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RELATIVE AMMONIUM ION AFFINITIES OF 18-CROWN-6 AND THE ISOMERS OF DICYCLOHEXANO-18-CROWN-6

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Abstract. Complexes of *cis-syn-cis-* and *cis-anti-cis*-dicyclohexano-18-crown-6 (DC18C6) with ammonium, methylammonium, propylammonium, isopropylammonium, butylammonium, isobutylammonium, and *tert*-butylammonium were generated and studied in the gas phase using Fourier transform ion cyclotron resonance mass spectrometry to measure exchange equilibrium constants of the guests with unsubstituted 18-crown-6 (18C6). Semiempirical calculations at the PM3 level were also performed for all the complexes. Both the experiments and the calculations indicate that sterically unhindered ammonium cations bind DC18C6 in preference to 18C6, but that preference decreases or vanishes for ammonium cations branched at the α carbon. The *cis-syn-cis* isomer has higher ammonium affinities than the *cis-anti-cis* isomer. The experiments and the calculations both suggest that in the *cis-syn-cis* isomer the ammonium cations preferentially bind on the face of the macroring enclosed by the cyclohexano units, but again this preference decreases for sterically crowded ammonium substituents. These trends are explained in terms of the ability of the substituents in the host to stabilize the charge of the guest.

Key words. Crown ether, ammonium ion, gas phase, mass spectrometry

1. Introduction

Crown ether - ammonium complexes are of fundamental interest as prototypical systems involving multiple hydrogen bonds. Study of these very simple multiply-bound complexes is a promising means of gaining insight into much more complex macromolecular systems, such as those involved in protein folding or in the pairing of nucleobases in polymeric nucleic acids. Crown ether - ammonium ion complexes involve materials volatile enough to enable gas-phase experiments, which can be conducted in the absence of any interfering effects from bulk solvation, and are sufficiently simple that they can be probed in detail using computational methods. The pairing of gas-phase experiments with computational chemistry is a natural and powerful one, since the experiments provide data

to test the results of calculations, while the calculations should be highly accurate for gas-phase conditions and often provide physical insights crucial for understanding the experimental results.

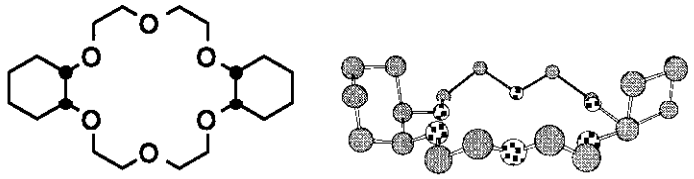
The fundamental importance of crown ether - ammonium ion systems has been recognized in a number of earlier gas-phase studies. Work by Kebarle in the early 1980's, using high-pressure mass spectrometry, quantified the enthalpies and entropies associated with protonation of crown ethers [1] as well as formation of complexes with hydronium ion and protonated methanol [2]. Meot-Ner generated both protonated crown ethers [3] and gas-phase crown ether - ammonium ion complexes [4] and characterized their thermochemistry, pointing out the importance of multiple hydrogen bond formation. More recently, collision-induced-dissociation methods have been used to compare the affinities of various simple crowns for NH_4^+, with the important finding that among the unsubstituted crown ethers intrinsic ammonium ion affinity increases in the order 12-crown-4 < 15-crown-5 < 18-crown-6 < 21-crown-7 [5]. Ligand-exchange methods gave similar results [6]. The dissociation behavior of crown ethers with substituted ammonium ions has also been examined [7], with the interesting observation that weakly-bound complexes, such as that between pyridinium ion and 18-crown-6, dissociate primarily either by loss of the ammonium cation or by loss of the neutral amine, while more strongly-bound complexes involving multiple hydrogen bonds often dissociate through fragmentation of the crown ether, reflecting the extra stability imparted by multiple hydrogen bonding.

