Effects of Alkyl Substitution on the Multidentate Attachment of Alkali Metal Cations by Ligands in the Gas Phase: Kinetics and Thermochemistry of Cation Binding by Isomers of Dicyclohexano-18-crown-6

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Abstract: Commercially-available dicyclohexano-18-crown-6 (DC18C6) is a mixture of two easily-resolved isomers, *cis*-syn-*cis* and *cis*-anti-*cis*, differing in whether the cyclohexyl rings are linked to the main macroring with both substituents on the same side or on opposite sides, respectively. We have investigated the reactions of DC18C6 and its alkali metal ion complexes in a solvent-free, gas-phase environment. Both isomers have greater free energies of alkali cation attachment in the gas phase than unsubstituted 18-crown-6 (18C6), with the greatest differences between the substituted and unsubstituted ligands (>10 kJ mol^{-1}) occurring for the smallest metal ions. This is rationalized in terms of the greater polarizability of DC18C6. Comparison with solution data indicates there must be a greater cost in free energy for desolvating the cavity of DC18C6 than for 18C6. The efficiency of metal transfer from 18C6 to DC18C6 is high (≥20% for all alkali metal ions with either isomer) and increases with decreasing alkali ion size, Li^+ being nearly a factor of 3 faster than Cs^+ for the anti isomer. The variation in rates with cation size can be explained on the basis of decreasing barrier height on the potential energy surface for cation transfer as the depths of the wells for metal binding increase. The syn and anti isomers differ measurably in free energy of cation attachment, in kinetics of cation uptake from 18C6−alkali metal complexes, and in the rates at which 2:1 ligand−metal complexes form. The latter for both isomers are slower than for unsubstituted 18C6, reflecting greater steric hindrance in the substituted crown.

Introduction

A major area of host−guest chemistry deals with the design of host compounds, accomplished by placing substituents in such a way that they either directly or indirectly interact with the binding site of the host. The underlying principles which control these interactions are increasingly important as ligand design and synthetic methods become more sophisticated, and ligands are built with highly specific recognition of a particular guest as the goal. For example, recognition of one member of an enantiomeric pair over the other is a challenging goal where understanding these principles is vital.

The addition of substituents may affect a receptor molecule in several ways. Substitution likely will influence the conformational mobility of the receptor, possibly also changing the effective size of the binding cavity. In addition, substitution may alter the electronic properties of the binding portion of the host. While steric changes arising from substitution can be examined using X-ray crystallography,[1] such studies are limited by the influences of crystal packing forces and the presence of counterions in the crystal (in the case of ionic species). Changes in electronic properties may be even more difficult to examine in condensed media, since they are easily masked by strong interactions between the host molecule and surrounding species.

However, in the simple environment of the gas phase, crystal packing, solvent, and counterion effects are all absent, suggesting that detailed studies of substituent effects might be more feasible under gas-phase conditions. Such studies reveal the intrinsic effects which arise on substitution, independent of other intermolecular effects. In addition, they provide a test for the various methods of molecular modeling which are in increasingly common use,[2−10] since the results are strongly dependent on molecular conformation, size, and shape relationships between host and guest, which modeling should address well. At the same time, the complexities of condensed media, which are difficult to model, are avoided.

With these kinds of goals in mind, we have undertaken a systematic study of host−guest chemistry in the gas phase. Our work, as well as that of several other groups, has examined crown ethers as prototypical host molecules. Structures and abbreviations for the crown compounds are given in Figure 1. Collision-induced dissociation (CID) experiments have established that crown ethers retain their structural integrity on complexation of guests such as alkali metal cations[11−14] and have led to rough estimates of alkali cation binding strengths

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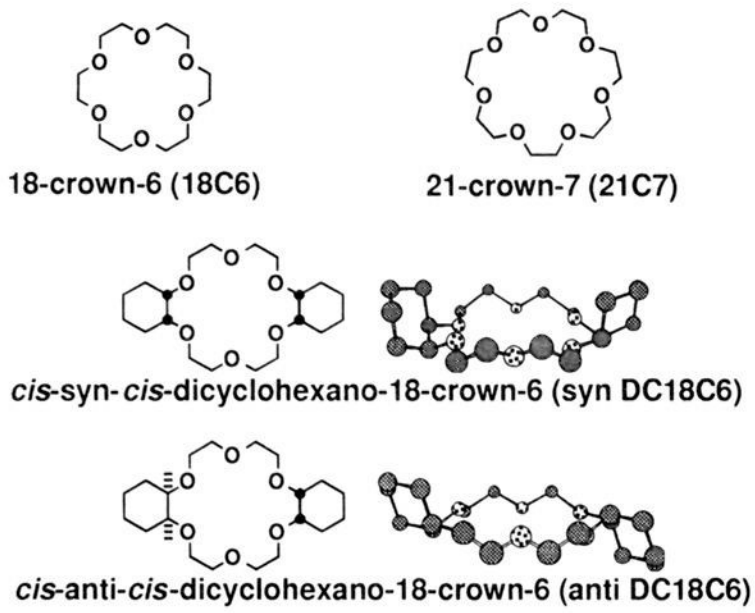

