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Crown Ether–Neutral Molecule Interactions Studied by Molecular Mechanics, Normal Mode Analysis, and Free Energy Perturbation Calculations. Near Quantitative Agreement between Theory and Experimental Binding Free Energies

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Abstract: We present a combined molecular mechanics, normal mode analysis, and free energy perturbation study of the 1:1 complexes of 18-crown-6 with malononitrile, nitromethane, and acetonitrile. In addition, the interactions of the host and guests with benzene were studied in order to qualitatively evaluate potential solvent–solute interactions. The calculated binding free energies of the 18-crown-6–neutral molecule complexes are remarkably close to the corresponding experimentally determined values in C_6D_6. The trends in the enthalpy and entropy of complexation were reproduced qualitatively. The *relative* binding free energies obtained with the free energy perturbation method agree quantitatively with the experimental numbers. By evaluating the contributions of electrostatic and van der Waals interactions to the relative free energies of complexation with a decoupled free energy perturbation method, our calculations indicate that in the complexes of 18-crown-6 with nitromethane and acetonitrile there is a substantial loss of attractive interaction relative to the complex of 18-crown-6 with malononitrile. This is explained in terms of the partial electrostatic charges and the electrostatic potential in the direction of the hydrogen atoms of the various neutral guest molecules.

The ability of synthetic receptor molecules such as crown ethers to complex cations or anions has received much attention during the last two decades.[1] However, another exciting property of macrocyclic host molecules is their ability to form well-defined, thermodynamically stable complexes with *uncharged* guest molecules. Such complexes may roughly be divided into water-soluble[2] and water-insoluble systems. In this paper we are mainly concerned with the latter type. Although a number of crystallographic[3] and thermodynamic studies[4] have been performed, the nature of the interactions between host and guest in such complexes is only partly understood specially in those cases where the guest is only capable of forming C–H···O hydrogen bonds. In this paper we present a theoretical study of some aspects of crown ether–neutral molecule complexes using a combination of molecular mechanics, normal mode analyses, and free energy perturbation calculations.

Computational methods have been applied on a variety of host–guest systems. With use of molecular mechanics,[5] molecular orbital methods,[6] and distance geometry calculations,[7] the interactions between crown ethers and cations were studied. Howard et al.[8] investigated the complexes between crown ethers and several cationic molecules, e.g., H_3O^+, NH_4^+, and Me_3NH^+. Gehin et al. studied the interactions between various ammonium cations and a number of crown ethers using molecular mechanics and dynamics.[9] A combined ab initio quantum mechanical and molecular mechanical method was applied by Singh and Kollman in order to simulate the gas-phase protonation of crown ethers.[10] Complexes of cations with the mostly larger, but less flexible molecules like the cryptands,[11] spherands,[12] and cavitands[13] were studied with molecular mechanics. The conformational space of uncomplexed crown ethers[14] and hemispherands[4d] could be explored with various approaches. All these calculations deal with isolated systems. The effect of a solvent on the conformational preferences of crown ethers was studied with Monte Carlo simulations of 18-crown-6 in a cluster of water molecules.[15] We are

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aware of only one example of a molecular mechanics study of crown ether–neutral guest complexes. Using the MM2 force field with an extra hydrogen bond term added, Uiterwijk et al.[16] studied the conformations of complexes of 18-crown-6 with urea and formamide. The hydrogen bonds in these complexes were of the N–H···O type.

Normal mode analyses have been performed for complexes of anisole spherands[12a] with cations in order to get estimations of the thermodynamic parameters of complexation.

Very recently, free energy perturbation methods have been used to study the preferences of a macrotricyclic receptor SC24 toward halogenide anions.[17] We have reported a study in which the same method was applied to the complexation of dibenzo crown ethers with the alkali cations in methanol.[18] Cieplak and Kollman have studied the free energy of association of nucleic acid bases in vacuo and water solution using a similar approach.[19]

In this paper we decided to study the 1:1 complexation of 18-crown-6 (18C6) with malononitrile (malo), nitromethane (nitr), and acetonitrile (acet). Accurate thermodynamic data are known for these complexes in an apolar solvent (C_6D_6) and, in addition, the X-ray structures of 18C6·malo (1:2),[20] 18C6·nitr (1:2),[4a,21] and very recently 18C6·acet (1:2)[22] have been reported in the literature. Since the thermodynamic parameters of complexation were determined in C_6D_6 (benz),[4a] we also studied the interactions between the host and the guests with this solvent. We were most interested in simulating and explaining the differences in the strength and nature of the binding in these host–guest·complexes. During the progress of the work Damewood and co-workers published a molecular mechanics (MM2) study addressing the same type of host–guest systems.[23] They focused on the simulation of the structural properties of the host–guest complexes and the simulation of the complexation enthalpy using various parameter development models. We, however, present a calculation of the complete thermodynamics of complexation, including binding enthalpy, entropy, and free energy. To our knowledge this is the first study of the complexes of macrocyclic hosts with uncharged guests in which normal mode analyses and free energy perturbation methods are applied and combined.

