Unexpected Roles of Guest Polarizability and Maximum Hardness, and of Host Solvation in Supramolecular Inclusion Complexes: A Dual Theoretical and Experimental Study

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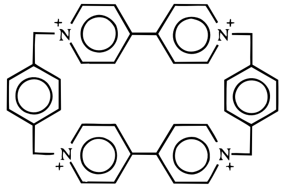
Abstract: The origin of differential binding affinity and structural recognition between the inclusion complexes of cyclobis(paraquat-*p*-phenylene), $\mathbf{1}^{4+}$, and 1,4-substituted phenyl or 4,4′-substituted biphenyl derivatives has been jointly determined by spectrometric techniques and ab initio and semiempirical molecular orbital methods. The unusual boxed geometry and tetracationic charge distribution in $\mathbf{1}^{4+}$ are key molecular features which produce strong intermolecular interactions with guest and solvent molecules. Solvation was addressed by including up to 12 acetonitrile molecules in the theoretical model, which realigned the predicted gas-phase supramolecular structures and energies into excellent agreement with experiment. The computed complexation enthalpies, ΔH_{bind}, from the semiempirical molecular orbital PM3 method are on average within 1 kcal/mol of the experimental free energy binding data collected from absorption spectroscopy in acetonitrile. In addition, the computed geometric penetration and positioning of $\mathbf{1}^{4+}$/benzidine and $\mathbf{1}^{4+}$/4,4′-biphenol complexes are consistent with that reported from NMR NOE data. The partitioning of self-consistent field complexation energies from both classical and quantum forces has been determined by using Morokuma's variational energy decomposition technique. It was determined that the primary basis for the molecular recognition between 1,4-substituted phenyl guests and $\mathbf{1}^{4+}$ is short-range stabilizing electrostatic forces complemented by small amounts of polarizability and charge-transfer. In contrast, the recognition force between 4,4′-substituted biphenyl guests and $\mathbf{1}^{4+}$ is dominated by polarizability with a small contribution from electrostatics. Therefore, the balance between molecular polarizability and electrostatics controls the differential binding affinity and structural recognition with $\mathbf{1}^{4+}$. For the first time, we report that individual molecular properties of substituted guests correlate with the binding energies of corresponding $\mathbf{1}^{4+}$ inclusion complexes. Direct correlations between the $\mathbf{1}^{4+}$ binding energies and the computed molecular polarizability, maximum hardness, softness, and electronegativity of the guest have been identified. It is now plausible to consider the design and construction of new supramolecular assemblies based upon a few select molecular properties of the constituent molecules.

Introduction

Recent advances in supramolecular chemistry have had a major impact on the understanding of structural and reactive aspects of biological chemistry and the design and manipulation of new materials.[1] The single concept common throughout supramolecular chemistry revolves around the study of molecular association. More specifically, the clear depiction of the structural, energetic, and dynamic character of the *intermolecular bond* can provide insight into the fundamental forces required for the rational design of nanoscale molecular devices and the spontaneous assembly of supramolecular systems.

Our interest in understanding intermolecular binding forces derives from the recent work with the tetracationic cyclophane receptor cyclobis(paraquat-*p*-phenylene), $\mathbf{1}^{4+}$.[2−6] The $\mathbf{1}^{4+}$ receptor has gained substantial prominence as a versatile molecular host and as a fundamental component of a large number of catenanes and rotaxanes.[3] As a receptor, $\mathbf{1}^{4+}$ shows considerable affinity for molecules containing electron-rich aromatic rings. It has been shown[3a] that $\mathbf{1}^{4+}$ forms stable inclusion complexes with a variety of π-donors, in which the aromatic ring of the donor guest penetrates the cavity of the host, establishing a balance of favorable and repulsive interactions between the host's electron deficient bipyridinium (paraquat) groups and the electron-rich ring(s) of the guest. In spite of the numerous



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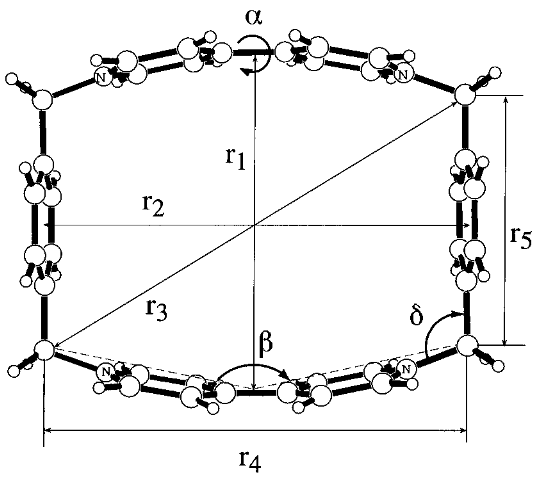
investigations in which host **1**$^{4+}$ has played a crucial role, the significant aspects of its selectivity and binding properties determined by intermolecular association are still poorly understood. For instance, charge-transfer interactions were originally thought to dominate the overall stability of **1**$^{4+}$ inclusion complexes, but recently have been determined to have a rather diminished role since *p*-phenylenediamine (PDA)[4] and benzidine (BZ)[3d,5] are two π-donor guests for which the order of π-donating ability (PDA > BZ) is opposite that of the stability of the corresponding inclusion complexes with **1**$^{4+}$ (BZ > PDA).

Given the importance of host **1**$^{4+}$ in the design and synthesis of electrochemically and chemically switchable rotaxanes,[6] photoactive rotaxanes,[3e] and other molecular devices,[7] it is both appropriate and timely to address the primary intermolecular factors which determine the stability of its inclusion complexes. It is our intention to evaluate the composition of intermolecular bonding which governs the overall strength and structure found in these particular supramolecular systems. We employed ab initio molecular orbital theory along with variational energy decomposition techniques to quantify the noncovalent forces prevalent in the inclusion complexes of **1**$^{4+}$. The long-term goal of this work is to provide a refined and more rational methodology to design new high-performance molecular devices.

Computational and Experimental Procedure

All calculations were performed using the SPARTAN 4.0/4.1,[8] GAUSSIAN 92/94,[9,10] and MONSTERGAUSS[11] software packages on an IBM RS/6000 Model 590 workstation equipped with 512 Mbyte of physical memory and 9 Gbyte of disk space. 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,[12] or with the MNDO, AM1, or PM3 semiempirical method.[13−15] No assumptions were made concerning the symmetry of the complexes, unless stated otherwise. Frequency calculations demonstrate that each complex is a true minimum on the potential energy surface. The details of each calculation are provided in the supporting information.

We have conducted UV−vis binding studies and compiled a comprehensive list of binding energies and charge-transfer band λ_{max} values for a variety of substituted phenyl and biphenyl compounds. UV−vis binding studies were conducted on a Shimadzu UV-2101PC computer-controlled scanning spectrophotometer with a temperature control module. In a typical experiment, a 0.8 mM cyclophane solution in dry CH_3CN was titrated with a 200 mM stock solution of the guest also containing 0.8 mM cyclophane to maintain a constant cyclophane concentration. Some guests were run at lower concentrations due to solubility limitations. Absorption readings were taken at λ_{max} for the charge-transfer band of the complex, and the absorption was corrected for any overlapping absorption of the guest in that region by blank subtraction when necessary. The data were fit to a binding isotherm equation using a least squares algorithm as described elsewhere.[3d]



α = (0.0, 32.4, 29.4, 19.9)
β = (156.2, 154.9, 158.6, 167.8)
δ = (109.8, 111.6, 110.4, 108.4)
r1 = (7.87, 7.47, 7.69, 6.82)
r2 = (9.81, 9.81, 10.04, 10.32)
r3 = (11.38, 11.34, 11.43, 11.52)
r4 = (9.79, 9.79, 9.83, 9.91)
r5 = (5.80, 5.81, 5.83, 5.76)

Figure 1. Distances (Å) and angles (degrees) of **1**$^{4+}$ given by PM3, AM1, RHF/6-31G(D), and X-ray crystallography.

Results and Discussion

Cyclobis(paraquat-*p*-phenylene). We have computed the gas-phase structure of **1**$^{4+}$ at several levels of theory and have made a detailed comparison with the X-ray crystal structure, as shown in Figure 1. The crystal structure of **1**$(PF_6)_4(MeCN)_3$ has been previously reported.[2] The solid state structure is most likely a good representation of **1**$^{4+}$ in the condensed liquid and gas phases since its cyclic constraints render an inflexible molecular framework with severely limited conformational freedom. Our first goal was to establish a level of theory which provided trustworthy structural information on the cyclophane as compared to X-ray crystallography.

