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Conformation of 18-Crown-5 and Its Influence on Complexation with Alkali and Ammonium Cations: Why 18-Crown-5 Binds More Than 1000 Times Weaker Than 18C6

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Stability constants of potassium, sodium, and benzylammonium salts with 18C5 are determined in water, methanol, and acetonitrile by potentiometric titrations. The corresponding free energies ΔG agree within the error with those obtained from calorimetric titrations. In comparison to 18C6 the ΔG values are lower by 14 to 16 kJ/mol, with methanol or acetonitrile as solvent and K^+ or benzylammonium salts. Differences in the calorimetrically determined binding enthalpies ΔH between 18C6 and 18C5 are usually even larger. In water, however, the ΔG differences between the 18C5 and 18C6 complexes become almost negligible. The D_3d-like conformation of such crown ethers can be evaluated for the first time by NOE methods using the less symmmetrical 18C5. The NMR data indicate also the absence of significant conformational changes upon complexation, in line with molecular mechanics calculations (CHARMm). These show that the low binding constants of K^+ with 18C5 are due to the expulsion of the cation due to one C−H bond pointing toward the cavity, leading to larger $K^+\cdots O$ distances. The CHARMm calculated gas phase energy difference between the K^+ crown complexes of 26 kJ/mol agrees approximately with experimental differences.

In spite of countless investigations on synthetic ionophores[1] some large variations in experimental binding constants still await a more quantitative analysis. The present paper deals with a classical case described already in 1977 by Cram et al.,[2] who observed a drop of association constants between 18C6 and 18C5 from, for example, $10^{6.5}$ to $10^{3.2}$ with *tert*-butylammonium salts. Cram et al.[2] rationalized that this essentially was based on the replacement of a favorable $O\cdots H-N$ interaction by an unfavorable $C-H\cdots H-N$ interaction in the 18C5 complex.

Table 1. Stability Constants and Thermodynamic Parameters (kJ/mol) for 1:1 Complexes of 18-Crown-5 with K^+, Na^+, and $BzNH_3^+$ in H_2O, MeOH, and MeCN at 298 K

no.	salt	solvent	log K[a]	$-\Delta G$	$-\Delta H$	$T\Delta S$	method[b]
1	NaI	H_2O	0.79[c]	4.5[d]			ISE
2	NaNCS	H_2O	[m]		≤2.5		Cal
3	NaI	MeOH	2.48	14.2			ISE
4	NaI	MeOH	2.46	14.0	23.5[e]	−9.5[e]	Cal
5	KI	H_2O	1.31	7.5			ISE
6	KNCS	H_2O	1.53[f]	8.7[g]	3.5[e]	5.2[h]	Cal
7	KI	MeOH	2.64[c]	15.1[d]			ISE
8	KCl	MeOH	2.42[c]	13.8[d]			ISE
9	KI	MeOH	2.79[c]	15.9[d]	25.3[e]	−9.4[i]	Cal
10	KNCS	MeOH	2.75	15.7	20.5	−4.8	Cal
11	KNCS	MeCN	2.82	16.1	9.0	7.1	Cal
12	$BzNH_3Cl$	MeOH	1.55	8.8			ISE
13	$BzNH_3Cl$	MeOH	1.37[j]	7.8[k]	14.4	−6.6[l]	Cal

[a] log K value for the reaction: $M^+ + L = ML^+$. [b] ISE: potentiometry using ion-selective electrodes; Cal: titration microcalorimetry. [c] Unless noted otherwise, uncertainties are given as standard deviations: in log K 0.05; in ΔG 0.3; in ΔH 0.5; in $T\Delta S$ 0.6; otherwise: [c]0.10; [d]0.6; [e]1.5; [f]0.25; [g]1.4; [h]2.0; [i]1.6; [j]0.15; [k]0.9; [l]1.0. [m] Only upper limit given, as the measured heat was approximately equal to the mixing heat.