Figure 1. Structures and abbreviations for crown compounds. The 3D representations are from X-ray data for complexes of syn with Ba^{2+} and anti with Na^+, both from ref 1.

in the absence of solvation.[15] Other work dealing with the mass spectrometry of crown ethers and their complexes was summarized in our earlier publication.[16]

Our own studies have primarily focused on the gas-phase ion−molecule chemistry of crown complexes. We have observed that efficiencies for formation of 1:1 metal−ligand complexes involving alkali metal cations and the simple crown ethers 12C4, 15C5, 18C6, and 21C7 are greatest for the smallest cations and decrease monotonically with increasing cation size.[16] In contrast to this simple behavior, the efficiency of forming 2:1 crown−metal complexes is strongly dependent on the relationship between the size of the ligand cavity and the size of the cation, with efficient reaction occurring only when the cations are too large to enter the ligand binding cavity.[16,17]

The intrinsic cation affinities of the simple crowns, measured using bracketing techniques, are quite different in the gas phase than in most solvents:[18,19] for all the alkali metal cations, gas-phase affinities are in the order 21C7 > 18C6 > 15C5 > 12C4, correlating with both the polarizabilities of the ligands and the number of ether oxygen donor groups they possess.[16] More detailed equilibrium constant measurements for alkali cation transfer between 18C6 and 21C7 reveal interesting variations in free energy,[16] enthalpy, and entropy[20] as cation size is varied, with the transfer of K^+ from 18C6 to 21C7 showing anomalous enthalpy and entropy, presumably arising from the size match between K^+ and 18C6.

This paper extends our work beyond the simple series of crown homologs to crowns which are alkyl substituted. Like 18C6, DC18C6 (Figure 1) has six ether oxygen donor groups in an 18-membered ring. Ignoring the conformational influence of the substituents, the cavity sizes of the unsubstituted and substituted ligands should be quite similar, and it is interesting to ask whether or not any cation size effects will be apparent when two ligands of similar cavity size are compared.

Comparison of 18C6 and DC18C6 also allows us to address the relative importance of ligand flexibility and polarizability in cation binding. Conformationally, the cyclohexyl groups of DC18C6 should act to stiffen the macrocyclic ring, making this ligand less flexible than its unsubstituted counterpart. Since ligand flexibility is required in order to maximize interactions between the heteroatom donors and the metal ions, if flexibility has a dominant influence we would expect DC18C6 to have *lower* intrinsic cation affinities than 18C6. On the other hand, addition of the cyclohexyl rings makes DC18C6 much more polarizable than 18C6. Prior measurements of complexation efficiencies[16,21] found that efficiencies fall with decreasing cation charge density. This suggests that polarizability may play a dominant role in the electrostatic interactions between alkali cations and crown ethers. If so, DC18C6 should have *higher* intrinsic alkali cation affinities than 18C6. One of our experimental objectives is to measure the relative cation affinities of 18C6 and DC18C6, in hopes of resolving whether ligand flexibility or polarizability is more important in determining binding efficiencies and affinities.

The resolution of structural isomers is a challenging problem in mass spectrometry, since isomers by definition are identical in mass. Isomers are typically distinguished mass spectrometrically by differences in their fragmentation patterns, or by differences in reactivity. We examine DC18C6 from the latter perspective. There are five isomerically-distinct ways of attaching the two cyclohexyl substituents. Commercially-obtained DC18C6, which is made by hydrogenation of dibenzo-18-crown-6,[22] typically is purchased as a mixture of the *cis*-syn-*cis* and *cis*-anti-*cis* isomers (hereafter referred to as "syn" and "anti," respectively), but these are easily separated using published methods.[23] This offers the possibility of studying the gas-phase chemistry of the syn and anti isomers separately. The two are difficult to distinguish on the basis of solution thermochemistry, their relative cation affinities being similar and solvent dependent.[19]

Finally, the asymmetry inherent in the syn isomer leads to interesting questions, because the placement of the cyclohexyl rings means that the two faces of this molecule are not equivalent. For cations too large to easily pass through the macrocycle, there are two binding sites, one on the same side of the macrocyclic ring as the cyclohexyl substituents (the "onaji" site) and one on the opposite side (the "hantai" site). Can the two binding sites be distinguished? Will one be preferentially populated? How might this change as the size of the cation increases?

Although DC18C6 has been extensively characterized in condensed media,[18,19,24] to our knowledge there are no prior reports of its gas-phase chemistry.

Experimental Section

The procedures used in these experiments have been discussed in detail.[16] In brief, all experiments employed Fourier transform ion cyclotron resonance mass spectrometry, using a commercial instrument (FTMS-1000, Extrel FTMS, Madison, WI) with inlet systems modified as has been described.[16] Neutral ligands were introduced into the vacuum system through vacuum locks on solid sample probes, which