The strengths and weaknesses of semiempirical methods have been reported.[16−22] The general conclusion derived from the existing literature is that it is necessary to critically examine the computational methods on model systems closely related to the chemistry of interest. Thus, we have compared MNDO, AM1, PM3, and ab initio methods against experimental structural data for 4,4′-substituted biphenyl systems.[23] Gas-

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Table 1. Computed Energies of Complexation between Monosubstituted Phenyl Guests and **1**$^{4+}$ [a]

system	no. of MeCN molecules	type	H_{guest}	H_{complex}	ΔH_{bind}	ΔG_{bind}	K	$\lambda_{\max}$	ϵ
benzene	0	π	23.455	1092.101	−2.29				
	4	π		1110.285	−1.39				
	12	π		1174.158	−0.52				
	0	σ		1089.044	−5.35				
	2	σ		1096.768	−4.03				
	4	σ		1108.316	−3.35				
	6	σ		1115.437	−3.06				
	12	σ		1173.003	−1.67	−1.68	17[b]	290	1295
toluene	0	σ	14.090	1078.063	−6.96				
	12	σ		1163.166	−2.14	−1.64	16[b]	319	1675
phenol	2	σ[c]	−21.672	1047.282	−8.39				
	2	σ[d]		1047.835	−7.84				
	12	σ[d]		1126.533	−3.01	−2.14	37	411	587
anisole	0	σ[e]	−14.553	1046.240	−10.14				
	12	σ[e]		1132.798	−3.87				
	12	σ[f]		1134.316	−2.35	−1.74	19	410	600
aniline	0	σ[g]	21.295	1082.587	−9.65				
	12	σ[g]		1169.210	−3.30				
	0	σ[h]		1082.587	−9.65				
	12	σ[h]		1171.148	−1.37				
	12	av[i]		1170.179	−2.33	−2.64	86	496	556
tert-butylbenzene	0	π	0.321	1064.246	−7.01				
	12	π		1149.033	−2.51				
	0	σ		1062.964	−8.29				
	12	σ		1148.400	−3.14	−0.95	5[b]	333	1040
thiophenol	2	σ	27.670	1095.220	−9.80				
	12	σ		1176.451	−2.44				
thioanisole	2	σ	23.243	1090.020	−10.57				
	12	σ		1170.972	−3.49	−1.71	18	445	656

[a] Binding is described as π type if it is truly an inclusion complex and as σ type if it is centered about but not completely inserted into the cyclophane. Energies are reported in kcal/mol, association constants in M^{-1}, $\lambda_{\max}$ in nm, and ϵ in $M^{-1}\,cm^{-1}$. [b] Data from Benniston, A. C.; Harriman, A.; Philp, D.; Stoddart, J. F. *J. Am. Chem. Soc.* **1993**, *117*, 5298. [c] The OH substituent is oriented away from the **1**$^{4+}$ cavity. [d] The OH substituent is oriented toward the **1**$^{4+}$ cavity. [e] The OMe substituent is oriented toward the **1**$^{4+}$ cavity. [f] The OMe substituent is oriented away from the **1**$^{4+}$ cavity. [g] The NH_2 substituent is oriented away from the **1**$^{4+}$ cavity. [h] The NH_2 substituent is oriented toward the **1**$^{4+}$ cavity. [i] The averaged value of two conformations is compared with experiment.

phase electron diffraction experiments[24] and high-level ab initio calculations[25] show that the twisted biphenyl conformations (~44°) are separated by coplanar and perpendicular transition structures. MNDO yields an incorrect potential energy surface, whereas AM1 and PM3 give qualitatively correct structures and energies.[23]

Our computational model for **1**$^{4+}$ involves the D_2 and C_1 structures. Frequency analysis reveals that the computed structures from each point group are local minima (except MNDO). The important geometric features of **1**$^{4+}$ are summarized in Figure 1. Upon close inspection, it is clear that both the AM1 and PM3 semiempirical and ab initio methods yield satisfactory agreement with the X-ray structure. The MNDO-generated structure is strongly distorted and resulted in the least satisfactory agreement with experiment.

The model was then redefined to include four chloride anions. The computations were carried out using AM1, PM3, MNDO, and RHF/STO-3G. The effect of the counterions improved some of the obvious structural deficiencies, but introduced more geometric and energetic error than the simple **1**$^{4+}$ model. Therefore, to probe binding energies and geometries, along with the forces operating within the binding cavity, we reverted back to the gas-phase **1**$^{4+}$ computational model with no counterions.

The energy differences between the D_2 and C_1 symmetric forms of **1**$^{4+}$ are less than 1 kcal/mol (excluding MNDO). This suggests that it is possible for **1**$^{4+}$ to have a number of accessible conformational states which may contribute to the phenomenon of guest inclusion or in the dynamic transfer of **1**$^{4+}$ along the thread of a rotaxane or molecular shuttle.[6] Therefore, we employed the method of "corner flapping"[26] to exhaustively explore the possibility of **1**$^{4+}$ ring conformations using the PM3 semiempirical method. The corner flapping method exploits the reduced conformational space of cyclic structures which avoids some of the inherent problems of random and systematic search procedures. We defined the central bipyridinium and corner methylene bonds as rotatable. In all, 59 trial conformations were generated and only 1 true conformation was retained using the PM3 Hamiltonian. The resulting D_2 structure is virtually identical with that of C_1. Thus, the potential energy surface of **1**$^{4+}$ is not complicated with many energy extrema. On the other hand, the energy cost to distort the bipyridinium and *p*-xylylene torsional angles is very small. The bipyridinium torsional angle can deviate 20° before destabilizing up to 1 kcal/mol, which may contribute to the dynamic behavior of rotaxanes and molecular shuttles in solution.[27]

Aromatic Molecule−Cyclophane Inclusion Complexes. Three earlier computational studies specifically targeted the understanding of **1**$^{4+}$ complexation with small aromatic guests.[28−30] Ricketts et al. used the CFF91 force field to account for nonbonding interactions between **1**$^{4+}$ and both simple and extended aromatic guest molecules.[28] The dominant binding forces were reported to be the electrostatic interactions between

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Figure 2. Electrostatic potential plot (+250 kcal/mol) of $\mathbf{1}^{4+}$.

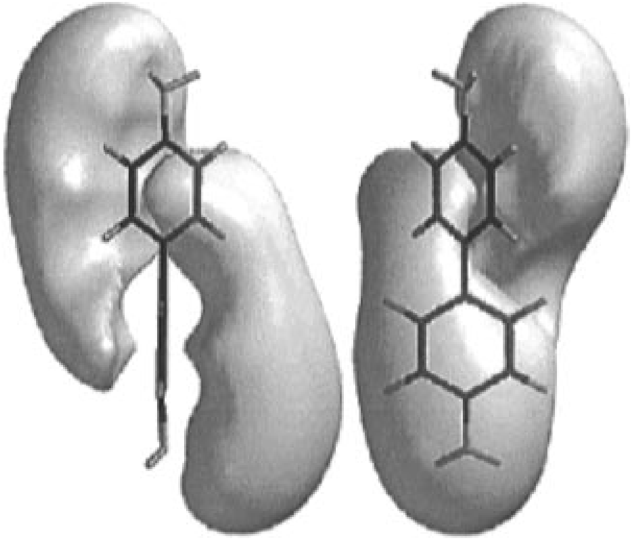
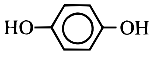


Figure 3. Electrostatic potential plot (−5 kcal/mol) of benzidine.

the phenolic oxygen lone pairs of the π-rich guest molecule and electron deficient parts of the paraquat units. Smit et al.[29] and Odell et al.[30] have applied AM1 to $\mathbf{1}^{4+}$ complexes of xylene and dicyanobenzene, and found strong electrostatic forces which yielded structures consistent with those reported by X-ray crystallography. Smit et al. also predicted that enthalpy controls the binding of complexation and not the entropy, where enthalpy changes follow electronic donor−acceptor considerations.[29]

The inclusion complexes of $\mathbf{1}^{4+}$ studied within this investigation involve 1,4-substituted phenyl and 4,4′-substituted biphenyl derivatives. The guests of greatest interest are hydroquinone (**2**), *p*-phenylenediamine (**3**), 4,4′-biphenol (**4**), and benzidine (**5**), since they are fundamental units of the docking stations used in recently reported rotaxanes[3,5] and molecular shuttles.[6] Over 20 substituted phenyl and biphenyl systems incorporating systematic electronic and structural changes have been examined with receptor $\mathbf{1}^{4+}$, as listed in Tables 1−4.



