JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 10, 369–382 (1997)

INCLUSION COMPLEXATION OF CYCLOBIS(PARAQUAT-*p*-PHENYLENE) AND RELATED CYCLOPHANE DERIVATIVES WITH SUBSTITUTED AROMATICS: COOPERATIVE NON-COVALENT CAVITY AND EXTERNAL INTERACTIONS

RENÉ CASTRO,[1] PABLO D. DAVIDOV,[1] KAIPEUCHERY A. KUMAR,[2] ALAN P. MARCHAND,[2]* JEFFREY D. EVANSECK[1]* and ANGEL E. KAIFER[1]*

[1] *Department of Chemistry, University of Miami, 1301 Memorial Drive, Coral Gables, Florida 33146-0431, USA*
[2] *Department of Chemistry, University of North Texas, Denton, Texas 76203, USA*

The cooperative nature of non-covalent interactions which give rise to inclusion complexes involving cyclobis(paraquat-*p*-phenylene), 1^{4+}, and related cyclophane derivatives, 2^{4+}–4^{4+}, with substituted 1,4-phenyl and 4,4′-biphenyl guests has been studied by spectroscopic techniques and *ab initio* and semiempirical molecular orbital methods. Inclusion complex formation and stability are primarily determined by the combination of two main interaction modes involving aromatic stacking of the guest within the cyclophane cavity and external interactions between guest side arms and the exterior of the cyclophane. A balance between cavity and external forces results in supramolecular association and is shown to change depending upon the functionality and substitution of the guest. Cavity binding was probed using 1,4-phenyl and 4,4′-biphenyl guests, where for the 1,4-phenyl guests the primary basis for energy stabilization with 1^{4+} is found to be short-range stabilizing electrostatic forces complemented by small amounts of polarizability and charge-transfer. In contrast, the cavity binding between substituted 4,4′-biphenyl guests and 1^{4+} is determined by almost equal contributions of polarizability and electrostatics. The effect of solvent is shown to have only a small effect on the computed geometry of 1^{4+} complexes, but its impact upon binding energies is substantial. The first solvation shell of the cyclophanes is computationally approximated by 12 acetonitriles and satisfies the requirements of the 16 relatively acidic protons on the bipyridinium groups. Good correlations between the computed (with solvation) and experimental 1^{4+} binding energies are found. The degree of linear correlation improves substantially when the comparison between computed and experimentally observed binding energies is restricted to structurally similar (number of aromatic rings, number of substituents and position of substitution) molecular guests. Furthermore, computed molecular properties, such as polarizability, maximum hardness, softness and electronegativity of the isolated guests, correlate well with 1^{4+} binding energies based upon the same requirement of guest similarity. The non-covalent forces associated with the external cyclophane interactions were studied with guest molecules built from symmetrical 1,4-extensions of hydroquinone composed of aliphatic or ethyleneoxy side arms. In particular, side arm length and functionality, and the position and type of heteroatoms along the chain, were systematically varied to define the external interactions between the guest side arms and different host cyclophanes. Specifically, the ethyleneoxy linkages are shown to provide a large chelate and cooperative effect which direct the binding with 1^{4+}. In order to probe further the special geometric and electronic character of 1^{4+}, we have synthesized and tested a new supramolecular host, 2^{4+}, similar to 1^{4+} but where a pentacycloundecane unit replaces one of the xylyl groups. Both experimental and computed data on the new host emphasize the ideal geometry and electronic nature of the 1^{4+} molecular receptor for aromatic guests. The inclusion complexes discussed in this paper are important not only because they, or similar entities, are the main components of

* *Correspondence to:* A. P. Marchand, J. D. Evanseck or A. E. Kaifer.
Contract grant sponsor: National Science Foundation; *Contract grant number:* CHE-9304262; *Contract grant number:* CHE-9633434.
Contract grant sponsor: Petroleum Research Fund; *Contract grant number:* PRF 30918-G4.
Contract grant sponsor: Department of Defense; *Contract grant number:* DAAH04-96-1-0311.
Contract grant sponsor: Robert A. Welch Foundation; *Contract grant number:* B-963.

 CCC 0894–3230/97/050369–14 $17.50

many rotaxanes, catenanes and other switchable molecules, but because the intermolecular interactions involved, such as electrostatics, polarizability and charge-transfer, are ubiquitous in supramolecular chemistry. The information reported on the specific interactions involving the 1^{4+}–4^{4+} molecular receptors with substituted aromatic guests can also be extended by analogy to many systems of broad interest. © 1997 by John Wiley & Sons, Ltd.

J. Phys. Org. Chem. **10**, 369–382 (1997) No. of Figures: 10 No. of Tables: 3 No. of References: 39

Keywords: inclusion complexation; cyclobis (paraquat-*p*-phenylene); cyclophanes; substituted aromatics; cooperative non-covalent cavity; external interactions

Received 30 September 1996; revised February 1997; accepted 21 February 1997

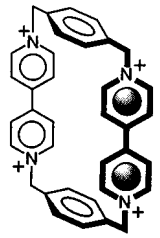
INTRODUCTION

The tetracationic host cyclobis(paraquat-*p*-phenylene), $\mathbf{1}^{4+}$, was first designed and prepared by Stoddart and co-workers.[1] During the last 8 years, this cyclophane has been shown to have very interesting and versatile receptor properties. Host $\mathbf{1}^{4+}$ has been used as a fundamental building block in a large number of catenanes, pseudorotaxanes, rotaxanes and other interesting molecules.[2] In addition, its water-soluble tetrachloride form is an effective receptor for aromatic amino acids,[3] neurotransmitters[4] and certain phenyl glycopyranosides.[5] The binding properties of $\mathbf{1}^{4+}$ are essentially determined by its rigid cavity, lined by two electron acceptor 4,4′-bipyridinium (paraquat) groups, which are separated by a distance approximately equal to the van der Waals thickness of an aromatic ring. Therefore, the cavity inclusion of an electron-rich aromatic residue gives rise to the development of strong non-bond interactions between the host's electron acceptor paraquat residues and the guest's electron donor ring. Owing to the ideal stacking of aromatic rings and the electronic character of such complexes, charge-transfer had been used as the main non-covalent interaction to explain the general affinity between compounds possessing electron-rich aromatic rings (π-donors) and host $\mathbf{1}^{4+}$.

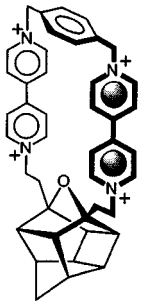
Some time ago, we asked ourselves how much of the receptor's binding strength was due to charge-transfer interactions and how much was the result of other intermolecular forces. If charge-transfer interactions were responsible for most of the observed complex stabilization, then the free energy of complex formation should correlate with the guest's oxidation potential, as a measure of its π-donor ability. With $\mathbf{1}^{4+}$, however, this is not always the case, as evidenced by comparing the two guests benzidine and *p*-phenylenediamine. The first oxidation potentials are +0·59 and +0·32 V vs Ag/AgCl in acetonitrile,[6] respectively. Obviously, *p*-phenylenediamine has the lower oxidation potential and is thus the strongest π-donor of the two. However, benzidine is more strongly bound to host $\mathbf{1}^{4+}$ (in acetonitrile solution, $\Delta G^\circ = -4{\cdot}1$ kcal/mol^{-1} (1 kcal = 4·184 kJ) for benzidine complexation vs $\Delta G^\circ = -2{\cdot}8$ kcal/mol^{-1} for *p*-phenylenediamine).[6] As such, the origin of intermolecular factors which control $\mathbf{1}^{4+}$ binding selectivity and affinity were not clearly understood.

In this paper, we collectively discuss our recent computational and experimental results[7,8] geared to provide an increased understanding of the balance between the non-covalent cavity and external binding forces operating between host $\mathbf{1}^{4+}$ and two classes of π-donor guests built from substituted 1,4-phenyl and 4,4′-biphenyl derivatives. Furthermore, the cooperative phenomenon between external host effects and cavity binding of $\mathbf{1}^{4+}$ was examined by the synthesis of a new supramolecular host, $\mathbf{2}^{4+}$, based on $\mathbf{1}^{4+}$. The idea was to alter both the electronic and geometric features of $\mathbf{1}^{4+}$ and similarly characterize the binding affinity of $\mathbf{2}^{4+}$ with 1,4-phenyl and 4,4′-biphenyl derivatives by using both experimental and computational methods.