Methods

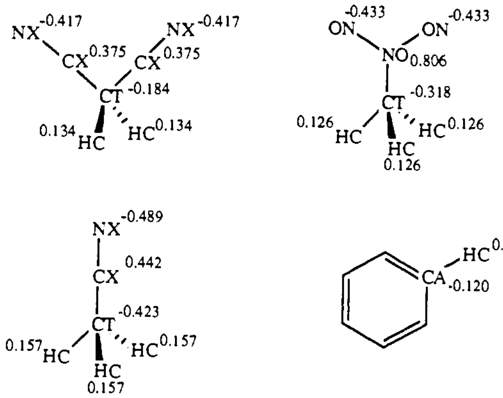
The AMBER package was used[24,25] for all computations described in this paper. The energy function is of the form

$$E_{\text{total}} = \sum_{\text{bonds}} K_r(r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}}\right] + \sum_{\text{H-bonds}}\left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}}\right] \quad (1)$$

Table I. Additional Force Field Parameters

bond	K_r (kcal mol^{-1} Å^{-2})	r_{eq} (Å)	
CT–CX	360.0	1.445	
HC–NX	1303.0	1.164	
CT–NO	240.0	1.46	
NO–ON	600.0	1.20	
angle	K_Θ (kcal mol^{-1} radian^{-2})	Θ_{eq} (deg)	
CT–CX–NX	35.0	180.0	
HC–CT–CX	35.0	109.5	
CX–CT–CX	35.0	112.0	
CT–NO–ON	70.0	119.0	
ON–NO–ON	80.0	118.0	
HC–CT–NO	35.0	109.5	
dihedral	$V_n/2$ (kcal mol^{-1})	γ (deg)	n
HC–CT–CX–NX	0.0	0.0	3
CX–CT–CX–NX	0.0	0.0	3
HC–CT–NO–ON	0.0	0.0	3
improper dihedral	V_n (kcal mol^{-1})	γ (deg)	n
ON–ON–NO–CT	20.0	180.0	2
VDW	R^* (Å)	ϵ (kcal mol^{-1})	
CX	1.80	0.06	
NX	1.75	0.16	
NO	1.75	0.16	
ON	1.65	0.15	

Chart I



The calculations were carried out on VAX8650 and FPS-264 computers. Throughout all calculations the all-atom force field was used, i.e. all atoms were explicitly represented by the force field. Most of the force field parameters have been previously published.[25b] A complete list of all additional parameters used in the present study is found in Table I. All bonding parameters for the bonds with a cyanide involved were derived from Allinger's MM2 force field[26] in the following manner. The equilibrium bond lengths and bond angles were taken directly from the MM2 parameters. The corresponding force constants were obtained by interpolation, using analogies between the parameters of the MM2 and AMBER force fields. The parameters involving a nitro functionality were generated from the 18-crown-6·nitromethane X-ray structure[21] and the AM1[27] optimized geometry of nitromethane. In order to calculate electrostatic point charges for the guest molecules under study, the molecules were fully optimized with AM1 after which a single-point ab initio calculation was carried out with the 6-31G* basis set with the GAUSSIAN 80 UCSF program.[28] Subsequently the charges were

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Table II. Results of Molecular Mechanics and Normal Mode Analysis Calculations on the 18-Crown-6–Neutral Molecule and Benzene–Neutral Molecule Complexes[a]

host	conformation[b]	guest	ΔE[c]	ΔElec[d]	ΔVdW[e]	ΔH[f]	$T\Delta S$[f]	ΔG[f]
18C6	D3d	malo	−15.0	−11.2	−3.8	−13.4 (−14.2)	−9.7 (−11.0)	−3.7 (−3.2)
18C6	D3d	nitr	−12.1	−7.7	−4.3	−10.5 (−7.6)	−9.9 (−7.5)	−0.6 (−0.1)
18C6	D3d	acet	−10.0	−6.6	−3.3	−8.7 (−6.0)	−8.2 (−6.6)	−0.5 (0.6)
18C6	D3d	benz	−6.0	−1.2	−5.1	−4.6	−7.3	2.7
benz	perp	malo	−5.0	−3.1	−1.9	−3.6	−5.5	1.8
benz	perp	nitr	−3.2	−1.7	−1.5	−1.8	−3.9	2.1
benz	copl	nitr	−5.0	−2.3	−2.6	−3.6	−5.3	1.7
benz	perp	acet	−2.7	−1.4	−1.3	−1.6	−3.4	1.9
benz	copl	acet	−3.6	−1.8	−1.8	−2.5	−4.1	1.6