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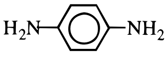

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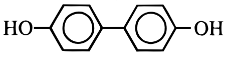

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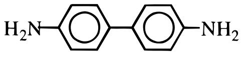

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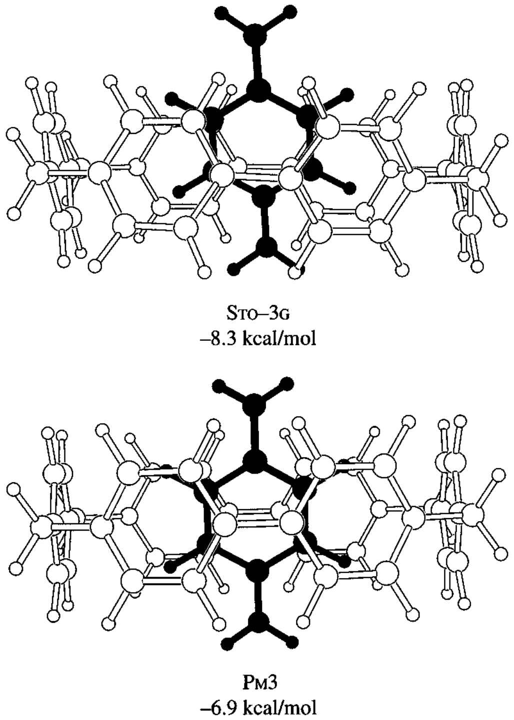

Figure 4. Comparison of RHF/STO-3G and PM3 complexes of $\mathbf{1}^{4+}$ and *p*-phenylenediamine.

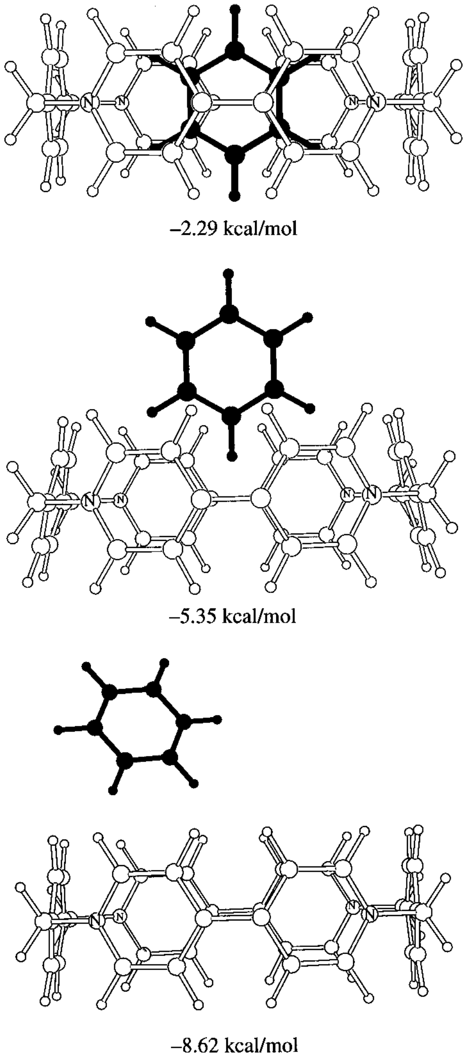

Figure 5. Three conformations and complexation energies of benzene and $\mathbf{1}^{4+}$ computed using PM3.

Table 2. Computed Energies of Complexation between Disubstituted Phenyl Guests and $\mathbf{1}^{4+\ a}$

system	no. of MeCN molecules	type	H_{guest}	H_{complex}	ΔH_{bind}	ΔG_{bind}	K	$\lambda_{\max}$	ϵ
p-xylene	0	π	4.740	1073.015	−2.66				
	12	π		1154.457	−1.50	−1.64	16^b	355	665
1,4-dichlorobenzene	0	π	10.112	1080.326	−0.72				
	12	π		1161.754	0.42				
	12	σ		1159.599	−1.73	−0.65	3^b	312	395
hydroquinone	0	π^c	−66.063	1004.611	−0.26				
	0	π^d		999.509	−5.37				
	0	σ		998.086	−6.79				
	12	σ		1082.696	−2.46	−1.71	18^b	473	620
1,4-dimethoxybenzene	0	σ	−51.899	1011.104	−7.93				
	12	σ		1096.081	−3.24	−1.64	16	472	420
p-phenylenediamine	0	π	19.489	1083.542	−6.88				
	12	π		1168.993	−1.71				
	0	π		1084.859	−5.57				
	0	σ		1080.918	−9.51				
	12	σ		1167.957	−2.75	−2.79	112^b	655	712
1,4-dimercaptobenzene	0	σ	32.001	1099.043	−3.90				
	0	σ		1094.379	−8.50				
p-chloroaniline (C_{2v})	2	σ^e	18.626	1089.037	−2.72				
	12	σ^e		1165.233	−4.61				
	12	av^i		1167.539	−2.31	−2.09	34	485	537
p-chlorophenol	0	σ^f	−28.390	1032.183	−10.36				
	12	σ^f		1120.026	−2.80				
	12	σ^d		1121.875	−0.95				
	12	av^g		1120.951	−1.88	−1.42	11	386	547
p-nitroaniline	0	σ^h	10.685	1046.585	−3.77				
	12	σ^h		1149.969	−11.93				
	12	av^i		1144.009	−5.97				
p-fluorotoluene	0	σ^j	−29.612	1029.749	−11.58				
	12	σ^j		1117.821	−3.79				
	12	av^i		1115.926	−1.90	−1.36	10^b	320	900
p-methoxytoluene	0	σ^d	−23.816	1040.571	−6.55				
	12	σ^d		1122.803	−4.60				
	12	av^i		1120.503	−2.30	−1.68	17	418	581

[a] Binding is described as π type if it is trulye an inclusion complex and σ type if it is centered about the cyclophane. Energies are reported in kcal/mol, association constants in M^{-1}, $\lambda_{\max}$ in nm, and ϵ in $M^{-1}\ cm^{-1}$. [b] Data from Benniston, A. C.; Harriman, A.; Philp, D.; Stoddart, J. F. *J. Am. Chem. Soc.* **1993**, *117*, 5298. [c] The guest is symmetrically oriented in $\mathbf{1}^{4+}$. [d] The OH substituent is oriented toward the $\mathbf{1}^{4+}$ cavity. [e] The NH_2 substituent is oriented toward the $\mathbf{1}^{4+}$ cavity. [f] The Cl substituent is oriented toward the $\mathbf{1}^{4+}$ cavity. [g] The averaged value of two conformations is compared with experiment. [h] The NO_2 substituent is oriented toward the $\mathbf{1}^{4+}$ cavity. [i] The conformer with the guest oriented in the opposite direction to $\mathbf{1}^{4+}$ yields a binding energy close to zero. [j] The F substituent is oriented toward the $\mathbf{1}^{4+}$ cavity.

Energy Minimizations. The electrostatic potentials (ESP) of receptor $\mathbf{1}^{4+}$ and different guests were computed. In the case of $\mathbf{1}^{4+}$, the ESP was generated at a constant 250 kcal/mol, as shown in Figure 2. The resulting narrow cavity of receptor $\mathbf{1}^{4+}$ is ideally configured for aromatic systems. In fact, the interior cavity width and length from X-ray crystallography[2] (6.8 × 10.3 Å) correspond to the dimensions found by theoretical considerations of stacked aromatic−aromatic interactions.[31] The ESP for **5** was generated at −5 kcal/mol, and is a good representation of other 4,4′-substituted biphenyl derivatives, as shown in Figure 3. To begin the energy minimizations, the SPARTAN graphics interface was used to visually insert guests into the cavity of host $\mathbf{1}^{4+}$ on the basis of the qualitative representations given by combining the ESP plots of the host and guest. Several starting orientations were used to initiate the energy minimizations using PM3, AM1, and RHF/STO-3G calculations. Often, the AM1 method did not find stable inclusion complexes; instead the guest preferred to bind to the outside of $\mathbf{1}^{4+}$, forming a "lidlike" structure. The PM3 semiempirical method provided stable inclusion complexes for all of the systems considered. One complex of **3** plus $\mathbf{1}^{4+}$ was energy minimized using the RHF/STO-3G level of theory, as shown in Figure 4. The difference in the computed interaction energy is 1.4 kcal/mol. The PM3 method tends to give a slightly more symmetric binding complex than that produced by the RHF/STO-3G method. On the basis of the comparison of semiempirical methods with experimental and ab initio structural and energetic data, the PM3 method was selected for the remaining computations.