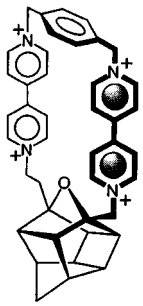
The new $\mathbf{2}^{4+}$ host was designed to perturb guest recognition and binding through the replacement of one



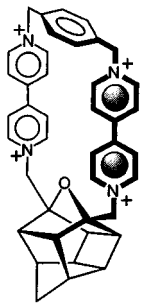
$\mathbf{1}^{4+}$



$\mathbf{2}^{4+}$



$\mathbf{3}^{4+}$



$\mathbf{4}^{4+}$

xylyl group by pentacycloundecane. In addition, a systematic alteration of cavity size was carried out computationally by subtracting the methylene units between the bipyridinium and pentacycloundecane groups resulting in $\mathbf{3}^{4+}$ and $\mathbf{4}^{4+}$. Neither $\mathbf{3}^{4+}$ nor $\mathbf{4}^{4+}$ has been synthesized or experimentally tested. In order to rationalize the geometric and electronic effects between $\mathbf{1}^{4+}$–$\mathbf{4}^{4+}$, and owing to the importance of $\mathbf{1}^{4+}$ as a building block for novel switchable molecules[9] and interfacial devices,[10] we started a detailed investigation of the non-covalent factors controlling the binding selectivity and strength between the cyclophane hosts $\mathbf{1}^{4+}$–$\mathbf{4}^{4+}$ and substituted 1,4-phenyl and 4,4′-biphenyl guests.

COMPUTATIONAL AND EXPERIMENTAL PROCEDURE

All computations were performed using the Spartan 4·1,[11] Gaussian 94,[12] and Monstergauss[13] software packages on IBM RS/6000 Model 590 and 591 workstations. Geometry optimizations were carried out using Restricted Hartree–Fock theory with the STO–3G, 3–21G, 6–31G(D) and 6–31G(P,D) basis sets for *ab initio* calculations,[14] or with the MNDO, AM1 or PM3 semiempirical methods,[15–17] as described previously.[7]

UV–VIS binding studies were conducted on a Shimadzu UV-2101PC scanning spectrophotometer with a tempera-

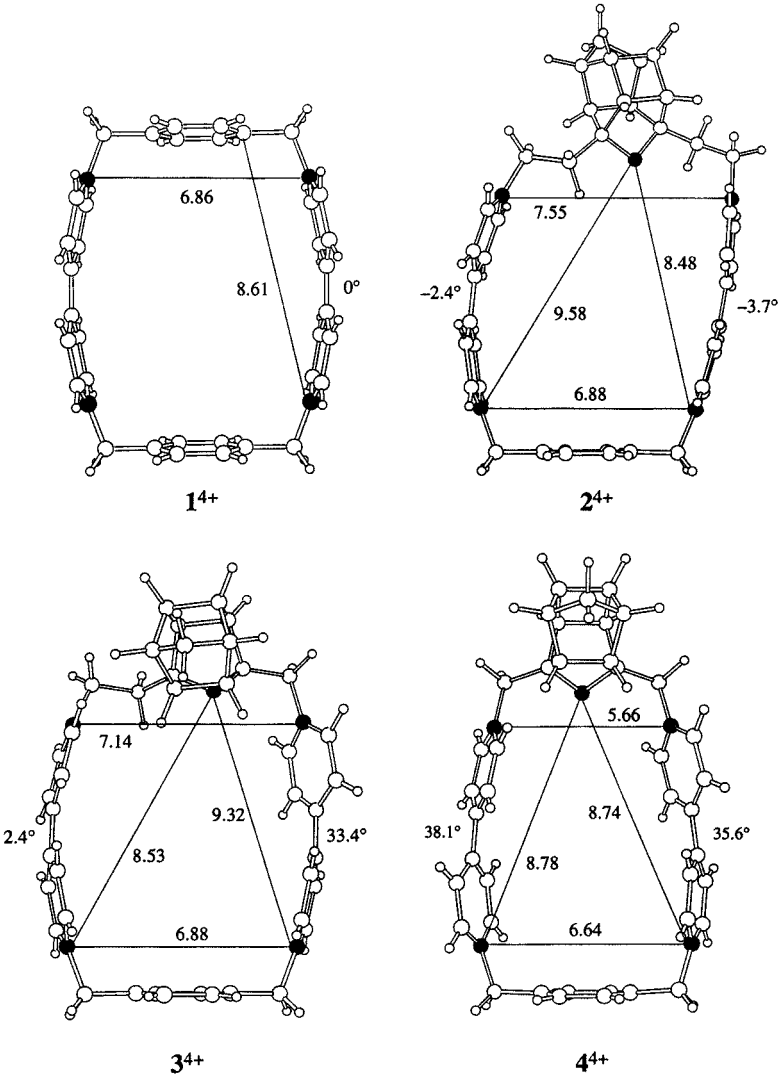
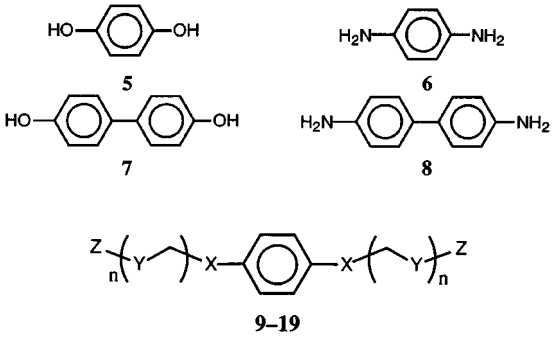


Figure 1. The four different cyclophane structures computed in vacuum using PM3. Distances are in Angstroms and angles in degrees.



ture control module. A charge-transfer band occurs if suitable intermolecular interactions develop between the guest and the host, which provides a straightforward signal to quantitate the free energy of complexation. The method to determine the binding constants monitors the charge-transfer band, since the cyclophane receptor is colorless in solution, until an aromatic guest is added. Syntheses, data collection and analysis were performed as described in detail elsewhere.[6]

RESULTS AND DISCUSSION

Cyclobis(paraquat-*p*-phenylene) and related cyclophane derivatives

Owing to the inherent limitations of empirical energy functions used in standard valence forcefield implementations, the description of induced electrostatics or polarizability,[18] especially for the cyclic tetracations, is problematic.[19] As a consequence, the most straightforward approach was to use semiempirical molecular orbital theory to model the cyclophanes and their complexes.[7] Problems with MNDO have been well documented for other molecular systems.[20] In this study, the MNDO computations produce an unrealistic geometry for $\mathbf{1}^{4+}$, whereas AM1, PM3 and *ab initio* calculations produce structures in good agreement with the crystal structure.[1, 7, 21] Consistent with that found for $\mathbf{1}^{4+}$, the computed PM3 and AM1 structures for $\mathbf{2}^{4+}$–$\mathbf{4}^{4+}$ are similar, but in contrast to that for $\mathbf{1}^{4+}$ do not dramatically distort when treated by MNDO. The computed dimensions of the $\mathbf{1}^{4+}$ cavity are practically constant when compared between the semiempirical and *ab initio* methods.[7] The largest structural change involves the dihedral angle across the bipyridinium units. The dihedral angle is 19° in the crystal structure and varies from 0 to 40° for the different levels of theory used. In addition, the distance across the bipyridinium units is computed to be consistently 1 Å larger than that reported from experiment. Electrostatic repulsion across the ring is believed to cause such an expansion of the cavity, since counterions and solvent were not included in the computations. The other cyclophanes were not compared with experiment, since the crystal structure of $\mathbf{2}^{4+}$ has not been determined, and cyclophanes $\mathbf{3}^{4+}$ and $\mathbf{4}^{4+}$ have not been synthesized. The cavity changes in geometry for the different cyclophanes were investigated by examining the distances from the bipyridinium nitrogens, as shown in Figure 1. A systematic and uneven expansion of the binding cavities is observed as the structure of the host is changed from $\mathbf{1}^{4+}$ to $\mathbf{2}^{4+}$. The symmetrical disposition of $\mathbf{1}^{4+}$ is clear. The effect of the extra methylene linkages in $\mathbf{2}^{4+}$ causes a considerable twist in the binding pocket of the cyclophane, as shown for the PM3 minimized structure. It is of interest that the oxygen lone pairs of the pentacycloundecane group introduce electron density into the cyclophane cavity while at the same time decrease the volume of the cavity owing to steric considerations.