[a] kcal mol^{-1}, T = 298 K. [b] "D3d" denotes the D_{3d} conformation of the crown ether in the complex; "perp" and "copl" indicate that the neutral molecule adopts an almost perpendicular or coplanar position, respectively, with respect to benzene; see also Figure 2. [c] $\Delta E = E_{\text{total}}(\text{Host·Guest}) - E_{\text{total}}(\text{Host}) - E_{\text{total}}(\text{Guest})$. [d] ΔElec = Elec(Host·Guest) − Elec(Host) − Elec(Guest); "Elec" denotes the electrostatic energy. [e] ΔVdW = VdW(Host·Guest) − VdW(Host) − VdW(Guest); "VdW" denotes the van der Waals energy. [f] Within parentheses the experimental values in C_6D_6 at 298 K, taken from ref 4a.

scaled in such a way that the calculated dipole moments were equivalent to the experimental gas-phase values.[29] These final charges were used when the energy of the guest molecules was minimized with AMBER. As a result of some minor geometrical changes upon minimization with AMBER the calculated dipole moments are no longer equivalent to the experimental values but the experimental trend is conserved. The calculated (experimental[30]) dipole moments for acet, malo, and nitr are 3.69 (3.92), 3.64 (3.73), and 3.59 (3.46) D, respectively. For the $-CH_2OCH_2-$ fragments the charges reported by Howard et al.[8] were used. All partial charges and AMBER atom types are found in Chart I.

Molecular Mechanics/Normal Mode Analysis. The starting geometries for the molecular mechanical calculations on the crown ether–neutral molecule complexes were obtained by docking the neutral guest in a position relative to the crown ether that maximized hydrogen bonding with the molecular graphics program MIDAS[31] on a Silicon Graphics system. A similar procedure was followed for obtaining the starting geometries of the (1:1) benzene–neutral molecule complexes. The geometries of the complexes were optimized with AMBER until the root-mean square (rms) energy gradient was less than 0.001 kcal mol^{-1} Å^{-1}. However, in case of the normal mode analyses the optimizations were continued until the rms energy gradient was less than 10^{-8}. It was ensured by checking the 6 lowest frequency vibrations that each local minimum was a true minimum and not a saddle point on the potential energy surface. Throughout all calculations a constant dielec with ϵ equal to 1.0 and a scale factor of 0.5 for the 1–4 VDW and 1–4 electrostatic interactions was used (SCNB = SCEE = 2.0).[25b,c] No cutoff for the nonbonded interactions was used.

The Free Energy Perturbation Method. The use of free energy perturbation theory[32] allows for the calculation of free energy differences between two states of a system, A and B. In the Gibbs module of AMBER, the two states A and B are linked to each other with a coupling parameter λ

$$H_\lambda = (1 - \lambda)H_A + \lambda H_B \tag{2}$$

where H_A and H_B are the Hamiltonians of states A and B. The free energy difference between the states at λ and $\lambda + \Delta\lambda$ is

$$\Delta G_\lambda = RT \ln \left\langle \exp\left\{ -\frac{H_{\lambda+\Delta\lambda} - H_\lambda}{RT} \right\} \right\rangle_\lambda \tag{3}$$

where R is the gas constant, T is the absolute temperature, and $\langle\,\rangle_\lambda$ denotes the ensemble average at intermediate positions along the conversion pathway from A to B characterized by the coupling parameter λ. The total change in free energy is obtained by accumulating the averages or so-called "thermodynamic windows".

$$\Delta G = \sum_{\lambda=0}^{\lambda=1} \Delta G_\lambda \tag{4}$$

Other methods to calculate free energies are the so-called "slow growth" and "thermodynamic integration" methods.[32] Free energy perturbation methods have been applied to a variety of systems including the simulation of site-specific mutagenesis in proteins,[33] the hydration properties of alkanes and alcohols,[34] anions,[35] cations,[36] DNA basepairs,[37] noble gases,[38] dipeptides,[39] and the thermodynamics of cavity formation in water.[40]

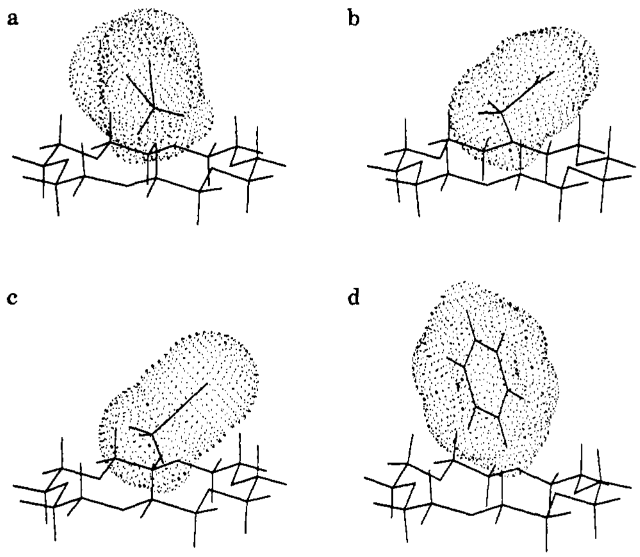

Figure 1. Side views of the molecular mechanics minimized complexes of 18C6 with malo (a), nitr (b), acet (c), and benz (d).

