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The thermochemical studies of protonated amine–crown ether complexes: Extension of the kinetic method

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Dedicated to Prof. Catherine Fenselau in deep appreciation of her invaluable mentorship and guidance.

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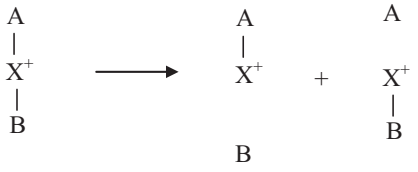
ABSTRACT

We have devised a new approach that extends the kinetic method to systems where the competitive dissociation (the cornerstone of the kinetic method) will occur not at one binding center but at two spatially different places. This approach was tested on dissociation of complexes of two symmetric doubly protonated diamines with seven different crown ethers resulting in the relative binding order of alkylammonium cation (half of the protonated diamine dication) to the crown ethers. For the experiments with 1,10-diaminodecane, leading to the n-alkylammonium binding ladder, the order was dicyclohexano-18-crown-6 > dibenzo-21-crown-7 > 18-crown-6 > dibenzo-24-crown-8 > dibenzo-18-crown-6 > 15-crown-5 > 12-crown-4. When N,N′-dimethyl-1,8-octanediamine was used, the experiments gave rise to the relative binding of N-methyl-n-alkylammonium cation, which was dibenzo-24-crown-8 > dicyclohexano-18-crown-6 > dibenzo-21-crown-7 > dibenzo-18-crown-6 > 18-crown-6 > 15-crown-5 > 12-crown-4. The observed binding trends were explained in terms of size of the alkylammonium cation, size of the cavity of the crown, flexibility of the crown substituents, and overall crown polarizability. Our data qualitatively correlate well to the literature gas-phase values for these systems as well as to the solution data (where available).

1. Introduction

The kinetic method [1–3] has established itself as one of the most common techniques for thermochemical measurements. Numerous applications of the kinetic method include determination of proton affinities and gas-phase basicities [4,5], with multiple contributions from Fenselau and co-workers [6–9]. Other applications of the method resulted in measuring metal ion binding energies [10–12], enantiomeric purity [13,14], gas-phase acidities [15], among many others. Developed by Cooks [16], this method takes advantage of a competitive dissociation at a binding center (Eq. (1)).



(1)

where X^+ can be a metal ion [10–12], a proton [2,5,6], or a small molecule (NO or NO_2) [17,18]. The charge can be reversed and anionic complexes could be probed instead [19].

As one can see from Eq. (1), a limitation of this technique is reached when X^+ is unable to bind A and B at the same time (e.g., for steric reasons). Even in systems where this binding can experimentally be observed, like in metal ion–aromatic amino acid complexes, X^+ may not reach an optimum binding arrangement with both A and B (which otherwise would be observed by binding only one of the ligands). This has led to discussions on whether the kinetic method should be employed for studying such systems [20].

Even more convincing are examples when X^+ simply cannot bind both A and B. Consider binding of a protonated primary amine RNH_3^+ to crown ether, as shown in Scheme 1. There the size of a crown ether cavity is normally sufficiently large to prevent the alkylammonium group from binding to another crown ether molecule.

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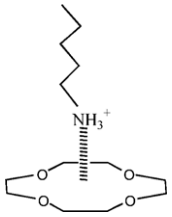
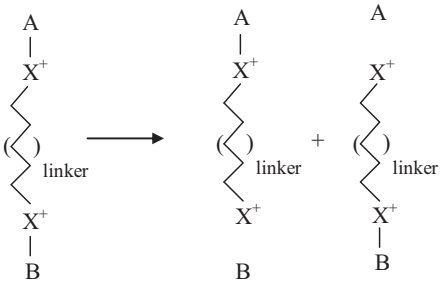


Scheme 1. Binding of an n-alkylammonium cation to a crown ether.

Thus, binding in this system cannot be studied by the "conventional" kinetic method.

In this work we present an extension of the kinetic method that will allow us to study systems like the one shown in Scheme 1.

