A Molecular Mechanics Study of 18-Crown-6 and Its Alkali Complexes: An Analysis of Structural Flexibility, Ligand Specificity, and the Macrocyclic Effect

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Abstract: We present molecular mechanics studies of different conformations of 18-crown-6, its alkali-cation complexes, and cation complexes of an open-chain analogue of this crown. For the crown and its complexes the lowest-energy conformers were those observed by X-ray crystallography. For the crown itself, several structures are found to be of comparable energy, the relative order depending on the dielectric constant. With a low dielectric constant, we calculate that the lowest-energy structure is of the same type (C_i symmetry) as that found in the crystal structure of 18-crown-6. However, in a more polar environment, we calculate that a D_{3d} structure becomes of similar energy. In fact, this is the structure that the crown adopts in some molecular crystalline adducts involving the dipole–dipole or H-bonding interactions of the adducts with the ether oxygens of the crown; this structure may also be present in polar solvents at low temperature, as suggested by ^{13}C NMR studies. We also predict the existence of a C_1 structure not heretofore structurally characterized, which is comparable in energy to the lowest-energy centrosymmetric C_i and D_{3d} structures, and whose contribution to the average properties of the crown can explain the significant temperature-dependent dipole moment of 18-crown-6. Although we find that the K$^+$/18-crown-6 complex is intrinsically less stable than the Na$^+$/18-crown-6 complex, we calculate it to have a more negative formation energy in aqueous solution, due to the fact that the calculated difference in hydration energies of Na$^+$ and K$^+$ is larger in magnitude than the calculated difference in intrinsic complexation energies. Calculations on cation–crown–H$_2$O complexes show that with complexation the crown cation affinity for H$_2$O is reduced; this is related to the facilitation of cation transport through membranes by carrier molecules.

The synthesis and study of macrocyclic ring systems and their interactions with guest molecules has been of interest to many chemists because such systems can display *discrimination* in binding to ligands.[1-7] Crown ethers are also of great interest to the theoretical chemist because they represent the simplest model system which might contain some of the features of enzyme specificity, i.e., a much stronger affinity for some guests than other, closely related ones. 18-Crown-6 (($CH_2CH_2O)_6$) is one of the most extensively characterized crown systems and as such, provides a good starting point for an analysis of the basis of crown structure, flexibility, and binding specificity.

The conformation of the crown can mainly be described by the sequence of dihedrals angles (for instance g$^+$, a, g$^-$) and the way they may repeat by symmetry. "Pseudocorners" and "genuine corners" are defined by the occurrence of g$^\pm$g$^\mp$ and g$^\pm$g$^\pm$ consecutive dihedrals, respectively.[8] Although deviations from the ideal symmetric structures may occur, we will use the notation of symmetry type to characterize the conformations (D_{3d}, C_i, C_2, C_1). Structural information comes mainly from X-ray studies: the uncomplexed crown is of C_i symmetry, with two pseudocorners.[9] A different conformation of C_i symmetry, with two genuine corners, is observed in the complex with benzenesulfonamide; we will refer to it by C_i'. The D_{3d} arrangement is observed in crystals[11-18] of complexes with K$^+$, Rb$^+$, and Cs$^+$, as well as in

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complexes where the crown is surrounded by polar O–H, C–H, or N–H bonds. In its Na⁺ complex,[19] the crown is highly distorted, without symmetry (C_1). Other conformations may be observed when O–C–C–O dihedrals are constrained by substituents like in dibenzo-18-crown-6[20] (C_2-type symmetry) or dicyclohexyl-18-crown-6 A (C_2) and B (C_i) cation complexes.[21,22] Spectroscopic, IR, and NMR studies in solution suggest that the conformation of the uncomplexed crown is the same in nonpolar solvents as in the solid phase,[23] but other conformers should be populated in polar media.[8] In solution the Na⁺ complexes contain conformers with genuine corners, while the K⁺, Rb⁺, and Cs⁺ complexes probably adopt a D_{3d}-type conformation.[8]

There are also thermodynamic data on the interaction enthalpies and entropies of various cations with 18-crown-6 as well as some analogues.[9,24,25] Previous theoretical studies of 18-crown-6 and its complexes with K⁺, Na⁺, and NH₄⁺ were carried out by Yamabe et al.,[26] employing the quantum-mechanical method CNDO/2. There have also been several previous molecular-mechanics studies of relevance to this work here. Bovill et al.[18] and Truter[27a] studied the properties of a number of ethers, including 18-crown-6. Hancock and McDougall[27b] compared the strain energy of a number of polyamines and their complexes with that of transition metals.

The molecular mechanics approach employed here lets us focus on three separate issues: (1) *structural flexibility*, or the tendency of crowns to adopt different conformations under different conditions; (2) *cation specificity*, or the preference (greater interaction free energy or enthalpy) of the crown for certain cations; and (3) the *macrocyclic effect*, or the greater binding free energy of the ligand to crowns than to open-chain analogues. Although our approach is an approximate one, we demonstrate that it is capable of answering detailed questions in each of the three areas given above. This has not been done before in all three areas, although Bovill et al.[18] examined issue 1, (in the absence of cation), Yamabe et al.,[26] issue 2, and Hancock and McDougall[27b] issue 3.

To address issue 1, we ask the basic question: is the fact that different structures are adopted by the various crown complexes, compared to uncomplexed crown, a crystal-packing effect or is it an "intrinsic" property of the individual structures? Our calculations suggest that the latter is the case.

To examine issue 2, we study the interaction energy and structure of alkali (M⁺ = Na⁺, K⁺, Rb⁺, Cs⁺) complexes of

Table 1. Interaction Energies and Parameters for M⁺⋯(OCH₃)₂ Complexes (M⁺ = Na⁺ and K⁺) and Parameters for M⁺ = Rb⁺ and Cs⁺

	M = Na⁺	M = K⁺	M = Rb⁺	M = Cs⁺
E_T,[a] kcal/mol	−25.6	−18.2	−16.3	−14.2
$R(O⋯M^+)$,[b] Å	2.20	2.69	2.88	3.15
q_0,[c] e⁻	−0.6	−0.6	−0.6	−0.6
R_M°,[d] Å	1.6	2.0	2.2	2.4
ΔH,[e] kcal/mol	−24.0	−17.9	−15.9	−13.7
ΔE(q.m.),[f] kcal/mol	−25.2	−17.5		
R(q.m.),[f] Å	2.25	2.69		

[a] In the molecular-mechanics model, the energies of M⁺ and O(CH₃)₂ are zero, so ΔE for the interaction is the total energy E_T of M⁺⋯(OCH₃)₂. The minimized energy had C_{2v} symmetry. [b] The optimized O⋯M⁺ distance. [c] The partial charge on oxygen ($q_C = -\frac{1}{2}q_0$). [d] The van der Waals radii for the cations; the N_{eff} values were 10.0, 18.5, 22.0, and 30 for Na⁺, K⁺, Rb⁺, and Cs⁺; the polarizability values (Å³) were 0.24, 1.23, 1.90, and 4.26 for Na⁺, K⁺, Rb⁺, and Cs⁺. [e] Experimental values for M⁺⋯OH₂ interaction from ref 32. [f] Calculated values with use of very accurate quantum-mechanical methods (ref 31) for M⁺⋯OH₂.

18-crown-6. We conclude, as did Yamabe et al.,[26] that relative solvation plays an important role in determining the selectivity of certain cations for the crown. Another important factor is the relative crown/cation size, and we find upon energy minimization that Cs⁺ moves slightly out of the center of 18-crown-6, as is observed in X-ray studies. Issue 3 is the macrocyclic effect, i.e., the fact that 18-crown-6 has a greater cation affinity than does its noncyclic analogue pentaglyme. By comparing the energy of pentaglyme in its all-trans and "pseudo-D_{3d}" conformation with the energy of its alkali complexes, we gain insight into enthalpic contributions to the macrocyclic effect.