The two states studied in this paper are complexes of 18-crown-6 with two different neutral guest molecules. Molecular dynamics was used in order to generate ensembles along the reaction pathway. Starting geometries for the molecular dynamics simulations were the energy minimized structures from the molecular mechanics studies. Before every molecular dynamics run the structures were equilibrated at 300 K for at

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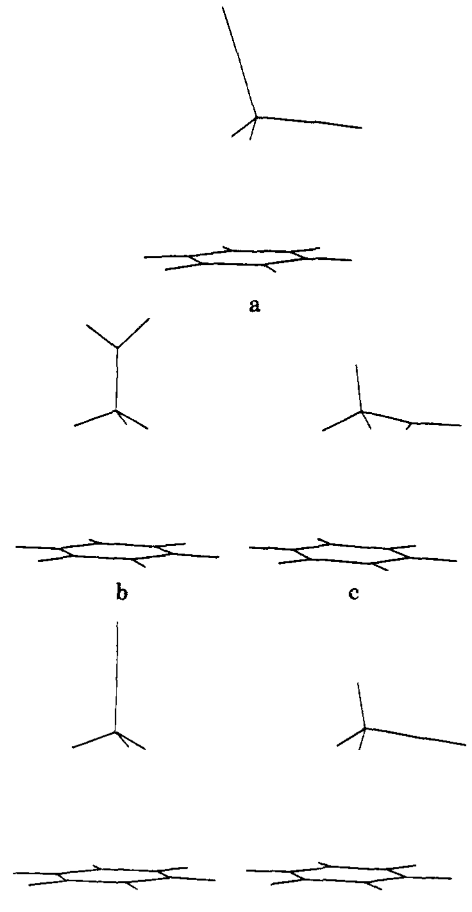

Figure 2. Side views of the molecular mechanics minimized complexes of benz with malo (a), nitr (b, perp; c, copl), and acet (d, perp; e, copl).

least 10 ps with a temperature relaxation time of 0.1 ps. It turned out to be necessary to apply a positional constraint of 2.0 kcal mol^{-1} (with a relaxation time of 0.1 ps) to the central carbon atom of the guest molecule in order to prevent the guest molecule from drifting away from the crown ether. Analysis of the molecular dynamics trajectories showed that the average movement of the constrained atom was less than 0.01 Å from its initial position and therefore no umbrella corrections were made. The translational and rotational motion about the center of mass of the system was removed every 200 steps. Each perturbation calculation consisted of 21 windows ($\Delta\lambda = 0.05$). At each window 500 steps of equilibration and 500 data collection steps were performed. Since the timestep was 0.001 ps the total time for one perturbation run amounts to 21 ps. All runs were performed forward (λ:1 → 0) and backward (λ:0 → 1). The Gibbs module also allows for the separate calculation of the electrostatic and van der Waals contributions to the free energies using so-called decoupled perturbation methods. The same protocol with respect to the number of windows, timestep, etc. was used as in the perturbation calculations described above. Since the ensembles were generated at constant temperature (300 K) and pressure (0 atm), the energies calculated may be regarded as "gas phase" Gibbs free energies. The time for a single perturbation run in which 21 ps of molecular dynamics was evaluated amounted to 1–2 CPU hours on a VAX8650 running under the VMS 4.6 operating system.

Results

Molecular Mechanics. The energy of the (1:1) complexes of 18C6 with the neutral molecules, obtained from model building, was minimized with AMBER. Since the thermodynamic parameters of complexation of these complexes are available in benzene, we also studied (1:1) complexes of benzene with the neutral guests and 18C6 in order to evaluate potential solvent effects. The results of the energy minimizations are found in Table II. Figures 1 and 2 display the structures of the minimized host–guest complexes. The conformations of the 18C6·malo and 18C6·nitr (1:1) complexes, are very similar to the X-ray structures of the corresponding 1:2 complexes. If the second guest molecule in the experimental structures is neglected, root-mean-square deviations between calculated and experimental structures[20,21] of 0.22 and 0.29 Å are calculated for respectively the 18C6·malo and 18C6·nitr complexes. Comparison of the different contributions to the total energy ΔE shows that the complexes involving 18-crown-6 are held together mainly by electrostatic rather than van der Waals interactions. The exception is the 18C6·benz complex that is mainly stabilized by van der Waals interactions. For the complexes of benz with the neutral molecules, the electrostatic and van der Waals interactions contribute almost the same to the total energies. Since hydrogen bonding is mostly of an electrostatic nature, the energy associated with the possible hydrogen bonds in the complexes is included in the ΔElec term, It must be noted that we did not use an explicit 10–12 hydrogen bond potential in the force field. Apparently the standard 6–12 van der Waals potential is sufficient to give good agreement between calculated and experimental structures in these complexes. When we treated C–H with the same 10–12 hydrogen bond parameters as N–H, we found that the interactions between host and guest were too strong, leading to very unrealistic structures.

