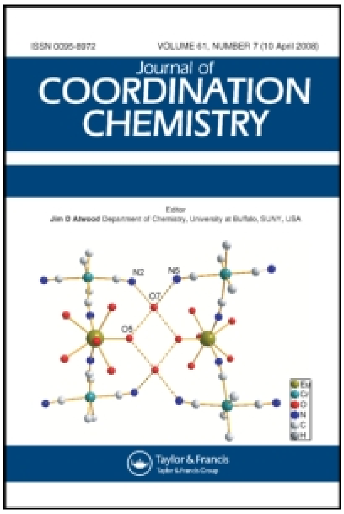

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THE INFLUENCE OF STRUCTURAL EFFECTS ON THE COMPLEXING ABILITY OF CROWN ETHERS

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THE INFLUENCE OF STRUCTURAL EFFECTS ON THE COMPLEXING ABILITY OF CROWN ETHERS

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Simple regression including interaction energies of the cation–ligand systems explains to some extent the variability in logarithms of stability constants of complexes formed by a series of nine 18-crown-6 ethers with potassium cations in methanol. The atomic charges were calculated for energy minimized structures, found during molecular dynamics computations. In order to mimic the residual solvation of complexed cations, two CH_3OH molecules were incorporated above and below the macrocyclic plane. Polarization effects of the metal cation on the resulting atomic charges were considered in calculations and found to be crucial for satisfactory correlations with experimental data.

Keywords: Crown ether complexes; stability constants; structural effects; molecular dynamics

INTRODUCTION

The development of macrocyclic ethers that are able to selectively complex the alkali metal cations has been an active field of research.[1–3] It is known, therefore, that cation–coronand interaction depends on several factors related to characteristic properties of the reacting ion and ligand. Among these, the effect of ligand structure is of great importance; it is often discussed and rationalized in qualitative terms which include cavity shape and topology as well as preorganization and complementarity.[4–6] Such a concept is fully understood but it does not explain quantitatively the existing trends in

