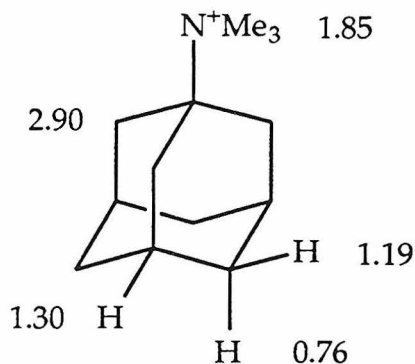


Figure 1.9. Calculated maximum upfield shifts (in ppm) for the protons of guest 30 upon binding to host P.

These results suggest that in the binding of cations to neutral aromatics a special kind of interaction takes place. This binding force has been named cation- π interaction.²⁵ The cation- π interaction can be intuitively envisioned as the electrostatic (attractive) force acting between a positively charged species and the electron rich face of benzene. The nature of this intermolecular force will be rigorously defined in chapter 2. For the moment we can notice that this kind of interaction was first observed in the binding of potassium ion and other small cations to benzene²⁶. Since then, it has been proposed by Burley and Petsko that this interaction may play a significant stabilizing role in the structure of proteins.²⁷ Also, after the Dougherty group reported its findings on host P and analogues, other groups, especially those of Collet²⁸ and Schneider²⁹ have observed this kind of interaction in simple host-guest systems. It must finally be mentioned that the Dougherty group has shown that binding of transition states having incipient positive charges by host P can lead to a novel form of catalysis.^{19b}

Starting from the initial observation on host P, our group has speculated about specific roles of the cation- π interactions in biological systems. This undertaking was especially prompted by the discovery that host P is able to bind the positively charged neurotransmitter acetylcholine (ACh hereafter). The binding constant of ACh to P has a $K_d=50\mu\text{M}$ in aqueous borate buffer (pH=9) at 298 K. This value is comparable to that of protein binding sites. Former group member Dave Stauffer proposed that the main interaction between ACh and its main associated enzyme acetylcholinesterase (AChEs), is due to cation- π interaction between the positive charge of ACh and aromatic sidechains in the binding site of AChEs.^{19d} It should be noted that, at the time of this proposal, the structure of AChEs was not known and the general opinion was that ACh was bound by carboxylates in the binding site of AChEs. Shortly after the publication of this hypothesis, the X-ray structure of AChEs from *Torpedo*, was solved by Sussman.³⁰ It showed the binding site lying at the bottom of a deep gorge. The gorge was lined with many aromatic sidechains, with aromatics being especially prominent at the active site. The hypothesis by Stauffer was therefore confirmed in a spectacular way. Since then, cation- π interactions have been invoked to explain other effects in biological systems. In particular, the Dougherty group proposed that cation- π interactions are the basis for the cation selectivity in K^+ channels.³¹ A detailed review of cation- π interactions in chemistry and biology can be found in ref. 24.

One of the main objections that can be made about the use of host P and related structures to study the cation- π interactions, is the presence of four negative external charges (the carboxylates) in the receptor. The effect, if any, of these negative charges is of paramount importance. In fact, the study of cation- π interactions ultimately reduces to the study of the binding affinities of positively charged guests. Therefore, any factor that can influence this binding must be carefully analyzed and quantified. For host P, one could say that the electrostatic field generated by the four carboxylates might be sufficient to explain the difference in binding seen between neutral and charged guests. Solvation in this case is fundamental, of course. The rigid structure of the ethenoanthracene unit keeps the carboxylates out of the binding cavity in any circumstances. The carboxylates are therefore completely exposed to the aqueous medium that will strongly solvate the four negative groups. In turn, this solvation should reduce the energy of interaction of the carboxylates with positively charged guests bound in the host cavity. However, while it is relatively easy to estimate the binding contribution due to the four carboxylates in the gas phase, it is difficult to do the same when the complex is solvated by water. For this reason, binding studies on hosts that have a different distribution of the solubilizing negatively charged groups or that do not have charged solubilizing groups, are of the greatest importance. In fact, these studies are essential to comprehend the binding nature of cyclophane related hosts in water and to quantify the intermolecular forces

that make binding possible. The synthesis, binding studies and unusual characteristics of an all neutral water-soluble cyclophane will be presented and discussed in detail in chapter 5. Chapter 6 will be dedicated to the description of the synthesis of two new and intriguing cyclophane structures. With this in mind, it is now time to examine the nature of the cation- π interaction more closely.

1.4 References

1. Wöhler, F., *Poggendorfs Ann. Physik* **1828**, 12, 253.
2. The amount of published literature on organic synthesis is so massive that is virtually impossible and out of the scope of this work to provide an appropriate reference citation. However, a perception of what has been accomplished by synthetic organic chemists can be found in the book Corey, E.J. *The Logic of Chemical Synthesis*, John Wiley & Sons, Inc., 1989.
3. See for example (a) Pauling L. *The Nature of the Chemical Bond*, Cornell University press, 3rd ed., 1960. (b) Israelachvili, J. *Intermolecular & Surface Forces*, 2nd Ed., Academic press, 1991.
4. See for example Stryer, L *Biochemistry*, 4th ed., W. H. Freeman and Company, 1995.
5. (a) Pedersen, C.J., *J. Am. Chem. Soc.* **1967**, 89, 2495. (b) Pedersen, C.J., *J. Am. Chem. Soc.* **1967**, 89, 7017.
6. Many excellent reviews exist on different aspects of supramolecular chemistry. However, a comprehensive overview of this field can be found in the following books: (a) Lehn, J-M *Supramolecular Chemistry: Concepts*

and Perspectives VCH, New York, 1995. (b) Balzani, V.; De Cola, L. Editors, *Supramolecular Chemistry*, NATO ASI, Series C, Mathematical and Physical Sciences, V. 371, Kluwer Academic Publishers, 1992. (c) Dietrich, B; Viout, P.; Lehn, J-M, *Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry*, VCH, New York, 1993, (d) Stoddart, J. F. editor, *Monographs in Supramolecular Chemistry*, The Royal Society of Chemistry. (e) Durr, H.; Schneider, H. J. *Frontiers in Supramolecular Organic Chemistry and Photochemistry*, VCH, New York, 1991. (f) Vögtle, F. *Cyclophane Chemistry: Synthesis, Structure and Reactions* John Wiley & Sons, New York, 1993.

7. An exhaustive list of all the known receptors using different intermolecular interactions and of all their authors is beyond the scope of this work. A partial list could be unfair towards the authors that would necessarily be left out. For these reasons, the reader is invited to consult the excellent and recent books reported in ref.6 in order to gain a first hand contact with the variety of structures and clefts that have been developed and that take advantage of different non-covalent forces.

8. Diederich, F. *Cyclophanes*, Monographs in Supramolecular Chemistry, vol.2, Serie Editor Stoddart, J. F, The Royal Society of Chemistry, 1994.

9. Pellegrin, M. M. *Rec. Trav. Chim. Pays-Bas*, 1899, 18, 457.

10. (a) Cram, D.J., Steinberg, H., *J. Am. Chem. Soc.* **1951**, *73*, 5691. (b) Cram, D.J., Allinger, N. L., Steinberg, H., *J. Am. Chem. Soc.* **1954**, *76*, 6132. (c) Cram, D.J., Bauer, R. H., Allinger, N. L., Reeves, R. A., Wechter, W. J., Heilbronner, E. *J. Am. Chem. Soc.* **1958**, *8*, 5977.
11. Odashima, K., Itai, A., Iitaka, Y., Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504.
12. Wudl, F., Gaeta, F. *J. Chem. Soc., Chem. Commun.* **1972**, 107.
13. Kyba, E. P., Siegel, M. G., Sousa, L. R., Sogah, G. D. Y., Cram, D. J., *J. Am. Chem. Soc.* **1973**, *95*, 2691.
14. Takahashi, I., Odashima, K., Koga, K. *Tetrahedron Lett.*, **1984**, *25*, 973.
15. (a) Smithrond, D. B., Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 339. (b) Ferguson, F. B., Diederich, F. *Angew. Chem. Int. Ed, Engl.*, **1986**, *25*, 1127. (c) Diederich, F., Dick, K., *J. Am. Chem. Soc.* **1984**, *106*, 8024. (d) Diederich, F., Dick, K. . *Tetrahedron Lett.*, **1982**, *23*, 3167.
16. (a) Dhaenens, M., Lehn, J.-M., Fernandez, M.-J. *New J. Chem.* **1991**, *15*, 873. (b) Lehn, J.-M. . *Angew. Chem. Int. Ed, Engl.*, **1988**, *27*, 89. (c) Dhaenens,

M., Lacombe, L., Lehn, J.-M., Vigneron, J.-P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097.

17. (a) Seel, c., Vögtle, F. *Angew. Chem. Int. Ed, Engl.*, **1991**, *30*, 442. (b) Vögtle, F., Merz, T., Wirtz, H. *Angew. Chem. Int. Ed, Engl.*, **1985**, *24*, 221.

18. (a) Adrian, J. C., Jr., Wilcox, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 1398. (b) Wilcox, C. S., Cowart, M. D. *Tetrahedron Lett.* **1986**, *27*, 5563.

19. (a) Kearney, P. C., Mizoue, L. S., Kumpf, R. A., Forman, J. E., McCurdy, A., Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907. (b) McCurdy, A., Jimenez, L., Stauffer, D. A., Dougherty, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10314. (c) Stauffer, D. A., Barrans, R. E., Jr., Dougherty, D. A. *J. Org. Chem.* **1990**, *55*, 2762. (d) Stauffer, D. A., Dougherty, D. A. *Science* **1990**, *250*, 1558. (e) Petti, M. A., Shepodd, T. J., Barrans, R. E., Jr., Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825. (f) Shepodd, T. J., Petti, M. A., Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1983. (g) Stauffer, D. A., Dougherty, D. A. *Tetrahedron Lett.* **1988**, *29*, 6039. (h) Shepodd, T. J., Petti, M. A., Dougherty, D. A. *J. Am. Chem. Soc.* **1986**, *108*, 6085. (i) Petti, M. A., Shepodd, T. J., Dougherty, D. A. *Tetrahedron Lett.* **1986**, *27*, 807.

20. (a) Petty, M. A., Thesis, California Institute of Technology, 1988. (b) Shepodd, T. J., Thesis, California Institute of Technology, 1988.

21. Kearney, P. C., Thesis, California Institute of Technology, 1994.
22. Hunter, C. A., Sanders, J. K. M., *J. Am. Chem. Soc.* **1990**, *112*, 5525.
23. Forman, J. E., Marsh, R. E., Schaefer, W. P., Dougherty, D. A. *Acta Cryst.* **1993**, *B49*, 892.
24. Forman, J. E., Barrans, R. E., Jr., Dougherty, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9213.
25. Dougherty, D. A. *Science*, **1996**, *271*, 163.
26. (a) Sunner, J., Nishizawa, K., Kebarle, P. *J. Phys. Chem.* **1981**, *85*, 1814.
Taft, R. W., Anvia, F., Gal, J.-F., Walsh, S., Capon, M., Holmes, M. C., Hosn, K., Oloumi, G., Vasanwala, R., Yazdani, S. *Pure & Appl. Chem.* **1990**, *62*, 17. (c) Deakyne, C. A., Meot-Ner, M. J. *J. Am. Chem. Soc.* **1985**, *107*, 469.
27. Burley, S. K., Petsko, G. A. *FEBS Lett.* **1986**, *203*, 139. (b) Burley, S. K., Petsko, G. A. *Weakly Polar Interactions in Proteins*; Academic Press, Inc., 1988, vol. 39, pp 125-189.

28. (a) Canceill, J., Lacombe, L., Collet, A. *J. Chem. Soc., Chem. Commun.* **1987**, 219. (b) Garel, L., Lozach, B., Dutasta, J. P., Collet, A. *J. Am. Chem. Soc.* **1993**, *115*, 11652. (c) Garel, L., Dutasta, J. P., Collet, A. *Angew. Chem. Int. Ed, Engl.* **1993**, *32*, 1169. (d) Collet, A. *Tetrahedron* **1987**, *43*, 5723. (e) Colet, A., Dutasta, J. P., Lozach, B., Canceill, J. *Topics in Current Chemistry* **1993**, *165*, 104.

29. (a) Schneider, H.-J., Schiestel, T., Zimmermann, P. *J. Am. Chem. Soc.* **1992**, *114*, 7698. (b) Schneider, H.-J. *Angew. Chem. Int. Ed, Engl.* **1991**, *30*, 1417.

30. (a) Tan, R. C., Truong, T. N., McCammon, J. A., Sussman, J. L. *Biochemistry* **1993**, *32*, 401. (b) Ripoll, D. R., Faerman, C. H., Axelsen, P.H., Silman, I., Sussman, J. L. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5128. (c) Harel, M., Schalk, I., Ehret-Sabatier, L., Bouet, F., Goeldner, M., Hirth, C., Axelsen, P. H., Silman, I., Sussman, J. L. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 9031. (d) Sussman, J. L., Harel, M., Frolow, F., Oefner, C., Goldman, A., Toker, L., Silman, I. *Science* **1991**, *253*, 872.

31. Kumpf, R. K., Dougherty, D. A. *Science* **1993**, *261*, 1708.

Chapter 2

The Nature of the Cation- π Interaction

2.1 Introduction

In chapter 1, the cation- π interaction has been defined as an attractive electrostatic interaction between a positively charged atomic or molecular species and the electron-rich face of benzene (Figure 2.1).

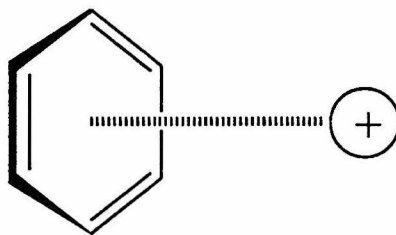


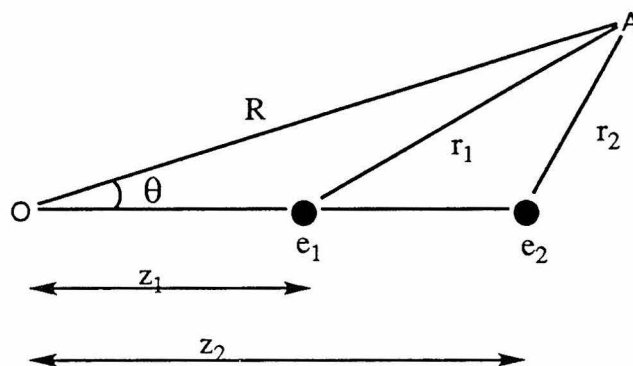
Figure 2.1. A pictorial representation of the cation- π interaction.

However, this definition does not specify or quantify the real forces that are responsible for the interaction. We can certainly say that a complete quantitative description of the cation- π interaction would involve a number of intermolecular forces, such as charge-quadrupole, charge-dipole, charge-induced dipole, charge transfer, dispersion forces and in some cases a hydrophobic component. One can then ask if, among all these different interactions, there is a specific force that plays a major role. We have previously proposed that, to first order, the major aspect of the cation- π interaction is electrostatic in nature.¹⁻³ How can that be? How can a neutral hydrocarbon molecule show affinity for positive charges? The answer to these questions lies in the electronic distribution in aromatic molecules. Consider benzene, the simplest aromatic. Benzene is a neutral

molecule, and it has D_{6h} symmetry. Its high symmetry makes the total dipole moment zero. However, higher order, even multipoles may have a value different from zero. In particular, the quadrupole moment of benzene is large, $-29.0 \times 10^{-40} \text{ Cm}^2$. The very existence of the quadrupole moment and its large value can be considered as the source of the electrostatic properties of aromatic molecules. Before going on, it is necessary to give some simple electrostatic definitions.

2.2 Molecular Quadrupole Moments.

Any system of electric charges has a set of electric multipole moments associated with it. Consider the potential V at an arbitrary point A due to the charges e_1 and e_2 at two points distant z_1 and z_2 from an origin O:



V is given by the following expression:

$$V = \frac{e_1}{r_1} + \frac{e_2}{r_2} = e_1 [R^2 - 2Rz_1 \cos \theta + z_1^2]^{-\frac{1}{2}} + e_2 [R^2 - 2Rz_2 \cos \theta + z_2^2]^{-\frac{1}{2}} \quad (2.1)$$

When, as in this case, R is greater than z_1 and z_2 , the expression for r_1^{-1} and r_2^{-1} can be expanded in powers of z_1/R and z_2/R leading to:

$$V = \frac{e_1 + e_2}{R} + (e_1 z_1 + e_2 z_2) \frac{\cos \theta}{R^2} + (e_1 z_1^2 + e_2 z_2^2) \frac{3 \cos \theta - 1}{2R^3} + (e_1 z_1^3 + e_2 z_2^3) \frac{5 \cos^3 \theta - 1}{2R^4} + \dots \quad (2.2)$$

Here, $(e_1 + e_2)$ is the zeroth moment, the charge, of the system of two charges; $(e_1 z_1 + e_2 z_2)$ is the first moment, the dipole moment; $(e_1 z_1^2 + e_2 z_2^2)$ is the second moment, the quadrupole moment; $(e_1 z_1^3 + e_2 z_2^3)$ is the third moment, the octopole moment, and so on.

The origin of the dipole moment in a molecule can be simply visualized as a separation of monopoles (charges). In the same way the origin of quadrupole moment can be seen in a separation of dipole moments. In general, any multipole n_{th} -moment can be thought of as originated by a separation of multipole $(n-1)_{th}$ -moments (Figure 2.2).

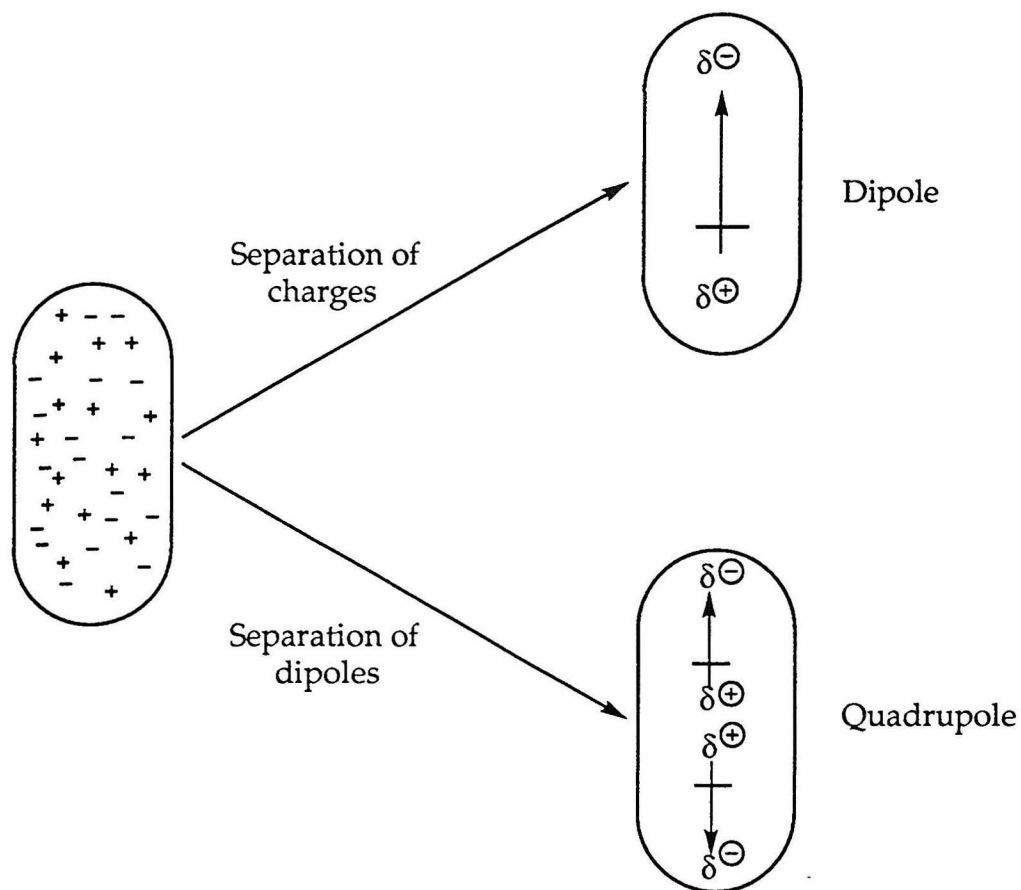


Figure 2.2. Generation of dipole and quadrupole moments from a separation of charges, and dipole moments respectively.

There has always been a great deal of confusion regarding the definition of quadrupole moments. The definition that we have given can be easily generalized for a system with i components, eq. 2.3.

$$\Theta = \sum_i e_i \mathbf{r}_i \mathbf{r}_i \quad (2.3)$$

However, a general treatment for long-range intermolecular interactions requires the evaluation of the perturbation of one molecule on the other by quantum-mechanical methods. This rigorous treatment is reported in

Appendix A of this chapter. For what is of immediate concern here, we notice that a more detailed and rigorous description of quadrupole moment is reached by defining it (see Appendix A for details) as the traceless tensor:

$$\Theta = \frac{1}{2} \sum_i e_i (3r_{i\alpha}r_{i\beta} - r_i^2\delta_{\alpha\beta}) \quad (2.4)$$

where $r_{i\alpha}$ is the x or y or z component of the vector $\mathbf{r}_i$ which defines the position of the charge e_i , as α takes the values 1, 2 or 3, and $\delta_{\alpha\beta}$ is the usual Kronecker delta ($\delta_{\alpha\beta}=1$ if $\alpha=\beta$, $\delta_{\alpha\beta}=0$ if $\alpha\neq\beta$). This is an important definition. In fact, for a linear charge distribution along the z-axis, or for a charge distribution cylindrically symmetric about the z-axis, the off-diagonal elements of Θ are zero, and the relationship between the three remaining components becomes:⁴

$$\Theta_{xx} = \Theta_{yy} = -\frac{1}{2}\Theta_{zz} \quad (2.5)$$

We can easily recognize that a charge distribution cylindrically symmetric is a property of any discrete charge distribution having an axis of symmetry which is at least threefold symmetric. Therefore, benzene, which has a D_{6h} symmetry, has a quadrupole moment characterized by eq. 2.5. It is common use for these kind of charge distribution to define the scalar Θ :

$$\Theta = |\Theta_{zz}| \quad (2.6)$$

Θ is usually called the quadrupole moment of the molecule. It is easy enough to develop an expression for the calculation of the theoretical interaction between a point charge and a quadrupole. This can be done in

two ways. We can make a theoretical quantum mechanical treatment starting from the expression for the electrostatic interaction in Appendix A (eq. 2.19). By substitution of the tensorial components of the quadrupole moment for a molecule such as benzene, we can then obtain a general expression that is valid for any change of variables (namely the angles that define the orientation of the molecule and therefore the polynomials that define the tensorial components). However the resulting expression is not easy to work with and it is not very informative, on a first analysis. On the other hand, for our considerations we can simply make a direct application of the Coulombic law of electrostatic interactions between a point charge A and a molecule B with cylindrical symmetry. Let's consider the system indicated in Figure 2.3.

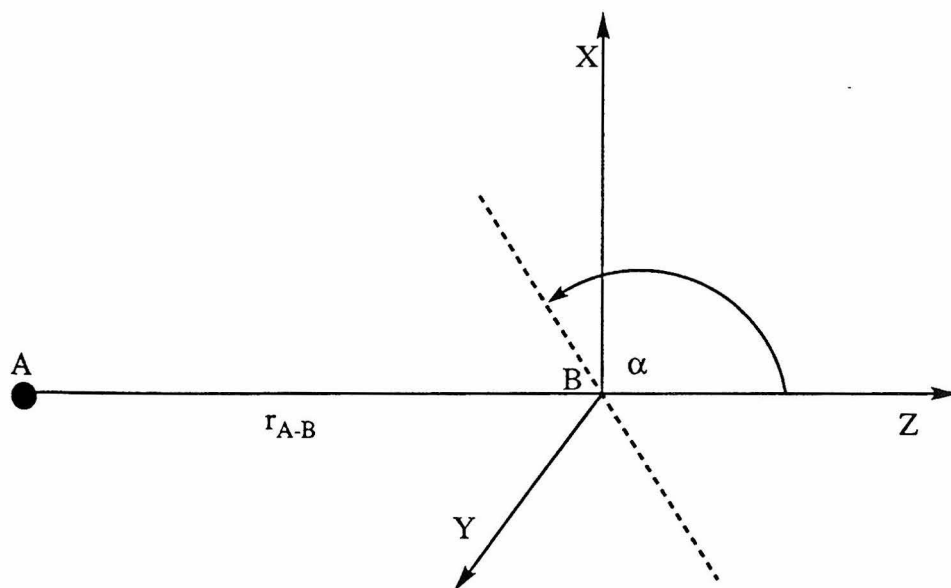


Figure 2.3. Laboratory reference frame for a point charge A and a molecule B. The dotted line through B indicates the axis describing the cylindrically symmetric quadrupole of B. The distance between A and B is indicated by r_{A-B} .

Some simple algebra immediately gives the formula for the interaction between the charge A and the quadrupole Θ of the molecule B:

$$E_{A,\Theta} = + \frac{C_A \Theta_B}{16\pi\epsilon_0 r_{A-B}^3} (3\cos^2 \alpha - 1)N \quad (2.7)$$

In the case of benzene, we substitute:

$$C_A = 1.602177 \times 10^{-19} \text{ C}$$

$$\Theta_B = -29.0 \times 10^{-40} \text{ Cm}^2$$

$$4\pi\epsilon_0 = 1.11265 \times 10^{-10} \text{ J}^{-1} \text{C}^2 \text{m}^{-1}$$

$$\alpha = 0^\circ \text{ or } 180^\circ$$

$$r_{A-B} = 2.47 \times 10^{-10} \text{ m}$$

$$N = 6.02214 \times 10^{23} \text{ mol}^{-1}$$

one obtains:

$$E_{A,\Theta} = -19.93 \text{ kcal/mol}$$

The distance $r_{A-B} = 2.47 \text{ \AA}$ is the distance found in the RHF/6-31G**//6-31G** optimization of the system benzene-Na⁺.^{3,9} The experimental and calculated value of the interaction between sodium and benzene is around 28 kcal/mol.^{3,5-9} Therefore, just considering a classical Coulombic attraction between a point charge and the quadrupole moment of benzene we can explain about 70% of the total interaction energy.

The charge distribution of molecules can be visualized with the help of electrostatic potential surfaces (EPS). The EPS for benzene is shown

in Figure 2.4 (this picture has been generated by HF/6-31G//6-31G** *ab initio* calculations). Here we can see the large asymmetric charge distribution: the area over the center of the ring is negatively charged (red means negative potential), while the protons are positively charged (blue means negative potential) to maintain the neutrality of the molecule. The cation- π effect originates from this large negative potential in the plane of the ring. In chapter 3, electrostatic potential surfaces and their use in the prediction of cation- π interactions will be discussed.

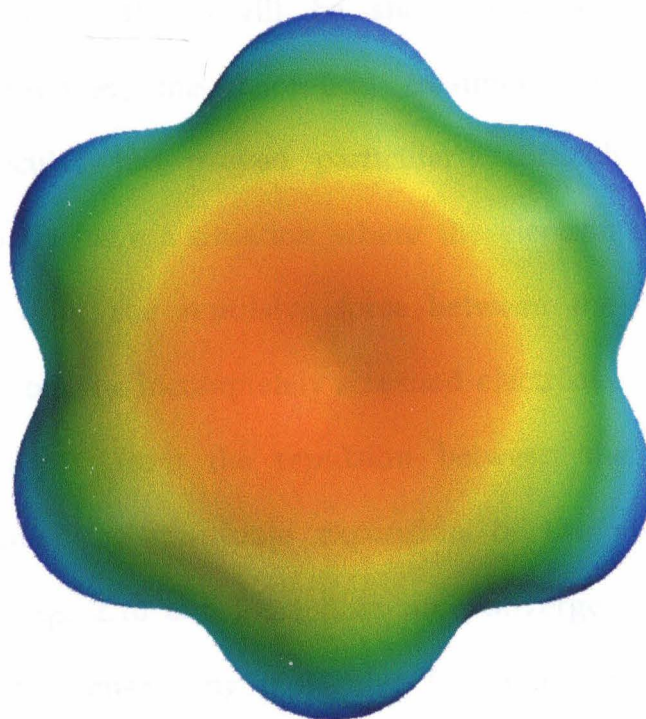


Figure 2.4. Electrostatic potential surface of benzene (HF/ 6-31G**).

2.3 Long-Range and Short-Range Intermolecular Forces

It is clear that any concept expressed until now is very qualitative. Even the interpretation of the simple quadrupole interaction between the quadrupole of aromatic molecules and charged species to explain the binding between these compounds, is not rigorous. This is because the treatment that is presented in Appendix A is valid only for long-range intermolecular interactions. The binding distance of 2.47Å discussed previously cannot be considered a real long-range intermolecular interaction. Clearly there will be short-range effects on the final interaction. However, the theoretical treatment of short-range forces between molecules has proved particularly difficult. For short-range forces, we usually have a situation where the electron clouds of the two molecules overlap. The repulsive force between the molecules clearly arises in part from the incompletely screened electrostatic repulsion of the nuclei and in part from the repulsion between the electrons of the molecules. Thus, the multipole expansion of the electrostatic energy (Appendix A, eqs. 2.10 and 2.19) does not converge when the electron clouds of the two interacting molecules (or atoms) appreciably overlap. Also, the wave function used in the evaluation of long-range forces no longer has the symmetry required by the Pauli exclusion principle. Finally, the perturbation of the energy of the two isolated systems is no longer small. This means that an initial unperturbated state as that employed in the treatment of long-range intermolecular forces, is not good anymore.

As a consequence, a variety of procedures have been developed to attempt the description of short-range electrostatic forces, most notably the approaches based on the valence bond method.¹⁰ We will not describe here these attempts but, once again, we want to emphasize that the interaction between two chemical species is never a simple one and it is never described by just one kind of intermolecular force, although there may be a force that plays a major role in the interaction.

2.4 Electrostatics as a Predictive Quantitative Tool for Cation- π Interactions in Aromatics.

Starting from these considerations, we have developed a more complete evaluation of the extent to which an electrostatic model can rationalize variations in cation binding abilities among various aromatic systems.⁹ We have found that for simple aromatics, electrostatics can account for 40-60% of the total binding energy, although there may be selected systems that show essentially no electrostatic binding. However, it is fundamental to emphasize that across all systems studied, electrostatics account for essentially 100% of the variations in cation binding. As such the electrostatic model is a powerful paradigm for rationalizing trends in cation- π interactions.

We have performed a series of *ab initio* computational studies on the binding of the sodium ion to the structures 1-11 (Figure 2.5).

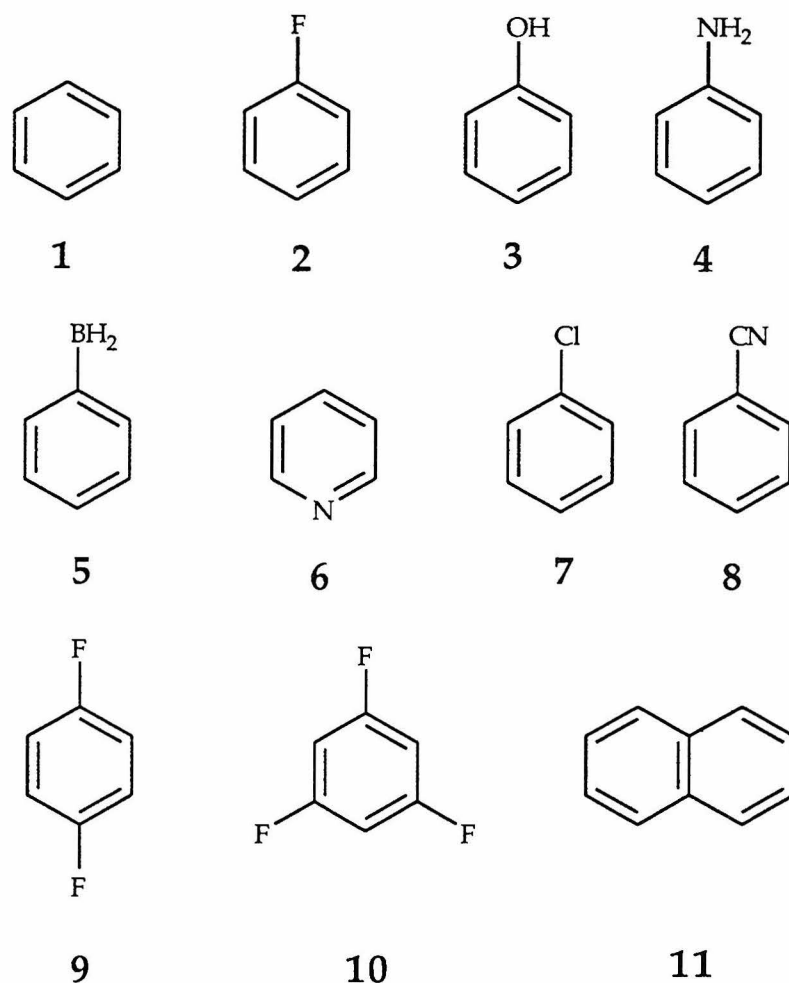


Figure 2.5. Aromatic structures evaluated in the present study.

We consider sodium complexes of these aromatics, a good model for the quantitative trends expected in the cation- π interactions. Thus, although experimental studies with cyclophane hosts such as P (chapter 1) are centered on the binding of ammonium or iminium guests, we believe

that sodium can yield correct results. In fact, we have shown that using the ammonium ion instead of sodium, does not alter in any way the results.¹¹ We have first evaluated the binding energies of compounds **1-11** to the sodium ion at the 6-31G**//6-31G** level using the Gaussian 92 package¹². In order to do this, we have placed the sodium atom above the ring centroid. In all the complexes, the sodium position and the geometry of the aromatic molecule were then optimized. An example of the geometry used, is reported in Figure 2.6 for the system benzene- Na^+ .

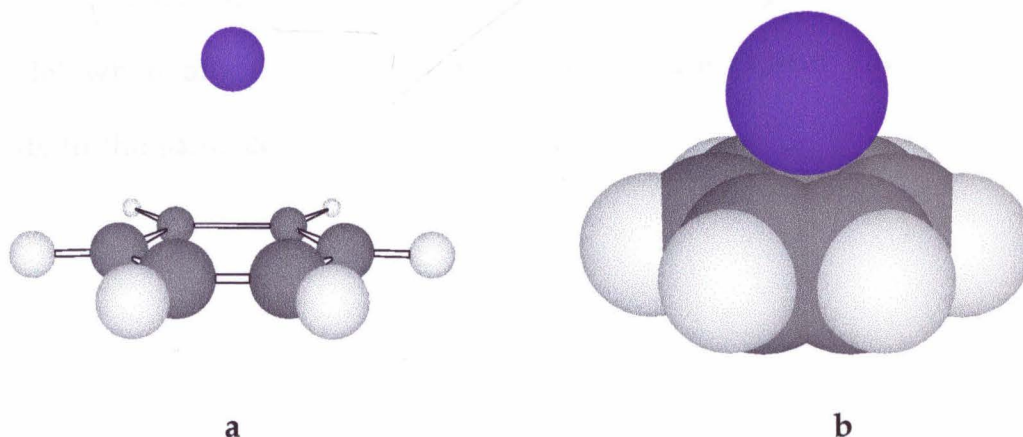


Figure 2.6. a) Optimized geometry for the complex benzene- Na^+ . b) The same complex in a CPK representation.

In the case of pyridine (**6**), no energy minimum was found over the ring. The optimized structure was a C_{2v} complex with the sodium in the plane of the aromatic ring and pointing toward the nitrogen. In order to estimate the binding energy of this aromatic to sodium (ion to face), the ion was fixed over the center of the ring and the complex optimized with this constraint.

The electrostatic contribution to binding was estimated by replacing the sodium ion of the optimized complex with a dummy, probe atom, and evaluating the electrostatic potential EP_{opt} at that point. For purposes of comparison, we also performed the same calculation using the geometry of the uncomplexed aromatic molecule and evaluating the potential at 2.47Å above the ring centroid, EP_{unopt} . The distance of 2.47Å is an average distance of Na^+ from the optimized complexes of molecules 1-11 (Table 2.1). This latter approach clearly verifies the validity of the electrostatic model when any distortions due to the Na^+ are absent. Either approach leads to the same conclusion.

Compound	HF Energy (H)	Na ⁺ to plane distance(Å)
1 (<i>D</i> _{6h})	-230.7138600	
2 (<i>C</i> _{2v})	-329.5636601	
3 (<i>C</i> _s)	-305.5737552	
4 (<i>C</i> _s)	-285.7475990	
5 (<i>C</i> _{2v})	-255.9720659	
6 (<i>C</i> _{2v})	-246.7046117	
7 (<i>C</i> _{2v})	-689.6123427	
8 (<i>C</i> _{2v})	-322.4477225	
9 (<i>D</i> _{2h})	-428.4109297	
10 (<i>D</i> _{3h})	-527.2607015	
11 (<i>D</i> _{2h})	-383.3693648	
Na ⁺	-161.6592883	
1•••Na ⁺ (<i>C</i> _{6v})	-392.4163047	2.451 Å
2•••Na ⁺ (<i>C</i> _s)	-491.2579659	2.496
3•••Na ⁺ (<i>C</i> ₁)	-467.2759556	2.459
4•••Na ⁺ (<i>C</i> _s)	-447.4576392	2.433
5•••Na ⁺ (<i>C</i> _s)	-417.6702063	2.455
6•••Na ⁺ (<i>C</i> _s)	-408.3957852 ^b	2.509
7•••Na ⁺ (<i>C</i> _s)	-851.3058568	2.489
8•••Na ⁺ (<i>C</i> _s)	-484.1320309	2.533
9•••Na ⁺ (<i>C</i> _{2v})	-590.0969364	2.545
10•••Na ⁺ (<i>C</i> _{3v})	-688.9398311	2.599
11•••Na ⁺ (<i>C</i> _s)	-545.0743541	2.430

Table 2.1 6-31G**//6-31G** Hartree-Fock energies in Hartree for 1-11, Na⁺, and the π -face complexes 1•••Na⁺-11•••Na⁺. Symmetry of the complexes are also reported together with the distance of sodium from the plane of the ring in the optimized complexes.

First of all, let's consider compounds 1-5. The atoms of the substituents in compounds 2-4 belong to the first row (periods 3-7) of the periodic table. Therefore, we can consider these compounds as the prototypical substituted benzenes. Looking to the binding energies of these compounds to Na⁺ (Table 2.2), we can see that there is a general trend: aniline is better

than benzene at binding sodium, and fluorobenzene is worse. Looking at phenol and phenylborane, we notice some peculiarities.

Complex	BE	EP _{opt}	EP _{unopt}
1...Na ⁺	-27.1	-15.6	-15.0
2...Na ⁺	-21.9	-10.5	-9.8
3...Na ⁺	-26.9	-15.8	-13.9
4...Na ⁺	-31.8	-20.7	-19.3
5...Na ⁺	-24.4	-12.1	-11.0
6...Na ⁺	-20.0	-8.9	-8.4
7...Na ⁺	-21.5	-9.8	-9.3
8...Na ⁺	-15.7	-3.7	-3.3
9...Na ⁺	-16.8	-5.2	-4.6
10...Na ⁺	-12.4	-1.2	0.3
11...Na ⁺	-28.7	-14.9	-14.2

Table 2.2. 6-31G**//6-31G** Hartree-Fock binding energies (BE) in kcal/mol and electrostatic contributions (EP_{opt}-EP_{unopt}) in kcal/mol to the binding energies for 1:1 complexes of compounds 1-11 with Na⁺

Thus, phenol, which in classic organic chemistry is described as an electron-rich system, is not better than benzene at binding Na⁺. Also, phenylborane, the full π - acceptor is not very different from fluorobenzene

2. Clearly, this trend cannot be explained through resonance arguments. However, a more careful analysis, shows that the binding data for 1-5 are in a somewhat rough agreement with a σ_m and a σ_m^+ Hammett plots (Figures 2.7 and 2.8).¹³

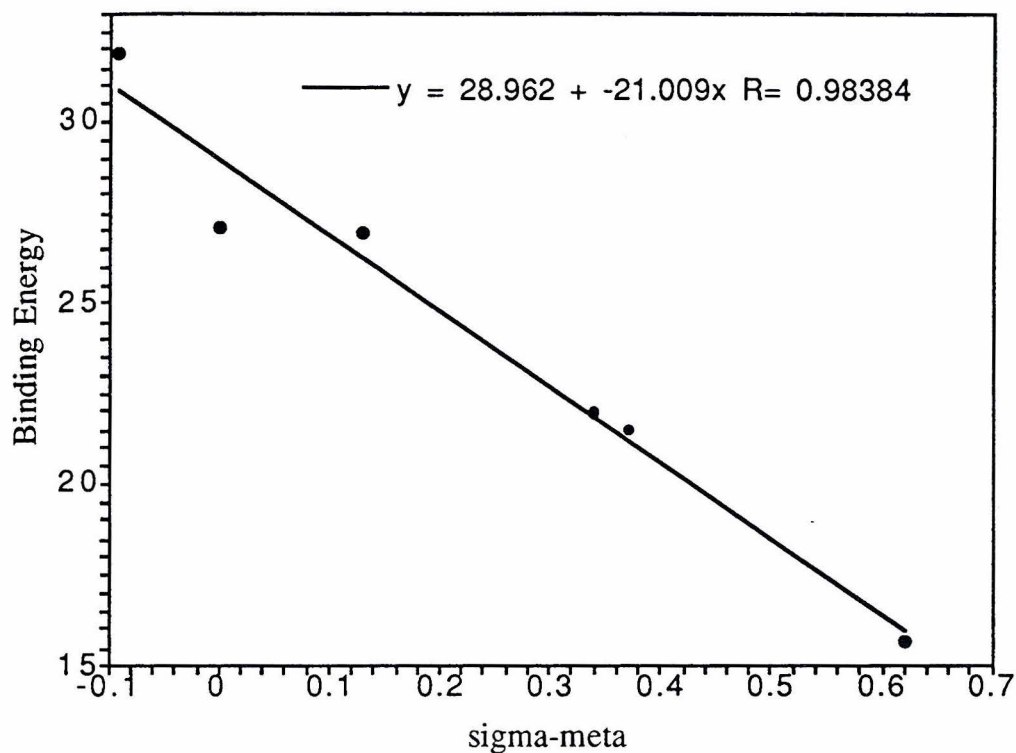


Figure 2.7. Hammett Plot for the binding constants of 1-11 to Na^+ and the substituent constant σ_m .

It may be noticed that a linear relation in the Hammett plots is *only* found when meta substituents are considered (σ_m and σ_m^+). This kind of agreement means that in the binding of these aromatics to Na^+ , the inductive effects are much more relevant than the resonance effects.

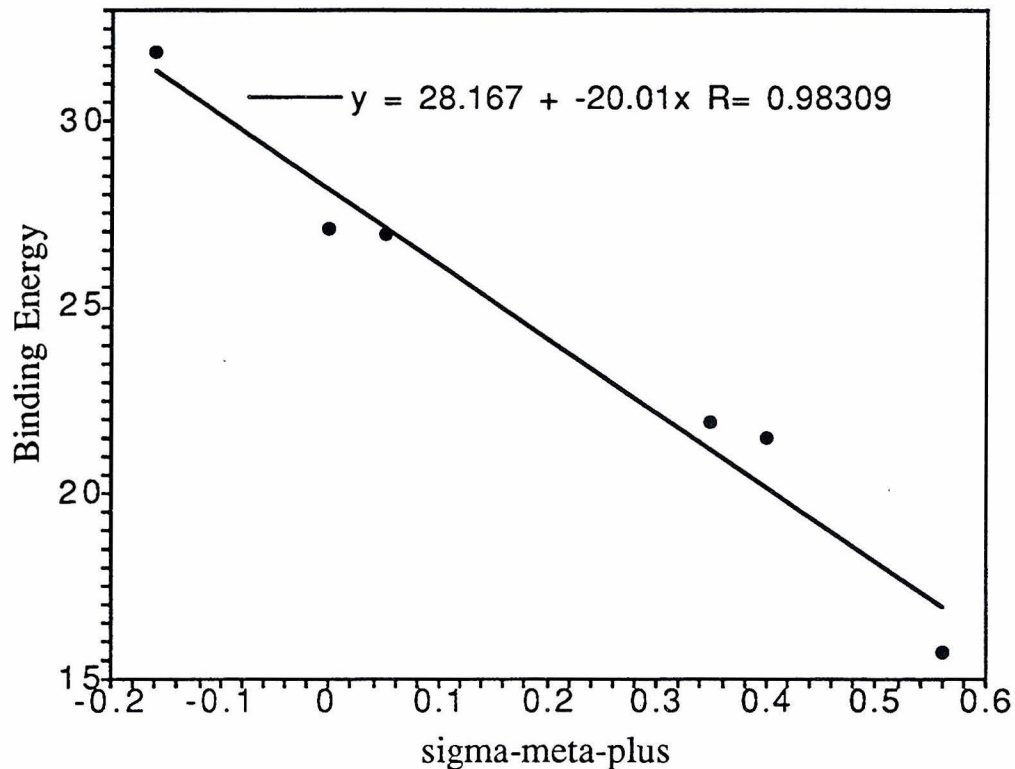


Figure 2.8. Hammett Plot for the binding constants of **1-11** to Na^+ and the substituent constant σ_{m}^+ . σ_{m}^+ for the substituent OH has not been measured. In its place and only for completeness, σ_{m} for OH has been used.

A much more satisfying rationalization comes from a plot of the electrostatic contribution to the binding energy EP_{opt} vs. the binding energy, Figure 2.9.

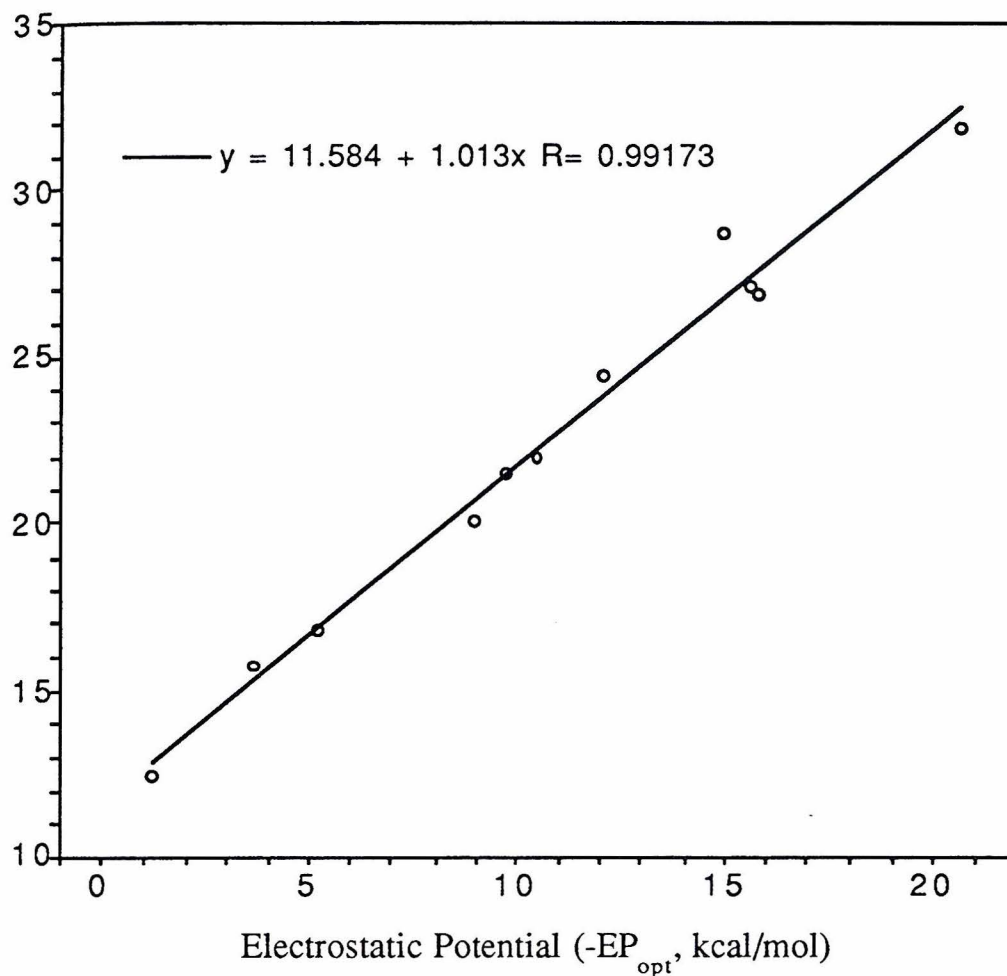


Figure 2.9. Correlation between binding energy and electrostatic potential (Ep_{opt}) for molecules 1-11 in their complexes with sodium cation .

This plot has many interesting features. First of all we can notice that the slope is 1.0 and the intercept 11.6. This means that essentially, *100% of the variation among 1-11 is reflected in the electrostatic term*. All other factors that one can think of, such as induced dipole, charge transfer, dispersion

forces, will account for a constant term worth 11.6 kcal/mol in this series. This means that a structure with no electrostatic component is predicted to have a binding energy of about 12 kcal/mol. Such a structure is 1,3,5-trifluorobenzene (**10**), a structure that is well known to have a quadrupole moment near zero.¹⁴ As we can see from Table 2.2, the binding energy of **10** to sodium is -12.4 kcal/mol, while the electrostatic contribution is near to zero. This is a strong confirmation of the value of these results. All these considerations are supported by the very high correlation coefficient of the plot (0.991).

We can also try to plot the binding energy vs. the electrostatic contribution to the binding energy, calculated at the fixed distance of 2.47 Å from the plane of the ring (EP_{unopt}), Figure 2.10.