Conformational Search. Since the $\mathbf{1}^{4+}$ host is tetracationic and the binding region has a narrow and well-defined cavity, the resulting complexes should be restricted to a limited conformational range. In order to probe the available conformational states for inclusion complexation, several random geometries were selected as the starting points for energy minimization for benzene plus $\mathbf{1}^{4+}$. For this particular system, energy minimizations using the PM3 Hamiltonian resulted in only three supramolecular complexes, as shown in Figure 5. The first computed complex has benzene centrosymmetrically located within the cyclophane cavity with a binding energy of −2.29 kcal/mol. The second complex has benzene symmetrically oriented in the pocket of the cyclophane, but slightly displaced (1−2 Å) along the axis of entry through $\mathbf{1}^{4+}$. The complexation energy of this configuration is more favorable at −5.35 kcal/mol. Finally, the third supramolecular complex is one where benzene is completely removed from the cavity region and strongly interacts (−8.62 kcal/mol) with the α and β protons on a paraquat group of $\mathbf{1}^{4+}$.

Jorgensen et al. have reported that the gas-phase optimization of a "tilted T" benzene dimer structure has an interaction energy of −2.31 kcal/mol.[31] This value is in excellent agreement with that reported from high-precision ionization measurements (−2.4 ± 0.4 kcal/mol).[32] The "shifted−stacked" structure was computed to be −2.11 kcal/mol in energy. The PM3-computed

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(31) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768.

Table 3. Computed Energies of Complexation between Monosubstituted Biphenyl Guests and **1**$^{4+}$ [a]

system	no. of MeCN molecules	type	H_{guest}	H_{complex}	ΔH_{bind}	ΔG_{bind}	K	λ_{max}	ϵ
biphenyl	0	π	47.578	1111.003	−7.51				
	12	π		1196.786	−2.01				
	0	σ		1108.152	−10.36				
	12	σ		1196.715	−2.08				
4-phenylphenol	0	π	2.415	1062.734	−10.62				
	12	π		1151.542	−2.09				
	0	σ^{b}		1061.227	−12.13				
	12	σ^{b}		1149.851	−3.78				
	0	σ^{c}		1063.030	−10.32				
	12	σ^{c}		1151.851	−1.78				
	12	av^{d}		1150.851	−2.78	−2.30	49	442	457
4-phenylanisole	0	σ^{e}	9.592	1066.995	−13.54				
	12	σ^{e}		1156.268	−4.54				
	0	σ^{f}		1069.580	−10.95				
	12	σ^{f}		1158.573	−2.24				
	12	av^{d}		1157.421	−3.39	−2.14	37	437	482
4-phenylaniline	0	π^{g}	45.272	1106.008	−10.20				
	0	π^{h}		1103.263	−12.95				
	0	σ^{h}		1100.983	−15.23				
	12	σ^{h}		1192.060	−4.43				
	0	σ^{g}		1106.138	−10.07				
	12	σ^{g}		1194.802	−1.69				
	12	av^{d}		1193.431	−3.06	−2.90	133	525	545

[a] Binding is described as π type if it is truly an inclusion complex and as σ type if it is centered about the cyclophane. Energies are reported in kcal/mol, association constants in M^{-1}, λ_{max} in nm, and ϵ in M^{-1} cm^{-1}. [b] The OH substituent is oriented away from the **1**$^{4+}$ cavity. [c] The OH substituent is oriented toward the **1**$^{4+}$ cavity. [d] The averaged value of two conformations is compared with experiment. [e] The OMe substituent is oriented away from the **1**$^{4+}$ cavity. [f] The OMe substituent is oriented toward the **1**$^{4+}$ cavity. [g] The NH_2 substituent is oriented toward the **1**$^{4+}$ cavity. [h] The NH_2 substituent is oriented away from the **1**$^{4+}$ cavity.

Table 4. Computed Energies of Complexation between Disubstituted Biphenyl Guests with **1**$^{4+}$ [a]

system	no. of MeCN molecules	type	H_{guest}	H_{complex}	ΔH_{bind}	ΔG_{bind}	K	λ_{max}	ϵ
4,4′-biphenol	0	π^{b}	−42.700	1020.699	−7.54				
	12	π^{b}		1105.902	−2.62				
	0	π^{c}		1019.153	−9.08				
	12	π^{c}		1114.703	−6.19				
	0	σ		1016.124	−12.11				
	12	σ		1103.478	−5.04				
	12	av^{d}		1104.690	−3.83	−2.93	140	500	438
benzidine	0	π^{c}	43.032	1099.581	−14.39				
	12	π^{c}		1193.553	−0.70				
	0	π^{b}		1099.060	−14.91				
	12	π^{b}		1189.403	−4.85	−4.12	1044	644	557
4,4′-dimethoxybiphenyl	0	π	−28.350	1031.235	−11.35				
	0	σ		1028.764	−13.82				
4,4′-dimercaptobiphenyl	0	π	55.948	1120.467	−6.42				
	0	σ		1117.531	−9.35				
4,4′-diphosphinobiphenyl	0	π	58.629	1123.695	−5.87				
	0	π^{b}	43.032	1098.994	−14.98				

[a] Binding is described as π type if it is truly an inclusion complex and as σ type if it is centered about the cyclophane. Energies are reported in kcal/mol, association constants in M^{-1}, λ_{max} in nm, and ϵ in M^{-1} cm^{-1}. [b] The guest is planar. [c] The guest is twisted. [d] The averaged value of two conformations is compared with experiment.

1^{4+}/benzene complexes (Figure 5) have been analyzed using the structural and energetic data provided by Jorgensen. For the centrosymmetric complex, the benzene guest is centered within the **1**$^{4+}$ cavity, resulting in two strong tilted T and four shifted−stacked interactions with the host. The two tilted T interactions should be roughly twice that reported by Jorgensen for the benzene dimer (−2.31 kcal/mol). The shifted−stacked interaction energies (−2.11 kcal/mol) can also be used to approximate the four benzene−paraquat interactions found in the **1**$^{4+}$ complex. Thus, a total interaction energy of −13.06 kcal/mol, based upon Jorgensen's work, can be used to estimate qualitatively the exclusion repulsive force (+10.75 kcal/mol) necessary to produce the predicted interaction energy of the **1**$^{4+}$/benzene complex (−2.31 kcal/mol). The origin of the second computed complex with benzene slightly outside the cyclophane binding pocket (Figure 5) is a direct result of relieving the repulsive exclusion force from the cavity at the expense of losing the two tilted T structures to gain extra stability (−5.35 kcal/mol). The third configuration is considered to be a gas-phase artifact, since no stationary point could be located when 12 acetonitriles were added.

UV−Vis Binding Studies. Receptor **1**$^{4+}$ is colorless in solution, until an aromatic guest is added. A charge-transfer band occurs if suitable intermolecular interactions develop between the guest and **1**$^{4+}$, which provides a straightforward method to quantitate the free energy of complexation. The binding constants obtained from the UV−vis titrations of host **1**$^{4+}$ with various guests show two major trends: (1) nitrogen-substituted aromatic molecules bind to **1**$^{4+}$ with greater affinity than oxygen-substituted systems and (2) 4,4′-substituted biphenyl molecules bind to **1**$^{4+}$ better than 1,4-substituted phenyl derivatives. Electron-withdrawing substituents decrease binding,

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(32) Grover, R.; Walters, E. A.; Hui, E. T. *J. Phys. Chem.* **1987**, *91*, 3233.

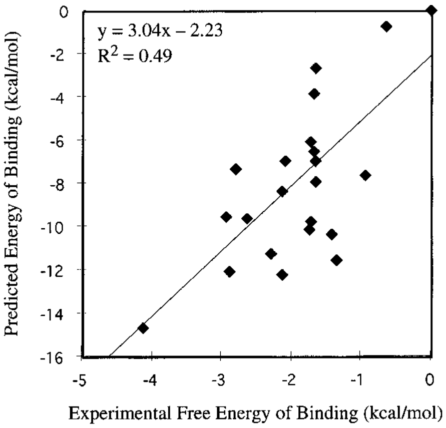
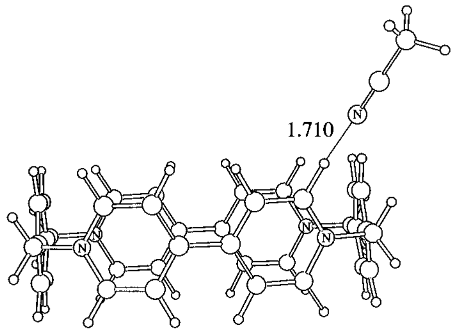


Figure 6. PM3-predicted enthalpic binding energies vs experimentally determined free energies of binding. The supramolecular model for the computations did not use any solvent.