The novelty of our approach is that the competitive dissociation (the cornerstone of the kinetic method) will occur not at one binding center (like in Eq. (1)) but at two different places, as shown in Eq. (2):



(2)

Here the design of the system requires two chemically identical groups X^+ be separated in space (by an inert linker, for instance). Mixed complexes of the ion containing two X^+ groups bound to A and B can be mass-selected in the mass spectrometer and from there on one can proceed with the "conventional" kinetic method with the result being relative binding of A and B to the group X^+ (plus the linker if X is small enough for binding to be affected by it).

While the systems suitable for this approach may seem quite elaborate, a logical first choice was to study the aforementioned binding of protonated primary amines to various crown ethers via 1,10-diaminodecane, the molecule in which alkylammonium groups RNH_3^+ correspond to X^+ and two different crown ethers would play the role of A and B in Eq. (2).

Mass spectrometry has been actively used for studying crown ether complexes with various protonated amines. Brodbelt group has determined the binding order of various crown ether complexes with protonated amines and peptides [21–25]. Julian and Beauchamp have used the strong binding between protonated primary amines and 18-crown-6 and its analogues as a probe for the lysine side chains and the peptide N-terminus [26,27]. Crumbliss et al. have looked at ionophore-siderophore host–guest supramolecular assemblies that utilize 18-crown-6, along with derivatives, binding to the alkylamine chain of ferrioxamine B for transport [28], thermodynamic parameters [29], and molecular recognition [30].

While numerous studies have confirmed the strong binding in primary alkylammonium–crown ether complexes, the thermochemistry of gas-phase binding has been explored in much less detail. Julian and Beauchamp have reported a binding energy of 182 kJ mol^{-1} for methylammonium–18-crown-6 complex based on PM3 calculations [26]. Colorado and Brodbelt [31] used an energy-variable CID technique to produce a value of >210 kJ mol^{-1} for n-butylammonium–18-crown-6 interaction. Data from studies in solution are not available for many crowns and/or alkylammonium ions and strongly depend on the choice of solvent [32,33].

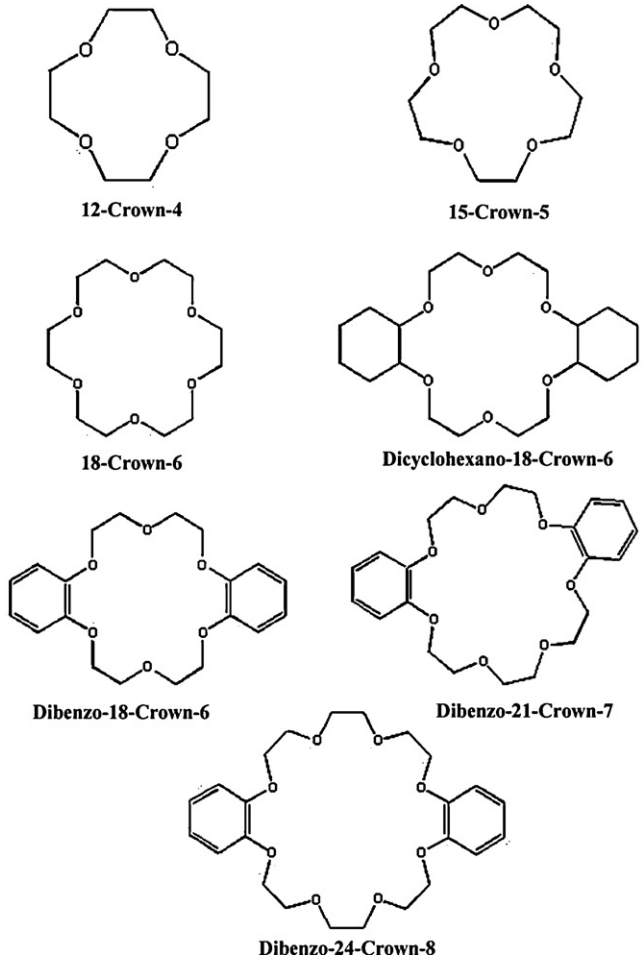


Fig. 1. Structures of crown ethers used in this study.