Crown ether - ammonium complexes have also been investigated computationally using molecular mechanics techniques [8]. This study considered both unsubstituted 18-crown-6 and a number of substituted derivatives interacting with a wide range of ammonium, amino acid, and dipeptide ions. Despite many approximations in the force-field methods employed, the calculations make several important predictions about crown ether - ammonium ion interactions. For example, in agreement with experiment [4] they show that binding affinities are in the order primary ammonium ion > secondary > tertiary. Further, they indicate that in general the ammonium ion affinity of the crown ether increases when substituents are added, due to additional stabilization arising from van der Waals interactions between the substituents and the guest ion. For similar reasons, increasing the length of an alkyl chain in a primary amine leads to increased binding. We provide experimental support for these latter findings in the present study.

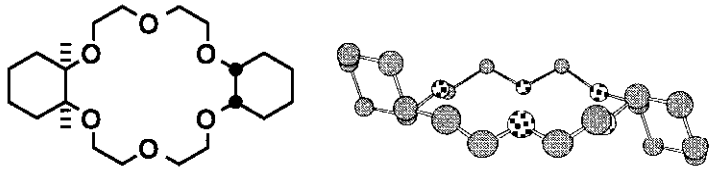
As part of an ongoing investigation of host-guest chemistry in the gas phase [9-19], this paper examines the relative affinities of 18-crown-6 (18C6) and its alkyl-substituted analog, dicyclohexano-18-crown-6 (DC18C6, Figure 1), for a group of substituted ammonium cations. We use two main techniques: Fourier transform ion cyclotron resonance mass

spectrometry, for measuring equilibrium constants for the exchange of ammonium guests between crown ether hosts; and PM3 semiempirical quantum mechanical calculations [20,21] of the geometries, heats of formation, and charge distributions of the complexes.

The goals and methods of this work parallel those of an earlier study that compared the alkali cation affinities of these same ligands [15]. That study found that the added polarizability imparted by the cyclohexano substituents more than compensates for the loss of flexibility in DC18C6 vs. 18C6, so that the affinity of DC18C6 for all of the alkali cations is greater than that of 18C6 for the corresponding metals. In this paper, we question whether or not this will still be true for ammonium ion guests, which in general should have much stronger orientational/conformational requirements than do the simple, spherically-symmetric alkali cations. In addition, we wish to examine the role of the substituents themselves (both on the crown ethers and on the ammonium cations) in the energetics of complexation. Do the substituents strengthen, weaken, or have little influence on the stability of the complexes? In asking these questions, we follow the same convention used earlier [15] of referring to relative free energies of binding in terms of relative cation affinities, although the term "affinity" is usually used to describe enthalpies.



cis syn cis dicyclohexano 18 crown 6 (syn DC18C6)



cis-anti-cis-dicyclohexano-18-crown-6 (anti DC18C6)

Figure 1. Structures and abbreviations for the isomers of dicyclohexano-18-crown-6.

All the amines examined have proton affinities [22] (see Table 2) which are much less than that of 18C6 (which has a proton affinity of about 961 kJ mol^{-1}) [1]. Although the proton affinity of DC18C6 has not been measured, based on their relative polarizabilities we expect the proton affinity of DC18C6 to be greater than that of 18C6. With such high proton affinities, it is interesting that the crowns do not simply abstract H^+ from the

ammonium ions. However, it is probable that the high proton affinities of the crown ethers arise because they can achieve very favorable geometries for multiple hydrogen bonding with protons [1,3]. For ammonium ions such as those studied here, multiple hydrogen bonding with the proton probably does not occur; rather, the crown ether most likely forms one hydrogen bond with each hydrogen of the ammonium group,[8] and the full intrinsic proton affinity of the crown ether is not operative. Therefore, we will refer to the guests as ammonium ions and to the hosts as neutral crowns.

Because DC18C6 is usually prepared via a *syn*-hydrogenation reaction of dibenzo-18-crown-6 [23], commercially-available DC18C6 usually consists of a mixture of *cis-syn-cis* and *cis-anti-cis* isomers, hereafter referred to as "syn" and "anti" for brevity (Figure 1). The syn isomer of DC18C6 is of particular interest as a simple host with two distinct binding sites (Figure 2): one on the same side of the main crown ring as the cyclohexano substituents (the "onaji" site, from the word for "same" in Japanese), and the other on the side opposite the cyclohexano substituents (the "hantai" site, from the Japanese word for "opposite") [15]. In contrast, the two sides of the anti isomer are indistinguishable. DC18C6 thus offers an opportunity to study a simple two-site host in hopes of learning whether or not one of the sites is preferentially occupied.