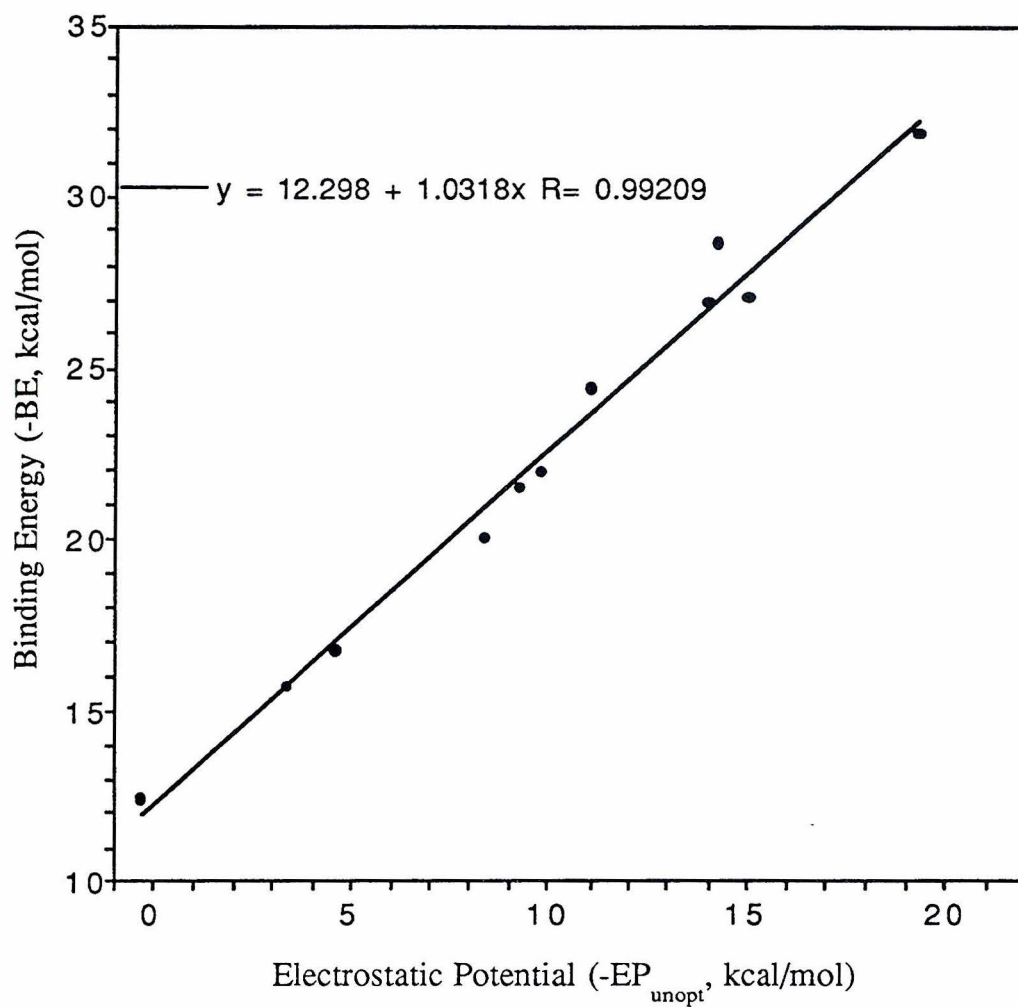


Figure 2.10. Correlation between binding energy and electrostatic potential (EP_{unopt}) for molecules 1-11 in their complexes with sodium cation. Sodium is kept at the fixed distance of 2.47Å in all the complexes.

As we can see not only didn't the situation change but the correlation coefficient is even slightly better.

In consideration of our discussion on short-range and long-range intermolecular forces, it is surprising how well a simple electrostatic model treats such a considerable variation in binding energy so well.

We also carried out additional calculations to determine the extent of the basis set superposition error (BSSE). Estimates of the BSSE were obtained by performing counterpoise calculations on the complexes **1-11** with sodium cation. The absolute BSSE was found to be small and in the range 1.4-1.8 kcal/mol for all the complexes. More significantly, Δ BSSE, that is the extent to which the BSSE preferentially stabilizes one complex vs. another, was found to be negligible (<0.3 kcal/mol) for all comparisons

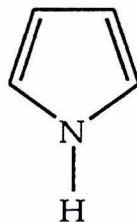
We also verified that the lack of electron correlation in the Hartree-Fock energies did not significantly alter the calculated binding energies. In order to do this, we calculated the binding energies for compounds **1**, **2**, and **4** at the MP2/6-31G**//6-31G** level. The addition of correlation, increased the binding energies of these complexes by 2.6 kcal/mol, 3.2 kcal/mol and 3.3 kcal/mol respectively. However, the corrections for zero point energy and BSSE at this level, almost completely compensate for the MP2 correction. Since the HF value for the benzene complex to sodium cation was found to be closer to the experimental value,⁵⁻⁸ and because the MP2 corrections did not alter the trends in the data, we relied on the Hartree-Fock results.

From the plots of Figure 2.9 and 2.10 we can see that there are very subtle deviations. Naphthalene is one of them. It lies above the correlation line. This is completely reasonable. As a matter of fact, the polarizability related terms, that should be the major terms after the electrostatic contribution, are larger for a molecule with a larger surface area. Still, this variation is fairly small and naphthalene correlates pretty well with the other points.

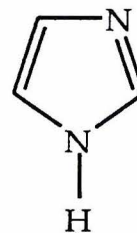
It is necessary to point out that the linear correlation seen for compounds 1-11 is specific for substituted benzenes. When other classes of aromatic molecules are investigated, they show similar linear correlations between binding energies and electrostatic contributions. However, while the slope is always 1, the intercepts are slightly different. Again, this is completely reasonable. For example, if we consider the series, furan, pyrrole, imidazole (12-14), it is natural that the contribution to the binding coming from polarizability-related terms and charge transfer effects are different from the same terms in the series of substituted benzenes (Figure 2.11).



12



13



14

In fact, the constant term, defined by the intercept, is specific for a class of compounds, for it derives from the specific geometric and electronic characteristic of those compounds. In this sense, 5-membered rings cannot behave as six-membered rings. However, the important points are that the linear relationship between binding energy and its electrostatic contribution holds, that the slope is 1 and that electrostatics are responsible for a major portion of the binding in most of the aromatics.

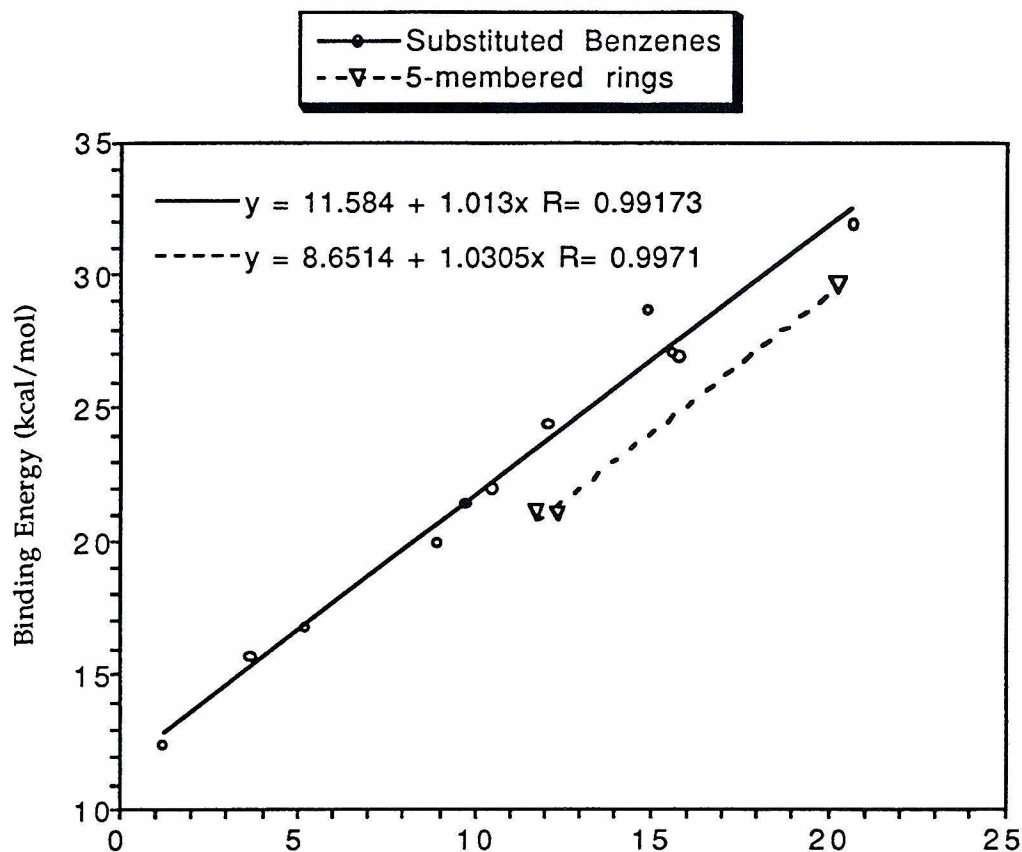


Figure 2.11. Binding energy/electrostatic potential plots for two classes of compounds, substituted benzenes 1-11 and 5-membered rings 12-14.

These results are consistent with other analyses of the cation- π interaction. In particular, Kollmann suggested that the electrostatic terms account for about 60% of the total binding energy for the system ethylene-lithium cation.¹⁵

Attempts at partitioning the binding energy in complexes between aromatic molecules and ammonium cations have also been recently reported in the literature.^{16, 17} These attempts are based on component analysis of the full wavefunction of the system. As such, the results are

always subject to complex interpretations. We believe that the simple, direct evaluation of electrostatic energy is a better way to describe the interactions in these complexes. This is particularly true in consideration of the fact that in most aromatic systems, electrostatic forces make a major contribution to the cation- π interaction.

The electrostatic arguments exposed so far, allow one to completely rationalize the trends across a series of related structures. This has important consequences for the design or the evaluation of new systems. However, *ab initio* calculations of the binding energies of the sodium cation to the aromatic molecule of interest are not an easy or affordable way to look at new structures. As such, we will present in the next chapter, a new methodology for the fast and direct evaluation of the strength of cation- π interactions in π -systems.

2.5 Appendix A

Theory of Long-Range Intermolecular Forces

The aim of a general theory of long-range intermolecular forces is to relate the intermolecular potential to the properties of the isolated molecules. Thus, if we consider the interaction between two molecules a and b we must assume that each molecule retains its identity. In particular, we assume that the effects of electron exchange are negligible. Any other effect that decreases exponentially with increasing molecular separation must also be negligible. This is the primary condition for long-range intermolecular interactions.

If this is true, we can then write the Hamiltonian of the system of the two molecules as:

$$H = H^a + H^b + H^{\text{int}} \quad (2.8)$$

where H^a and H^b are the Hamiltonians of the free molecules and H^{int} is the interaction. H^{int} can be considered a perturbation to $H^a + H^b$. If the two molecules a and b are in the states n_a and n_b , we can use standard quantum mechanical perturbation theory¹⁰, to express the perturbed wavefunction in terms of the eigenfunctions of $H^a + H^b$:

$$|\psi_{ab}\rangle = |n_a n_b\rangle + \sum_{p_a p_b} \frac{\langle p_a p_b | H^{\text{int}} | n_a n_b \rangle}{E_{m_a} + E_{m_b} - E_{p_a} - E_{p_b}} |p_a p_b\rangle + \dots \quad (2.9)$$

where the sum is over the complete set of unperturbed states $p_a p_b$ and only the first-order perturbation is reported. The energy of the pair of molecules is then:

$$E_{m_a, m_b} = \frac{\langle \psi_{m_a m_b} | H | \psi_{m_a m_b} \rangle}{\langle \psi_{m_a m_b} | \psi_{m_a m_b} \rangle} = E_{m_a} + E_{m_b} + \langle m_a m_b | H^{\text{int}} | m_a m_b \rangle - \sum_{p_a p_b} \frac{|\langle p_a p_b | H^{\text{int}} | m_a m_b \rangle|^2}{E_{p_a} + E_{p_b} - E_{m_a} - E_{m_b}} + \dots \quad (2.10)$$

In eq. 2.10, the first-order energy $\langle m_a m_b | H^{\text{int}} | m_a m_b \rangle$ is the unperturbed expectation value of the perturbation H^{int} and it is by definition, the electrostatic interaction energy. The second-order energy in eq. 2.10 may be separated into two factors, the induction energy and the dispersion energy. In this treatment, we will not specifically derive expressions for these two latter terms.

The next step in deriving a general equation for the electrostatic energy, is to expand H^{int} in a multipole series. To do this we need to consider the reference frame described in Figure 2.12.

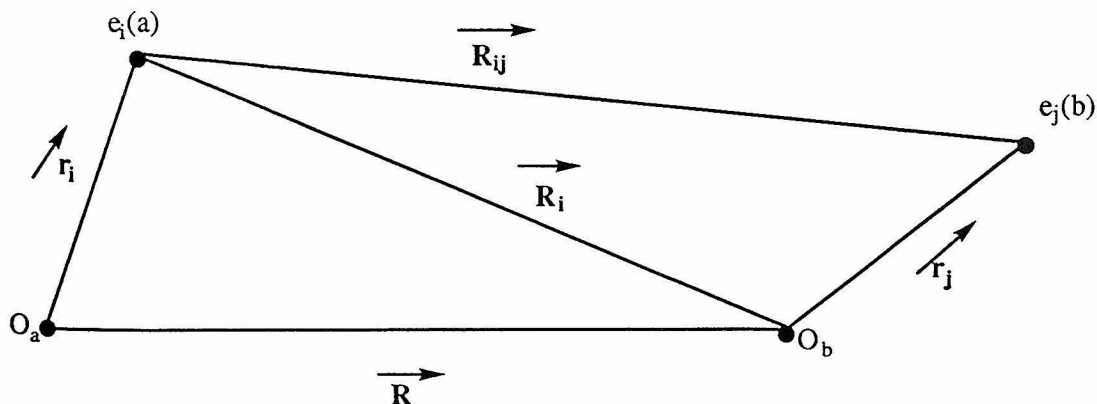


Figure 2.12. Definition of the relative position of the charges e_i and e_j of the molecules a and b respectively.

If we call e_i and e_j charges in the molecules a and b, we can define their relative position using the vector $\mathbf{R}_{ij}$ (Figure 2.10). The trick is that $\mathbf{R}_{ij}$ is obviously defined by:

$$\mathbf{R}_{ij} = \mathbf{R} + \mathbf{r}_i - \mathbf{r}_j \quad (2.11)$$

and it can be expanded as a power series in R^{-1} , where R is the distance between the origins O_a and O_b fixed in each molecule. The interaction Hamiltonian can then be written as:

$$H^{\text{int}} = (4\pi\epsilon_0)^{-1} \sum_{i,j} \frac{e_i e_j}{R_{ij}} = \sum_i e_i \phi_i = \sum_j e_j \phi_j \quad (2.12)$$

where:

$$\phi_j = (4\pi\epsilon_0)^{-1} \sum_i \frac{e_i}{R_{ij}} \quad (2.13)$$

is the potential at the j th charge of the molecule b due to all charges in the molecule a. Expanding eq. 2.13 as a Taylor series we have:

$$\begin{aligned} H^{\text{int}} &= \sum_j e_j \left[\phi^b + (\nabla_\alpha \phi^b)_0 r_{j\alpha} + \frac{1}{2} (\nabla_\alpha \nabla_\beta \phi^b)_0 r_{j\alpha} r_{j\beta} + \dots \right] = \\ &= q^b \phi^b - \mu_\alpha^b F_\alpha^b - \frac{1}{3} \Theta_{\alpha\beta}^b F_{\alpha\beta}^b - \dots \frac{1}{1 \cdot 3 \cdot 5 \cdot \dots (2n-1)} \xi_{\alpha\beta\gamma\dots\nu}^{nb} F_{\alpha\beta\gamma\dots\nu}^b - \dots \end{aligned} \quad (2.14)$$

In eq. 2.14 we have that $F_\alpha^b = -(\nabla_\alpha \phi^b)_0$ is the electric field at the fixed origin of molecule b (O_b in Figure 2.11) due to the instantaneous charge distribution of the molecule a. $F_{\alpha\beta}^b = -(\nabla_\alpha \nabla_\beta \phi^b)_0$ is the field gradient. q^b (charge), μ_α^b (dipole), $\Theta_{\alpha\beta}^b$ (quadrupole) and $\xi_{\alpha\beta\gamma\dots\nu}^b$ (ν th multipole) are the electric

multipole tensors of the molecule b. We have already given the definition for the quadrupole moment (eq. 2.4). $\xi_{\alpha\beta\gamma\dots v}^b$ is defined as:

$$\xi_{\alpha\beta\gamma\dots v}^b = (-1)^n (n!)^{-1} \sum_j e_j^b r_j^{2n+1} \frac{\partial}{\partial r_{i\alpha}} \frac{\partial}{\partial r_{j\beta}} \frac{\partial}{\partial r_{\gamma}} \dots \frac{\partial}{\partial r_{iv}} \left(\frac{1}{r_i} \right) \quad (2.15)$$

The number of independent multipole moments for molecules having symmetry elements can be determined by group theory methods.

In eq. 2.14 the potential ϕ and the fields F can be expressed in terms of the multipole moments of a molecule. This is reached by expanding R_i^{-1} as a Taylor series:

$$\begin{aligned} \phi_j &= (4\pi\epsilon_0)^{-1} \sum_i \frac{e_i}{R_i} = (4\pi\epsilon_0)^{-1} \sum_i e_i^a \left[R^{-1} - r_{i\alpha} \nabla_\alpha R^{-1} + \frac{1}{2} r_{i\alpha} r_{i\beta} \nabla_\alpha \nabla_\beta R^{-1} \dots \right] = \\ &= q^a T - \mu_\alpha^a T_\alpha + \frac{1}{3} \Theta_{\alpha\beta}^a T_{\alpha\beta} - \frac{1}{15} \Omega_{\alpha\beta\gamma}^a T_{\alpha\beta\gamma} + \dots \\ &\quad \dots (-1)^n \frac{1}{1 \cdot 3 \cdot 5 \dots (2n-1)} \xi_{\alpha\beta\gamma\dots v}^{na} T_{\alpha\beta\gamma\dots v} \end{aligned} \quad (2.16)$$

where $T_{\alpha\beta\lambda\dots v} = (4\pi\epsilon_0)^{-1} \nabla_\alpha \nabla_\beta \nabla_\lambda \dots \nabla_v R^{-1}$ is a tensor that is symmetric with respect to interchange of any pair of suffixes and is reduced to zero on contraction.

Considering that the field F^b is:

$$\begin{aligned} F_\alpha^b &= -\nabla_\alpha \phi^b = -q T_\alpha + \mu_\beta^a T_{\alpha\beta} - \frac{1}{3} \Theta_{\beta\gamma}^a T_{\alpha\beta\gamma} \dots \\ F_{\alpha\beta}^b &= -\nabla_\alpha \nabla_\beta \phi^b = -q^a T_{\alpha\beta} + \mu_\gamma^a T_{\alpha\beta\gamma} - \frac{1}{3} \Theta_{\gamma\delta}^a T_{\alpha\beta\gamma\delta} + \dots \end{aligned} \quad (2.17)$$

we can express the interaction Hamiltonian in eq. 2.14 as:

$$\begin{aligned}
H^{\text{int}} &= Tq^a q^b + T_\alpha (q^a \mu_\alpha^a - q^b \mu_\alpha^a) + T_{\alpha\beta} \left(\frac{1}{3} q^a \Theta_{\alpha\beta}^b + \frac{1}{3} q^b \Theta_{\alpha\beta}^a - \mu_\alpha^a \mu_\beta^b \right) + \dots = \\
&= \sum_{n=0}^{\infty} \sum_{n'=0}^{\infty} (-1)^{n'} \frac{1}{1 \cdot 3 \cdot 5 \cdot \dots (2n-1)} \frac{1}{1 \cdot 3 \cdot 5 \cdot \dots (2n'-1)} \cdot T_{\alpha\beta\gamma \dots \nu \alpha' \beta' \gamma' \dots \nu'} \xi_{\alpha\beta\gamma \dots \nu}^{nb} \xi_{\alpha' \beta' \gamma' \dots \nu'}^{n'a}
\end{aligned}
\tag{2.18}$$

At this point, the electrostatic interaction energy can be immediately expressed in terms of the permanent multipole moments of molecules a and b, combining eq. 2.10 and eq. 2.18:

$$\begin{aligned}
E_{\text{electrostatic}} &= \langle m_a m_b | H^{\text{int}} | m_a m_b \rangle = Tq^a q^b + T_\alpha (q^a \mu_\alpha^{n_b} - q^b \mu_\alpha^{n_a}) + \\
&\quad + T_{\alpha\beta} \left(\frac{1}{3} q^a \Theta_{\alpha\beta}^{n_b} + \frac{1}{3} q^b \Theta_{\alpha\beta}^{n_a} - \mu_\alpha^{n_a} \mu_\beta^{n_b} \right) + \dots = \\
&= \sum_{n=0}^{\infty} \sum_{n'=0}^{\infty} (-1)^{n'} \frac{2^{n+n'} (n)!(n')!}{(2n)!(2n')!} T_{\alpha\beta\gamma \dots \nu \alpha' \beta' \gamma' \dots \nu'} \xi_{\alpha\beta\gamma \dots \nu}^{n,nb} \xi_{\alpha' \beta' \gamma' \dots \nu'}^{n',na}
\end{aligned}
\tag{2.19}$$

Although eq. 2.19 appears as a complex expression, symmetry elements in the molecules a and b and their spatial orientation allow enormous simplifications, so that eq. 2.19 is actually a simple expression to use. Also, if only the dipole moments μ and the quadrupole moments Θ are considered (μ and Θ are the multipole moments that are measurable) eq. 2.19 is substantially simplified.

2.6 Appendix B

Sample of Input Files for the Calculation of Binding Energies and Electrostatic Potentials

All the calculations were performed on an IRIS 4D/220GTX workstation using the GAUSSIAN 92 package.¹²

In this appendix, the input files used for aniline will be presented. All the calculations performed on the other compounds were made with similar input files and using the symmetry constraints indicated in Table 1.1.

HF/6-31G** Optimization of Aniline.

```
$RunGauss
#p rhf/6-31g** fopt pop=min test
```

```
aniline - 6-31G C2v opt
```

```
0,1
C
X,1,1.0
C,1,r1,2,90.0
X,3,1.0,1,90.0,2,0.0
C,1,r2,2,90.0,4,a1
C,1,r2,2,90.0,4,-a1
C,5,r3,1,a2,6,0.0
C,6,r3,1,a2,5,0.0
H,5,r4,1,a3,6,180.0
H,6,r4,1,a3,5,180.0
N,1,r5,2,90.0,4,180.0
H,3,r6,4,90.0,2,180.0
H,7,r7,3,a4,12,0.0
H,8,r7,3,a4,12,0.0
H,11,r8,1,a5,2,90.0
H,11,r8,1,a5,2,-90.0
```

```

r1=2.80467798
r2=1.39696813
r3=1.38473634
r4=1.07417033
r5=1.38042996
r6=1.07228085
r7=1.07370684
r8=0.98896431
a1=59.30988156
a2=120.40301668
a3=119.54254536
a4=119.92317899
a5=121.07073133

```

HF/6-31G**/6-31G** Optimization of the Complex Aniline-Na⁺.

```

$RunGauss
#p rhf/6-31g** fopt pop=min test

```

aniline - 6-31G** C2v opt

```

1,1
C
X,1,1.0
C,1,r1,2,90.0
X,3,1.0,1,90.0,2,0.0
C,1,r2,2,aa1,4,a1
C,1,r2,2,aa1,4,-a1
C,5,r3,1,a2,6,d1
C,6,r3,1,a2,5,-d1
H,5,r4,1,a3,6,d2
H,6,r4,1,a3,5,-d2
N,1,r5,2,aa2,4,180.0
H,3,r6,4,aa3,2,180.0
H,7,r7,3,a4,12,d3
H,8,r7,3,a4,12,-d3
H,11,r8,1,a5,2,d4
H,11,r8,1,a5,2,-d4
Na,11,rna,1,ana,2,180.0

```

```

rna=2.35

```

```

ana=91.0
r1=2.80359974
r2=1.39560226
r3=1.3823014
r4=1.0768049
r5=1.37369928
r6=1.07482848
r7=1.07650066
r8=0.98937209
a1=59.26852333
a2=120.37000712
a3=119.58255259
a4=119.89079902
a5=120.9570248
aa1=90.01
d1=0.01
d2=180.01
aa2=90.02
aa3=90.03
d3=0.02
d4=90.04

```

Electrostatic Potential (EP_{opt}) Calculation.

```

$RunGauss
#p rhf/6-31g** pop=min prop=potential scf=(tight,direct) test

```

aniline + Na+ - EP

```

0,1
C
X,1,1.0
C,1,r1,2,90.0
X,3,1.0,1,90.0,2,0.0
C,1,r2,2,aa1,4,a1
C,1,r2,2,aa1,4,-a1
C,5,r3,1,a2,6,d1
C,6,r3,1,a2,5,-d1
H,5,r4,1,a3,6,d2
H,6,r4,1,a3,5,-d2
N,1,r5,2,aa2,4,180.0

```

H,3,r6,4,aa3,2,180.0
 H,7,r7,3,a4,12,d3
 H,8,r7,3,a4,12,-d3
 H,11,r8,1,a5,2,d4
 H,11,r8,1,a5,2,-d4
 X,1,1.38,2,90.0,11,180.0
 Bq,17,rna,1,ana,2,180.0

rna=2.44130365
 ana=92.62699529
 r1=2.79874822
 r2=1.39277401
 r3=1.38310272
 r4=1.07683961
 r5=1.3947993
 r6=1.07497409
 r7=1.07632956
 r8=0.99564723
 a1=59.35522927
 a2=120.38827003
 a3=119.59274805
 a4=119.95094019
 a5=114.61867046
 aa1=90.04392204
 d1=0.1036308
 d2=180.48927479
 aa2=91.94714335
 aa3=89.90712356
 d3=-0.03821906
 d4=65.27359952

Estimate of the Basis Set Superposition Error

\$RunGauss
 #p rhf/6-31g** pop=min message scf=(tight,direct) test
 aniline + Na+ - at opt geo
 1,1
 C
 X,1,1.0

C,1,r1,2,90.0
 X,3,1.0,1,90.0,2,0.0
 C,1,r2,2,aa1,4,a1
 C,1,r2,2,aa1,4,-a1
 C,5,r3,1,a2,6,d1
 C,6,r3,1,a2,5,-d1
 H,5,r4,1,a3,6,d2
 H,6,r4,1,a3,5,-d2
 N,1,r5,2,aa2,4,180.0
 H,3,r6,4,aa3,2,180.0
 H,7,r7,3,a4,12,d3
 H,8,r7,3,a4,12,-d3
 H,11,r8,1,a5,2,d4
 H,11,r8,1,a5,2,-d4
 X,1,1.38,2,90.0,11,180.0
 Na,17,rna,1,ana,2,180.0

rna=2.44130365
 ana=92.62699529
 r1=2.82166931
 r2=1.4038059
 r3=1.38915224
 r4=1.07596125
 r5=1.37430552
 r6=1.07414892
 r7=1.07568324
 r8=0.99560181
 a1=59.10339702
 a2=120.56734207
 a3=119.5715073
 a4=119.90640232
 a5=116.78118825
 aa1=90.77303323
 d1=2.72698075
 d2=179.37743978
 aa2=91.77232881
 aa3=87.47177529
 d3=-1.11224968
 d4=68.90002616

1 0 0.0
 2 0 0.0
 3 0 0.0
 4 0 0.0
 5 0 0.0
 6 0 0.0

7 0 0.0
 8 0 0.0
 9 0 0.0
 10 0 0.0
 11 0 0.0
 12 0 0.0
 13 0 0.0
 14 0 0.0

\$RunGauss
 #p rhf/6-31g** pop=min message scf=(tight,direct) test

aniline + Na+ - at opt geo

0,1
 C
 X,1,1.0
 C,1,r1,2,90.0
 X,3,1.0,1,90.0,2,0.0
 C,1,r2,2,aa1,4,a1
 C,1,r2,2,aa1,4,-a1
 C,5,r3,1,a2,6,d1
 C,6,r3,1,a2,5,-d1
 H,5,r4,1,a3,6,d2
 H,6,r4,1,a3,5,-d2
 N,1,r5,2,aa2,4,180.0
 H,3,r6,4,aa3,2,180.0
 H,7,r7,3,a4,12,d3
 H,8,r7,3,a4,12,-d3
 H,11,r8,1,a5,2,d4
 H,11,r8,1,a5,2,-d4
 X,1,1.38,2,90.0,11,180.0
 Na,17,rna,1,ana,2,180.0

rna=2.44130365
 ana=92.62699529
 r1=2.82166931
 r2=1.4038059
 r3=1.38915224
 r4=1.07596125
 r5=1.37430552
 r6=1.07414892
 r7=1.07568324
 r8=0.99560181
 a1=59.10339702

```

a2=120.56734207
a3=119.5715073
a4=119.90640232
a5=116.78118825
aa1=90.77303323
d1=2.72698075
d2=179.37743978
aa2=91.77232881
aa3=87.47177529
d3=-1.11224968
d4=68.90002616

```

```
15 0 0.0
```

RMP2/6-31G** Calculation of the Energy of the Complex Aniline-Na⁺

```

$RunGauss
#p rmp2(full)/6-31g** pop=min scf=(tight,direct) MaxDisk=32000000 test

```

aniline + Na⁺ - at opt geo

```

1,1
C
X,1,1.0
C,1,r1,2,90.0
X,3,1.0,1,90.0,2,0.0
C,1,r2,2,aa1,4,a1
C,1,r2,2,aa1,4,-a1
C,5,r3,1,a2,6,d1
C,6,r3,1,a2,5,-d1
H,5,r4,1,a3,6,d2
H,6,r4,1,a3,5,-d2
N,1,r5,2,aa2,4,180.0
H,3,r6,4,aa3,2,180.0
H,7,r7,3,a4,12,d3
H,8,r7,3,a4,12,-d3
H,11,r8,1,a5,2,d4
H,11,r8,1,a5,2,-d4
X,1,1.38,2,90.0,11,180.0
Na,17,rna,1,ana,2,180.0

```

rna=2.44130365
ana=92.62699529
r1=2.82166931
r2=1.4038059
r3=1.38915224
r4=1.07596125
r5=1.37430552
r6=1.07414892
r7=1.07568324
r8=0.99560181
a1=59.10339702
a2=120.56734207
a3=119.5715073
a4=119.90640232
a5=116.78118825
aa1=90.77303323
d1=2.72698075
d2=179.37743978
aa2=91.77232881
aa3=87.47177529
d3=-1.11224968
d4=68.90002616

2.7 Appendix C

The Binding of the Hydronium Ion to Benzene

We will describe here the special case of the binding of the hydronium ion, H_3O^+ , to benzene. The structure for the calculation was generated by placing the pyramidal structure of H_3O^+ over the plane of benzene, so that the final structure was characterized by a C_{3v} symmetry (Figure 2.13).

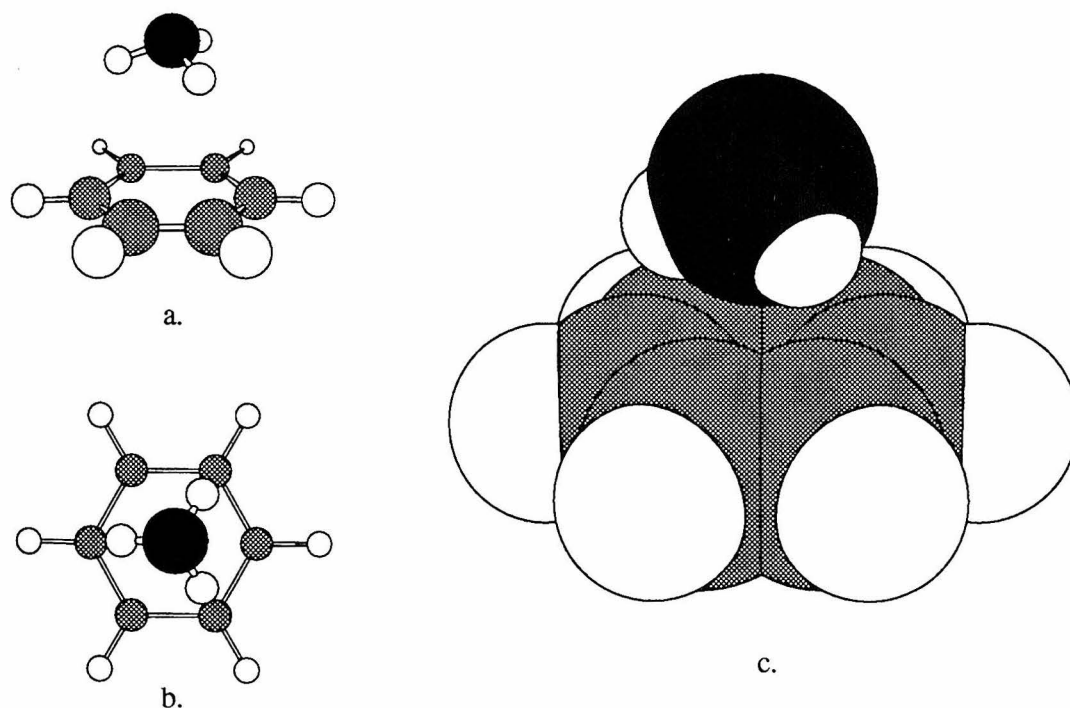


Figure 2.13. Geometry of the optimized complex between benzene and H_3O^+ . a) side view. b) view from above the plane. c) CPK representation of system a.

Benzene and H_3O^+ were first optimized at the HF/6-31G** level. During the optimization of H_3O^+ it was noted that at the 6-31G level (used as

starting point for the HF/6-31G** calculation), the cation was optimized as a planar structure. Clearly, the 6-31G level is not adequate for this optimization. H_3O^+ was therefore optimized starting from a pyramidal structure and carrying out the optimization directly at the 6-31G** level. This procedure gave a structure that is not very different from the pyramidal structures reported from experimental and theoretical studies over H_3O^+ .¹⁸

After this, a Hartree-Fock 6-31G**//6-31G** optimization of the complex was performed.

The following results were obtained:

HF Energy of H_3O^+ = -76.3103248 ion

HF Energy of benzene = -230.71386

HF Energy of the Complex = -307.0550251

Binding Energy_{benzene- hydronium ion} = 19.35 kcal/mol

Distance oxygen-ring centroid = 2.89 Å

∠ H-O-H = 107.57 Å

2.8 Appendix 4

Multipole Moments for Compounds 1-11

The multipole moments for molecule 1-11 are reported in this section. They have been calculated during the Hartree-Fock optimization of the molecules at the level 6-31G** (HF/6-31G**//6-31G**). The numbers reported are the sum of the atomic contributions to the multipole moments. The actual quadrupole moments can be calculated applying eq. 2.4.

$$1 \text{ Debye-Angstrom} = 3.3356 \times 10^{-40} \text{ Cm}^2$$

BENZENE

Charge= 0.0000 electrons

Dipole moment (Debye):

X= 0.0000 Y= 0.0000 Z= 0.0000 Tot= 0.0000

Quadrupole moment (Debye-Ang):

XX= -31.3942 YY= -31.3942 ZZ= -39.6825

XY= 0.0000 XZ= 0.0000 YZ= 0.0000

Octapole moment (Debye-Ang**2):

XXX= 0.0000 YYY= 0.0000 ZZZ= 0.0000 XYY= 0.0000

XXY= 0.0000 XXZ= 0.0000 XZZ= 0.0000 YZZ= 0.0000

YYZ= 0.0000 XYZ= 0.0000

Hexadecapole moment (Debye-Ang**3):

XXXX= -262.8693 YYYY= -262.8693 ZZZZ= -42.7205 XXXY= 0.0000

XXXZ= 0.0000 YYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000

ZZZY= 0.0000 XXYY= -87.6231 XXZZ= -61.1531 YYZZ= -61.1531

XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

FLUOROBENZENE

Charge= 0.0000 electrons
 Dipole moment (Debye):
 X= 0.0000 Y= 0.0000 Z= -1.6762 Tot= 1.6762
 Quadrupole moment (Debye-Ang):
 XX= -42.9537 YY= -33.8977 ZZ= -40.0554
 XY= 0.0000 XZ= 0.0000 YZ= 0.0000
 Octapole moment (Debye-Ang**2):
 XXX= 0.0000 YYY= 0.0000 ZZZ= -0.5811 XYY= 0.0000
 XXY= 0.0000 XXZ= 9.0306 XZZ= 0.0000 YZZ= 0.0000
 YYZ= 4.7318 XYZ= 0.0000
 Hexadecapole moment (Debye-Ang**3):
 XXXX= -43.4735 YYYY= -256.6082 ZZZZ= -453.7368 XXXY= 0.0000
 XXZ= 0.0000 YYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000
 ZZZY= 0.0000 XXYY= -61.3446 XXZZ= -88.2659 YYZZ= -111.3303
 XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

PHENOL

Charge= 0.0000 electrons
 Dipole moment (Debye):
 X= -1.5990 Y= -0.5719 Z= 0.0000 Tot= 1.6982
 Quadrupole moment (Debye-Ang):
 XX= -42.7480 YY= -38.1576 ZZ= -36.2688
 XY= -4.8687 XZ= 0.0000 YZ= 0.0000
 Octapole moment (Debye-Ang**2):
 XXX= -2.5162 YYY= 3.6772 ZZZ= 0.0000 XYY= -13.3350
 XXY= 10.7348 XXZ= 0.0000 XZZ= 0.0195 YZZ= 1.3836
 YYZ= 0.0000 XYZ= 0.0000
 Hexadecapole moment (Debye-Ang**3):
 XXX= -45.6162 YYYY= -477.3345 ZZZZ= -262.8575 XXXY= -0.2117
 XXXZ= 0.0000 YYYX= -33.1761 YYYZ= 0.0000 ZZZX= 0.0000
 ZZZY= 0.0000 XXYY= -87.6654 XXZZ= -62.3159 YYZZ= -124.7697
 XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.9786

ANILINE

Charge= 0.0000 electrons

Dipole moment (Debye):

X= 0.0000 Y= 0.0000 Z= 1.6028 Tot= 1.6028

Quadrupole moment (Debye-Ang):

XX= -46.7484 YY= -36.0042 ZZ= -32.8246

XY= 0.0000 XZ= 0.0000 YZ= 0.0000

Octapole moment (Debye-Ang**2):

XXX= 0.0000 YYY= 0.0000 ZZZ= 24.3086 XYY= 0.0000

XXY= 0.0000 XXZ= 2.2741 XZZ= 0.0000 YZZ= 0.0000

YYZ= 5.9968 XYZ= 0.0000

Hexadecapole moment (Debye-Ang**3):

XXXX= -49.1445 YYYY= -273.3837 ZZZZ= -454.9395 XXXY= 0.0000

XXXZ= 0.0000 YYYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000

ZZZY= 0.0000 XXYY= -64.3195 XXZZ= -114.4397 YYZZ= -114.4609

XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

PHENYLBORANE

Charge= 0.0000 electrons

Dipole moment (Debye):

X= 0.0000 Y= 0.0000 Z= 1.3849 Tot= 1.3849

Quadrupole moment (Debye-Ang):

XX= -44.8540 YY= -38.5329 ZZ= -42.1893

XY= 0.0000 XZ= 0.0000 YZ= 0.0000

Octapole moment (Debye-Ang**2):

XXX= 0.0000 YYY= 0.0000 ZZZ= 37.8391 XYY= 0.0000

XXY= 0.0000 XXZ= -0.2556 XZZ= 0.0000 YZZ= 0.0000

YYZ= 8.6337 XYZ= 0.0000

Hexadecapole moment (Debye-Ang**3):

XXXX= -48.1280 YYYY= -283.7356 ZZZZ= -682.1987 XXXY= 0.0000

XXXZ= 0.0000 YYYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000

ZZZY= 0.0000 XXYY= -65.7238 XXZZ= -115.0311 YYZZ= -159.5141

XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

PYRIDINE

Charge= 0.0000 electrons

Dipole moment (Debye):

X= 0.0000 Y= 0.0000 Z= -2.3103 Tot= 2.3103

Quadrupole moment (Debye-Ang):

XX= -37.7793 YY= -28.9136 ZZ= -36.0950

XY= 0.0000 XZ= 0.0000 YZ= 0.0000

Octapole moment (Debye-Ang**2):

XXX= 0.0000 YYY= 0.0000 ZZZ= -15.5940 XYY= 0.0000

XXY= 0.0000 XXZ= 1.4569 XZZ= 0.0000 YZZ= 0.0000

YYZ= 2.4175 XYZ= 0.0000

Hexadecapole moment (Debye-Ang**3):

XXXX= -38.9640 YYYY= -241.7206 ZZZZ= -273.8954 XXXY= 0.0000

XXXZ= 0.0000 YYYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000

ZZZY= 0.0000 XXYY= -56.5946 XXZZ= -54.7673 YYZZ= -77.4475

XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

CHLOROBENZENE

Charge= 0.0000 electrons

Dipole moment (Debye):

X= 0.0000 Y= 0.0000 Z= -2.1486 Tot= 2.1486

Quadrupole moment (Debye-Ang):

XX= -51.4062 YY= -41.7561 ZZ= -46.1895

XY= 0.0000 XZ= 0.0000 YZ= 0.0000

Octapole moment (Debye-Ang**2):

XXX= 0.0000 YYY= 0.0000 ZZZ= -7.7141 XYY= 0.0000

XXY= 0.0000 XXZ= 6.2009 XZZ= 0.0000 YZZ= 0.0000

YYZ= -1.6189 XYZ= 0.0000

Hexadecapole moment (Debye-Ang**3):

XXX= -55.7182 YYYY= -265.7650 ZZZZ= -774.0081 XXXY= 0.0000

XXXZ= 0.0000 YYYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000

ZZZY= 0.0000 XXYY= -64.9192 XXZZ= -159.5929 YYZZ= -177.0941

XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

CYANOBENZENE

Charge= 0.0000 electrons
 Dipole moment (Debye):
 X= 0.0000 Y= 0.0000 Z= -4.8517 Tot= 4.8517
 Quadrupole moment (Debye-Ang):
 XX= -48.9793 YY= -38.9322 ZZ= -56.5794
 XY= 0.0000 XZ= 0.0000 YZ= 0.0000
 Octapole moment (Debye-Ang**2):
 XXX= 0.0000 YYY= 0.0000 ZZZ= -77.4329 XYY= 0.0000
 XXY= 0.0000 XXZ= 3.0890 XZZ= 0.0000 YZZ= 0.0000
 YYZ= -3.8114 XYZ= 0.0000
 Hexadecapole moment (Debye-Ang**3):
 XXXX= -50.8507 YYYY= -259.0511 ZZZZ= -1064.4995 XXXY= 0.0000
 XXXZ= 0.0000 YYYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000
 ZZZY= 0.0000 XXYY= -63.2158 XXZZ= -165.7060 YYZZ= -184.0684
 XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

1,4-DIFLUOROBENZENE

Charge= 0.0000 electrons
 Dipole moment (Debye):
 X= 0.0000 Y= 0.0000 Z= 0.0000 Tot= 0.0000
 Quadrupole moment (Debye-Ang):
 XX= -46.2035 YY= -36.4330 ZZ= -51.6645
 XY= 0.0000 XZ= 0.0000 YZ= 0.0000
 Octapole moment (Debye-Ang**2):
 XXX= 0.0000 YYY= 0.0000 ZZZ= 0.0000 XYY= 0.0000
 XXY= 0.0000 XXZ= 0.0000 XZZ= 0.0000 YZZ= 0.0000
 YYZ= 0.0000 XYZ= 0.0000
 Hexadecapole moment (Debye-Ang**3):
 XXXX= -44.1823 YYYY= -250.5619 ZZZZ= -739.5206 XXXY= 0.0000
 XXXZ= 0.0000 YYYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000
 ZZZY= 0.0000 XXYY= -61.5171 XXZZ= -115.9033 YYZZ= -139.7898
 XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

1,3,5-TRIFLUOROBENZENE

Charge= 0.0000 electrons
 Dipole moment (Debye):
 X= 0.0000 Y= 0.0000 Z= 0.0000 Tot= 0.0000
 Quadrupole moment (Debye-Ang):
 XX= -50.1265 YY= -50.1265 ZZ= -49.5831
 XY= 0.0000 XZ= 0.0000 YZ= 0.0000
 Octapole moment (Debye-Ang**2):
 XXX= 0.0000 YYY= -17.2002 ZZZ= 0.0000 XYY= 0.0000
 XXY= 17.2002 XXZ= 0.0000 XZZ= 0.0000 YZZ= 0.0000
 YYZ= 0.0000 XYZ= 0.0000
 Hexadecapole moment (Debye-Ang**3):
 XXXX= -577.1563 YYYY= -577.1563 ZZZZ= -45.1879 XXXY= 0.0000
 XXXZ= 0.0000 YYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000
 ZZZY= 0.0000 XXYY= -192.3854 XXZZ= -102.3713 YYZZ= -102.3713
 XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

NAPHTHALENE

Charge= 0.0000 electrons
 Dipole moment (Debye):
 X= 0.0000 Y= 0.0000 Z= 0.0000 Tot= 0.0000
 Quadrupole moment (Debye-Ang):
 XX= -64.8350 YY= -51.2457 ZZ= -51.3821
 XY= 0.0000 XZ= 0.0000 YZ= 0.0000
 Octapole moment (Debye-Ang**2):
 XXX= 0.0000 YYY= 0.0000 ZZZ= 0.0000 XYY= 0.0000
 XXY= 0.0000 XXZ= 0.0000 XZZ= 0.0000 YZZ= 0.0000
 YYZ= 0.0000 XYZ= 0.0000
 Hexadecapole moment (Debye-Ang**3):
 XXXX= -70.2205 YYYY= -1066.0316 ZZZZ= -466.3665 XXXY= 0.0000
 XXXZ= 0.0000 YYYX= 0.0000 YYYZ= 0.0000 ZZZX= 0.0000
 ZZZY= 0.0000 XXYY= -236.9262 XXZZ= -109.2962 YYZZ= -261.2558
 XXYZ= 0.0000 YYXZ= 0.0000 ZZXY= 0.0000

2.9 References

1. Dougherty, D. A. *Science*, **1996**, *271*, 163.
2. Dougherty, D. A., *Comprehensive Supramolecular Chemistry*. J.-M. Lehn, Ed., Vol.2, Pergamon Press, 1996.
3. Kumpf, R. K., Dougherty, D. A. *Science* **1993**, *261*, 1708.
4. Hirschfelder, J. O., Curtiss, C. F., Bird, R. B. *Molecular Theory of Gases and Liquids*, John Wiley & Sons, 1964.
- 5) Sunner, J., Nishizawa, K., Kebarle, P. J. *Phys. Chem.* **1981**, *85*, 1814.
6. Taft, R. W., Anvia, F., Gal, J.-F., Walsh, S., Capon, M., Holmes, M. C., Hosn, K., Oloumi, G., Vasanwala, R., Yazdani, S. *Puer & Appl. Chem.* **1990**, *67*, 17.
7. Guo, B. C., Purnell, J. W., Castleman, A. W., Jr., *Chem. Phys. Lett.* **1990**, *168*, 155.
8. Deakine, C. A, Meot-Ner, M. J. *Am. Chem. Soc.* **1985**, *107*, 469.

9. Mecozzi, S., West, A. P., Jr., Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307.
10. Pauling, I., Wilson, E. B., Jr. *Introduction to Quantum Mechanics*, McGraw-Hill, New York, 1935.
11. Kearney, P. C., Mizoue, L. S., Kumpf, R. A., Forman, J. E., McCurdy, A., Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907.
12. Gaussian92/DFT, Revision F.4, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Gill, P. M. W., Johnson, B. G., Wong, M. W., Foresman, J. B., Robb, M. A., Head-Gordon, M., Replogle, E. S., Comperts, R., Andres, J. L., Raghavachari, K., Binkley, J. S., Gonzalez, C., Martin, R. L., Fox, D. J., Defrees, D. J., Baker, J., Stewart, J. J. P., Pople, J. A. Gaussian, Inc., Pittsburgh, PA 1993.
13. (a) Brown, H. C., Okamoto, Y., *J. Am. Chem. Soc.* **1958**, *80*, 4979. (b) March, J. *Advanced Organic Chemistry* 4th ed., John Wiley & Sons, 1993, p. 280.
14. William, J. H. *Acc. Chem. res.* **1993**, *26*, 593.
15. Caldwell, J. W., Kollmann, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 4177.

16. Basch, H., Stevens, W. J. *Theochem.* **1995**, 338, 305.
17. (a) Kim, K. S., Lee, J. Y., Lee, S. J., Ha, T.-K., Kim, D. H. *J. Am. Chem. Soc.* **1994**, 116, 7399. (b) Lee, J. Y., Lee, S. J., Choi, H. S., Cho, S. J., Kim, K. S., Ha, T.-K. *Chem. Phys. Lett.* **1995**, 232, 67.
18. (a) Rodwell, W. R., Radom, L. *J. Am. Chem. Soc.* **1981**, 103, 2865. (b) Symons, M. C. R. *J. Am. Chem. Soc.* **1980**, 102, 3982. (c) Petek, H., Nesbitt, D. J., Owrutsky, J. C., Gudeman, C. S., Yang, X., Harris, D. O., Moore, C. B., Saykally, R. J. *J. Chem. Phys.* **1990**, 92, 3257.

Chapter 3

Electrostatic Potential Surfaces as a Qualitative

Guide for Cation- π Interactions

3.1 Introduction

In Chapter 2, we have defined the nature of the cation- π interaction. We have seen that simple intuitive concepts of classical organic chemistry, such as resonance, cannot rationalize the variation in binding energy of a series of substituted benzenes to the sodium cation. However, we have also seen that electrostatic considerations account for *any* variation in the binding energy of aromatic compounds to a cation.¹ In order to show this fundamental aspect of the cation- π interaction, we evaluated the HF/6-31G**//6-31G** binding energy of prototype aromatic systems to the sodium cation. However, it is not always practical to calculate the *ab initio* binding energy of an aromatic to a cation in order to know its ability to participate in cation- π interactions. This is especially true for a large molecule. In fact, in most cases, *ab initio* calculations are limited to molecules with no more than 30 atoms, and for molecules of this size, the calculation can require extensive CPU time. This is, of course, a serious limit to the analysis (from the point of view of the cation- π interactions) of molecules of biological and medicinal interest.

Considering the results presented in chapter 2, we thought that one should be able to qualitatively, and perhaps even semi-quantitatively, evaluate new ring systems as potential cation binders by considering only the electrostatic surface of the molecules. We report now that this is

possible and present a series of electrostatic potential surfaces (EPS hereafter) for a large number of aromatic molecules. We also show that intermolecular interactions, such as hydrogen bonds, to an aromatic, can deeply modify its ability to participate in cation- π interactions.