Thus, measuring the bond dissociation energies in these systems remains a challenge. In this work we use the proposed extension of the kinetic method to measure the bond energy differences in alkylammonium complexes with seven different crown ethers. The structures of the crown ethers used in this study are shown in Fig. 1.

2. Experimental

2.1. Materials

All crown ethers used in this study (listed in Fig. 1), 1,10-diaminodecane, and N,N′-dimethyl-1,8-octanediamine were purchased from Sigma–Aldrich (Milwaukee, WI) and used without further purification. Acetonitrile and acetic acid (glacial) were obtained from Fisher Scientific (Pittsburgh, PA). Solutions of crown ethers and 1,10-diaminodecane were prepared in 50:50 acetonitrile:water with 1% acetic acid added, resulting in final concentrations of 10 μM. For the preparation of mixed complexes, solutions of 1,10-diaminodecane and two crown ethers of interest were mixed in 1:1:1 ratio and used in the mass spectrometry experiments without further dilution. Solutions of N,N′-dimethyl-1,8-octanediamine and two crown ethers of interest were mixed in 1:3:3 ratio.

2.2. Mass spectrometry experiments

All experiments were carried out using a commercial quadrupole ion trap mass spectrometer equipped with electrospray

ionization (ESI) (Bruker Esquire 3000, Bremen, Germany). The samples were introduced to the mass spectrometer at a flow rate of 4 μL/min. The sheath gas, needle voltage and temperature were adjusted to *ca* 10 arb. units, 3.0 kV and 200 °C, respectively. The CID experiments were performed using standard procedures by mass selecting the desired precursor ion, with an activation window of 2 *m*/*z*; and then subjecting it to CID. The CID excitation voltage was kept low (typically, below 0.4 V_{pp}) resulting in dissociation of some of the precursor ions. Branching ratios of the product ions were measured after averaging at least 20 scans. All ratio measurements were repeated three or four times.

3. Results and discussion

3.1. Formation and gas-phase dissociation of diamine–crown complexes

Electrospray mass spectra of a mixture of diamine (DA) and two crown ethers (C1 and C2) resulted in several major peaks. Protonated diamine $[DA+H^+]^+$ was always prominent. Protonated crowns $[C1+H^+]$ and $[C2+H^+]$ were present. There were singly charged adducts of diamine and one crown $[C1+H^++DA]^+$ and $[DA+H^++C2]^+$ as well as doubly charged "symmetric" complexes of two crowns with the diamine $[C1+H^++DA+H^++C1]^{2+}$ and $[C2+H^++DA+H^++C2]^{2+}$. However, the mixed crown–diamine doubly protonated complex of interest $[C1+H^++DA+H^++C2]^{2+}$ was always present in high enough intensity that allowed it to be isolated and subjected to collision-induced dissociation in the ion trap.

CID of the mixed crown–diamine doubly protonated complex also resulted in multiple products. Formation of the products of interest, the doubly charged complexes of the diamine with one crown, $[C1+H^++DA+H^+]^{2+}$ and $[H^++DA+H^++C2]^{2+}$, formed according to the generic Eq. (2), is shown below in Eqs. (3a) and (3b). Along with these, some other reaction channels were present, like the formation of singly charged crown–diamine complexes $[C1+H^++DA]^+$ and $[DA+H^++C2]^+$ (Eqs. (4a) and (4b)), and secondary dissociation products (Eqs. (4c) and (4d)). Reactions (4a)–(4d) were relatively minor under 'mild' CID conditions, where the excitation amplitude was chosen so that the precursor ion $[C1+H^++DA+H^++C2]^{2+}$ was still visible in the spectrum. More importantly, the branching ratio of the products of reactions (3a) and (3b) stayed fairly constant under those 'mild' CID conditions independent of the excitation amplitude used.