To search for the possible conformations of $\mathbf{1}^{4+}$, the technique of 'corner flapping'[22] was employed using the PM3 semiempirical method. Only one conformation was located from the 59 starting configurations generated by the search method. As such, the potential energy surface of $\mathbf{1}^{4+}$ is not complicated with many energy extrema, although an important feature of the $\mathbf{1}^{4+}$ potential energy surface is that geometric distortion of the bipyridinium and *p*-xylylene torsional angles requires only a small amount of energy. For example, the bipyridinium torsional angle can deviate 20° before destabilizing up to 1 kcal mol^{-1}, which may contribute to the dynamic behavior of rotaxanes and molecular shuttles in solution.[23] Cyclophanes $\mathbf{2}^{4+}$–$\mathbf{4}^{4+}$ are considerably more flexible than $\mathbf{1}^{4+}$, owing to the extra methylene units connecting the bipyridinium and pentacycloundecane groups. Even though a systematic approach to exploring the accessible conformations of the other cyclophanes was not carried out, several initial geometries were used as starting points, and two important conformations were located in the gas phase. It is of interest to quantitate the structural and energetic differences between the two conformations of the $\mathbf{2}^{4+}$ cyclophane, since both could contribute to the binding phenomenon. The main structural difference involves the positioning of the pentacycloundecane unit with respect to the cavity entrance of the cyclophane, as shown in Figure 2. Two important observations are made which could influence the binding properties of $\mathbf{2}^{4+}$. First, the observed 90° twist of the pentacycloundecane unit acts as a gate above the cavity modulating guest entry; this could be exploited to act as a switch for guest binding. Second, the lone pairs on the oxygen atom of the pentacycloundecane unit are directed either into or away from the cavity of $\mathbf{2}^{4+}$ depending on the conformation. This can have a large electronic impact on the molecular receptor and subsequently on the binding of guests.

Cyclophane inclusion complexes

Two general classes of substituted 1,4-phenyl and 4,4′-biphenyl guest were used to understand better the cavity binding processes with the cyclophanes. Hydro-

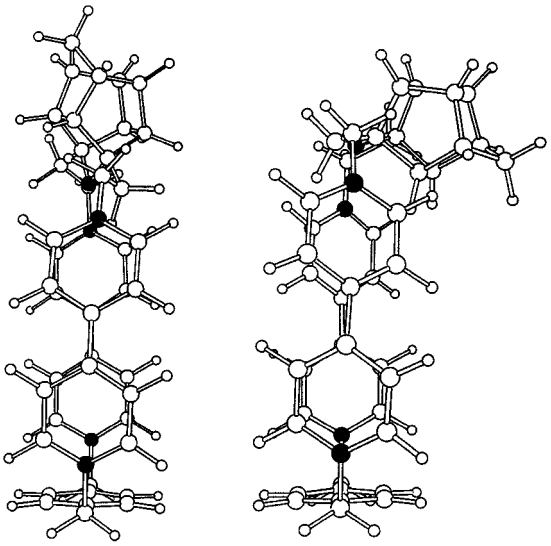


Figure 2. Two PM3 energy minimized conformations of $\mathbf{2}^{4+}$ in vacuum

quinone (**5**), *p*-phenylenediamine (**6**), 4,4′-biphenol (**7**) and benzidine (**8**) were four important guests in our studies, since heteratom differences and delocalization could be directly examined. Moreover, each of these guests are fundamental units of the docking stations used in recently reported rotaxanes[6] and molecular shuttles.[9] Several systematic electronic and structural changes have been made with substituted 1,4-phenyl and 4,4′-biphenyl systems and the energies of complexation with $\mathbf{1}^{4+}$ have been reported previously.[7] The absolute energies (E), computed enthalpies of complexation (ΔH_{bind}), and experimental free energies of binding (ΔF_{bind}) are given in Table 1.. Guests **9**–**19** were synthesized with systematic variations in side arm length (n) and functionality (X, Y and Z) to elucidate the electronic and structural factors which control the external factors in binding with $\mathbf{1}^{4+}$, as summarized in Table 2.

The supramolecular complexes were computationally built by using the Spartan graphics interface to insert the guests visually into the cavity of the cyclophane. Two issues of concern involve the placement of the guests' aromatic unit within the cavity of the cyclophane, and, the orientation of the extended side arm's ethyleneoxy oxygens with respect to the acidic α- and β-protons on the bipyridinium units of the hosts. Alignment of the aromatic portion of the guest was accomplished by placing the guest according to the independently computed electrostatic potential plots (ESP) for the host and guest. In order to probe the available configurations for inclusion complexation, several random geometries guided by the ESP were selected as the starting

Table 1. Computed absolute energies (kcal mol^{-1}) using RHF/6–31G(D) and polarizabilities (Å^3) using the RHF/3–21G and RHF/6–31G(D) levels of theory, with computed enthalpy of complexation, ΔH_{bind}, and experimental free energy of binding, ΔG_{bind}, between $\mathbf{1}^{4+}$ and each guest given in kcal mol^{-1} [a]

Molecule	E(6–31G*)	α_{3-21G}	α_{6-31G*}	ΔH_{bind}	ΔG_{bind}
Benzene	−230·70314	64·9	68·1	−1·67	−1·68
Toluene	−269·74016	81·3	85·3	−2·14	−1·64
Phenol	−305·55768	71·4	74·8	−3·01	−2·14
Anisole	−344·58171	87·7	90·9	−2·35	−1·74
Aniline	−285·73070	79·9	82·9	−2·33	−2·64
tert-Butylbenzene	−386·83767	116·8	122·2	−3·14	−0·95
p-Xylene	−308·77700	98·8	103·6	−1·50	−1·64
1,4-Dichlorobenzene	−1148·50183	115·9	116·9	−1·73	−0·65
Hydroquinone	−380·40887	77·5	80·8	−2·46	−1·71
1,4-Dimethoxybenzene	−458·45783	110·9	114·1	−3·24	−1·64
1,4-Phenylenediamine	−340·75424	93·2	96·9	−2·75	−2·79
p-Chloroaniline	−744·63086	106·0	107·8	−2·31	−2·09
p-Chlorophenol	−764·45704	84·7	98·6	−1·88	−1·42
p-Methoxytoluene	−383·61802	88·6	109·2	−2·30	−1·68
Biphenyl	−460·25385	159·5	169·5	−2·08	n/a
4-phenylphenol	−535·10868	169·0	179·1	−2·78	−2·30
4-Phenylanisole	−574·13400	189·2	199·3	−3·39	−2·14
4-Phenylaniline	−515·28159	181·7	191·0	−3·06	−2·90
4,4′-Biphenol	−609·96327	177·7	187·8	−3·83	−2·93
Benzidine	−570·30344	200·6	213·5	−4·85	−4·12

[a] All guests have been verified as ground-state minima by frequency analysis.