The complexation enthalpies ΔH, shown in Table II, were calculated as the difference in the total energy of the complex and the sum of the total energies of its components minus RT. By using a normal modes analysis of the vibrations of each complex it is possible to retrieve gas-phase molar entropies of the complexes. Again the entropies of the complexes were calculated as the difference between entropy of the complex and the sum of the entropies of its components. The molar entropies at 300 K for the separate molecules are 150.8 (18C6), 69.9 (malo), 71.5 (nitr), 59.2 (acet), and 71.8 (benz) cal mol^{-1} K^{-1}. It must be noted that the entropic contributions $T\Delta S$ to the complexation free energies, as given in Table II, were corrected by substracting RT ln (1/22.4), which amounts to −1.84 kcal mol^{-1} at 298 K, in order to correct the translational entropies to the 1 M standard state.[19] The binding free energies were obtained as the difference between the ΔH and $T\Delta S$ terms at $T = 298$ K.

As expected the entropy term for all complexes is negative. The 18C6·benz complex excepted, all enthalpies of complexation are negative. However, when looking to the free energies of complexation only three complexes of all those listed in Table II are likely to be formed. The calculations strongly suggest that the 18C6·benz and benz·neutral molecule complexes are thermodynamically not stable. Mosier-Boss and Popov recently examined the role of some of these complexes in complexation equilibria of 18C6 with neutral guests in organic solvents.[4b] In the case of the acet/benz system spectral data did not allow a distinction between dimerization and complex formation of the components. Our results confirm the choice they made to analyze their data in terms of dimerization rather than complex formation equilibria.

Consider the thermodynamic cycle

$$\begin{tikzcd}
(\mathrm{Host})_g \arrow[d, "\Delta G_g(\mathrm{Host})"] & + & (\mathrm{Guest})_g \arrow[d, "\Delta G_g(\mathrm{Guest})"] \arrow[r, "\Delta G_{\mathrm{compl,g}}"] & (\mathrm{Host{\bullet}Guest})_g \arrow[d, "\Delta G_g(\mathrm{Host{\cdot}Guest})"] \\
(\mathrm{Host})_g & + & (\mathrm{Guest})_g \arrow[r, "\Delta G_{\mathrm{compl,s}}"] & (\mathrm{Host{\bullet}Guest})_{\mathrm{compl,s}}
\end{tikzcd}$$

in which g and s denote the gas-phase and solvated state, respectively. The free energy of complexation is expressed by eq 5. Since the calculations suggest that the interactions between

$$\Delta G_{\mathrm{compl,s}} = \Delta G_{\mathrm{compl,g}} + \Delta G_{\mathrm{s}}(\mathrm{Host{\cdot}Guest}) - \Delta G_{\mathrm{s}}(\mathrm{Host}) - \Delta G_{\mathrm{s}}(\mathrm{Guest}) \quad (5)$$

both the host and guests with the solvent (benz) are rather weak, we assume that the free energies of solvation for the host, guest, and host–guest complex are small and cancel out, i.e. $\Delta G_{\mathrm{s}}(\mathrm{Host{\cdot}Guest}) = \Delta G_{\mathrm{s}}(\mathrm{Host}) + \Delta G_{\mathrm{s}}(\mathrm{Guest})$. Under this assumption, the free energies of complexation in the gas phase and solution are equal, and the calculated gas-phase binding free energies may be compared with the experimental data.