3.2. *Ab Initio* Calculation of Binding Energies

We started from the series of *ab initio* binding studies presented in chapter 2 for compounds 1-14, and calculated the binding energy to Na⁺ for three more molecules, indole (15), azulene (16), and cyclohexane (17), Figure 3.1.²

All of these calculations, of course, refer to a gas-phase environment, as is appropriate for evaluating the fundamental nature of the cation- π interaction. In most instances, though, cation- π interactions have been invoked in solution. Certainly, in considering the differences among various cations in cation- π interactions, solvation-desolvation arguments are of paramount importance.³ However, in the current study the ion is held constant. We expect that differential solvation-desolvation effects among the various aromatics will be small, and so the calculations

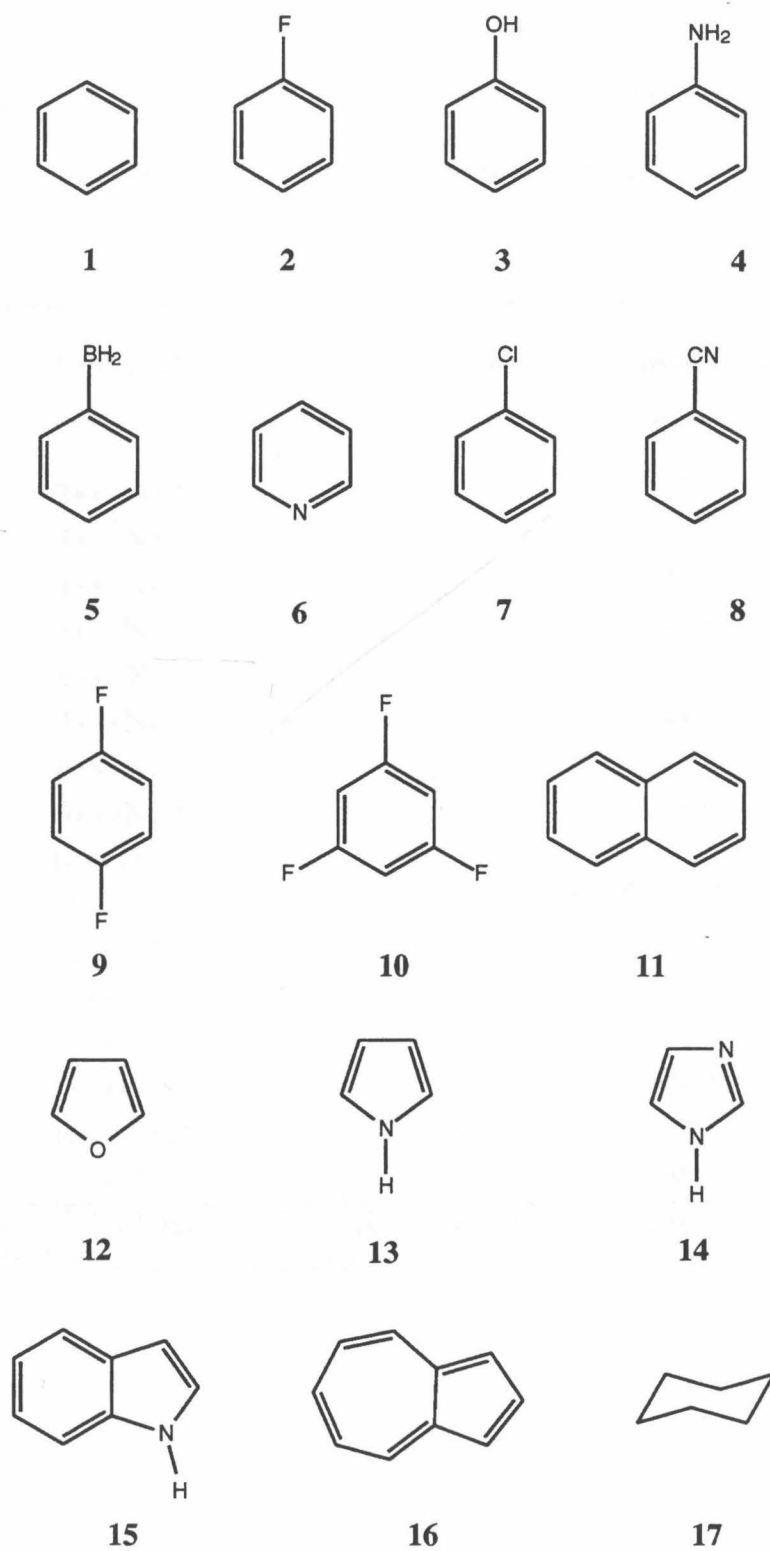


Figure 3.1. Structures of compounds 1-17.

will be of value to experimentalists interested in designing new systems. The quantitative data of our calculations are summarized in Table 3.1. The final structures of all the optimized cation- π complexes are reported in Figure 3.2.

Complex	Binding Energy (kcal/mol)
1...Na ⁺	-27.1
2...Na ⁺	-21.9
3...Na ⁺	-26.9
4...Na ⁺	-31.8
5...Na ⁺	-24.4
6...Na ⁺	-20.0
7...Na ⁺	-21.5
8...Na ⁺	-15.7
9...Na ⁺	-16.8
10...Na ⁺	-12.4
11...Na ⁺	-28.7(C _s) / -26.5(C _{2v})
12...Na ⁺	-21.0
13...Na ⁺	-29.6
14...Na ⁺	-21.0
15...Na ⁺	-32.6
16...Na ⁺	-34.1
17...Na ⁺	-8.4

Table 3.1. Calculated HF/6-31G**//6-31G** binding energies for compounds 1-17 with sodium cation.



Figure 3.2. Structures of the optimized complexes between aromatics 1-17 and Na^+ .

Among these simple systems, we can see that an amino group as the one in aniline (4) strongly enhances the cation- π interaction while withdrawing groups, such as the cyano group (8), are deactivating.

Turning our attention to the heterocyclic systems 6 and 11-16, we see that pyridine is deactivated, while pyrrole (13) is activated. Furan (12) is significantly poorer than benzene at making cation- π interactions even though it is more reactive toward electrophiles. This effect was noted before in our group and it was confirmed by cyclophane binding studies (host F in chapter 1).⁴ Indole (15) is the best overall binding molecule. From Figure 3.2 we can see that in the complex with Na^+ , the cation is over the six-membered ring, rather than on the pyrrole ring, suggesting that in cation- π interactions, indole is better thought of as a derivative of aniline rather than pyrrole. Naphthalene (11) is slightly better than benzene and the geometry of the complex is characterized by C_s symmetry, so that the sodium is actually over the center of one ring rather than over the molecular center. However, the C_{2v} complex is only 2.2 kcal/mol less stable than the C_s complex. Azulene (16) is an interesting molecule. The electronic distribution between the seven-membered ring and the five-membered ring divides the molecule into a strong dipole: negative charge is centered on the five-membered ring; positive charge is centered on the seven-membered ring. As such, Na^+ is centered over the five-membered ring. Finally cyclohexane, is included for comparison purposes. In fact,

cyclohexane is a structure of comparable size to some of the aromatic molecules, but it does not have any significant electrostatic binding, because its quadrupole moment is near zero.⁵ Its very low binding energy to Na^+ is then another demonstration of the importance of electrostatics in cation- π interactions. In fact, cyclohexane is more polarizable than benzene, so that if polarizability were an important factor in establishing the magnitude of a cation- π interaction, one might have expected cyclohexane to outperform benzene.

In compounds 2, 3, 4, 6, 8, 10, and 14, the heteroatom bears a substantial amount of negative charge. In all these cases, binding of the cation on the heteroatom is possible. The binding energies for these heteroatom-complexes are given in Table 3.2. The corresponding optimized geometries of the complexes are shown in Figure 3.3.

Complex	Binding Energy (kcal/mol)
2a...Na ⁺	-22.3
3a...Na ⁺	-27.4
4a...Na ⁺	-33.17
6a...Na ⁺	-33.4
8a...Na ⁺	-36.5
14a...Na ⁺	-39.5

Table 3.2. Calculated HF/6-31G**//6-31G** binding energies for heteroatom complexes of compounds 2, 3, 4, 6, 8, 10, and 14 with sodium cation.

For **2**, **3**, and **4**, heteroatom binding is competitive with cation- π binding. In contrast, for **6**, **8**, and **14** the heteroatom binding is stronger than the cation- π binding, and in the case of **6** and **14**, only the binding to the nitrogen represents a true minimum. It should be noted that the cation- π binding energies for these two compounds were obtained by forcing the Na^+ to stay over the π system, and therefore, must be considered approximate.

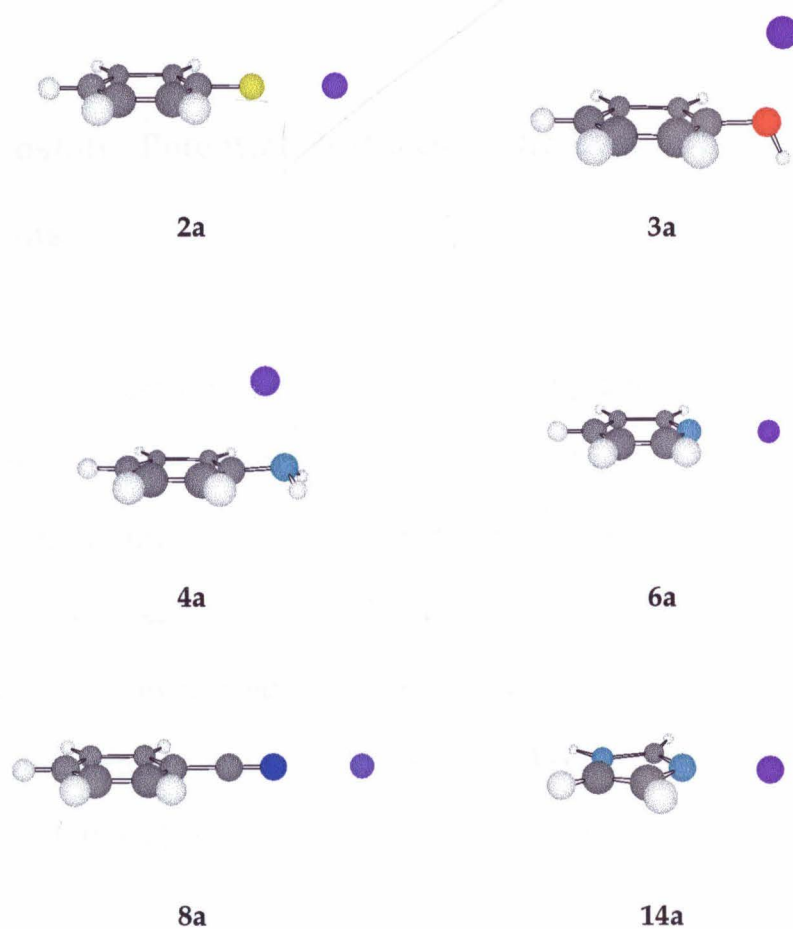


Figure 3.3. Structures of the optimized complexes between heteroatom and Na^+ in compounds **2**, **3**, **4**, **6**, **8**, **14**.

The heteroatom binding sites are, of course, extremely relevant in the gas phase. However, in solution, solvation issues become critical. In fact, one would expect the energy penalty for desolvating the heteroatoms to be much more severe than for the aromatic. If we consider biological structures, one expects that the proteins may orient aromatic sidechains (bearing a heteroatom in the ring or as a substituent) so that only the face of the aromatic or the heteroatom is available for binding.

3.3 Electrostatic Potential Surfaces in the Evaluation of Cation- π Interactions.

The goal of the present work is to provide a simple tool to predict cation- π interactions, without resorting to full *ab initio* calculations of the molecule-cation complexes. Based on the findings described in chapter 2, and using the results presented in the last section as quantitative benchmarks, we evaluated the electrostatic potential surfaces of the uncomplexed, ground state molecules 1-17. We expected that the simple inspection of the electrostatic surfaces would be of value to anticipate cation- π interactions. We found that this is so.

Methodology. Electrostatic potential surfaces of the aromatic compounds 1-17 were generated by mapping HF/6-31G** electrostatic potentials onto

surfaces of molecular electron density ($0.002 \text{ e}/\text{\AA}^3$) and color-coding, using the program SPARTAN⁶. In all surfaces the potential energy values range from +25 kcal/mol to -25 kcal/mol, with red signifying a value greater than or equal to the maximum in negative potential and blue signifying a value greater or equal to the maximum in positive potential. In some regions of these surfaces, the electrostatic potentials lie beyond the ± 25 kcal/mol range. This is particularly true for the regions associated with the heteroatoms. The range ± 25 kcal/mol was chosen to emphasize the variations in the aromatic region. Semi-empirical AM1 calculations⁷ of the same surfaces were also performed in order to compare the two levels of theory.

Results. Figures 3.4-3.6 shows the *ab initio* HF/6-31G//6-31G** electrostatic potential surfaces for structures 1-17. Inspection of the aromatic ring region shows that there is remarkable agreement between the quantitative binding results described in section 3.2 and the electrostatic potential surfaces.

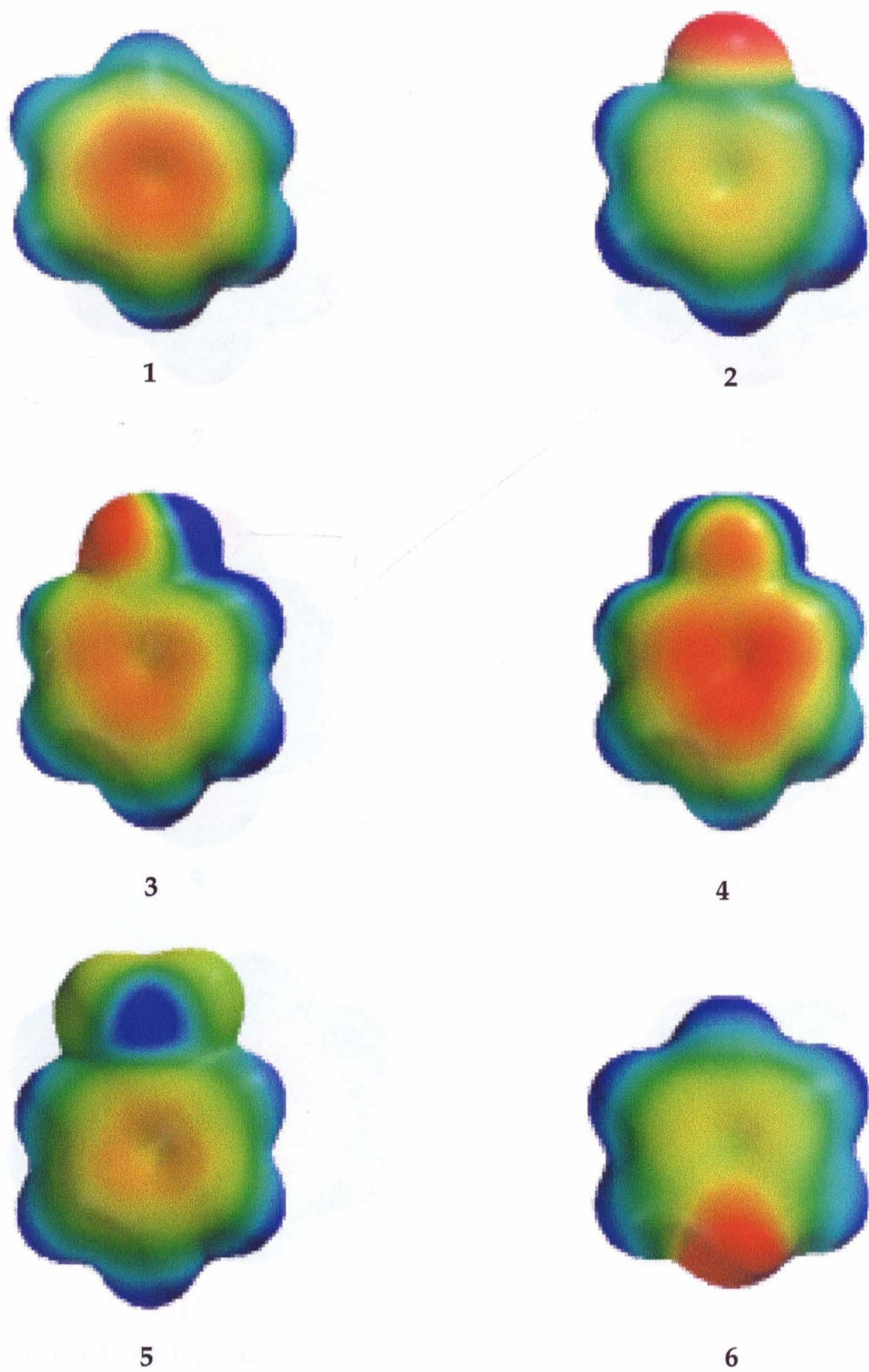


Figure 3.4. *Ab initio* 6-31G** electrostatic potential surfaces for compounds 1-6.

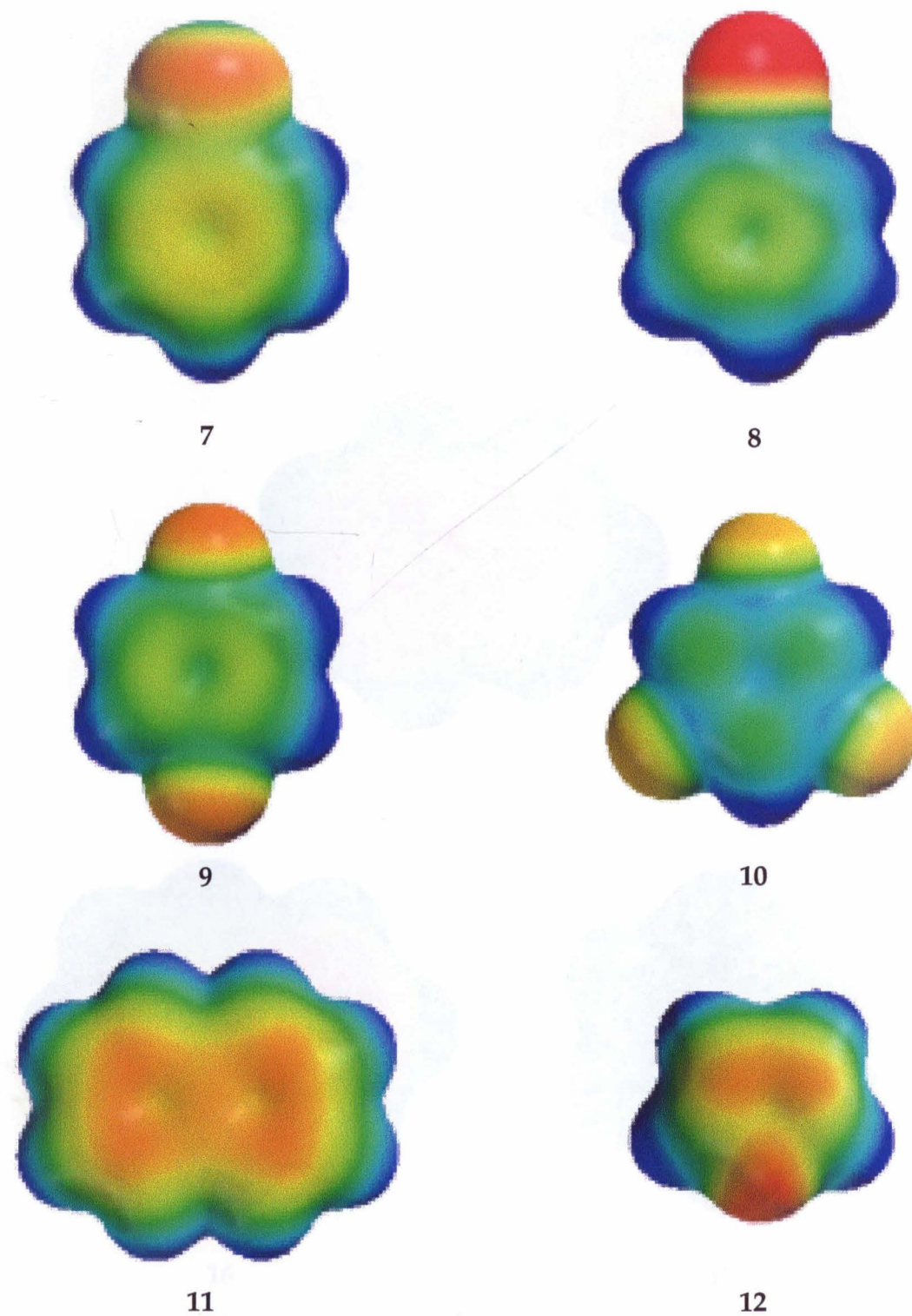
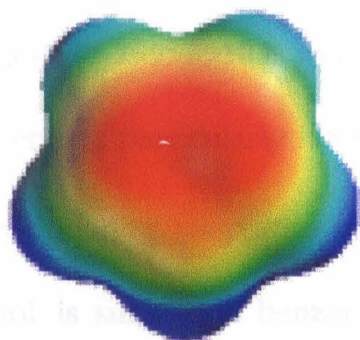
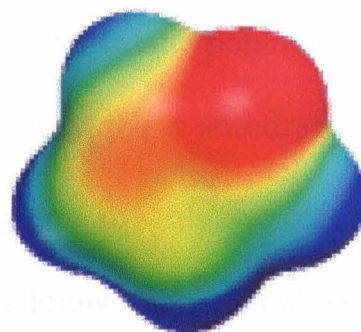


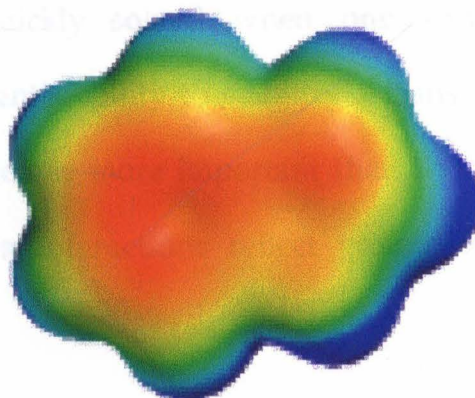
Figure 3.5. *Ab initio* 6-31G** electrostatic potential surfaces for compounds 6-12.



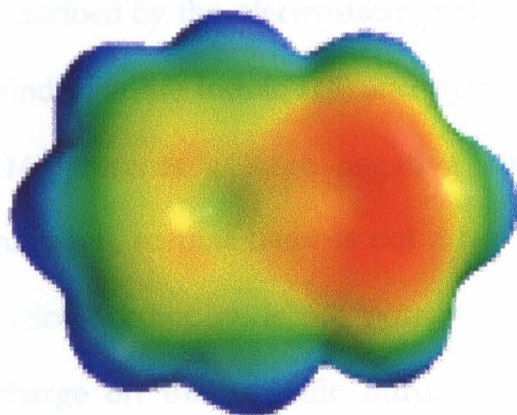
13



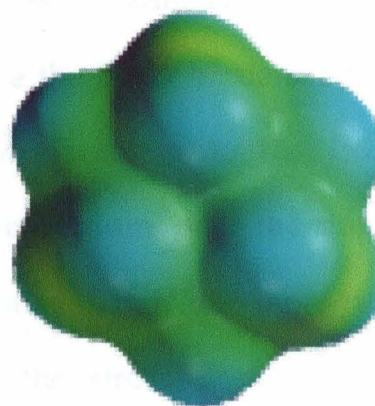
14



15



16



17

Figure 3.6. *Ab initio* 6-31G** electrostatic potential surfaces for compounds 13-17.

In these surfaces, the cation- π binding of the simple benzenes $4 > 1 \geq 3 > 5 > 2 > 7 > 9 > 8 > 10$ is well reproduced. The electrostatic potential surface of phenol is particularly interesting. It appears that the σ -withdrawing and the π -donating properties of the phenolic group roughly cancel, so that phenol is similar to benzene. However, we know that phenol is much more reactive than benzene toward electrophilic reagents. This apparent contradiction is quickly solved when one considers that reactivity concerns a substituent's ability to stabilize a transition state. In this case, resonance issues become more important than inductive effects. This also means that cation- π interactions reflect ground state properties of the aromatic.

The behavior of heterocycles **6**, **12**, **13**, **14**, and **15** is also very well described by the electrostatic potential surfaces. Pyridine (**6**) is the weakest binder, while indole (**15**) and pyrrole (**13**) are the better binders. Imidazole (**14**) presents a large negative charge corresponding to the iminium nitrogen, so that there is not a real energy minimum over the ring and a cation- π complex is not possible. On the other hand, this large negative charge on that specific nitrogen explains the strong basic character of imidazole. Indole and pyrrole are also very interesting. Both present a clear peak in the negative electrostatic potential over the π system. However, indole more closely resembles a substituted aniline than pyrrole, and the most negative ring is the six-membered ring, as an *ab*

initio optimization of the complex indole- Na^+ had shown. The large difference between furan (12) and pyrrole (13) can be accounted for by the introduction, in pyrrole, of a strong N-H dipole. Also, the electrostatic potential surface of furan shows that now the σ -withdrawing properties of oxygen overwhelm the π -donating and the ring is deactivated compared to benzene. Azulene (16) is perhaps the most peculiar molecule in this series. The electrostatic potential surface shows a large polarization in the system as expected. The 5-membered ring is the most negative region of the molecule.

Given these results, it can be said that the use of electrostatic potential surfaces for evaluating cation- π interactions is a full success. However, even if the calculation of an *ab initio* surface is less computer intensive than the evaluation of the full complex with a cation, it is still prohibitive for larger molecules. For this reason, we have evaluated the semi-empirical electrostatic potential surfaces for compounds 1-17.

Different semi-empirical methods are available today. The most used and reliable are AM1, PM3 and MNDO. In order to check which of these methods was better for the calculation of electrostatic potential surfaces, we calculated the EPS for benzene with the three methods and compared them to the *ab initio* surface. Figure 3.7 shows the results.

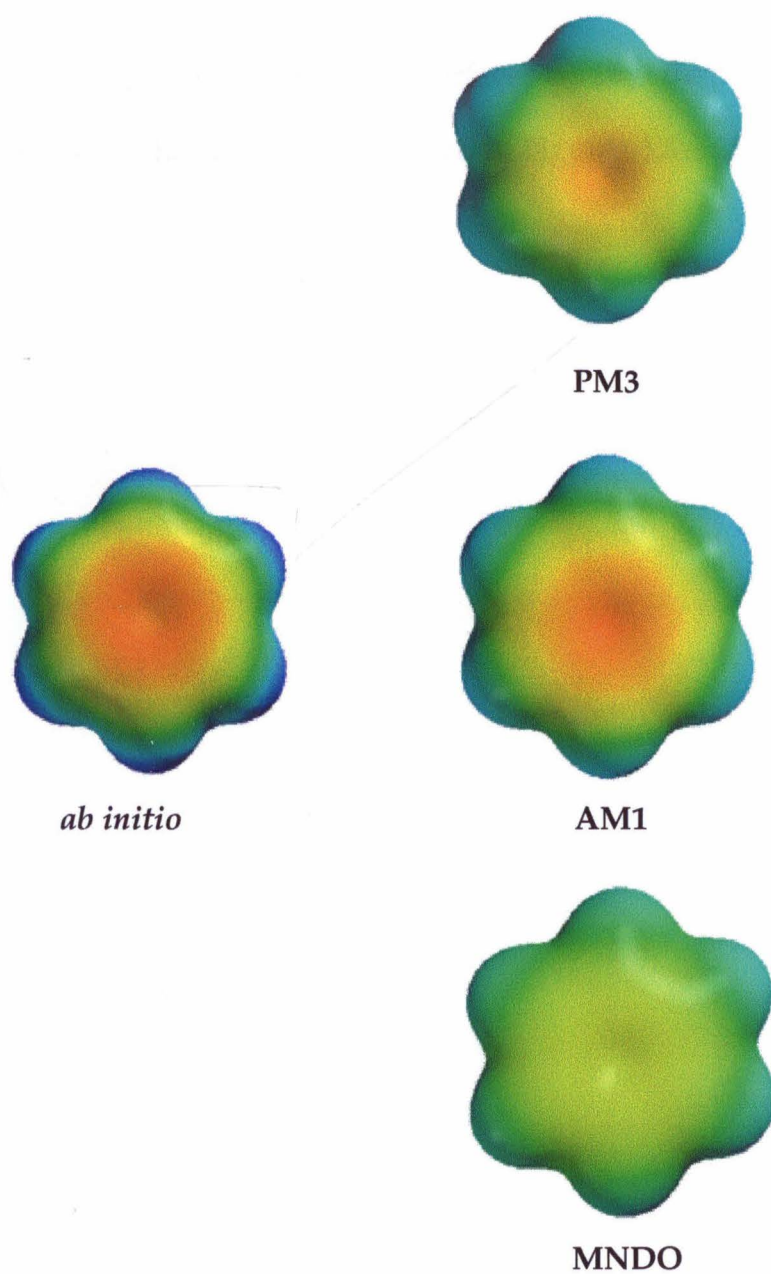


Figure 3.7. The electrostatic potential surface of benzene calculated by *ab initio* and PM3, AM1, and MNDO methods.

We can see that the AM1 electrostatic potential surface is by far the closest to the *ab initio* surface.

AM1 electrostatic potential surfaces were then calculated for compounds 1-17. The surfaces are shown in Figures 3.8-3.10

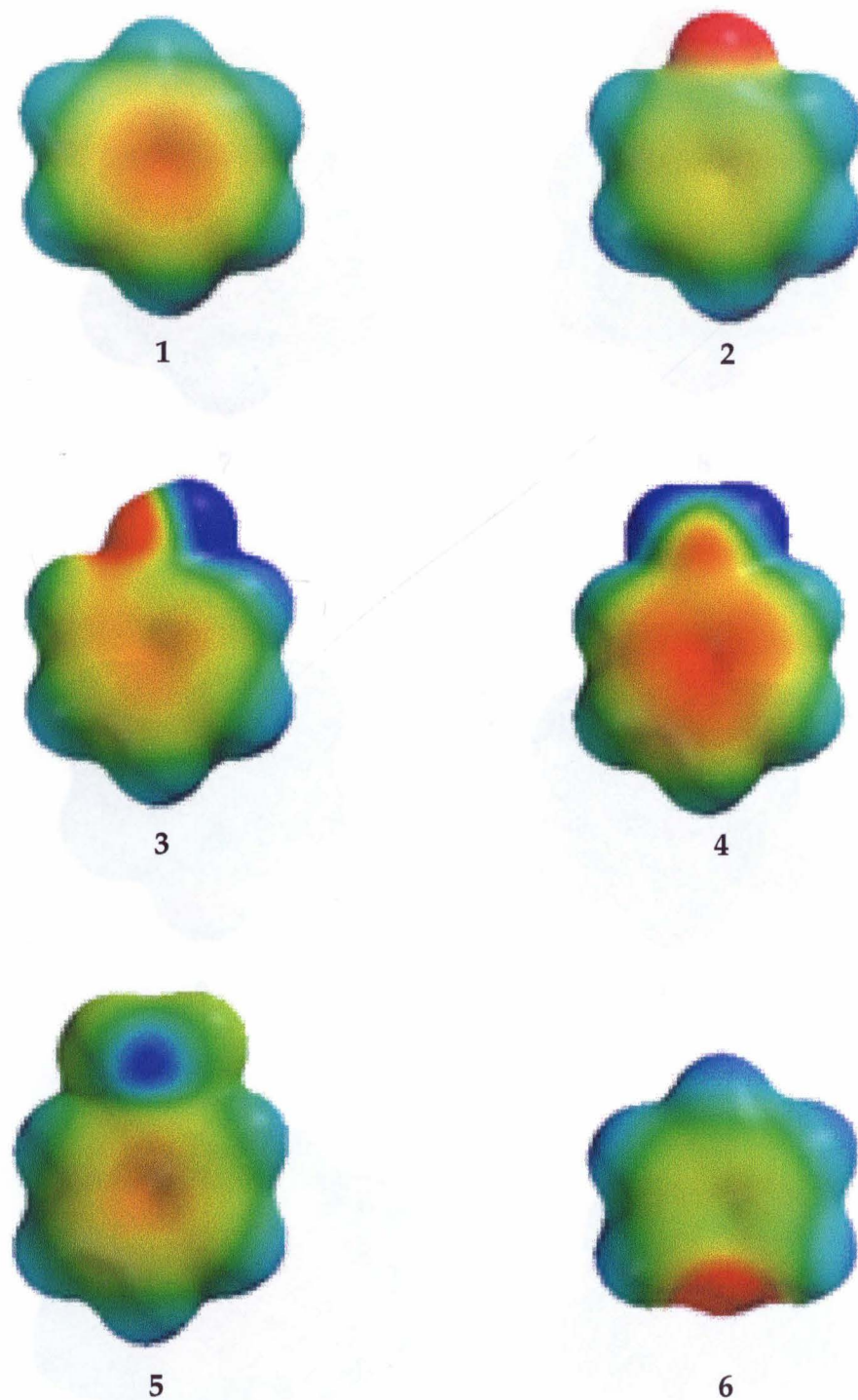


Figure 3.8. AM1 electrostatic potential surfaces for compounds 1-6.

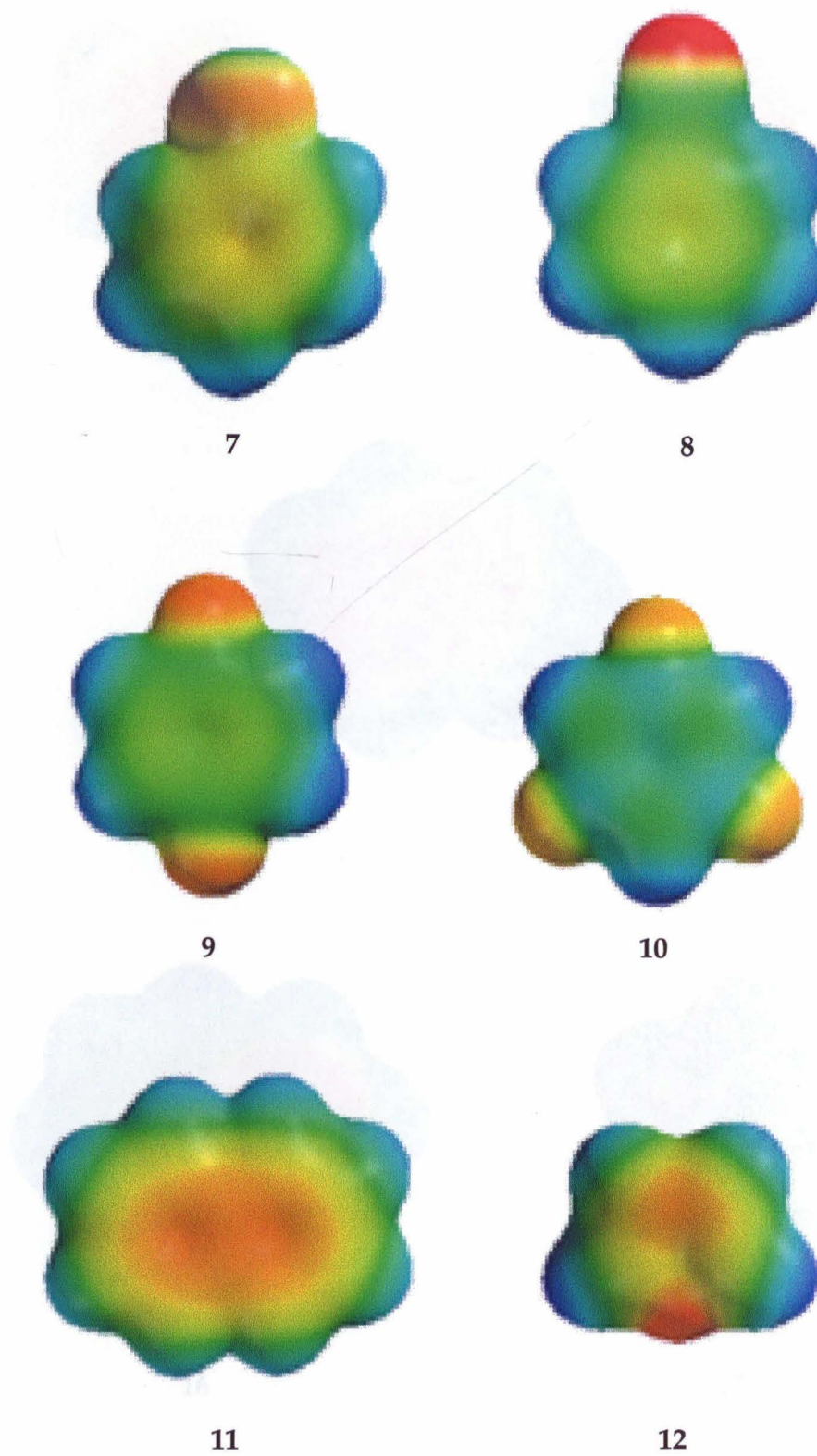
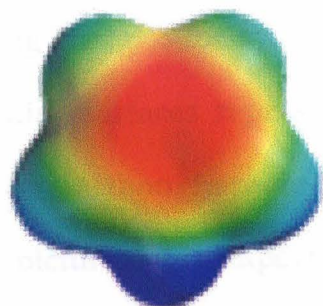
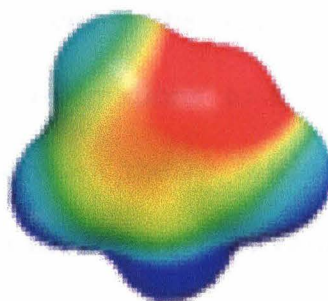


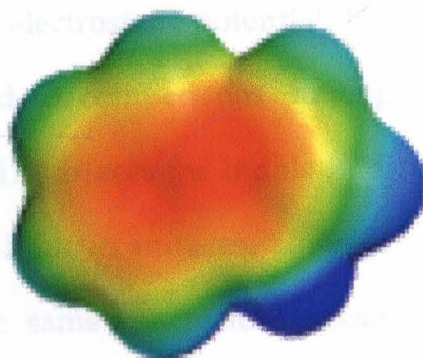
Figure 3.9. AM1 electrostatic potential surfaces for compounds 7-12.



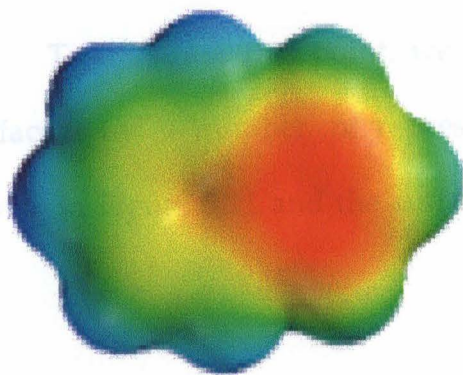
13



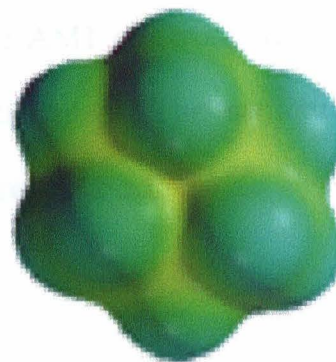
14



15



16



17

Figure 3.10. AM1 electrostatic potential surfaces for compounds 13-17.

It is known that AM1 is not very successful at reproducing *ab initio* binding energies for systems of this type.⁸ However, the AM1 electrostatic potential surfaces represent very good approximations to the *ab initio* surfaces. Although there are differences between the *ab initio* and the AM1 pictures, it is important to note that in the same series, variations are the same. Thus, for example, the AM1 surface of benzene is different from the *ab initio* surface, with the semi-empirical surface showing generally smaller variations in electrostatic potential. However, this effect persists in the other systems and so, comparisons among the AM1 surfaces are very informative. The AM1 surfaces for indole and naphthalene are noticeably different from the *ab initio* surfaces. However, in the same series, it is possible to reach the same conclusions about cation- π binding energies. This suggests that for more complex systems, for which *ab initio* calculations may not be feasible, AM1 can provide a useful guideline.

To illustrate this point, we provide the AM1 electrostatic potential surfaces for a number of representative structures. The structures are shown in Figure 3.11 and the surfaces in Figures 3.12-3.15.

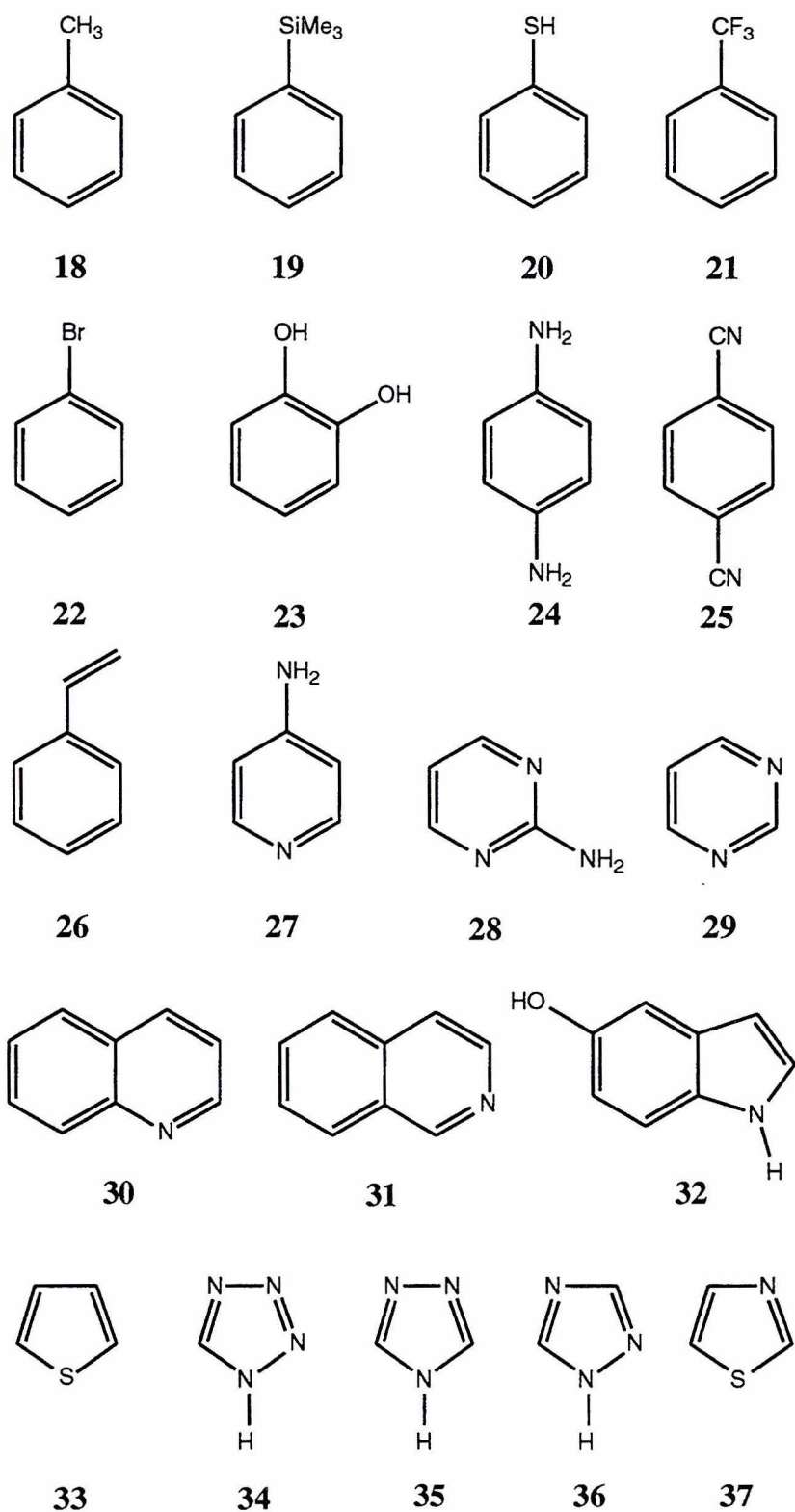


Figure 3.11. Representative structures for which AM1 electrostatic potential surfaces have been calculated

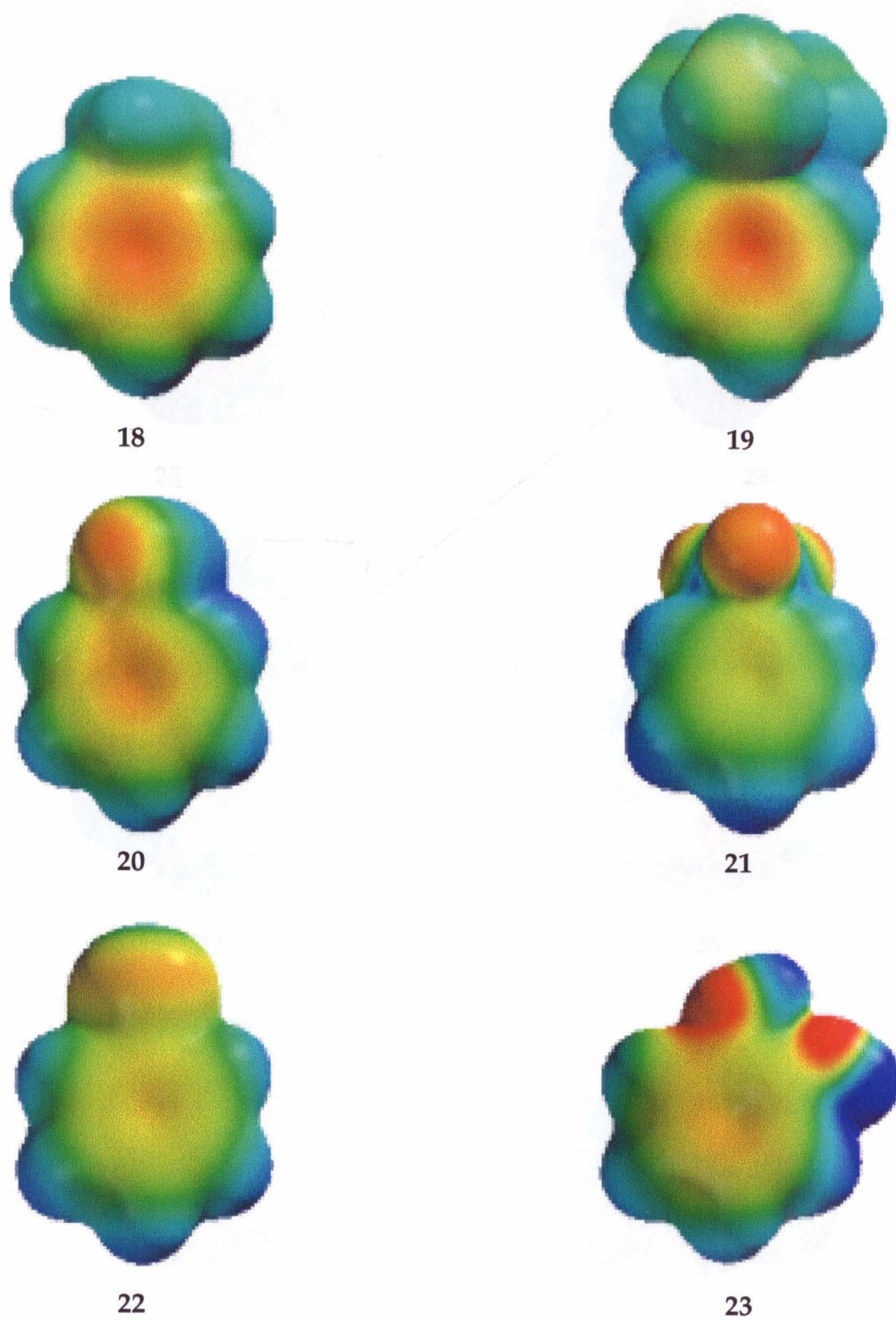


Figure 3.12. AM1 electrostatic potential surfaces for compounds 18-23.

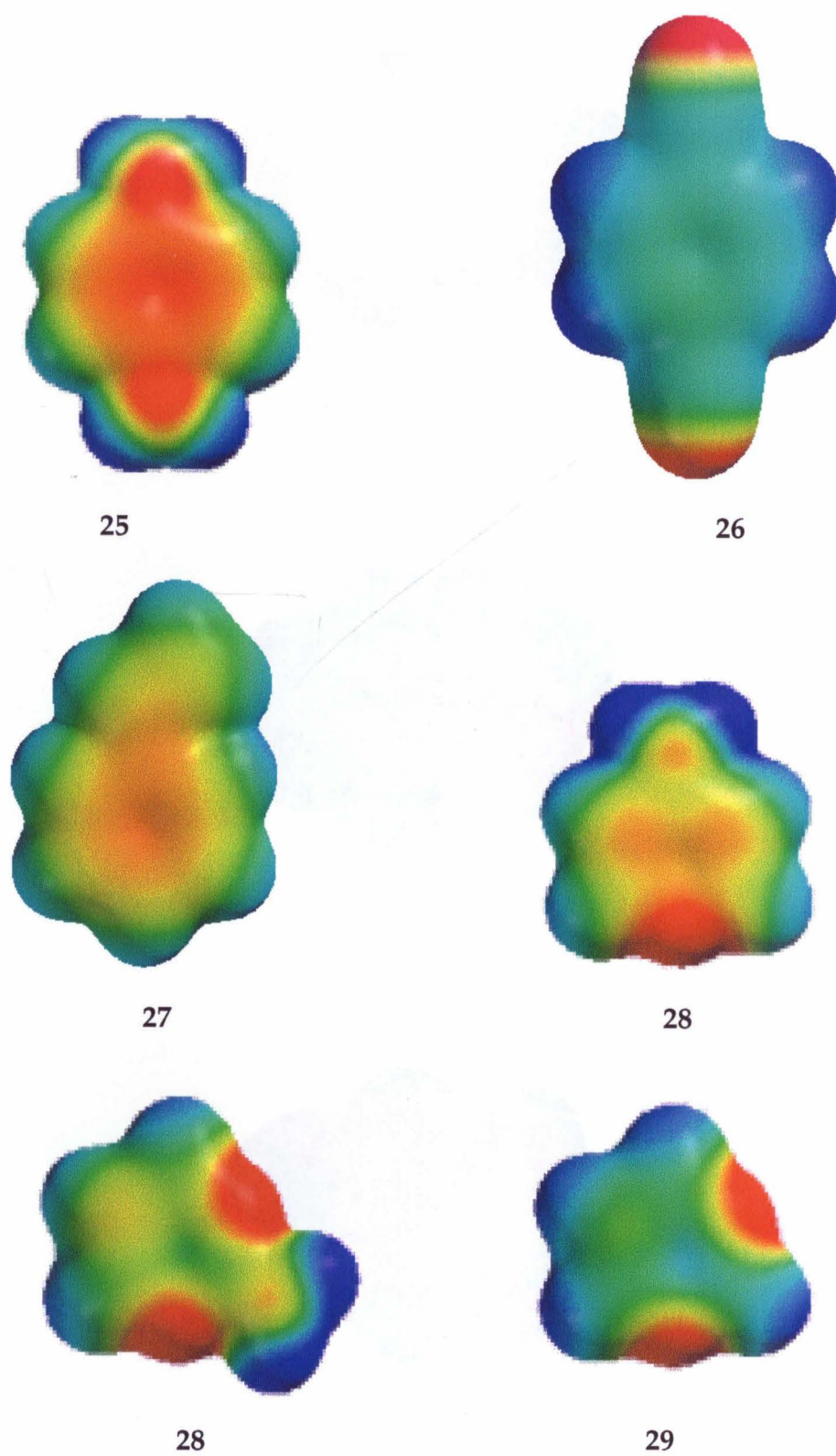
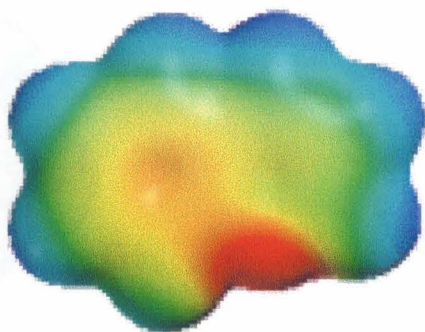
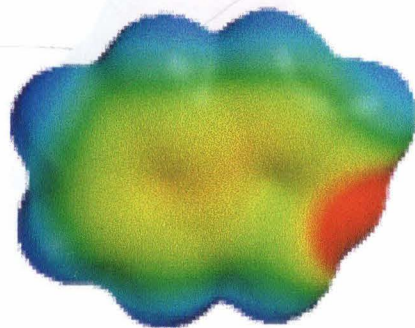


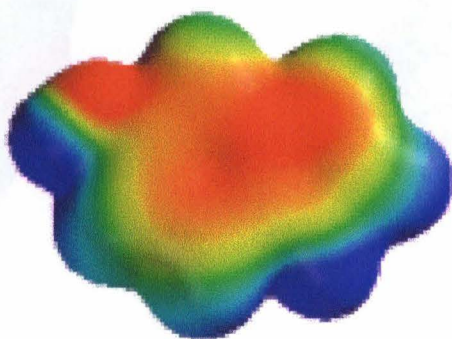
Figure 3.13. AM1 electrostatic potential surfaces for compounds 24-29.