Methods of Procedure

The work we describe here was carried out with use of the molecular-mechanics software AMBER,[29] which uses an energy function of the form:

$$E = \sum_{bonds} k_b(r - r_b)^2 + \sum_{angles} k_a(\theta - \theta_a)^2 + \sum_{dihedrals} \frac{k_d}{2}[1 +$$

$$\cos(n\phi - \gamma)] + \sum_{nonbonded} \left[B_{ij}r_{ij}^{-12} - A_{ij}r_{ij}^{-6} + \frac{q_iq_j}{\epsilon_{ij}r_{ij}} \right]$$

where the nonbonded terms are summed over all atom–atom pairs i and j, which are separated by at least three bonds. The parameters are reported in the Appendix, Table X; most of these parameters come from our previous studies of nucleotides,[30] but the nonbonded parameters of the cations Na⁺, K⁺, and Cs⁺ and the partial atomic charges on the atoms had to be determined from appropriate model systems. The total and interaction energies are quite sensitive to the charges, so we usually carried out the calculations with at least two different sets of atomic charges, in order to ensure as much as possible that the calculated results are independent of parameter choice. This also gives insight into the effect of the dielectric constant of the medium. A united atom approximation for the aliphatic hydrogens was used.[30]

For each calculation, the energy was minimized with respect to all degrees of freedom by using analytical first derivatives. The calculation was terminated when the root-mean-squared energy gradient was less than 0.1 kcal/Å or when the change in energy was less than 10⁻³ kcal/mol. The final converged energies were not sensitive to using different starting guesses or small random displacements in structure.

When we performed calculations on the C_2' structures, corresponding to the crown conformation in dibenzo-18-crown-6, the two cis OCCO dihedrals were constrained to remain zero. This C_2' geometry is not a local minimum for 18-crown-6 but is a

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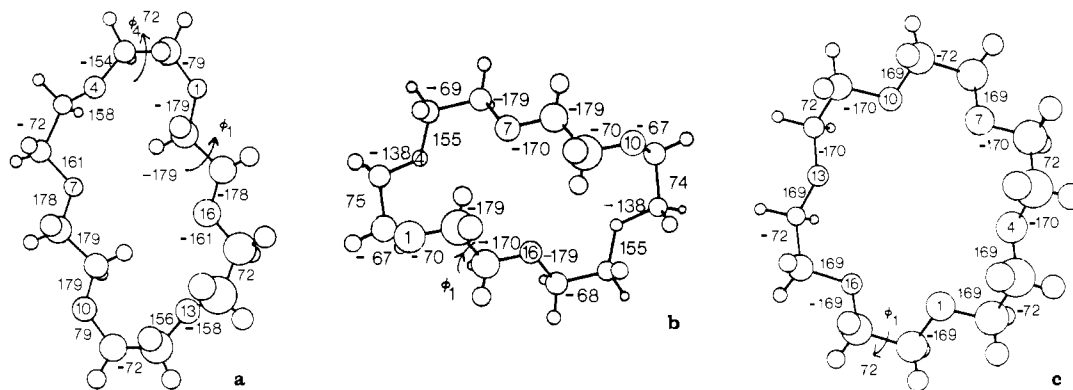
Figure 1. (a) A plot of energy-optimized C_i structure ($q_0 = -0.3$) with dihedral angles indicated. (b) A plot of energy-optimized C_2 structure ($q_0 = -0.3$). (c) A plot of energy-optimized D_{3d} structure ($q_0 = -0.3$).

reasonable representation of the conformation and properties of dibenzo-18-crown-6.

Results

A. Analysis of Empirical Parameters To Use in the Calculations and Studies of Cation–Dimethyl Ether and Cation–Water Interactions.

The parameters determined in this study are the following; (a) the partial atomic charges on oxygen and CH_2 (or CH_3) groups and (b) the nonbonded parameters to use for the alkali cations. We also needed to find appropriate partial charges to use for O and H atoms of the water.

Our first set of calculations was on the complexes $Na^+\cdots O$-$(CH_3)_2$ and $K^+\cdots O(CH_3)_2$. The excellent agreement between quantum-mechanically[31] calculated and experimental[32] ΔH for the $K^+\cdots OH_2$ and $Na^+\cdots OH_2$ complexes leads us to expect that the calculated $R(M^+\cdots O)$ distances are substantially correct. Experiments[33] and calculations[34] on $Li^+\cdots(OCH_3)_2$, $Li^+\cdots$ $(HOCH_3)$, and $Li^+\cdots(OH_2)$ and calculations on $K^+\cdots O(CH_3)_2$, $K^+\cdots(HOCH_3)$, and $K^+\cdots(OH_2)$[35] lead us to conclude that the experimental $\Delta H(K^+\cdots O(CH_3)_2)$ is comparable to $\Delta H(K^+\cdots OH_2)$ and $R(M^+\cdots O)$ is likely to be nearly identical for these two complexes.[36] We thus varied the charge on the oxygen q_0 and the nonbonded parameters for Na^+ and K^+, using the Slater–Kirkwood approach[37] in order to fit the "experimental" ΔH and $R(M^+\cdots O)$. Table I contains the corresponding results. From these results we extrapolate parameters for Rb^+ and Cs^+. A limited variation of the polarizability α of the cation revealed that ΔE and R were relatively insensitive to this parameter. Since the various ionic radii scales[39] indicated $R(Na^+) < R(K^+)$ by ~ 0.4 Å, we attempted to use a set of parameters with $R(K^+) - R(Na^+)$ = 0.4. The reproduction of the "experimental" ΔH's (for $K^+\cdots OH_2$ and $Na^+\cdots OH_2$) required a q_0 of -0.6. Such a charge leads to a calculated dipole moment of 2.48 D, significantly larger than the dipole moment of dimethyl ether. On the other hand $q_0 = -0.3$ leads to a calculated dipole moment for dimethyl ether in good agreement with experiment ($\mu = 1.3$ D). Thus, a charge on oxygen of -0.3 seems most appropriate for the crown itself and a charge on oxygen of -0.6 seems most appropriate for the cation/crown complex.

Table II. Interaction Energy and Geometry of Cation-Hydrate Complexes and $(H_2O)_6$

complex	$q_0 = -0.6$		$q_0 = -0.8$			
	$-E_T{}^a$	$R,^b$ Å	$-E_T{}^a$	$R,^b$ Å	$-\Delta H_{\text{exptl}}{}^c$	$-\Delta H_{\text{solv}}{}^d$
$Na^+\cdots OH_2$	18.4	2.25	25.8	2.19	24.0	
$Na^+\cdots(OH_2)_6$	89.2	2.31	113.0	2.28	96.4	106.1
$K^+\cdots OH_2$	12.9	2.74	17.9	2.67	17.9	
$K^+\cdots(OH_2)_6$	65.4	2.79	84.0	2.75	79.7	86.1
$Rb^+\cdots OH_2$	11.4	2.93	15.9	2.86	15.9	
$Rb^+\cdots(OH_2)_6$	58.6	2.98	75.6	2.93	e	81.0
$Cs^+\cdots OH_2$	9.9	3.20	13.6	3.13	13.7	
$Cs^+\cdots(OH_2)_6$	51.4	3.26	66.4	3.21	e	75.2
$(H_2O)_6$	36.4	2.48	82.3	2.30		

a Total energy of complex = total interaction energy (kcal/mol). b O···M distance for cation complexes; O···O distance for $(H_2O)_6$. c Experimental mono- or hexahydration enthalpy (ref 32). d Experimental total solvation energy of the appropriate cation (ref 40). e The hexahydrate energies for these cations were not determined in ref 32.

The relative insensitivity of the Na^+ and K^+ energies and distances to N_{eff} and α caused us to take extrapolated values of these parameters for Rb^+ and Cs^+. For the van der Waals radius of these ions, we used the fact that the experimental ionic radius of Rb^+ is 0.2 Å larger than K^+ and the ionic radius of Cs^+ is another 0.2 Å larger.[39]

Because we want to examine the relative hydration and crown complexation energies of cations, we turn to calculations on $M^+\cdots OH_2$ and $M^+\cdots(OH_2)_6$ interactions. Table II contains the results of calculations on $M^+\cdots OH_2$ and $M^+\cdots(OH_2)_6$ complexes as a function of the charge on oxygen. To reproduce the monomer dipole moment of water requires $q_0 = -0.6$; on the other hand, a charge of $q_0 = -0.8$ fits the experimental ΔH's for Na^+ and $K^+\cdots OH_2$ interactions better.