Table 2. Guest structure and UV–VIS binding data in CH_3CH at 298 K

Guest	R	K (l mol^{-1})	ε (l mol^{-1} cm^{-1})	λ_{max} (nm)
5	—OH	18	670	473
9	—O⁄⁄OH	340	479	472
10	—O⁄⁄O⁄⁄OH	3400	434	465
11	—O⁄⁄OCH_3	290	470	469
12	—O⁄⁄O⁄⁄OCH_3	3200	210	468
13	—O⁄⁄	28	389	478
14	—O⁄⁄O⁄⁄	320	212	465
15	—O⁄⁄O⁄⁄SH	180	492	468
16	—O⁄⁄⁄⁄⁄⁄OH	54	555	477
17	⁄⁄O⁄⁄O⁄⁄OH	3200	3817	330
18	—O⁄⁄⁄⁄⁄⁄	22	371	479
19	—O⁄⁄O⁄⁄O⁄⁄SH	1200	314	460

points for energy minimization for the benzene–$\mathbf{1}^{4+}$ complex. Only three supramolecular complexes were computed in vacuum for this particular system, as shown in Figure 3. The first complex has a binding enthalpy of $-2{\cdot}29$ kcal-mol^{-1} with benzene centrosymmetrically located within the cyclophane cavity. This configuration is the least stable of the three, but is probably the most relevant structure, since the binding association should be dominated by

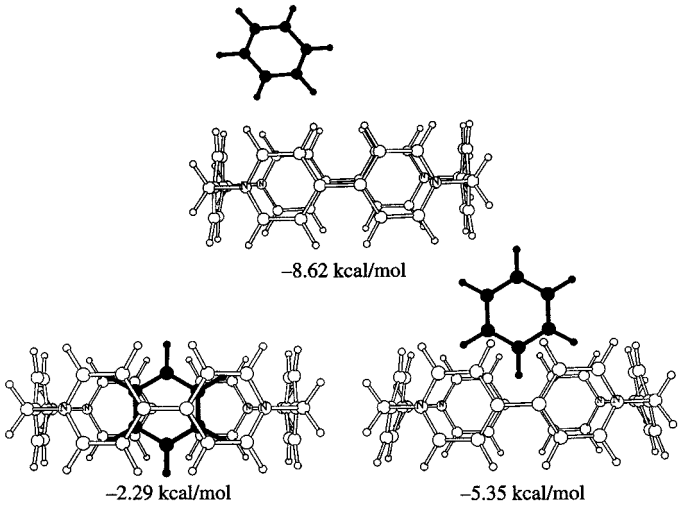


Figure 3. Three conformations and complexation energies of benzene and $\mathbf{1}^{4+}$ computed using PM3

interactions originating from the cyclophane cavity. The second complex has benzene slightly displaced (1–2 Å) along the axis of entry through $\mathbf{1}^{4+}$. The complexation enthalpy of this configuration is more favorable at $-5{\cdot}35$ kcal mol^{-1}. As discussed later, the possible origin of additional stability is that an artificial interaction with the acidic α- and β-protons of the bipyridinium units of the cyclophane occurs owing to the lack of solvent interaction with the cyclophane host. Finally, the third supramolecular complex is one where benzene is completely removed from the cavity region and strongly interacts ($-8{\cdot}62$ kcal mol^{-1}) with the α- and β-protons on a paraquat group of the cyclophane. Again, the strength of this binding would be reduced with the presence of solvent, since acetonitrile would effectively compete for the acidic protons. Almost all of the 1,4-substituted phenyl guests followed this pattern of behavior in producing the three general classifications of complexes. Since our interest is to better understand the non-covalent interactions that govern the phenomena of inclusion complexation, the data pertaining to the configuration of maximum penetration of the guest into the host was used as the basis of our interpretations.

Energy minimizations were carried out and compared between the PM3, AM1 and RHF/STO-3G calculations. One complex involving **5** and $\mathbf{1}^{4+}$ was energy minimized using several levels of theory, and the difference between the computed PM3 and RHF/STO–3G interaction energies was 1·4 kcal mol^{-1}. Other comparisons between *ab initio* and semiempirical treatments of complexes involving **6**, **7** and **8** with the $\mathbf{1}^{4+}$ receptor result with stronger energies of binding from the *ab inito* calculations by approximately the same amount of energy. In addition, the PM3 method gives a slightly more symmetric complex than that produced by the RHF/STO–3G method. Only the PM3 method (compared with MNDO and AM1) yielded stable inclusion complexes bound in the $\mathbf{1}^{4+}$ cavity for all of the guests considered. MNDO produced wildly distorted complexes, none of which were inclusion complexes, and often AM1 computations resulted in 'lid-like' complexes where the guest would cover the entrance of the cyclophane cavity. The PM3 method was therefore selected for the remaining computations owing to favorable structural and energetic comparisons with experimental and *ab inito* data.

In order to construct the elongated guest complexes, the hydroquinone–cyclophane complex was minimized and then the side arms were added visually to the guest structure. Care was taken to maximize the favorable electrostatic interactions between the ethyleneoxy oxygens of the guest and the exterior of $\mathbf{1}^{4+}$. In other words, the oxygen lone pairs were placed and directed towards the α- and β-protons of the bipyridinium units of $\mathbf{1}^{4+}$. The resulting complex was then minimized using the PM3 method. A detailed search of the accessible configurations was not attempted. By maximizing the strong electrostatic interaction between the guest and host, one of the lowest possible energy complexes was almost certainly identified and a qualitative view of the important intermolecular interactions could be made. A few starting geometries were tried for the elongated guests in order to qualitatively assess the conformational space of the system. The energies of the different minimizations for the same guest were roughly equal (within 6% of the total interaction energy), although the side arms were notably flexible and variable in their final conformation about the host. In all cases, the central aromatic core of the elongated guests resided in the cavity of the host and the side arms wrapped around the cyclophane after the energy minimization.

The UV–VIS titrations of host $\mathbf{1}^{4+}$ with the substituted 1,4-phenyl and 4,4′-biphenyl guests (Table 1) yield binding constants which show that nitrogen substituted aromatic molecules bind with greater affinity to $\mathbf{1}^{4+}$ than oxygen substituted guests, and that 4,4′-substituted biphenyl molecules bind to $\mathbf{1}^{4+}$ better than 1,4-substituted phenyl derivatives. The traditional ideas of donor–acceptor interactions in these systems typically do not hold since combinations of the best donor substituents on the same guest do not always give the best cyclophane binders. In addition, 4,4′-substituted biphenyl systems have less localized electron density than the phenyl systems, yet are better guests for $\mathbf{1}^{4+}$. Consequently, some property other than charge transfer must be governing the binding, a property of the system as a whole that takes into account not only the number and type of substituents, but how they interact with each other and with the ring system to which they are attached.

A direct comparison between the experimental free energies and PM3 computed enthalpies of binding (vacuum) results in a moderate correlation when simultaneously considering all of the possible guest complexes. In the event that multiple complexes were identified for an individual guest, the resulting energies of binding for each minimized conformation were averaged and then compared with experiment. In this work we consider only carbon-, nitrogen-, oxygen- and chlorine-containing guests. In previous reports, the binding energies from sulfur and fluoride molecular guests were included.[7] Methodological problems associated with the semiempirical treatment of these specific atoms could skew correlations between the experimental and computed binding energies, and thus they were removed from the current data set. In vacuum, the square of the linear correlation coefficient, r^2, also known as the coefficient of determination, is 0·63 for 17 points, as shown in Fig. 4. As such, 63% of the variance in the computed binding energies linearly correlates with the experimental data. Comparison between vacuum calculations and experimental determination of the binding energies shows that the computed enthalpies of complexation are about three times greater than the free energies of complexation found by the UV–VIS experiments. The theoretical binding energies are determined by subtracting the energies computed for the isolated guest and the host from the energy of the supramolecular system. The overestimated binding energies and the moderate correlation between the experimental and computational binding constants could be influenced by the

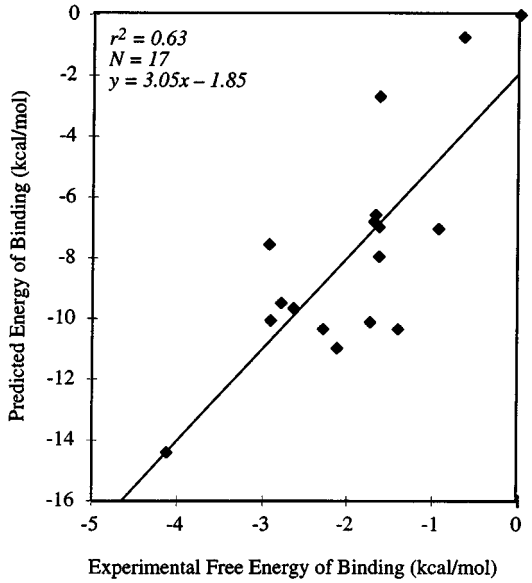


Figure 4. PM3 predicted enthalpies of binding compared with the experimental free energies of binding. The supramolecular model did not include any solvation

absence of counterions and solvent,[24] incomplete description of the conformation distributions,[25] level of theory used for evaluation[26] or by a constant entropic term.