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Table 1. Rate Constants, $k(\times 10^{10}$ cm^3 molecule^{-1} s^{-1}), and Reaction Efficiencies for Cation Transfer from 18C6 to Isomers of DC18C6

	cis-syn-*cis*		*cis*-anti-*cis*	
metal	k	$k/k_{Langevin}$	k	$k/k_{Langevin}$
Li^+	9.9 ± 1.0	0.85 ± 0.09	8.0 ± 0.5	0.69 ± 0.04
Na^+	10.1 ± 1.4	0.88 ± 0.12	6.7 ± 0.5	0.59 ± 0.04
K^+	7.0 ± 0.6	0.62 ± 0.05	5.1 ± 0.5	0.45 ± 0.05
Rb^+	6.9 ± 0.7	0.64 ± 0.06	4.7 ± 0.7	0.43 ± 0.06
Cs^+	6.3 ± 0.6	0.59 ± 0.06	2.5 ± 0.4	0.23 ± 0.04

Table 2. Rate Constants, $k(\times 10^{12}$ cm^3 molecule^{-1} s^{-1}), and Reaction Efficiencies for Formation of $(DC18C6)_2M^+$

	cis-syn-*cis*[a]		*cis*-anti-*cis*[a]	
metal	k	$k/k_{Langevin}$	k	$k/k_{Langevin}$
Li^+	*	*	*	*
Na^+	*	*	*	*
K^+	*	*	*	*
Rb^+	*	*	5 ± 1	0.005 ± 0.001
Cs^+	14 ± 6	0.014 ± 0.006	35 ± 8	0.035 ± 0.008

[a] An asterisk indicates no reaction observed.

were not heated for these experiments (the temperature was estimated to be approximately 310 K in the vacuum chamber, based on readings from a thermocouple mounted on the solid sample probe adjacent to the trapping cell). This generated sufficient vapor pressures for all experiments. Alkali metal cations were laser-desorbed into the gas phase from nitrate salt mixtures deposited on the face of a solid sample probe situated adjacent to the ion trapping cell of the instrument. Typically, three or more alkali metal cations were examined concurrently to ensure that the metals experienced the same neutral partial pressures and thus improve the reliability of relative rate and equilibrium constant measurements. All values are reported as the mean of at least three separate determinations ± one standard deviation.

Rate constant determinations were made by ejecting product ions to define the time = 0 point, then following disappearance of reactants and formation of products as a function of time. Plots of log(ion intensity) versus reaction time were linear as expected under pseudo-first-order conditions. To estimate absolute rate constants, ligand pressures were estimated by measuring rates of proton attachment to the ligands. Attachment was assumed to be 100% efficient, and comparison of measured attachment rates with collision rates calculated using Langevin theory[25] yielded absolute neutral pressure estimates which are probably within a factor of 5 of the correct values.

Equilibrium constants were measured using the ratio of product ion to reactant ion intensities at long reaction times, along with relative pressure ratios for the two neutral ligands being compared. The latter were measured as previously described,[16] from the relative rates of proton attachment to the two ligands. All equilibria were approached in both the forward and reverse directions, to ensure that true equilibrium was attained.

All the alkali metal nitrates, as well as the neutral ligands 18C6 and DC18C6 (mixture of *cis*-syn-*cis* and *cis*-anti-*cis* isomers), were obtained from Aldrich Chemical Co. All were used as supplied, except DC18C6, for which the isomers were separated using published procedures.[23]

Results

Rate Constants. Rate constants measured for reactions 1 and 2 are listed in Tables 1 and 2, respectively. We estimate the absolute values of the rate constants are within approximately a factor of 5 of the true values (with most of the uncertainty arising from uncertainty in the pressure measurements), while because they were measured concurrently, the relative magnitudes of the constants for different metals reacting with a given ligand are accurate to about ±10%.

$$(18C6)M^+ + DC18C6 \rightarrow 18C6 + (DC18C6)M^+ \quad (1)$$

$$(DC18C6)M^+ + DC18C6 \rightarrow (DC18C6)_2M^+ \quad (2)$$

Reaction 1 is seen to be highly efficient, with between 20 and 90% of collisions resulting in cation transfer. In general, transfers of the smaller cations are most efficient, and efficiency decreases monotonically with increasing alkali metal cation size. Reactions involving the *cis*-syn-*cis* isomer are significantly more efficient than those of the *cis*-anti-*cis* isomer.

Reaction 2, the "sandwiching" reaction (Table 2), is in general more than an order of magnitude less efficient than reaction 1, and is too slow to observe for all but the largest alkali metal cations. In contrast to reaction 1, reactions of the *cis*-anti-*cis* isomer are more efficient than those of the syn isomer.

Equilibrium Constants. Equilibrium constants for reaction 1, with the corresponding free energies at 310 K, are listed in Table 3. Similarly, Table 4 gives equilibrium constants and free energies for alkali cation transfer from 21C7 to the two isomers of DC18C6, reaction 3.

$$(21C7)M^+ + DC18C6 \rightleftharpoons 21C7 + (DC18C6)M^+ \quad (3)$$

The constants for both reactions decrease with increasing alkali metal size. For reaction 1 involving the syn isomer with M = Li, the equilibrium constant was too large to measure using our methods (i.e., reaction was only observed in the forward direction as indicated, even with the largest practical excess pressure of 18C6 we could generate), and likewise, for reaction 3 involving the anti isomer with M = Rb and Cs, the constant was too small to measure (reaction was only observed in the reverse direction). In all cases the constants are larger for the syn isomer than for anti, with differences generally greater for the smaller metals than for the larger ones.