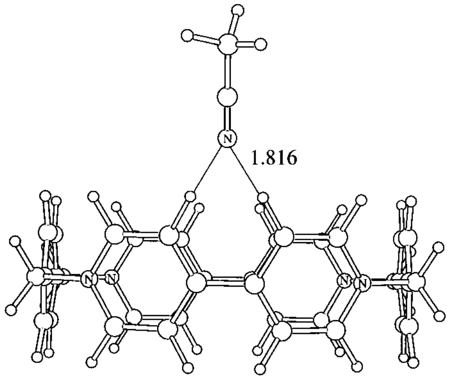
as in *p*-chloroaniline, *p*-chlorophenol, *p*-aminobenzoic acid, and *p*-aminobenzoic acid methyl ester. Two donating *para* substituents enhance binding, except for hydroquinone and its bis(methyl ether), which are actually poorer binders than phenol and anisole. Replacement of a phenol with its methyl ether reduces the binding except for hydroquinone which seems to have the same value whether one or both of the phenols are methylated. Since both phenol and anisole similarly insert into the cavity of $\mathbf{1}^{4+}$, a steric effect could be in operation or the difference could be due to a favorable proton–aromatic ring type interaction which methylation eliminates. Methylation of the amines cannot be similarly rationalized since rotation of the dimethylamino group, and thus delocalization of its electron pair, is hindered with respect to the amino group, and monomethylation still leaves one amino hydrogen whereas the methylated phenol has none. Replacement of oxygen with sulfur lowers the binding constant contrary to the notion that a softer sulfur would be a better donor and therefore increase the binding. Unfortunately, this trend could not be examined further because thiophenol and other related compounds with a thiol or dimethylphosphino group reduce $\mathbf{1}^{4+}$ to its 3+ cation radical. Hence, only the corresponding methyl sulfides could be used. An interesting case is presented by *p*-aminophenol. While its binding constant is much larger than phenol's, it is also larger than the binding constant for *p*-phenylenediamine. This is strange since nitrogen is a much better donor. Possibly, the asymmetry of the system could be a factor.

Obviously, simple additive effects are not the general rule in these systems since combinations of the best donors do not always give the best binders. The biphenyl systems have less localized electron density than the phenyl systems, yet are better binders with $\mathbf{1}^{4+}$. Some other property 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 also how they interact with each other and with the ring system to which they are attached.

Solvation. The gas-phase enthalpies of complexation have been computed using the PM3 method, as listed in Tables 1–4. The binding energies are determined by subtracting the energies computed for the isolated guest and the solvated host from the energy of the supramolecular system. The comparison between the experimental free energies and PM3-computed enthalpies is shown in Figure 6. A linear trend results, but the computed enthalpies of complexation are ca. 3 times greater than the free energies of complexation found by the UV–vis experiments. The computed absolute binding energies could be influenced by the absence of counterions and solvent,[33] incomplete description of the conformation distributions,[34] level of theory used for evaluation,[35] or a constant entropic term.



α–hydrogen complex



β–hydrogen complex

Figure 7. PM3-minimized complexes of $\mathbf{1}^{4+}$ with acetonitrile.

Our curiosity concerning the overestimated binding energies was further enhanced by the fact that when either acetonitrile or water was placed into the center of the $\mathbf{1}^{4+}$ cavity, both solvents energy minimized to either the α or β protons on the paraquat units of $\mathbf{1}^{4+}$, as shown in Figure 7. PM3 yields −20.7 kcal/mol for the acetonitrile/$\mathbf{1}^{4+}$ system at the β-protons and −23.3 kcal/mol at the α-proton. The β-proton complex forms a bifurcated system where the acetonitrile nitrogen is equally shared between the two protons. In order to test the unique strength of these interactions, a model system of methyl viologen plus acetonitrile was computed, as shown in Figure 8. The PM3, RHF/3-21G, and RHF/6-31G(D) methods yield −23.2, −27.8, and −23.4 kcal/mol for the α-interactions. In comparison, the β-interactions were computed to be −20.7, −22.5, and −18.5 kcal/mol, respectively. These results suggest that the protons are highly solvated and that the computed results will be improved by including solvent in these specific positions.

The influence of solvent upon computed binding affinity was further investigated by systematically adding solvent molecules to $\mathbf{1}^{4+}$. First, two acetonitriles were added to the regions corresponding to the paraquat β-protons on one face of $\mathbf{1}^{4+}$. PM3 geometry optimizations resulted in a symmetric structure, as shown in Figure 7, for one acetonitrile. Two bifurcated hydrogen bonds result, with each acetonitrile sharing both bipyridinium β-protons from the paraquat units. Thus, a second pair of acetonitriles was subsequently added to the opposite face of the cyclophane for the shared β-protons, and

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[33] (a) Mirzoian, A.; Kaifer, A. E. *J. Org. Chem.* **1995**, *60*, 8093. (b) Denti, T. Z. M.; van Gunsteren, W. F.; Diederich, F. *J. Am. Chem. Soc.* **1996**, *118*, 6044.

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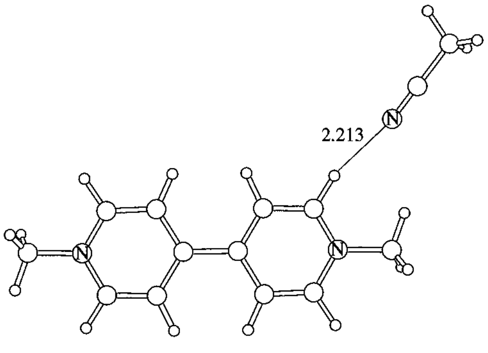
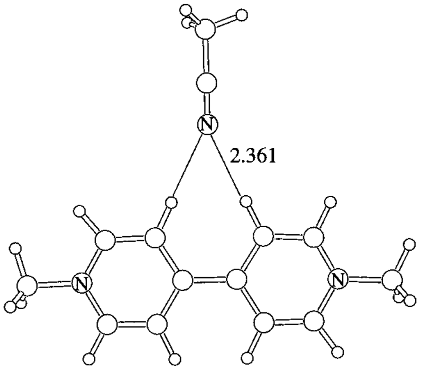
[35] Ochterski, J. W.; Petersson, G. A.; Wiberg, K. B. *J. Am. Chem. Soc.* **1995**, *117*, 11299.



α–hydrogen complex



β–hydrogen complex

Figure 8. 6-31G(D)-minimized complexes of methyl viologen with acetonitrile.

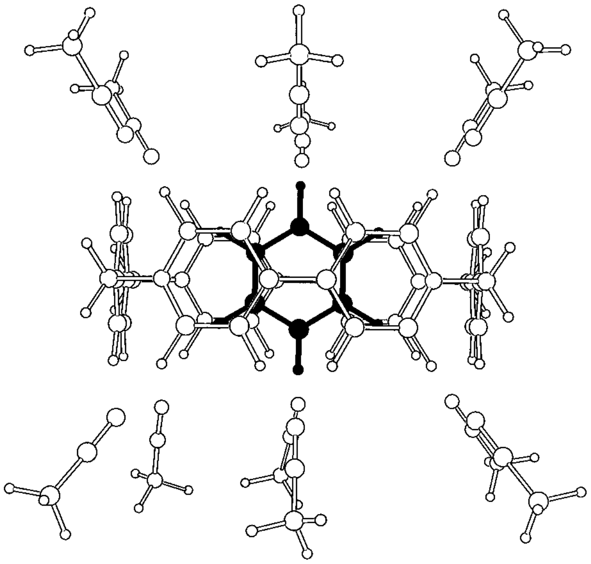


Figure 9. Supramolecular complex of 12 acetonitriles, benzene, and 1^{4+}.

Table 5. PM3-Computed Effect of Acetonitrile on Binding Energies

system	H_{form}	ΔH_{bind}	ΔH_{bind}/CH$_3$CN
acetonitrile	23.285		
$\mathbf{1}^{4+}$	1070.937		
$\mathbf{1}^{4+}$ + 2MeCN	1077.346	−40.2	−20.1
$\mathbf{1}^{4+}$ + 4MeCN	1088.215	−75.9	−19.0
$\mathbf{1}^{4+}$ + 6MeCN	1095.045	−115.6	−19.3
$\mathbf{1}^{4+}$ + 12MeCN	1151.218	−199.1	−16.6

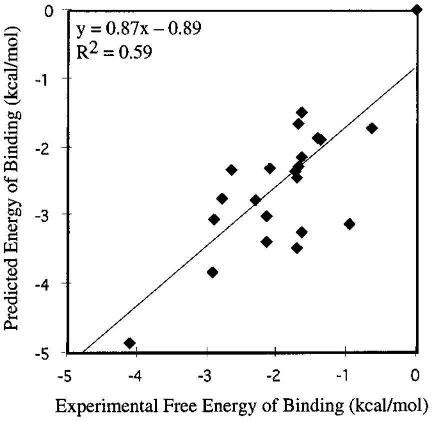


Figure 10. PM3-predicted enthalpic binding energies vs experimentally determined free energies of binding. The supramolecular model for the computations used 12 solvent molecules.

one acetonitrile was added for every α-proton for a total of twelve acetonitriles per cyclophane, as shown in Figure 9. The computed energies for incremental addition of solvent molecules are given in Table 5.