Solvation and cavity interactions

The effect of solvent was accounted for by systematically adding solvent molecules to $\mathbf{1}^{4+}$. A limited number of acetonitriles were added (stepwise) to satisfy the strong interactions of the bipyridinium α- and β-protons. Eight acetonitriles are required to interact with the eight α-protons. Four more acetonitriles are required to interact with the β-protons in a bifurcated manner, as shown in Fig. 5. We decided to treat all the complexes using the same number of acetonitriles to provide a consistent approximation of the first solvation shell. A secondary reason for stopping at the first solvation shell is the computational cost of such calculations. For example, the complex of $\mathbf{1}^{4+}$, biphenol and 12 acetonitriles involves 454 electrons and 438 basis functions using PM3. Addition of a complete second solvation shell would be beyond reasonable reach of available computational resources.

The computed enthalpic energy of binding between benzene and $\mathbf{1}^{4+}$ is $-5{\cdot}35$ kcal mol^{-1} with no solvent, and $-4{\cdot}03$, $-3{\cdot}35$, $-3{\cdot}06$ and $-1{\cdot}67$ kcal mol^{-1} with two, four, six and twelve acetonitriles, respectively. In this particular case, the agreement between theory and experimental binding energies is within $0{\cdot}01$ kcal mol^{-1}, but in general, the computed binding enthalpy is within 1 kcal

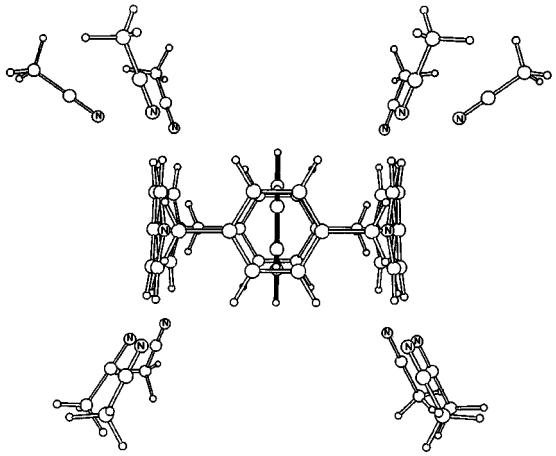


Figure 5. Supramolecular complex of 12 acetonitriles, benzene and $\mathbf{1}^{4+}$

mol^{-1} of the experimental free energy of binding. The computed enthalpies of complexation, when compared with the experimental free energies, result in a slightly better correlation coefficient of $0{\cdot}67$, but more importantly the slope decreased to $0{\cdot}96$, as shown in Fig. 6. Thus, the first 12 acetonitriles as the first solvation sphere can be used to approximate effectively the energetic consequences of solvation included in our computational model.

A concern of the study was the lack of a strong correlation coefficient between the predicted and observed

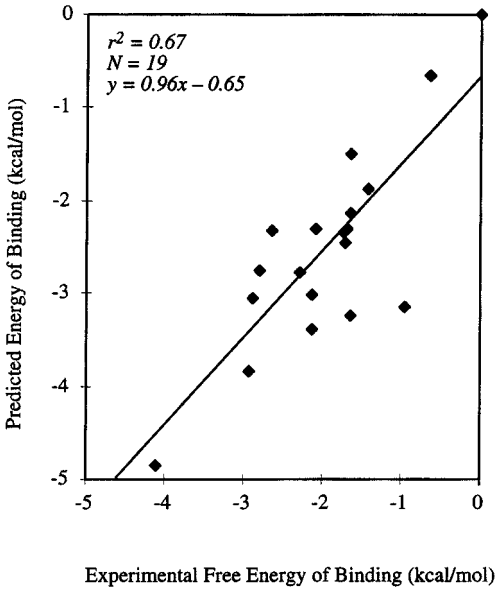


Figure 6. PM3 predicted enthalpies of binding compared with the experimental free energies of binding. The supramolecular model included 12 acetonitrile molecules

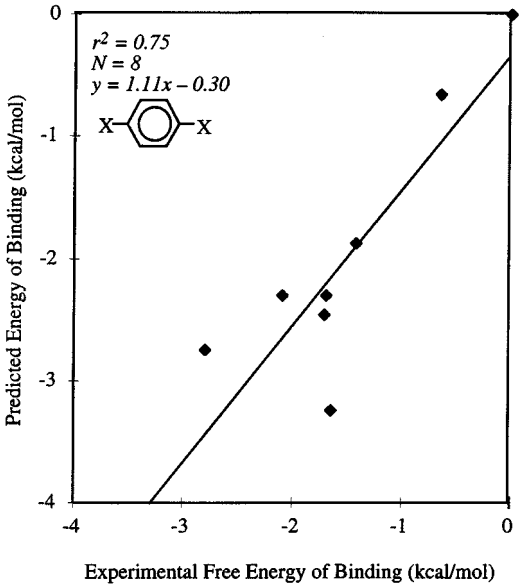


Figure 7. PM3 predicted enthalpies of binding compared with the experimental free energies of binding. The supramolecular model included 12 acetonitriles and the 1,4-substituted phenyl guests

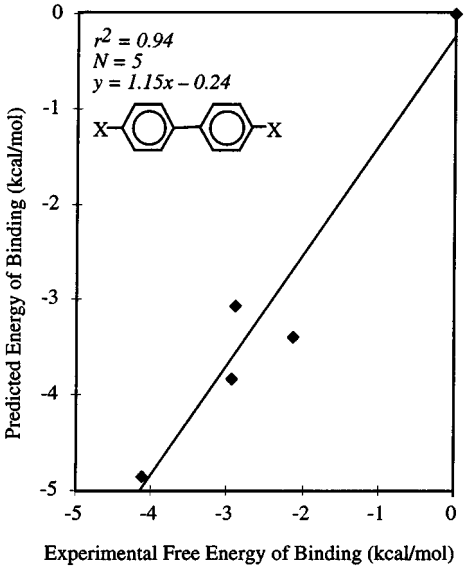


Figure 8. PM3 predicted enthalpies of binding compared with the experimental free energies of binding. The supramolecular model included 12 acetonitriles and the 4,4′-substituted biphenyl guests

binding data for all of the complexes studied. The molecular guests were divided into 1,4-substituted and 4,4′-substituted groups. Furthermore, each class could be subdivided into mono- and disubstituted systems. Comparison between predicted and observed binding data was carried out based on the four different classes of molecular guests. The results were striking. Eight 1,4-phenyl-substituted guests gave a coefficient of determination of 0·75, which is a substantial improvement over the value obtained when all the guests were considered, as shown in Fig. 7. In addition, the 4,4′-substituted biphenyl guests yielded a coefficient of determination of 0·94 using the five available points, as shown in Fig. 8. A detailed comparison of the mono-substituted phenyls produced almost no correlation between the experimental and computed data. The resulting coefficient of determination was below 0·3. The lack of correlation could result from a number of factors, most probably due to the inadequate description of multiple complex configurations, or the accuracy of determining very weak binding constants (less than 25 l mol^{-1}). When the binding constants are of moderate strength, we find that strong correlations between the theoretical and experimental binding data result and, as a consequence, we can accurately predict the binding energies of structurally related molecules.