Discussion

Influence of Alkyl Substitution on Alkali Cation Affinities. The proton affinity of a gas-phase compound refers to $-\Delta H°$ for reaction 4,

$$A + H^+ \rightleftharpoons AH^+ \quad (4)$$

while its gas-phase basicity is $-\Delta G°$ for the same reaction.[26] Measurement of $\Delta H°$ or $\Delta G°$ for proton transfer between two gas phase species yields the difference between their proton affinities or gas-phase basicities, respectively. Reactions 1 and 3 are analogous to reaction 4, but involve transfers of alkali metal cations, rather than protons. To be rigorously faithful to this analogy, relative cation affinities should be determined from $\Delta H°$ data for the cation transfer reactions. The $\Delta G°$ data derived from the equilibrium constants of Tables 3 and 4 yield the differences in the gas-phase Lewis basicities of 18C6 and DC18C6, and 21C7 and DC18C6, respectively, toward the alkali metal cations. However, to avoid this cumbersome terminology, we will refer to these differences as relative cation affinities, while recognizing this is not a strictly correct use of the term.

Figure 2 plots $\Delta G°$ for reactions 1 and 3 versus cation size, graphically showing trends in the relative cation affinities of 18C6 and 21C7 versus the syn and anti isomers of DC18C6. The affinities of both isomers of DC18C6 for Li^+, Na^+, K^+, Rb^+, and Cs^+ are higher than those of unsubstituted 18C6 ($\Delta G°$ for reaction 1 is negative for all the alkali metals). Further, the difference in alkali cation affinities between the substituted and unsubstituted ligands decreases with increasing alkali cation size.

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Table 3. Equilibrium Constants, K, and Free Energies (kJ mol^{-1}) for Cation Transfer from 18C6 to DC18C6

	cis-syn-*cis*		*cis*-anti-*cis*	
metal	K	$\Delta G°_{310}$	K	$\Delta G°_{310}$
Li^+	*	*	25 ± 4	-8.3 ± 0.2
Na^+	550 ± 50	-16.3 ± 0.1	11 ± 1	-6.2 ± 0.1
K^+	7.3 ± 0.6	-5.1 ± 0.1	2.4 ± 0.4	-2.3 ± 0.2
Rb^+	6.6 ± 0.6	-4.9 ± 0.1	1.8 ± 0.4	-1.5 ± 0.2
Cs^+	3.4 ± 0.2	-3.2 ± 0.1	1.0 ± 0.1	-0.08 ± 0.06

[a] An asterisk indicates equilibrium was not observed; only the DC18C6 complexes were observed at long reaction times.

Table 4. Equilibrium Constants, K, and Free Energies (kJ mol^{-1}) for Cation Transfer from 21C7 to DC18C6

	cis-syn-*cis*		*cis*-anti-*cis*	
metal	K	$\Delta G°_{310}$	K	$\Delta G°_{310}$
Li^+	350 ± 30	-15 ± 0.1	6.1 ± 0.5	-4.7 ± 0.1
Na^+	14 ± 1	-6.8 ± 0.1	0.40 ± 0.02	2.4 ± 0.1
K^+	1.5 ± 0.1	-1.0 ± 0.1	0.40 ± 0.3	2.4 ± 0.1
Rb^+	0.18 ± 0.03	4.4 ± 0.2	*	
Cs^+	0.11 ± 0.01	5.6 ± 0.1	*	

[a] An asterisk indicates equilibrium not observed.

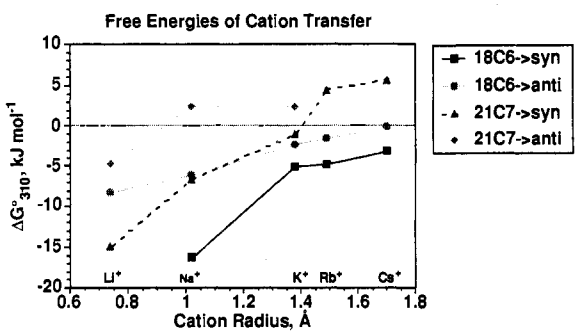

Figure 2. Free energies for cation transfer from unsubstituted crowns to isomers of DC18C6, derived from equilibrium constant data using the measured trapping cell temperature of 310 K.

Similar trends are seen in data comparing DC18C6 and 21C7, reaction 3. Remarkably, the syn isomer has a higher affinity for Li^+, Na^+, and K^+ than 21C7, while the Li^+ affinity of anti is also higher than that of 21C7, despite the presence of an additional donor atom in 21C7!

In rationalizing the differences in the cation affinities of 18C6 and DC18C6, it is useful to compare the two ligands. Both have six donor oxygens and are expected to have cavities of very similar size based on X-ray crystallographic data.[1] Steric bulk is greater for the two DC18C6 isomers. Conformational mobility is expected to be less for the substituted ligand. Finally, DC18C6 has considerably higher polarizability than 18C6.

Steric bulk is unlikely to account for the higher alkali cation affinities of DC18C6; one would expect increased steric bulk to lead to *lower*, rather than higher, affinities. In any event, the steric requirements to accommodate small cations like Li^+ are small, while the observed effects are largest for the smallest cations. Thus, differences in steric requirements cannot explain the experimental observations.