It is sensible that the model with $q_0 = -0.8$, which contains a dipole moment for H_2O greater than that of the isolated monomer, is required to quantitatively fit these ΔH values for monohydration, since quantum-mechanical studies show that the polarization energy is the second-largest attractive component of cation–water interaction energies.[28,35]

We also carried out calculations on the cyclic hexamer of $(H_2O)_6$ with the same parameters, using no van der Waals repulsion between H and O, as has precedent in the work of Hagler et al.[41] With $q_0 = -0.6$, this leads to a reasonable $-\Delta E$,[42] but a too small R (2.48 Å).[43]

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Table III. Summary of Total Energies of 18-Crown-6 Uncomplexed and Complexed

oxygen charge	conformation						
	D_{3d}	C_i	C_i'	C_2	C_2'	C_1	d
uncomplexed crown							
−0.6	193.3	181.4	196.2	184.3	197.4	202.3	180.2
−0.4	87.2	82.5	89.2		98.0		
−0.3	48.3	47.2	50.2	49.7	58.8	56.6	49.3
a	7.8	0.0	5.0			4.4	
M$^+$···complexes							
Na$^+$ −0.6	114.6	137.6	120.6		123.4	111.5	
−0.4	29.0	48.8[b]	34.7		34.5	27.2	
−0.3			8.8			3.4	
K$^+$ −0.6	119.6	134.7	131.6		131.9	126.7	
−0.4	33.5	57.3	43.8		43.7	41.6	
−0.3	3.5						
Rb$^+$ −0.6	124.6	136.1[c]	139.9		138.2	133.9	
−0.4	38.8	39.2[c]			51.6	46.8	
−0.3	12.4						
Cs$^+$ −0.6	132.9	136.6[c]	157.8		146.1	140.7	
−0.4	45.1	53.4[c]			56.5	51.5	
−0.3	16.9						

[a] Relative energies calculated by Bovill et al. (ref 18).   [b] Highly distorted; however, it is 6.7 kcal/mol more stable than the structure of exact C_i symmetry.   [c] The converged structure becomes of D_{3d} type in the case of Rb$^+$ and Cs$^+$ (see Table VI), due to the instability of the initial structure when the cation is at the center of the cavity (see text). The corresponding K$^+$ C_i structure is already very distorted compared to the uncomplexed C_i structure (compare Tables IV and V).   [d] C_2 distorted structure (see text).

Table IV. Results of Calculations of 18-Crown-6 Uncomplexed

	oxygen charge = −0.6 with the following conformations[a]						oxygen charge = −0.3 with the following conformations[a]							
	D_{3d}	C_i	C_i'	C_2	C_2'	C_l	D_{3d}	C_i	C_i^g	C_i'	C_2	C_2'	C_1	C_1'
energy results														
$E_T{}^b$	193.3	181.4	196.2	184.3	197.4	202.3	48.3	47.2		50.2	49.7	58.0	56.6	47.9
el^a	184.7	175.4	186.6	174.2	183.6	189.7	49.8	45.4		50.3	45.4	51.6	52.2	47.6
VdW^d	−4.8	−4.7	−4.0	−5.0	−3.7	−3.5	−5.0	−4.5		−3.8	−4.1	−4.7	−4.1	−4.7
internal^e	13.5	10.7	13.7	15.2	17.4	16.1	3.6	6.3		3.7	8.3	11.2	8.5	5.0
dihedral angles^f														
ϕ_1	87	179	81	−179	1	−79	72	−179	174	66	−179	1	−62	72
ϕ_2	−161	180	−150	−66	171	152	−169	−179	170	−168	−70	171	158	−178
ϕ_3	161	−75	166	−56	−76	−162	169	−79	−79	167	−67	−168	−174	177
ϕ_4	−87	76	−82	80	75	88	−72	72	75	−69	75	72	68	−73
ϕ_5	161	−147	−141	−142	−170	−146	169	−154	−155	−166	−138	166	−158	176
ϕ_6	−161	147	163	126	170	157	−170	158	166	−176	155	165	164	−178
ϕ_7	87	−81	−80	−74	−170	−90	72	−72	−68	−65	−69	−73	−58	73
ϕ_8	−161	160	162	−178	77	158	−170	161	176	173	−179	170	180	−165
ϕ_9	161	−179	−74	−139	−170	−159	169	178	175	−76	−170	−174	−166	171
ϕ_{10}	−87	−179	−82	−178	1	75	−72	179	−175	−66	−179	0	37	−69
ϕ_{11}	160	180	150	−64	171	60	169	179	−170	167	−70	172	79	164
ϕ_{12}	−160	75	−166	−57	−76	−154	−170	79	80	−167	−67	−167	−155	−166
ϕ_{13}	87	−76	82	81	75	83	72	−72	−75	69	74	72	67	71
ϕ_{14}	−161	147	141	−140	−170	−165	−170	156	155	166	−138	−166	−170	−140
ϕ_{15}	161	−147	−163	125	168	58	169	−158	−166	176	155	164	77	168
ϕ_{16}	−87	81	80	−75	−76	48	−72	72	68	65	−68	−73	37	180
ϕ_{17}	161	−160	−162	−177	78	101	169	−161	−176	−173	−179	171	114	−175
ϕ_{18}	−161	178	74	−137	−172	−67	−169	−178	−175	76	−170	−175	−75	−85
nonbonded distances, Å														
O$_1$···O$_{10}$	6.4	7.3	6.7	6.7	6.3	5.9	6.0	7.2	7.0	6.3	7.1	5.7	5.5	6.6
O$_4$···O$_{13}$	6.4	7.4	5.0	5.8	6.2	4.3	6.0	7.0	6.8	4.7	6.0	6.2	4.1	6.3
O$_7$···O$_{16}$	6.4	4.4	7.1	3.5	6.3	5.7	6.0	4.5	4.3	6.8	3.5	5.6	5.2	5.6

[a] Optimized structures starting with the crystal structure of 18-crown-6 complexed with K$^+$ (D_{3d}); uncomplexed (C_i); complexed with PhSO$_2$NH$_2$ (C_i'); generated from half of C_i structure, setting ϕ_2 and ϕ_{11} gauche (C_2); complexed with Na$^+$ (C_1); from dibenzo-18-crown-6 complexed with Na$^+$ (C_2').   [b] Total energy in kcal/mol; E_T = el + VdW + internal.   [c] Total electrostatic energy.   [d] Total van der Waals energy.   [e] Sum of bond-length, bond-angle, and dihedral-angle strain.   [f] Optimum torsional angles (in deg); ϕ_1, ϕ_4. ..., ϕ_{16} are the angles of rotation around the C–C bonds.   [g] Experimental values (ref 9).

B. Calculations on 18-Crown-6 and Its K$^+$ and Na$^+$ Complexes.

We now turn to calculations on the 18-crown-6 itself. We have carried out such calculations with q_0 = −0.3 and −0.6, starting with the geometry of the crystal of 18-crown-6[9] (C_i) and its

complexes with benzenesulfonamide, (C_i'), K$^+$ (D_{3d}), and Na$^+$ (C_1), as well as a C_2 symmetry structure with internal coordinates derived from the C_i structure (see Figure 1b). . The 18-crown-6 fragment of the Na$^+$/dibenzo-18-crown-6 complex[20] was also considered; it will be referred to as C_2'. The results are reported in Table IV. We also used a distance geometry approach[44] to

(43) With q_0 = −0.8, −ΔE is far too large and R far too small for (H$_2$O)$_6$. It thus appears that for studies of hydrogen bonding, at least a small H···O repulsion is required to give a reasonable ΔE and R for (H$_2$O)$_6$. That is not the focus of this study, however, and here we only make use of the (reasonable) −ΔE for (H$_2$O)$_6$ with q_0 = −0.6.

(44) Kuntz, I. D.; Crippen, G. M.; Kollman, P. A.; Kimelman, D. *J. Mol. Biol.* **1976**, *106*, 983.