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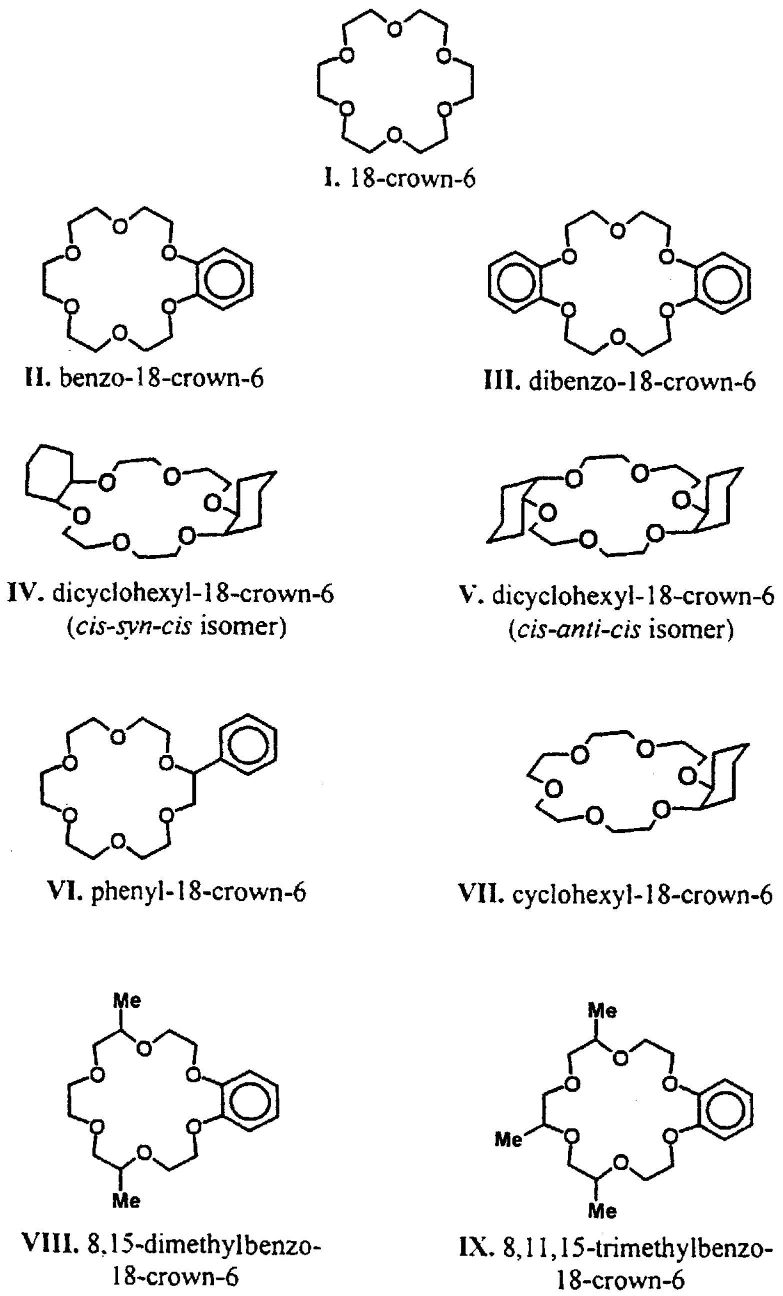
complex stability. Molecular mechanics (MM) and molecular dynamics (MD) modelling have been used to calculate interaction energies for a series of metal ions with a single coronand in an effort to rationalize the observed selectivity patterns. Earlier results of these calculations have been reviewed.[7–10] Yet, in spite of extensive computational efforts, quantitative relationships for predicting how the three-dimensional structure of a crown ether molecule will affect the stability of its complexes are very limited. In the light of this fact, the results of Hay *et al.*[11,12] are quite exceptional. Their studies on MM and *ab initio* calculations indicated convincingly that the strain energy approach may be useful in rationalizing the effect of coronand structure on complex stability. It was found[11] that $\log K_s$ values (K_s stands for stability constant) available for potassium complexes of selected hexadentate crown ether ligands in methanolic solutions are strongly correlated with differences in strain energy between the free ligand and its complex. It should be pointed out that this finding represents the first quantitative structure–stability relationship that has been reported for crown ether complexes. Note, however, that considerations have been focussed on ligands containing aliphatic substituents and that systems with aromatic nuclei were not included in the investigated series. Later, a detailed study of the influence of alkyl substitution on structural organization of ethylene-bridged-bidentate ether donor ligands for alkali metal cations was carried out.[13] Quite recently, structural requirements for strain-free metal ion complexation were investigated through the use of both electronic structure calculations and MM calculations with an extended MM3 force field.[14,15] Thus, differences in complex stability would be expected to arise from differences in spatial orientation of the oxygen atoms rather than from the differences between their electron donating properties. It is important to note, however, that the respective strain energies were computed for isolated molecules. Neither inner- nor outer-sphere solvent effects were included in the treatment, whereas none of the cations complexed by 18C6 are completely shielded from the solvent, and their coordination numbers depend on charge and ion size.

More generally, trends in structural changes of $\log K_s$ can be understood in terms of at least two dominant contributors: (i) the strain energy, as demonstrated by Hay *et al.*[11] and (ii) interaction energy, E_{int}, between the positively charged ion and the ether oxygen atoms together with the donor atoms of the solvent molecules participating in the residual solvation of the complexed cation. In the present work we describe the utility of the E_{int} approach in order to gain more information about factors responsible for variations in $\log K_s$. Nine crown ethers and their potassium complexes in methanol were examined. As can be seen from the Scheme, the series under


I. 18-crown-6
II. benzo-18-crown-6
III. dibenzo-18-crown-6
IV. dicyclohexyl-18-crown-6 (*cis-syn-cis* isomer)
V. dicyclohexyl-18-crown-6 (*cis-anti-cis* isomer)
VI. phenyl-18-crown-6
VII. cyclohexyl-18-crown-6
Me
Me
VIII. 8,15-dimethylbenzo-18-crown-6
Me
Me
Me
IX. 8,11,15-trimethylbenzo-18-crown-6

SCHEME I-IX

study contained the ligands with both aliphatic and aromatic side groups joined to the main macrocyclic ring of the 18C6 type.

EXPERIMENTAL AND COMPUTATIONAL PROCEDURES

Compounds **I–III** (Scheme) were commercial samples (Merck) used without purification. *Cis-syn-cis* (**IV**) and *cis-anti-cis* (**V**) isomers were isolated from the commercial sample of dicyclohexyl-18-crown-6 (Merck) by the method proposed by Izatt and his group.[16] Coronands **VI** and **VII** (Ref. 17) as well as **VIII** and **IX** (Ref. 18 and corresponding references therein) were synthesized and purified according to the procedures described in the literature; satisfactory elemental analyses were obtained for all compounds (C, ±0.34; H, ±0.25). Analytical grade $KClO_4$ from Merck was used without purification except for drying over P_2O_5 at 120°C. Tetraethylammonium perchlorate served as supporting electrolyte in cyclic voltammetric experiments. The compound was prepared from tetraethylammonium chloride and purified by repeated recrystallization from triply distilled water and then dried at 60°C *in vacuo*. Methanol was purchased as a Fluka certified reagent for UV spectroscopy and used without purification.