The difference in conformational mobilities of the unsubstituted and substituted ligands is difficult to quantify. One possibility is to use molecular dynamics/modeling studies, but even these are not practical with the computing equipment available to us, due to the very long times required for the ligands to reach statistically meaningful thermal equilibrium. For example, a recent molecular dynamics study indicates that molecular motions must be allowed to evolve for 6 ns or longer in order for 18C6 to reach thermodynamic equilibrium at 500 K, and even this is not long enough to eliminate statistical fluctuations due to incomplete sampling.[27] Even longer times would probably be required for the more complex DC18C6.

Conformationally, it is possible that the cyclohexyl rings could promote especially favorable orientations of the donor atoms for binding the metal ions, but several lines of reasoning suggest that is not the case. First, donor orientation, and whatever advantages it confers, should be significantly different in the syn and anti isomers. It is unlikely that the two isomers would both enjoy large conformational advantages over 18C6, yet both have higher cation affinities than 18C6. Second, donor orientational requirements for optimum binding undoubtedly change with changes in cation size, so it is unlikely that a donor orientation favorable for binding Li^+ would also account for enhanced binding of Cs^+. Yet, DC18C6 has higher affinities for *all* the alkali metal cations, not just a few as would be expected if conformation were the controlling factor.

Given the similarity of 18C6 and DC18C6, it is difficult to explain the greater alkali cation affinities of the substituted ligand in terms of factors other than polarizability. The observed trends are consistent with a dominant role for polarizability in determining the alkali cation affinities of multidentate ether ligands. The polarizabilities of the ligands can be accurately estimated using the method of atomic hybrid components.[28,29] By this method, the polarizability of DC18C6 (39.1 Å^3) is much higher than those of either 18C6 (25.9 Å^3) or 21C7 (30.2 Å^3). We would expect the relative importance of polarizability to be greatest for the smallest metals, which are the strongest polarizers, and to decrease with increasing metal size. This is exactly what is observed.

The influence of polarizability on the Li^+ affinities of small organic molecules has been noted previously.[30] Likewise, examination of K^+ affinity data for small N- and O-donor ligands[31] shows a roughly linear dependence of cation affinity on polarizability (Figure 3). In this light, it is not surprising that the alkali affinities of DC18C6 should be greater than those of 18C6, but it is interesting that polarizability effects can be so important for multidentate ligands, even to the extent that they overwhelm the influence of the additional donor group of 21C7, which is known to have higher intrinsic alkali cation affinities than 18C6.[16] It is noteworthy that the latter occurs only for the smaller alkali metal cations, where polarization should be strongest and the benefits of the additional donor group are minimized due to the greater strain involved in orienting the ligand to optimize donor interactions with the smaller cations. For the larger cations such as Rb^+ and Cs^+, which are weaker polarizers and better fits to the larger ligand, 21C7 has higher affinity than DC18C6.

Cation Size Effects. Since the binding cavities of 18C6 and DC18C6 are similar in size, this pair of ligands affords an opportunity to examine the relationship between cation size and the efficiency of the transfer reaction between two ligands (reaction 1) where neither presents a markedly better "fit" to any of the cations. In effect, the transfer reaction probes the relative labilities of the various cations in their 18-crown-6 complexes. One might expect the reaction efficiencies to

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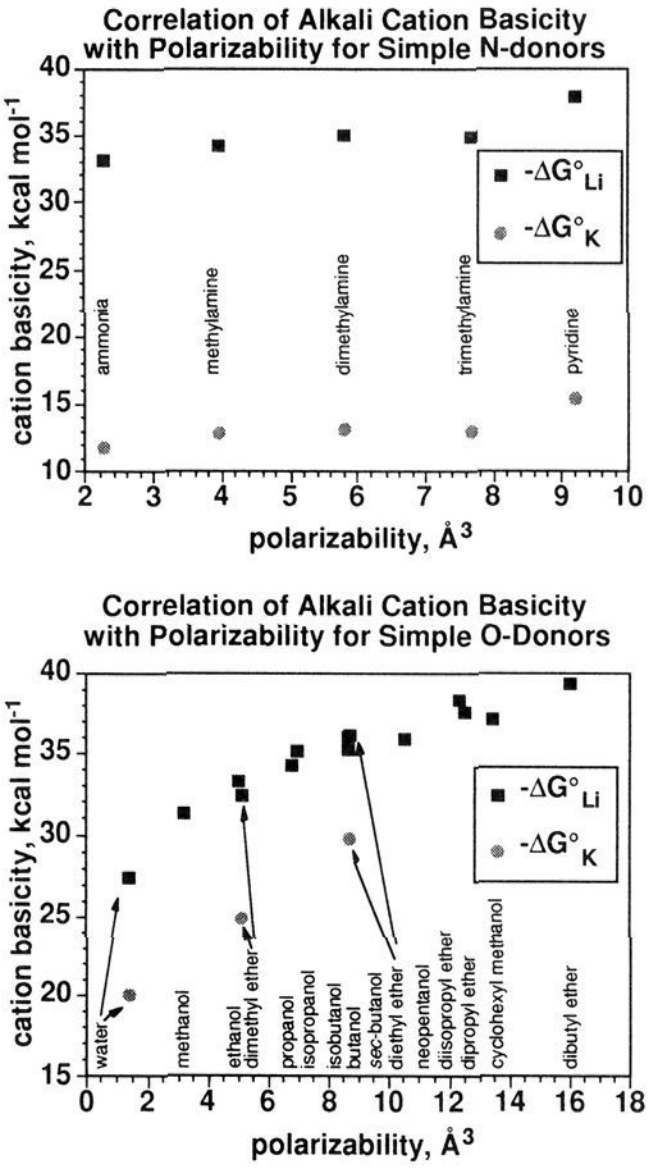