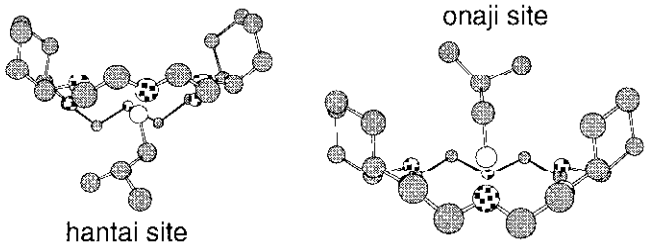


Figure 2. Complexes of isobutylammonium with *cis-syn-cis*-dicyclohexano-18-crown-6, with the ammonium bound in the hantai and onaji binding sites. Structures determined from PM3 semiempirical calculations.

Finally, it is interesting to envision what takes place in a guest exchange reaction like those studied here. We imagine that exchange involves approach of DC18C6 to the RNH_3^+•18C6 complex, probably from the same side occupied by the guest, followed by attack of the DC18C6 oxygens on the ammonium ion's hydrogen atoms. This likely involves a long-lived collision complex. Eventually, displacement of 18C6 by DC18C6 occurs, and the collision complex dissociates to the 18C6 and RNH_3^+•DC18C6 exchange products. The kinetics of the exchange process will likely yield some information on the exchange mechanism, but in this paper we will only deal with the thermochemistry of exchange and leave kinetics for a future study.

2. Experimental

2.1 FTICR/MS EXPERIMENTS

The instrumentation and experimental techniques used in this study have been described [12,13,15,16]. In brief, DC18C6 and 18C6 were introduced into the trapping cell of a Fourier transform ion cyclotron resonance mass spectrometer via two unheated direct-insertion solids probes. One of the probes was inserted collinear with the axis of the solenoidal magnet that encloses the trapping cell and vacuum chamber, while the other was inserted transverse to the magnet axis. The end of the collinear probe was typically located within about 10 cm of the trapping cell, while the end of the transverse probe was typically up to 100 cm from the trapping cell. Hence, the less volatile DC18C6 was placed on the collinear probe, while the much more volatile 18C6 was placed on the transverse probe. The amine(s) of interest was also introduced, through a precision variable leak valve. Ions were created by firing an electron gun through the trapping cell, followed by a delay to allow formation of crown ether - ammonium ion complexes by ion-molecule reactions. The ions of interest were isolated in the trapping cell using conventional RF [24] and SWIFT [25] ion ejection techniques. A thermocouple mounted on the collinear solids probe indicated a temperature of 310 K during these experiments, although the walls of the trapping cell may have been at a somewhat higher temperature since the cell is closer than the probe to the filament of the electron gun.

The presence of the ammonium ion and both neutral hosts in the trapping cell enabled the measurement of equilibrium constants for exchange of ammonium guest ions between the two neutral crown ether hosts (reaction 1). Abundances of the ionic reactant and product were determined from peak intensities in the mass spectra obtained after long reaction times. These abundances were always measured by approaching equilibrium in both the forward and reverse directions, with identical results. The ratio of the partial pressures of the two neutral hosts is also required to measure the equilibrium constant. Pressure ratios were determined from the relative rates of proton attachment to the two hosts, as has been described [16].

$$18C6{\bullet}RNH_3^+ + DC18C6 \rightleftharpoons 18C6 + DC18C6{\bullet}RNH_3^+ \qquad (1)$$

2.2 SEMIEMPIRICAL CALCULATIONS

All calculations were carried out using the Spartan modeling package, version 4.1.1 (Wavefunction, Inc.; Irvine, CA). Starting geometries for

DC18C6 were obtained from X-ray crystal structures of the Ba^{2+} (*cis-syn-cis*) and Na^{+} (*cis-anti-cis*) complexes [26]. Ammonium ions were added with substituents arranged by visual inspection to minimize steric hindrance and maximize hydrogen bonding interactions. Preliminary geometry optimization was carried out using the Sybyl force field supplied with Spartan, followed by full optimization at the PM3 semiempirical level. No attempts at conformational searching were made. Heats of formation and Mullikan charges are as reported by Spartan.