Cyclic voltammetric measurements were carried out with an apparatus described previously.[19] Procedures connected with potentiometric titrations were similar to those reported earlier.[20] Experiments were performed at 25 ± 0.5°C.

Structures of the complexes were generated and minimized by the use of the HyperChem 5.0 program[21] with the AMBER force field package and with the representation of potential energy described in the paper.[22] In all MM calculations an all-atom force field was used, *i.e.*, all atoms were explicitly represented by the force field, and all the parameters were taken from the most recent version of AMBER.[23] In order to mimic the residual solvation of the complexed cations, two CH_3OH molecules were added to the coronates. Calculations of atomic charges appropriate for the complexes were performed using the AM1 method[24] in quantum-classical mode, including the polarization effect of the metal cation. To this purpose, a crown ether molecule was subjected to the semiempirical AM1 procedure, whereas the alkali metal cation was treated as a perturbation. This was carried out in HyperChem 5.0 by simple selection of a coronand molecule, while the cation remained unselected. The selected and unselected atoms were treated as the quantum and classical atoms, respectively. In the case involving use of a solvent, all the ensemble except the metal cation was selected for quantum mechanics single-point calculations of charges. The atomic charges resulting from AM1 computations were subsequently used in MM optimization of structure, and then the whole system was returned to AM1. The procedure was carried out until self-consistency of atomic charges and structure of the system was reached. It should be pointed out that polarization effects of the cation calculated in the above manner were found to be crucial for satisfactory correlations of the resulting values with experimental data.

Subsequent 100 ps MD in 300 K starting from different initial structures revealed an array of conformations which were taken into account in order to find the global, or close to global, minimum energy for a given complex. All the conformers withdrawn from the run of MD were subjected to the above-described procedure of charge-structure calculations, and the data appropriate for the lowest energy conformer of each complex were correlated with the experimental $\log K_s$ values.

The simulations were carried out at the Interdisciplinary Centre for Mathematics and Modelling at the University of Warsaw, using a CRAY-YMP supercomputer.

RESULTS AND DISCUSSION

Similarly as in our previous paper,[19] the determination of the stability constants of complexes was based on the measurements of ΔE, the changes of the redox potentials of K^+ cations, brought out by the ligand added to the solution. The cyclic voltammetric curves (scan rate $0.1\,V\,s^{-1}$), recorded in solutions containing 0.5 mM $KClO_4$ and 0.10 M tetraethylammonium perchlorate, were reversible. The shift in potentials towards more negative values upon stepwise addition of excess ligand was observed to be in agreement with the simple Lingane equation. In our experiments c_L, the analytical concentration of the ligand, usually varied from about 5 to about 50 mM and the plots of ΔE against $\log c_L$ were linear with slopes of 58 ± 4 mV. This result may be treated as evidence that only 1 : 1 complexes are formed in all systems under study.

The methanol stability constants presented in Table I illustrate the effect of the side groups on the complexing ability of the main ligand ring. It should be pointed out that these values were verified by potentiometric titration,[20] and the reproducibility in $\log K_s$ determined voltammetrically and potentiometrically was found to be ± 0.1 log units. Moreover, some results are available in the literature for comparison. It is noteworthy,

TABLE I Experimental stability constants, K_s, and calculated interaction energies (in kcal/mol)[a] for the potassium coronates in gas phase, $(E_{int})_{gas\ phase}$ and with regard to two microsolvating methanol molecules, $(E_{int})_{solv}$

Ligand	log K_s	$(E_{int})_{gas\ phase}$	$(E_{int})_{solv}$
I	6.0_6	−39.19	−47.01
II	5.1_4	−38.47	−44.43
III	5.0_1	−36.52	−44.84
IV	5.9_4	−40.02	−47.29
V	5.3_9	−39.54	−46.16
VI	5.5_0	−38.95	−45.80
VII	5.7_4	−40.56	−46.07
VIII	4.9_3	−38.89	−45.55
IX	4.3_3	−38.90	−43.75

[a] Here, 1 cal = 4.184 J.

therefore, that the data presented in Table I are generally in good agreement with those reported,[25,26] except for the complexes formed by **VIII** and **IX**, for which the authors[18] obtained the values of log K_s 4.39 and 3.91, respectively.