The energetic effect of acetonitrile addition on $\mathbf{1}^{4+}$ complexes is shown in Tables 1−4. The experimental free energy of binding between $\mathbf{1}^{4+}$ and benzene is −1.68 kcal/mol. The computed enthalpic energy of binding is −5.35 kcal/mol with no solvent and −4.03, −3.35, −3.06, and −1.67 kcal/mol for two, four, six, and twelve acetonitriles, respectively. In this particular case, the agreement between theory and experimental binding energies is within 0.01 kcal/mol, but in general, the computed binding enthalpy is within 1 kcal/mol of the experimental free energy of binding. Each substituted phenyl and biphenyl system was recomputed in the presence of the 12 acetonitriles. In a few cases, more than one stable complex was located. In the event that multiple complexes were identified, the resulting energies of binding for each minimized conformation were averaged and then compared to experiment. The computed enthalpies of complexation, when compared to the experimental free energies, provide a linear correlation, as shown in Figure 10. *Thus, the energetic consequences of the first solvation sphere of these complexes can be approximated by the 12 specific acetonitriles included in our computational model.* Interestingly, no counterions were necessary to describe the structural and energetic behavior of $\mathbf{1}^{4+}$ complexes with substituted phenyl and biphenyl compounds.

The structural behavior of 4,4′-substituted biphenyl guests emphasizes the importance of solvation in these particular host−guest systems.[23−25] The planar transition structure (D_{2h}) which separates the equivalent minima of biphenyl has low activation barriers for PM3, RHF/3-21G, and RHF/6-31G(D),[23] consistent with the experimental value of 1.43 kcal/mol.[36] For example, we compute that when benzidine initially inserts into $\mathbf{1}^{4+}$ that the large biphenyl twist prevents complete penetration into the cavity. The resulting complexation energy is −0.7 kcal/mol, but as the benzidine flattens and inserts deeper into the $\mathbf{1}^{4+}$ cavity the binding energy drops to −4.9 kcal/mol. The observed destabilization is caused by the twisted phenyl unit interfering with the strong electrostatic interaction between the bifurcated acetonitriles and the β-hydrogens on $\mathbf{1}^{4+}$. As shown in Figure 11, two acetonitriles are displaced 1 Å away from the region of maximum electrostatic interaction with the β-protons on $\mathbf{1}^{4+}$. The disrupted solvents are computed to regain their optimal positions around $\mathbf{1}^{4+}$ as benzidine inserts to provide a maximum solvation effect. The implication is that the supramolecular system gains additional stability from the solvent as the guest molecule passes through the center of $\mathbf{1}^{4+}$, since it must become

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(36) Bastiansen, O.; Samdal, S. *J. Mol. Struct.* **1985**, *128*, 115.

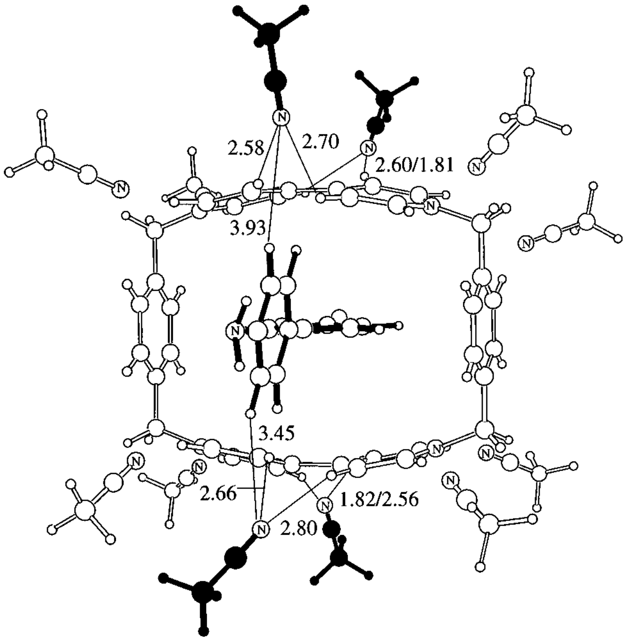

Figure 11. The twisted conformation of benzidine disrupts solvation. The acetonitriles (black) show the 1 Å movement away from the β-protons on $\mathbf{1}^{4+}$.

planar to thread through the center of the cyclophane. *Thus, solvent is computed to be a major contributor to the driving force of inclusion complexation and can possibly be a factor in the threading mechanism required for rotaxane formation.*

In addition to the solvent effect, the binding of **4** with $\mathbf{1}^{4+}$ should not occur in the same symmetric fashion as with **5**, since the hydroxyl lone pair will necessarily tilt the biphenyl entry in order to maximize the electrostatic binding within the cavity of $\mathbf{1}^{4+}$. The energy of complexation should be stronger for **5** as compared to **4**, since the benzidine amino substituents are stronger Lewis bases than the hydroxyls of biphenol. NMR NOE studies on the different inclusion complexes (**4** and **5** plus $\mathbf{1}^{4+}$) were recently reported.[6] Due to the geometry of the inclusion complex between **4** and $\mathbf{1}^{4+}$, an NOE was detected between the hydroxyl hydrogen of biphenol and the bipyridinium β-protons of $\mathbf{1}^{4+}$. No NOE could be detected between the amine hydrogens of benzidine and the bipyridinium β-protons of $\mathbf{1}^{4+}$. PM3 energy minimizations were carried out on both complexes using 12 acetonitriles, as shown in Figure 12 (solvent removed for clarity). In agreement with the qualitative predictions made above, there are major differences in the binding structures. The resulting PM3 $\mathbf{1}^{4+}$/benzidine complex is centrosymmetric in the cavity of the cyclophane. Both phenyl rings penetrate into the cavity and become planar so that solvation of the β-protons on $\mathbf{1}^{4+}$ can be achieved. Therefore, the amine hydrogens are far removed from the β-protons involved in the NOE experiments. The closest distance between the two sets of protons is 4.37 Å. The computed complex structure for $\mathbf{1}^{4+}$/biphenol reflects the difference in the electrostatics between **4** and **5**. In order to position the available lone pair of biphenol near the paraquat nitrogens, the biphenol enters the cavity in a diagonal fashion. Therefore, the depth of penetration is more shallow than found with **5**. The result is that the hydroxyl hydrogen is oriented closer to the β-protons being irradiated in the NOE experiments. The closest computed distance is 4.08 Å, which is close enough to yield an NOE signal, as found by experiment.[6]

Variational Energy Decomposition of the Intermolecular Bond. The components of intermolecular complexation include a variety of well-known forces, and range from moderately strong to weak interaction energies.[37,38] The collective strength of intermolecular bonds often provides a significant driving force to yield unique supramolecular structures, energetics, and properties.[1] Experimental results have indicated that van der Waals interactions, electrostatic interactions, and desolvation are significant factors in the processes of molecular recognition.[38a] 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.[38a] One goal of our study is to address the origin of intermolecular forces responsible for $\mathbf{1}^{4+}$ complexes, since the current literature invokes charge-transfer to rationalize $\mathbf{1}^{4+}$ binding.[2,3a]

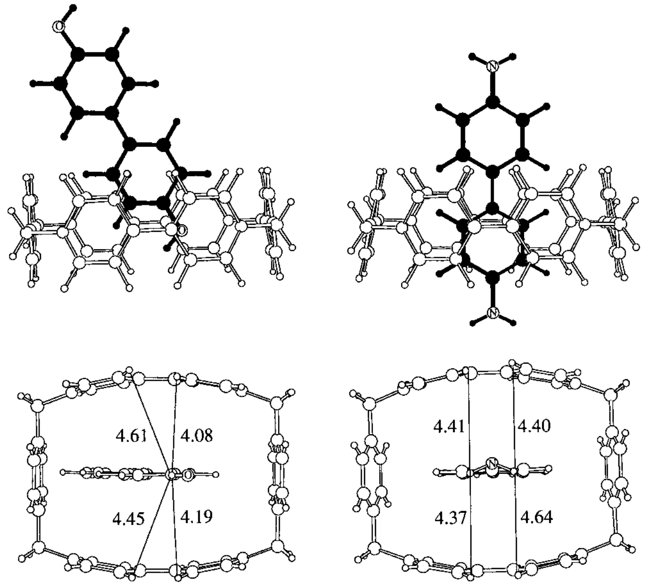

Figure 12. Two views of the PM3-minimized complexes of $\mathbf{1}^{4+}$ with 4,4′-biphenol and benzidine. The 12 acetonitriles were removed for clarity.