3. Results

3.1 OBSERVED COMPLEXES

Both 18C6 and the isomers of DC18C6 readily form complexes with ammonium ions in the gas phase under low-pressure conditions, in agreement with earlier observations of 18C6 - ammonium ion complexes generated using high-pressure mass spectrometry techniques [4] and using quadrupole ion trap mass spectrometry [5,6]. In some cases, crown ether - ammonium ion complexes can also be formed by reaction of *protonated* crowns with *neutral* amines [19]. However, this reaction is not general; protonated 18C6 forms complexes with a variety of amines, but the protonated DC18C6 isomers were never observed to form complexes [19].

3.2 EQUILIBRIUM CONSTANTS FOR AMMONIUM EXCHANGE

The results from the equilibrium constant measurements are shown in Table I, which includes free energy changes derived from the equilibrium constants assuming a temperature of 310 K. For most of the guests, both isomers of DC18C6 have higher ammonium ion affinities than unsubstituted 18C6. Exceptions occur in cases where the guest ion is highly branched. Comparison of the results for the two DC18C6 isomers shows that the syn isomer has higher ammonium affinity than the anti isomer for all the ammonium ions examined.

Examination of the results for ammonium, methylammonium, propylammonium, and butylammonium ions shows the effect of the length of the alkyl chain on the exchange equilibrium constants. For the syn isomer, the number of carbon atoms in the alkyl chain has little effect on the equilibrium constants, while for the anti isomer the equilibrium constants decrease monotonically with increasing chain length. However, the size of the decrease is small enough that it may not be statistically significant.

Table I. Equilibrium constants and free energy changes for the reaction
$18C6(RNH_3^+) + DC18C6 \rightleftharpoons 18C6 + DC18C6(RNH_3^+)$ at 310 K.

	cis-syn-cis DC18C6		*cis-anti-cis* DC18C6	
R	K	$-\Delta G^\circ_{310}$ (kJ mol^{-1})	K	$-\Delta G^\circ_{310}$ (kJ mol^{-1})
H	8.4 ± 0.7	5.5 ± 0.1	3.9 ± 0.2	3.5 ± 0.1
methyl	4.5 ± 0.3	3.9 ± 0.1	2.2 ± 0.1	2.0 ± 0.1
propyl	5.3 ± 0.2	4.3 ± 0.1	2.2 ± 0.1	2.0 ± 0.2
isopropyl	2.7 ± 0.1	2.6 ± 0.1	0.7 ± 0.1	-0.8 ± 0.1
butyl	6.8 ± 0.1	5.0 ± 0.1	1.5 ± 0.1	1.0 ± 0.1
isobutyl	6.7 ± 0.7	4.9 ± 0.1	1.7 ± 0.8	1.4 ± 0.1
tert-butyl	0.6 ± 0.1	-1.4 ± 0.1	0.5 ± 0.1	-1.6 ± 0.1

For amines with branched alkyl chains, the proximity of the branch point to the amine functional group strongly affects the equilibrium constants. Comparison of the results for propylammonium and isopropylammonium ions, as well as those for butylammonium, isobutylammonium, and *tert*-butylammonium ions shows that the preference of the ammonium cations for DC18C6 decreases as the degree of branching increases. It is interesting to note that this effect is strong for branching at the α-carbon (for example, compare results for propyl- and isopropylammonium ions, or for butyl- and *tert*-butylammonium ions), while branching at the β-carbon has little effect (compare butyl- and isobutylammonium ions). In fact, the effect is so large in the case of *tert*-butylammonium ion that 18C6 has higher affinity for this guest than does DC18C6. Finally, it is interesting to compare the syn and anti isomers. The difference in free energies between the propyl- and isopropylammonium ion guests is about 1.7 kJ mol^{-1} for the syn isomer, and about 2.8 kJ mol^{-1} for the anti isomer. Considering butyl- and *tert*-butylammonium ions, the difference between the isomers is larger: more than 6 kJ mol^{-1} for the syn isomer, but only about 2.6 kJ mol^{-1} for the anti isomer.