30

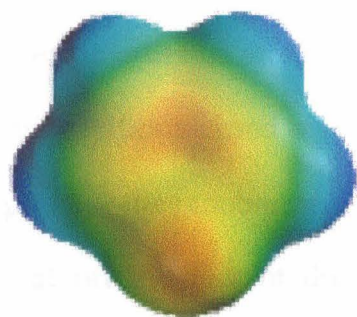


31

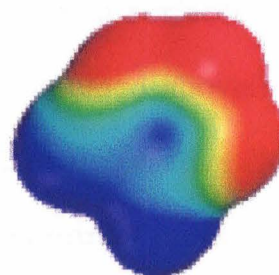


32

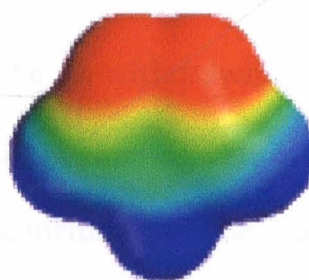
Figure 3.14. AM1 electrostatic potential surfaces for compounds 30-32.



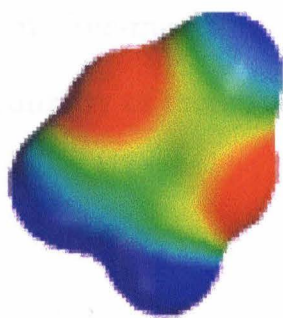
33



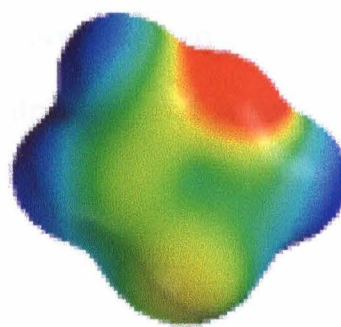
34



35



36



37

Figure 3.15. AM1 electrostatic potential surfaces for compounds 33-37.

All the surfaces for these compounds present interesting characteristics. However, it must be stressed that the results for these surfaces are in line with expectations based on the model system discussed above. Thus, for example, 1,4-dicyanobenzene (25) presents a relatively positive electrostatic potential on the face of the ring, due to the withdrawing effects of two cyano groups. On the other hand, 1,4-diaminobenzene (24) presents a strong negative electrostatic potential on the ring. Catechol (23) shows that two hydroxyl groups actually deactivate the aromatic ring relative to benzene showing that the σ -withdrawing properties of the hydroxyl groups are fundamental in evaluating cation- π interactions, as anticipated above. We can therefore conclude that the effect of additional substituents on the same ring is roughly additive. The effects of the groups CF_3 (21), SiMe_3 (19) and vinyl (26) are also very interesting. All show the specific electrostatic properties of these groups. Finally, some medically important, five-membered heterocycles are represented in surfaces 34-37. The peculiarity of these surfaces is certainly intriguing and is suggestive of further studies.

We expect this semi-empirical approach for anticipating cation- π interactions, to be of the greatest value in the design of molecules of pharmaceutical interest. In fact it is possible to generate AM1 surfaces for almost any kind of structural unit of interest. The only limitation is

related to some transition metals and heavier elements, for which AM1 parameters are not available.

3.4 Biological Considerations

The results presented here also offer a way to rationalize the extent to which nature uses aromatic residues to fashion cation binding sites in proteins.⁹ The three aromatic amino acids, tryptophan, tyrosine, and phenylalanine are all present in a number of cation binding sites.⁹ However it appeared to us that the various aromatic sidechains do not appear with equal frequency at potential cation- π binding sites. Trp is prominent and this is especially suspicious, because Trp is the least frequently used amino acid.¹⁰ Tyr is used almost as much as Trp and Phe is used sometimes. Also we can notice that histidine is never present at cation- π sites. The electrostatic potential surfaces reported in this chapter nicely rationalize these observations. Trp represented by indole (15) is the best amino acid for cation- π interactions. On the other hand, His modeled by imidazole (14) is the worst. Also, as anticipated above, His is a powerful base that can be protonated at physiological pH. Protonation will destroy any possible cation- π interactions. The electrostatic potential surfaces of benzene, for Phe, and of phenol, for Tyr, are very similar. One possible explanation for the preference of Tyr over Phe at cation- π sites, is that the

phenolic OH could interact with hydrogen bond acceptors. This interaction would help position the ring, and it could also have an effect on the cation- π interaction. In order to test this hypothesis, we considered the system phenol-formamide (Figure 3.16). Distance and angles between the oxygen on formamide and the phenolic hydroxyl were chosen according to published values for hydrogen bond networks in analogous systems.¹¹

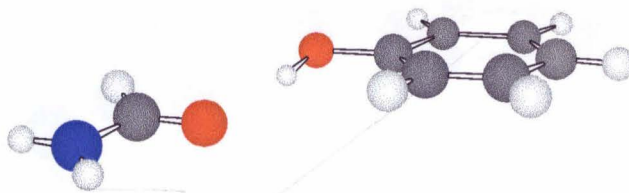


Figure 3.16. The hydrogen bond complex between phenol and formamide.

We first calculated the 6-31G** surface of this system, Figure 3.17.

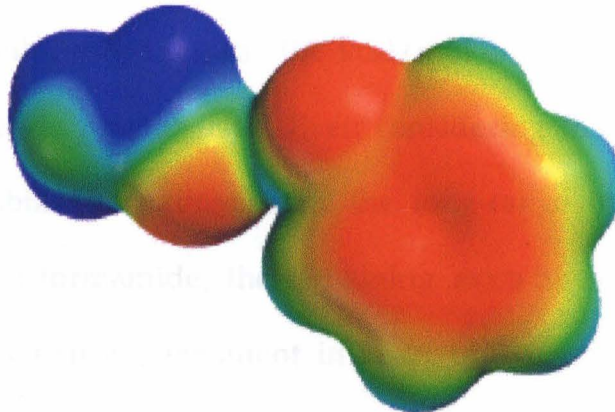


Figure 3.17. Electrostatic potential surface for the system depicted in Figure 3.9.

Comparing this surface to the surface of phenol (3), it is clear that the interaction of phenol with a hydrogen bond acceptor will strongly increase the amount of negative charge on the ring. This means that the cation- π

interaction will be stronger than in simple phenol. We confirmed these predictions by an *ab initio* calculation. We considered the system depicted in Figure 3.18, where we placed a sodium cation, on the phenol-complex, at the optimized position for phenol.

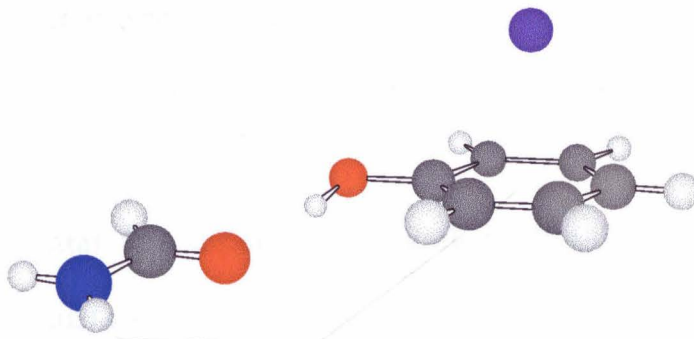


Figure 3.18. Binding of the complex phenol-formamide to Na^+ . The distance between the sodium ion and the phenolic ring is the same as in the optimized complex between phenol and sodium (chapter 2)

We then performed a single point energy calculation of the binding energy to Na^+ . The resulting value was 9.2 kcal/mol higher than the binding energy of sodium to phenol itself. Even considering that ca. 5.8 kcal/mol of this extra stabilization come from the long-range interaction of Na^+ with the dipole of formamide, the remaining extra binding energy (ca. 3.4 kcal/mol) makes a strong argument in favor of the presence of hydrogen bonded Tyr in cation- π binding sites.

3.5 Final Remarks

Although electrostatic potential surfaces are extremely appealing for the simplicity of their interpretation and the ability of predicting phenomena in molecular recognition, a few strict rules must be followed when using EPS's.

- 1) It is fundamental to compare any new electrostatic potential surface to some reference surface.
- 2) The potential energy range must be the same for the surfaces that need to be compared.
- 3) Surfaces of neutral molecules cannot be compared to surfaces of charged molecules.
- 4) The electron density cutoff must be the same for all the compared surfaces. In the case that van der Waals radii are used, one must be sure that the differences in van der Waals radius among the compared molecules do not significantly alter their electrostatic potential surfaces.
- 5) The image processing for the surfaces must absolutely be the same for all the compared surfaces.
- 6) In order to use electrostatic potential surfaces to predict or evaluate intermolecular interactions, other than the cation- π interaction, it is first necessary to establish that the interaction under consideration is well described by a predominantly electrostatic model. Only in this case, can

electrostatic potential surfaces be of some value. For example, we can consider the interaction between the four nucleic bases, Figures 3.19-3.20.

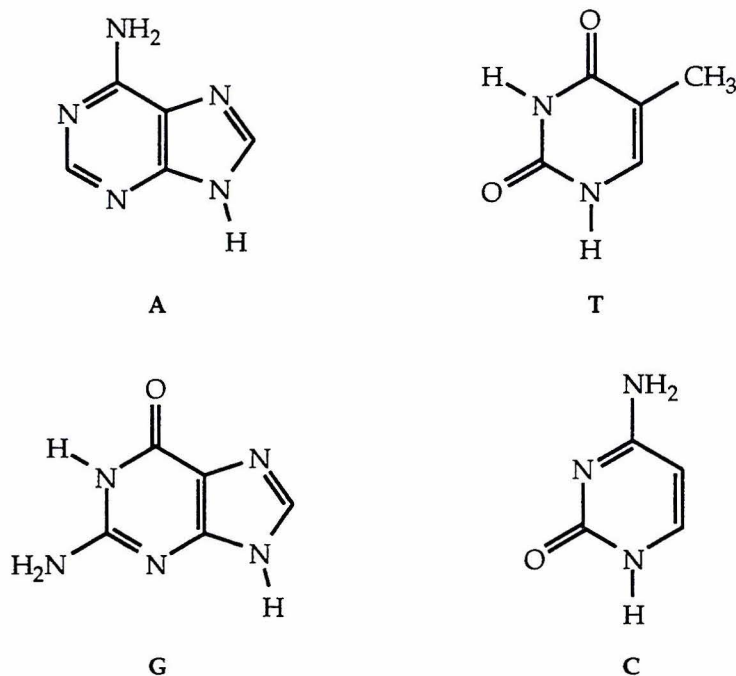


Figure 3.19. The nucleic bases adenine (A), guanine (G), thymine (T), and cytosine (C).

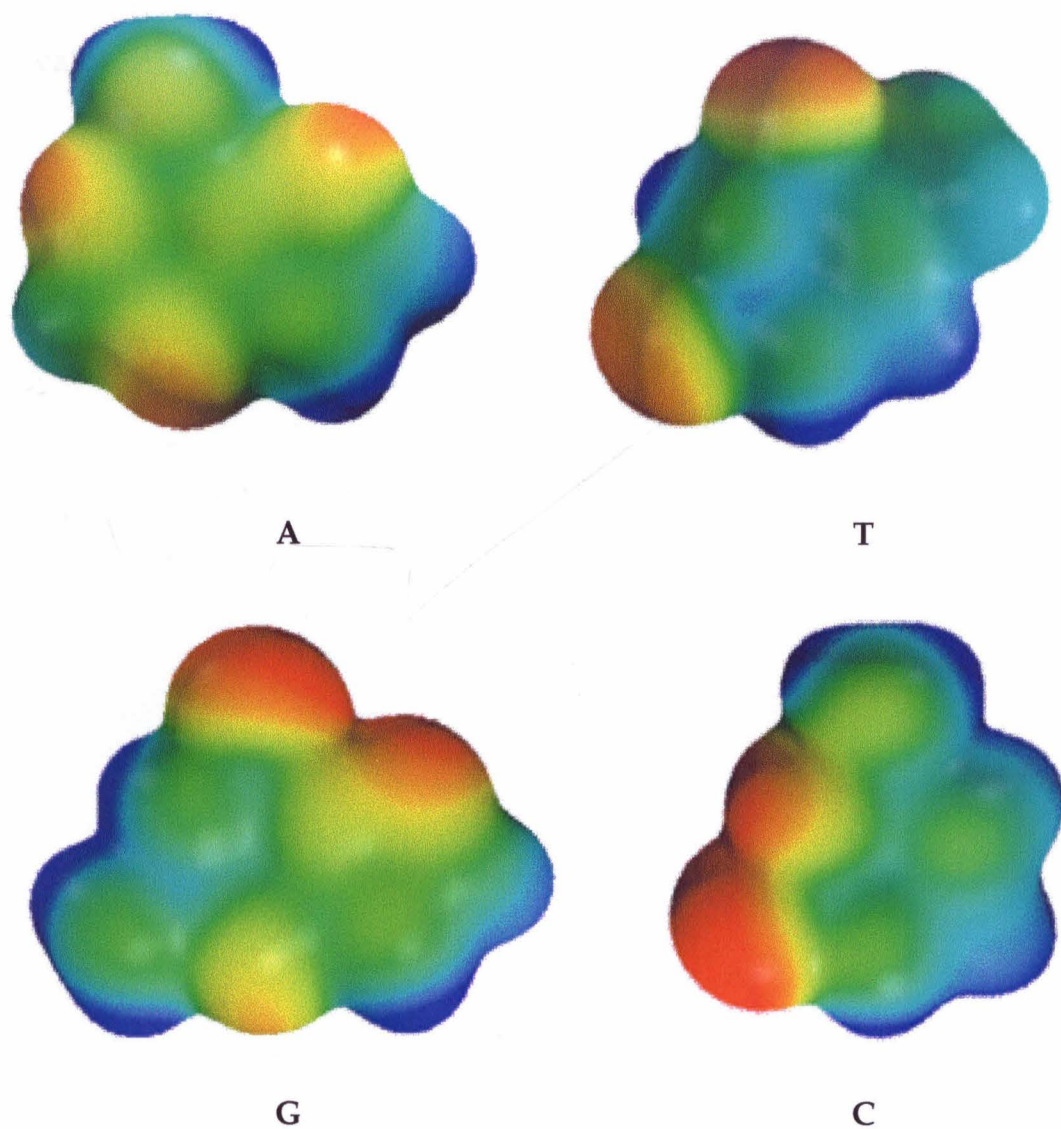


Figure 3.20. *Ab initio* HF/6-31G//6-31G** electrostatic potential surfaces for ATGC.

In this case, the strong π -dipoles introduced by the carbonyl groups in the rings and the presence of many heteroatoms make the analysis based on electrostatic potential surfaces much more problematic. *Ab initio* studies on the binding of these molecules to an ion must first be performed in

order to be sure that the electrostatic model is applicable. Only after this has been proven can the electrostatic potential surfaces be considered to be of value.

3.6. References

- 1) Mecozzi, S., West, A. P., Jr., Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307.
- 2) The methodology used for the calculation of the binding energy of these three molecules to Na⁺ is the same that was used for compounds 1-11 in chapter 2, and it will not be repeated here.
3. Kumpf, R. A., Dougherty, D. A. *Science* **1993**, *261*, 1708.
4. Kearney, P. C., Mizoue, L. S., Kumpf, R. A., Forman, J. E., McCurdy, A., Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907.
5. Craven, I. E., Hesling, M. R., Laver, D. R., Lukins, P. B., Ritchie, G. L. D., Vrbancich, J. J. *Phys. Chem.* **1989**, *93*, 627.
6. Spartan Version 2.1 (1992), Wavefunction, Inc., Irvine, CA.
7. Dewar, M. J. S., Zoebisch, E. G., Healy, E. F., Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
8. Basch, H., Stevens, W. J. *Theochem* **1995**, *338*, 303.

9. Dougherty, D. A. *Science* **1996**, 271, 163.
10. Doolittle, R. F. *Of Urfs and Orfs: A Primer on How to Analyze Derived Amino Acid Sequences* University Science Books, Mill Valley, CA, 1986.
11. Jasien, P. G., Stevens, W. J. *J. Chem. Phys.* **1986**, 84, 3271.

Chapter 4

A Neutral Water-Soluble Cyclophane Receptor

4.1 Introduction

In chapter 1, the syntheses and the binding properties of a series of cyclophane receptors have been described. All of the hosts (P, C, O, S, CP, TMP, TBP, TMTBP) present strong arguments in favor of a role of the cation- π interaction in the binding of positively charged guests.¹ As mentioned in the same chapter, all of the hosts are water-soluble by virtue of four external carboxylates (Figure 4.1).

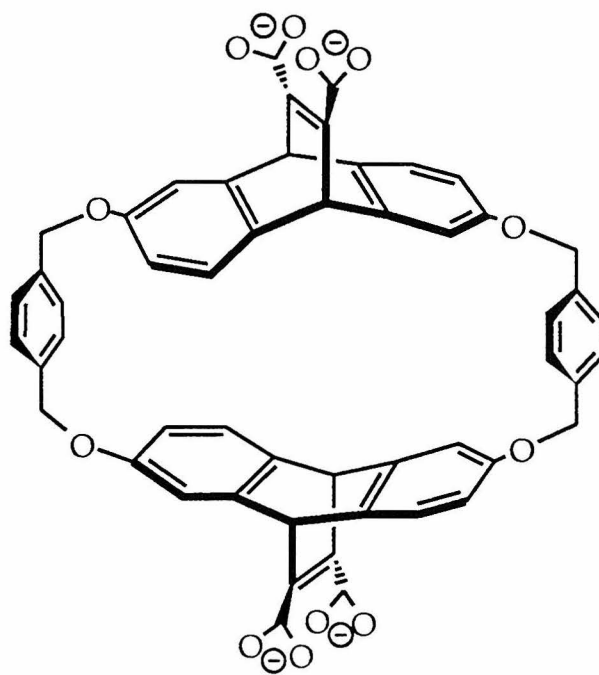


Figure 4.1. Host P and its analogous cyclophane hosts owe their water-solubility to the four external carboxylates.

From the above picture and from the CPK models from Figure 1.8, it is evident that these carboxylates cannot enter in the binding cavity and therefore cannot *directly* interact with the guests. Furthermore, an

aqueous medium should strongly solvate these charged groups, resulting in a general isotropic decrease of the electrostatic field generated by the four carboxylates. However, it must be remembered that the highest binding constants are seen with positively charged guests. The fact that this happens when four negative charges are positioned at an average distance from the center of the binding cavity of about 8 Å (this is an estimate, based on the crystal structure of host P_E) is, to say the least, highly suspicious. Certainly, one can explain the increase in the binding constants of positive guests (compared to neutral guests) by invoking cation- π interactions. As stated above, there should be no doubts that this happens. However, a quantitative evaluation of these interactions in an aqueous medium, is not easily done. One could then say, that, as a working hypothesis, the high binding constants that have been measured for positively charged guests are due to a combination of cation- π interactions and long-range electrostatic interactions with the four external carboxylates.

Let's consider two elementary charges at the distance R. The interaction energy between the two charges is described by eq. 4.1:

$$E_{a,b} = \frac{q_a q_b}{4\pi\epsilon R} N \quad (4.1)$$

In our case we can substitute:

$$q_a = -q_b = 1.602177 \times 10^{-19} \text{ C}$$

$$4\pi\epsilon_0=1.11265\times 10^{-10} \text{ J}^{-1}\text{C}^2\text{m}^{-1} \text{ (in the vacuum)}$$

$$4\pi\epsilon=78.54\times 4\pi\epsilon_0=8.73640\times 10^{-9} \text{ J}^{-1}\text{C}^2\text{m}^{-1} \text{ (in water)}$$

$$R=8\times 10^{-10} \text{ m}$$

$$N=6.02214\times 10^{23} \text{ mol}^{-1}$$

and we obtain:

$$E_{a,b}=41.49 \text{ kcal/mol (in the vacuum)}$$

$$E_{a,b}=0.53 \text{ kcal/mol (in water)}$$

Considering that there are four carboxylates, the total interaction could be worth 2.0 kcal/mol. However, it must be stressed that this is a very elementary and rough estimate of the effect of the carboxylates. Too many different effects can play a role in a system such as host P in an aqueous medium.

A similar situation is also present in some biological systems. For example looking carefully at the crystal structure of the enzyme acetylcholinesterase, one can find two very interesting features.² The first is the clear and important role of aromatic residues in the binding of acetylcholine. As detailed in chapter 1, the binding site lies at the bottom of a deep gorge. The gorge is lined with many aromatic sidechains, with aromatics being especially prominent at the active site. The second feature of this structure, much less evident than the first, is the presence of a number of carboxylates (from Glu and Asn) that lie beyond the gorge and

beyond the active site. Some of these carboxylates are at an average distance of 7Å from the aromatics of the binding site. The obvious question is "why are they there?". One logical explanation is that they occupy those specific positions in order to generate a global dipole moment of the molecule. In fact, the negatively charged residues of the protein are all concentrated in the half part of the molecule that contains the binding site. The other half of the molecule is obviously positively polarized. This dipole moment can drive acetylcholine into the gorge, and this explains how the substrate finds the entrance to the gorge. This is a perfectly appropriate explanation. However, the carboxylates could be there *also* to help in the binding of acetylcholine via long-range electrostatic interactions. This is also reasonable. In the interior of the protein the dielectric constant should be much lower than that of the solvent, so that classical electrostatic interactions can be strong. Also, the placement of the negative charges behind a wall of hydrophobic aromatics avoids the always possible formation of strongly bound ion pairs, that could be counterproductive for the enzymatic reaction. It must be pointed out that this possible secondary role of the negatively charged residues in acetylcholinesterase, does not diminish in any way the fundamental importance of cation- π interactions in the binding of acetylcholine. It is proven that acetylcholine is primarily bound by the aromatics in the binding site. It is also clear that ACh is helped in its journey through the gorge by cation- π interactions with the aromatics lining on the walls of the

gorge. The hypothesis proposed here is just a secondary interaction involving peripheral carboxylates and a cationic substrate. It is clear that a unique answer to all these questions can be found only by carefully designed experimental studies. In this regard, the synthesis and the study of the binding properties of a neutral water-soluble cyclophane receptor are of paramount importance. The next sections of this chapter will be devoted to this aspect of cyclophane chemistry.

4.2 Design and Synthesis of a Neutral Water-Soluble Cyclophane Host

Host P (Figure 4.1) is a very special molecule. It is water-soluble, however it has an extremely hydrophobic binding cavity. If we take away the four external carboxylates, we are left with a hydrophobic skeleton that is highly insoluble. This is the challenge of making a neutral water-soluble cyclophane host: find neutral groups that can solubilize a hydrocarbon in water.

A neutral group that is appropriate to solubilize our class of cyclophane hosts, must meet several requirements:

- 1) In order to impart water-solubility, it must contain strongly polarized groups. However, these groups must not dissociate or be protonated at the

pH's used for the binding studies (a reasonable range of safe pH is from 7 to 10).

2) These groups should be introduced early in the synthesis of the host, in order to limit the number of reactions on the precious cyclophanes. However, a strongly polar group (as the neutral water-solubilizing group should be) is rarely unreactive and this would imply synthetic problems. A possible protection/deprotection sequence is also not very efficient, synthetically speaking, for the number of groups involved and for the sensitive nature of some parts of the cyclophane structure (such as the benzylic ether linkage). A compromise would be finding a group that could be introduced in just one step by reaction with the tetramethyl-ester of the chosen host.

3) This one-step reaction must have high yield.

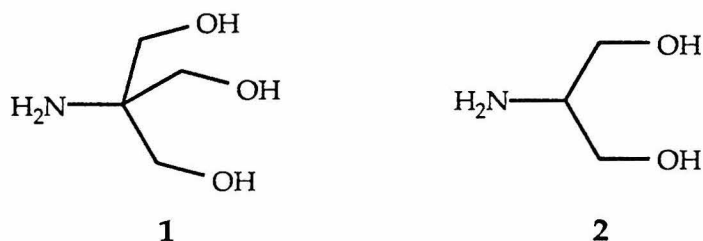
4) The resulting product must retain the symmetry elements of the starting host, i.e. the host must be substituted by these neutral groups in a symmetric fashion. This is important because the host must have a symmetric binding cavity and because in this way the NMR spectra are simplified. This also means that the single step reaction of point 2 must take place on multiple sites (with high yield).

5) The neutral groups must contain the minimum number of non-exchangeable hydrogens. This is important because the ^1H -NMR spectrum of the host must be as simple as possible. This, in turn, is necessary in

order to easily follow the movements of the guest peaks during an NMR binding study.

If we combine all these requirements, we are tempted to say that such a group, if it exists, should be very hard to find. Some of the main attempts made in this direction are presented below. We can anticipate that our search was successful.

We started by noting that one of the best groups for increasing the solubility of organic compounds in water is the hydroxyl group. Almost immediately, our attention was attracted by two common compounds, tris-(hydroxymethyl)-aminomethane (common name Tris) **1**, and bis (hydroxymethyl)-aminomethane (common name serinol), **2**.



The challenge with these compounds is to find a reaction where the amino group is reactive while the three hydroxyl groups are relatively unreactive. Considering the general structure of the class of cyclophane hosts developed in our group (Figure 1.3, chapter 1; Figure 4.2 in this chapter shows the tetramethyl ester of host P, P_E), an aminolysis reaction on the four external ester groups would be an ideal reaction.

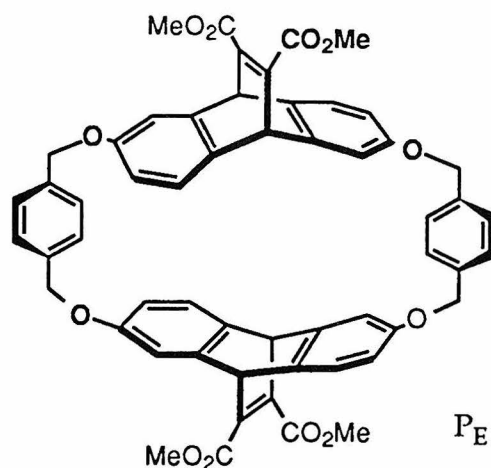
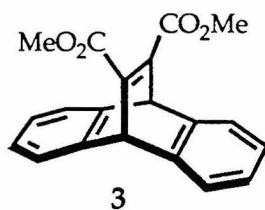


Figure 4.2. The tetramethylester P_E . For details on its synthesis and how to make host P (Figure 4.1) starting from it, see chapter 1.

However one can immediately see that the conditions for an aminolysis (basic pH and/or catalytic or stoichiometric amounts of a nucleophile) could very well catalyze a transesterification reaction. Considering that there are three (in Tris) hydroxyl groups for one amino group, the reaction should favor transesterification. Despite these possible problems, we decided to attempt an aminolysis reaction between Tris and the model (and relatively inexpensive) compound 3.



Various conditions, bases and nucleophiles commonly used for aminolysis³ were tried. Figure 4.3 presents some of these attempts.

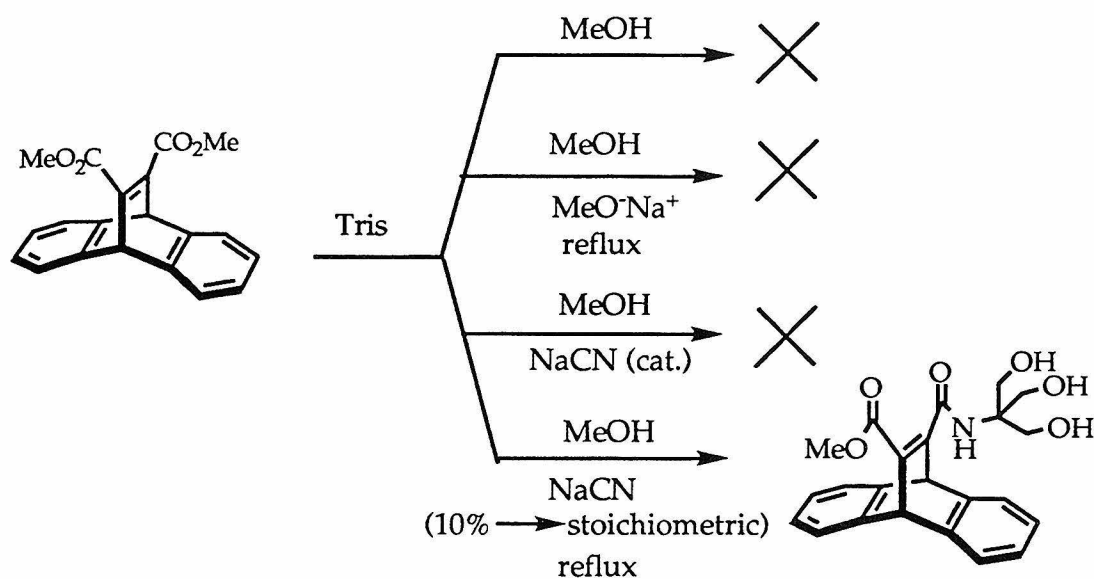
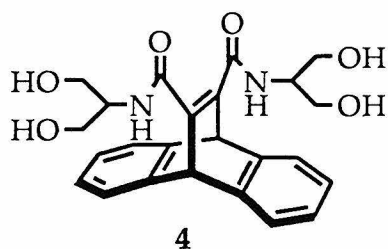


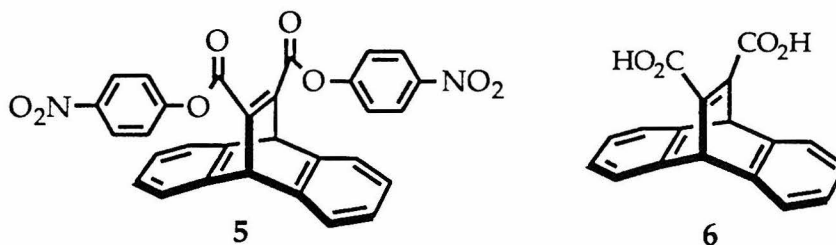
Figure 4.3. Attempted aminolysis by classical methods.

Models for the intermediate of the cyanide catalyzed aminolysis (the amine reacts with the cyano compound coming from the nucleophilic addition of CN⁻ and elimination of MeO⁻) show that the steric hindrance of the Tris molecules is a problem. The same set of reactions was then tried with serinol (2). In this case the reaction in refluxing MeOH with 10% NaCN gave the desired product 4.



4 is partially water-soluble at room temperature, but completely water-soluble at 60°C. However, the reaction of the tetramethyl-ester of host P (P_E hereafter) with serinol never gave the tetrasubstituted product,

probably due to the low efficiency of the aminolysis reaction. Furthermore, it was thought that the presence of a total of 8 hydroxyls would not be sufficient to water-solubilize a hydrophobic molecule such as P_E . Further reactions were then tried with the Tris molecule. The Tris-aminolysis of p-nitrophenyl esters **5**, and the coupling of the diacid **6** with Tris using various dicyclohexylcarbodiimides were all unsuccessful.



It then came to our attention that a different methodology, first introduced by Newcome in the synthesis of arborols,⁴ could be used for the introduction of Tris in our molecules. The reaction uses DMSO as a solvent and potassium carbonate as a base. In these conditions, one of the hydroxyls of Tris is deprotonated and can transesterify the methyl ester. The intermediate ester then undergoes an intramolecular aminolysis to yield the final product (Figure 4.4).

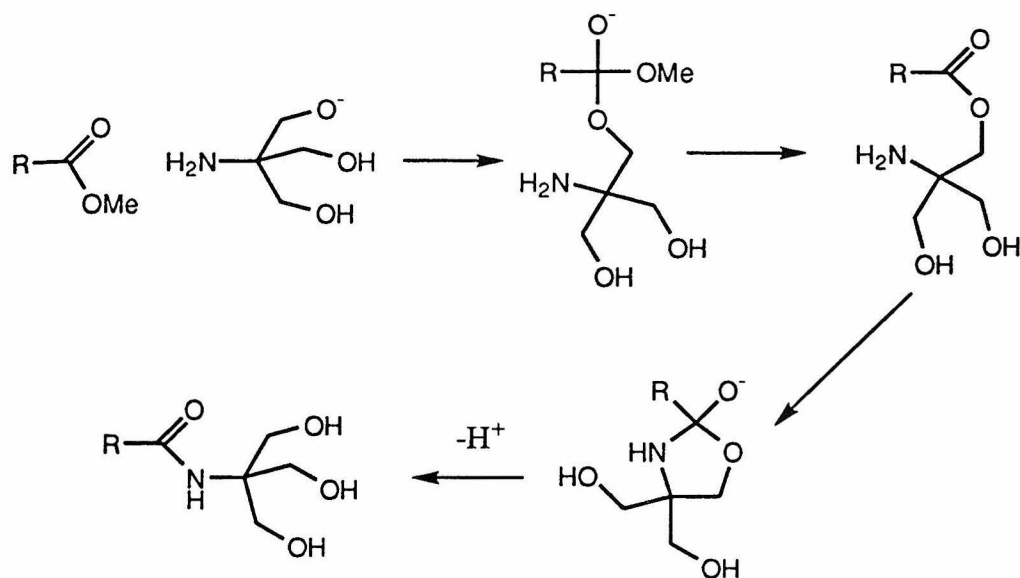
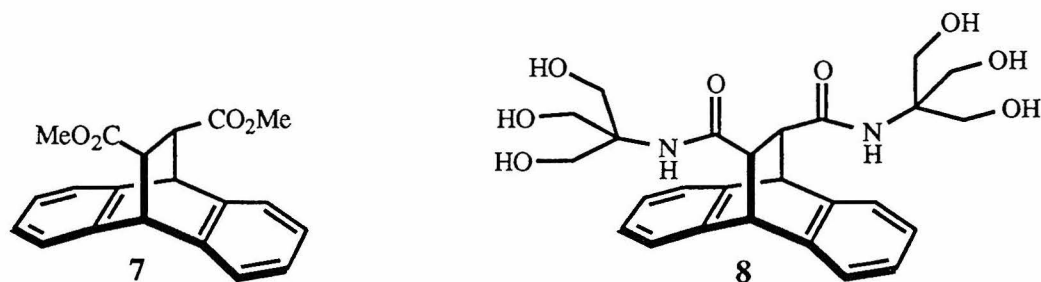


Figure 4.4. Mechanism for the reaction between a methyl ester and Tris in DMSO using K_2CO_3 as a base.

However, to our disappointment, when we tried this method on the dimethylester **3**, the reaction did not occur. After a few more attempts under different conditions, we reached the conclusion that the ethenoanthracene system would make the reaction too sterically hindered to happen efficiently. We then prepared compound **7** by a Diels-Alder reaction between anthracene and dimethylfumarate, and tried to condense Tris on the ethanoanthracene compound.



After a few trials to optimize the reaction, we were able to make the desired compound **8**. Compound **8** is water-soluble at room temperature at

concentrations higher than 5 mM. Encouraged by the synthesis and the properties of **8** we proceeded to synthesize hosts **9** and **10** (Figure 4.5) by a slight variation in the synthesis described in chapter 1 for host P.

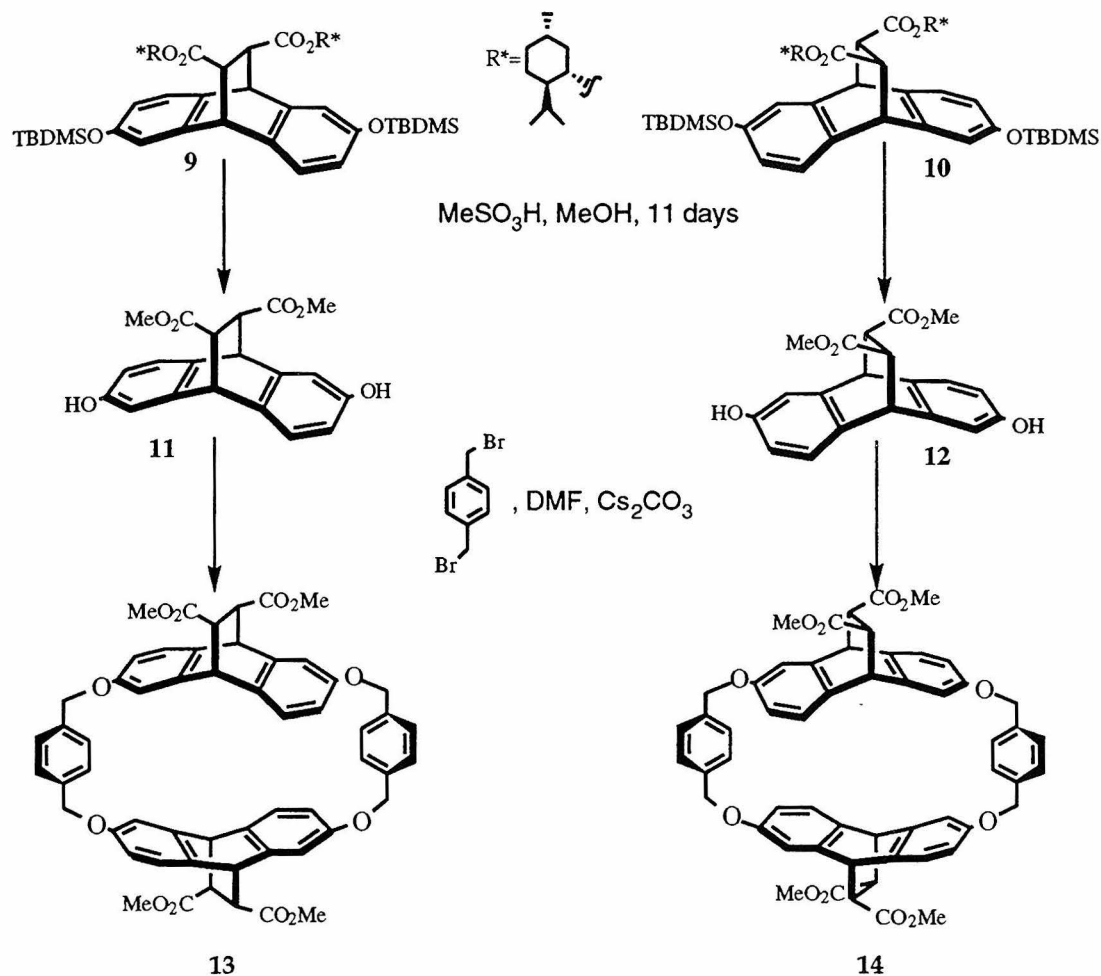
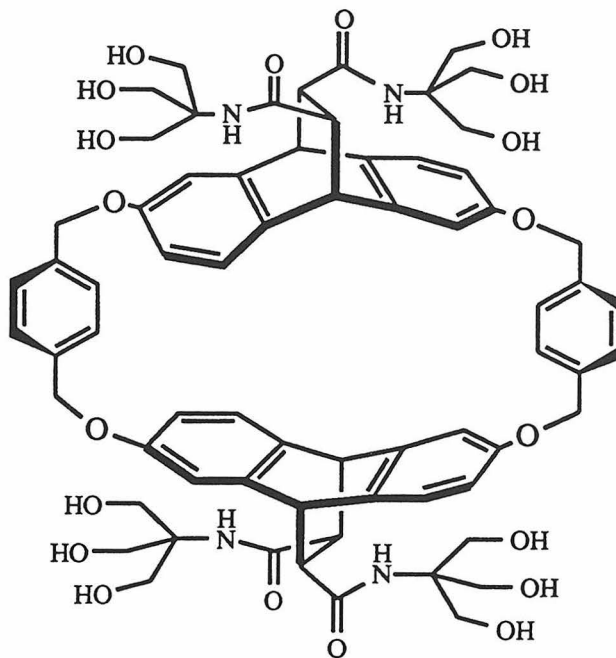
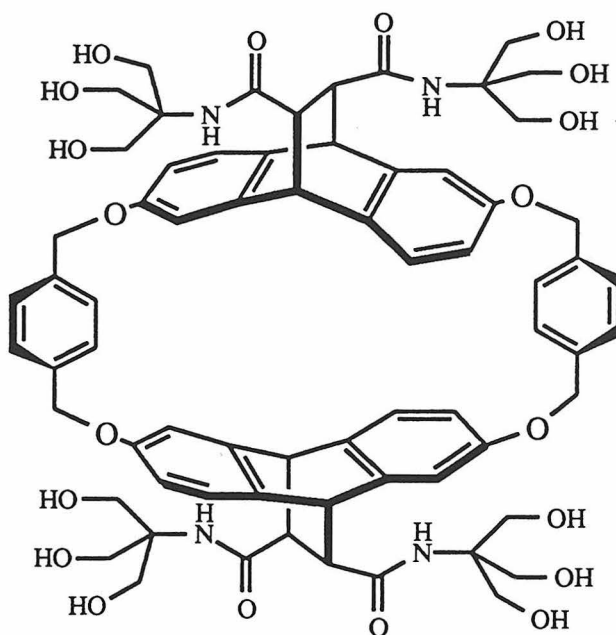


Figure 4.5. Synthesis of hosts **13** and **14**.

We then found that it was possible to have a reaction on all four the methyl esters of **13** and **14** under very specific conditions and in the presence of a large excess of Tris (DMSO , 60°C , 2 days, molar ratio tetramethylester/Tris/ $\text{K}_2\text{CO}_3 = 1/10/5$). We were thus able to make the neutral cyclophane receptors **15** and **16**.



15 (S,S,S,S,S,S,S)-NSP



16 (R,R,R,R,S,S,S,S)-NSP

Purification of these hosts was at first a problem due to the large excess of Tris used in the reaction. Tris is a very simple molecule and it is not UV active, so that its presence is not easily revealed under the conditions used

in the common methods of separation (column chromatography, HPLC). All these problems were solved when an extremely sensitive, specific test for primary amine was used (0.5% alizarin in EtOH).

Depending on the efficiency of the reaction with Tris (presence or not (TLC) of unreacted intermediates), simple column chromatography or HPLC were used to isolate pure neutral hosts. Host **11** was called anti-NSP, anti for the anti configuration of the phenolic and the amide groups and NSP for Neutral Saturated (because it is an ethanoanthracene) P. Host **12** was, in analogy, called syn-NSP.

4.3 Binding Studies of Host NSP

The properties of the neutral host were immediately studied. These compounds are water-soluble but not at the millimolar concentrations required for NMR binding experiments. At those concentrations, the host aggregates. While these solubility properties could be disappointing, it is necessary to recall that a compound that is *almost* water-soluble at the required concentrations can be made *completely* soluble by addition of small amounts of a less polar solvent such as acetonitrile. The addition of 10% acetonitrile by volume to solutions of the host in aqueous medium was found to suppress aggregation, allowing NMR titrations to be performed using host concentrations of at least 500 μM . This procedure has been used previously in our group for the most hydrophobic hosts such as TBP or TMTBP (chapter 1). Also, in order to compare the binding

results for all of the hosts, measurements of the binding constants of host P in 10% MeCN/borate buffer had been previously performed for a large variety of guests.^{1a} We have seen for host P and other hosts^{1a}, that in changing from borate buffer to 10% MeCN/borate buffer, the binding affinities decrease, for all the positively charged guests, by 2.5 kcal/mol. Therefore, in our choice of guests for NSP, we were limited to those guests that present a high (>3.5 kcal/mol) affinity in the mixed solvent. This limit depends on the sensitivity of the NMR titration method, that, in our hands, does not allow measuring binding constants lower than 3.5 kcal/mol (for details, see experimental section-determination of binding constants, at the end of this chapter).

Binding constants of host NSP with a variety of guests have been measured. The results are shown in Table 4.1.

Finally, we must notice that the main goal in making a neutral host, was to measure binding constants when no other charges are present on the host. Considering the peculiar properties of the hydroxyls in Tris, that are deprotonated by potassium carbonate in DMSO, we decided to use neutral solutions for the binding experiments. We dissolved the host in MeCN/aqueous 10mM NaCl 1:9 in volume, in order to have the same ionic strength of the borate buffer. We thought that the binding constants measured this way were comparable to the binding constants measured in MeCN/borate buffer 1:9 by volume.

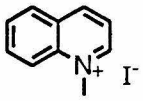
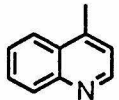
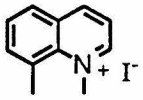
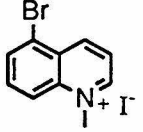
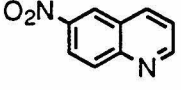
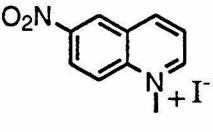
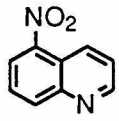
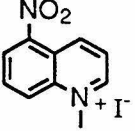
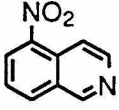
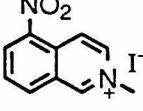
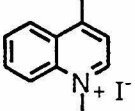
<u>Guest</u>	<u>anti-NSP</u>	<u>syn-NSP</u>	<u>Host P</u>
 17	4.4±0.4		5.8
 18	not measurable		not measurable
 19	5.7±0.2		6.3
 20	4.7±0.4		6.1
 21	5.8±0.4	5.6±0.2	4.6
 22	4.3±0.4	5.1±0.1	unknown
 23	4.8±0.3	4.8±0.2	4.3
 24	6.0 6.1	5.7±0.2	unknown
 25	5.1±0.2	5.3±0.3	4.6
 26	3.8±0.2	4.1±0.2	unknown
 27		5.1±0.3	5.9

Table 4.1. $-\Delta G^{\circ}_{298}$ for binding to hosts anti-NSP and syn-NSP in 10% MeCN/aqueous NaCl 10mM, and for binding to host P in 10% MeCN/borate buffer (ionic strength=10 mM).

Table 4.1 shows many interesting peculiarities. First of all we can see that for “classical” guests such as N-methylquinolinium (NMQ, 17) and 5-bromo-N-methylquinolinium 20, there is a decrease in binding of almost 1.5 kcal/mol relative to host P. The data for NMQ, were particularly interesting, because this guest does not have any functionality that could interact with the host in other ways. The binding energy for NMQ and anti-NSP was then measured in 10 mM aqueous NaCl (i.e., no added MeCN) using CD techniques. It was determined to be 6.9 kcal/mol, i.e., exactly 1.5 kcal/mol less than the binding of NMQ for host P in borate buffer. This value, as all the binding constants measured by NMR, was completely reproducible. However, the surprises did not stop here. Considering that, in 10% MeCN, we would have a decrease in binding, compared to host P in borate buffer, of $2.5+1.5=4$ kcal/mol, we were unable to measure the binding constants of many guests. One exception was the nitro-substituted quinolinium salts. These compounds have very large binding constants, such that for host P they often exceed the upper limit (8 kcal/mol) for NMR titrations. Thus we decided to look to the binding of these guests, and the results were unusual, at least. We can see from Table 4.1, that the binding of the nitro guests to NSP is stronger than the binding of the same guests (those for which the binding constant is known) to host P. Furthermore, the syn and anti isomer of NSP show a reproducible

difference in binding for 6-nitroquinolinium. This was highly surprising and suggestive of different interactions. An astonishing result was the binding of the pairs 5-nitro-isoquinoline (25) / 5-nitro-N-methyl-isoquinolinium (26) and 6-nitroquinoline (21) / 6-nitro-N-methylquinolinium (22) to host anti-NSP: in these cases, the neutral guests bind more than the charged guests by as much as 1.5 kcal/mol! In order to rationalize these results, a series of 2D-COSY experiments was performed on the nitro-guests. These studies allowed assignment of the right chemical shift to each proton and as a consequence to make a careful analysis of the D values for the binding of these guests. We define D values as the differences in the chemical shift between the free and the bound guest. D values are obtained by measuring the resonances of the protons of the guest, in a solution of the guest and in a solution of the host-guest complex, with the host in large excess, so to have the highest percentage of bound guest. The differences between the two sets of chemical shifts give the D values. Knowing the complex of the D values for a guest may result in the assembly of a "picture" of the guest in its complexed state. These differences are then normalized by assigning 1 to the largest value and reporting the other differences as percentages. If two guests of similar size have different D values, one can conclude that they are bound in different conformations by the host. Figure 4.6 reports the D values for the binding of neutral and charged nitro-guests to host anti-NSP.