Exterior 1^{4+} interactions with guest side arms

Most of the applications of host $\mathbf{1}^{4+}$ involve guests that are elongated in some way with side arms of varying functionality, but usually these side arms are ethyleneoxy chains. These chains are used to attach other groups to the guests without interfering with the site of complexation. It is important, therefore, to understand how this modification modulates the association with the host. Many factors in these seemingly innocuous chains could potentially exert major influences on the association process. The length of the chain, type of functionality along the chain and the number and position of the functionality could all have some effect on the complex stabilization. All of these factors were taken into consideration and a set of systematically modified elongated guests were designed and synthesized around a common core in order to try to separate these different contributions.

Table 2 shows the structure of the elongated guests used in this study and the relevant information from the UV–VIS binding studies with $\mathbf{1}^{4+}$. Evidence showing that increasing the length of an attached ethyleneoxy chain on an aromatic guest increases the binding constant can be found in the literature along with crystal structures suggesting interaction between the ethyleneoxy side arms and the host.[27] How the side arms are interacting with the host is not exactly clear, however. Guests **5**, **13** and **18** were synthesized to determine if elongation of a guest with aliphatic side arms with no heteroatoms is enough to increase the binding constant. The data show that this is not a factor in the association with $\mathbf{1}^{4+}$. The strong increase in association seen with the ethyleneoxy chains (guests **5**, **9** and **10**) is therefore due to the oxygen atoms and not simply the length of the chain. The interaction of these oxygen atoms with the host could conceivably take on many forms. They could

interact with the positively charged nitrogen atom of the bipyridinium rings or a more generalized electrostatic interaction between the positive charge delocalized over the rings and the oxygens could be happening. Another possibility is that the oxygen atoms are taking part in some sort of hydrogen bonding type association with acidic protons on the host. Bipyridinium is known to have relatively acidic protons and our cavity investigations showed how the acetonitrile molecules aligned themselves in selective interactions with the α- and β-protons of the bipyridinium units. These facts were very suggestive. PM3 semiempirical molecular orbital calculations suggested that this was the cause of the ethyleneoxy association with the host as the closest distances of approach of the arms to the host are from the oxygen atoms on the arms to the protons on the bipyridinium units of the host, not the nitrogen atoms or the π faces of the rings. The increase in the binding constant of the guests elongated with ethyleneoxy functionality is seen to die off after the first few ethyleneoxy units.[26] This can be understood by noting that after the protons on the paraquat units of the host have been 'solvated' by the oxygen atoms of the guest (Figure 9), elongating the arms with more ethyleneoxy functionality becomes useless because the sites of attraction (the paraquat protons) are already occupied. This hydrogen bonding-like interaction prompted us to investigate the involvement of the terminal hydroxyl group of these guests for possible effects. Comparing guests **9** with **11** and **10** with **12** showed that methylation of the hydroxyl group had little effect on the binding constant and thus no effect due to the terminal hydroxyl hydrogen atom was noted. The polarizability of the heteroatom might also mitigate the association of the arms with the host so we investigated guest **15** and compared its binding constant with that of guest **10**. The lower value for the sulfur containing guest suggests that higher polarizability does not help association and implies that the hardness of the oxygen is important, again pointing towards hydrogen bonding-like behavior.

Next to be investigated was the positioning of these heteroatoms on the side arm. Since guests **14** and **16** both have two oxygen atoms along the chain, they might be expected to associate similarly with $\mathbf{1}^{4+}$. Interestingly, the binding constant for **14** is much higher. The only difference is that the second oxygen atom is closer to the aromatic ring along the chain. The initial suggestion that the simple increase in distance is causing the difference does not seem reasonable since the chain is flexible enough for the oxygen to wrap in and interact with the host and furthermore this terminal placement allows for better possible interaction with the host. The oxygen atoms must be taking part in a chelate effect in which nearby oxyen atoms direct the complexation of each other and their overall complexation is much stronger than the sum of the individual ones. The length of the chain is important only due to the extra oxygen atoms added along the chain and the position of these oxygen atoms is also critical in optimizing the overall association.

Now that the separate effects of the two parts of the elongated guests had been investigated, it became important to gauge the relative contribution of the two parts and the effect of one on the other. Guest **17** was synthesized just for this purpose. The oxygen atoms attached to the ring are here moved one methylene group away so that we can gauge the effects of the chain without any delocalization of the oxygen electron density into the ring. The similarity in the binding constant to guest **10** shows that the chain is responsible for most of the increase in binding, since the core binds so weakly. Might we be able to get away with no ring at all since the chains do all of the work? ^{1}H NMR experiments with hexa(ethylene glycol) were conducted to investigate the strength of its interaction with $\mathbf{1}^{4+}$. The lack of charge-transfer due to the absence of an aromatic ring in the guest negates the use of the UV–VIS method. Separate experiments involving excess (5 equiv.) of either the host or hexa(ethylene glycol) in CD_3CN showed no effect on the proton resonances of either compound. Therefore, the guest needs an aromatic core to position itself in the host even

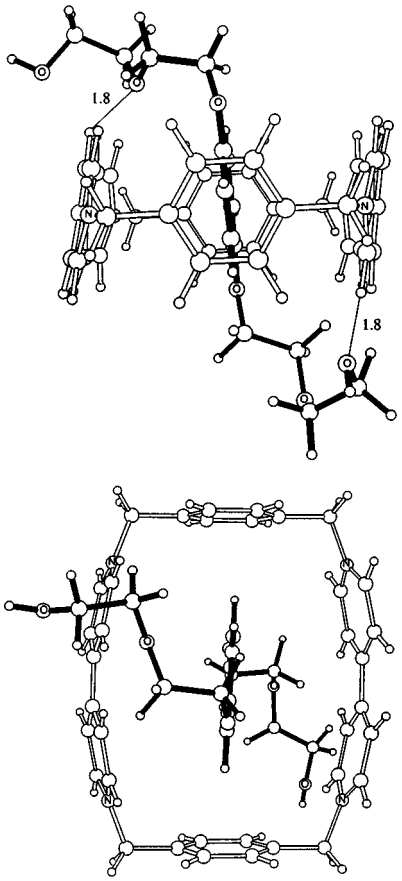


Figure 9. Two views of tan elongated hydroquinone core complexed with $\mathbf{1}^{4+}$ computed using PM3

Table 3. Variational energy decomposition using the STO-3G basis set on $\mathbf{1}^{4+}$ with guest molecules (**5**–**8**), with energies reported in kcal mol^{-1}

System	ΔE	ES	PL	EX	CT	MIX
Hydroquinone (**5**)	−3·9	−6·7	−1·2	6·8	−3·2	0·4
BSSE corrected	−1·3			8·4	−2·6	0·9
p-Phenylenediamine (**6**)	−7·3	−10·1	−1·0	6·7	−3·1	0·3
BSSE corrected	−4·2			8·6	−2·5	0·8
4,4′-Biphenol (**7**)	−7·7	−4·4	−6·8	5·3	−2·2	0·4
BSSE corrected	−5·8			6·5	−1·8	0·7
Benzidine (**8**)	−12·0	−9·4	−7·0	7·6	−3·7	0·5
BSSE corrected	−8·9			9·3	−3·0	1·2

though the ethyleneoxy chains do most of the work. This cooperative effect between the aromatic core and the glycol side arms is therefore extremely important and complements the chelate effect found with the oxygen atoms themselves.