When comparing the calculated with the experimental values for the thermodynamic parameters of complexation, it is clear that the agreement is almost quantitative with respect to the

Table III. Results of the Free Energy Calculations (kcal mol^{-1}) on the 18-Crown-6–Neutral Guest Complexes

guest-1	guest-2	$\Delta\Delta G_{calc}{}^{a}$	$\Delta\Delta G_{elec}{}^{b}$	$\Delta\Delta G_{vdw}{}^{b}$	$\Delta G_4{}^{b}$	$\Delta\Delta G_{exp}{}^{c}$
malo	nitr	3.1	3.1 ± 0.2	0.6 ± 0.2	3.1 ± 0.1	3.1
malo	acet	3.3	2.7 ± 0.3	0.9 ± 0.2	4.1 ± 0.6	3.8

[a] Calculated from the data in Table II that were obtained by molecular mechanics/normal mode analysis. [b] The abbreviations elec and vdw denote that only the contributions of electrostatic respectively van der Waals interactions to the free energy were calculated. In the undecoupled free energy perturbation calculation all nonbonding interactions are evaluated, resulting in the ΔG_4. [c] Calculated from the experimental values determined in C_6D_6 at 298 K, see ref 4a.

binding free energies. The trends for the entropy and enthalpy terms are reproduced rather well, although these terms are somewhat over-estimated in the calculations. However, it appears that the over-estimation of these terms must be of the same magnitude since they cancel out in the calculation of the free energy. For the 18C6·acet complex our calculation of the binding free energy (−0.5 kcal mol^{-1}) is closer to the value reported by Popov (0.0 kcal mol^{-1})[4b] than to the value reported by Reinhoudt (0.6 kcal mol^{-1})[4a] and co-workers.

The molecular mechanics and normal mode calculations were all carried out for only one conformation of 18C6. Although other conformations of 18C6 of relatively low energy may exist in the complexes studied in this paper, we feel that our choice for taking the D_{3d} conformation for 18C6 is justified by the fact that in the solid state only this conformation has been observed in complexes of 18C6 with uncharged molecules. However, molecular dynamics calculations are very much suited for spanning a larger part of conformational space for the complexes under study. In addition relative binding free energies can be obtained by using the free energy perturbation method.

Free Energy Perturbation Calculations on the Host–Guest Complexes. In the molecular mechanics calculations only one structure for each complex was studied. In order to span a larger part of the conformational space of the 18C6·neutral molecule complexes, a free energy perturbation method was applied. We used the thermodynamic cycle

$$\begin{tikzcd}
(\mathrm{Host})_g + (\mathrm{Guest\text{-}1})_g \arrow[r, "\Delta G_1"] \arrow[d, "\Delta G_3"] & (\mathrm{Host{\bullet}Guest\text{-}1})_g \arrow[d, "\Delta G_4"] \\
(\mathrm{Host})_g + (\mathrm{Guest\text{-}2})_g \arrow[r, "\Delta G_2"] & (\mathrm{Host{\bullet}Guest\text{-}2})_g
\end{tikzcd}$$

By using the perturbation method it is possible to calculate ΔG_4. Since we do not include intramolecular terms in our free energy approach[24] ΔG_3 equals 0.0. Therefore, the difference in binding free energies for the Host·Guest-1 and Host·Guest-2 complexes, $\Delta G_1 - \Delta G_2$, is equal to ΔG_4 since the free energy is a state function. The results of the calculations are found in Table III. In Table III the contributions of van der Waals and electrostatic interactions to the relative free energies were calculated separately by decoupling the free energy perturbation into electrostatic and van der Waals components. Ideally, the sum of $\Delta\Delta G_{elec}$ and $\Delta\Delta G_{vdw}$ should equal ΔG_4. However, since somewhat different trajectories were followed in each perturbation calculation, this is not completely true. The quantitative agreement between the calculated and experimental relative free energies is very encouraging. It is obvious that the relative free energies calculated by the perturbation method are closer to the experimental values than the corresponding values calculated by molecular mechanics/normal mode analyses. This time our calculation of the difference in binding free energy between 18C6·malo and 18C6·acet, amounting to 4.1 kcal mol^{-1}, shows more agreement with the corresponding value based on Reinhoudt's data (3.8 kcal mol^{-1}) rather than Popov's data (3.2 kcal mol^{-1}). When mutating 18C6·malo into 18C6·acet the ratio $\Delta\Delta G_{elec}/\Delta\Delta G_{vdw}$ amounts to 3.0. This is significantly smaller than the corresponding value for the 18C6·malo to 18C6·nitr perturbation, being 5.0. Apparently the loss of electrostatic interactions when going from the 18C6·malo complex to the 18C6·nitr complex is more important than going to the 18C6·acet complex. Damewood and co-workers reported ab initio studies of the interaction between H_2O and acet,[41a] nitr,[41b] and malo.[41b] They found no evidence for C–H···O hydrogen bond formation between H_2O and acet or nitr. Under the assumption that H_2O is a good model for the ether units of 18C6, the decrease in the electrostatic interactions in the corresponding complexes with 18C6 could be due to the (partial) loss of hydrogen bonding.