Figure 3. Correlation between basicity (toward Li^+ and K^+) and polarizability of the base, for a number of N- and O-donor monodentate bases. Li^+ basicities are from ref 30, and K^+ basicities are from ref 31.

increase with increasing cation size, since bond strengths are expected to decrease as the metals become larger, poorer polarizers.

Consideration of Figure 4 shows just the opposite. For the anti isomer, efficiency *decreases* monotonically with increasing cation size. The trends are similar for the syn isomer, although it accepts the cation more readily than anti. Thus, this experiment suggests that cation lability is *greatest* for the smallest alkali metals, despite the fact that they are almost certainly bound the strongest. Similar results have been found in studies of the exchange of alkali cations between isotopically labeled 21C7 ligands,[32] where the exchange is thermoneutral rather than exothermic as in the present case.

One possible explanation for these counterintuitive results is illustrated in Figure 5, which schematically depicts potential energy surfaces for the transfer reaction. The discussion which follows assumes that transfer proceeds via an associative mechanism, which seems reasonable since free metal ions are never observed in the mass spectra after formation of the complexes. In the figure, it is also assumed that the wells associated with binding the alkali metal ion to each neutral crown are Gaussian in shape. The actual well shape is not known, but we expect that the width of the well along the reaction coordinate should increase with increasing well depth. The Gaussian function nicely accounts for such an effect, and so would seem an appropriate choice conceptually. A further key assumption is that the barrier between the two wells results from incomplete overlap. Because the width of the wells increases as their depths increase, overlap increases with increasing depth and the height of the barrier decreases.

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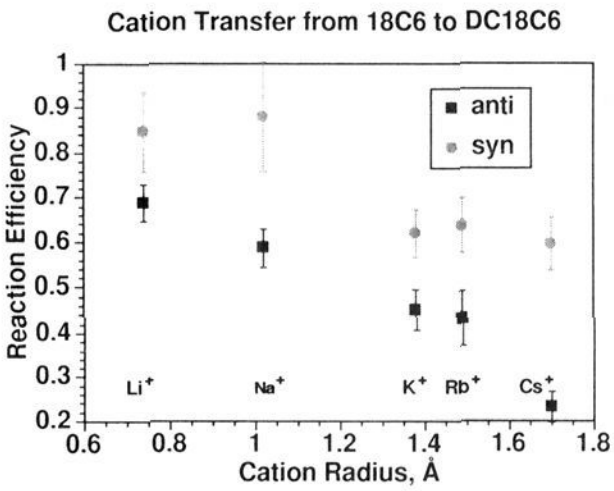
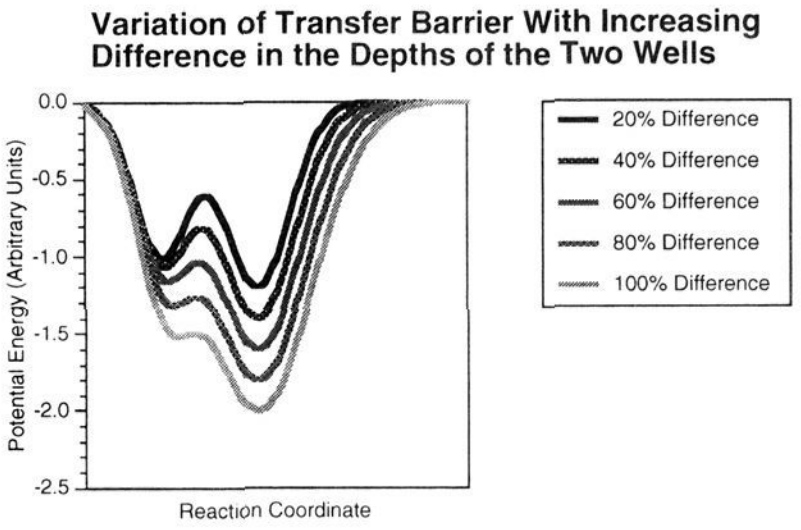


Figure 4. Reaction efficiencies (reaction rate/collision rate) for transfer of alkali metal cation from 18C6 to isomers of DC18C6. Error bars represent one standard deviation.