Variational energy decomposition of intermolecular cavity interactions

Unique supramolecular structures, energetics and properties are determined by the collective strength of intermolecular bonds and their arrangements.[2] It is well known that intermolecular complexation is composed of a variety of forces, which range from moderately strong to weak noncovalent interaction energies.[28–30] Computational techniques have been developed which decompose the interaction energy between two molecular fragments into their respective non-covalent contributions. The methods have been applied to gain a deeper insight into supramolecular phenomena, such as hydrogen bonding,[31, 32a, 33] donor–acceptor (EDA) complexes,[31–33] metal–ligand interactions[34] and clustering of alkali metal cations.[35] One particular variational energy decomposition technique, the energy and charge distribution methods (ECDD) by Morokuma and co-workers,[31, 36] has proven to be a powerful tool for the direct evaluation of molecular interactions. Experimental results have indicated that van der Waals interactions, electrostatic interactions, and desolvation are significant factors in the processes of molecular recognition.[29a] In addition, there is increasing evidence that charge-transfer and electron donor–acceptor forces are negligible when compared to the effects of electrostatics upon molecular recognition.[29a] In fact, the π–cation interaction has been proposed as a basic intermolecular force, which, depending upon the molecular system, can be dominated by polarizability or electrostatics.[37] A primary goal of our study is to quantitate the components of the intermolecular forces responsible for $\mathbf{1}^{4+}$ complexes, since the current literature invokes charge-transfer to rationalize $\mathbf{1}^{4+}$ binding.[1, 27] To delineate the forces involved in the computed binding enthalpies in our study, four molecular complexes formed by the guests **5**–**8** and host $\mathbf{1}^{4+}$ were subjected to the ECDD method (Table 3). The minimized PM3 geometries of the complexes were used.

Energy decomposition provides a detailed description of the individual energy components involved in cyclophane inclusion complexation. First, the electrostatic contribution for both the substituted phenyl and biphenyl complexes with $\mathbf{1}^{4+}$ is expected to be underestimated, as reported previously for the water dimer using the STO–3G basis set.[36] Despite this expectation, the electrostatic term is computed to dominate the energetic interactions between $\mathbf{1}^{4+}$ with either **5** or **6**. In addition, the computations clearly show that the electrostatic contribution is approximately twice as large for the nitrogen-containing guests as that found with their oxygen counterparts (compare **5** with **6** and **7** with **8**). The repulsion-exchange term cancels the electrostatic stabilization provided by oxygen-substituted guests, yet only partially counterbalances the electrostatic stabilization from nitrogen-substituted systems. A significant find is that the charge-transfer contribution is relatively constant (*ca* 2 kcal mol^{-1}) for the four complexes examined. Therefore, the charge-transfer stabilization does not reflect the experimentally determined differences in binding energies, as traditionally believed.[1, 27] The energy decompositions also provide an interpretation of the extra stability observed and computed for $\mathbf{1}^{4+}$ complexes with biphenyl molecules **7** and **8** as compared with the analogous phenyl guests **5** and **6**. Polarizability was computed to be the largest computed differential property between the complexes. The contribution from polarizability increases from 1 to 7 kcal mol^{-1} on replacing the phenyl with a biphenyl guest. The delocalization resulting from extending the π-system of the guest significantly enhances the polarizability of the entire supramolecular complex. Therefore, the change in polarizability (not charge-transfer) of the supramolecular complex explains the differential binding effects that have been previously reported and experimentally observed.

Molecular polarizability

Since polarizability was deemed to control the differential binding of the $\mathbf{1}^{4+}$ supramolecular complexes, it was natural to extend the investigation to study the possibility that

individual guest properties would correlate with the computed binding energies with $\mathbf{1}^{4+}$. The 3–21G and 6–31G(D) basis sets were used to compute the electrical moments and polarizabilities of each isolated guest using restricted Hartree–Fock theory. The component of polarizability along the principal molecular (biphenyl) axis is reported in Table 1. A linear trend between the computed polarizability for each guest and the enthalpy of binding of the $\mathbf{1}^{4+}$ complex (12 acetonitriles) results, as shown in Figure 10. Highly polarizable molecules can electronically adapt to the rigid binding cavity of $\mathbf{1}^{4+}$ and this results in stronger binding energies. Several molecular guests were tested, and we find that a meaningful response in the binding energy occurs only between a polarizability of 60 and 200 Å^3. Polarizabilities outside this region have only a constant effect on the binding energies. For the first time, a direct correlation between computed molecular polarizability of the guest, within a certain window of polarizabilities, and the stability of the resulting $\mathbf{1}^{4+}$ complex has been shown.

Principle of maximum hardness

The maximum hardness of an organic molecule can provide an intuitive understanding into its chemical behavior and reactivity.[38, 39] In hardness–softness terms, the softness of a molecule can be regarded as its capacity to accept electronic charge, which is closely related to the polarizability of a molecule. Formally, the hardness (η) and the electronic chemical potential (μ) are defined as the derivative of the energy (E) for a given number of electrons (N), potential due to nuclei (ν) and any other external potential.[7] In practice, the hardness and chemical potential are related to the ionization potential and electron affinity. By invoking Koopman's theorem, the orbital energies of the highest occupied (HOMO) and lowest unoccupied (LUMO) orbitals can be used to approximate both equations. As such, the softness has been defined as the reciprocal of the hardness. Previous correlations between the hardness, polarizability, and size of atoms, molecules and clusters have been demonstrated.[39c, d] The maximum hardness of a molecule has also been shown to be an excellent measure of aromaticity.[39] In addition, the principle of maximum hardness in a chemical system is a measure of its resistance to change in electronic configuration. Other novel relationships between the cube root of the polarizability and the dipole moment for both positively and negatively charged ions have been reported.[39e]

Electronic structure calculations were carried out for over 20 substituted 1,4-phenyl and 4,4′-substituted biphenyl guests. The correlation between molecular hardness and the computed $\mathbf{1}^{4+}$ binding affinities is not as good as found with the molecular polarizability. The computed trend between molecular hardness of the individual guest molecules and the binding energies of $\mathbf{1}^{4+}$ complexes is consistent with the idea that guests which resist changes in their electronic configuration also result in low binding energies with $\mathbf{1}^{4+}$.

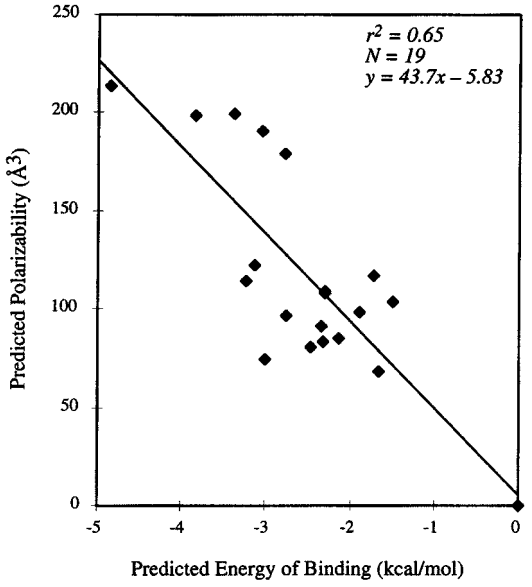


Figure 10. Comparison of the PM3 computed binding energies and the 6–31G(D) computed molecular polarizability of the guests

CONCLUSIONS

The cooperativity between cavity and external interactions involving the tetracationic cyclophane receptors $\mathbf{1}^{4+}$–$\mathbf{4}^{4+}$ and 1,4-phenyl and 4,4′-substituted biphenyl guests is primarily determined by the combination of two main interaction modes involving aromatic stacking of the guest within the cyclophane cavity and external interactions between guest side arms and the exterior of the cyclophane. A balance between cavity and external forces results in supramolecular association and is shown to change depending upon the functionality and substitution of the guest. The primary basis for cavity binding within $\mathbf{1}^{4+}$ is found to be short-range stabilizing electrostatic forces complemented by small amounts of polarizability and charge-transfer. In contrast, complexes of substituted 4,4′-biphenyl guests and $\mathbf{1}^{4+}$ are determined by almost equal amounts of polarizability and electrostatics. Two main chemical factors which rationalize the differential binding have been identified and linked to the (1) Lewis basicity of nitrogen vs oxygen-containing substituents and (2) electron delocalization in the biphenyl vs phenyl units of the guest molecule. A new supramolecular host, $\mathbf{2}^{4+}$, was synthesized in which a pentacycloundecane unit replaces one of the xylyl groups. Computed $\mathbf{2}^{4+}$ results emphasize the ideal geometry and electronic nature of the $\mathbf{1}^{4+}$ molecular receptor for aromatic guests. The role of solvent has been addressed and a first solvation shell of 12 acetonitriles has been shown to account for many of the observed structural and energetic properties of the complexes. For the first time, we have shown a direct

correlation between computed molecular properties of the guest and the strength of the resulting $\mathbf{1}^{4+}$ complex. Molecular polarizability and maximum hardness of the guest can be used as predictive tools in the design of new complexes, rotaxanes and catenanes. The binding of elongated aromatic core molecules to the cyclophane hosts is governed almost entirely by the heteroatoms on the side arms. Their number and placement along the chain are crucial to the association with the host. Not only do the oxygen atoms of the chain take part in a strong chelation effect, but also the aromatic core and the side arms have to work in conjunction. Cooperativity between the core and the side arms is essential since neither one of the components alone binds strongly to the host. While $\mathbf{1}^{4+}$ is a unique receptor, the methods and conclusions presented here to understand the structure and energetics of the *intermolecular bond* are applicable to more generalized situations in supramolecular chemistry.