Different techniques have been reported which decompose the energetic contributions to the intermolecular bond energy in order to better understand phenomena such as hydrogen bonding,[39] donor−acceptor (EDA) complexes,[39,40] metal−ligand interactions,[41] and clustering of alkali metal cations.[42] The energy and charge distribution methods (ECDD) by Morokuma and Kitaura-Morokuma have proven to be powerful tools for the direct evaluation of molecular interactions.[39,43] The ECDD method is based upon the removal of specified elements from the Hartree−Fock matrix which define the individual components of the interaction energy. The interaction energy is partitioned into electrostatic (ES), polarization (PL), repulsive exchange (EX), charge-transfer (CT), and residual (MIX) terms:

$$\Delta E_{\mathrm{SCF}} = \Delta E_{\mathrm{ES}} + \Delta E_{\mathrm{PL}} + \Delta E_{\mathrm{EX}} + \Delta E_{\mathrm{CT}} + \Delta E_{\mathrm{MIX}} \quad (1)$$

Since the intermediate wave functions used to compute the ES and PL terms are not antisymmetrized, the ECDD method yields

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(37) (a) Morokuma, K.; Kitaura, K. In *Molecular Interactions*; Ratajczak, H., Orville-Thomas, W. J., Eds.; John Wiley and Sons: Bath, England, 1980; Vol. 1. (b) Benniston, A. C.; Harriman, A.; Lynch, V. M. *J. Am. Chem. Soc.* **1995**, *117*, 5275.

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Table 6. Variational Energy Decomposition of $\mathbf{1}^{4+}$ with Various Guest Molecules[a]

	Δ*E*	ES	PL	EX	CT	MIX
			Hydroquinone (**2**)			
STO-3G//PM3	−3.9	−6.7	−1.2	6.8	−3.2	0.4
BSSE corrected	−1.3			8.4	−2.6	0.9
			p-Phenylenediamine (**3**)			
STO-3G//STO-3G	−8.9	−11.6	−1.4	6.6	−2.8	0.2
BSSE corrected	−1.3			8.9	−2.2	0.7
STO-3G//PM3	−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 (**4**)			
STO-3G//PM3	−7.7	−4.4	−6.8	5.3	−2.2	0.4
BSSE corrected	−5.8			6.5	−1.8	0.7
			Benzidine (**5**)			
STO-3G//PM3	−12.0	−9.4	−7.0	7.6	−3.7	0.5
BSSE corrected	−8.9			9.3	−3.0	1.2

[a] Energies are reported in kcal/mol.

components that can potentially violate the Pauli exclusion principle.[42,44] Hence, critical examination of these terms is required since they are not upper bounds on the exact energy. Failure of the ECDD can potentially occur with extended basis sets and in unnatural and compressed fragment separations. Despite the claim of problems with the model wave functions, the ECDD method has proven to be successful when carefully monitored.

The PM3 method yields structures which compare well with experiment and higher level theory for the complexes of interest. Typically, ab initio wave functions are used for the ECDD treatment of ab initio structures. The question which remains is whether the PM3-generated structures are appropriate for an ab initio ECDD analysis. Thus, ECDD was carried out on the PM3-minimized water dimer geometry using the STO-3G, 3-21G, 6-31G(D), and 6-31G(P,D) basis sets. The energetic components from the ECDD method on the PM3-minimized geometries were computed to be within 0.2 kcal/mol of the energies from the corresponding ab initio structures.

To delineate the forces which cause the computed binding enthalpies in our study, four molecular complexes, **2**−**5** plus $\mathbf{1}^{4+}$, were subjected to the ECDD method (Table 6). The minimized PM3 geometries of the complexes were used. The largest basis set affordable for ECDD with molecular complexes of 98 atoms was the STO-3G basis set. Each integral file used in the energy evaluation grew to be 1.9 Gbyte. The current maximum size of any UNIX file on modern computer workstations is 2 Gbyte. We are currently implementing direct SCF procedures to alleviate this current limitation. Our first observation is that basis set superposition error (BSSE) of the computed complexes was not as great as found with the water dimer.[43] The proportion of BSSE correction to the total computed interaction energy ranged from 25 to 67% for the **2**−**5** plus $\mathbf{1}^{4+}$ complexes. The computed interaction energy from both PM3 and STO-3G is greater for **3** as compared to **2**, and for **5** with respect to **4**.

The ECDD decomposition yields interesting insights into the processes and energies of inclusion complexation. First, the electrostatic contribution for both the substituted phenyl and biphenyl complexes with $\mathbf{1}^{4+}$ is expected to be underestimated as previously computed for the water dimer using the STO-3G basis set.[43] Surprisingly, the electrostatic term is computed to dominate the energetic interactions between $\mathbf{1}^{4+}$ and either **2** or **3**. For both the phenyl and biphenyl systems, the electrostatic contribution is approximately twice as large for the nitrogen-substituted guests as that found with their oxygen counterparts (compare **2** with **3** and **4** with **5**). The repulsion-exchange term almost completely cancels the electrostatic stabilization provided by oxygen-substituted guests, yet only partially cancels the electrostatic stabilization from nitrogen-substituted systems. The charge-transfer contribution is relatively constant in the range between 2 and 3 kcal/mol for complexes **2**−**5** with $\mathbf{1}^{4+}$. Therefore, the charge-transfer stabilization does not reflect the experimentally determined differences in binding energies, as traditionally believed.[2,3a] The ECDD computations show that the stability of $\mathbf{1}^{4+}$ complexes is greater for the biphenyl systems **4** and **5** as compared to the analogous phenyl guests **2** and **3**. The largest computed differential effect was seen in the polarizability of the complexes. We compute that the stabilization provided by polarizability increases from 1 to 7 kcal/mol when phenyl is replaced with biphenyl in the molecular systems studied. The delocalization resulting from extending the π-system of the guest significantly enhances the polarizability of the entire supramolecular complex. *Thus, for all of the energetic components examined, the change in polarizability (not charge-transfer) is determined to be responsible for the differential binding effects that have been theoretically and experimentally observed.*

Molecular Polarizability. It is now common practice to compute molecular electrical moments and polarizabilities.[45] Such computations have recently provided an advanced understanding of molecular properties and reactivity in chemical systems.[46] The molecular properties of interest are defined as derivatives of an energy. For example, the dipole moment is formulated as the first derivative of the energy with respect to the strength of an applied field. The second derivative is defined to be the polarizability. The influence of basis set quality upon computed electrical properties has recently been examined in detail.[46]

The main result of the energy decomposition study is that the change in polarizability of the $\mathbf{1}^{4+}$ complex is determined to be responsible for the differential binding effects in 1,4-substituted phenyl and 4,4′-substituted biphenyl derivatives. Due to well-documented problems with ECDD,[44] we decided to explore the possibility that individual molecular properties of the guests would correlate with the computed binding energies with $\mathbf{1}^{4+}$. Such a correlation would support the ECDD studies. 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 computed polarizability component along the principal molecular (biphenyl) axis is reported in Table 7. The polarizability values were compared with the associated enthalpies of binding and observed free energies of binding with $\mathbf{1}^{4+}$. The 3-21G polarizability along the principal molecular axis is a few percent lower than that computed using the 6-31G(D) basis set. A linear correlation 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 13. The interpretation formulated is that a more polarizable molecule can electronically adapt to the unusual binding cavity of $\mathbf{1}^{4+}$, and this results in stronger binding energies.

Benzidine yields the strongest observed and computed association constant for the series of 1,4-substituted phenyl and 4,4′-substituted biphenyl molecules tested. In addition, benzidine has the largest molecular polarizability component along the main axis of the biphenyl unit. Our intention was to use a

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Table 7. Computed Polarizabilities (Å^3) Using the RHF/3-21G and RHF/6-31G(D) Levels of Theory[a]

molecule	E(6-31G*)	$\alpha_{3\text{-}21\text{G}}$	$\alpha_{6\text{-}31\text{G}*}$	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
thiophenol	−628.21031	94.7	98.3	−2.44	n/a
thioanisole	−668.24501	124.0	129.2	−3.49	−1.71
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	−0.40	−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
4,4′-diphosphinobiphenyl	−913.28249	275.1	145.1	n/a	n/a
water	−76.01075	3.6	4.8	n/a	n/a
ammonia	−56.18436	3.6	5.3	n/a	n/a
acetonitrile	−131.92753	29.5	31.8	n/a	n/a

[a] The computed enthalpy of complexation, ΔH_{bind}, and experimental free energy of binding, ΔG_{bind}, between **1**$^{4+}$ and each guest is given in kcal/mol. All guests have been verified as ground state minima by frequency analysis.