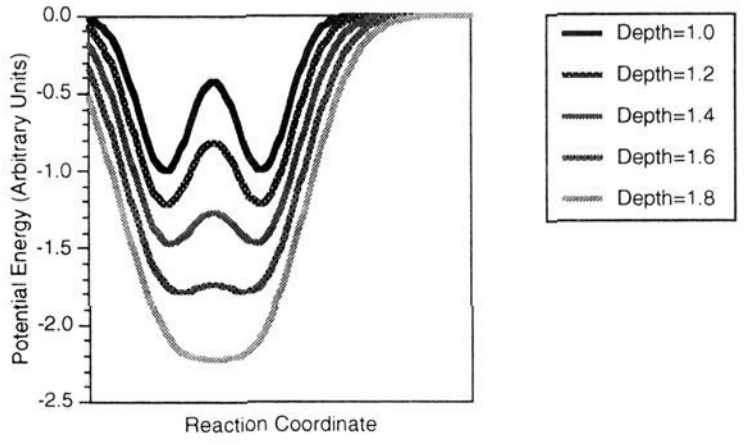


Figure 5. Schematic representation of effects of changes in well depth on barrier height. Wells are assumed to have Gaussian shape and their separation along the reaction coordinate is held constant. The barrier between the wells arises from their incomplete overlap.

From the equilibrium data noted above, it is clear that the well depths for binding alkali metals to 18C6 are less than those for binding to DC18C6, and that the difference in well depth for the two ligands increases with decreasing metal size. To a first approximation, the rate of cation transfer from 18C6 to DC18C6 will depend on the height of the barrier between the two wells. As Figure 5 suggests, the largest barrier occurs when the two wells have similar depths, such as would occur for Cs^+ transfer. As the well corresponding to DC18C6 binding deepens, the potential energy surface is pulled down and the barrier decreases. As a result, the barrier for transferring a more strongly-held cation, such as Li^+, *decreases*, and the rates *increase* for the smaller metals.

The discussion above is centered around the idea that the difference in well depths increases as the metal ions become smaller. However, extension of this idea to the case of thermoneutral metal transfer suggests the effect should be

observed even when both wells have the same depth, as long as the absolute depth of both wells increases (Figure 5, bottom). Further, it is possible this effect would be observed even if the height of the barrier relative to the bottom of the well does not change, as long as the energy of the barrier relative to separated reactants and products decreases, because the density of reactive states at the top of the barrier will increase as the top of the barrier moves to lower energy. We are now designing thermoneutral exchange experiments using isotopically-labeled ligands to test these ideas.

Isomer Differentiation. As was noted in the Introduction, DC18C6 is commonly available in two isomeric forms, referred to in this paper as the syn and anti isomers. In the early literature, these were referred to as the "A" and "B" isomers, respectively.[1] Each isomer has been characterized in the solid state using X-ray crystallography. The uncomplexed[33] syn isomer is observed to have a pseudo-2-fold rotation axis in crystals, with the two cyclohexyl groups and the main macrocyclic ring forming a cup shape. The two faces of the ligand are therefore nonequivalent. We term the face of the ligand on the same side of the macroring as the cyclohexyl substituents the "onaji" face, and the other side the "hantai" face (from Japanese for "same" and "opposite", respectively). The uncomplexed anti isomer[33] has a crystallographic center of symmetry, making its two faces equivalent.

The syn and anti isomers of DC18C6 are easily distinguished in the gas phase on the basis of their ion−molecule reaction kinetics, and by differences in cation affinities. Analysis of the differences yields information relative to the mechanism of cation binding and the structure of the complex ions.

Consideration of Figure 4 reveals that reaction 1, cation transfer from 18C6, is more efficient for the syn isomer than for the anti isomer, by 20% or more. This is somewhat surprising, since on the basis of the X-ray data one would expect the two faces of the syn isomer to be nonequivalent in the gas phase such that one approach direction might be preferred in the transfer reaction. For example, if the cyclohexyl rings sterically interfere with approach of the 18C6/metal ion complex, then only approaches on the "hantai" side would lead to metal transfer. For the anti isomer, both faces are equivalent so both should be equally reactive.

The data show that there is no strongly preferred direction of approach for the transfer reaction, both because the syn isomer reacts more efficiently than the anti isomer and because the efficiency of the reaction for the syn isomer is greater than the 50% maximum efficiency which would be found if only approach on one face or the other led to transfer. Rather, the collision complexes leading to transfer must be sufficiently long-lived that no "memory" of the approach direction is retained. Long-lived complexes are not at all surprising in thermal collisions of such large molecules containing many internal degrees of freedom, as can quickly be seen from very approximate RRKM descriptions of the expected transition states. The data also imply that the transition state for cation transfer must be relatively "late", because only with a late transition state would rates for the two isomers differ significantly, as is observed. We defer discussion of why transfer is faster for the syn isomer until after discussion of thermochemistry for the two isomers, below.

Reaction efficiencies for "sandwiching", reaction 2, also differ for the two isomers, as noted in Table 2. Consistent with earlier observations for unsubstituted 18C6,[16] which showed addition of a second ligand to be very slow when the metal ion is small enough to be "encapsulated" in a 1:1 complex, reactions of both isomers with Li^+, Na^+, and K^+ are too slow for us to measure. For Rb^+, the syn isomer reacts too slowly to measure, while the anti isomer undergoes sandwiching at approximately 0.5 ± 0.1% efficiency (about a factor of 3 slower than unsubstituted 18C6). Likewise, for Cs^+ the syn isomer reacts at 1.4 ± 0.6% efficiency, the anti isomer at 3.5 ± 0.8% (compared with 9.6 ± 2.4% for unsubstituted 18C6).