Table V. Comparison of 18-Crown-6 Na$^+$ and K$^+$ Complexes (Oxygen Charge = -0.6)[a]

	Na$^+$ with the following conformations					K$^+$ with the following conformations				
	D_{3d}	C_i	$C_i{}'$	$C_2{}'$	C_1	D_{3d}	C_i	$C_i{}'$	$C_2{}'$	C_1
energy results										
E_T	115.7	137.6	120.6	123.4	111.5	119.6	134.7	131.6	131.9	126.7
crown itself										
el	221.1	186.1	218.0	230.2	226.3	214.6	207.2	211.1	217.5	210.8
VdW	−4.4	−3.6	−4.1	−3.2	−3.5	−4.7	−4.8	−4.5	−4.3	−4.6
internal	6.3	15.8	9.5	14.5	12.1	4.8	22.5	11.8	17.3	12.2
crown···M$^+$ interaction										
el	−107.5	−66.3	−104.4	−118.5	−126.8	−98.0	−96.3	−93.4	−103.7	−100.0
VdW	0.2	5.5	1.6	0.3	3.3	2.9	6.0	6.4	5.2	8.2
total	−107.2	−60.8	−102.9	−118.2	−123.4	−95.1	−90.3	−86.9	−98.6	−91.8
dihedral angles										
ϕ_1	46	−161	44	−1	−42	46	−61	45	−2	−50
ϕ_2	177	171	178	−174	−167	−175	171	180	−175	162
ϕ_3	180	−76	−176	180	172	178	−137	−175	−177	180
ϕ_4	−53	54	−38	37	44	−52	24	−37	−177	50
ϕ_5	−177	−179	−168	175	−172	−176	178	−164	41	−170
ϕ_6	180	170	167	−175	−178	180	173	167	179	179
ϕ_7	48	−29	−48	−43	−44	48	−9	−52	−179	−51
ϕ_8	−177	157	175	−178	−173	−174	172	180	−43	176
ϕ_9	176	165	−91	173	−173	175	178	−96	173	−165
ϕ_{10}	−43	161	−48	−1	36	−49	61	−45	173	44
ϕ_{11}	−175	−172	180	−171	87	180	−171	−179	−171	81
ϕ_{12}	174	76	178	−177	−163	176	137	173	−175	−161
ϕ_{13}	43	−55	43	41	47	54	−25	37	40	55
ϕ_{14}	−179	179	168	172	−166	−175	−178	164	177	−163
ϕ_{15}	177	−170	−169	−176	88	172	−174	−166	−178	82
ϕ_{16}	−44	29	45	−38	32	−50	9	49	−40	34
ϕ_{17}	−179	−157	−176	−170	120	−177	−173	180	−173	117
ϕ_{18}	177	−165	93	166	−82	179	−179	95	166	−79
M$^+$···oxygen distances, Å										
M$^+$···O$_1$	3.01	3.93	2.78	2.63	2.59	2.82	3.31	2.78	2.90	2.76
M$^+$···O$_4$	3.06	3.05	2.65	2.63	2.56	2.84	2.81	2.65	2.84	2.84
M$^+$···O$_7$	2.87	2.26	3.18	2.74	2.45	2.89	2.67	3.18	2.78	2.69
M$^+$···O$_{10}$	2.53	3.93	2.86	2.80	2.54	2.90	3.31	2.86	2.78	2.75
M$^+$···O$_{13}$	2.51	3.05	2.70	2.67	2.32	2.94	2.81	2.70	2.81	2.84
M$^+$···O$_{16}$	2.87	2.26	3.04	2.58	2.58	2.94	2.67	3.04	2.84	2.75
average	2.81	3.08	2.87	2.67	2.51	2.89	2.93	2.87	2.82	2.77

^{a} See footnotes for Table IV for the definitions of E_T, el, and VdW. In the M$^+$···crown complexes, the total energy E_T is the sum of the energy of the crown itself (el + VdW + internal) and of the crown···M$^+$ total interaction energy.

generate a number of ring-closed structures with randomly generated dihedral angles, and after energy refinement, they all had significantly higher energies than those reported in Table IV. With $q_0 = -0.3$ (the most reasonable charge set for uncomplexed crown), the structure with the lowest energy is the one with C_i symmetry. Figures 1a–c illustrate this C_i structure, as well as C_2 and D_{3d} structures.

In order to examine the flexibility of the crown itself, we carried out calculations on the $C_i \rightarrow D_{3d}$ conversion for a one-step symmetrical process. Using the optimized dihedral angles for the C_i structure (Table IV; the signs of all of the dihedral angles of D_{3d} should be reversed to allow the maximum congruence of the C_i and D_{3d} angles), ϕ_1, ϕ_3, ϕ_{10}, and ϕ_{12} were constrained in $\sim 20°$ increments to change linearly from their values in the C_i structure to that of the D_{3d}. The remaining dihedral angles, bond angles, and bond lengths were energy minimized at each step of the conversion. Such a calculation led to a calculated barrier of 7.6 kcal/mol ($q_0 = -0.3$).

We have carried out the energy calculations on the alkali M$^+$ crown complexes, starting with the geometries of the uncomplexed crown (C_i) of complexes with benzenesulfonamide ($C_i{}'$), Na$^+$ (C_1), K$^+$ (D_{3d}), and of the 18-crown-6/Na$^+$ fragment of the dibenzo-18-crown-6/Na$^+$ complex ($C_2{}'$). In the case of C_i and $C_i{}'$ and D_{3d} crown complexes, we used the computer-graphics program CHEM[45] to dock the cations to a location near the center of the crown,
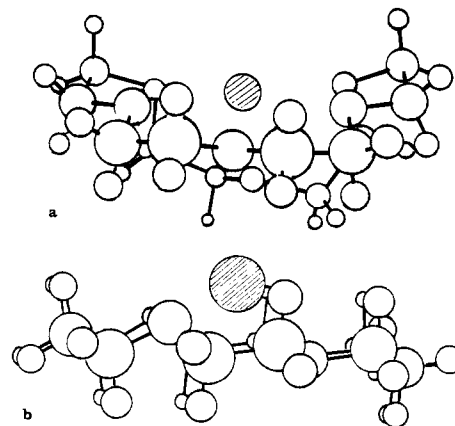
(45) Dearing, A., CHEM program, unpublished work.

Figure 2. (a) The optimized structure for Na$^+$–crown complex (C_1). (b) The optimized structure for Cs$^+$–crown.

Table V summarizes the results of such calculations and Figure 2a shows the Na$^+$ C_1 structure. It is encouraging to find that for the Na$^+$ complex the lowest-energy structure is the (observed) C_1 structure, and for the K$^+$ complex the lowest energy is also the observed (D_{3d}) structure. A comparison of the energy components indicates that the basis for the differentiation is the cation/crown interaction energy, which for Na$^+$ greatly favors the C_1 structure but for K$^+$ slightly favors D_{3d}. For each cation complex, the internal energy of the crown is much lower for D_{3d} than for C_1. We also carried out a parallel set of calculations with

Table VI. Comparison of 18-Crown-6 Na^+ and K^+ Complexes (Oxygen Charge = -0.4)[a]