$$[C1 + H^+ + DA + H^+ + C2]^{2+} \rightarrow [C1 + H^+ + DA + H^+]^{2+} + C2 \quad (3a)$$

$$[C1 + H^+ + DA + H^+ + C2]^{2+} \rightarrow C1 + [H^+ + DA + H^+ + C2]^{2+} \quad (3b)$$

$$[C1 + H^+ + DA + H^+ + C2]^{2+} \rightarrow [C1 + H^+ + DA]^+ + [H^+ + C2]^+ \quad (4a)$$

$$[C1 + H^+ + DA + H^+ + C2]^{2+} \rightarrow [C1 + H^+]^+ + [DA + H^+ + C2]^+ \quad (4b)$$

$$[C1 + H^+ + DA + H^+ + C2]^{2+} \rightarrow [DA + H^+]^+ + [C1 + H^+] + C2 \quad (4c)$$

$$[C1 + H^+ + DA + H^+ + C2]^{2+} \rightarrow [DA + H^+]^+ + [C2 + H^+] + C1 \quad (4d)$$

Sample MS/MS spectra for complexes of 1,10-diaminodecane with 18-crown-6 and dibenzo-18-crown-6 as well as for N,N′-dimethyl-1,8-diamine with dibenzo-21-crown-7 and dibenzo-24-crown-8 are given in Figs. 2 and 3, respectively.

3.2. The kinetic method analysis of CID data

The simple kinetic method treatment of Eq. (1) provides a route for obtaining relative $\Delta(\Delta H)$ binding of A and B to X^+ via Eq. (5):

$$\ln\left(\frac{k_1}{k_2}\right) = \ln\left(\frac{[A - X^+]}{[B - X^+]}\right) \approx \frac{\Delta(\Delta H)}{RT_{eff}} \quad (5)$$

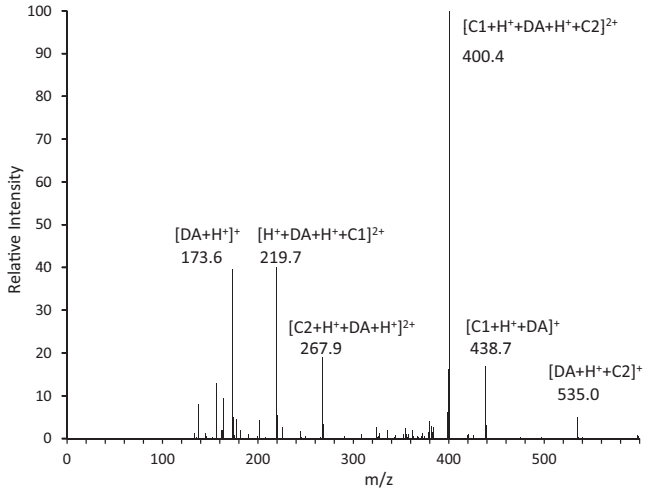


Fig. 2. CID of the complex of doubly protonated 1,10-diaminodecane (DA) with 18-crown-6 (C1) and dibenzo-18-crown-6 (C2).

where T_{eff} is the effective ion temperature inside the trap. The value of T_{eff} in CID experiments in quadrupole ion traps has been a matter of multiple studies. The general consensus is that it is very close to the room temperature for ions prior to CID (Gronert reported 315 K using a temperature-sensitive equilibrium reaction [34]). During collisional activation the temperature will be somewhat higher. Afonso et al. [35] found that when the excitation amplitude is kept low, T_{eff} is close to 350 K for the dissociation of proton-bound dimers of amino acids. That value increases to 390 K with moderate increases of CID amplitude. Brodbelt-Lustig and Cooks [36] measured T_{eff} = 335 K during the dissociation of proton-bound pyridine dimers. While many modifications to the simple kinetic method [35,5], including works by Fenselau's group [6,7,37], allow for determination of T_{eff} via varying the collision energy, for our proof-of-principle study we decided to use T_{eff} = 350 K. We realize that the resulting uncertainty in the $\Delta(\Delta H)$ obtained with this approximation will be higher, but the focus of this study was to show that the kinetic method can be applied to systems with competitive dissociations at two different locations.