Several reasons led us to reinvestigate the strikingly large difference between 18C6 and 18C5. First of all, the loss of one interaction alone can hardly explain the observed binding energy differences, which therefore must have reasons connected to conformational effects. The 18C5 conformations, which to the best of our knowledge have not been analyzed before, were therefore studied with molecular mechanics calculations and NMR measurements. This should also complement our earlier approach to the prediction of ionophore complex stabilities,[3] which actually is based in the first approximation on counting the number of contacts between binding sites and cation, and ascribing electron donor capacities to the different ligand fragments on the basis of hydrogen bond factor values; these go back to a large basis of hydrogen bond measurements in carbon tetrachloride. There were also until now few experimental data on 18C5 complexes, and these were largely determined by less reliable extraction methods. For potassium and 18C5 we found in the literature only one value measured in chloroform.[2] We therefore measured association constants for potassium, sodium, and benzylammonium ($BzNH_3^+$) salts with 18C5 in several frequently used solvents (Table 1), using both titrations with ion-selective electrodes (ISE) and calorimetric titrations. The latter allow not only to check the ΔG values derived from ISE titrations, but also provide insight as to whether the differences between 18C5 and 18C6 complexes are due to enthalpy ΔH or entropy $T\Delta S$ variations. Values with 18C6 for comparison were either available form the literature[4] or were new determinations (Table 2).

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Table 2. Stability Constants and Thermodynamic Parameters (kJ/mol) for 1:1 Complexation of 18-Crown-6 with K^+, Na^+, and $BzNH_3^+$ in H_2O, MeOH, and MeCN at 298 K

no.	salt	solvent	log *K*	$-\Delta G$	$-\Delta H$	$T\Delta S$	ref
1	NaCl	H_2O	0.8	4.6	9.4	−4.8	4a,b
2	NaCl	MeOH	4.36	24.9	35.1	−10.2	4c,d
3	KCl	H_2O	2.03	11.6	26.0	−14.4	4a,b
4	KCl	MeOH	6.05	34.5	56.1	−21.6	4c,d
5	KSCN	MeCN	5.52	31.5	15.9	15.6	4e
6	$BzNH_3Cl^c$	H_2O	1.44^d	8.2^e	6.5	1.7^f	a
7	$BzNH_3Cl^c$	MeOH	4.22	24.1	43.2^g	-19.1^h	a
	$BzNH_3Cl^c$	MeOH	4.43	25.3	−	−	b

[a] Calorimetric data of this work. [b] ISE data of this work. [c] Unless noted, uncertainties for *a* and *b* data are given as standard deviations: in log *K* 0.10; in ΔG 0.6; in ΔH 0.3; in $T\Delta S$ 0.6; otherwise: [d]0.04; [e]0.2; [f]0.4; [g]1.5; [h]1.6.

Table 3. Comparison of Stability Constants and Thermodynamic Parameters (kJ/mol) for 1:1 Complexation of 18-Crown-5 and 18-Crown-6 with K^+ and Na^+ in H_2O, MeOH, and MeCN at 298 K

no.	salt	solvent	$\Delta\Delta G$	$\Delta\Delta H$
1	KSCN	MeCN	15.8	6.9
2	KCl^b	MeOH	18.6	30.8
3	KCl^b	H_2O	4.1	c
4	$NaCl^b$	MeOH	10.9	11.6
5	$NaCl^b$	H_2O	0.1	c
6	$BzNH_3Cl$	MeOH	16.3	28.8
7	$Me_3CNH_3^d$	$CDCl_3$	18.5	−

[a] Data (kJ/mol) from Tables 1 and 2; see footnotes there. [b] Data for 18C5 complex with iodide instead of chloride. [c] No reliable calorimetric data available due to too small reaction heat. [d] SCN salts; data from ref 2.

Experimental Section

Materials. 18C5 was synthesized according to ref 2. Benzylammonium chloride ($BzNH_3Cl$) was obtained by adding HCl to fresh distilled benzylamine; the salt was recrystallized twice from methanol and dried under vacuum. KI (99.9%) and NaI (99.7%) were purchased from Merck and used without further purification. Tetraethylammonium iodide (TEAI) (99.7%) was recrystallized twice from methanol, washed with ether, and dried under vacuum. Methanol (MeOH) was rectified over magnesium methanolate under nitrogen.

Stability Constant Measurements. Potentiometric measurements were carried out with using ion-selective and reference electrodes, one in the reaction vessel, the other in the reference cell. The two half cells were connected with a salt bridge filled with a 0.05 M tetraethylammonium iodide solution. Ionic strength of the solutions were constant in all three compartments. The reference electrode used in all titrations was a Ag/Ag^+ electrode which was immersed in the same solvent as that under investigation.