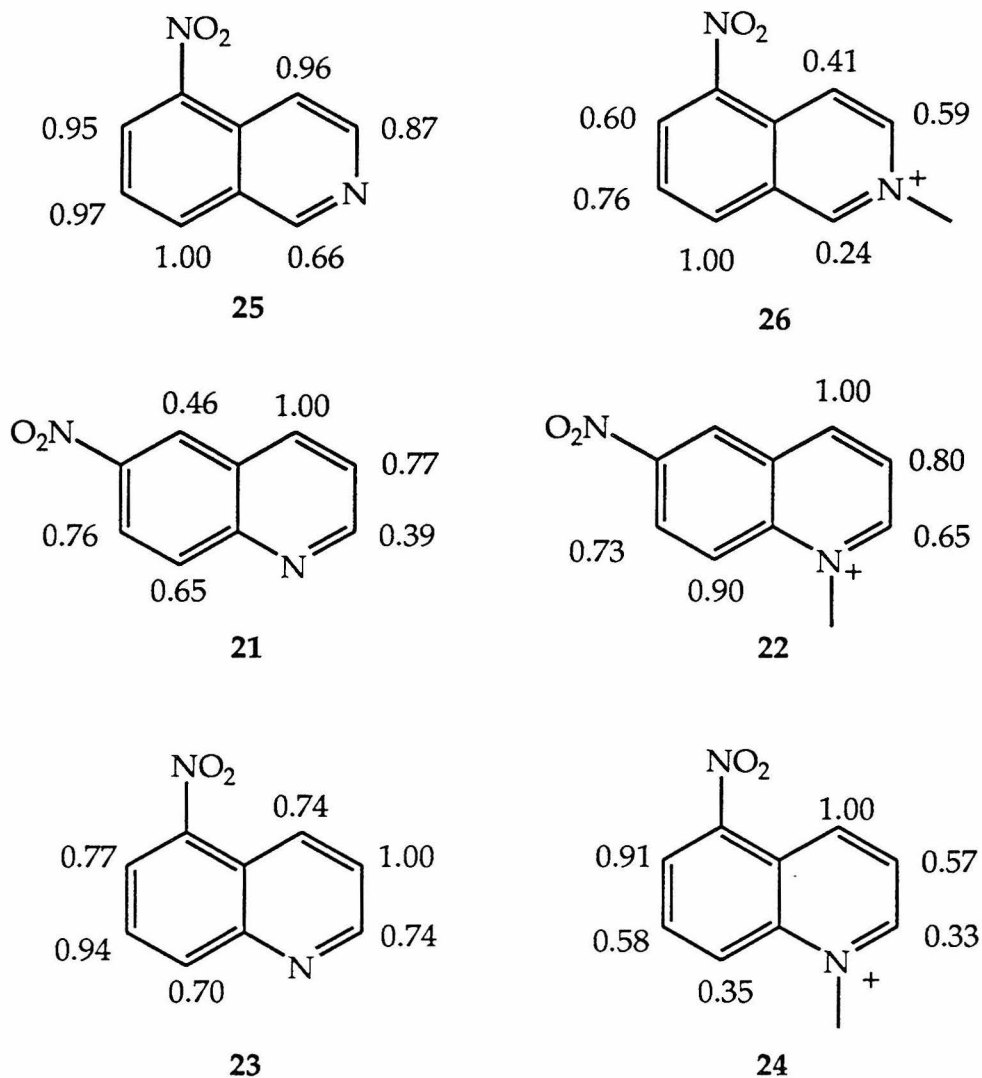


Figure 4.6. D values for the binding of nitro guests to anti-NSP (Table 4.1).

For the pair **25** and **26**, one can see that, going from the charged to the neutral guest, the D values generally increase. This allows us to say that the quinolinium salt is not as deeply buried in the binding cavity as it is the neutral guest. In the case of the pair **21** and **22** the charged guest is now positioning more deeply in the binding cavity than the neutral guest. In

the case of the “regular” pair **23** and **24**, there are definite changes in the binding conformation going from the neutral to the charged guests.

While it is not possible to outline definite conclusions from these studies, we can make the following observations.

- 1) All the nitro-guests show different conformations for the binding of the neutral and of the charged guests.
- 2) Interestingly, 6-nitro-N-methylquinolinium and 5-nitro-N-methyl-isoquinolinium present the same molecular graph (Figure 4.7):

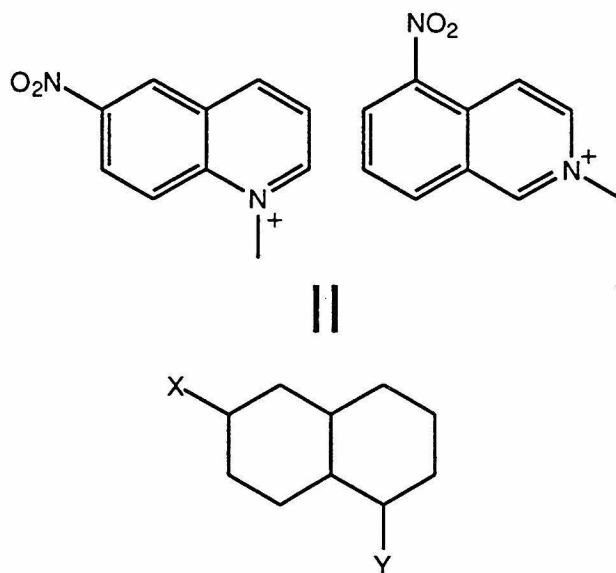


Figure 4.7. Guests **22** and **26** have the same molecular graph.

The differences in the binding that are seen for the neutral and the charged guests, could therefore be due for the two pairs to two different possible causes:

- a) Steric hindrance in the binding of the charged guests.

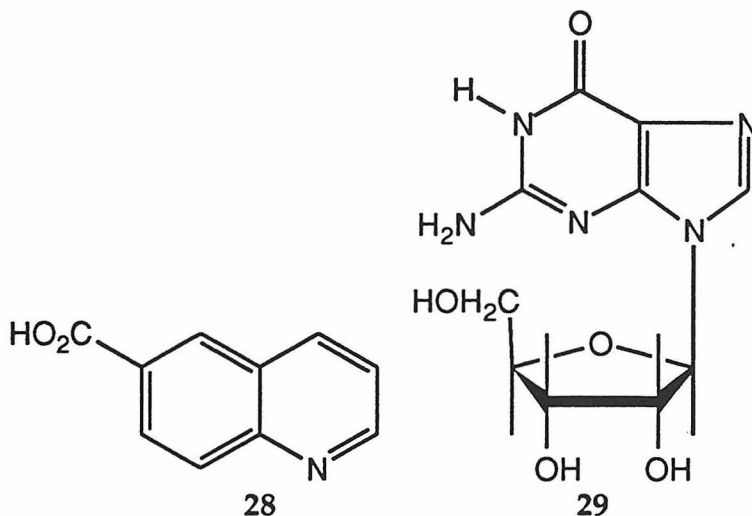
b) The binding conformation of the charged guests does not allow interactions that are possible upon binding the neutral guests.

We propose here that there could be hydrogen bonds between the nitro groups of the guests and the hydroxyl groups of the host. The steric hindrance of the quaternary methyl of the charged guests would then make these interactions difficult, if not impossible. Interestingly, in guests 23 and 24 where the steric hindrance should be reduced, this effect is not noted and the charged guest presents the highest binding constant measured for the nitrocompounds. This hypothesis could also partially explain the differences in binding between anti and syn NSP. CPK models show that, due to the twisting of the chiral host, the anti and the syn hosts place the Tris groups in slightly different positions. This difference of positions could then translate in a difference of strength of the interaction.

It did not escape the author's attention that the hypothesis presented in point b is debatable, at least. In fact, the presence of hydrogen bond interactions, in water, has been seen very rarely⁵. Furthermore, the hydroxyl groups should be strongly solvated, even if the anisotropic distribution of the medium (it contains 10% MeCN) could provide local zones richer in MeCN.

In order to test the hydrogen bond hypothesis, binding experiments were performed with guests potentially able to interact with the hydroxyls

of the host. Guests 28 and 29 (guanosine) were selected for this trial. No binding was measured for these guests. However, it is necessary to stress that the negative results of the latter experiments do not show that the lack of hydrogen bond interactions in the binding of the nitro guests. They show that guests 28 and 29 do not bind to NSP.



The hydrogen bond hypothesis could also be tested by measuring binding constants in solvents different from water, because host NSP is soluble in a variety of solvents. However, these studies, even if positive, would not prove that there are hydrogen bonds in water, and were thus not performed.

It was also thought that these differences in binding constants were the result of a particular specific conformation of host NSP. This brings us back to the general problem raised by this host: the binding constants of positively charged guests are up to 1.5 kcal less than the corresponding binding constants for host P. Is this the result of the absence of the four

external carboxylates or is it due to the binding conformation of this molecule?

There are two main differences between host NSP and host P. One is obviously the presence of the neutral solubilizing groups. The second is a geometry change in the bridge of the anthracene. We have an ethenoanthracene for host P and an ethanoanthracene for host NSP. Could this geometry change cause the differences that we were seeing? In order to answer to this question, we synthesized host SP, **30** (Figure 4.8) by basic hydrolysis of host **14**.

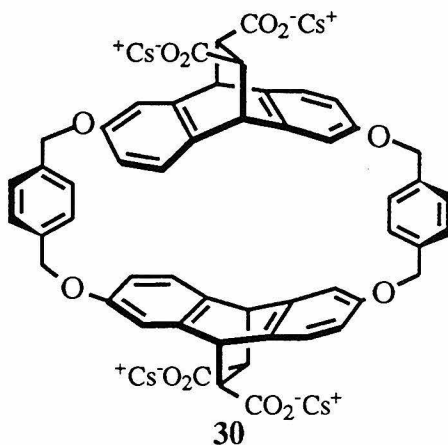


Figure 4.8. Host SP (Saturated P)

The binding properties of host SP are reported in Table 4.2.

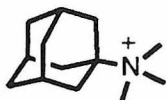
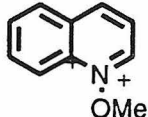
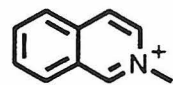
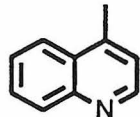
				
Host P	6.7	7.4	7.3	5.9
Host SP	6.7	7.4	7.5	5.8

Table 4.2. $-\Delta G^{\circ}_{298}$ for binding of selected guests to hosts P and SP in borate buffer. Error in the free energies of binding is approximately ± 0.2 kcal/mol.

The binding constants for hosts P and SP can be considered identical. Thus, the change in geometry in the bridge of the anthracene unit does not bring a change in binding. The remaining possibility for explaining the binding constants of NSP, without invoking an absence of the peripheral negative charges, is that the introduction of the Tris groups changed the binding conformation of the host. In order to study this possibility, two efforts were undertaken. We tried to crystallize host NSP, but we found that a better option would be to crystallize model compound **8**. We were able to grow beautiful crystals of **8** and an X-ray structure did not show any particular change in the geometry of the anthracene unit, when compared to the crystal structure of host P. However, while **8** did not give any new insights, it showed an unusual solid state structure that is pictorially described in Figures 4.9-4.12.

The solid is a regular bilayer. Particularly interesting are the series of channels visible in the structure at different angles.

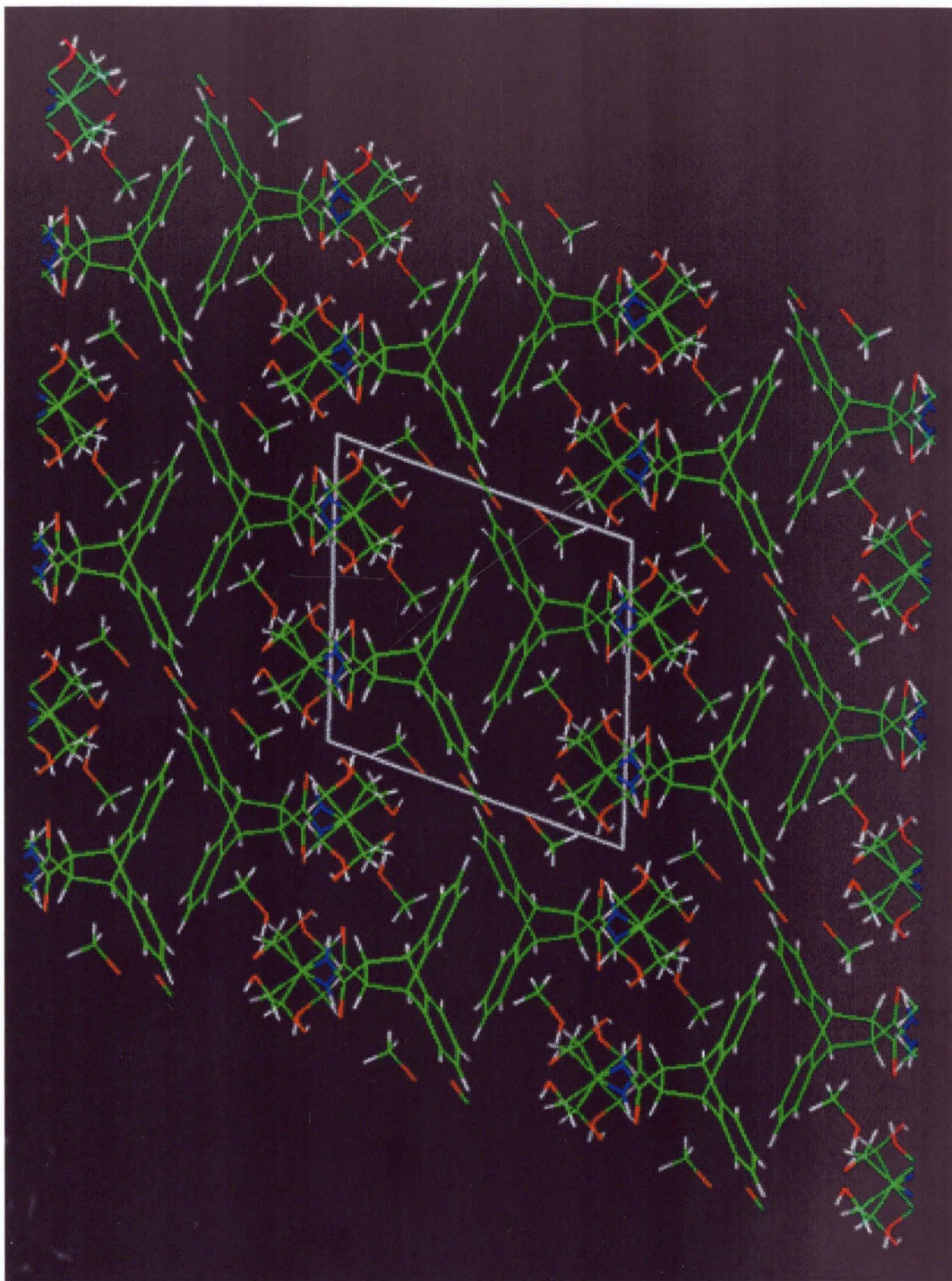


Figure 4.9. X-ray structure of **8**. The white borders at the center of the picture describe the unit cell. This is actually a cube of 3x3x3 molecules. Solvent molecules (MeOH) are clearly trapped hydrogen bond interactions with the hydrophilic part of the molecule. The bilayer structure is self-evident.

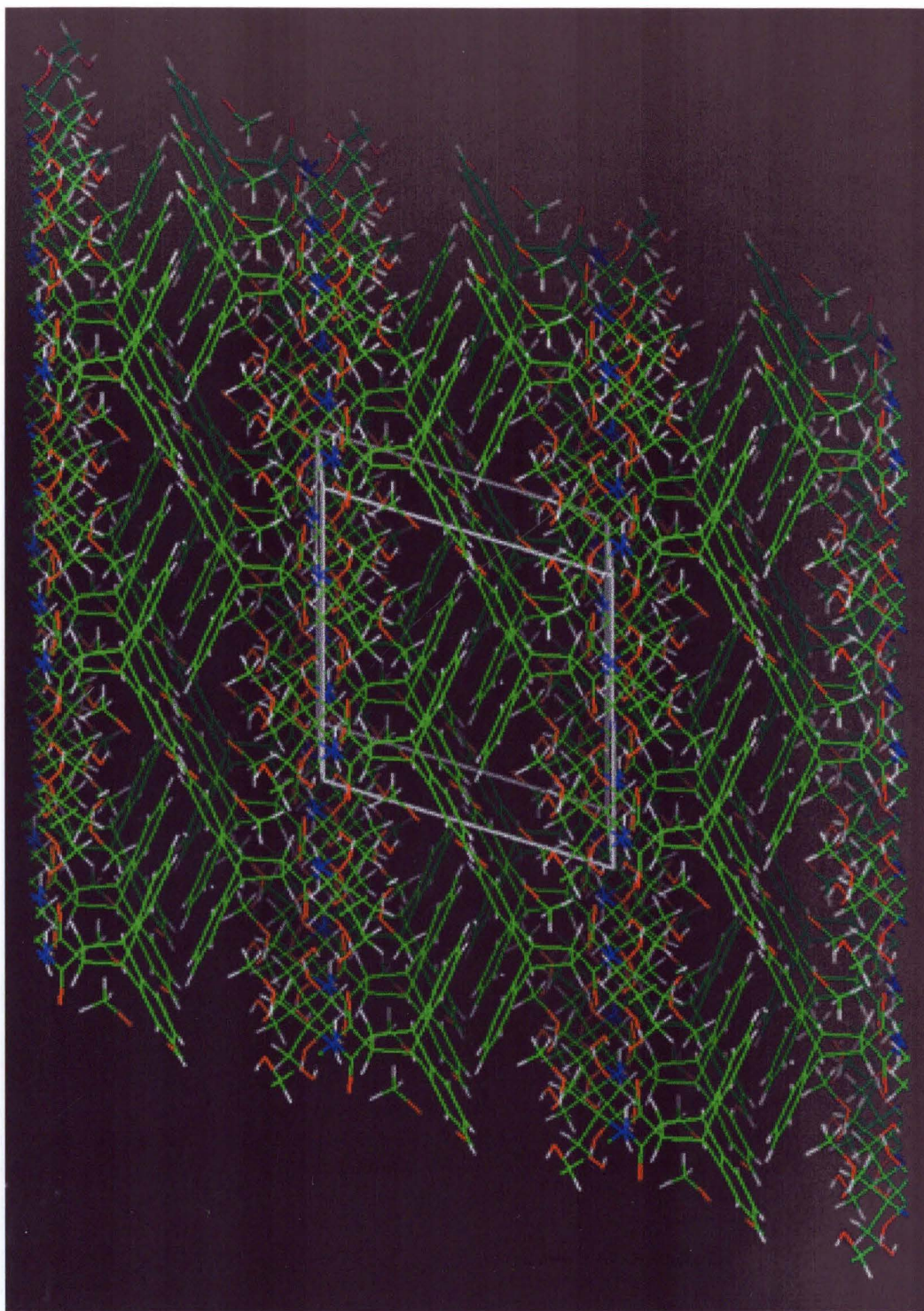


Figure 4.10. Rotation of about 20° from the $3 \times 3 \times 3$ cube of Figure 4.8, gives a sense of the three-dimensional structure

Figure 4.10 shows a 3D model of the diamond crystal structure. The atoms are represented by green, red, and blue spheres, and the bonds are shown as lines. The structure is rotated approximately 20° from the perspective shown in Figure 4.8, giving a sense of the three-dimensional structure.

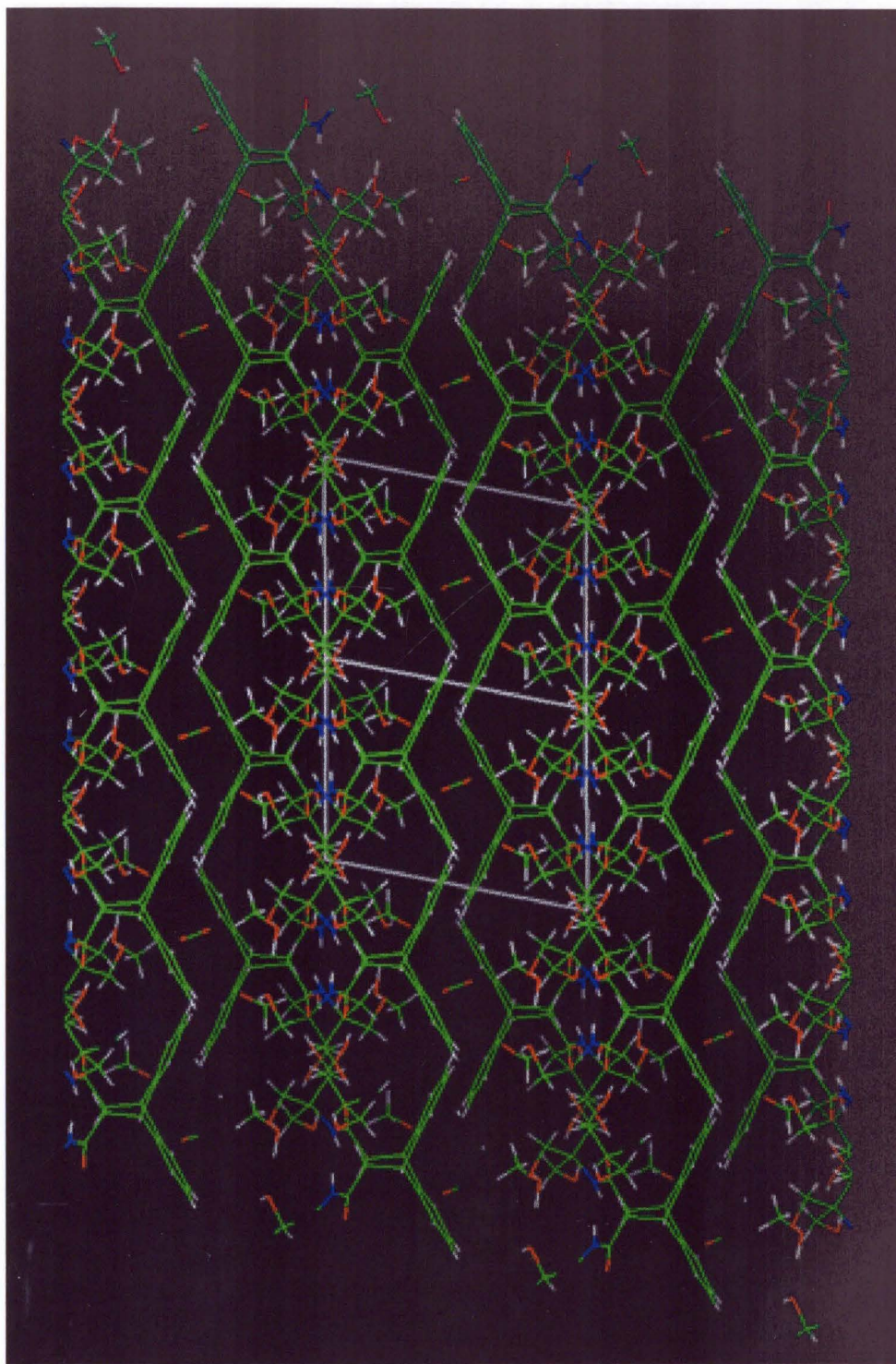


Figure 4.11. Rotation of 45° from picture 4.8 shows the regularity of the bilayers. Solvent molecules trapped in the channels of the structure (the OH of one solvent molecule is disordered, so it appears at both the extremities of the molecule).

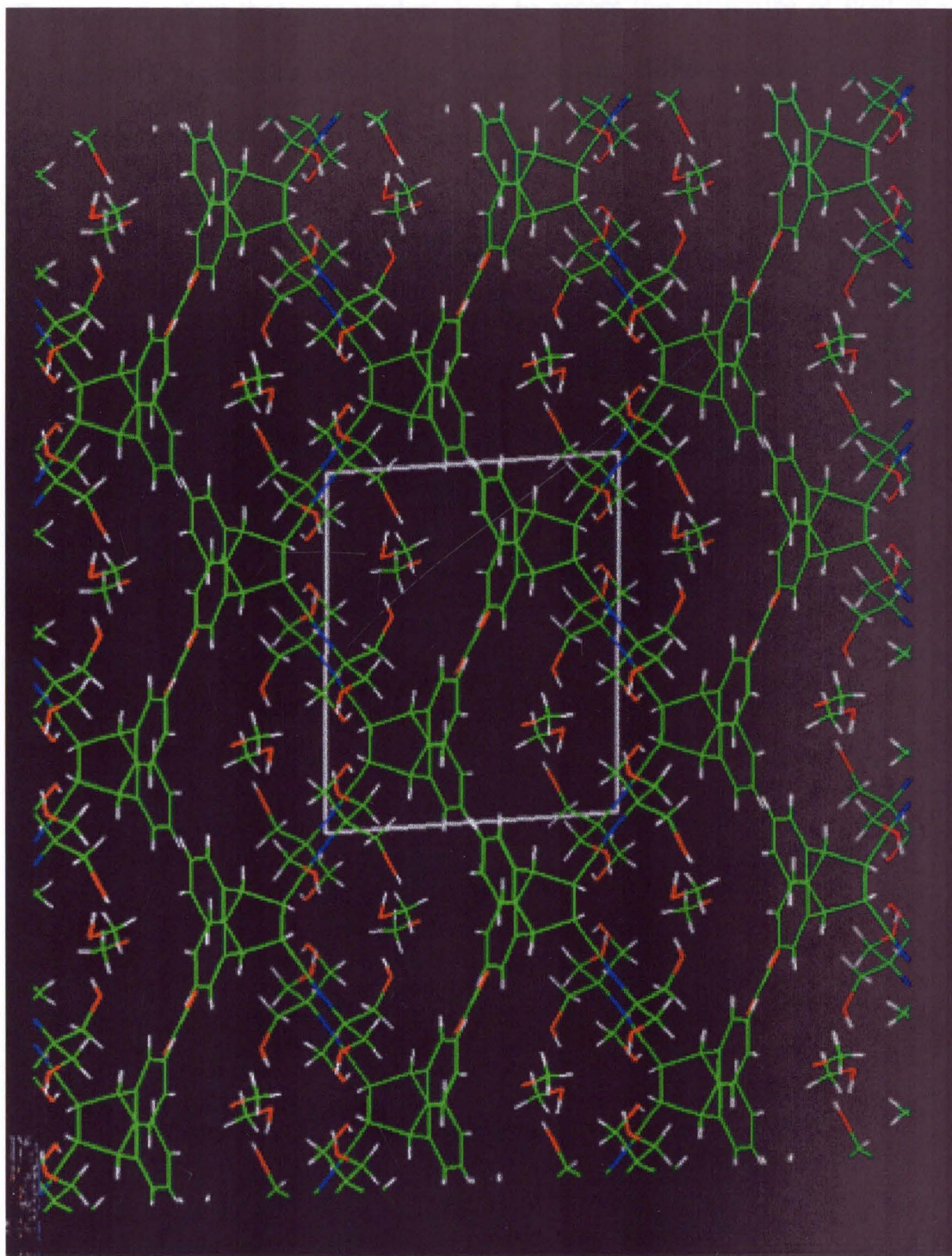


Figure 4.12. Rotation of other 45° , (90° from Figure 4.8) shows another series of well defined channels. Solvent molecules are trapped inside.

The second effort that was undertaken to assess the structure of host NSP is a series of molecular modelling studies using different force fields. The results are reported in Figures 4.13-4.14.

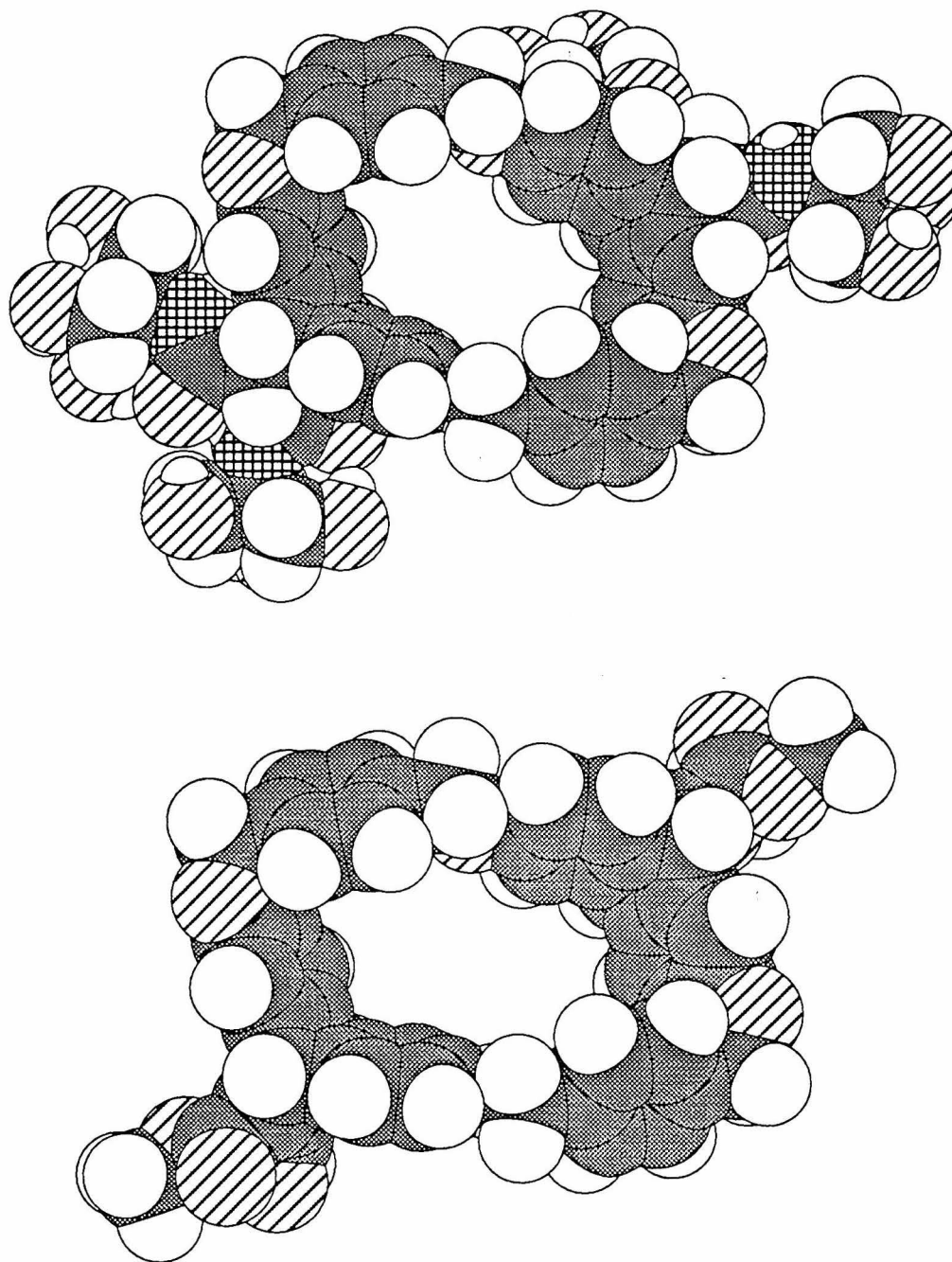


Figure 4.13. Host P (bottom) and host syn-NSP (top) optimized by molecular mechanics calculations using the force field CFF91.

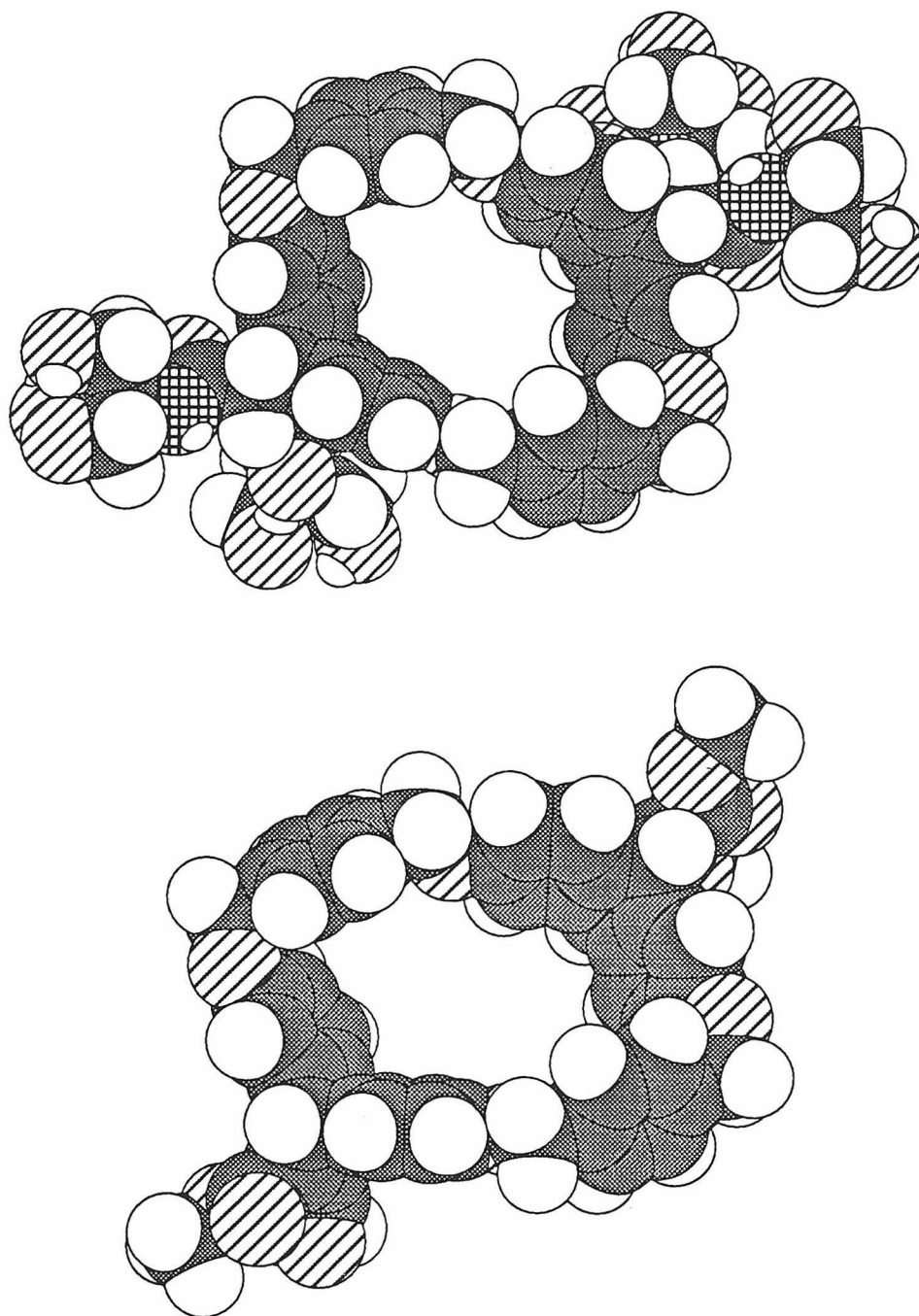


Figure 4.14. Host P (bottom) and host syn-NSP (top) optimized by molecular mechanics calculations using the force field CVFF.

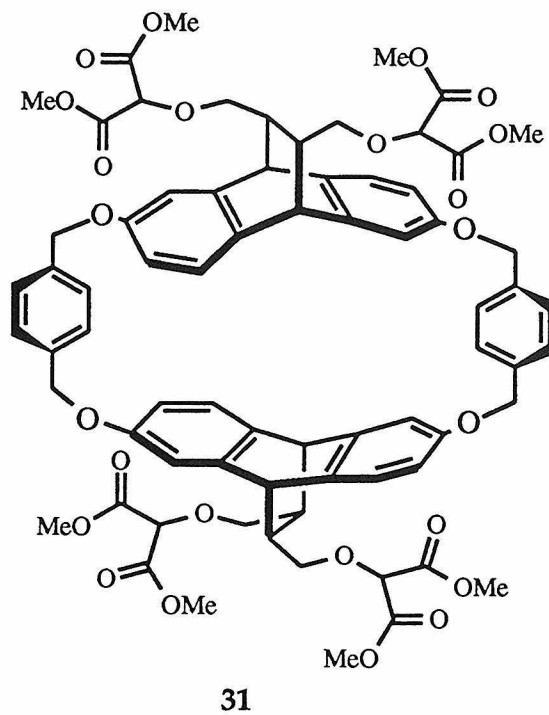
Both calculations show that the binding cavities of host P and host syn-NSP are almost identical. An analogous calculation made using the AMBER force field gave different cavities for the two hosts. However, CVFF and CFF91 are much better force fields for our molecules, and we decided to base our conclusions on these two force fields.

One last aspect of the differences between host P and NSP is the rigidity of the binding cavity. In fact, the binding cavity modifies its shape to better accommodate the guest. It could be that the strong solvation of the Tris groups makes it difficult for the cavity to change its shape (when compared to host P). This effect would have an impact on the resulting binding constant. However the nitro-guests bind to NSP more tightly than to P. So, unless there are *very strong* hydrogen bonds between NSP and the nitro groups, the rigidity of the binding cavities of P and NSP should not be very different. All the discussions developed so far, brings about another possibility: the decrease in binding seen for host NSP is due to the absence of the four carboxylates. This means that long-range electrostatic interactions should be worth approximately 1.5 kcal/mol in water for four carboxylates at the average distance of 8 Å from the center of the binding cavity. Thus, each carboxylate should be worth about 0.35 kcal/mol. Is this possible? The answer to this question can be articulated in experimental and theoretical studies. From the experimental point of view, the most logical course of action can be, once again, divided in two ways.

- 1) The binding constants of other guests to host NSP would certainly be valuable. As discussed above, we were limited in the choice of our guests by the poor binding abilities of NSP. The use of CD techniques that allow binding constants to be taken into aqueous media, should solve this problem. However, we need to point out that CD measurements of binding constants for this host have proven to be particularly difficult compared to host P. The only known CD binding constant for NSP is the one for NMQ-Cl. It was measured after many failed attempts.
- 2) A millimolar water-soluble neutral host could be synthesized. We will now briefly discuss here this possibility.

4.4 Attempts to Improve the Water-Solubility of Host NSP

The reaction between **14** and Tris to make host NSP works well and with high yields. It is then only natural to try to improve the water solubility of the host by increasing the number of Tris groups. This means that the number of methyl ester groups must increase. The most simple starting molecule is therefore **31**.



From **31**, host **32** should be a feasible target.

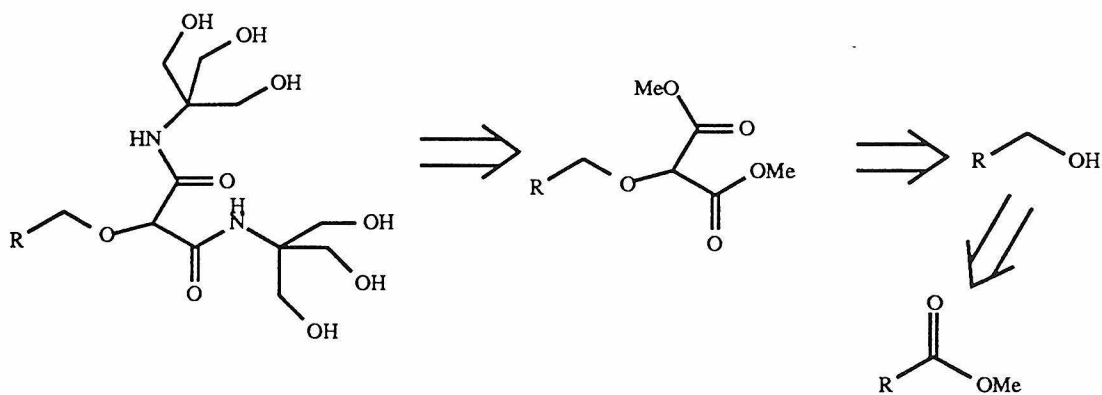
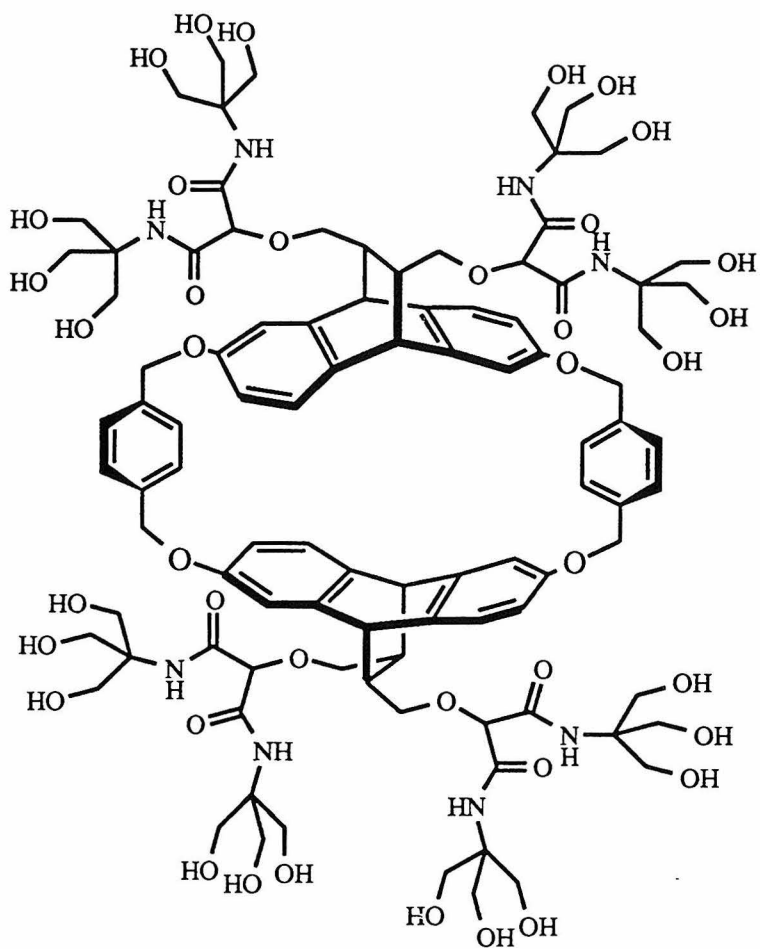


Figure 4.15. Retrosynthetic analysis for the introduction of two Tris groups starting from one methyl ester.



32

Different reactions were tried to make 31.

Specifically, some reactions were tried on model compound 33. The most significant reactions are reported in Figure 4.16.

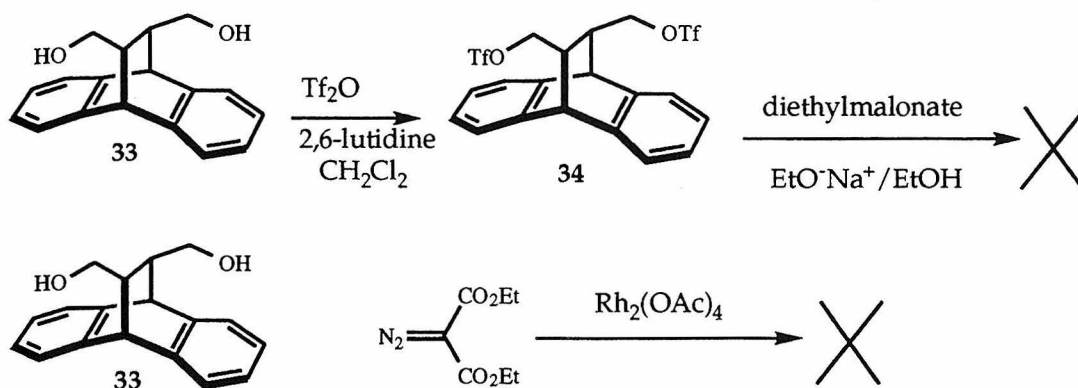


Figure 4.16. Steric hindrance affected the alkylation of diethylmalonate by 22, while diazomalonate proved to be an extremely stable compound.

Alkylation of diethylmalonate did not work, possibly for steric reasons. The diazomalonate turned out to be a very stable compound and it did not react under a variety of reactions. At this point another approach was used. It is shown in Figure 4.17

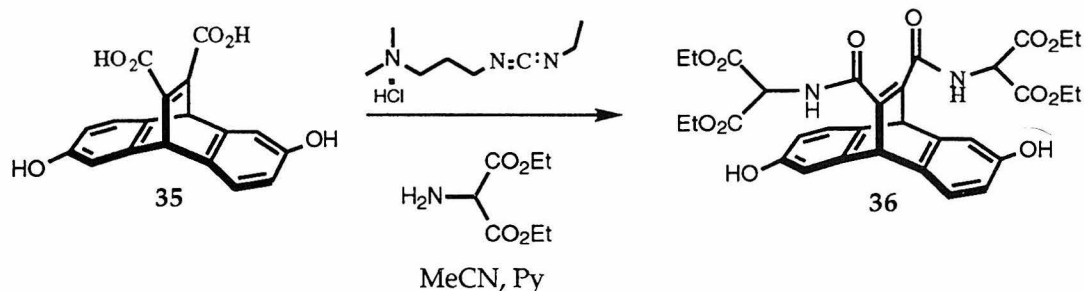
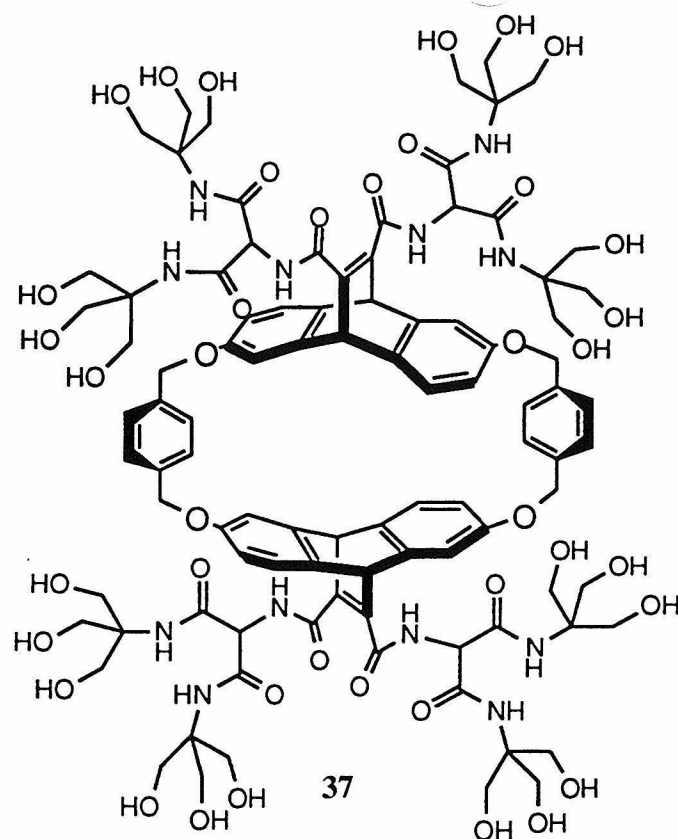


Figure 4.17. Condensation of aminodiethylmalonate with 35 yielded the tetraester 36.

Compound 36 was isolated without problems. Macrocyclization of 36 was expected to give an octaester that after reaction with Tris should yield host 37.



The macrocyclization proved unsuccessful because the hydrogen of the CH in the malonate portion is highly acidic, and it is deprotonated under the macrocyclization conditions. This generates four anionic centers that strongly interfere with the addition of Tris. Of course, one way to solve this problem is to reduce the acidity of that specific proton. This may be done by interposing one or more CH_2 's between the malonate NH and the CH as in compound 39 (Figure 4.18).

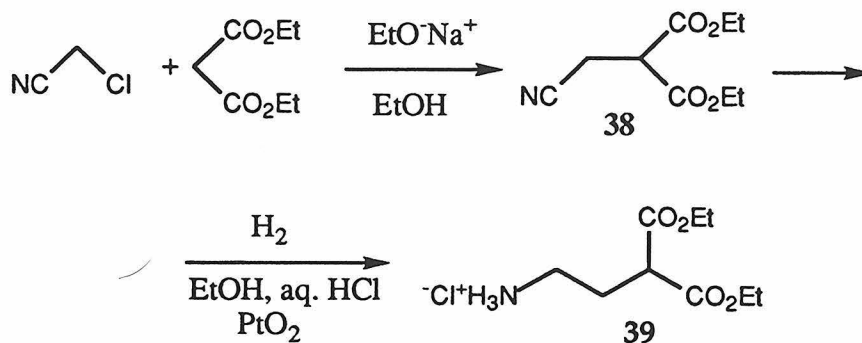


Figure 4.18. Synthesis of the amine 39.

The DCC coupling procedure shown in Figure 4.17 should allow easy attachment of this chain to the ethanoanthracene 35. It was also thought that because of the distance between the malonate moiety and the amino group, the sterical requirements of compound 39 should be less than those of 36. The coupling reaction was therefore performed on the ethenoanthracene 40 (Figure 4.19). Coupling of 39 to 40 gave compound 41. Macrocyclization of 41 could then give host 42 (Figure 4.19). Unfortunately the macrocyclization reaction did not proceed in an efficient manner. A number of products were obtained and among them the desired 42 was not found.

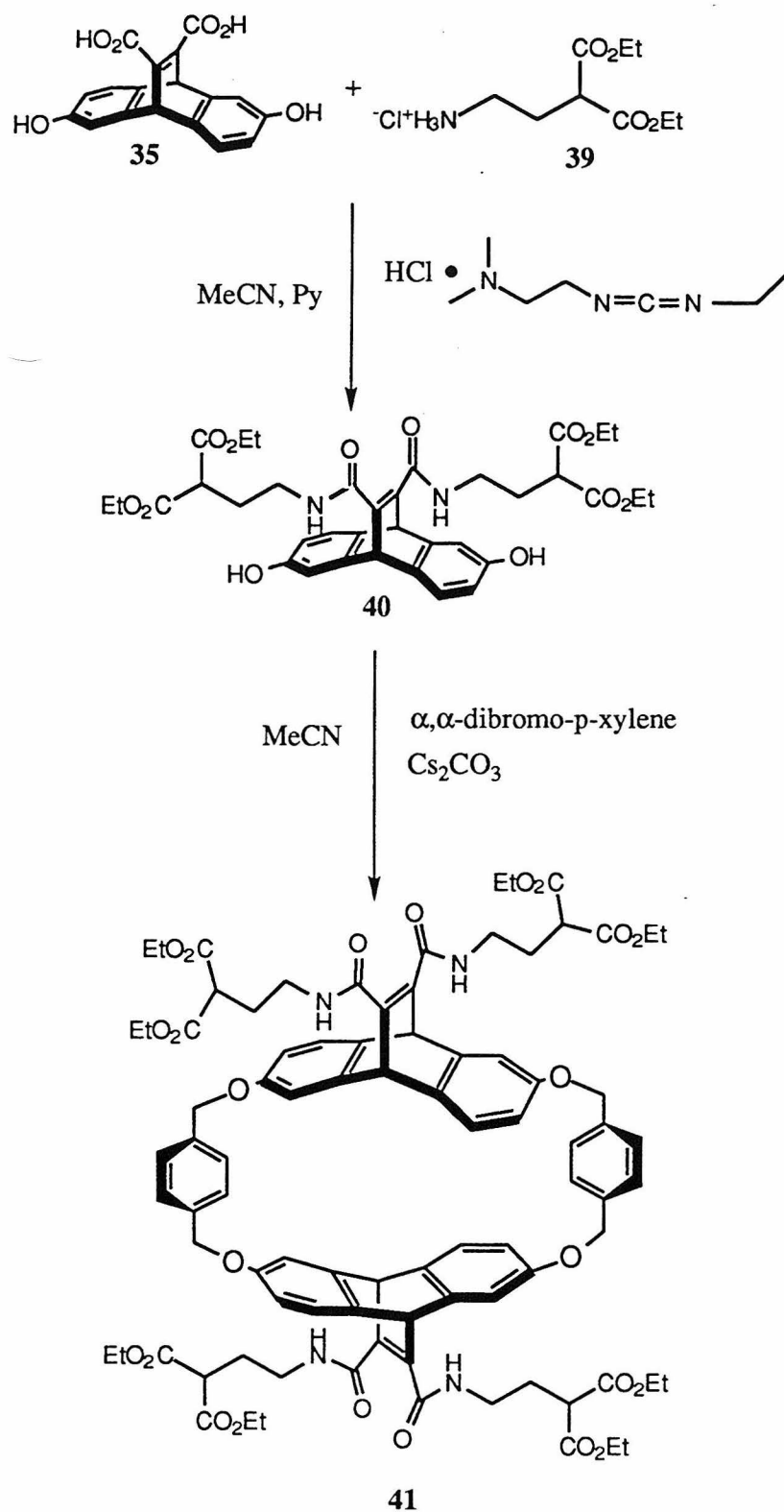


Figure 4.19. Attempted synthesis of host 41.