Initial MD calculations were performed on gas phase systems. The results demonstrated convincingly that in the complexes with K^+ the macrocyclic ring generally adopts a conformation in which all six oxygen atoms coordinate equatorially to the cation in the centre of the cavity. This finding is not surprising; similar conclusions were reported in the previous papers describing MD modelling of the complexes formed by **I**[27] and **III**.[28] Such structures were used as starting geometries for the calculations of the interaction energy, E_{int}, defined as the difference of the total energy of the complex in its lowest energy conformation and the same system without a metal cation. The resulting $(E_{int})_{gas\ phase}$ values are also given in Table I.

The results of Table I show that the stability constants for the coronands are quite sensitive to structural effects. In order to clarify this observation we have first correlated log K_s with the corresponding $(E_{int})_{gas\ phase}$ values. It appeared, however, that these quantities are colinear to very limited extent; correlation coefficient $r = 0.426$. Taking into account the fact that in solution the cation–crown complexes are surrounded by solvent molecules, this result seems justifiable. Then, as a subsequent step of our analysis, we have computed the corresponding $(E_{int})_{solv}$ energies, *i.e.*, values with regard to solvation of the systems of interest.

MD simulations based on classical force field[29,30] and hybrid quantum mechanical–molecular mechanical studies[31,32] are able to incorporate several hundred solvent molecules with a cation–crown complex. On the other hand, however, it is evident that the residual solvation (*i.e.*, microsolvation) of the cation bound to coronands plays an important part in thermodynamics of complexation.[33–35] Thus, taking into account the results described for 18-crown-6 complexes in water,[33,34] we have considered the effect of two microsolvating CH_3OH molecules attached to the complexed cation.

As follows from initial MD modelling performed on the gas phase systems, there is a room for methanol coordination at the complexed potassium ion, above and below the macrocyclic plane. Therefore, in order to mimic the microsolvation effect, computations were performed with regard to two CH_3OH molecules placed in the abovementioned positions. For all the coronates coordination was maintained after minimization; the diagrams reproduced in Figure 1 should be treated as examples.

Such structures were used for the calculation of $(E_{int})_{solv}$ energies; resulting values are collected in the last column of Table I. Comparison of these data with experimentally determined stability constants, $\log K_s$, shows a linear relationship. Correlation analysis leads to a relation in the following form:

$$\log K_s = (-0.43 \pm 0.17)(E_{int})_{solv} - (14.40 \pm 7.79) \qquad (1)$$

which holds with $r = 0.915$ and a mean square standard deviation in $\log K_s$ of $s = 0.21$ (Figure 2). Errors in regression coefficients were calculated using Student's distribution with a confidence level of 0.95. Thus, the correlation is rather poor, but an application of the Fisher test ($F = 35.85$) indicates that it is statistically significant at the 0.95 level. This confirms that the $(E_{int})_{solv}$ value is an important factor determining the complexation equilibria in the systems considered in the present work. Hence we can conclude that Equation (1) is indeed "robust".

The results presented above show that the significant part of the variation of interaction energy is attributable to microsolvation effects. This can be related to the pattern of the optimized structures of the complexes, where the cation is coordinated not only with the crown ether but also with the solvent molecules in the resulting cluster. Next, the $\log K_s$ values are proportional to the free energy of complexation which can be expressed in terms of enthalpy and entropy, while the calculated $(E_{int})_{solv}$ quantities do not include the entropic effect. The question thus arises as to whether the entropy changes are relatively constant, or linearly related to the enthalpy changes for all members belonging to the series investigated. A definite answer is