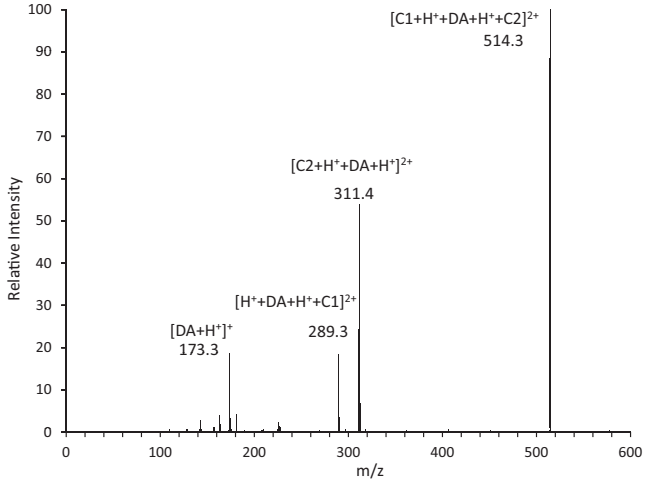


Fig. 3. CID of the complex of dibenzo-21-crown-7 (C1) and dibenzo-24-crown-8 (C2) with doubly protonated N,N′-dimethyl-1,8, octanediamine (DA).

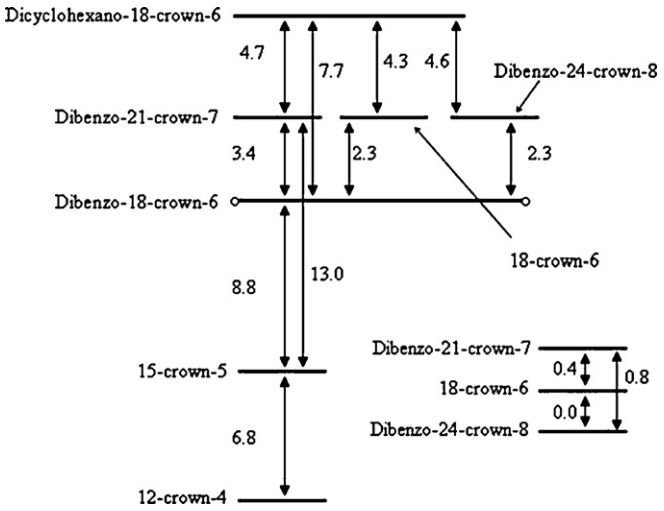


Fig. 4. Binding ladder of crown ethers to the n-alkylammonium moiety. The results are average of four runs. Standard deviations (not including the uncertainty in the T_{eff} value of 350 K) are ±0.2 kJ mol^{-1}.

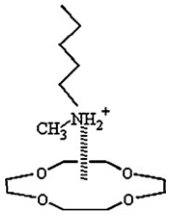
For the dissociation of the mixed crown–diamine doubly protonated complex, Eq. (5) can be re-written as (6):

$$\ln\left(\frac{k_1}{k_2}\right) = \ln\left(\frac{[C1 + H^+ + DA + H^+]^{2+}}{[H^+ + DA + H^+ + C2]^{2+}}\right) \approx \frac{\Delta(\Delta H)}{RT_{eff}} \quad (6)$$

By taking experimental ratios of products in Eq. (6) (obtained from CID mass spectra similar to Figs. 2 and 3), we calculated $\Delta(\Delta H)$ of binding of different crown ethers to "half" of a doubly protonated diamine, or to an alkylammonium moiety in case of 1,10-diamine and to the N-methyl-alkylammonium moiety in case of N,N′-dimethyl-1,8-diamine.