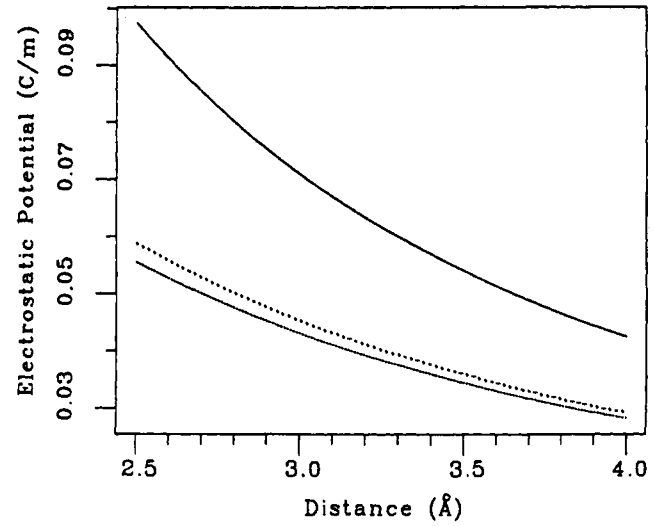

Figure 3. Electrostatic potential calculated for malo (—, top), nitr (- - -, middle) and acet (···, bottom), as a function of the distance between the central carbon atom and points lying on the symmetry axes in the direction of the hydrogen atoms.

Preference of 18-Crown-6 for Malononitrile. Finally we would like to address the question of why 18C6 forms such relatively strong complexes with malo when compared to nitr and acet. Neither the dipole moments nor the acidities of the protons of the guests suggest the observed differences. The protons involved in the bonding to the oxygen atoms of 18C6 all have partial charges of the same order as can be seen in the Chart I. However, a closer look to the partial charge distribution reveals that the carbon attached to the hydrogens is the least negatively charged for malo (−0.18) and bears significantly more negative charge for nitr (−0.32) and acet (−0.42). This suggests that the repulsive electrostatic interactions between this carbon and the negatively charged oxygen atoms in the host–guest complex dominate the thermodynamic complex stabilities. Because of the important role of the charge distribution in the guest molecules we calculated the electrostatic potential, defined as

$$V = \sum_{\mathrm{atoms}} \frac{q_i}{r_i} \tag{6}$$

where q_i is the partial charge of atom i and r_i the corresponding distance to the central carbon atom of the guest, for several points along the symmetry axes of the guests in the direction of the hydrogen atoms. The results are depicted in Figure 3. It clearly shows that the gradient in the electrostatic potential is steepest for malo followed by nitr and acet. Therefore the strength of the interaction between the crown dipoles and the neutral molecules follows the same trend.

Discussion and Conclusions

We have presented molecular mechanics/normal mode calculations on the complexes of 18-crown-6 with malononitrile, nitromethane, and acetonitrile and have calculated *absolute* free energies for gas-phase association in very good (within 0.5–1.1 kcal mol^{-1}) agreement with experimental association free energies determined in benzene. This agreement has been achieved because (a) differential solvation effects between host and guest and their complexes are apparently small, (b) the structures used in the molecular mechanics study are close to the correct local minimum

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(41) (a) Damewood, J. R., Jr.; Kumpf, R. A. *J. Phys. Chem.* **1987**, *91*, 3449–3452. (b) Kumpf, R. A.; Damewood, J. R., Jr. *J. Chem. Soc., Chem. Commun.* **1988**, 621–622.

J. Am. Chem. Soc. 1989, 111, 4051–4063

for the complexes, and (c) the empirical energy function used in reasonable and well-balanced. The agreement with the experimental enthalpies and entropies of association is less quantitative, but the trend of increasing $-T\Delta S$ parallelling increasingly negative ΔH is observed in both experiment and theory. The relative electrostatic interaction energy is the key to the relative free energy of association for these molecules and the calculations have given qualitative insight (Figure 3) into why malononitrile interacts more strongly with 18-crown-6 than either nitromethane or acetonitrile. The trend in free energies cannot be explained by the relative dipole moments; rather the relative electrostatic potential gradient in the direction of the crown is the critical determinant. This ties in nicely with such an analysis for hydrogen bonding interactions.[42]

Using the free energy perturbation approach, we have been able to calculate the relative free energies of association for malononitrile vs nitromethane and malononitrile vs acetonitrile to within experimental and calculational error. In this approach, unlike the molecular mechanics/normal mode method, dynamic effects are taken into account and many effects that are similar in both guests cancel; thus, it is not suprising that the agreement with experiment is more quantitative in the free energy perturbation approach. Nonetheless, it is encouraging that the agreement is so quantitative, given that a constraint had to be applied to prevent host/guest decomplexation during the simulations. These results further validate the power of the free energy method. The fact that such agreement was achieved with no empirical adjustment of molecular mechanical parameters (standard atom types for van der Waals interactions and electrostatic potential derived charges) provides important validation of the robustness of this approach on this well-defined model system.