The stability constants of 18C5 with Na^+ or K^+ were determined by potentiometric titration of a ligand solution (6.02−6.96 mmol/L) with a NaI (1.25−13.5 mmol/L) or KI (1.05−11.2 mmol/L) solution at 298 K. The concentration of the free Na^+ or K^+ ions was measured with a solid state sodium or potassium selective electrode from Moscow Institute of General and Inorganic Chemistry. The electrode responses in pure MeOH were 54.7 mV for K^+, and 53.9 mV for Na^+, and those in H_2O were 55.1 for K^+ and 54.4 mV for Na^+. Potentials were measured with a diode-modulating impedance transformer (Knick, Type 646).

The stability constant of 18C5 and 18C6 with $BzNH_3^+$ was determined by competition potentiometric titration of the ligand/$BzNH_3Cl$ ($C°_L$ 3.58−3.99 mmol/L, $C°_{BzNH3}$ 7.27−8.31 mmol/L) solution with KI ($C°_{KI}$ 1.05−10.2 mmol/L), for 18C5, and the ligand/$BzNH_3Cl$ ($C°_L$ 3.37−3.89 mmol/L, $C°_{BzNH3}$ 16.4−18.9 mmol/L) solution with KI ($C°_{KI}$ 2.31−15.1 mmol/L) for 18C6 at 298 K.

Calorimetric measurements were performed at 298.15 K as described earlier[1d,5] using a LKB-2107 microcalorimetry system (Model 2107/112). Heats of complexation of 18C5 with Na^+ and K^+ metal cations and $BzNH_3^+$ cation were measured in H_2O, MeOH, and MeCN solvents. The solutions of 18C5 (2 mL, concentrations see below) in the calorimetric vessel were titrated with 0.04 mL portions of salt solutions (concentrations see below) contained in a 1 mL gas-tight motor-driven Hamilton syringe. Dilution heats of 18C5 with the titrations were neglected. The justification of this was checked by adding 0.04 mL portions of pure solvent into 2 mL volumes of crown-ether solutions; the observed dilution heats were smaller than the random error of heat measurements. Dilution heats of salts were automatically taken into account using differential calorimetry by simultaneously adding salt solutions to pure solvent and to 18C5 solution. The syringe volumes were checked by weighing doubly distilled water portions at 25 °C.

Reliability of the calorimetric system was checked by measuring stability constants and enthalpies of a well-known reaction. For the 1:1 complexation of 18C6 with K^+ as KNO_2 salt in H_2O at 298 K, values of log *K* 1.98(±0.01) and ΔH −25.8(±0.2) kJ/mol were obtained. This compares well with published calorimetric data for the same complex (log *K* 2.03, ΔH −26.0 kJ/mol).[4a,b]

Potentiometric and calorimetric experimental data were analyzed by using the multipurpose computer program CHEM-EQUI as described earlier.[1d] CHEM-EQUI is written in the programming languages C and Pascal for MS-DOS PCs; it is based on a general nonlinear least square method for the estimations of the stoichiometry, stability constants, and related physical quantities. The least square method collection allows calculation of the equiliblium constants from simple $2A = A_2$ or $A + B = AB$ reactions up to multimetal-multiligand systems. The optimization uses gradient Newton-Raphson, Simplex, and Monte-Carlo algorithms. Variable transformation and scaling is performed to avoid underflows and overflows during the calculations. A singular value decomposition method is applied for searching stochiometry of complexes present in solution.

In our investigations we tested several possible equilibria: $mM^+ + nL = M_mL_n^{m+}$ (M = Na, K, $BzNH_3$, L = 18C5, m = 1,2, n = 1,2, taking into consideration all possible combinations of the complexes. The best agreement with experimental potentiometric and calorimetric data was found for the simple ML^+ model, based on the Hamilton *R*-factor for hypothesis testing,[6] and residuals analysis for fitness test. Only in the cases of Na^+ and K^+ complexes in MeOH did we find ML_2^+ complexes with the following values: (a) with NaI/18C5/MeOH, log β_2 4.87 , ΔH_2 14.3 kJ/mol, (b) with KI/18C5/MeOH, log β_2 4.85, ΔH_2 36.9 kJ/mol, (c) with KNCS/18C5/MeOH, log β_2 4.53 , ΔH_2 33.6 kJ/mol.

NMR measurments were carried out with a Bruker Avance DRX500 spectrometer with the processing software UXNMR on a Bruker Aspect station I. All measurements were done in D_2O at 303 K. For 2D-NOESY experiments we used the standard Bruker NOESY parameter set, with a 2 s relaxation delay and 1 s mixing time.