3.3 RESULTS OF PM3 CALCULATIONS

Heat of formation results from the semiempirical calculations are given in Table II. Comparison of the two binding sites of the syn isomer is quite interesting. For all of the ammonium ion guests, binding in the onaji site results in a lower heat of formation for the complex than binding in the hantai site, often by 10 kJ mol^{-1} or more. The complexes of the anti isomer are enthalpically a few kJ mol^{-1} less stable than the most stable syn isomer complexes for all the guests examined except isopropylammonium and *tert*-butylammonium ions.

Table II. Heats of formation for ammonium ion complexes with *cis-syn-cis* and *cis-anti-cis*-DC18C6 calculated at the PM3 semiempirical level.

	Amine proton affinity [22], kJ mol^{-1}	$\Delta H^{\circ}_{f,298}(RNH_3^+ \bullet DC18C6)$, kJ mol^{-1}		
R		syn(hantai)	syn(onaji)	anti
H	854	-613.8	-615.6	-616.2
methyl	896	-599.9	-611.4	-608.9
propyl	912	-660.3	-670.5	-668.0
isopropyl	915	-670.2	-676.0	-681.1
butyl	914	-683.1	-693.7	-687.4
isobutyl	916	-680.8	-700.9	-686.4
tert-butyl	924	-703.9	-704.9	-717.4

Table III. Sum of Mullikan charges on the eight cyclohexano carbons not part of the main crown ring for $RNH_3^+ \bullet DC18C6$ complexes from PM3 semiempirical calculations.

	Sum of Mullikan Charges on Cyclohexano Carbons		
R	syn(hantai)	syn(onaji)	anti
H	-0.902	-0.900	-0.903
methyl	-0.902	-0.915	-0.909
propyl	-0.904	-0.920	-0.910
isopropyl	-0.905	-0.912	-0.909
butyl	-0.904	-0.921	-0.908
isobutyl	-0.900	-0.951	-0.907
tert-butyl	-0.903	-0.921	-0.942

Mullikan population analysis was used to compute formal charges on each of the atoms in the complexes, and the sum of the Mullikan charges for the eight cyclohexano carbon atoms not part of the main crown ether ring is given in Table III for each of the complexes. In general, for a given guest the lowest absolute value of the Mullikan sum is found in cases where the guest is bound in the hantai site of the syn isomer, and the highest occurs when the guest is bound in the onaji site of the syn isomer. Binding to the anti isomer generally yields intermediate values.

Table IV gives the calculated mean N-O distance for the hydrogen bonded pairs in each of the complexes, along with the associated standard deviation. For most of the systems examined, the mean separation is about

2.85 Å, although it is somewhat less for the NH_4^+ guest and significantly greater for the isopropylammonium and *tert*-butylammonium ion complexes of the syn isomer when bound in the onaji site, and for the *tert*-butylammonium guest bound to the anti isomer. The large values are the result of considerable asymmetry among the three hydrogen bonds, as can be seen in the large standard deviations for the three cases noted above.

Table IV. Mean and standard deviation of calculated N-O distances involving hydrogen bonding in RNH_3^+•crown ether complexes from PM3 semiempirical calculations.

	Calculated N-O Distances, Å			
R	18C6	syn(hantai)	syn(onaji)	anti
H	2.805±0.000	2.801±0.009	2.794±0.008	2.796±0.015
methyl	2.831±0.001	2.837±0.008	2.835±0.020	2.838±0.006
propyl	2.850±0.014	2.858±0.027	2.851±0.008	2.844±0.004
isopropyl	2.870±0.002	2.883±0.015	2.969±0.198	2.854±0.010
butyl	2.850±0.014	2.857±0.026	2.850±0.008	2.854±0.018
isobutyl	2.851±0.017	2.859±0.016	2.859±0.010	2.870±0.015
tert-butyl	2.900±0.000	2.923±0.002	3.094±0.355	2.969±0.255