Host **41** would have been an ideal molecule. By reaction with Tris, one could have made host **42** and by simple basic hydrolysis one would have made an octanegatively charged host, **43** (Figure 4.20).

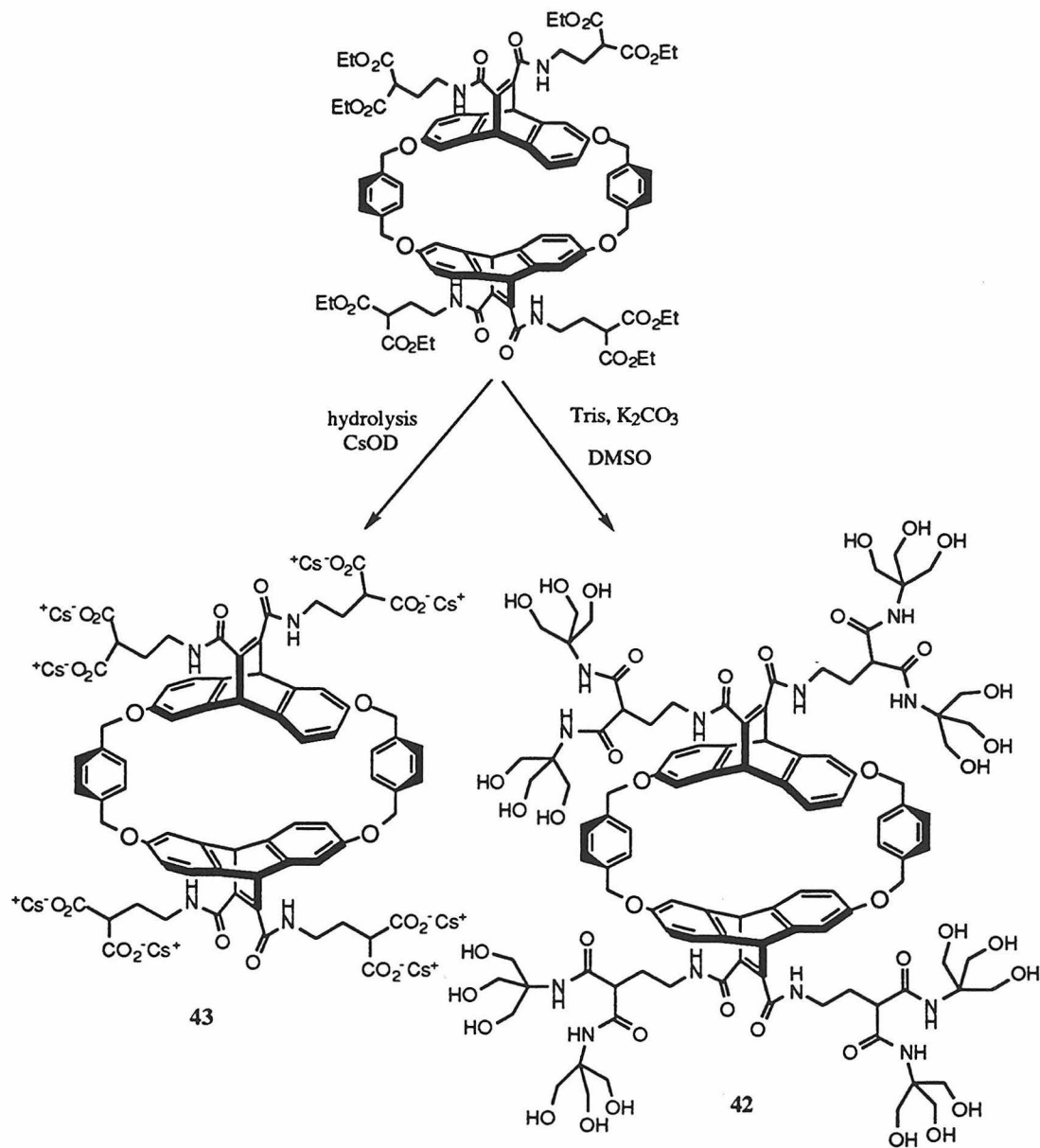
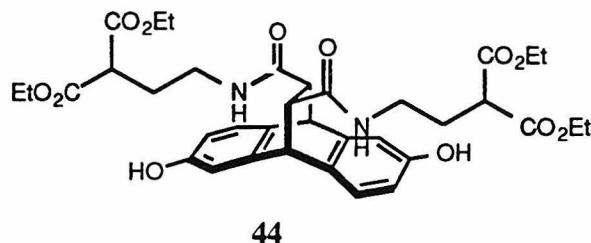


Figure 4.20. Two interesting molecules could be made starting from host **41**.

The reasons for the failure of the macrocyclization of **40** are not evident. They could be related, once again, to the ethenoanthracene system.

Compound **41** could be too bulky. An improvement would be to use the anti-ethanoanthracene system **44**. In this building block, the bulky groups have a very different position than in **40**. In our experience, the ethanoanthracene units have always been relieved of steric hindrance compared to the ethenoanthracene systems.



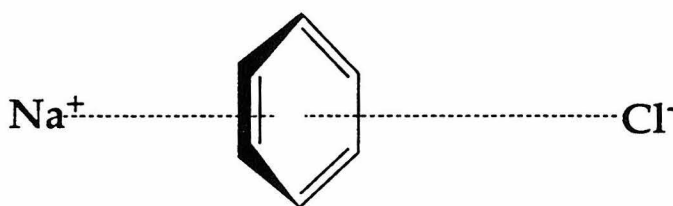
While this is certainly a worthwhile approach, it could not be tried due to time limitations.

4.5 Theoretical Studies

The decrease in binding seen for NSP can be explained by the absence of the four remote carboxylates. This raises the question of how long-range electrostatic interactions can be so effective in this system. One possibility is that the aromatic rings of the host provide an especially effective intervening medium for transmitting long-range electrostatic effects. We have tried to model this hypothesis computationally.

We have performed a variety of *ab initio*, 6-31G** calculations on simple model systems. We believe that this level of theory provides good

estimates of the kinds of interactions of interest here. Based on the crystal structure of P_E ,⁶ we estimated that the average distance from the center of one carboxylate to the center of the closest aromatic ring on the ethenoanthracene unit is 5.1 Å. We thus placed a chloride ion at 5.1 Å from the center of a molecule of benzene and we placed a sodium ion (on the other side of the aromatic), at the optimized distance of 2.45 Å from the benzene (Figure 4.21),



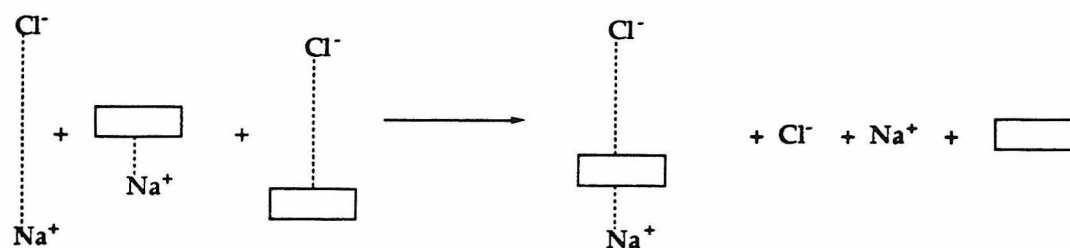
$$R \text{ Na}^+ \text{---benzene} = 2.45 \text{ \AA}$$

$$R \text{ benzene---Cl}^- = 5.10 \text{ \AA}$$

$$R \text{ Na}^+ \text{-----Cl} = 7.55 \text{ \AA}$$

Figure 4.21. The system used to model the interaction of remote carboxylates and positively charged guests in host P.

HF 6-31G** energy calculations were performed and the results (Figure 4.22) were that the presence of the benzene molecule between the sodium and the chloride confers an extra 5 kcal of stabilization to the system.



System	Energy (H)
Na^+	-161.6592883
Cl^-	-459.5259970
$\text{Na}^+ \text{---} \text{Cl}^-$	-621.2559633
benzene	-230.7138600
$\text{Na}^+ \text{---} \text{benzene}$	-392.4157508
$\text{benzene} \text{---} \text{Cl}^-$	-690.2357337
$\text{Na}^+ \text{---} \text{benzene} \text{---} \text{Cl}^-$	-852.0163940

$$\Delta E = -5.08 \text{ kcal/mol}$$

Figure 4.22. Energies in Hartrees for the system sodium cation-benzene-chloride anion described in Figure 4.21. The extra-stabilization energy due to the intervening benzene has been calculated by considering the cycle for the formation of the complex (top), where  represents benzene.

Note that the Coulombic interaction in vacuum between sodium and chloride at a distance of 7.55 Å, is worth 44 kcal/mol. This result shows that an intervening benzene ring does enhance the long-range electrostatic interaction by a significant amount. This enhancement has a clear physical basis: it is better to have a polarizable molecule between the two charges, than just vacuum, i.e., the benzene ring behaves as a medium with a dielectric constant >1 . In this explanation the word polarizable is crucial. In fact, different orientations of the benzene ring will give

different results because the polarizability will change with the orientation. Of course, these are gas-phase calculations and their real impact on a system in an aqueous medium is not easy to estimate. It can only be concluded that the aromatic rings of host P can favor the long-range electrostatic interaction between the external carboxylates and the positively charged guests. The amount of this extra stabilization in water, is not known at the present.

A pictorial representation of the this model is presented in Figure 4.23.

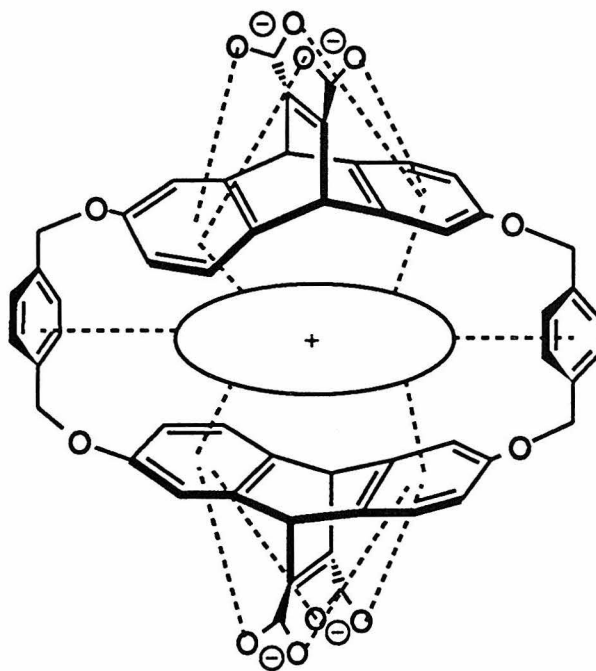


Figure 4.23. Pictorial representation of the hypothesized transmission of electrostatic interactions by the aromatic rings.

The results obtained with this simple model system, prompted us to try to establish if benzene was a special molecule for the transmission of

electrostatic forces. We performed a series of calculations on the systems sodium-benzene-chloride and sodium-cyclohexane-chloride (Figure 4.24).

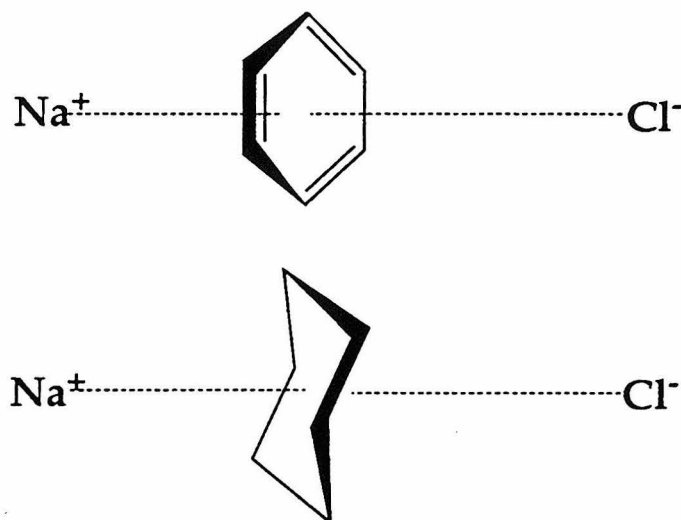
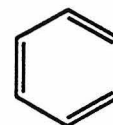


Figure 4.24. Orientation of cyclohexane and benzene in the two model systems studied.

In the two complexes, we optimized the distances between the ions and the molecule by HF/6-31G** calculations. Once we had the optimized distances (see Appendix 1 in this chapter for values), we performed an MP2 single point energy calculation for the extra-stabilization energy due to the intervening molecule in the two complexes. The results, completely reported in Appendix 1, are summarized in Table 4.3.



Distance to Na ⁺ (Å)	3.11	2.45
Distance to Cl ⁻ (Å)	3.51	3.21
Distance Na ⁺ - Cl ⁻ (Å)	6.62	5.66
Extra-Stabilization Energy (kcal/mol)	-10.04	-8.93

Table 4.3. Summary of results for the MP2/6-31G** calculations on the two systems of Figure 4.24.

Table 4.3 shows that cyclohexane outperforms benzene in the transmission of electrostatic forces between the two ions. Cyclohexane has a higher extra-stabilization energy, even if the two ions are at a larger distance than in the benzene system. When the stabilization energy in the benzene complex is estimated choosing the distances for the two ions as the optimized distances in the cyclohexane complex, the result is only -7.31 kcal/mol! These results are not completely surprising. Cyclohexane is known to have a larger polarizability along the z axis, than benzene.⁸ Thus, it should perform better than benzene in the transmission of electrostatic forces by induced dipoles. More importantly, these results tell us that benzene is not a special molecule in this regard and that its many

special properties, such as the cation- π interaction, cannot be the result of induced dipoles.

4.6 Final Remarks

In this chapter we have investigated the properties of a neutral water-soluble cyclophane receptor. We have seen that in the binding of positively charged guests, this host does not perform as well as analogous hosts with remote negative charges. We have analyzed and eliminated possible structural reasons that could account for this behavior. We are left with the conclusion that the four remote negative charges do have an effect on the binding of quaternary ammonium compounds. This conclusion is supported by computational studies.

It is only fair to mention that studies in our group regarding the binding properties of a host bearing five carboxylates (four on the ethenoanthracene bridge as in P and one on the aromatic linker) do not show particular enhancements in binding, despite the fact that the fifth carboxylate is much closer to the binding cavity.⁷ Clearly, a complete rationalization of all the binding data available requires more studies. The synthesis of new hosts bearing a higher number of remote negative charges, and/or negative charges in strategic points of the molecule, seems

the best way to overcome the present impasse. In the next chapter synthetic strategies toward some of these novel structures will be presented. It is hoped that the study of these new receptors will solve once for all the problem of long-range and short-range electrostatic interactions in water.

4.7 Experimental Section

General NMR spectra were recorded on Bruker AMX500, Bruker AM500, or General Electric QE-300 spectrometers. Routine spectra were referenced to the residual proton signals of the solvents and are reported in ppm downfield of 0.0 as δ values. All coupling constants, J , are in Hz. All aqueous host solutions for study were prepared in acetonitrile- d_3 / aqueous deuterated 10mM sodium chloride 1:9 by volume.. Spectra for binding studies in this medium referenced to the residual proton signal of acetonitrile (δ 1.94). All circular dichroism experiments were carried out using a JASCO J-600 spectropolarimeter with either 1.0 or 0.5 cm pathlength cells. Preparative centrifugal chromatography was performed on a Harrison Research Chromatotron model 7924T using silica plates. HPLC was performed on a Waters dual 510 pump liquid chromatograph system equipped with a Waters 996 photodiode array detector and a

Waters 490E wavelength detector. Mass spectral analyses were performed at the University of California, Riverside.

Binding Constants Determination. All host solutions for NMR binding studies were prepared in acetonitrile- d_3 /aqueous deuterated 10mM sodium chloride. The initial concentration of host was approximately 500 μ M. The host solutions were quantified by NMR integrations against a standard solution of dimethylglutaric acid (DMG) in the same mixed solvent. The DMG solution was quantified by a primary standard solution of potassium phthalate. This is necessary because solid DMG is not easy to weigh and because it is not possible to know precisely the amount of water in it (it may range from 1% to 2%). Solid potassium phthalate is dried overnight at 130°C before use. Guest solutions for NMR binding studies were prepared by dissolution of the compounds in the appropriate volumes of the mixed solvent. Guest solution concentrations were determined gravimetrically, by weight of solute, or through NMR integrations against DMG. All binding studies were performed by subsequent addition of aliquots of guest solutions to an NMR tube containing a solution of host. Binding data were fit to an appropriate association constant, using the MULTIFIT or EMUL programs.⁹ Errors bars on the NMR binding constants measurements were calculated through the analysis packages PORTIA and LUCIUS.¹⁰

Solutions for CD binding studies were prepared in aqueous 10mM sodium chloride prepared from water passed through a Milli-Q purification system. Host concentrations varied between 2-5 μ M. Calibration curves for hosts anti-NSP and syn-NSP were built for concentrations varied between 1-10 μ M. $\Delta\epsilon$ values for the hosts were calculated from these calibration curves. CD spectra recorded during the binding titration and the $\Delta\epsilon$ values were fit to an association constant using the CDFIT program.¹¹ Error bars for CD measurements were not determined. N-methylquinolinium iodide was exchanged for chloride using Dowex[®] 1X8-400 ion exchange resin.

Tetrahydrofuran and diethyl ether were distilled from benzophenone diketyl, methylene chloride and acetonitrile were distilled from calcium hydride, anhydrous N,N-dimethylformamide and anhydrous dimethylsulfoxide were purchased from Aldrich and used without further treatment.

All the neutral guests were available from commercial sources. The N-methyl quaternary salts were synthesized by stirring the corresponding neutral compounds with methyl iodide for 3 hours (yield>95%).

Compounds 9, 10, and 35 were prepared according to literature.^{1,10}

Compound 4. Into a 25 ml, three-necked round bottom flask fitted with a stopper, a septum and an argon gas adapter, were placed 100 mg of 11,12-dicarbomethoxyethenoanthracene **3** (0.287 mmol), 261 mg of serinol **2** (2.874 mmol), and a catalytic amount of sodium cyanide. The flask was purged with argon and 10 ml of anhydrous methanol were injected in the solution. The solution was refluxed with stirring for two days. The solvent was then evaporated and the residue was mixed with 3 ml of aqueous saturated sodium chloride and 20 ml of ethyl acetate. The organic layer and another extraction of the aqueous layer were combined, dried with MgSO_4 filtered and concentrated. The residue was then chromatographed over flash grade silica (dichloromethane/methanol 9:1) to yield the purified product **4** (100mg, 0.228 mmol, 80%). $^1\text{H-NMR}$ (methanol- d_4) δ 7.42 (m, 4H), 7.01 (m, 4H), 5.53, (s, 2H), 3.63 (m, 8H). FAB-MS m/e 439 (MH^+).

Compound 8. Into a 25ml round bottom flask were placed 500 mg of ester **3** (1.553 mmol) 1.136 g of Tris (9.311 mmol) and 643 mg of dry potassium carbonate (dried overnight at 350°C). 6 ml of anhydrous DMSO was injected and the slurry was stirred at 50°C for 2 days. The mixture was then cooled and filtered to eliminate most of the potassium carbonate and the undissolved Tris. The solution was frozen and lyophilized. The residue was dissolved in water (5ml), frozen and lyophilized again. This procedure was repeated until a dry white solid was obtained. The residue

was then chromatographed over flash grade silica (chloroform/methanol 8:2) to yield the purified product **8** (582 mg, 1.16 mmol, 75%). $^1\text{H-NMR}$ (D_2O) δ 7.42 (d, $J=3$, 2H), 7.32 (d, $J=3$, 2H), 7.18 (m, 4H), 4.67 (s, 2H), 3.78 (AB pattern, 12H), 3.22 (s, 2H). $^{13}\text{C-NMR}$ (D_2O) δ 175.44, 142.82, 140.53, 127.27, 127.13, 125.52, 124.18, 62.45, 61.30, 48.75. FAB-MS m/e 501 (MH^+).

2,6-dihydroxy-(9R, 10R)-dihydro-(11S, 12S)-dicarbomethoxyethano-anthracene 11 or **2,6-dihydroxy-(9S, 10S)-dihydro-(11S, 12S)-dicarbomethoxyethano-anthracene 12**. Into a 100 ml round-bottomed flask was placed 1.615 g (1.94 mmol) of 2,6-bis-[*tert*-butyldimethylsilyloxy] - 9R, 10R-dihydro - (11S, 12S)- dicarbomethoxyethanoanthracene (**9**) or of 2,6-bis-[*tert*-butyldimethylsilyloxy] - 9S, 10S-dihydro - (11S, 12S)-dicarbomethoxyethanoanthracene (**10**). 30 ml of methanol was added and the resulting suspension was stirred. 2g of methanesulfonic acid was then added. All the solids dissolved. Solution was refluxed for 11 days. 50 ml of ethyl acetate and 20 ml of potassium phosphate buffer were then added. The organic layer and two more extractions of the aqueous layer, were combined and dried over MgSO_4 . Solvent was then removed under reduced pressure and the yellow solid was purified via flash chromatography on silica eluted with petroleum ether/diethyl ether 35:65. 554 mg of a white solid were recovered (1.57 mmol, 81% yield).

Syn isomer (**11**) $^1\text{H-NMR}$ (CDCl_3) δ 7.15 (d, $J=8$, 2H), 6.72 (d, $J=2$, 2H), 6.53 (dd, $J=2,8$, 2H), 4.56 (s, 2H), 3.60 (s, 6H), 1.93 (s, 2H).

Anti isomer (**12**): $^1\text{H-NMR}$ (CDCl_3) δ 7.19 (d, $J=8$, 2H), 6.79 (d, $J=2$, 2H), 6.58 (dd, $J=2,8$, 2H), 4.88 (s, 2H), 3.69 (s, 6H), 1.61 (s, 2H).

Hosts 13, 14. Hosts **13** and **14**, were synthesized according to the same procedure. 277mg of **11** or **12** (0.783 mmol) and 207 mg of α,α -dibromopxylene (0.783 mmol) were placed in a dried 100 ml flask and dissolved in 10 ml of anhydrous DMF. This solution, along with two 5 ml rinsings of the flask were drawn into a 30 ml syringe and this syringe was placed in a syringe pump. Clean DMF (30 ml) and cesium carbonate (1.27 g, 3.89 mmol) were added to the reaction flask and addition was started so that the solution would be added to the reaction at 0.45 ml/h. The reaction was run in the dark and stirred rapidly. Twelve hours after the addition finished, the reaction was filtered and the DMF was evaporated under reduced pressure. The crude products were purified by flash chromatography over silica (dichloromethane/ethyl acetate 97:3) to afford a white solid (68 mg, 19% yield).

Syn isomer (**13**): $^1\text{H-NMR}$ (CDCl_3) δ 7.38 (s, 8H), 7.23 (d, $J=8$, 4H), 6.93 (d, $J=2$, 4H), 6.70 (dd, $J=8,2$, 4H), 5.28 (AB, 8H), 4.69 (s, 4H), 3.82 (s, 12H), 3.55 (s, 4H). $^{13}\text{C-NMR}$ (CDCl_3) δ 173.34, 157.56, 142.61, 137.54, 134.75, 127.14, 124.80, 113.06, 112.17, 70.06, 52.79, 48.46, 46.573. FAB-MS, m/e 913 (MH^+).

Anti isomer (**14**): $^1\text{H-NMR}$ (CDCl_3) 7.21 (s, 8H), 6.95 (d, $J=8$, 4H), 6.82 (d, $J=2$, 4H), 6.49 (dd, $J=8,2$, 4H), 5.11 (AB, 8H), 4.48 (s, 4H), 3.61 (s, 12H), 3.33 (s, 4H). FAB-MS, m/e 913 (MH^+).

Host 15. Into a 5 ml round bottom flask were placed 25 mg of host **14** (0.027 mmol), 68 mg of Tris (0.56 mmol) and 50 mg of potassium carbonate (dried overnight at 350 °C). The flask was fitted with a septum and 0.25 ml of anhydrous DMSO was injected. The slurry was vigorously stirred at the temperature of 60 °C (the reaction vessel was covered with foil to shield the reactants and the products from light). After 60 hours (TLC, CHCl₃/MeOH 7:3) the solution was cooled, 0.5 ml of DMSO was added and the solid (mainly K₂CO₃) was filtered away. The DMSO solution was then frozen and lyophilized. The remaining residue was dissolved in 2 ml of water, frozen and lyophilized again. This procedure was repeated twice in order to eliminate any trace of DMSO. The lyophilization products (white powder) were dissolved in 3ml of MeOH and undissolved solid, mainly Tris, was filtered away. The methanolic solution was concentrated and depleted of the excess of Tris by a fast column chromatography (CHCl₃/MeOH 7:3). Pure host **15** was recovered by a second column chromatography using a solvent gradient (95-75% chloroform in methanol) (21.5 mg 0.017 mmol, 62%). ¹H-NMR (methanol-d₄) δ 7.21 (s, 8H), 7.02 (d, J=8, 4H), 6.88 (d, J=2, 4H), 6.54 (dd, J=2,8, 4H), 5.07 (AB, 8H), 4.33 (s, 4H), 3.65 (AB, 24H), 3.19 (s, 4H). ¹³C-NMR (methanol-d₄) δ 174.30, 156.76, 144.56, 137.06, 132.51, 126.66, 125.06, 111.49, 111.36, 69.12, 62.13, 61.27. FAB-MS *m/e* 1291 (MNa⁺). Host **16** is synthesized in the same way starting from **13**.

Host 30. 30 mg of tetraester **14** were dissolved in 3 ml of DMSO into a 25 ml round-bottomed flask. 0.4 ml of 1.10 M aqueous cesium deuteroxide were added. Solution was sonicated for five minutes. It was then stirred for five hours. Three ml of water were then added and the solution was stirred overnight. Solution was then frozen and lyophilized. Residue was taken with three ml of water and the solution was frozen and lyophilized to eliminate any trace of DMSO. Solid was then dissolved in borate buffer. ^1H NMR (deuterated borate buffer) δ 6.93 (s, 8H), 6.86 (d, $J=8$, 4H), 6.73 (d, $J=2$, 4H), 6.37 (dd, $J=8,2$, 4H), 4.81 (s, 8H), 4.25 (s, 4H), 2.82 (s, 4H).

Compound 36. Into a 25 ml three-necked round-bottomed flask equipped with a stopper, a septum and an argon inlet, was placed 229 mg of diacid **35** (0.71 mmol). 5ml of anhydrous acetonitrile and 218 μl of anhydrous pyridine were injected and the solid was dissolved. 310 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.62 mmol) and 343 mg of aminomalonate hydrochloride (1.62 mmol) were added. Solution was stirred overnight. Solvent was then evaporated under reduced pressure and the residue was partitioned between dichloromethane (50 ml) and 2N hydrochloric acid (15 ml). aqueous layer was extracted with dichloromethane (3X50 ml).The organic layers were then combined and dried over anhydrous magnesium sulfate. Solvent was then evaporated under reduced pressure. A white solid was recovered

(408 mg, 90% yield). No further purification was necessary. ^1H NMR (CDCl_3) δ 8.08 (d, $J=2$, 2H), 6.82 (d, $J=8$, 2H), 6.69 (s, 2H), 6.12 (d, $J=8$, 2H), 5.32 (s, 2H), 5.16 (d, $J=4$, 2H), 4.07 (q, 8H), 1.11 (t, 12H). ^{13}C NMR 166.56, 154.94, 148.08, 146.34, 135.45, 124.79, 112.436, 111.57, 63.43, 57.60, 53.00, 14.44.

Compound 38. Into a 100ml three-necked, round-bottomed flask, 175 mg of sodium (7.6 mmol) was placed. 10 ml of anhydrous ethanol was added. 1.228 g of diethylmalonate (7.58 mmol) were weighted directly in an additional funnel. 15 ml of anhydrous methanol was added into the additional funnel containing the malonate. When the sodium was completely reacted, the malonate solution was added to the alkaline solution. 572 mg of chloroacetonitrile (7.58 mmol) dissolved in 5 ml of anhydrous methanol was added to the alkaline solution of the malonate via a second additional funnel. Solution was then refluxed for thirty minutes and its pH was tested. It was neutral. The solvent was then evaporated under reduced pressure and the remaining residue was taken with 100 ml of diethyl ether and enough water (10 ml) to solubilize all the salts. The two layers were separated and the aqueous layer was extracted with 50 ml of ether. combined ethereal layers were dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (petroleum ether/ether 6:4) to yield a white powder (1.371 g, 90% yield). ^1H NMR (CDCl_3) 4.19 (q,

4H), 3.66 (t, J=8, 1H), 2.84 (d, J=8, 2H), 1.23 (t, 6H). ^{13}C NMR 167.03, 117.42, 63.03, 48.44, 17.39, 14.44.

Compound 39. Into a 100 ml round-bottomed flask was placed 500 mg of nitrile 38. 50 ml of absolute ethanol was added. When the compound dissolved, a catalytic amount of platinum dioxide was added. Flask was evacuated and filled with hydrogen. A balloon full of hydrogen was then attached to the flask via a septum and the solution was stirred for 5 hours. Hydrogen was then evacuated from the flask. Suspension was filtered using size 1 filter paper. solvent was evaporated under reduced pressure. The remaining residue was dissolved in dichloromethane and the minimum amount of methanol. Calcium chloride dried hydrogen chloride was then bubbled into the solution for 20 minutes. Solvent was then evaporated and the residue dried under high vacuum. ^1H NMR (D_2O) δ 4.27 (q, 4H), 3.74 (t, J=6, 1H), 3.10 (t, J=4, 2H), 2.25(q, J=6,4, 2H) 1.29 (t, 6H).

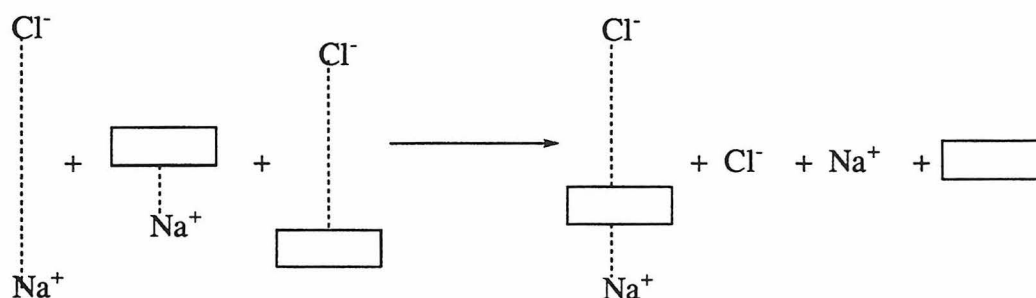
Compound 40. Into a 25 ml three-necked round-bottomed flask equipped with a stopper, a septum and an argon inlet, was placed 100 mg of diacid 35 (0.308 mmol). 5ml of anhydrous acetonitrile and 146 μl of anhydrous pyridine were injected and the solid was dissolved. 136 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.71 mmol) and 343 mg of aminomalonate hydrochloride (1.058 mmol) were added.

Solution was stirred overnight. Solvent was then evaporated under reduced pressure and the residue was partitioned between dichloromethane (50 ml) and 2N hydrochloric acid (15 ml). aqueous layer was extracted with dichloromethane (3X50 ml).The organic layers were then combined and dried over anhydrous magnesium sulfate. Solvent was then evaporated under reduced pressure. A white solid was recovered (193 mg, 90% yield). No further purification was necessary. ^1H NMR (CDCl_3) δ 7.42 (t, $J=4$, 2H, exchangeable), 7.19 (d, $J=8$, 2H), 6.97 (s, 2H, exchangeable), 6.90 (d, $J=2$, 2H), 6.39 (dd, $J=2,8$, 2H), 5.34 (s, 2H), 4.08 (m, 8H), 3.39 (t, $J=6$, 1H), 3.27 (q, $J=4,4$, 2H), 2.01 (q, $J=6,4$, 2H), 1.17 (t, $J=8$, 12H). ^{13}C NMR 169.17, 166.32, 146.84, 135.64, 124.19, 119.25, 111.624, 110.384, 61.346, 52.096, 49.483, 37.226, 28.099, 13.422.

4.8 Appendix

Energies in Hartrees for the Complexes $\text{Na}^+\text{-C}_6\text{H}_6\text{-Cl}^-$ and $\text{Na}^+\text{-C}_6\text{H}_{14}\text{-Cl}^-$ Discussed in Section 4.4

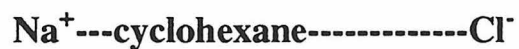
The following cycle has been used to calculate the extra-stabilization energy (ΔE) coming from the molecule (benzene or cyclohexane) interposed between Na^+ and Cl^- .



Here, the symbol $\boxed{}$ identifies either benzene or cyclohexane. At the end of any set of energies, the interaction energy between just the two ions (that is without benzene or cyclohexane) is reported.

Three complexes were studied by MP2/6-31G** calculations:

1)



$$R \text{ Na}^+ \text{---cyclohexane} = 3.11 \text{ \AA} \text{ (opt.)}$$

$$R \text{ cyclohexane} \text{----Cl}^- = 3.51 \text{ \AA} \text{ (opt.)}$$

$$R \text{ Na}^+ \text{-----Cl}^- = 6.62 \text{ \AA} \text{ .}$$

System	Energy (H)
Na ⁺	-161.6607843
Cl ⁻	-459.6618249
Na ⁺ -----Cl ⁻	-621.4050854
cyclohexane	-235.1208854
Na ⁺ ---cyclohexane	-396.7992660
cyclohexane-----Cl ⁻	-694.7961510
Na ⁺ ---cyclohexane-----Cl ⁻	-856.5733086

$$\Delta E = -10.04 \text{ kcal/mol}$$

$$\text{Na}^+ \text{-----Cl}^- - \text{Na}^+ - \text{Cl}^- = -51.75 \text{ kcal/mol}$$

2)



$$R \text{ Na}^+ \cdots \text{benzene} = 2.45 \text{ \AA} \text{ (opt.)}$$

$$R \text{ benzene} \cdots \cdots \text{Cl}^- = 3.21 \text{ \AA} \text{ (opt.)}$$

$$R \text{ Na}^+ \cdots \cdots \cdots \text{Cl}^- = 5.66 \text{ \AA}$$

System	Energy (H)
Na ⁺	-161.6607843
Cl ⁻	-459.6618249
Na ⁺ -----Cl ⁻	-621.4212718
benzene	-231.5352383
Na ⁺ ---benzene	-393.2421431
benzene-----Cl ⁻	-691.1883370
Na ⁺ ---benzene-----Cl ⁻	-853.0081341

$$\Delta E = -8.93 \text{ kcal/mol}$$

$$\text{Na}^+ \cdots \cdots \text{Cl}^- - \text{Na}^+ - \text{Cl}^- = -61.91 \text{ kcal/mol}$$

3)



Same distances of the optimized cyclohexane system
(calculation No.1 in this Appendix)

$$R \text{ Na}^+ \cdots \text{benzene} = 3.11 \text{ \AA}$$

$$R \text{ benzene} \cdots \cdots \text{Cl}^- = 3.51 \text{ \AA}$$

$$R \text{ Na}^+ \cdots \cdots \cdots \text{Cl}^- = 6.62 \text{ \AA}$$

System	Energy (H)
Na^+	-161.6592883
Cl^-	-459.5259970
$\text{Na}^+ \cdots \cdots \cdots \text{Cl}^-$	-621.2662859
benzene	-230.7138600
$\text{Na}^+ \cdots \text{benzene}$	-392.4057014
$\text{benzene} \cdots \cdots \cdots \text{Cl}^-$	-690.2292155
$\text{Na}^+ \cdots \text{benzene} \cdots \cdots \cdots \text{Cl}^-$	-852.0144068

$$\Delta E = -7.75 \text{ kcal/mol}$$

$$\text{Na}^+ \cdots \cdots \cdots \text{Cl}^- - \text{Na}^+ - \text{Cl}^- = -50.83 \text{ kcal/mol}$$

4.9 References

1. (a) Kearney, P. C., Mizoue, L. S., Kumpf, R. A., Forman, J. E., McCurdy, A., Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907. (b) McCurdy, A., Jimenez, L., Stauffer, D. A., Dougherty, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10314. (c) Stauffer, D. A., Barrans, R. E., Jr., Dougherty, D. A. *J. Org. Chem.* **1990**, *55*, 2762. (d) Stauffer, D. A., Dougherty, D. A. *Science* **1990**, *250*, 1558. (e) Petti, M. A., Shepodd, T. J., Barrans, R. E., Jr., Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825. (f) Shepodd, T. J., Petti, M. A., Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1983. (g) Stauffer, D. A., Dougherty, D. A. *Tetrahedron Lett.* **1988**, *29*, 6039. (h) Shepodd, T. J., Petti, M. A., Dougherty, D. A. *J. Am. Chem. Soc.* **1986**, *108*, 6085. (i) Petti, M. A., Shepodd, T. J., Dougherty, D. A. *Tetrahedron Lett.* **1986**, *27*, 807.

2. (a) Tan, R. C., Truong, T. N., McCammon, J. A., Sussman, J. L. *Biochemistry* **1993**, *32*, 401. (b) Ripoll, D. R., Faerman, C. H., Axelsen, P.H., Silman, I., Sussman, J. L. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5128. (c) Harel, M., Schalk, I., Ehret-Sabatier, L., Bouet, F., Goeldner, M., Hirth, C., Axelsen, P. H., Silman, I., Sussman, J. L. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 9031. (d) Sussman, J. L., Harel, M., Frolow, F., Oefner, C., Goldman, A., Toker, L., Silman, I. *Science* **1991**, *253*, 872.

3. (a) Hogberg, T., Ström, P., Ebner, M., Råmsby, S. *J. Org. Chem.* **1987**, 52, 2033. (b) De Fevand, R. J., Strickler, P. D. *J. Org. Chem.* **1963**, 28, 2915.
4. (a) Newkome, G. R., Baker, G. R., Arai, S., Saunders, M. J., Russo, P. S. *J. Am. Chem. Soc.* **1990**, 112, 8458. (b) Newkome, G. R., Hu, Y. F., Saunders, M. J., Fronczek, F. R. *Tetrahedron Lett.* **1991**, 32, 1133.
5. Kato, Y., Conn, M. M., Rebek, J. *Proc. Natl. Acad. Sci. USA* **1995**, 92, 1208.
6. Forman, J. E., Marsh, R. E., Schaefer, W. P., Dougherty, D. A. *Acta Cryst.* **1993**, B49, 892.
7. Kearney, P. C. *Ph. D. Thesis*, California Institute of Technology, 1993.
8. Craven, I. E., Hesling, M. R., Laver, D. R., Lukins, P. B., Ritchie, G. L. D., Urbancich, J. *J. Phys. Chem.* **1989**, 93, 627.
9. Barrans, R. E., Jr., Dougherty, D. A. *Supramolecular Chem.* **1994**, 4, 121.
10. Barrans, R. E., Jr. *Ph. D. Thesis*, California Institute of Technology, 1993.
11. (a) Forman, J. E., Barrans, R. E., Jr., Dougherty, D. A. *J. Am. Chem. Soc.* **1995**, 117, 9213.

Chapter 5

Synthesis of Model Cyclophane Receptors for the Study of Long-Range and Short-Range Electrostatic Interactions in Aqueous Media

5.1 Introduction

In chapter 4, we have explored the unusual binding properties of a neutral water-soluble cyclophane receptor (1). We have learned that the four external carboxylates in host P (2), could have an impact in the binding of positively charged guests. The Interaction of each carboxylate with a cationic guest seems to be worth about 0.3kcal/mol. We have also briefly mentioned at the end of the chapter that binding studies performed in our group¹ on a different host (3) bearing five carboxylates, one of which is in close vicinity to the binding cavity, do not show significant enhancements in the binding of cationic guests. We will now briefly review the results for host 3. We will then describe some experiments that will help solve the problem of long-range and short-range electrostatic interactions in water.

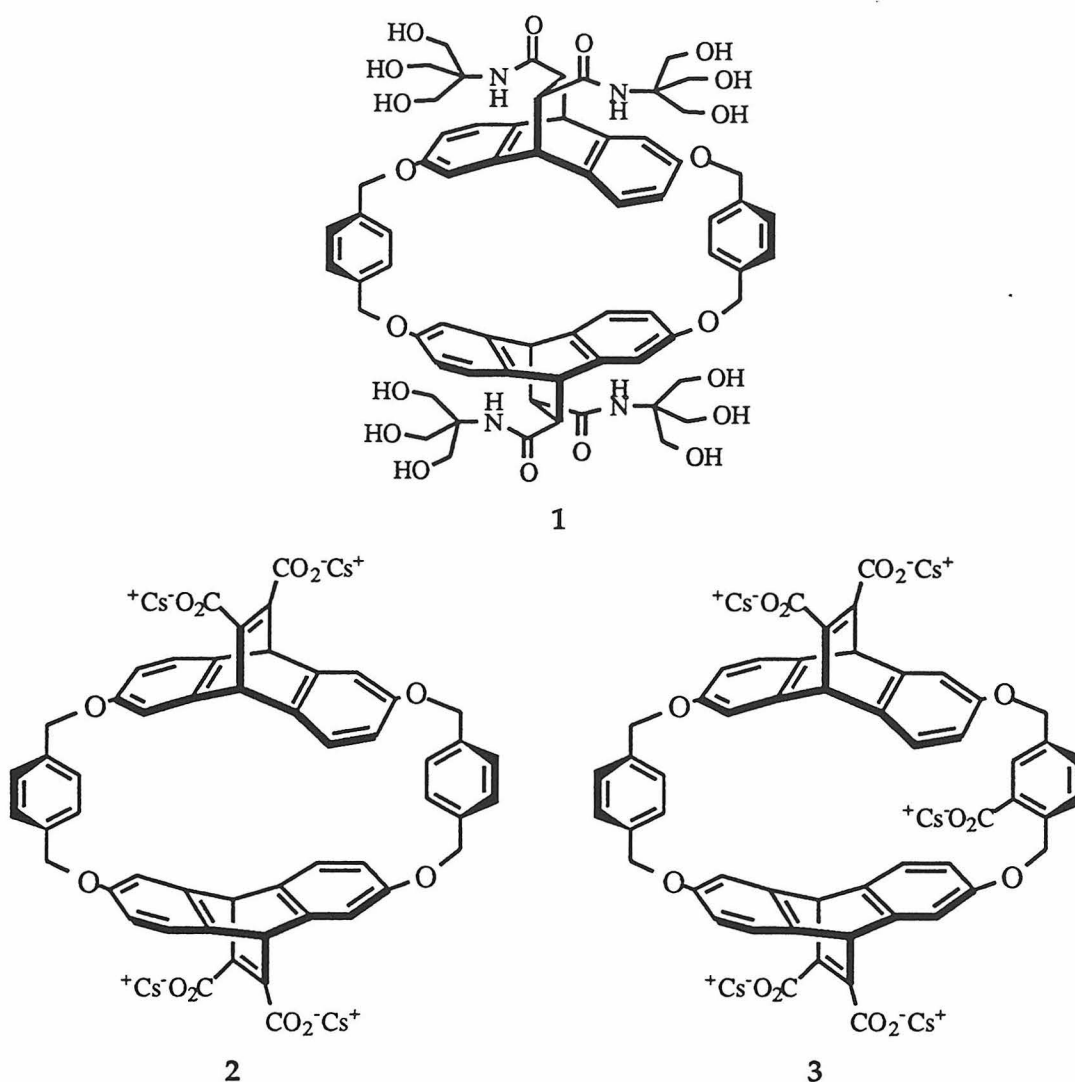


Figure 5.1. Structure of hosts NSP (1), P (2), and CP (3). The name CP comes from Carboxy-P.

5.2 Binding Properties of the PentaCarboxy Host.

The pentacarboxy host **3** (3 has been called CP for Carboxy-P) has been synthesized through minor variations of the synthesis of host P.¹ Here we are interested in the binding properties of this host, in particular

in the binding of positively charged guests. Table 5.1 reports the binding constants of **3** for some selected guests.

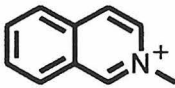
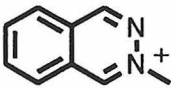
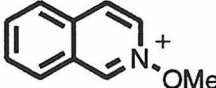
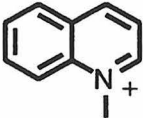
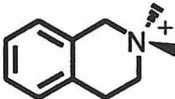
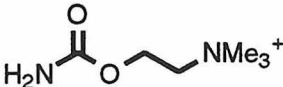
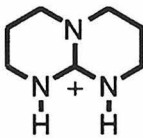
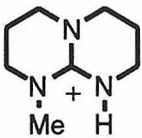
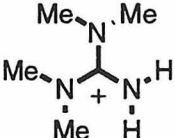
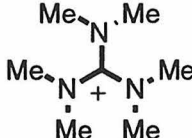
			
7.8/7.2	6.9/6.5	7.3/6.8	8.7/8.4
			
6.6/6.7	4.7/4.8	6.7/6.4	4.6/4.5
			
5.8/5.0	6.7/6.2	5.1/4.7	5.0/4.9

Table 5.1. $-\Delta G^{\circ}_{298}$ (kcal/mol) in borate buffer (pD=9) for binding to hosts CP (**3**) and P (**2**). These data have been taken from reference 1.

It is immediately apparent that the fifth carboxylate does not seem to have a large role in the binding of cationic guests. This is very surprising, especially considering the results for host NSP (**1**). The fifth carboxylate is now closer to the binding cavity than the external four carboxylates, however, it seems to have in some cases a negligible effect. In Table 5.1, one can see that there are some guests for which there is an enhancement. In all of these cases, the increase in binding ranges from 0.3 to 0.8 kcal/mol. These enhancements could be in line with the expectations of

electrostatic interactions between the fifth carboxylate and the guests. However, what is troubling is the fact that other positively charged guests do not show any change at all in the binding constant, compared to host P. The situation becomes even more complex if the D values of the guests are taken into consideration.¹ In fact, the D values of the guests, show that there are no real differences of binding conformations going from host 2 to host 3. The author of the studies on host 3, Pat Kearney, then proposed to look at the electrostatic potential surfaces of the guests. He discovered that the guests that show an enhancement in the binding constant also have a region of positive charge that could, in theory, be accessible to the fifth carboxylate. On the contrary, the guests that do not show an enhancement in binding have a region of positive charge that is buried in their structure, and that therefore, cannot be exposed to the fifth carboxylate. These findings clearly reduce the importance of long-range electrostatic interactions: if what could be an ion pair is worth 0.3-0.5 kcal/mol, the contribution to the binding from the remote carboxylates cannot be of the same order of magnitude. It could also be true that the fifth carboxylate is actually engaged in other kinds of interactions (such as hydrogen bond) with the guests. This possibility would further reduce the importance of the external negative charges. One can also notice that the fifth carboxylate is from an aromatic acid, while the other four are from substituted fumaric acids. This should not be an issue in the medium used for the binding studies (borate buffer, pD=9), but it is always a difference. It is

possible that this specific carboxylate is more solvated than the other four, so that its electrostatic interactions are reduced. Also, a strongly solvated carboxylate would certainly be as far as possible from the hydrophobic binding cavity. In order to do this, the aromatic ring bearing the fifth carboxylate could rotate, with its edge now pointing toward the cavity. This would translate in a decrease of the binding (that aromatic ring could not contribute anymore), that could compensate part of the increase due to classical electrostatic interactions between the guest and the carboxylate. Whatever the reasons for the specific binding behavior of **3**, it should be clear, at this point, that progress in the understanding of long-range and short-range electrostatic interactions in aqueous media can be reached only through new receptors that amplify or combine the properties of the hosts **1** and **3**, so any ambiguities can be explained. In the following sections of this chapter, we will present the design and synthesis of two of such receptors.

5.3 Increasing the Number of Peripheral Negative Charges.

The decrease in binding seen with host NSP (**1**) has been, in the first analysis, attributed to the absence of the four external negative charges. If such an effect is real, increasing the number of remote negatively charged groups should give an increase in binding, compared to host P (**2**). A

external negative charges. One obvious approach would have been to hydrolyze the eight ester groups in compound 4. However, as described in chapter five, the last step to produce this host, the macrocyclization of molecule 5 with α,α -dibromo-*p*-xylene did not work.

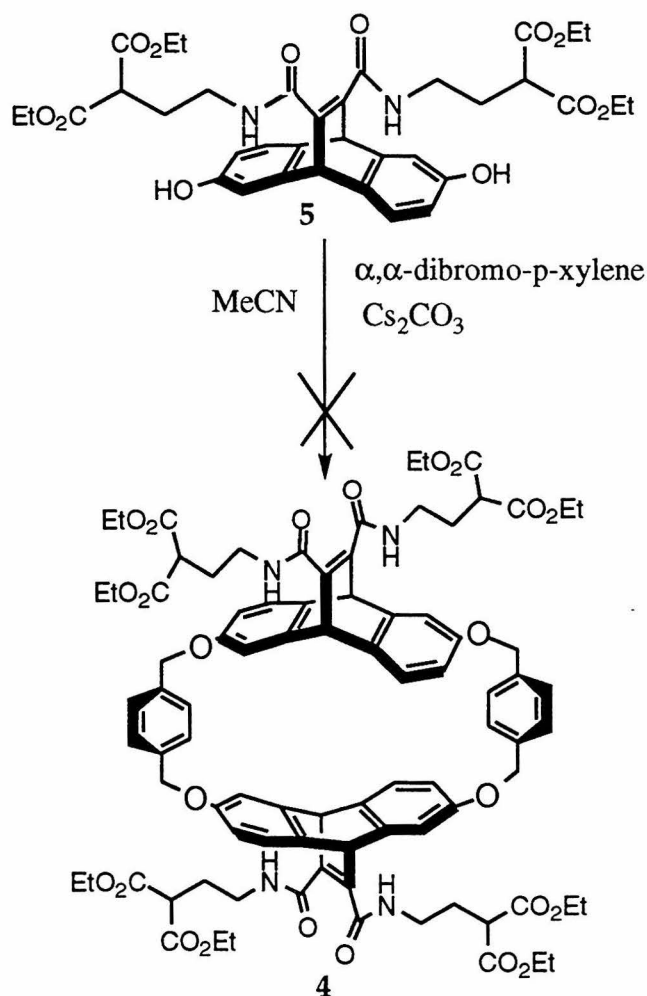


Figure 5.2. The macrocyclization to yield host 4 did not give any good product (see chapter 4 for details).