The following general question arises: when is the neglect of solvation energies justified in calculations such as those reported here? This approach is likely to work if the specific interactions between solutes and solute complexes with the solvent are weak. This is true for aliphatic hydrocarbon solvents with any neutral organic solute. For aromatic hydrocarbon solvents, such as benzene, neglect of solvation appears to be justified for solutes without proton donor functionality, such as studied here. The approach we have used is unlikely to work well for polar solvents and/or ionic solutes. Nonetheless, even in those cases it may be interesting to carry out the gas-phase simulations in order to quantitate and understand the solvation effect.

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Registry No. 18-Crown-6/malononitrile, 63726-93-2; 18-crown-6/nitromethane, 82064-74-2; 18-crown-6/acetonitrile, 60336-83-6.

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On the Thermal Behavior of Schiff Bases of Retinal and Its Analogues: 1,2-Dihydropyridine Formation via Six-π-Electron Electrocyclization of 13-Cis Isomers[1a]

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Abstract: Reaction of 13-*tert*-butyl-13-*cis*-retinal (**3a**) with *n*-butylamine affords *n*-butyl Schiff base **3b**, which affords the electrocyclized dihydropyridine (DHP) **7b** with a half-life of ~11 min at 23 °C in benzene-d_6. The corresponding 11,13-*dicis* Schiff base **5b** isomerizes to the same DHP-**7b** with a half-life of ~4 min at 78 °C. For *tert*-butyl Schiff bases 13-*cis*-**3c** and 11,13-*dicis*-**5c**, an equilibrium is established at 78 °C between **3c**, **5c**, and DHP-**7c** in a ~5/2/3 ratio, respectively. The parent 13-*cis*-retinal *n*-butyl Schiff base **2b** undergoes similar electrocyclization, but geometric isomerization occurs as a competing process. Because of the considerably more complex thermal behavior of the parent series, *n*-butyl and *tert*-butyl Schiff bases of aldehydes *all-trans*-**1a**, 13-*cis*-**2a**, and 9-*cis*-**11a** were prepared and then in parallel experiments subjected to thermal isomerization at 78 °C. For the *tert*-butyl Schiff bases **1c**, **2c**, and **11c**, only geometric isomerism leading to ~50–60% of **1c**, near equal amounts (~20% each) of **2c** and **11c**, and minor amounts (~6–12%) of 9,13-*dicis*-**13c** occurs on prolonged heating. The *n*-butyl Schiff bases behave in a qualitatively similar manner except that 13-*cis*-**2b** produces significant amounts of DHP-**9b** and that in all cases prolonged heating leads to a myriad of minor components as indicated by ^{1}H NMR monitoring. For the seven-membered ring fused, 12-s-cis-locked series of *n*-butyl Schiff base analogues, 13-*cis*-**4b**, 11,13-*dicis*-**6b**, 9,11,13-*tricis*-**14b**, and 9,13-*dicis*-**16b**, similar thermal experiments were conducted, and the results resembled those of the 13-*tert*-butyl isomers 13-*cis*-**3b** and 11,13-*dicis*-**5b**, which are thought to be biased in 12-s-cis conformations. The remarkable facility with which 13-cis isomers of 13-*tert*-butyl and 12-s-cis-locked Schiff base analogues undergo electrocyclization to DHP's is attributed to their strongly biased or locked 12-s-cis conformations. Finally, it was shown that DHP-**7b**, which is formed exclusively when either 13-*cis*-**3b** or 11,13-*dicis*-**5b** is heated, is stable to prolonged heating (78 °C, 14 h) in benzene-d_6 and cannot be induced to undergo ring opening to protonated Schiff base **18** by protonation. Instead, protonation of DHP-**7b** afforded 2,3-dihydropyridinium salt **19**.

Schiff base derivatives of *all-trans*-(**1a**) and 13-*cis*-retinal (**2a**) (Chart I) with *n*-butylamine, namely, **1b** and **2b**, respectively, have been used extensively as models to reproduce the spectroscopic and chemical properties of the several pigments of Halobacteria, particularly bacteriorhodopsin.[2] This pigment, which contains *all-trans*-retinal (**1a**) as chromophore bound to the ε-amino group of a lysine residue of the protein bacterioopsin, functions as a

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[1] (a) A preliminary account of this work has appeared: Okamura, W. H.; de Lera, A. R.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 4462. (b) NATO Postdoctoral Fellow, 1985–1987. Present address: Department of Organic Chemistry, University of Santiago, Spain. (c) Present address: Department of Organic Chemistry, University of Vienna, Austria.

[2] (a) Stoeckenius, W. *Acc. Chem. Res.* **1980**, *13*, 337. (b) Stoeckenius, W.; Bogomolni, R. A. *Annu. Rev. Biochem.* **1982**, *52*, 587. (c) Oesterhelt, D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 17.

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