The data suggest that the cyclohexyl substituents cause steric hindrance which decreases the efficiency of reaction 2 relative to the same reaction involving 18C6. Reactions for the anti isomer are consistently about a factor of 3 slower than for 18C6. This implies that closer approach of the two colliding ligands may be necessary to form a 2:1 sandwich complex than is required for simple metal transfer, which proceeds with high efficiency (20% or greater, as noted above). It is also interesting that in the one case where the data allow comparison (the Cs^+ efficiencies), the efficiency for syn is only about half that for anti. It is tempting to conclude that there *is* a preferred direction of approach for the sandwiching reaction. For instance, it is easy to imagine a situation where the metal binds in the less hindered, "hantai" site, and sandwiches only form when the hantai site of the second ligand is oriented toward the metal. Likewise, if binding to the first ligand involves the "onaji" site, steric hindrance could require the second to approach the "hantai" side first. Unfortunately, the data do not allow these situations to be distinguished, but if there is a preferred approach direction similar rate differences should be observed for other large monopositive metal ions reacting with the two isomers.

The two isomers also differ measurably in alkali cation affinities. In methanol solution, the complexes of syn with Na^+, K^+, and Cs^+ have stability constants slightly *smaller* than those of the corresponding 18C6 complexes, while complexes of the anti isomer are considerably weaker.[22] The situation is similar in aqueous solution (although all the constants are smaller than they are in methanol), with the syn isomer and 18C6 having nearly identical stability constants and the anti isomer having constants which are somewhat smaller.[34,35] From the solution studies, no clear pattern emerges in the differences between 18C6 and DC18C6 binding constants as the cation size is varied.

Consideration of Figure 2 shows the gas-phase trends for comparison. In the gas phase, in contrast to what is observed in solution, both DC18C6 isomers clearly bind the alkali cations *more strongly* than unsubstituted 18C6. Therefore, there must be a larger cost to displacing solvent from the substituted ligands than from 18C6. The observed decrease in stability constants for the anti isomer relative to 18C6 is indeed a solvation effect, as was postulated in one of the earliest solution studies.[34]

In the gas phase, syn binds all the alkali metal cations more strongly than anti, by about 3 kJ mol^{-1} for K^+, Rb^+, and Cs^+, and by 10 kJ mol^{-1} or more for the smaller alkali ions. The larger binding constants for the syn isomer relative to the anti isomer observed in solution and now confirmed in the gas phase must therefore arise from intrinsic differences between the two isomers and are *not* solely dependent on differences in solvation. In contrast to the solution results, the difference between 18C6 and DC18C6 cation affinities clearly decreases as the size of the cation increases, and this probably arises from intrinsic polarizability effects as noted above. It is unclear why syn should have intrinsically higher affinities than anti. The most satisfying explanation consistent with all the data is that the

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(34) Izatt, R. M.; Nelson, D. P.; Rytting, J. H.; Haymore, B. L.; Christensen, J. J. *J. Am. Chem. Soc.* **1971**, *93*, 1619−1623.

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metal binds preferentially in the "onaji" site, and that ion-induced dipole stabilization is greater when the two cyclohexyl groups are both oriented close to the bound cation. However, an equally likely explanation might be that the oxygen donor groups are more favorably oriented in the syn isomer than in anti, revealing nothing about whether "onaji" or "hantai" is the preferred site. Perhaps molecular mechanics or higher level calculations can shed some light on this question.

The difference in the alkali cation affinities of the two isomers also helps explain why the transfer rates from 18C6 to the two isomers differ. Since syn has higher cation affinities than anti, by the analysis given above the barriers to cation transfer are less for syn than for anti. It follows that transfer rates for syn should be faster than for anti, as is observed.

Summary

The substitution of cyclohexyl groups on the 18C6 macroring strongly affects the reactivity of the ligand. In particular, the free energy of complexation with alkali metal ions is greater for the substituted ligand, more so for the small metals than for the large ones, despite the fact that the ligands each have six donor groups and similar-size binding cavities. This is obscured in solution by solvation effects. The relative cation affinities can be simply explained on the basis of differences in polarizability between 18C6 and DC18C6, while differences in ligand flexibility do not appear to have a significant effect. The efficiency of cation transfer from 18C6 to DC18C6 increases as the metal ions become smaller. This can be rationalized by decreases in the barrier height for cation transfer as the differences in well depths for binding the metal, as well as the absolute depths of the wells, increase with decreasing metal size. Polarizability appears to have very large influence on the kinetics and thermochemistry of multidentate ligand–metal cation binding in the gas phase, but more subtle effects arising from structural details of the complexes are also readily observable.

For example, the *cis*-syn-*cis* and *cis*-anti-*cis* isomers of DC18C6 differ from each other in the gas phase both thermochemically and kinetically. The syn isomer has higher alkali cation affinities, and accepts alkali cations from 18C6 faster, than the anti isomer. However, syn forms 2:1 ligand–metal complexes more slowly than anti. It is tempting to infer that the deeper cavity afforded by the syn isomer leads to greater cation affinities and transfer rates, but slower sandwiching rates. However, additional data are needed before such a conclusion can be more than speculative.

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