3.3. Relative binding order for n-alkylammonium (~RNH_3^+)

Relative binding enthalpies of alkylammonium moiety to different crown ethers are shown in Fig. 4. At the bottom of the binding ladder are 12-crown-4 (weakest binder) and 15-crown-5. Their cavities are simply too small to accommodate the alkylammonium moiety efficiently. The cavity of a crown-6 is considered to be the "perfect" size for alkylammonium. For instance, Julian et al. used 18-crown-6 to count the number of accessible Lys side chains (which is an n-alkylammonium moiety) in a protein [26,27,38,39]. Not surprisingly, 18-crown-6 displays much stronger binding than 12-crown-4 or 15-crown-5 in our experiments as well. Among the three members of crown-6 family in our study, 18-crown-6 is in the middle of binding strength. The dibenzo-18-crown-6 has two rigid aromatic rings that do not allow the crown cavity to adjust its size for the optimum binding of alkylammonium cation, thus it binds 2.3 kJ mol^{-1} less strongly. On the other hand, dicyclohexano-18-crown-6 binds 4.3 kJ mol^{-1} more strongly than 18-crown-6, because its cyclohexano substituents are flexible and do not impede with the optimum hydrogen-bond formation while increasing the overall polarizability of the crown. This is consistent with findings of Dearden and Chu [40] who in addition pointed out that binding of dicyclohexano-18-crown-6 to protonated amines is dependent on the crown conformation. As one increases the cavity size to dibenzo-21-crown-7 and dibenzo-24-crown-8, the polarizability of the crown increases, but the cavity becomes too large to accommodate the alkylammonium group in an optimum way. These two factors seem to cancel each other out, as both of these crowns bind alkylammonium cation about equally strongly to 18-crown-6. In fact, an inset to Fig. 4 shows that these three crowns are within 0.8 kJ mol^{-1} of each other on the binding scale. A recent work [41] suggests that the gas-phase NH_4^+ binding of 21-crown-7 should be higher than that of 18-crown-6, but we could not confirm it as unsubstituted 21-crown-7 was not available to us. However, we can indirectly confirm this by noticing that dibenzo-21-crown-7 binds an alkylammonium moiety 3.4 kJ mol^{-1} more strongly than dibenzo-18-crown-6. Overall, our gas-phase binding order correlates well with solution data as well, at least in the general picture 12-crown-4 < 15-crown-5 < 18-crown-6. While the individual branching ratios for Eqs. (3a) and (3b) are very reproducible resulting in the measurement error of ±0.2 kJ mol^{-1}, a better assessment of the data self-consistency can be done by comparing the obtained via different routes (Fig. 4). For instance, dibenzo-18-crown-6 and dicyclohexano-18-crown-6 differ in their ammonium affinities by 7.7 kJ mol^{-1} when compared directly, and by 2.3 + 4.3 = 6.6 kJ mol^{-1} when compared indirectly, through 18-crown-6. On the other hand, going through dibenzo-21-crown-7 gives the $\Delta(\Delta H)$ value of 4.3 + 3.7 = 8.1. These fluctuations, which could be due to uncertainties in T_{eff} and to entropy effects, provide a more realistic value of the error range as being 1.0–1.5 kJ mol^{-1}.



Scheme 2. Binding of an N-methyl-n-alkylammonium cation to a crown ether.

3.4. Relative binding order for N-methyl-alkylammonium (~RNH_2^+-CH_3)

Another system that was tested by our approach was complexes of doubly protonated N,N′-dimethyl-1,8-octanediamine with crown ethers. The proposed analysis of the kinetic method data for this system results in relative binding values between N-methyl-n-alkylammonium cation and the series of crown ethers shown in Scheme 2.

An important difference between n-alkylammonium and N-methyl-alkylammonium cations binding to crowns is the number of hydrogen bonds: the former has three hydrogens available, while the latter has only two. Schalley and Springer [41] showed that tertiary ammonium cations such as trialkylammonium or pyridinium (that have only one hydrogen atom available for hydrogen bonding) show virtually no preference for a cavity size of the crown, while n-alkylammonium cations for the reasons of symmetry prefer 18-crown-6 and its derivatives.

A sample CID spectrum of a mixed complex between doubly protonated N,N′-dimethyl-1,8-octanediamine with dibenzo-21-crown-7 and dibenzo-24-crown-8 is shown in Fig. 3. Analysis of spectra like that one by Eq. (6) resulted in the relative binding ladder reported in Fig. 5. An obvious trend is that binding increases with the increase in the cavity size (crown-5 < crown-6 < crown-7 < crown-8). Experiments were also performed with 12-crown-4 but CID of its mixed complexes resulted in the exclusive loss of 12-crown-4 which did not allow us to measure the branching ratio for reactions (3a) and (3b). Obviously, 12-crown-4 was a much weaker binder than the next weakest crown, 15-crown-5. Within the same crown cavity size, the binding order was 18-crown-6 < dibenzo-18-crown-6 < dicyclohexano-crown-6. If one imagines than no more than four oxygen atoms from the crown can participate in interactions with the two hydrogen atoms of the N-methyl-alkylammonium moiety, then the observed overall binding order simply follows the overall polarizability of the crown ethers, with