ACKNOWLEDGMENTS

We are grateful to the National Science Foundation (to A. E. K., Grants CHE-9304262 and 9633434), the Summer Award in Natural Science and Engineering and the University Research Council from the University of Miami (to J.D.E.), the Petroleum Research Fund (to J.D.E., Grant PRF 30918-G4), and the Department of Defense (to J.D.E., Grant DAAH04-96-1-0311) for financial support of this research.

REFERENCES

1. B. Odell, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *Angew. Chem., Int. Ed. Engl.* **27**, 1547 (1988).
2. For two recent reviews, see (a) D. B. Amabilino and J. F. Stoddart, *Chem. Rev.* **95**, 2725 (1995); (b) D. Philip and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.* **35**, 1154 (1996).
3. T. T. Goodnow, M. V. Reddington, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc.* **113**, 4335 (1991).
4. A. R. Bernardo, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc.* **114**, 10624 (1992).
5. (a) S. A. Staley and B. D. Smith, *Tetrahedron Lett.* **37**, 283 (1996). (b) M. A. Lipton, *Tetrahedron Lett.* **37**, 287 (1996).
6. E. Córdova, R. A. Bissell and A. E. Kaifer, *J. Org. Chem.* **60**, 1033 (1995).
7. R. Castro, M. J. Berardi, E. Córdova, M. Ochoa de Olza, A. E. Kaifer and J. D. Evanseck, *J. Am. Chem. Soc.* **118**, 10257 (1996).
8. R. Castro, K. R. Nixon, J. D. Evanseck and A. E. Kaifer, *J. Org. Chem.* **61**, 7298 (1996).
9. For instance, see R. A. Bissell, E. Córdova, A. E. Kaifer and J. F. Stoddart, *Nature* (*London*) **369**, 133 (1994).
10. The accessible redox chemistry of host $\mathbf{1}^{4+}$ has been utilized to design voltammetric molecular sensors: see, for instance, (a) A. R. Bernardo, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc.* **114**, 10624 (1992); (b) M. T. Rojas and A. E. Kaifer, *J. Am. Chem. Soc.* **117**, 5883 (1995).
11. *Spartan 4.0 and 4.1*. Wavefunction, Irvine, CA.
12. M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, *Gaussian 94, Revision B.3*. Gaussian, Pittsburgh, PA (1995).
13. M. Peterson, University of Toronto and R. Poirier, Memorial University of Newfoundland, *Monstergauss* (1991).
14. W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*. Wiley, New York (1986).
15. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.* **99**, 4899 (1977).
16. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.* **107**, 3902 (1985).
17. J. J. P. Stewart, *Comput. Chem.* **209**, 221 (1989).
18. H.-J. Schneider, *Angew. Chem., Int. Ed. Engl.* **30**, 1417 (1991).
19. W. L. Jorgensen, Yale University, personal communication.
20. For example, see (a) W. Thiel, *Tetrahedron Lett.* **44**, 7393 (1988); (b) D. A. Smith, C. W. Ulmér II and M. J. Gilbert, *J. Comput. Chem.* **13**, 640 (1992); (c) P. Scano and C. Thomson, *J. Comput. Chem.* **12**, 172 (1991); (d) J. M. L. Martin, J. P. François and R. Gijbels, *J. Comput. Chem.* **12**, 52 (1991).
21. M. Ochoa de Olza, C. A. Davey and J. D. Evanseck, in preparation.
22. (a) H. Goto and E. Osawa, *J. Am. Chem. Soc.* **111**, 8950 (1989); (b) H. Goto, E. Osawa and M. Yamato, *Tetrahedron* **49**, 387 (1993).
23. A. E. Kaifer and J. D. Evanseck, to be published.
24. (a) A. Mirzoian and A. E. Kaifer, *J. Org. Chem.* **60**, 8093 (1995); (b) T. Z. M. Denti, W. F. van Gunsteren and F. Diederich, *J. Am. Chem. Soc.* **118**, 6044 (1996).
25. H. Frauenfelder and P. G. Wolynes, *Phys. Today* 58 (1994).
26. J. W. Ochterski, G. A. Petersson and K. B. Wiberg, *J. Am. Chem. Soc.* **117**, 11299 (1995).
27. (a) P. L. Anelli, P. R. Ashton, R. Ballardini, V. Balzani, M. Delgado, M. T. Gandolfi, T. T. Goodnow, A. E. Kaifer, D. Philp, M. Pietraszkiewicz, L. Prodi, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vicent and D. J. Williams, *J. Am. Chem. Soc.* **114**, 193 (1992).
28. (a) K. Morokuma and K. Kitaura, in *Molecular Interactions*, Vol. 1, edited by H. Ratajczak and W. J. Orville-Thomas. Wiley, Chichester (1980). (b) A. C. Benniston, A. Harriman and V. M. Lynch, *J. Am. Chem. Soc.* **117**, 5275 (1995).
29. (a) C. A. Hunter, *Chem. Soc. Rev.* 101 (1994); (b) H. A. Hunter and J. K. M. Sanders, *J. Am. Chem. Soc.* **112**, 5525 (1990); (c) T. Dahl, *Acta Chem. Scand.* **48**, 95 (1994); (d) G. R. Desiraju, *Acc. Chem. Res.* **29**, 441 (1996).
30. A. J. Stone, *The Theory of Intermolecular Forces*. Clarendon Press, Oxford (1996).
31. (a) K. Morokuma, *Acc. Chem. Res.* **10**, 294 (1977); (b) W. Chen and M. S. Gordon, *J. Phys. Chem.* **100**, 14316 (1996).
32. (a) H. Umeyama and K. Morokuma, *J. Am. Chem. Soc.* **99**, 1316 (1997); (b) A. Sevin and C. Giessner-Prettre, *Tetrahedron* **50**, 5387 (1994).
33. E. D. Glendening and A. Streitwieser, *J. Chem. Phys.* **100**,

2900 (1994).
34. R. Frey and E. R. Davidson, *J. Chem. Phys.* **90**, 5555 (1989).
35. E. D. Glendening, *J. Am. Chem. Soc.* **118**, 2473 (1996).
36. (a) K. Morokuma, *J. Chem. Phys.* **55**, 1236 (1971); (b) K. Kitaura and K. Morokuma, *Int. J. Quantum Chem.* **10**, 325 (1976).
37. D. A. Dougherty, *Science* **271**, 163 (1996).
38. W. Yang and R. G. Parr, *Proc. Natl. Acad. Sci. USA* **82**, 6723 (1985).
39. (a) P. K. Chattaraj, A. Cedillo, R. G. Parr and E. M. Arnett, *J. Org. Chem.* **60**, 4707 (1995); (b) R. G. Parr, W. Yang, *Density-Functional Theory of Atoms and Molecules*. Oxford University Press, New York (1989); (c) T. K. Ghanty and S. K. Ghosh, *J. Phys. Chem.* **97**, 4951 (1993); (d) T. K. Ghanty and S. K. Ghosh, *J. Phys. Chem.* **100**, 12295 (1996); (e) S. Pal and A. K. Chandra, *J. Phys. Chem.* **99**, 13865 (1995); (f) G. J. Makov, *J. Phys. Chem.* **99**, 9337 (1995).