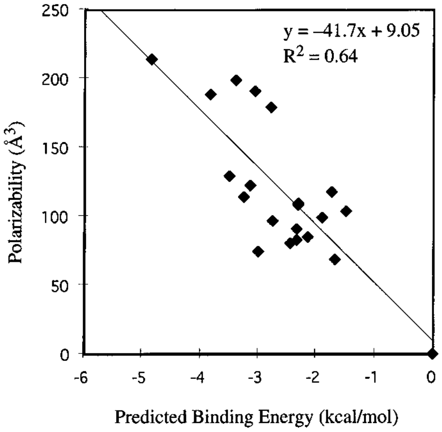

Figure 13. Comparison of the 6-31G(D)-computed binding energies and the molecular polarizability of the guests.

more polarizable molecule, such as 4,4′-diphosphinobiphenyl, with the expectation that it would bind better with **1**$^{4+}$. Unfortunately, we could not determine the experimental binding constant of 4,4′-diphosphinobiphenyl with **1**$^{4+}$ due to the reduction of **1**$^{4+}$. In addition, the predicted energies of complexation for both 4,4′-diphosphinobiphenyl and 4,4′-dimercaptobiphenyl are actually smaller than found with the benzidine/**1**$^{4+}$ system, as shown in Table 4. The results indicate that a meaningful response in the binding energy occurs only between 60 and 200 Å^3, where benzidine defines the upper limit. Polarizabilities outside of this region have only a constant effect on the binding energies. *Therefore, for the first time, we have shown a direct correlation between computed molecular polarizability of the guest, within a certain window of polarizabilities, and the stability of the resulting* ***1***$^{4+}$ *complex.*

Principle of Maximum Hardness. It has been recently pointed out that the maximum hardness of an organic molecule can provide an intuitive understanding into its chemical behavior and reactivity.[47,48] In hardness−softness terms, the softness of a molecule can be regarded as its capacity to accept electronic charge. 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. In practice, eqs 2 and 3 are

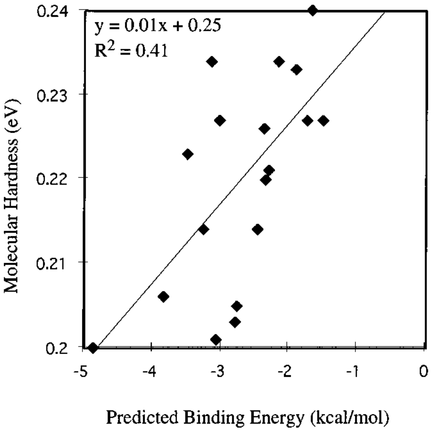

Figure 14. Comparison of the 6-31G(D)-computed binding energies and the molecular hardness of the guests.

$$2\eta = (\partial^2 E/\partial N^2)_{\nu,T} = (\partial\mu/\partial N)_{\nu,T} \qquad (2)$$

$$\mu = (\partial E/\partial N)_{\nu,T} \qquad (3)$$

replaced by a finite difference approximation which relates the chemical hardness (η) and chemical potential (μ) 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:

$$\eta = (\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}})/2 \qquad (4)$$

$$\mu = (\epsilon_{\text{LUMO}} + \epsilon_{\text{HOMO}})/2 \qquad (5)$$

The softness has been defined as the reciprocal of the hardness. Previous correlations among the hardness, polarizability, and size of atoms, molecules, and clusters have been demonstrated.[48c] The maximum hardness of a molecule has also been shown to be an excellent measure of aromaticity.[48] In addition, the principle of maximum hardness in a chemical system is a measure of its resistance to changes 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.[48d]

In an effort to better understand the electronic nature of **1**$^{4+}$, the orbital energy levels and electron affinities have been computed. The HOMO and SHOMO are doubly degenerate and stay closely spaced at all the levels of theory considered. This is consistent with the experimentally known two consecutive electron reduction potentials of **1**$^{4+}$ to **1**$^{2+}$ and **1**.[3a] Previous use of Koopman's theorem has shown that Hartree−Fock calculations with the minimal basis set are particularly inadequate for predicting electron affinities in other supramolecular systems, yet semiempirical methods when used with Koopman's theorem have been shown to provide surprisingly accurate

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Table 8. Computed RHF/6-31G(D) Orbital Energies of Mono- and 1,4-Disubstituted Phenyl and Biphenyl Guests[a]

system	E(6-31G(D))	E_{HOMO}	E_{LUMO}	hardness	softness	EN
benzene	−230.70314	−0.331	0.150	0.240	4.16	−0.091
toluene	−269.74015	−0.319	0.148	0.234	4.28	−0.086
chlorobenzene	−689.60335	−0.335	0.132	0.234	4.28	−0.102
phenol	−305.55768	−0.309	0.144	0.227	4.42	−0.083
anisole	−344.58171	−0.305	0.147	0.226	4.42	−0.079
aniline	−285.73070	−0.289	0.151	0.220	4.55	−0.069
tert-butylbenzene	−386.83767	−0.319	0.149	0.234	4.27	−0.085
thiophenol	−628.20892	−0.306	0.319	0.223	4.49	−0.084
phenylphosphine	−571.99284	−0.314	0.132	0.223	4.48	−0.091
p-xylene	−308.77696	−0.308	0.146	0.227	4.41	−0.162
1,4-dichlorobenzene	−1148.50183	−0.338	0.116	0.227	4.41	−0.111
hydroquinone	−380.40887	−0.292	0.135	0.214	4.68	−0.079
1,4-dimethoxybenzene	−458.45783	−0.285	0.142	0.214	4.68	−0.072
p-phenylenediamine	−340.75424	−0.262	0.147	0.205	4.89	−0.058
1,4-dimercaptobenzene	−1025.71376	−0.293	0.128	0.211	4.75	−0.083
1,4-diphosphinobenzene	−913.28249	−0.304	0.119	0.212	4.73	−0.093
p-fluorotoluene	−368.59127	−0.332	0.134	0.233	4.29	−0.099
p-mercaptophenol	−703.06217	−0.292	0.132	0.212	4.72	−0.080
p-methoxytoluene	−383.61802	−0.296	0.146	0.221	4.52	−0.075
biphenyl	−460.25385	−0.300	0.117	0.209	4.80	−0.092
4-phenylphenol	−535.10868	−0.282	0.124	0.203	4.93	−0.079
4-phenylaniline	−515.28159	−0.274	0.128	0.201	4.98	−0.073
4,4′-biphenol	−609.96327	−0.279	0.133	0.206	4.85	−0.073
benzidine	−570.30344	−0.258	0.141	0.200	5.01	−0.059
4,4′-diphosphinobiphenyl	−913.28249	−0.304	0.119	0.212	4.73	−0.093

[a] HF energies are reported in kcal/mol, and orbital energies are in eV. The absolute hardness is defined as $(E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}})/2$, the softness as the reciprocal, and the electronegativity as $(E_{\mathrm{LUMO}} + E_{\mathrm{HOMO}})/2$.

electron affinities.[49] In our specific system, the energy between the degenerate HOMO and degenerate virtual orbitals is between 0.25 and 0.26 eV for MNDO, PM3, and AM1. The Hartree–Fock-predicted differences are higher at 0.35, 0.34, and 0.33 eV using the STO-3G, 3-21G, and 6-31G(D) basis sets.

Electronic structure calculations were carried out for over 20 substituted phenyl and biphenyl guests, as listed in Table 8. The correlation between molecular hardness and the computed $\mathbf{1}^{4+}$ binding affinities is shown in Figure 14, which 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 $\mathbf{1}^{4+}$.

Conclusions

The energy components of the intermolecular bond have been evaluated in inclusion complexes involving the tetracationic cyclophane receptor $\mathbf{1}^{4+}$ and 1,4-substituted phenyl and 4,4′-substituted biphenyl guests. Excellent agreement between observed and predicted structures and binding affinities have been found. 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 $\mathbf{1}^{4+}$ complexes. We have shown by using semiempirical and ab initio molecular orbital theory that the basis of molecular recognition is governed by cavity binding composed of strong electrostatic and small charge-transfer forces for 1,4-substituted phenyl systems. The largest intermolecular differential force driving the inclusion complexation in 1,4-substituted phenyl and 4,4′-substituted biphenyl guests is polarizability. 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. The molecular polarizability and maximum hardness of the guest can be used as predictive tools in the design of new and useful molecular devices. 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) delocalization of biphenyl vs phenyl units of the guest molecule. 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.

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Supporting Information Available: Semiempirical and ab initio energies, structures, and frequencies in either GAUSSIAN or SPARTAN archive format (163 pages). See any current masthead page for ordering and Internet access instructions.

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