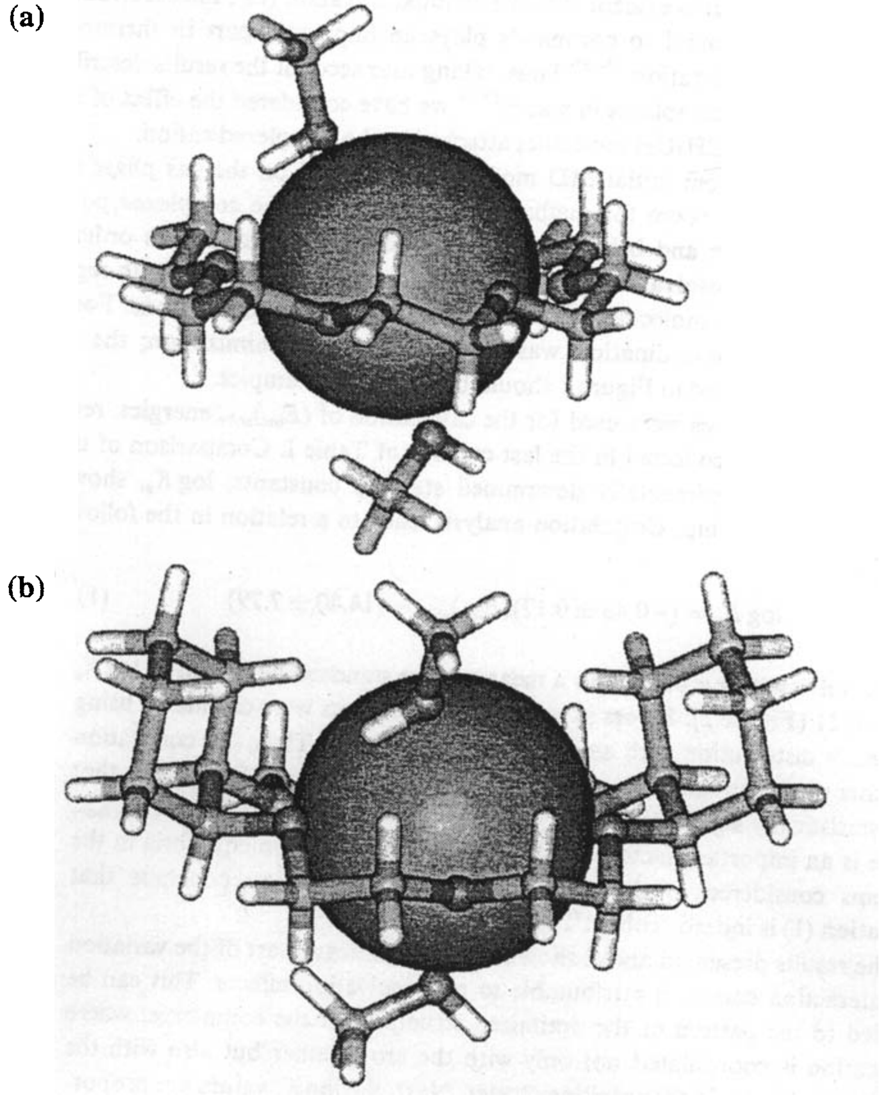


FIGURE 1 A view of the molecular dynamics minimized clusters of 18-crown-6 (a) and *cis-syn-cis* dicyclohexyl-18-crown-6 (b) with the potassium cation and two microsolvating methanol molecules.

impossible, but we are able to say that colinearity between $\log K_s$ and $(E_{\text{int}})_{\text{solv}}$ is also observed for rubidium and cesium complexes formed by the ligands **I**–**IX** in methanol solution. This problem will be discussed in a further communication.

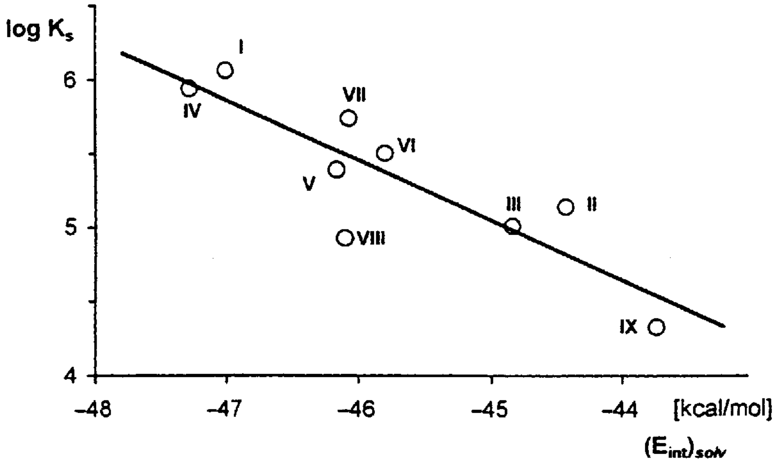


FIGURE 2 Plot of the log K_s values for potassium coronates *vs* interaction energies, $(E_{int})_{solv}$.

Acknowledgments

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