	Na^+ with the following conformations						K^+ with the following conformations					
	D_{3d}	C_i	C_i'	C_2'	C_1	C_1[b]	D_{3d}	D_{3d}[b]	C_i	C_i'	C_2'	C_1
energy results												
E_T	29.0	54.1	34.7	34.5	27.2	3.4	33.5	3.5	57.3	43.8	43.7	41.6
crown itself												
el	99.1	83.7	98.3	103.1	101.7	57.2	96.8	55.7	83.1	94.6	97.5	95.5
VdW	-4.3	-3.7	-3.9	-2.9	-3.0	-2.9	-4.6	-4.3	-5.0	-4.4	-4.2	-4.5
internal	5.3	12.3	10.9	13.7	9.9	8.8	3.7	4.6	11.5	9.5	14.1	10.7
crown···M^+ interaction												
el	-71.2	-41.5	-71.9	-79.7	-84.3	-62.2	-65.4	-52.4	-34.6	-62.6	-79.7	-66.7
VdW	0.0	3.5	1.5	0.4	2.8	2.5	3.1	-0.1	4.1	6.6	6.0	6.6
total	71.1	-38.0	-70.4	-79.3	-81.4	-59.7	-62.3	-52.5	-32.3	-55.9	-63.8	-60.1
dihedral angles												
ϕ_1	47	-164	43	-1	-45	-47	47	48	-147	47	-1	-51
ϕ_2	180	172	179	-174	167	167	-179	180	165	-179	-176	163
ϕ_3	-178	-80	-176	179	172	172	-179	-178	-108	-174	-179	181
ϕ_4	-52	53	-39	38	48	50	-52	-53	58	-41	44	49
ϕ_5	-177	178	-170	174	-173	-173	-176	-177	177	-164	179	-171
ϕ_6	179	176	167	-175	-177	-177	179	179	-175	169	-179	180
ϕ_7	48	-35	-41	-45	-47	-49	49	49	-62	-51	-51	-48
ϕ_8	-179	156	176	-178	-172	-173	-178	180	150	178	179	177
ϕ_9	178	170	-98	174	-175	-174	178	179	-172	-95	176	-166
ϕ_{10}	-45	164	-43	0	39	42	-51	-47	147	-47	1	42
ϕ_{11}	-176	-172	-179	-172	84	82	180	-178	-166	179	-172	84
ϕ_{12}	175	80	175	-178	-167	-168	-177	176	108	174	-176	-162
ϕ_{13}	47	53	38	42	49	51	57	50	-58	41	44	51
ϕ_{14}	179	-178	170	172	-170	-172	-178	179	-177	164	176	-163
ϕ_{15}	179	-176	-167	-176	87	86	175	179	174	-169	-179	87
ϕ_{16}	-46	35	41	-41	36	37	-52	-48	62	50	-45	35
ϕ_{17}	-178	-157	-177	-169	120	119	-177	-178	-150	178	-173	119
ϕ_{18}	178	-170	97	167	-82	-81	178	178	172	95	168	-80
M^+···oxygen distances, Å												
M^+···O_1	2.97	3.84	2.75	2.62	2.57	2.58	2.82	2.97	3.70	2.81	2.83	2.76
M^+···O_4	3.04	3.00	2.40	2.62	2.57	2.58	2.86	3.05	2.82	2.67	2.81	2.88
M^+···O_7	2.85	2.36	3.06	2.71	2.46	2.47	2.86	2.85	2.91	3.07	2.79	2.72
M^+···O_{10}	2.57	3.84	2.75	2.76	2.53	2.54	2.89	2.60	3.70	2.81	2.79	2.77
M^+···O_{13}	2.53	3.00	2.40	2.65	2.38	2.41	2.89	2.55	2.82	2.67	2.79	2.92
M^+···O_{16}	2.87	2.36	3.06	2.58	2.55	2.55	2.94	2.89	2.91	3.07	2.79	2.76
average	2.80	3.07	2.74	2.66	2.51	2.52	2.88	2.82	3.14	2.85	2.80	2.80

[a] See footnotes for Table V. [b] These results are obtained with $q_0 = -0.3$.

$q_0 = -0.3$ and $q_0 = -0.4$, and the results are qualitatively similar to those with $q_0 = -0.6$.

C. Calculations on the 18-Crown-6 Complexes with Rb⁺ and Cs⁺. Because the free energy and enthalpy of association in solution of 18-crown-6 complexes differ significantly for the different cations, we carried out calculations on the Rb⁺ and Cs⁺ 18-crown-6 complexes (Table VI). In both the crown/Rb⁺ and crown/Cs⁺ complexes, $q_0 = -0.6$, we found a large preference for the D_{3d} structure over C_i and C_1. We report the results for only some of these calculations in Table VI.

The optimized structure of Cs⁺ crown is shown in Figure 2b; note that upon optimization, starting with the geometry of K⁺ crown, the Cs⁺ moves about 1 Å out of the mean plane of the ring. Such a structure has been observed in the X-ray structure of a Cs⁺/crown complex,[13] If, however, the Cs⁺ is constrained to be at the center of symmetry, the energy increases by 3.7 kcal/mol ($q_0 = -0.6$) and 9.0 kcal/mol ($q_0 = -0.3$), respectively, while the O–C–C–O dihedral angle increases by 16°. Most of this higher energy for the "constrained" structure is due to crown–cation van der Waals repulsion. In the crown itself, the higher internal strain energy is mainly compensated by the lower electrostatic energy (see Table VI, structures referred to as D_{3d} and C_i).

D. Calculations on Cation/Crown–Water Complexes. Because the hydration of the crown/cation complex plays an important role in determining the thermodynamics of crown complexation, we studied the interaction of two water molecules with the cation/crown complexes, starting with the water molecules at O···M⁺ distances near the minima found in the M⁺···OH₂ interaction, with approximate local C_{2v} symmetry for the M⁺···OH₂ interaction and with one water "at each face of" the crown/cation complex. We

used the energy-minimized structures for the crown/cation complex to start the calculation. The energies and energy components for the M⁺/crown···2H₂O complexes are reported in Table VII.

E. Calculations on the Cation Interaction with Pentaglyme. The open-chain analogue of 18-crown-6 is pentaglyme, CH₃O(CH₂-CH₂O)₄OCH₃, for which we have considered three conformers: The first is an all-trans structure, because it is probably one of the most stable uncomplexed forms, based on the results of calculations on different conformers of the smallest parent compound, dimethoxyethane.[46] The second conformer is of "pseudo-D_{3d}" symmetry, derived from the geometry of the D_{3d} crown ether, with the end methyls rotated away from each other, This structure may correspond to the conformation of pentaglyme in its cation complexes, by analogy with the Hg²⁺ complex of tetraethylene glycol–dimethyl ether.[47] The third conformer

(46) We carried out calculations on dimethoxyethane, employing the parameters used in the crown studies, with different q_0 (-0.3, -0.4, -0.6) and V_2(OCCO) = 1.5 kcal/mol, as well as the V_2(OCCO) = 1.0 kcal/mol, employed in most of these studies and in the calculations on nucleotides. All calculations find that among the five structures considered (aaa, ag⁺g, ag⁺g⁺, aga, and aag), aaa is the most stable and ag⁺g⁺ is the least stable. The calculations with $q_0 = -0.3$, V_2(OCCO) = 1.0 kcal/mol give the aga structure 0.4 kcal/mol higher in energy than the aaa structure. When degeneracy is taken into account, that set of parameters lead to approximately equal populations of gauche and anti conformers around the C–C bond. Changing V_2 to 1.5 kcal/mol leads to equal stability of aga and aaa conformers. For experimental results on dimethoxyethane, see: Snyder, R. G.; Zerbi, G. *Spectrochim. Acta, Part A* **1967**, *23A*, 391. Ogawa, Y.; Ohta, M.; Matsuura, H.; Harada, I.; Shimanouchi, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 650. Astrup, E. E. *Acta Chem. Scand., Ser. A* **1979**, *A33*, 655 and references cited.

(47) Iwamoto, R. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1114.

Table VII. Energies and Optimized Structures for
M⁺/Crown···2H₂O Complexes[a]

	conformations for Na⁺, K⁺, Rb⁺, and Cs⁺					
	Na⁺		K⁺		Rb⁺	Cs⁺
	D_{3d}	C_1	D_{3d}	C_1	D_{3d}	D_{3d}
energy results						
E_T	97.1	96.0	106.9	128.9	111.2	118.6
crown itself						
el	213.4	218.6	207.6	202.6	203.5	197.4
VdW	−4.7	−4.6	−4.8	−5.4	−4.9	−4.9
internal	6.6	28.2	6.4	22.7	7.0	6.7
crown···M⁺						
el	−99.1	−123.5	−90.5	−61.6	−85.6	−69.1
VdW	0.1	5.1	1.3	3.0	5.1	3.7
crown···(OH₂)₂						
el	15.3	2.4	11.3	−24.6	10.0	1.2
VdW	−2.8	−0.6	−2.6	0.3	−2.4	−0.8
M⁺···(OH₂)₂						
el	−34.5	−34.3	−25.1	−12.1	−23.0	−16.8
VdW	2.0	3.9	3.0	3.1	1.6	1.0
M⁺···OH₂						
distances, Å	2.33	2.32	2.76	2.63	3.0	3.33
	2.54	2.29	2.75	4.93[b]	3.0	3.26

[a] The total energy E_T is the sum of the energy of the crown itself and of the different crown···M⁺, crown···(OH₂)₂, M⁺···(OH₂)₂, and H₂O···OH₂ (not included in the table; less than 1 kcal/mol) interaction energies. [b] During the optimization this water molecule became hydrogen bonded to the crown, rather than bonded to K⁺.

corresponds to a helical type structure with aga units as observed in the polymer poly(ethylene oxide).[48] We calculated it to be less stable than the all-trans conformer (by 1.3 kcal/mol, $q_0 = -0.3$, and by 12.8 kcal/mol, $q_0 = -0.6$). Table VIII contains the results of energy minimization on pentaglyme uncomplexed (all-trans and pseudo-D_{3d}) and on its M⁺ complexes ("pseudo-D_{3d}").