We then started looking for new groups and functionalities that could dissociate in a moderately basic aqueous solution (pH=9-10 would be appropriate; higher pH's could make difficult the interpretation of the

results). Approximately at that time, a methodology used to introduce phosphate groups in nucleotides and oligonucleotides came to our attention.² In this reaction, an alcohol is reacted with the phosphoramidite **6** in acetonitrile (Figure 5.2) using tetrazole as a catalyst. The resulting coupled product **7** is then oxidized with iodine in a THF/H₂O solution to yield the phosphate **8**. Phosphate **8** is deprotected from the propionitrile groups by treatment with a mild base (NH₄OH in water/dioxane/methanol) in a sealed tube to yield the free phosphate **9**.

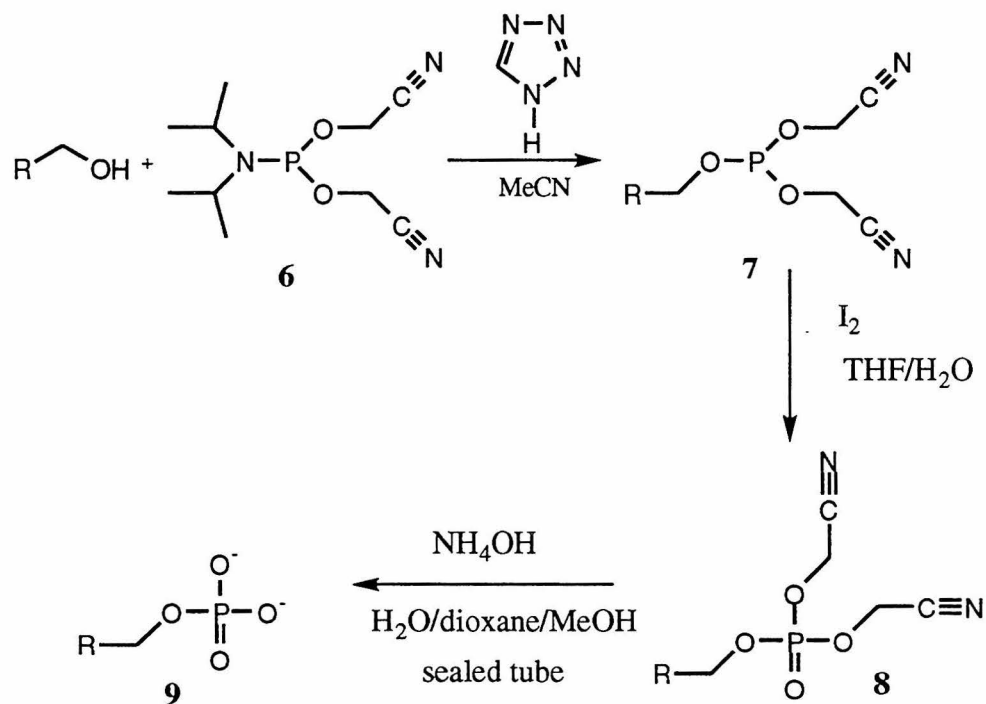


Figure 5.3. Introduction of phosphate groups in a molecule containing a primary alcohol.

6 is made according to the synthetic scheme in Figure 5.4

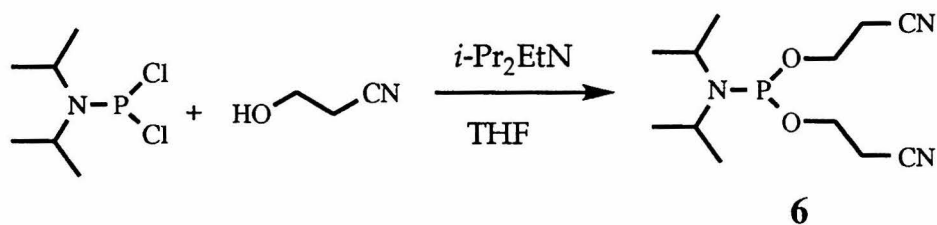


Figure 5.4. Synthesis of phosphoramidite **6**.

Considering that each phosphate group contains two negative charges, when fully dissociated, we thought that this could be a good approach. The synthetic target host **10** was then set (Figure 5.5).

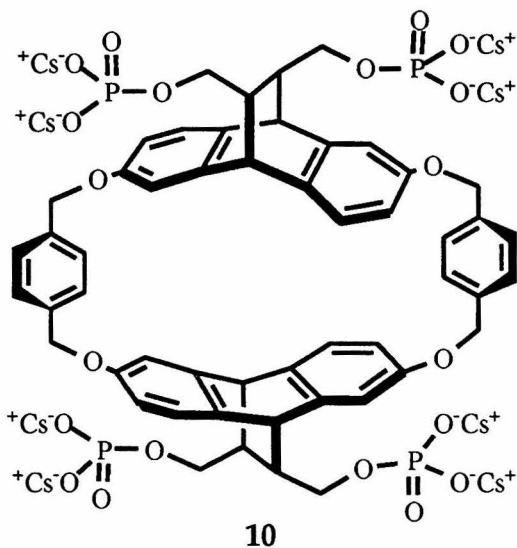


Figure 5.5. A host bearing eight external negative charges can be built using phosphate groups.

Synthetic schemes in Figures 5.6 and 5.8 describe the synthesis of **10**.

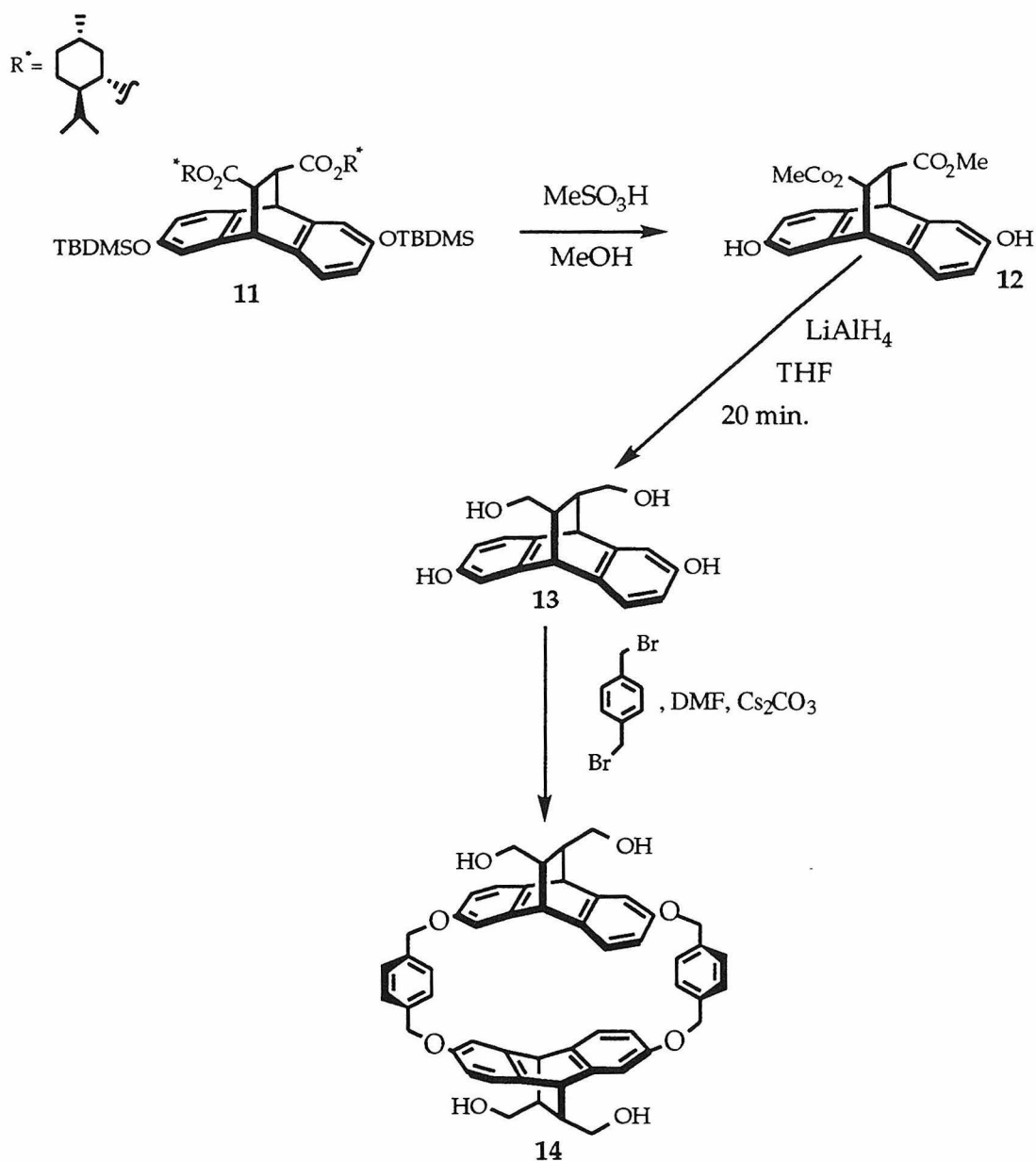


Figure 5.6. Synthetic scheme for the synthesis of host 14.

The half molecule **11** (coming from a diastereoselective Diels-Alder reaction-see chapter 1 for details) is transesterified with methanesulfonic acid in refluxing methanol to yield compound **12**. Reduction of **12** with lithium aluminum hydride gives the compound **13**. The difference in

reactivity of the phenolic and the alcoholic hydroxyls allows the macrocyclization of **13** with α,α -dibromo-*p*-xylene to yield receptor **14**.

The tetraalcohol **14** is then transformed in the tetraphosphate host **10** by the sequence of reactions described in Figure 5.8 and by dissolving the tetraphosphoric acid in borate buffer (pD=9).

All the intermediates of this synthetic sequence, have been characterized. However, the tetraacid **16** is not recovered pure from the reaction with ammonia. During this reaction, the cyanoethyl groups are removed from the phosphate atoms by a simple elimination reaction, during which acrylonitrile is formed (Figure 5.7).

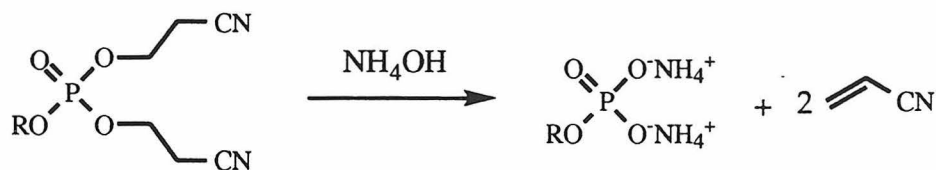


Figure 5.7. Deprotection of the phosphate groups

The boiling point of acrylonitrile is 77°C. This means that this compound should be easy to eliminate during lyophilization. However, the NMR spectrum of recovered compound **16** in pure water shows residual signals in the region corresponding to the proprionitrile groups. These signals can clearly come from some unreacted material or intermediate (only two or three phosphates could, for example, have been introduced in molecule **16**) or they can come from decomposition products of this molecule. In fact,

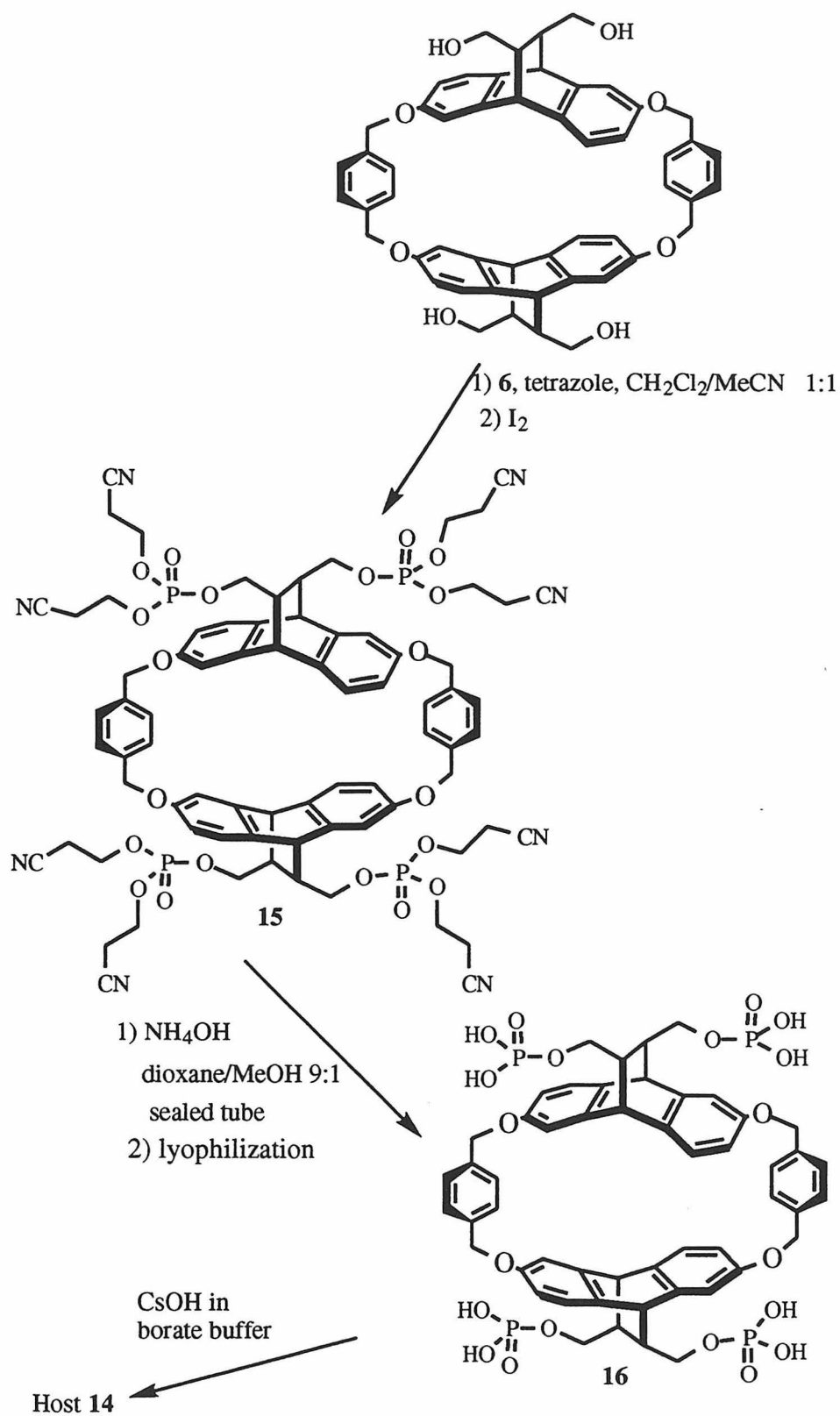


Figure 5.8. Synthetic scheme for the synthesis of host 10.

the conditions of this reaction, concentrated aqueous ammonia in a sealed tube at 65°C for 2 days, could originate some decomposition. However, only part of the material should have been affected judging from the NMR spectrum in borate buffer (Figure 5.8). Therefore, it is the opinion of the author, that this is probably only a purification problem (HPLC - gradient-70% to 30% acetonitrile in 25 mM ammonium acetate should solve the problem). When the tetraacid **16** is dissolved in pure water, at a 5mM concentration (approximately), it shows aggregation. This is not something completely unexpected for this host. In fact, it must be considered that in a water solution of this compound, there are many equilibria involving the dissociation of the phosphate groups (the solution is, of course, strongly acidic, pH=2) and in these conditions aggregation is always a possibility. When the aqueous solution of **16** was lyophilized and the residue dissolved in borate buffer the NMR spectrum changed dramatically. The compound no longer aggregates. The assignment of peaks corresponding to the aromatic region are particularly self-explanatory (Figure 5.9). The purification and characterization of this host have not been performed, due to time limitations on the graduate carrier of the author. Nevertheless, host **10** may be considered practically done. A simple HPLC purification of the mixture coming from the deprotection of **15** should yield the right compound. It is highly hoped that this will be done in the future.

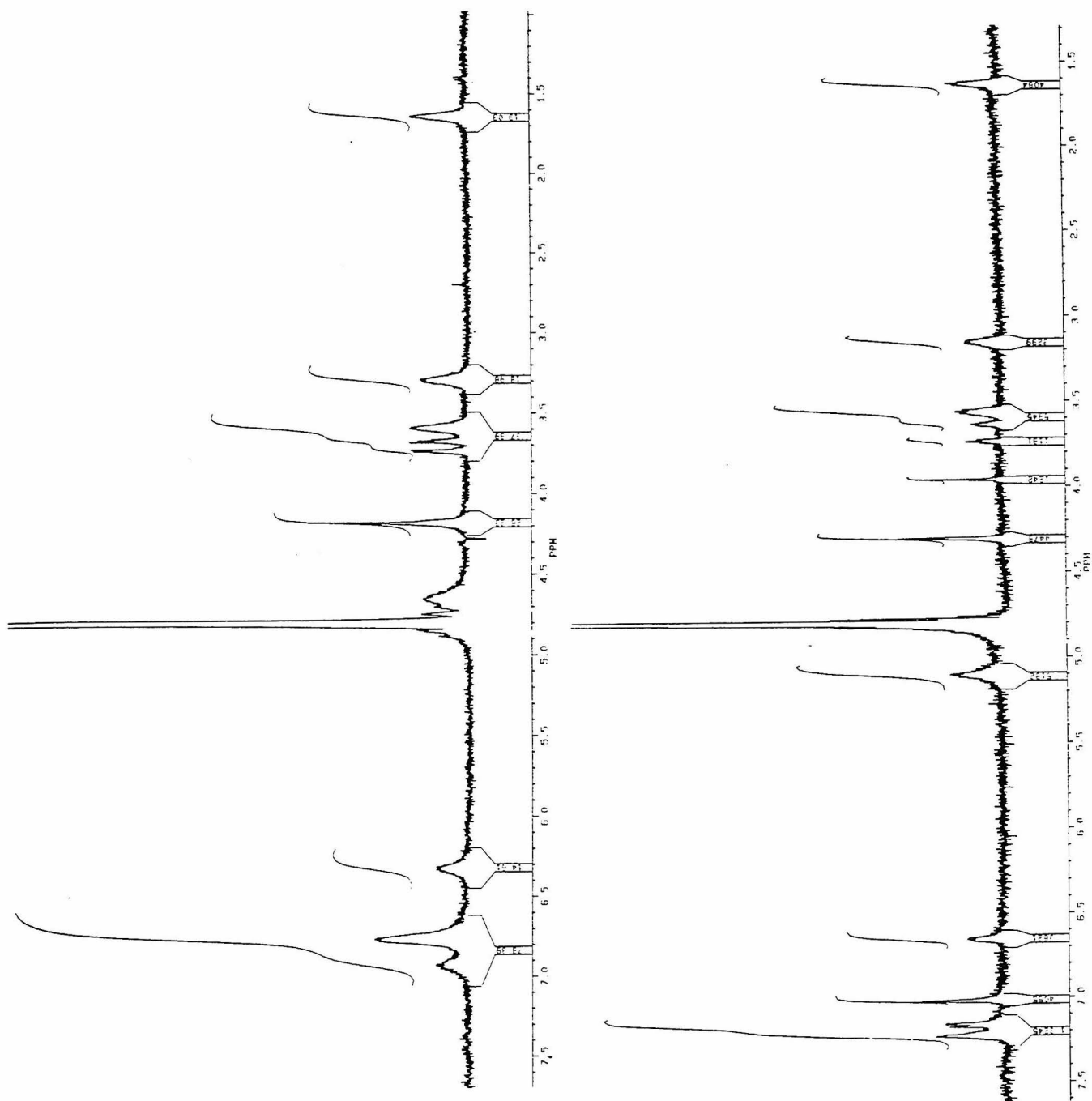
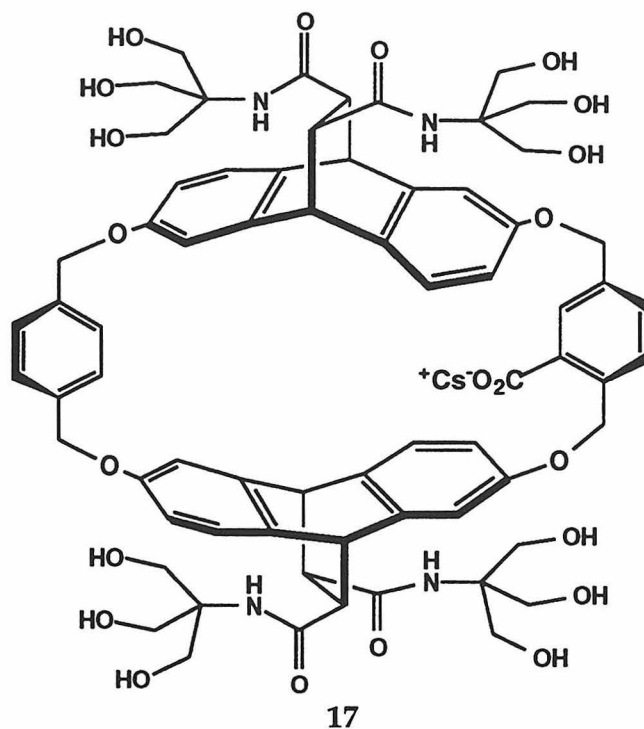


Figure 5.9. Top: ^1H -NMR spectrum of **10** in pure D_2O . Bottom: ^1H -NMR spectrum of **10** in borate buffer.

The study of the binding properties of host **10** is particularly crucial for the interpretation of the data regarding the neutral host. Any enhancement or lack of enhancement of the free energies of binding of this host to positively charged guests, relative to host **P**, will allow to make specific conclusions on the nature of long-range electrostatic forces in water.

5.4 A Cyclophane Receptor for the Study of Short-Range Electrostatic Forces.

The results for host **CP (3)**, described in section 5.2, predict that an ion pair in water should be worth just about 0.5 kcal/mol. They also show that long-range electrostatic interactions from the four remote carboxylates should not be worth much. In order to test these hypotheses, we started designing a receptor that had no remote negative charges and only one charge on the side. The result was host **17**.



Clearly, host **17** is just a combination of the neutral host NSP (**1**) and host CP (**3**). This host should now present only the effect due to the side charge, with no possible interference from the remote carboxylates. If the results reached with host CP (**3**) are true, they should be reproducible with host **17**. If, on the other hand, the remote carboxylates have an effect, it should be seen with host **17**. In fact, one objection that can be made concerning host CP (**3**) is that the negative electrostatic field originating from the remote negatively charged groups, could be as high as to make the effect due to the addition of a fifth carboxylate negligible. If this is the case, then only those guests that can go very close to the side carboxylate can show the effect of the fifth charge. It is clear, then, that different scenarios may be envisioned to explain the results for host CP (**3**) and for host NSP (**1**). Cyclophane receptor **17** will help in selecting the correct answer.

The synthesis of host **17** is different from the synthesis of any other host described so far. This is due to the “fifth” carboxylate, the carboxylate on the side, that introduces an element of discontinuity in the symmetry of the molecule. This means that a macrocyclization reaction between an ethenoanthracene moiety and a difunctional linker, is not possible anymore: the molecule must be built piece by piece.

The synthesis starts with the condensation of an excess of the diphenol **18** with α,α -dibromo-*p*-xylene to give molecule **19** (Figure 5.10).

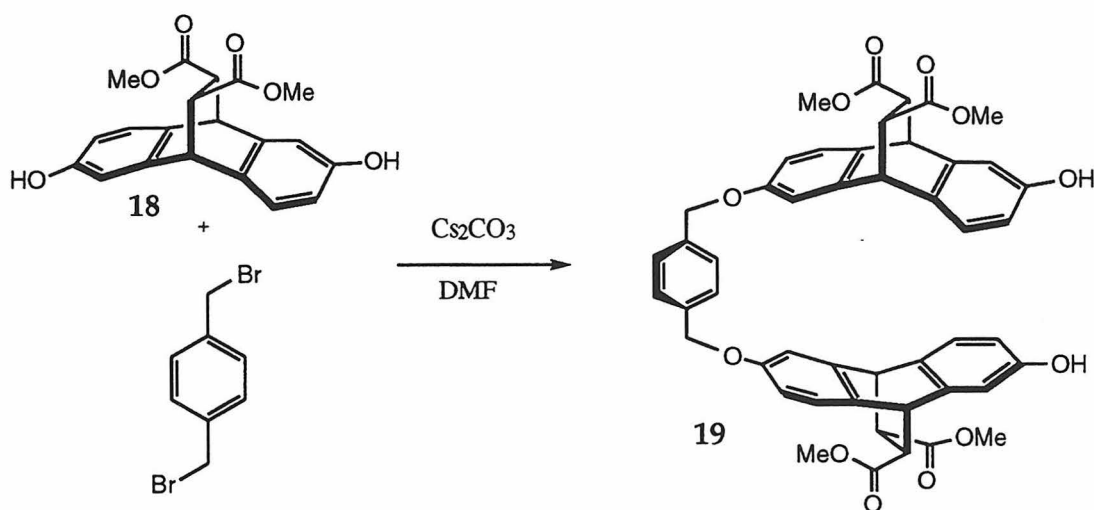


Figure 5.10. Synthesis of the 3/4 molecule **19**.

A carboxybutyl substituted α,α -dibromo-*p*-xylene **23** is then prepared through the sequence of reactions described in Figure 5.11.

2,5-dimethylbenzoic acid **20** is transformed to the acyl chloride by reaction with thionyl chloride. The chloride **21** is refluxed in *t*-butyl alcohol to yield

the *t*-butyl ester **22**. Reaction of **22** with N-bromosuccinimide gives the dibromide **23**.

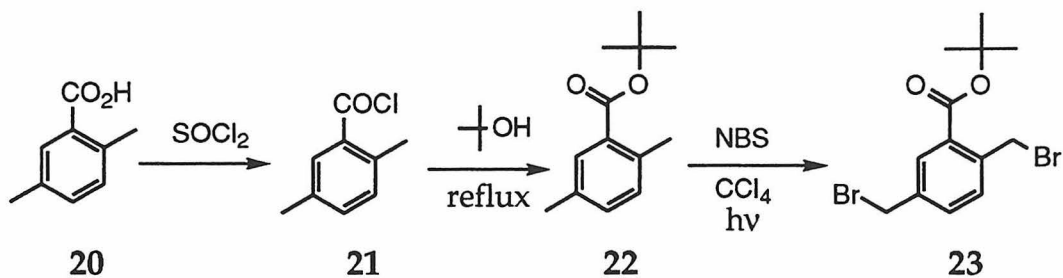


Figure 5.11. Synthesis of linker **23**.

3/4 molecule **19** and dibromide **23** were then condensed to yield macrocycle **24**. The *t*-butyl ester is then hydrolyzed with trifluoromethanesulfonic acid to give the monoacid **24**. **24** was purified by preparative HPLC and then reacted with Tris under the conditions developed for the preparation of the neutral host NSP (Figure 5.12).

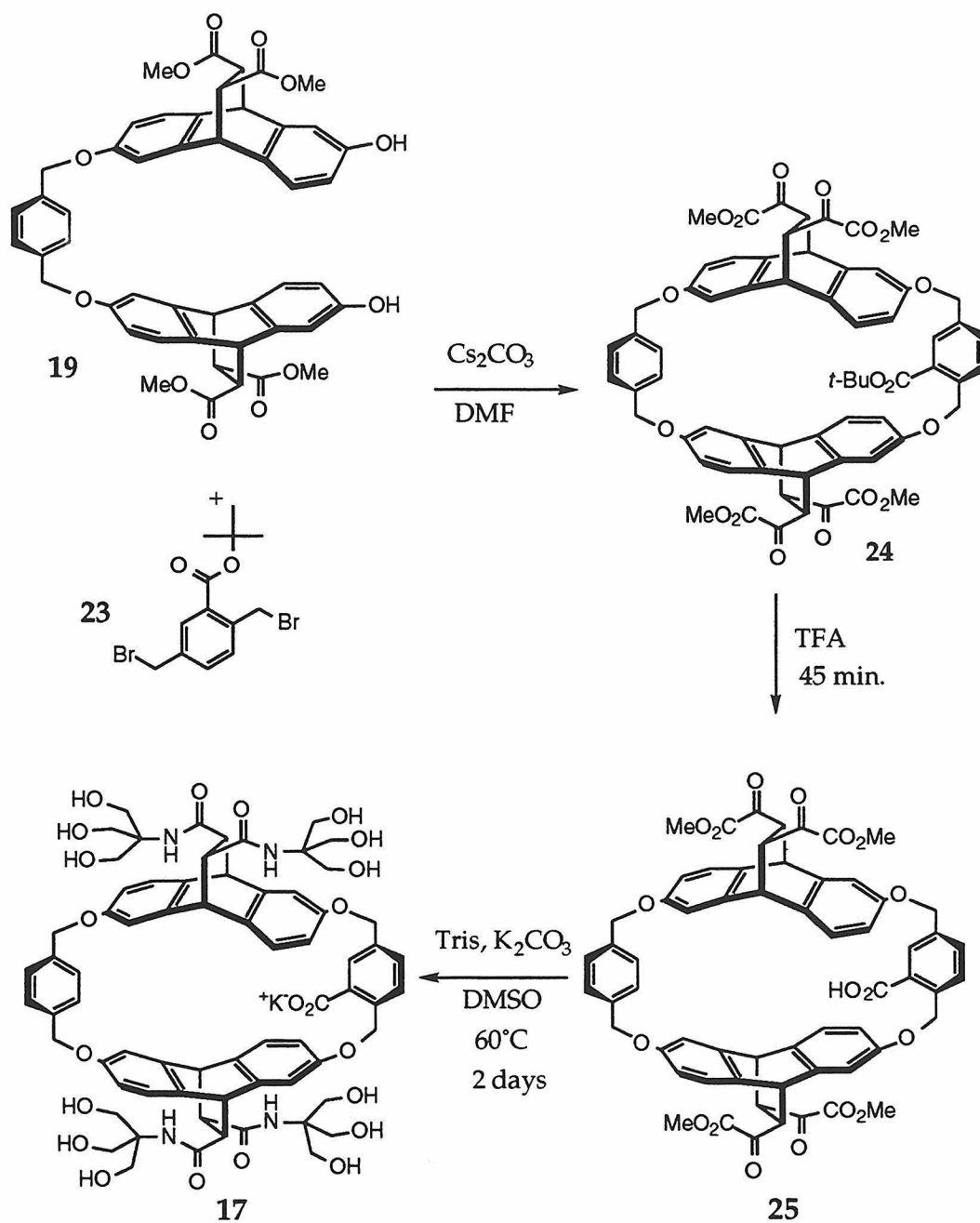


Figure 5.12. Final steps in the synthesis of host 17.

All the reactions in the synthesis scheme until compound 25 worked cleanly and with high yields. 17 has not been isolated in a pure form. Although the final reaction from 25 to 17 should not give any problem

from the point of view of reactivity³, the final mixture is especially difficult to purify. This is due to the fact that Tris and the host seem to have a similar polarity so that actually even repeated HPLC runs were not sufficient to have a pure compound.⁴ An ion exchange column on a strongly acidic resin did not help. The solution to this problem should come from the careful choice of HPLC conditions. It is anticipated that the similarity in polarity between Tris (present in a 20-fold excess) and **17** cannot be the same when the carboxylate in **17** is dissociated and when it is not dissociated. Therefore, the purification procedure will be based on the use of a basic or an acidic buffer and on the use of an appropriate gradient of HPLC solvents (acetonitrile/buffer or methanol/buffer). It is the opinion of the author that, although difficult, this separation is possible and actually very close to being reached. One encouraging aspect in the synthesis of **17**, is that the mixture coming from the final reaction is completely water-soluble. A clear solution is immediately obtained upon addition of water to the solids recovered from the aminolysis of **25**. It is highly hoped that in the near future host **17** will be purified and appropriately characterized. It is anticipated that the results reached in studying the binding properties of cyclophane **17** will be invaluable to assess the validity and to quantify correctly the model of short-range electrostatic forces associated with host CP (**3**).

5.5 Final Remarks

In section 5.2, the synthesis of an octanegatively charged host (**10**) has been discussed. In the last section, the synthesis of a water-soluble cyclophane (**17**) with a carboxylate very close to the binding cavity has been described. Both the hosts are indispensable for the construction of a general theory of long-range and short-range electrostatic forces in an aqueous medium. The results reached in the study of the neutral host NSP (**1**) and the monocarboxy host CP (**3**) are somewhat in disagreement. They should be clarified and actually complemented by the evaluation of the binding properties of **10** and **17**. Conclusions reached considering only the properties of host NSP or only those of host CP, do not allow formulating a general, consistent and experimentally safe theory of electrostatic forces in water. It is only through a systematic analysis of the effect of each charged group, that a unifying theory can be developed. Hosts **10** and **17** follow this direction and the evaluation of their properties will certainly be of great benefit to the comprehension of ion-pairs and long-range electrostatic interactions in water.

Finally, it is necessary to specify that the negative charges associated with the carboxylates (or phosphates) in hosts **2**, **3**, **10**, and **17**, are not point charges. We should always remember that these hosts are dissolved in a 10 mM buffer solution. This concentration is at least ten times higher than

the concentration of the host in the solutions used for binding studies. This means that the carboxylates cannot be considered “naked” but they are associated with a certain number of counterions. For the sake of simplicity, we can imagine that just one counterion, for example a cesium ion, is associated with one carboxylate. This association must not be considered as an ion-pair, but rather as the average neutralization of a charge from the surrounding medium. If we consider such a system, we can say that the interaction between the remote carboxylates (or the side carboxylate in 3 and 17) and the guest bound in the cavity of the host, is better described by the interaction between a point charge and a dipole moment⁵, the dipole moment being generated by the pair carboxylate-counterion.

We can then use eq. 2.19 in appendix A of chapter 2 to calculate the interaction between a point charge and a dipole. It is easily seen that this interaction is described by eq. 5.1.

$$E_{A,\mu} = -\frac{q\mu}{4\pi\epsilon_0 r^2}(\cos\alpha)N \quad (5.1)$$

Here, q is the charge, μ is the dipole moment of the pair carboxylate-counterion, r is the distance between the center of the dipole moment and the charge, and α is the angle defined in Figure 5.13.

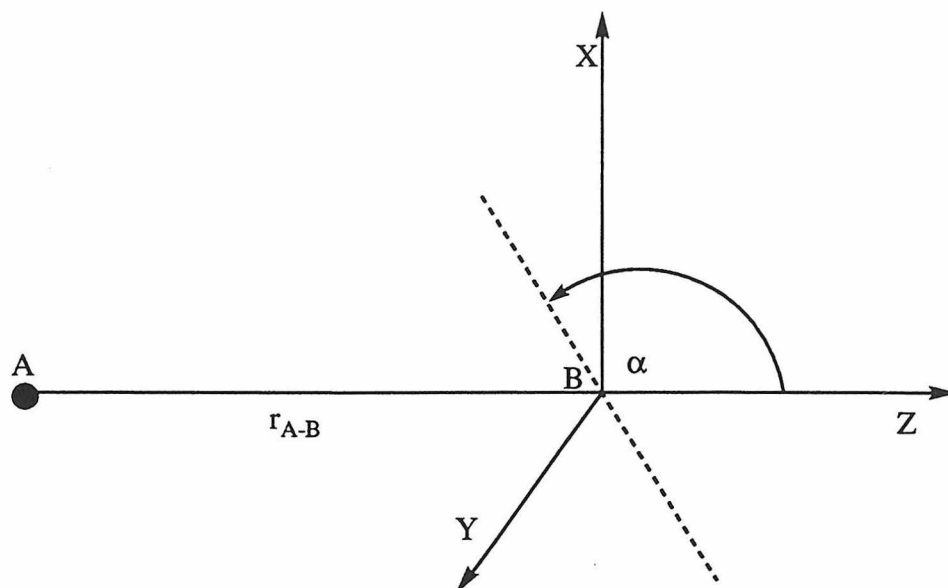


Figure 5.13. Schematic representation of the interaction between a point charge A and a dipole moment. The dotted line through B represents the axis of the molecule(in this case the system carboxylate-counterion).

A dipole is defined as two equal and opposite charges $+q$ and $-q$ separated by a distance l . The dipole moment μ of this system is given by :

$$\mu = ql \quad (5.2)$$

In our case we can substitute:

$$l = 2 \times 10^{-10} \text{ m}$$

$$q = 1.602177 \times 10^{-19} \text{ C}$$

$$4\pi\epsilon_0 = 1.11265 \times 10^{-10} \text{ J}^{-1} \text{ C}^2 \text{ m}^{-1} \quad (\text{in the vacuum})$$

$$\alpha = 0^\circ \text{ or } 180^\circ \text{ (to maximize the interaction)}$$

$$r = 8 \times 10^{-10} \text{ m}$$

$$N = 6.02214 \times 10^{23} \text{ mol}^{-1}$$

and we obtain:

$$E_{A,\mu}=10.37 \text{ kcal/mol}$$

This value is approximately four times lower than the interaction we can calculate for two point charges at the same distance (chapter 4, section 4.1). Is the dipole-charge a realistic situation? First of all, an ideal dipole is defined as one in which l approaches zero as q approaches infinity, so that their product remains constant. This is hardly the situation represented here. Also, eq. 5.1 is valid only when the size of the dipole, defined by l , is negligible relative to distance between the charge and the center of the dipole. This condition is clearly not satisfied here ($r/l=4$). Finally, the distance l , defining the dipole, has been arbitrarily set to $2\text{\AA}$. A proper distance is not easy to estimate. However, the important point is that if carboxylate-counterion associations are real, the electrostatic interaction of the remote carboxylates with the cationic guest will be definitely reduced. A similar situation is also true for the side-carboxylate, the fifth carboxylate in host 3. However, the situation in this case is slightly different. Due to the vicinity of this carboxylate to the binding cavity, the formation of an association with a counterion could completely neutralize the interaction with a cation trapped in the cavity. In fact, this is what happens when the ratio r/l is too low. Figure 5.14 illustrates this concept.

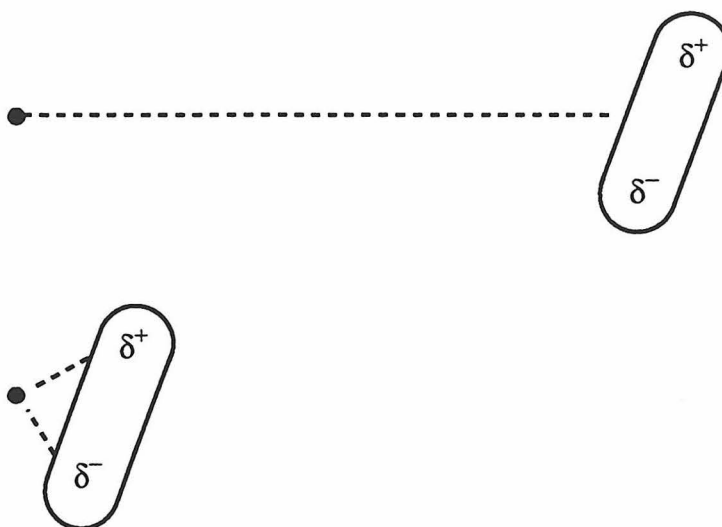


Figure 5.14. Top: when the dipole moment and the point charge are far from each other ($r/l \gg 1$) an interaction dipole-charge can be described by classical electrostatic laws.

Bottom: when the dipole and the charge are very close to each other, the total interaction is the sum of the interactions of all the separated charges in the dipole with the point charge. This sum can very well be close to zero.

If this situation is real, it could well explain the binding behavior of the CP host: only those guests that can get close enough to the fifth carboxylate, and in so doing reduce its association with counterions, can show an increase (modest) in binding energies. Once again, the experimental results that the hosts **10** and **17** will provide, will be determining in proving this fascinating hypothesis.

As the very last sentence of this chapter, the author wants to express his wonder for what a simple model system can teach us. Host P is an extremely carefully designed model receptor. It is the perfect receptor for organic cations. It is also a simple compound, compared to biological

molecules. Yet, the study of the properties of this host and of its analogs still presents "dark zones", where our theories and hypotheses are put to a test. Those are the moments when human mind faces the unknown, the undefined, the never-seen-before. A scientist lives for those moments, because it is in these challenges that he finds a chance to build up new knowledge and to build the science of tomorrow.

5.6. Experimental Section

General NMR spectra were recorded on Bruker AMX500, Bruker AM500, or General Electric QE-300 spectrometers. Routine spectra were referenced to the residual proton signals of the solvents and are reported in ppm downfield of 0.0 as δ values. All coupling constants, J , are in Hz. Preparative centrifugal chromatography was performed on a Harrison Research Chromatotron model 7924T using silica plates. HPLC was performed on a Waters dual 510 pump liquid chromatograph system equipped with a Waters 996 photodiode array detector and a Waters 490E wavelength detector. Mass spectral analyses were performed at the University of California, Riverside.

Tetrahydrofuran and diethyl ether were distilled from benzophenone diketyl, methylene chloride and acetonitrile were distilled from calcium hydride, anhydrous *N,N*-dimethylformamide and anhydrous

dimethylsulfoxide were purchased from Aldrich and used without further treatment.

Phosphoramidite **6** was prepared as described in the literature.² 2,6-bis-[*tert*-butyldimethylsilyloxy] - 9R, 10R-dihydro - (11S, 12S)- dicarbomethoxy ethanoanthracene **11** was also prepared according to the literature.⁶

2,6-dihydroxy-(9R, 10R)-dihydro-(11S, 12S)-dicarbomethoxyethanoanthracene 12. Into a 100 ml round-bottomed flask were placed 1.615 g (1.94 mmol) of 2,6-bis-[*tert*-butyldimethylsilyloxy] - 9R, 10R-dihydro - (11S, 12S)-dicarbomethoxyethanoanthracene. 30 ml of methanol was added and the resulting suspension was stirred. 2g of methanesulfonic acid was then added. All the solids dissolved. Solution was refluxed for 11 days. 50 ml of ethyl acetate and 20 ml of potassium phosphate buffer was then added. The organic layer and two more extractions of the aqueous layer, were combined and dried over MgSO₄. Solvent was then removed under reduced pressure and the yellow solid was purified via flash chromatography on silica eluted with petroleum ether/diethyl ether 35:65. 554 mg of a white solid were recovered (1.57 mmol, 81% yield). ¹H-NMR (CDCl₃) δ 7.19 (d, J=8, 2H), 6.79 (d, J=2, 2H), 6.58 (dd, J=2,8, 2H), 4.88 (s, 2H), 3.69 (s, 6H), 1.66 (s, 2H).

2,6-dihydroxy-(9R, 10R)-dihydro-(11S, 12S)-dihydroxymethyl ethano-anthracene 13. Into a 250 ml three-necked round-bottomed flask equipped with a additional funnel, a septum, and an argon gas adapter, was placed 454 mg of lithium aluminum hydride (12 mmol). 70 ml of anhydrous THF was injected into the flask. A solution of 700 mg of **12** (1.99 mmol) in 10 ml of anhydrous THF was then added dropwise (*caution: gas evolution*) via the additional funnel over a period of 5 minutes. Solution was stirred for thirty minutes at room temperature. 3ml of methanol was then added to destroy the excess of lithium aluminum hydride. The mixture was then treated with 2N sulfuric acid until two clear layers formed (about 50 ml). The two layers were separated and the aqueous layer was extracted twice (100 ml) with diethyl ether. The organic layers were combined and washed with 5% aqueous sodium bicarbonate. Solvent was then evaporated under reduced pressure. The residue was purified via flash chromatography on silica eluted with a gradient of 9:1 to 8:2 (v/v) chloroform/methanol affording a white solid. ^1H NMR (methanol- d_4) δ 7.04 (d, $J=8$, 2H), 6.78 (d, $J=2$, 2H), 6.52 (dd, $J=2,8$, 2H), 4.14 (s, 2H), 3.25-2.99 (AB, 4H), 1.38 (s, 2H). ^{13}C NMR 155.32, 143.70, 135.78, 123.84, 113.20, 112.22, 65.86, 47.09, 45.83. FAB-MS m/e 297 (MH^+).

Compound 14. 442mg of **13** (1.48 mmol) and 391 mg of α,α -dibromopxylene (1.48 mmol) was placed in a dried 100 ml flask and dissolved in 10

flask were drawn into a 30 ml syringe and this syringe was placed in a syringe pump. Clean DMF (30 ml) and cesium carbonate (2.4 g, 7.4 mmol) were added to the reaction flask and addition was started so that the solution would be added to the reaction at 0.45 ml/h. The reaction was run in the dark and stirred rapidly. Twelve hours after the addition finished, the reaction was filtered and the DMF was evaporated under reduced pressure. The crude products were purified by HPLC using a Whatman Magnum 9 column (50 cm, Partisil 10, ODS-3). A gradient 70:30 to 0:100 acetonitrile/water over 60 minutes was used. The desired product eluted after about 16 minutes (note: the main product of this macrocyclization is the trimer host. It is eluted in the conditions reported above, after about 27 minutes). Solution containing the product was frozen and lyophilized to afford a white solid. ^1H NMR (methanol- d_4) δ 7.26 (s, 8H), 7.02 (d, $J=8$, 4H), 6.86 (d, $J=2$, 4H), 6.57 (dd, $J=8,2$, 4H), 4.99 (s, 8H), 4.13 (s, 4H), 3.20-2.91 (AB, 8H), 1.33 (s, 4H). ^{13}C NMR 156.31, 142.57, 136.75, 135.92, 126.75, 123.06, 112.56, 123.06, 112.65, 111.18, 69.05, 64.28, 45.77, 44.60. FAB-MS m/e 801 (MH^+).

Host 15. 20.22 mg of host 14 (25.27 μmol) and 15 mg of tetrazole (0.21 mmol) was placed in a 50 ml 3-necked, round-bottomed flask. 2 ml of anhydrous methylene chloride was added. A solution of 56 mg of di-2-(cyanoethyl)- N,N -diisopropylaminophosphoramidite 6 (0.13 mmol) in 2 ml of dry dichloromethane was then injected into the reaction flask. After

ml of dry dichloromethane was then injected into the reaction flask. After an hour the reaction is complete (TLC, chloroform/methanol 8:2). A solution of iodine (prepared dissolving 752 mg of iodine in 5 ml of 2:1:0.08 v/v/v of THF/H₂O/pyridine) is then added dropwise to the solution until the brown color of iodine persists (it is necessary to add an excess of iodine compared to the starting host 14, because iodine also reacts with 6). Therefore, the volume of iodine solution added, will vary depending on the amounts of 14 and 6). Solution was stirred for ten minutes and then the solvent was removed under reduced pressure. The dark residue was redissolved in 20 ml of chloroform. This solution was extracted with a 0.05% aqueous sodium bisulfite (20 ml). Organic layer was then washed once with water (10 ml) and once with brine (10 ml). It was then dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure. Residue was purified with flash chromatography on silica eluted with a gradient 95:5 to 7:3 chloroform/methanol. ¹H-NMR (CDCl₃) δ 7.22 (s, 8H), 7.05 (d, J=8, 4H), 6.81 (d, J=2, 4H), 6.56 (dd, J=8,2, 4H), 5.148 (AB, 8H), 4.28 (q, 16H), 4.12 (s, 4H), 3.82 (m, 4H), 3.65 (m, 4H), 2.79 (q, 16H), 1.77 (s, 4H). ¹³C NMR 156.97, 141.55, 136.95, 134.46, 126.55, 116.68, 108.96, 101.02, 62.48, 44.11, 19.85, 19.75.

Host 16. 23 mg of host 15 (15.4 μmol), 10 ml of aqueous concentrated ammonium hydroxide and 3 ml of dioxane/methanol 1:9 were placed into a Kontes flask equipped with a stir bar. The flask was sealed and

heated to 60°C for 48 hours. The flask was then cooled to room temperature, and a flow of argon was passed through the solution to remove most of the ammonia. The solution was then frozen and lyophilized. A light-brown solid was recovered. This solid was dissolved in water and its purification was attempted by HPLC. Products coming from a first purification were analyzed by FAB mass spectrometry. A weak MH^+ peak for host 16 was found. However, as discussed in the main sections, product still needs a better purification.

Host 17. Into a 5 ml round bottom flask were placed 8.2 mg of host 25 (8.4 μ mol), 21 mg of Tris (0.17 mmol) and 24 mg of potassium carbonate (dried overnight at 350°C). The flask was fitted with a septum and 0.5 ml of anhydrous DMSO was injected. The slurry was energetically stirred at the temperature of 60°C (the reaction vessel was covered with foil to shield the reactants and the products from light). After 60 hours (TLC, $CHCl_3/MeOH$ 7:3) the solution was cooled, 0.5 ml of DMSO was added and the solid (mainly K_2CO_3) was filtered away. The DMSO solution was then frozen and lyophilized. Residue was dissolved in 2 ml of water, frozen and lyophilized again. This procedure was repeated twice in order to eliminate any trace of DMSO. The products coming from the lyophilization (white powder) were dissolved in 3ml of MeOH. Undissolved solid, mainly Tris, was filtered away. The methanolic solution was concentrated and analyzed via HPLC. Semipreparative purification was attempted, but it was not

not seem to contain methyl esters anymore. It was not possible to assess if the fifth carboxylate, on the side of the molecule, reacted or not. In fact, the NMR signal corresponding to the tris groups in the molecule is covered from an enormous peak coming from the excess of Tris used in the reaction.

Compound 19. Into a 100 ml three-necked round-bottomed flask fitted with a stopper, a septum, and an argon gas adapter, were placed 2.3 g of cesium carbonate (7.0 mmol) and 500 mg of (9S, 10S)-2,6-dihydroxy-(11S, 12S)-dicarbomethoxyethanoanthracene **18** (1.4 mmol). The flask was then purged with argon and 40 ml of anhydrous N, N-dimethylformamide was injected into the vessel. A solution of α,α -dibromo-*p*-xylene (75 mg, 0.29 mmol) in 10 ml of anhydrous DMF was then delivered via syringe pump into the ethanoanthracene solution over 10 hours. The reaction mixture was then allowed to stir at room temperature for one day. Both the reaction vessel and the gas-tight syringe used in the reaction were covered with foil to shield the reactants and products from light. The solvent was then stripped off in vacuo. The residue was dissolved in 10 ml of water and 70 ml of chloroform. pH of the aqueous layer was adjusted to pH=7 with HCl 2N and pH=7 phosphate buffer. Organic layer and other two extractions of the aqueous layer were combined and dried over MgSO_4 . Solvent was then stripped off in vacuo. Residue was dissolved in the minimum amount of chloroform and silica gel was added until the

minimum amount of chloroform and silica gel was added until the solution became a slurry mixture. Solvent was then evaporated and the solid was chromatographed over flash grade silica (80-0% petroleum ether in ether) to yield the desired product **19** (135 mg, 0.17 mmol, 57% yield).

$^1\text{H-NMR}$ (CDCl_3) δ 7.42 (s, 4H), 7.24 (d, $J=6$, 2H), 7.18 (d, $J=6$, 2H), 6.91 (d, $J=1$, 2H), 6.78 (d, $J=1$, 2H), 6.72 (dd, $J=6,1$ 2H), 6.54 (dd, $J=6,1$, 2H), 5.51 (s, 2H, exchangeable protons), 5.02 (AB, 4H), 4.65 (s, 4H), 3.69 (s, 6H), 3.61 (s, 6H), 3.45 (s, 4H). $^{13}\text{C NMR}$ 173.59, 163.55, 157, 83, 155.47, 142.88, 142.70, 137.34, 134.99, 133.88, 128.21, 125.08, 125.10, 113.21, 112.87, 112.44, 112.29, 70.34, 52.92, 48.64, 48.60, 46.74, 46.59, 37.30, 32.25.