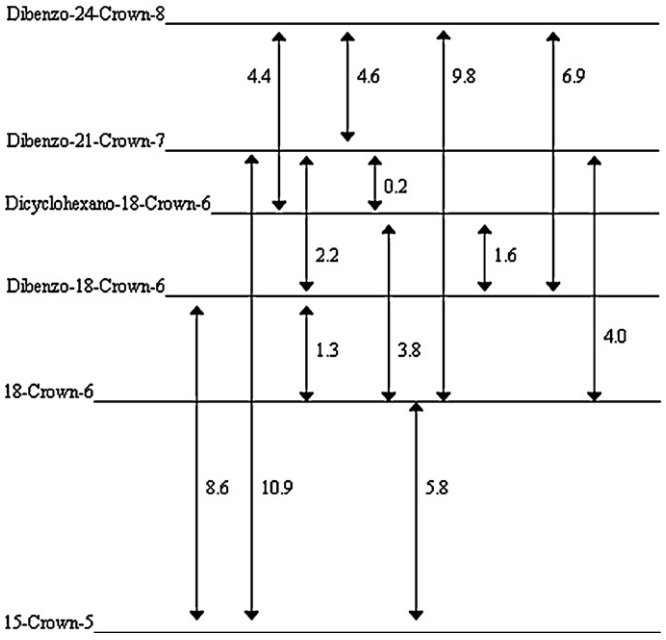


Fig. 5. Binding ladder of crown ethers to the N-methyl-n-alkylammonium moiety. The results are average of three runs. Standard deviations (not including the uncertainty in the T_{eff} value of 350 K) are ± 0.2 kJ mol^{-1}.

little or no selectivity displayed. While no "anchors" have so far been reported in the literature for this system, one should expect a substantially weaker binding of the N-methyl-alkylammonium by crowns compared to the alkylammonium, simply on the basis of the number of hydrogen bonds formed in the complex.

N-methyl-alkylammonium moieties are present in ε-N-methylated lysine, an important post translational modification in proteins, especially in histones [42,43]. An important conclusion from our binding studies is that it is going to be fairly difficult to "map" N-methyl-Lys residues on the surface by forming non-covalent complexes with crown ethers (as Julian and Beauchamp have done for Lys [27]), especially in the presence of unmodified Lys residues. Further studies will be carried out to compare binding enthalpies for crown complexes of alkylammonium vs N-methyl-alkylammonium, especially to investigate if any favorable interactions between the N-methyl group and crown non-polar substituents can be explored.

4. Conclusions

A modification to the kinetic method experiment is described where the competitive dissociation occurs not at one but rather at two spatially different places. If the system is designed properly, its symmetry can be the rationale for applying the standard kinetic method treatments to such variations. Numerous charge/symmetry designs can be envisioned for our approach. The two examples shown in this work are dicationic diamine/crown or N,N′-dimethyl-diamine/crown complexes, resulting in relative binding order of n-alkylammonium/crown and N-methyl-n-alkylammonium/crown complexes, respectively. The binding ladders that were obtained in this work can easily be combined with one of the literature "anchors" to produce absolute binding enthalpies, available for one of these systems. While our kinetic method treatment was simplified by assuming the effective ion temperature to be 350 K, in principle, any more sophisticated treatment can be utilized instead. Our limitation in this respect was that we were not able to vary the effective ion temperature enough by changing CID excitation amplitude, as the doubly charged ions of interest produced constant branching ratios (Eqs. (3a) and (3b)) within the experimental range of CID voltages. Using a different instrumental setting (like a triple-quadrupole-based mass spectrometer) may solve this problem. Future studies will be conducted to assess whether the linkage length is sufficient to eliminate the effects of the remote substituent on the measured binding strength.

Acknowledgments

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