Discussion

A. Lowest-Energy Structures. 1. 18-Crown-6 Uncomplexed. It is clear from the results of our calculations (Table III) that we would predict the C_i structure of the crown to be more stable than the D_{3d}, C_i', C_2, C_2', or C_1 in the gas phase, with the dielectric constant $\epsilon = 1$. The fact that this is the actual structure observed in the crystal and in nonpolar solvents is encouraging and suggests that crystal-packing forces do not change the relative stabilities of the different structures. The magnitudes of the energy difference between structures are, however, sensitive to the electrostatic charges on the atoms and, thus, to a change in dielectric constant. The energy components reported in Table IV make it clear that if ϵ becomes large, the D_{3d} structure is expected to be the most stable conformer of 18-crown-6, as observed in more polar solvents at low temperatures.[8] This is also supported by calculations with no electrostatic charges ($\epsilon = \infty$), which show that the D_{3d} structure is more stable than C_i (3.4 kcal/mol).

The major reason why the C_i structure is the lowest-energy structure (with $q_0 = -0,3$) is its low internal electrostatic energy. Only the C_2 structure has a comparably low electrostatic energy, but it has more internal strain than the C_i (Table IV).

The root-mean-square difference between the atomic positions of the calculated and experimental C_i structures is 0.15 Å. The torsional angles calculated ($q_0 = -0.3$) for 18-crown-6 C_i are in good agreement with the X-ray values, the largest deviation being 15°.

The dependence of dihedral angle on charge is worthy of note (Table IV). Not surprisingly, the gauche OCCO angles in the various structures are larger for $q_0 = -0.6$ than for $q_0 = -0.3$, reflecting the greater O···O repulsion in the former case. With

$q_0 = -0.3$, the crown also tends to become slightly more compact, as indicated by the O···O distances reported in Table IV.

The observation of a significant temperature dependent dipole moment for 18-crown-6[49] is apparently inconsistent with the X-ray observation of only C_i and D_{3d} structures for the crown itself. We thus used distance-geometry techniques to generate a new crown structure (C_1') that is a linear combination of C_i and D_{3d}. Since the D_{3d} structure can be described as (g⁺ttg⁻tt)₃ and the C_i as (g⁺ttg⁻ttttg⁺)₂, we took the C_i structure and replaced its last three dihedral angles by g⁺tt. This structure, when energy refined, had an energy only 0.7 kcal/mol above the C_i structure (Table IV) and a dipole moment ($q_0 = -0.3$) of 1.92 D. The presence of a reasonable population of such a conformer in solution is consistent with the dielectric measurements.[50]

2. The Alkali Complexes of 18-Crown-6. K⁺ "prefers" the D_{3d} structure while Na⁺ "prefers" the C_1 structure. Why is this? In both cases, as was noted for the uncomplexed crown, the D_{3d} structure is intrinsically more stable than the C_1 structure from the point of view of internal and electrostatic strain. It is also clear that K⁺ does not fit as well into the C_1 as into the D_{3d} structure (note the larger crown-M⁺ van der Waals repulsion in the former case). Na⁺ is able to overcome the greater internal strain of the C_1 structure because of the significantly more favorable Na⁺···crown interaction in this conformer. The net crown Na⁺···crown interaction energy for the C_1 structure, $q_0 = -0.6$, is almost five times the individual dimethyl ether···Na⁺ interaction energy, whereas in the D_{3d} structure, the net interaction is closer to four times an individual ether···Na⁺ interaction. The C_1 structure allows the shortest O···M⁺ contacts and this is presumably why Na⁺ intrinsically prefers this structure even without the additional stabilization brought about by one water molecule in the crystal structure.[9]

It can be seen from the ϕ_i angles that the "D_{3d}" complexes of Na⁺ and K⁺ reported in Table V are not of exact D_{3d} symmetry; this is because the cation was not located initially exactly at the center of the crown. In particular, there are two shorter Na⁺···O distances of 2.5 Å in this structure, consistent with the intrinsic preference of Na⁺ for such closer contacts. These results suggest that the deviation from exact D_{3d} symmetry observed in the K⁺/crown complex is not only due to crystal or counterion effects but may be an intrinsic property of the structure.

The remaining structures (C_i, C_i', C_2) all have significantly less favorable M⁺···crown interaction energies. This can be related to the fact that none of these structures affords the possibility of six simultaneous good M⁺···O interactions. Particularly in the most stable uncomplexed C_i structure, the O₁···O₁₀ and O₄···O₁₃ distances are too long, and the O₇···O₁₆ distance is too short. (Compare Figures 1a (C_i) and 1c (D_{3d}).) The results suggest the need of conformational change prior to complexation, which our calculations on the $C_i \rightarrow D_{3d}$ one-step conversion suggest to be rather facile. It is of interest that the C_2' structure, which is the structure found in the Na⁺/dibenzo crown complex, also has the second most favorable Na⁺···crown interactions and the best M⁺···crown interactions in the K⁺, Rb⁺, and Cs⁺ cases. Experimentally, this dibenzo crown has a larger affinity for these cations than does 18-crown-6 in some solvents.[25c]

For the K⁺, Rb⁺, and Cs⁺ crown complexes the D_{3d} structure has the lowest energy. This structure has nearly the most favorable M⁺···crown interaction (with the exception of C_2') and has a significantly lower energy for the crown itself than all the other structures considered. It is of interest that the Cs⁺/crown C_i structure optimized starting with the cation at the center of symmetry refines to a structure of D_{3d} symmetry. This large conformational change is presumably caused by the large M⁺···O van der Waals repulsion when M⁺ = Cs⁺, since O₇···O₁₆ in this

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(50) For example, using our calculated relative energies for C_i (0), C_i' (0.7 kcal/mol), and D_{3d} (1.1 kcal/mol) and relative degeneracies of these structures (3:6:2), we would predict a dipole moment of 0.8 D at 298 K, which is of the right magnitude to explain the experimental results.[49]

Table VIII. Energies of Pentaglyme and Its Complexes (kcal/mol)

	uncomplexed				complexed				
	all-trans		D_{3d}		Na$^+$ D_{3d}	K$^+$ D_{3d}		Rb$^+$ D_{3d}	Cs$^+$ D_{3d}
oxygen charge	−0.3	−0.6	−0.3	−0.6	−0.6	−0.6	0.3	−0.6	−0.6
energy results									
E_T	37.5	143.4	43.6	156.0	91.9	97.0	7.3	101.2	108.7
crown alone									
el	35.5	140.2	41.3	150.1	183.8	180.1	45.2	174.8	170.2
VdW	−3.1	−3.1	−4.7	−3.7	−2.6	−4.6	−4.8	−5.1	−5.1
internal	5.1	6.3	6.1	9.7	9.8	12.4	9.6	11.8	14.7
pentaglyme···M$^+$ interaction									
el					−99.1	−95.3	−46.8	−87.4	−81.6
VdW					0.1	4.4	4.2	7.2	10.6
total					−99.0	−90.9	−42.6	−80.2	−71.1
M$^+$···oxygen distance(Å)									
minimum					2.55	2.80	2.82	2.93	3.07
maximum					3.01	2.92	2.95	2.97	3.11

structure is only about 4.5 Å. A conformational change from C_i → D_{3d} prior to complexation would permit the formation of the most stable "out-of-plane" complex, without the initial bad M$^+$···crown van der Waals contacts.

Comparison of calculations with $q_0 = -0.6$ and with $q_0 = -0.4$ shows that the dihedrals and the M$^+$···O distances are rather insensitive to the choice of q_0. The torsional angles calculated for C_1 Na$^+$/crown and D_{3d} K$^+$/crown are in qualitative agreement with experiment, with all of the largest deviation involving the OCCO angles (about 17° smaller than the experimental values ($q_0 = -0.6$)).