Molecular mechanics and dynamics calculations were performed on a Silicon Graphics workstation INDY using the program QUANTA (release 4.0) from MSI/BIOSYM and the forcefield CHARMm (release 22).[7] Minimizations were done

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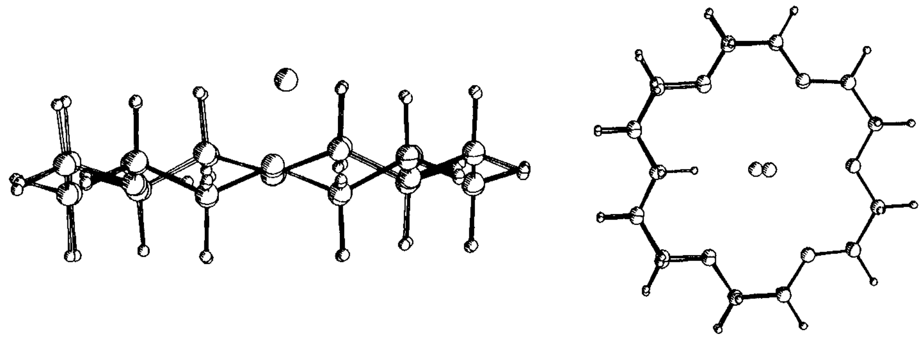


Figure 1. Superposition of 18-crown-5 and 18-crown-6 structures with K^+ (from CHARMm calculations).

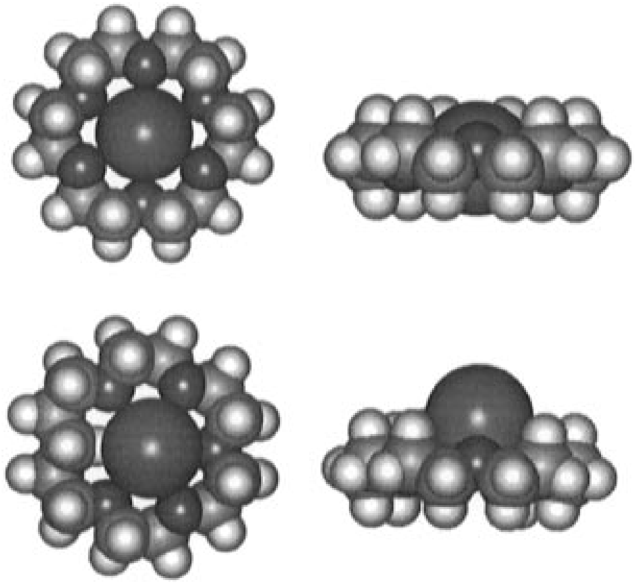
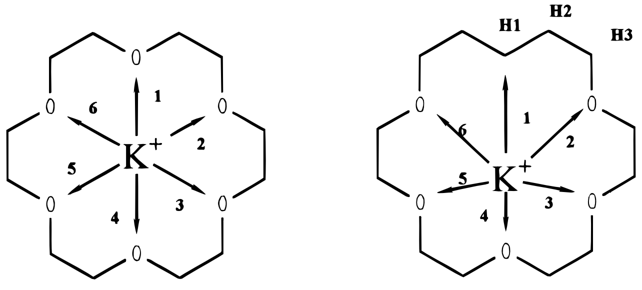


Figure 2. Top and side view of CPK models of 18-crown-5 and 18-crown-6 complexes with K^+ (from CHARMm calculations).



1 = K^+-O1	3.08
2 = K^+-O2	3.02
3 = K^+-O3	3.08
4 = K^+-O4	3.02
5 = K^+-O5	3.08
6 = K^+-O6	3.02

1 = K^+-C1	3.45[a)]
2 = K^+-O3	3.53
3 = K^+-O4	3.10
4 = K^+-O5	3.04
5 = K^+-O1	3.10
6 = K^+-O2	3.53

[a)] K^+ - C1-H - distance: 2.76Å.

Figure 3. Distances (Å) in the 18-crown-5 and 18-crown-6 complexes with K^+ (from CHARMm calculations).