2,5-dimethyl-benzoyl chloride 21. 10g. of 2,4-dimethylbenzoic acid was placed in a 100 ml round-bottomed flask and 20 ml of thionyl chloride was added. Flask was fitted with a reflux condenser and a calcium chloride drying tube was attached to the condenser. Solution was stirred and refluxed overnight. Thionyl chloride was then removed under reduced pressure and the residual compound was immediately used for the subsequent reaction.

***t*-butyl 2,5-dimethylbenzoate 22.** 5 g of 2,4-dimethylbenzoyl chloride **21** was placed in a 100 ml round-bottomed flask and 60 ml of *t*-butyl alcohol were added. The solution was stirred and refluxed for two days, Solvent was then stripped off in vacuo and the colorless liquid was dried under high

vacuum. 5.6 g of **22** were recovered (99% yield). ^1H NMR (CDCl_3) δ 7.57 (s, 1H), 7.06 (d, $J=4$, 1H), 7.01 (d, $J=4$, 1H), 2.46 (s, 3H), 2.26 (s, 3H), 1.53 (s, 9H).

23. *t*-butyl 2,5-bis-(bromomethyl)-benzoate **23**. 3g of *t*-butyl 2,5-dimethyl benzoate **22** (14.5 mmol) was placed in a 250ml round bottomed flask equipped with a stir bar, a reflux condenser and an argon inlet. 50 ml of carbon tetrachloride and 5.695 g. of N-bromosuccinimide (32.0 mmol) was then added. The solution was heated to refluxing. The flask was then irradiated for 10 minutes using a GE model RSKB sunlamp with a 275W bulb. The solution was allowed to reflux for four hours. It was then cooled and filtered, to remove succinimide, and concentrated. The residue was chromatographed over silica gel eluted with 99:1 petroleum ether/ ether, to remove the products of hyperbromination. The purified material was an off-white solid compound. ^1H NMR (CDCl_3) δ 7.92 (s, 1H), 7.50 (d, $J=4$, 1H), 7.43 (d, $J=4$, 1H), 4.94 (s, 2H), 4.52 (s, 2H), 1.68 (s, 9H). ^{13}C NMR 166.06, 139.07, 138.74, 132.89, 132.61, 132.17, 83.06, 32.60, 31.70, 28.73.

Host 24. Cesium carbonate (180 mg, 0.55 mmol) was placed in a 100 ml three-necked round-bottomed flask fitted with a stopper, a septum and an argon inlet adapter. The system was purged with argon and charged with 40ml of anhydrous N,N-dimethylformamide. In a separate flask, compound **19** (90 mg, 0.11 mmol) and *t*-butyl 2,5-bis-(bromomethyl)-benzoate (41 mg, 0.11 mmol) were dissolved in 15 ml of anhydrous DMF.

This solution, along with two 5 ml rinsings of the flask were drawn into a 25 ml gas-tight syringe and this syringe was placed in a syringe pump. the solution was then injected into the cesium carbonate suspension over 448 hours. After the injection was complete, the solution was stirred for an additional 24 hours. The syringe and the main reaction vessel were shielded from light throughout the course of the reaction. The DMF solution was then filtered to remove cesium salts. The collected solids were washed twice with approximately 10 ml of DMF. The filtrate and washings were then combined and the solvent was removed under reduced pressure. The crude material was then purified via flash chromatography over silica with a gradient 100:0 to 93:3 v/v of dichloromethane/diethyl ether that yielded 21 mg of host **24** (21 μ mol, 19%). ^1H NMR (CDCl_3) δ 7.86 (s, 1H), 7.33 (m, 2H), 7.22 (s, 4H), 7.06 (m, 4H), 6.64 (m, 4H), 6.53 (m, 4H), 5.58 (s, 2H), 5.15 (s, 2H), 5.12 (s, 4H), 4.53 (s, 4H), 3.65 (s, 12H), 3.34 (s, 4H), 1.64 (s, 9 H). ^{13}C NMR 172.98, 172.95, 166.23, 157.269 157.17, 157.14, 143.74, , 143.69, 143.64, 138.96, 137.21, 137.15, 136.76, 132.54, 132.31, 132.27. 132.22, 129.77, 129.24, 126.37, 125.24, 111.17, 101.04, 82.10, 69.26, 52.47, 52.26, 48.00, 47.97, 47.93, 46.18, 45.98. FAB-MS m/r 1035 (MNa^+).

Host 25. 20 mg of host **24** was placed in a 10 ml round-bottomed flask equipped with a stir bar and a stopper. 4 ml of trifluoromethanesulfonic acid was then added. The reaction was run in the dark and stirred rapidly.

Reaction was complete after 45 minutes (^1H NMR in CD_2Cl_2 does not show any presence of *t*-butyl groups). A flow of argon was then passed through the solution until all the triflic acid was evaporated. The last residues of triflic acid were eliminated putting the contents of the flask under high vacuum at room temperature for ten minutes. Compound was then purified by HPLC using a Whatman Magnum 9 column (50 cm, Partisil 10, ODS-3). A gradient 70:30 to 0:100 acetonitrile/water over 45 minutes was used. The desired product eluted after about 30 minutes. ^1H NMR (CDCl_3) δ 8.15 (m, 1H), 7.65 (m, 2H), 7.39 (s, 4H), 7.18 (m, 4H), 6.89 (s, 4H), 6.71 (m, 4H), 5.43 (s, 2H), 5.04 (s, 2H), 5.01 (s, 4H), 4.62 (s, 4H), 3.62 (m, 12H), 3.42 (s, 4H). FAB-MS m/r 979 (MNa^+).

5.7. References

1. Kearney, P. C. *Ph. D. Thesis*, California Institute of Technology, 1993.
2. Uhlmann, E., Engels, J. *Tetrahedron lett.* **1986**, *27*, 1023.
3. NMR of the product mixture shows minor signs of residual methyl esters. Another possible reason of concern is the fifth carboxylate on the aromatic linker. It is hoped that the dissociated carboxylate will not be esterified under the conditions used for the aminolysis of the methyl esters. In fact, a dissociated carboxylate should be of extremely low reactivity in a nucleophilic addition.
4. The similar polarity of Tris and host 17 is complicated by the difficulty to reveal Tris (present in a 20-fold excess). The Tris molecule is not UV active and its presence is usually revealed by chemical reaction with a 0.5% alizarine solution in ethanol. Traces of unreacted intermediates are also difficult to purify, due to the very high polarity of these molecules.
5. A guest is certainly not a point charge. However, it may be approximated to this model system if we consider that there should not be water, and therefore counterions, in the hydrophobic binding cavity of all the considered hosts. The positive charge of the guest will then be distributed

considered hosts. The positive charge of the guest will then be distributed on its surface according to the structure of the molecule. This distribution will depend from the symmetry of the molecule and it will not be, in general, isotropic. As a consequence of the large number of molecules of host and guest present in solution, we will only see a statistical average of the interaction of each carboxylate with different parts of the guest. This is the meaning we attribute to a point charge-dipole interaction.

6. Petti, M. A., Shepodd, T. J., Barrans, R. E., Jr., Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825.

Appendix A

A Catalyst for Enantioselective Radical Reactions

Since the studies of Gomberg on triphenylmethyl radical in 1900¹, radical chemistry has acquired more and more importance. The alkyl radicals were initially discovered by Paneth² in 1920. In 1937 Hey and Waters³, and Kharasch⁴ were the first to use free radicals in organic synthesis. In the following years Mayo, Lewis and Walling⁵ started to apply the principles of radical chemistry to polymerization reactions and for many years radical species were primarily used in the polymer field. In fact, the use of radical species in the synthesis of non-polymer organic compounds has been limited for some decades due to the lack of selectivity. However, within the last decade radical reactions that allow formation of specific carbon-carbon bonds in the synthesis of even complex molecules have emerged⁶.

Specifically, radical-initiated cyclizations have been explored only in recent years⁷⁻⁹. The substrates for this kind of reaction usually contain a functional group that can generate a radical under specific conditions, and a π system that can be intramolecularly attacked by the radical.

The control of the cyclization strongly depends on steric effects as well as orbital overlap of the π system and the electron-deficient reacting radical center. If we consider for example, a 1-hexenyl-6-radical, radical cyclizations usually give five-membered rings under kinetic control, six-membered rings are obtained by the electronic stabilization of the initial

reacting radical center¹⁰. The general requirement is having at least three atoms between the multiple bond and the reacting center.

Nowadays, several methods are known to generate radicals from various functional groups, frequently with high selectivity. Intramolecular radical cyclizations can be carried out using C-C, C-O, and C-N multiple bonds as radical traps. In general, free radical reactions must be chemo-, regio-, diastereo- and/or enantioselective in order to be useful for the organic chemist. While it is often possible to obtain chemo- and regio-selectivity using an appropriate substrate and changing the reagents and the reaction conditions⁶, enantioselectivity from simple substrates is not easy to achieve with radical reactions. Of course, one method of producing enantioselective compounds is to use chiral precursors. However there is another approach that one can consider. Cyclization occurs when the chain loops up out of the plane of the alkene allowing the radical to attack the π orbital of the alkene. This process is thought to proceed through helical transition states. It is clear that enantioselectivity can then be reached by preferentially stabilizing one of the two transition states.

For some time we have tried to develop a catalyst for enantioselective radical cyclizations. Our initial design was based on molecule 1 illustrated in figure A.1.

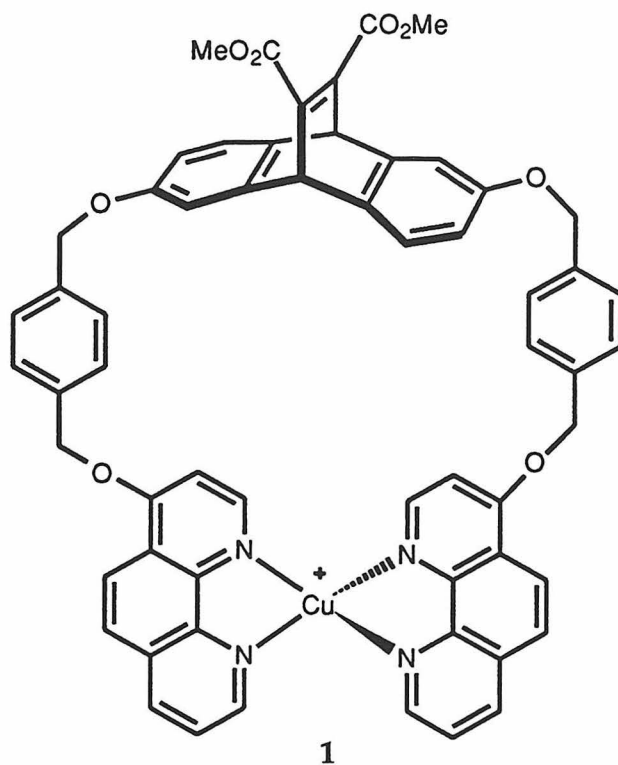


Figure A.1. The initial design of a catalyst for enantioselective radical reactions.

This system was developed to catalyze the radical cyclization of diazonium salts such as **2** (figure A.2)

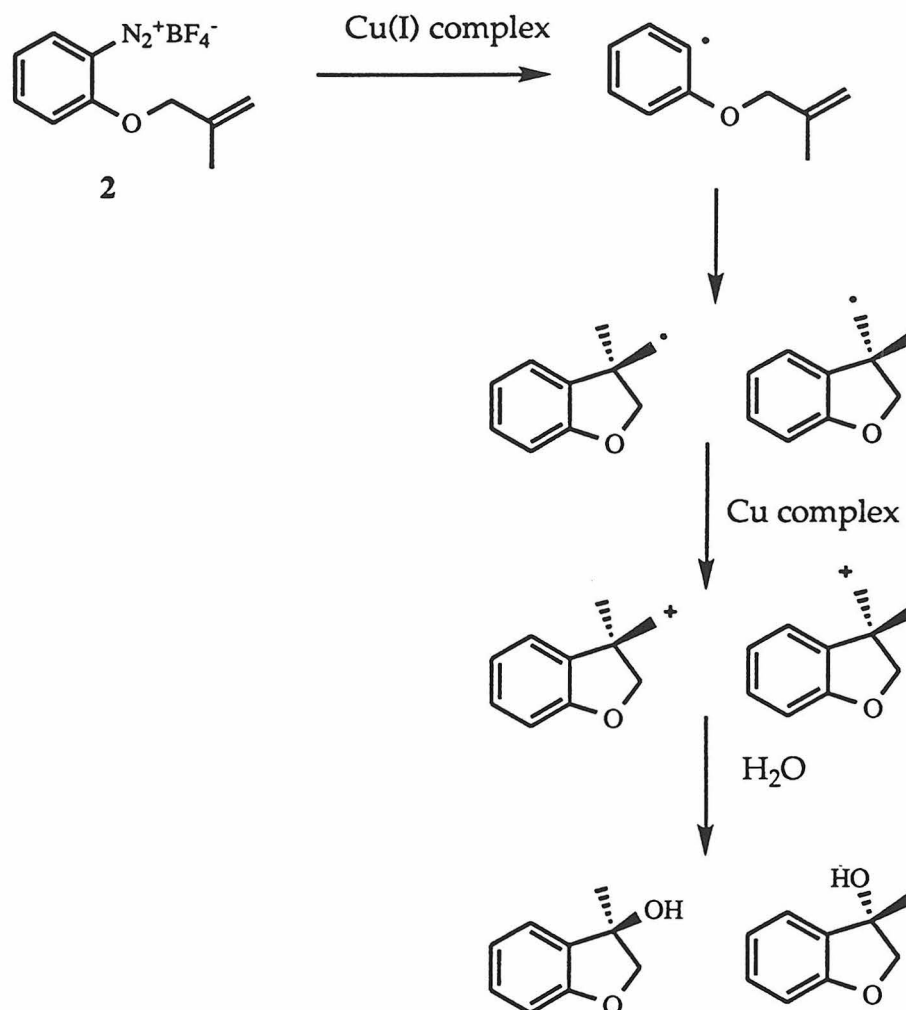


Figure A.2. Reaction of diazonium salts with copper(I) complexes generates radicals that will cyclize if the aliphatic chain is long enough.

We expected that receptor **1** would bind the diazonium salt **2** in the same way that host **P** binds organic quaternary cations. The copper-phenanthroline complex would then initiate the radical cyclization. Due to the chirality of **1**, only one of the two transition states would be stabilized, so that the net result of the reaction would be the preferential formation of an enantiomer.

The synthesis of compound **1** is reported in figure A.3. Alkylation of 4-hydroxyphenanthroline **3** and of the diphenol **4** should give molecule **1**.

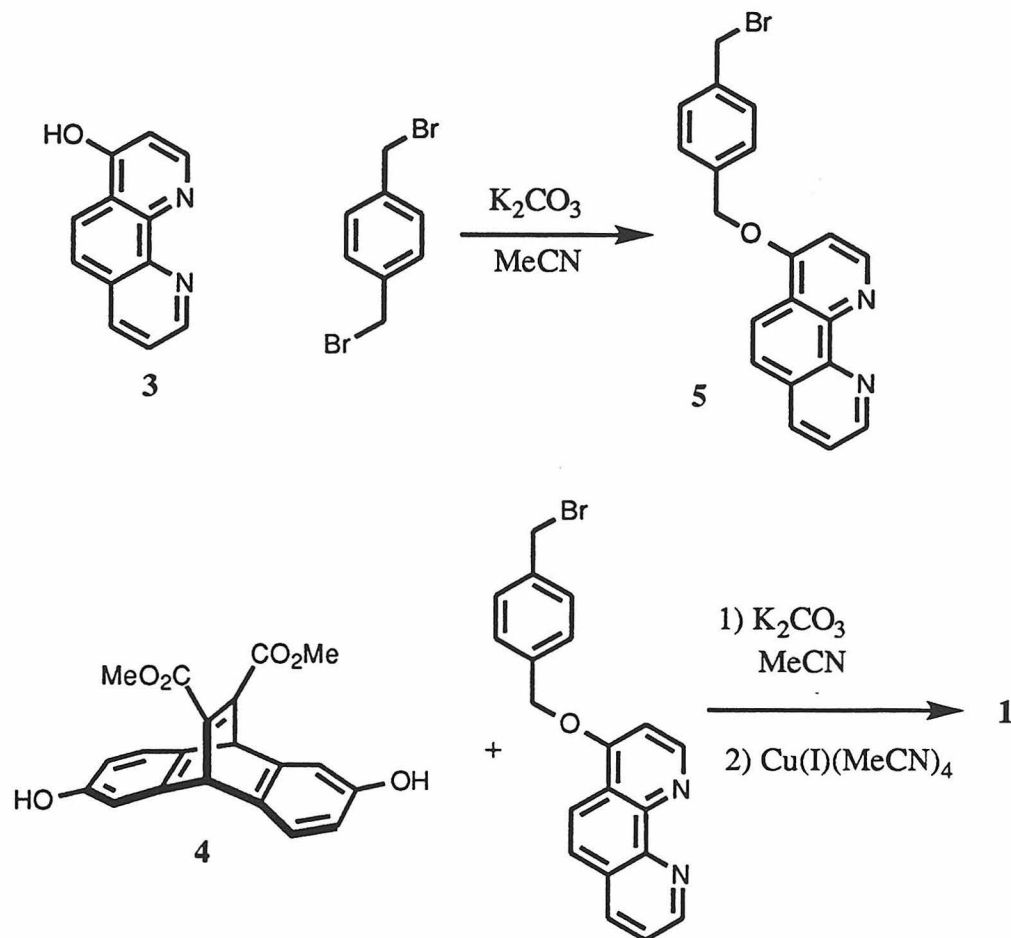


Figure A.3. Attempted synthesis of receptor **1**

However, when we tried to bind copper with the alkylation product **1**, we had the surprise that the copper did not bind. This was a peculiar result, because phenanthroline is the best known binder for copper. We then realized that during the alkylation of 4-hydroxyphenanthroline **3**, we did

not alkylate the oxygen, but the nitrogen (figure A.4). This clearly explains why the hypothesized molecule 1 did not bind copper.

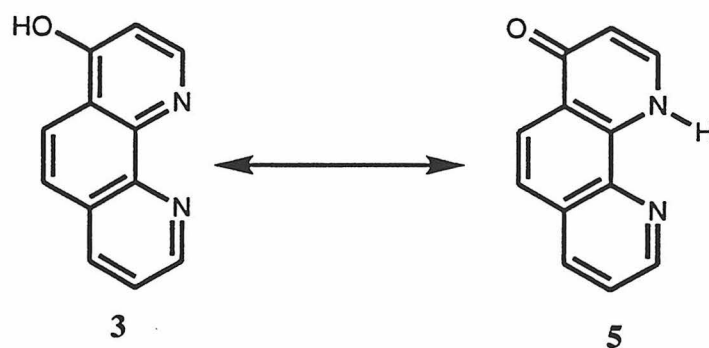
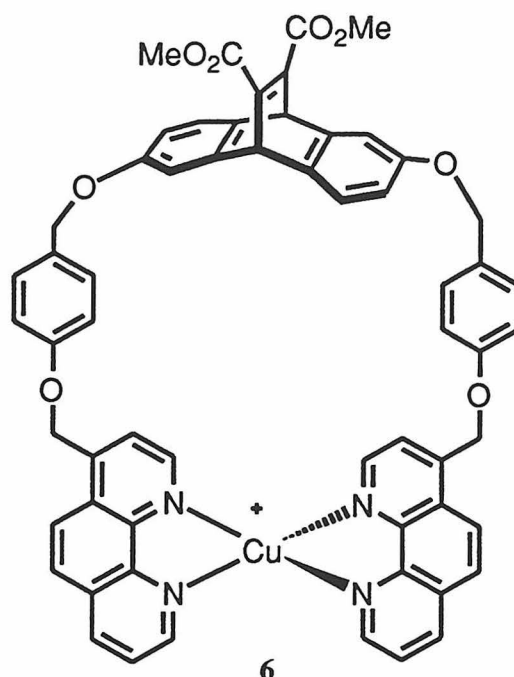


Figure A.4. 4-hydroxyphenanthroline 3, can exist in two tautomeric forms. Form 5 is more reactive than 3.

We then proceeded to redesign the whole system. We decided that small changes could solve the problem of the competition between oxygen and nitrogen in 3. In particular, introducing a spacer between the OH and the phenanthroline eliminates the tautomerism. Thus, we proposed molecule 6 as the next generation of catalysts for enantioselective reactions.



The size and the shape of molecule 6 were chosen to match the reaction that it should catalyze. Even minimum variations in the structure could mean a failure. It is clear that in the design of this molecule, the synthesis of an appropriate 4-substituted phenanthroline is crucial. Unfortunately, position 4 in phenanthroline is the least reactive of the whole molecule. After many attempts, the sequence of reactions described in figure A.5 was developed.

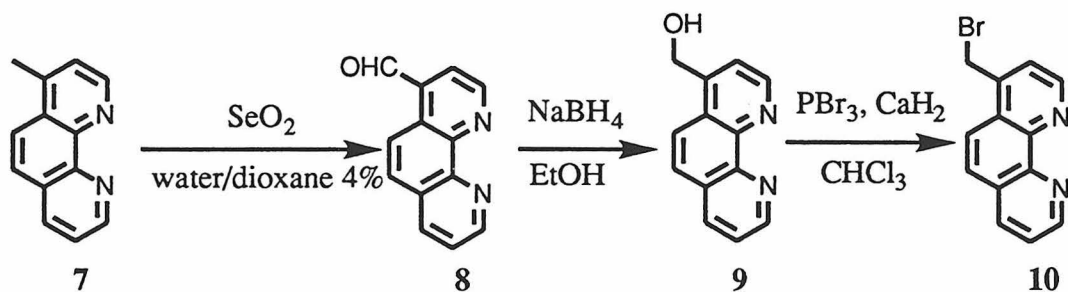
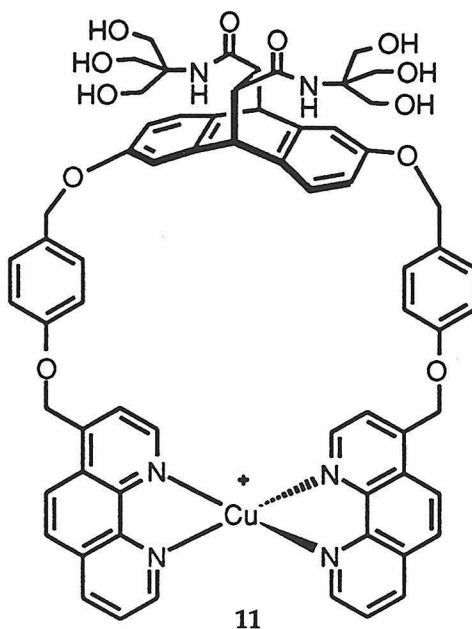


Figure A.5. The synthesis of 4-substituted phenanthrolines such as 9 and 10 is crucial for the synthesis of 6.

Commercially available 4-methylphenanthroline is oxidized with selenium dioxide to aldehyde 8. Reduction of 8 gives 4-hydromethylphenanthroline 9, that can be transformed to the bromide 10.

A final consideration on the structure of 6 regards its solubility. It is reasonable to assume that the simple complexation with copper will not confer enough water-solubility to this hydrophobic molecule. On the other hand, the hydrolysis of the methyl esters to give two carboxylates, would certainly make the copper complex water-soluble. However, the presence of opposite charges in the same molecule (the cationic copper and the anionic carboxylates) could give aggregation problems. We then decided that the best choice would be to use neutral water-solubilizing groups. Molecule 11 is proposed.



A synthetic scheme for molecule 11 is described in figure A.6.

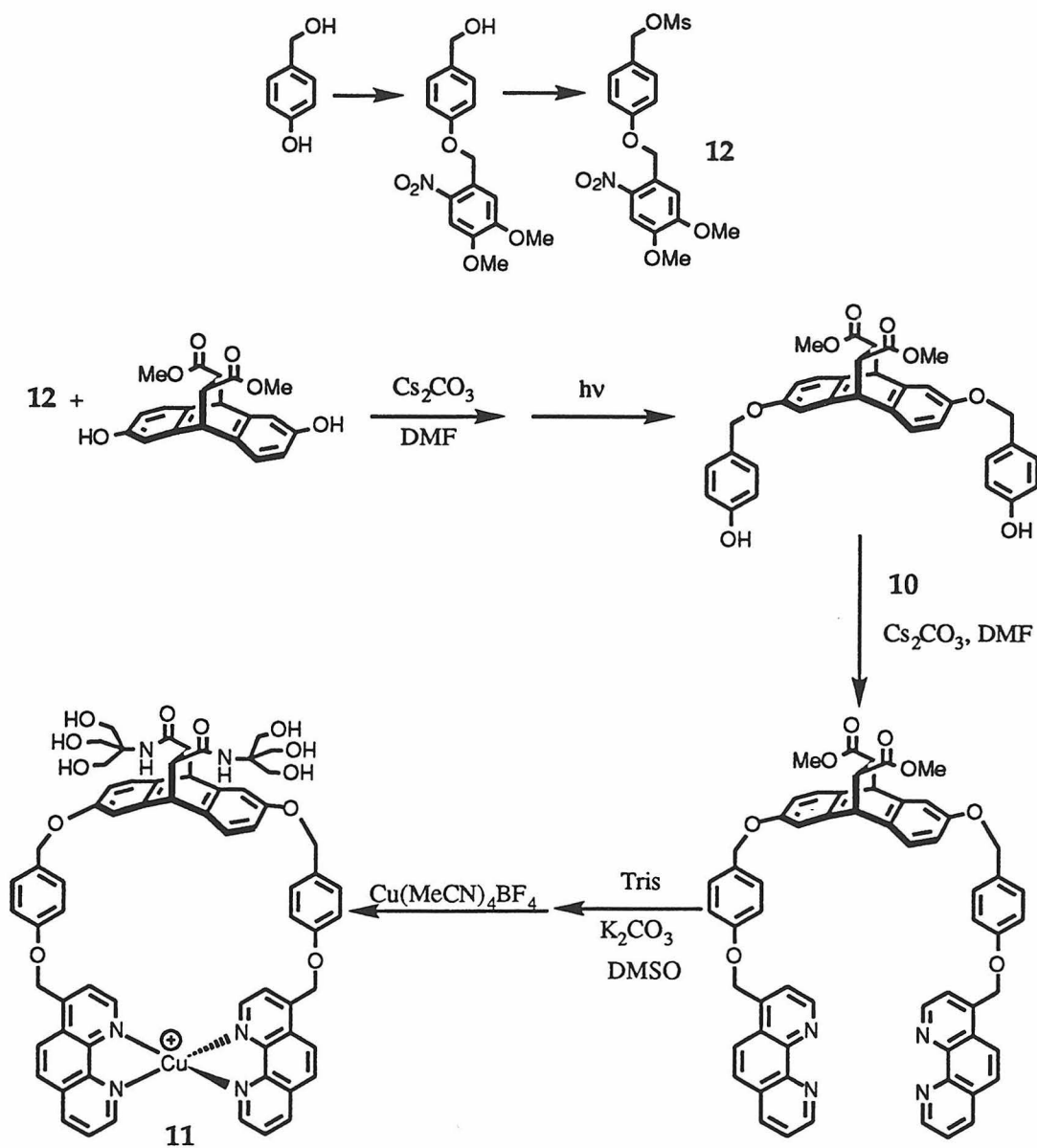


Figure A.6. A proposed synthetic scheme for molecule 11.

While it is not possible to say at this point that this synthetic scheme will work, it certainly represents a major improvement over the original starting molecule 1.

Experimental Section

General NMR spectra were recorded on Bruker AMX500, Bruker AM500, or General Electric QE-300 spectrometers. Routine spectra were referenced to the residual proton signals of the solvents and are reported in ppm downfield of 0.0 as δ values. All coupling constants, J , are in Hz. Mass spectral analyses were performed at the University of California, Riverside.

4-methylphenanthroline **7** is commercially available.

4-formylphenanthroline 8. Into a 50 ml 3-necked, round-bottomed flask equipped with a stopper, a reflux condenser, and an addition funnel, were placed 204 mg of selenium dioxide (1.80 mmol) and 2ml of 96:4 dioxane/water. Temperature was gradually raised (to 55°C) until all the selenium dioxide was dissolved. A solution of 250 mg of 4-methylphenanthroline (1.29 mmol) in 10 ml of dioxane was then added dropwise through the addition funnel to the selenium dioxide solution. The solution was brought to reflux and vigorous stirring was maintained throughout the reaction. The solution turned clear-orange after 20 minutes and the bottom of the flask became coated with black colloidal selenium. The

solution was filtered and an orange suspension was recovered. Solvent was removed under reduced pressure. The solid residue was laced with colloidal selenium. The mixture was redissolved in chloroform and the suspension was centrifuged. A clear solution was separated. Solvent was evaporated and traces of selenium were still found in the residue. The procedure, dissolution in chloroform-centrifugation-removal of the solvent, was repeated seven times, until all of the selenium was eliminated (note: colloidal selenium seems to have a reduced solubility in anhydrous chloroform. Therefore, the use of this solvent decreases the number of steps of purification necessary to eliminate the selenium). The solvent was then removed under reduced pressure to yield a yellow solid (233 mg, 1.12 mmol, 87% yield). ^1H NMR (CDCl_3) δ 10.60 (s, 1H), 9.48 (d, $J=4.5$, 1H), 9.25 (dd, 2.7, 0.9, 1H), 9.02 (d, $J=8$, 1H), 8.31 (dd, $J=3.3$, 0.9, 1H), 8.03 (d, $J=4.5$, 1H), 7.98 (d, $J=8$, 1H), 7.71 (dd, $J=2.7$, 3.3). IR, C=O stretching at 1698 cm^{-1} . EI-MS m/e 208 (M^+).

4-hydroxymethylphenanthroline 9. 500 mg of sodiumborohydride (13.16 mmol) was placed in a 250 ml three-necked, round-bottomed flask equipped with a septum, a stopper and an additional funnel. 100 ml of ethanol was then added and the suspension was stirred. A solution of 1.630 g of aldehyde 8 (7.84 mmol) in 10 ml of ethanol was added dropwise via the addition funnel. After the addition was completed, the solution was stirred for four hours. 20 ml of water was then added and the mixture

was stirred for twenty minutes, to destroy all the excess of sodium borohydride. The mixture was then extracted three times (100 ml) with chloroform. Combined organic layers were dried over anhydrous MgSO_4 and the solvent was removed under reduced pressure. A white solid (1.596 g, 7.6 mmol, 97 % yield) was recovered. ^1H NMR ($\text{DMSO}-d_6$) δ 9.05 (m, 2H), 8.45 (dd, $J=6.6, 1.5$, 1H), 8.05 (d, $J=9$, 1H), 7.96 (d, $J=9$, 1H), 7.79 (d, $J=6.6$, 1H), 7.73 (m, 1H), 5.60 (broad, 1H), 5.10 (s, 2H). ^{13}C NMR ($\text{DMSO}-d_6$) 150.86, 150.61, 148.80, 146.90, 146.30, 136.93, 129.00, 127.35, 126.93, 124.09, 123.16, 121.41, 61.09. EI-MS 210 (M^+).

4-bromomethylphenanthroline 10. 30 mg of alcohol 9 (0.143 mmol) and 20mg of calcium hydride (0.48 mmol) were placed in a 25 ml three-necked, round-bottomed flask equipped with a septum, a stopper and an argon inlet. 8 ml of anhydrous chloroform was injected into the vessel. Solution was stirred. 6.76 μl of phosphorous tribromide was then added. The solution was stirred at room temperature for three hours. 10ml of chloroform, 5 ml of ethyl acetate, and 10 ml of 5% aqueous sodium bicarbonate were then added. The aqueous layer was extracted twice (50ml) with ethyl acetate and the combined organic layers were dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure. Residue was dried under high vacuum (32 mg, 82% yield). ^1H NMR (CDCl_3) δ 9.19 (dd, $J=4,2$, 1H), 9.13 (d, $J=2$, 1H), 8.25 (dd, $J=4,2$, 1H), 8.10 (d, $J=9$, 1H), 7.89 (d, $J=9$, 1H), 7.68 (m, 2H), 4.89 (s, 2H). ^{13}C

NMR (CDCl₃) 150.69, 150.19, 146.86, 146.37, 142.54, 136.06, 128.45, 127.17, 126.50, 123.39, 121.82, 120.90, 28.481. EI-MS 272-274 (bromine doublet).

References

1. M. Gomberg, *J. Am. Chem. Soc.* 22, 757 (1900).
2. F. Paneth, W. Hofeditz, *Chem. Ber.*, 62, 1335 (1929).
3. D. H. Hey, W.A. Waters, *Chem. Rev.*, 21, 169 (1927).
4. M.S. Kharasch, E.T. Margolis, F.R. Mayo, *J. Org. Chem.* 12, 393 (1937).
5. F.R. Mayo, F. M. Lewis, *J. Am. Chem. Soc.*, 66, 1594 (1944).
6. See for example the excellent reviews: M. Ramaiah, *Tetrahedron*, 43, 3541 (1987) and D.P. Curran, *Synthesis*, 417 and 489 (1988). For a more general description of the C-C bond formation see B. Giese, Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon Press, N.Y., N.Y., 1986.
7. A.L.J. Beckwith, D.H. Roberts, *J. Am. Chem. Soc.* 108, 5893 (1986).

8. B. Giese, *Angew. Chem.Int. Ed.*, 22, 753 (1983).
9. D. J. Hart, *Science*, 223, 883 (1984).
10. M. Julia, *Acc. Chem. Res.* 4, 386 (1971).

Appendix B

The Interaction Between Benzene and Hexafluorobenzene

In chapter 2 of this thesis we have shown that the molecule of benzene has a large negative quadrupole on its surface.¹ It has also been shown that the quadrupole moment can be thought as originated from a separation of dipoles in the structure of the molecule. In the case of benzene, the dipole moments are due to the six C-H bonds. Benzene is a D_{6h} molecule, and this means that its global dipole moment is zero. However, the orientation of the local dipole moments of the C-H's gives rise to the quadrupolar distribution. It is only logical to think that if we invert the direction of the local dipole moments, we should have a molecule with a large positive quadrupole moment on its surface. This is exactly what happens with hexafluorobenzene. Using the concepts exposed in chapter 3, we can use electrostatic potential surfaces to illustrate this concept. In figure B1, the electrostatic potential surfaces for benzene and hexafluorobenzene are reported.² The inversion in the quadrupole moment going from C_6H_6 to C_6F_6 is evident.

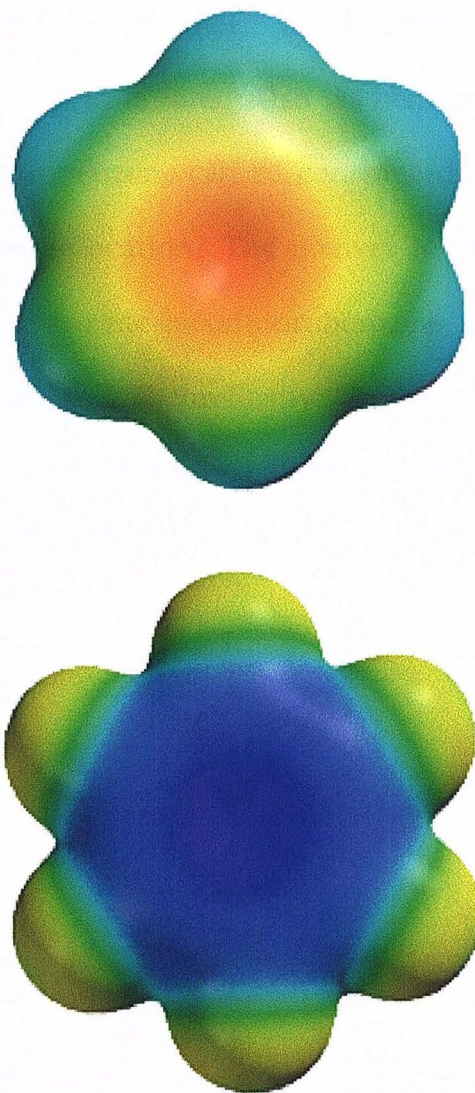


Figure B1. Electrostatic Potential surfaces of benzene (top) and hexafluorobenzene (bottom). The inversion of the quadrupole moments is clear.

The quadrupole moment of hexafluorobenzene has been measured^{1,3-6} and calculated⁷. Its value is large and positive, $31.7 \times 10^{-40} \text{ Cm}^2$. In hexafluorobenzene, the electron charge density is evidently due to the high electronegativity of the six fluorine atoms that are in the plane of the molecule.

Now, we can expect that, as benzene can bind cations, hexafluorobenzene can bind anions. Also, as benzene can be considered a pseudoanion, hexafluorobenzene can be considered a pseudocation. Can a pseudoanion bind a pseudocation? The answer to this question is already known. Structures of benzene-hexafluorobenzene complexes have been studied experimentally and theoretically. Experimentally, benzene and hexafluorobenzene have been cocrystallized to yield structures where the electrical properties of the two molecules are self-evident (figure B2).^{1,8}

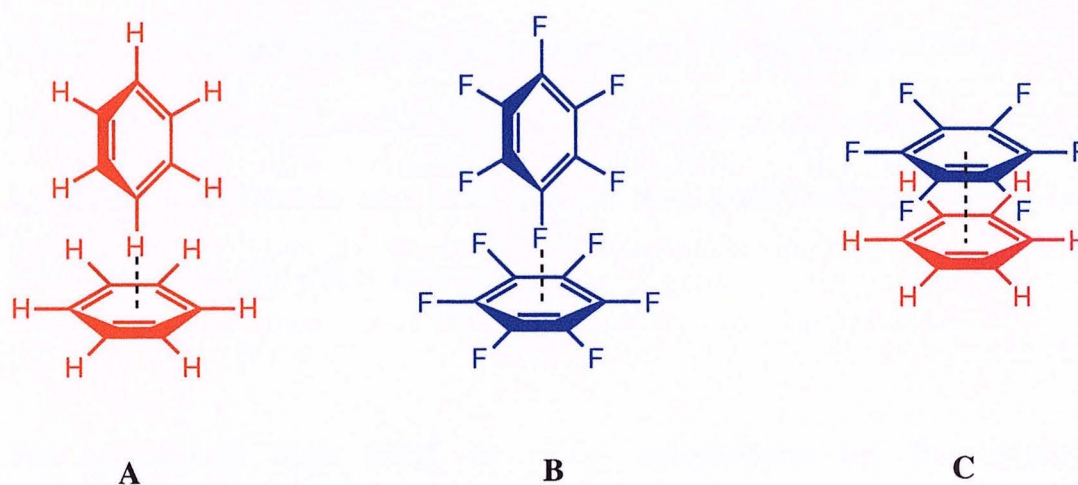
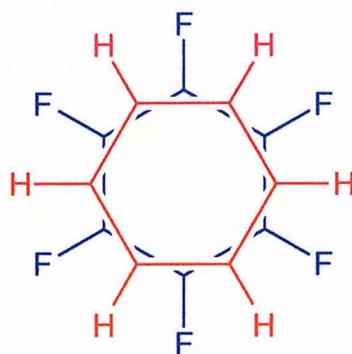


Figure B2. Approximated solid state interactions in solid benzene (A), solid hexafluorobenzene (B) and a cocrystallized mixture of benzene-hexafluorobenzene.

In the mixed complex C (figure B2), the distance between the parallel planes was estimated to be $3.77\text{\AA}$.¹

Also, theoretical studies have shown that the preferred binding conformation of benzene and hexafluorobenzene in mixed complexes has the molecular planes parallel to each other with a twist angle of 30° .⁹



Finally, the quadrupolar interaction energy between benzene and hexafluorobenzene has been estimated by approximate classical electrostatics calculations, to be worth 15.3 kcal/mol.¹⁰ One could argue that charge-transfer effects could be important in this kind of interaction. However, Siegel and Cozzi have analyzed a series of stacked aryl groups in 1,8-diarylnaphthalenes and have shown that polar/ π -electrostatic effects dominate over any other interaction.¹¹

We performed high level *ab initio* calculations on the complex benzene/hexafluorobenzene using the GAUSSIAN 92¹² package. We first optimized the geometry of the complex where the twist angle α between the two molecules is zero with a Hartree-Fock calculation at the 6-31G** level. We found that at this level, the optimized distance between parallel benzene and hexafluorobenzene is 4.08 Å, 0.31 Å longer than the distance found in the crystal structure of the complex. We then took into account the effect of the electronic correlation with a single point energy MP2/6-31G** calculation of the interaction energy between the two molecules at

the HF optimized distance. We also calculated the interaction energy, at the same distance, but with the two molecules having a twist angle of 30° (figure B3). Results are reported in table B1.

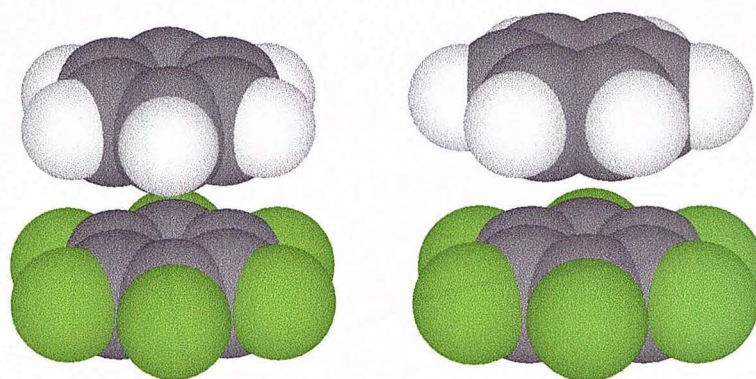


Figure B3. The complex benzene-hexafluorobenzene has been studied at two different geometries. In both the geometries the molecules were parallel to each other. Twist angle α was 0° in one case (left) and 30° in the other case (right).

Twist Angle	0°	30°
HF Energy in kcal/mol	-1.51	-1.50
MP2 Energy in kcal/mol	-4.00	-3.96

Table B1. HF/6-31G** and MP2/6-31G** energies for the complex benzene-hexafluorobenzene, at the geometries shown in figure B2.

From the data on table 1 one can immediately see the relevance of the electron correlation in calculating the interaction energy between the

two molecules. We then proceeded in calculating an energy-distance curve. This curve was first estimated by Hartree-Fock 6-31G** calculations and is reported in figure B4.

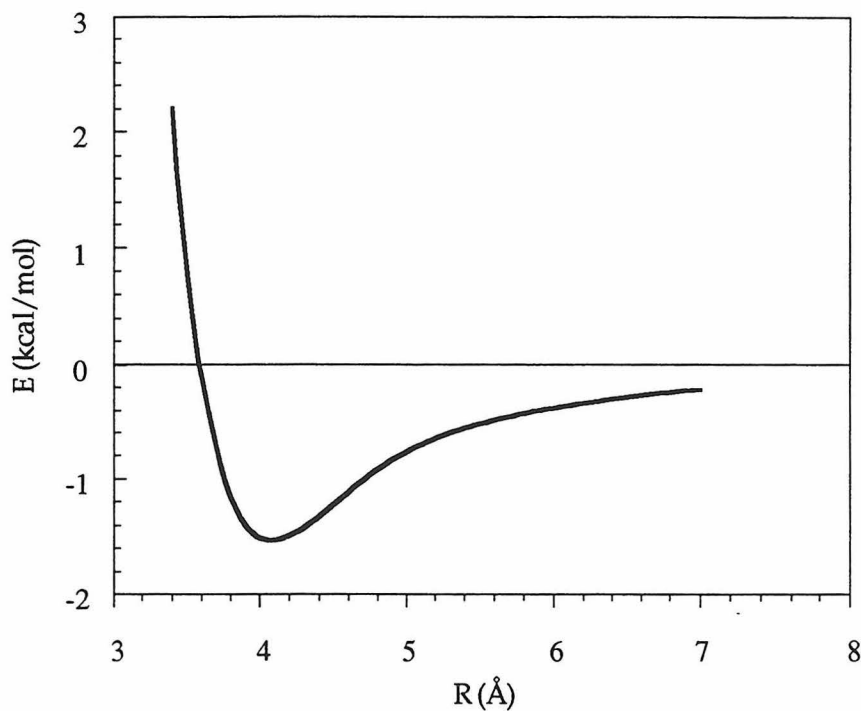


Figure B4. Energy-distance curve for the complex benzene-hexafluorobenzene estimated through HF/6-31G** calculations. The distance R is the distance between the centroids of the two parallel molecules. The twist angle between the two molecules is zero.

The attractive region of the plot can be fit and the dependence from R can be estimated (figure B5):

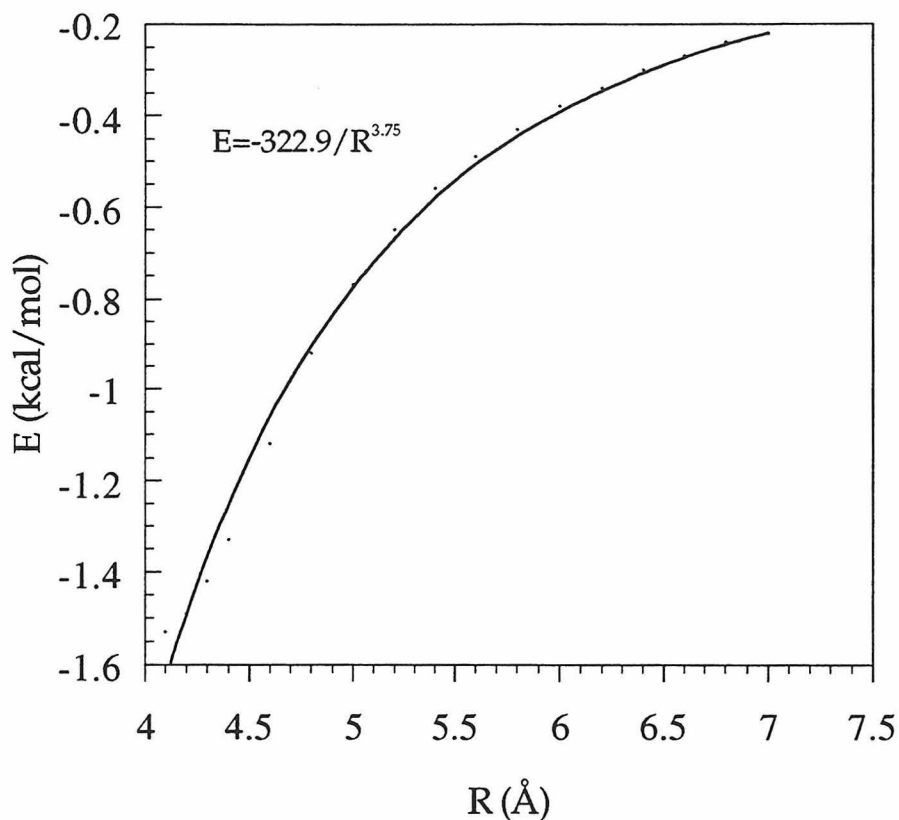


Figure B5. Fit of the interaction energy/distance curve for the attractive region of the plot.

Theoretically, the R dependence of the interaction of two quadrupoles is proportional to R^{-5} . Therefore, the HF calculations show that a simple quadrupolar interaction is not sufficient to completely describe the system. This is hardly surprising considering the size of the molecules and their distance. In consideration of these results, we then proceeded to calculate interaction energies at different distances R by MP2/6-31G** calculations. Results are reported in table 2.

Distance R (Å)	4.08	3.90	3.77	3.65	3.55
MP2 Energy	4.00	4.88	5.53	6.11	6.52

Table B2. MP2/6-31G** calculation of the interaction energy (kcal/mol) in the complex benzene/hexafluorobenzene. The molecules are parallel to each other and the twist angle is zero.

The curve minimum is now reached around 3.5Å (crystal structure distance) and the interaction energy is 4 kcal/mol higher than the energy calculated in the HF optimization! This discrepancy between the HF and the MP2 calculations is not unexpected but its magnitude is somewhat surprising.

Clearly, the interaction between benzene and hexafluorobenzene is not easy to model. However, the data presented in this appendix represent a substantial improvement on the data currently available in the literature. It is anticipated that the present results will be instrumental in the design of systems based on the benzene-hexafluorobenzene interaction.

References

1. Williams J.H. *Acc. Chem. Res.* **26**, 593 (1993).
2. Electrostatic potential surfaces of benzene and hexafluorobenzene were generated by mapping HF/6-31G** electrostatic potentials onto surfaces of molecular electron density ($0.002 \text{ e}/\text{\AA}^3$) and color-coding, using the program SPARTAN (ref. 6 chap. 4). In the two surfaces the potential energy values range from +25 kcal/mol to -25 kcal/mol, with red signifying a value greater than or equal to the maximum in negative potential and blue signifying a value greater or equal to the maximum in positive potential.
3. Vrbancich, J.; Ritchie, G. L. D. *Chem. phys. Lett.* **94**, 63 (1983).
4. Battaglia, M. R.; Buckingham, A. D.; Williams, J. H. *Chem. Phys. Lett.* **78**, 421 (1981).
5. Vrbancich, J.; Ritchie, G. L. D. *J. Chem Soc. Faraday II* **76**, 648 (1980).
6. Gentle, I. R.; Ritchie, G. L. D. *J. Phys. Chem.* **93**, 7740 (1989).
7. Laidig, K. E. *Chem. Phys. Lett.* **185**, 483 (1991).

8. a) Williams, J. H. *Mol. Phys.* **73**, 113 (1991). b) Williams, J. H.; White, R. P. *Chim. Phys.* **89**, 1755 (1992).
9. Jain, D. V. S.; Nandel, F. S. *Proc. Indian Acad. Sci. (Chem. Sci.)* **91**, 295 (1982).
10. Hernandez-Trujillo, J; Costas, M.; Vela, A. J. *Chem. Soc. Faraday Trans.* **89**, 2441 (1993).
11. a) Siegel, J. S.; Cozzi, F. *Pure & Appl. Chem.* **67**, 683 (1995). b) Cozzi, F.; Ponzini, F.; Annunziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem. Int. Ed. Engl.* **34**, 1019 (1995).
12. Gaussian92/DFT, Revision F.4, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Gill, P. M. W., Johnson, B. G., Wong, M. W., Foresman, J. B., Robb, M. A., Head-Gordon, M., Replogle, E. S., Comperts, R., Andres, J. L., Raghavachari, K., Binkley, J. S., Gonzalez, C., Martin, R. L., Fox, D. J., Defrees, D. J., Baker, J., Stewart, J. J. P., Pople, J. A. Gaussian, Inc., Pittsburgh, PA 1993.