3. Cation/Crown–2H$_2$O Complexes. "Solvating" the crown K$^+$ and crown Na$^+$ complexes with two water molecules does not alter the relative preferences for D_{3d} and C_1 structures, respectively. The two waters ($q_0 = -0.6$) interact more strongly with Na$^+$ [ΔE(Na$^+$···2OH$_2$) = −30 kcal/mol; R(O···Na$^+$) = 2.5 Å in both D_{3d} and C_1 structures] than with K$^+$ [ΔE = −22 kcal/mol; R-(O···K$^+$) = 2.8 Å]. In the case of K$^+$, only the D_{3d} structure is hydrated very favorably, with the net stabilizing effect of K$^+$··· ·2H$_2$O interactions and a lowering of the crown energy compensated by repulsive crown–2H$_2$O repulsion and reduced crown–K$^+$ interactions, resulting in a net stabilization of about −13 kcal/mol (Table VII). It is also worth noting that "dihydration" of the Na$^+$ complex reduces the energy difference between the D_{3d} and C_1 structures from 4 to 1 kcal/mol ($q_0 = -0.6$), suggesting that even if the C_1 structure is intrinsically preferred, as is observed in the crystal, the D_{3d} conformer is also likely to be populated in aqueous solution. This result is also consistent with the fact that in the crystal structure of dicyclohexyl-18-crown-6/Na$^+$ complex (isomer B), where the coordination sphere of Na$^+$ is completed by two H$_2$O molecules, the ring adopts a D_{3d}-type conformation.[22]

Although the K$^+$···OH$_2$ and Na$^+$···OH$_2$ calculated interaction energies are about 13 and 18 kcal/mol, respectively (Table II), the total energy lowering on dihydration of the crown/M$^+$ complexes is only 13–16 kcal/mol. The interaction-energy analysis (Table VII) also indicates a much smaller M$^+$···O interaction energy per H$_2$O molecule in the M$^+$/crown···2H$_2$O complex than found in M$^+$···OH$_2$ itself. This is due to destabilizing crown–2H$_2$O interactions, the reduced (less favorable) crown–M$^+$ interaction, and the higher internal energy of the crown in the presence of 2H$_2$O.

This energy lowering per H$_2$O molecule is comparable to the interaction energy per water molecule calculated in a cyclic hexamer (C_6 symmetry; $q_0 = -0.6$) of about 6 kcal/mol per H bond (Table II). These results suggest that upon cation–crown complexation, the cation affinity of the water is reduced and becomes comparable to the hydrogen bonding between water molecules in aqueous solution. This may be of significance in the elucidation of the mechanisms of cation transport across hydrophobic membranes. Once a cation interacts with the crown (and this process is thermodynamically favorable)[25] we find that there is no longer a significant water attraction for the cation. Thus, we can see how cation transport can be facilitated from both a

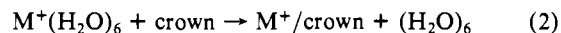Table IX. Calculated Reaction Energies for Reactions 1 and 2 (kcal/mol)

reaction 1				reaction 2		
M$_1$$^+$	M$_2$$^+$	ΔE_{calcd}^{a}	ΔH_{exptl}^{b}	M$^+$	ΔE_{calcd}^{a}	ΔH^c
K$^+$	Na$^+$	−15.7	−3.96	Na$^+$	−15.3	−2.25
Rb$^+$	K$^+$	−1.8	2.39	K$^+$	−31.0	−6.21
				Rb$^+$	−32.8	−3.82
Cs$^+$	Rb$^+$	1.1	0.03	Cs$^+$	−31.7	−3.79

^{a} Calculated with use of lowest-energy structures, Table III, q_0 = −0.6. ^{b} Calculated from experimental enthalpies of ref 25a. ^{c} Enthalpies of complexation from ref 25a.

thermodynamic and a kinetic point of view by complexation with crown ethers.[51]

B. Crown–Cation Specificity. We find that the most stable Na$^+$ complex (C_1) is intrinsically more stable than the most stable K$^+$ complex (D_{3d}) (Table III). However, it is known that 18-crown-6 interacts more strongly with K$^+$ (ΔH = −6.21 kcal/mol, log K = 2.03) than with Na$^+$ (ΔH = −2.25 kcal/mol, log K = 0.8) in aqueous solution[25a] as well as in other solvents (methanol, Me$_2$SO, DMF[25c]), and so it is interesting to examine what out calculations can say about this specificity.

To do this, we examine the energetics of reactions 1 and 2.

$$M_1^+(H_2O)_6 + M_2^+/crown \rightarrow M_2^+(H_2O)_6 + M_1^+/crown \quad (1)$$

$$M^+(H_2O)_6 + crown \rightarrow M^+/crown + (H_2O)_6 \quad (2)$$

Using the total energies of the lowest-energy conformers from Table III and all oxygen charges of −0.6, we calculate a −ΔE for reaction 1 (M_1 = K$^+$, M_2 = Na$^+$) of 15.7 kcal/mol (Table IX). With any reasonable set of charges (e.g., $q_0 = -0.3$ to −0.6), a negative ΔE is obtained. This result is consistent with a calculated crown preference for K$^+$. This preference comes, as has also been found by Yamabe et al.,[26] from the fact that the difference between the hydration energies of Na$^+$ and K$^+$ is greater than the differences between their interaction energies with 18-crown-6. When solvents less polar and weaker solvating than H$_2$O (e.g., THF) are used, Na$^+$ complexation becomes favored over K$^+$ complexation.[52]

We calculate ΔE of reaction 1 for the remaining alkali cations (Table IX) and the calculations show that the crown–cation selectivity in aqueous solution peaks at Rb$^+$, with K$^+$, Cs$^+$, and Na$^+$ interacting less strongly. Experimentally, the enthalpy peaks at K$^+$. Thus, both experiment and theory find a "peaking" of −ΔE when one increases the size of the cation, although the theory does not correctly predict where the peak occurs. These energies (reaction 2) are compromises between the hydration energy of

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(52) Wong, K. H.; Konizer, G.; Smid, J. *J. Am. Chem. Soc.* **1970**, *92*, 666.

the cation and the crown–cation interaction energy.

What is the driving force for crown–cation association? By calculating the energy for reaction 2, we attempt to model the competition between the crown and water for cation complexation, taking into account the ability of water molecules to hydrogen bond with each other when they are not complexed, This ΔE is negative for all of the cations (Table IX). Despite the simplicity of this model, it illustrates the tendency for crowns to be complexed by alkali cations in water environments. This tendency comes about because the H bonding of the water molecules released when the cation complex forms compensates for the fact that these waters interact more favorably with the cation than does the crown. However, it is clear from our calculations that the intrinsic interaction energy of cations with the crown is $Na^+ > K^+ > Rb^+ > Cs^+$. It is the solvation energy of the cation which changes these relative affinities in aqueous solution; when solvation effects are less important (as in THF[52]), the Na^+ affinity for the crown will exceed that of K^+,

It is of interest to relate these studies to the findings of Warshel,[53] who has noted that crown ethers might be an analogue of an enzyme-active site, which he has suggested as being capable of solvating a substrate (transition state) more favorably than the corresponding solvation in aqueous solution. Our interpretation of the tendency of crowns to bind cations (reaction 2) is somewhat different, since, as noted above, water interacts *more* favorably with M^+ than does the crown and, despite this, reaction 2 has a negative ΔH due to the instability of the crown (compared to H_2O) in the absence of M^+. If the analogy between crowns and enzyme-active sites holds, then it suggests that a modeling of the enzyme-active site in both the presence and the absence of substrate may be necessary for an understanding of enzyme specificity.

C. The "Macrocyclic Effect". Why does K^+ have a significantly higher affinity for 18-crown-6 than for pentaglyme? Our calculations find a ΔE for K^+/18-crown-6 of 61.8 kcal/mol ($q_0 = -0.6$) with use of the energy of the C_i structure for the uncomplexed crown and D_{3d} for the complex. This is comparable to the interaction energy of 59.0 kcal/mol for the reaction K^+ + pentaglyme "(D_{3d})" → complex "(D_{3d})". However, pentaglyme is significantly more stable in the all-trans conformation and so the net reaction for its interaction with K^+ is reduced to 46 kcal/mol ($q_0 = -0.6$), Thus, the significantly greater affinity of K^+ for the crown than for pentaglyme ("macrocyclic effect")[12] could have an important enthalpic contribution coming from the greater stability of conformations other than those that can effectively interact with the cation. Even though it is hard to give a more precise estimate for this enthalpic contribution to the macrocyclic effect,[12] its qualitative features are clear from our calculations, which show that the all-trans → "D_{3d}" ΔE is mainly associated with electrostatic repulsions in the D_{3d} structure. The "macrocyclic effect" is thus expected to decrease when the dielectric constant of the medium increases, as observed experimentally Of course, the entropy contribution to the "macrocyclic effect" may also affect the relative complexing ability of 18-crown-6 compared to its more rigid dibenzo or dicyclohexyl derivatives.