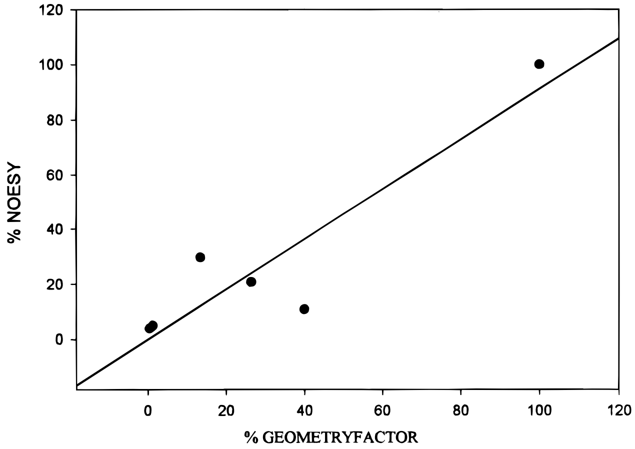


Figure 4. NOESY integrals *vs* r^{-6} geometry factors with distances from CHARMm calculations. The integrals were normalized using the biggest observed interaction (between H_2 and H_3) as reference.

with a constant dielectric constant of 3.0, using the Adopted Basis Newton Raphson (ABNR) algorithm after 200 steps preminimization by the steepest descent method (SD). The charges on the crown ether atoms were obtained with the Gasteiger-Marsili algorithm.[8] As stop criteria we used a RMS of 0.001 kcal/mol, or a maximum stepnumber of 5000. A water box calculation was carried out by putting the crowns or their complexes in a TIP3[9] water box with 428 water molecules inside. For investigations of complex and host geometries we used additional MD calculations at 1200 K, with 10000 steps simulation time after heating and equilibration.

Results and Discussion

Experimental Binding Energies. The free energies or stability constants for 18C5 complexes with Na^+, K^+, and $BzNH_3^+$ cations (Table 1) from two calorimetric and ISE titrations agree within the error limits of both methods. In water the complexation between Na^+ and 18C5 was not determined by calorimetry in view of the low interaction enthalpy. In the case of 18C5 complexes with K^+ in H_2O and MeOH the calorimetric method gave higher ΔG/log K values than the ISE method, opposite to the complexation of $BzNH_3Cl$ with 18C5. However, the values still were within the intervals of confidence for both methods.

Comparisons between the 18C5 and 18C6 complexes (Table 3) show that with K^+ and $BzNH_3^+$ cations the differences reach 16−18 kJ/mol for methanol, chloroform, and acetonitrile as solvent, whereas they become almost negligible in water. Calorimetric data are available for MeOH as solvent and show that the differences are even larger in ΔH, in contrast to MeCN as solvent. The data suggest enthalpy−entropy compensation effects which are well documented for many ionophore complexes.[10] With the Na^+ ion the difference between 18C5 and 18C6 is much smaller than with the other cations, obviously

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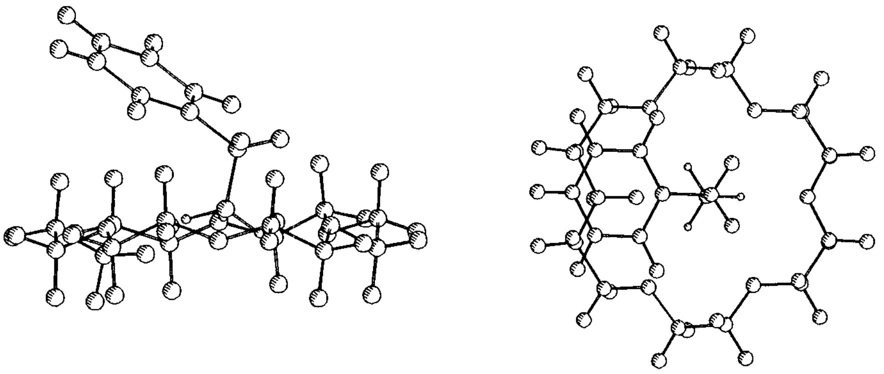

Figure 5. Side and top views of the $BzNH_3^+$−18-crown-5 complex.