4. Discussion

4.1 EFFECTS OF ALKYL SUBSTITUENTS ON AMMONIUM ION AFFINITY

As was done earlier for alkali cation guests [15], comparison of the ammonium ion affinities of 18C6 and DC18C6 allows the relative importance of ligand flexibility and polarizability with respect to complex stability to be investigated. The results show that the intrinsic affinity of DC18C6 for ammonium cations is greater than that of unsubstituted 18C6, with the exception of the highly crowded cations isopropylammonium ion (for the anti isomer) and *tert*-butylammonium ion (for both isomers). This result is consistent with earlier findings for alkali cation guests in solution [27] and in the gas phase [15], which showed higher alkali cation affinities for DC18C6 than for 18C6. It also supports the predictions of molecular mechanics calculations [8], which found that substituted 18C6 derivatives in general have higher ammonium ion affinities than 18C6. The observed differences in the affinities of the two ligands for unbranched ammonium cations fall within a relatively small range (2.6-5.5 kJ mol^{-1}, syn isomer; 1.0-

3.5 kJ mol^{-1}, anti isomer), in contrast with a much larger range for alkali metal ions (3.2-16.3 kJ mol^{-1}, syn isomer; 0-8.3 kJ mol^{-1}, anti isomer) [15]. This is not surprising in light of the fact that the ammonium functional groups on all the guests examined here are quite similar, such that differences in ammonium ion affinities arise from secondary interactions with the substituents, rather than from direct donor-acceptor interactions.

The explanations offered for the relative alkali cation affinities of 18C6 and the DC18C6 isomers can probably be extended to the current results, with additional refinements arising from the directional preferences of hydrogen bonds [2]. Specifically, the substituted ligands, being more polarizable than 18C6 (by the method of atomic hybrid components [28,29], the polarizabilities of 18C6 and DC18C6 are 25.9 $Å^3$ and 39.1 $Å^3$, respectively), are better able to accommodate charged guests than the unsubstituted crown, as long as the substituents do not interfere with the formation of the hydrogen bonds necessary for stabilization of the complex. Alkyl substitution does not confer a large enough difference in ligand flexibility to significantly hinder complexation of ammonium ion by DC18C6, and the larger, more polarizable ligand has the higher affinity for ammonium cations which do not interfere sterically with host substituent groups.

In cases where the guest is bulky (such as *tert*-butylammonium), the relatively more crowded binding site of the substituted hosts leads to lower affinities for the DC18C6 isomers than are observed for 18C6. Examination of molecular models generated from the PM3 calculations suggests that steric interference between branched alkyl groups and the cyclohexano substituents occurs when the alkyl branch point is α to the ammonium functionality, but there is little interference when the branch point is on the β-carbon. This is consistent with the experimental results, which show large decreases in equilibrium constants for α-branched ammonium cations (isopropyl- and *tert*-butylammonium ions) vs. the straight-chain isomers, but essentially no difference between β-branched isobutylammonium and unbranched butylammonium. Comparing the two α-branched guests, the effect is much larger for *tert*-butylammonium ion than for the less crowded isopropylammonium ion. It is very likely that for these bulky guests steric interactions prevent the attainment of optimum bond lengths and angles for hydrogen bond formation [30,31]. The data of Table IV provide support for this idea: for guests which encounter steric interferences with the host substituents (isopropylammonium and *tert*-butylammonium ions bound in the onaji site of the syn isomer, and *tert*-butylammonium ion bound to the anti isomer), the calculations find the average hydrogen bond donor-acceptor distance is significantly increased, generally because one of the distances is abnormally large. In addition, it is possible in these cases that the entropic penalty associated with attaining the proper bonding geometry [7] is high.

4.2 DIFFERENTIATION OF DC18C6 ISOMERS

Both the equilibrium constant measurements and the PM3 heats of formation indicate that all of the ammonium ion guests distinguish between the syn and anti isomers of DC18C6, with the syn complexes being more stable than the anti complexes for all the guests studied. What is the origin of these differences? We examine possible explanations based on donor arrangement, steric factors, and the ability to solvate the charge of the guest.

It might be argued that the arrangement of the oxygen donor groups in the syn isomer is more optimal for multiple hydrogen bond formation than that of the anti isomer. However, examination of molecular models suggests the two isomers have very similar donor oxygen placements. Furthermore, the hydrogen bond donor-acceptor distances for the anti isomer are not significantly larger than those for the syn isomer (Table IV). We therefore believe donor arrangement is a minor factor in distinguishing between the two isomers.