D. Comparison with Previous Studies. Yamabe et al. calculate that K^+ interacts more strongly with the crown than with $6H_2O$, in disagreement with our results. We calculate a $-\Delta E$ for $K^+ \cdots (OH_2)_6$ of 65.4 kcal/mol and a $-\Delta E$ of 61.8 kcal/mol for $K^+ \cdots$crown ($q_0 = -0.6$). Some of this difference between our results and those of Yamabe et al.[26] may be due to the fact that CNDO/2 significantly overestimates cation–oxygen interactions (e.g., they predict that the hydrate of Na^+ has a $-\Delta E$ of 43 kcal/mol, compared to the experimental $\Delta H = -24$ kcal/mol). We also disagree with their interpretation of cation–crown complexation as a charge-transfer interaction. They concluded this on the basis of comparison of calculations with and without p orbitals on the cation; we suggest their result is a CNDO/2

artifact. Ab initio energy component calculations[35,28] on alkali cation···oxygen complexes suggest that the main attractive forces are electrostatic and polarization, with charge transfer actually smaller than second-order exchange. The reasonableness of our results on crown complexation is suggestive evidence that charge transfer is not an essential element of these cation–crown interactions.

We are in agreement with Yamabe et al.[26] on their interpretation of why K^+ interacts more strongly with 18-crown-6 than does Na^+ in aqueous solution.

Bovill et al.[18] have carried out molecular mechanics studies on uncomplexed 18-crown-6. It is encouraging to us that our average error for the torsional angles in the C_i structure of 18-crown-6 is actually lower (5.6°) than that found with the more complex force field of Bovill et al. (7°). That study also found the C_i structure of lowest energy for the crown itself, with the C_1 structure 4.4 kcal/mol and the D_{3d} 7.8 kcal/mol higher in energy.

Summary and Conclusions

We have presented molecular mechanics studies on 18-crown-6 and its complexes with alkali cations. A simple model, in which the major attractive term in the $M^+ \cdots$crown association is electrostatic, has been employed; the generally good agreement with experiment validates the use of such a model.

The structure calculated to be of lowest energy for uncomplexed 18-crown-6 is the C_i conformation observed in the crystal; also of low energy is the D_{3d} conformation and a new C_1' conformation, heretofore not characterized. We predict that the solution dielectric properties of 18-crown-6 are due to a significant population of this conformer. The observation of the D_{3d} conformation in crystals with H-bond-donating groups is also consistent with our calculations, since the stronger interaction energies of polar X–H bonds[14-18] with the D_{3d} conformation of the crown can help compensate for the fact that this structure has larger intramolecular electrostatic repulsion than does the C_i structure.

The lowest-energy conformation of the Na^+/crown structure is of the type C_1 that is observed in the solid state; the lowest-energy conformation of K^+/crown is of the D_{3d} type that is observed in the solid state. Na^+ favors the C_1 conformation because it allows significantly better $M^+ \cdots$crown interactions than the other conformation. K^+ favors the D_{3d} conformation despite the fact that it does not have the lowest-energy $M^+ \cdots$crown interaction, since this conformation also has a very low internal strain energy.

The above results clearly delineate the *structural flexibility* of the crown and its tendency to adopt different conformations appropriate to its environment. An example of *cation mobility* inside the crown was afforded by the calculations on the $Na^+ \cdots D_{3d}$ structure, in which the "hole" for the cation is too large and an example of the *constraint of crown size* was afforded by $Cs^+ \cdots$ crown, in which the Cs^+ moved out of the cavity upon energy refinement.

Our calculations also have given insight into the cation specificity of 18-crown-6 in solution. As we have seen, this specificity is a delicate balance between the energies of crown–cation interactions and cation solvation. Of the alkali cations, Na^+ is sufficiently more strongly hydrated in aqueous solution than K^+, Rb^+, and Cs^+ that its crown–cation interaction enthalpy becomes greater and its affinity less than that of K^+.

Comparison of the calculated complexation energy of a cation with crown ethers and their open-chain analogue pentaglyme shows that there is likely to be an enthalpic contribution to the "macrocyclic effect" (the greater affinity of alkali cations for 18-crown-6 than for pentaglyme).

Our calculations find that the interaction energy of H_2O with the 18-crown-6 Na^+ and K^+ complexes is not more favorable than the likely H_2O interaction energy with its neighbors in liquid water, providing a specific example of how crowns can shield cations from H_2O and transport them through hydrophobic environments.

The success of our molecular mechanics model in analyzing intermolecular interactions in this system is encouraging and suggests that such an approach can be fruitfully applied to many other complex molecular processes. Such energy evaluations will

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Table X. Appendix: Force-Field Parameters and Nonbonded Interactions

Force-Field Parameters Used

bond	k_b	r_b, A
C–C	300	1.525
C–O	300	1.430

angle	k_a	θ_a, deg
O–C–C	46.5	112
C–O–C	46.5	111

dihedral	$k_{d,2}$	$k_{d,3}$	γ
O–C–C–O	1.0	3.0	0
C–C–O–C		1.0	0

Nonbonded Interactions

atom	α	N_{eff}	R_i^0
C	1.77	7.0	1.90
O	0.64	7.0	1.6
Na$^+$	0.24	10.0	1.6
K$^+$	1.23	18.5	2.0
Rb$^+$	1.90	22.0	2.2
Cs$^+$	4.26	30.0	2.4

^{a} Units are kcal/A^2/mol for k_b, kcal/radian^2/mol for k_a, kcal/mol for $k_{d,n}$. The relation between the polarizability, α, the effective atomic number, N_{eff}, the ionic radius, R_i^0, and the parameters A and B is given in reference 38.

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Complete Theoretical Structures for the Classical and Nonclassical Forms of the 2-Norbornyl Cation and for Edge-Protonated Nortricyclene

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Abstract: Fully optimized geometries for the classical and nonclassical structures of the 2-norbornyl cation and for an edge-protonated nortricyclene have been determined with use of a split valence 4-21G basis set and a gradient procedure. At these optimized geometries the relative SCF energies in kcal/mol were as follows: classical structure 0.0, nonclassical structure +0.2, and edge-protonated nortricyclene +17.3. Additional calculations at these geometries with a standard C(9s5p/4s2p), H(4s/2s) double-ζ basis set yielded the following energy differences: classical form (0.0), nonclassical form (+1.0), and edge protonated nortricyclene (+17.8). The 4-21G basis set augmented by sets of d polarization functions on *all seven carbons* predicted the relative SCF energies: classical (0.0), nonclassical (−0.2), and edge protonated (+12.4). Thus, the classical and nonclassical forms are essentially equal (within tenths of a kcal/mol) in energy at these levels of theory. However, if one is justified in assuming that the effects of electron correlation will be analogous to what is found for smaller carbonium ions, then the nonclassical norbornyl cation will ultimately prove to lie lower in energy. The classical structure is predicted to be closer in geometry to the nonclassical one than was found in previous work. The geometry suggests that the classical isomer might best be viewed as an unsymmetrically bridged species.

One of the longest lasting controversies in physical organic chemistry has been concerned with the structure of the cation formed from the solvolysis of *exo*-2-norbornyl derivatives.[2a] A vast amount of experimental effort over the past 30 years has attempted to clearly establish whether the classical norbornyl cation **1** or the nonclassical structure **2** is more stable (or exists?) and whether one or the other form can best rationalize the considerable experimental data. More recently, new techniques[2b] such
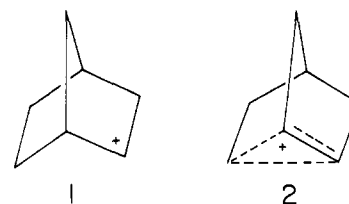
as carbon-13 NMR and X-ray photoelectron spectroscopy have been brought to bear on this problem. The orthodox view that the norbornyl cation has a nonclassical structure has recently been succinctly but forcefully restated by Schleyer and Chandrasekhar.[3] They conclude that the secondary 2-norbornyl cation has an extra stabilization of 6 ± 1 kcal/mol in stable ion media. Although

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