Table 4. CHARMm-Calculated Energies (kJ/mol) for Crown Complexes with K^+

crown	FSE_{cr}[a]	FSE_{cpx}[b]	$FSEcoul_{cpx}$[c]	E_{cpx}[d]	FSE_{incpx}[e]	SE[f]
18C6	10.6	−70.6	−59.2	−81.1	11.9	1.3
18C5	4.2	−51.3	−40.6	−55.5	7.7	3.5

[a] Final steric energy FSE of the crown in its uncomplexed form. [b] FSE of the complexes. [c] Coulomb contribution to FSE_{cpx}. [d] Energy of complexation: $E_{cpx} = FSE_{cpx} - FSE_{cr}$. [e] Strain energy of the crown in its compexed form. [f] Strain energy in the crown due to complexation: $SE = FSE_{incpx} - FSE_{cr}$.

connected to the insuffient fit of the smaller Na^+ cation into the cavity of both ligands (see below).

The enormous influence of the solvent on the absolute binding constants has been shown by us recently to be essentially a linear function of the cation free solvation energies in the different solvents.[4e] We now see that solvent changes affect the relative binding energies much beyond what one would expect by an attenuation factor which would reflect the dampening effect of water on the absolute scale. That 18C5 shows only in water almost no difference to 18C6, in sharp contrast to methanol, implies a connection to specific hydration effects (see below).

Molecular Mechanics Calculations and NMR Analyses. Detailed analysis of 18C6 conformations with advanced calculation techniques by Kollman and others[11] have shown the highly symmetric D_3d to be the most stable one. By CHARMm force field application we obtained invariably the same conformation for 18C5 as global minimum by energy minimizations starting from quite different geometries like those given by Shamovsky and Szentpaly.[12] Energy minimizations for the 18C5 complex with ammonium ions show similarly a D_3d-like conformation (Figure 5). Figure 1 illustrates that indeed the 18C6 and 18C5 structures become virtually superimposable, however, with the potassium cation distinctly above the ring in 18C5. This is the consequence of those C−H bonds protruding into the ring, which belong to the methylene group replacing the oxygen in going from 18C6 to 18C5. The CPK models of the force field-minimized K^+ ion complex structures (Figure 2) make it clear that there is an enforced loss of many ideal contacts between the K and oxygen atoms in 18C5 compared to 18C6. This effect is smaller for the complexes with sodium, where the distances are not ideal also with 18C6, and this explains the smaller 18C6/5 difference here.

The enlarged K····O distances in 18C5 (see Figure 3) lead to a decrease of CHARMm-calculated Coulomb energies around 19 kJ/mol compared to 18C6−K^+. Van der Waals and other contributions differ much less between 18C6 and 18C5 potassium ion complexes (only about 1 kJ/mol)). The strain energy changes upon complexation within the crown were calculated by comparing the total energies of the energy-minimized crown with and without a guest and are below $\Delta\Delta H = 2.2$ kJ/mol. The CHARMm-calculated total energy difference between the 18C6 and 18C5 potassium complexes is 26 kJ/mol (see Table 4) not very far from the experimentally observed one (Table 3) for chloroform as solvent with $Me_3CNH_3^+$ (18.5 kJ/mol), or with $BzNH_3^+$ in MeOH (28.8 kJ/mol). Calculations taking into account only van der Waals changes and only the Coulomb interactions between the cation and the different oxygens, as suggested by Lokuvits,[13] show strongly exaggerated differences between the 18C6 and 18C5 potassium complexes, with values of up to $\Delta\Delta H = 95$ kJ/mol.

NMR studies of 18C5 offer for the first time an experimental proof for the D_3d conformation of such crown ethers, as the loss of symmetry in comparison to 18C6 allows application of NOE techniques. NOESY spectra of 18C5 in D_2O showed several cross peaks with intensities correlating approximately with geometry factors as calculated from CHARMm-generated intramolecular distances (Figure 4). The D_3d conformation shown this way does not change significantly by complexation, as evident also by ^1H and ^{13}C NMR shift differences below 0.07 ppm for ^1H and below 0.1 ppm for ^{13}C before and after adding potassium salts.

Finally we address the question why the binding differences between 18C6 and 18C5 become much smaller in water compared to the other solvents. Molecular dynamics simulations in a 15 Å diameter TIP3[9] water box indicate that with 18C6 nine hydrogen bonds of water to the crown can build up, in contrast to 18C5 with only about four corresponding bonds. Although one also observes significant and difficult to quantify distortions of the water network outside the cavities, the tentative conclusion is that the wider 18C6 cavity will lose more hydrogen bonds upon complexation than will 18C5. The smaller cavity desolvation energy for 18C5 would then be responsible for the diminution of the $\Delta\Delta G$ values in water.

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