It is possible that different steric requirements for the guests might differentiate the two hosts. If the preferred binding site for the syn isomer is the hantai site, this site is less sterically hindered than the binding site of the anti isomer, and the syn isomer would therefore have the higher ammonium ion affinities. However, the data suggest that the onaji site, not the hantai site, is preferred (see below). If so, the onaji site of syn is *more* crowded than the binding site of the anti isomer, and steric arguments would favor anti over syn, contrary to the experimental findings. Steric effects, therefore, probably do not explain the results.

A third rationale deals with the relative abilities of the two host isomers to accommodate and "solvate" the charge of the guest. The onaji site of the syn isomer forms a cleft to hold the ammonium ion, with the cyclohexano substituents assisting in solvating the charge center. In the anti isomer, one of the cyclohexano substituents is on the wrong side of the crown ring to interact with the guest, and cannot provide such stabilization. All of our data are consistent with this explanation, which is discussed further in the following section which deals with site preferences in the syn isomer.

4.3 BINDING SITE PREFERENCES IN THE SYN ISOMER

As was noted above, the *cis-syn-cis* isomer is a simple case of a host molecule with two distinct binding sites. Is one of the binding sites preferentially populated, and if so, is this apparent in the results of either the semiempirical calculations or the equilibrium constant measurements? The data suggest that there is a general preference for the onaji binding site.

The semiempirical calculations indicate in at least two ways that the onaji binding site is favored. First, the heats of formation for the

ammonium complexes with the syn isomer in the hantai and onaji sites (Table II) show that the onaji-bound ammonium ion is lower in energy than hantai-bound ammonium ion, for each of the guests examined. The differences between the two sites are small in three cases: NH_4^+, isopropylammonium, and *tert*-butylammonium ions. In the NH_4^+ case, hydrogen is such a small substituent that it probably does not approach the cyclohexyano groups closely enough for the difference in sites to be appreciable. The other two guests both involve branching on the α-carbon of the alkyl substituent, which causes steric hindrance for guests bound in the onaji site, and disrupts the hydrogen bonds anchoring the guest in the host (Table IV). This is particularly striking in the case of *tert*-butylammonium ion, where the calculated preference for the onaji site is only about 1 kJ mol^{-1}, in contrast with the less bulky guests which exhibit enthalpic site preferences of 10 kJ mol^{-1} or more.

The preference for binding in the onaji site is somewhat surprising, since this site clearly involves more steric crowding than the hantai site. The explanations noted above for the differences between the ammonium affinities of the syn and anti isomers could also be invoked here for explaining the differences between the onaji and hantai binding sites, with the same results. The ligand appears to be sufficiently flexible that oxygen donor placement would not favor either binding site appreciably, and steric arguments predict a preference opposite to the results of the calculations. The third explanation, stabilizing solvation of the guest charge by the substituent groups in the onaji site, bears further examination.

The sums of Mullikan charges in Table III provide additional evidence that the onaji binding site is preferred, and support the substituent solvation ideas for explaining this preference. For every guest except NH_4^+ (which, as noted above, has too small an R group for such effects to be appreciable), the sum of Mullikan charges on the substituent carbon atoms is more negative for the onaji site than for the hantai site. Charges on the substituent carbons of the anti isomer are in all cases (again, with the exception of the NH_4^+ guest, and also the *tert*-butylammonium guest, where steric effects are probably quite large) intermediate between those for the syn binding site variants, which is consistent with the notion that the anti isomer's binding site is intermediate between the two syn isomer sites. The trends in substituent charges vs. binding sites highlight the likely role of the substituents in solvating and stabilizing the charge on the ammonium ion guest: onaji site substituents, with greater negative partial charges, are best able to accommodate the guest ammonium cation. This rationale begins to break down when the guest is very small (as for NH_4^+), because the guest is too far from the substituents for the stabilization to be effective, and when the guest is very bulky (as for *tert*-butylammonium ion), when steric repulsions become large and counteract the stabilizing effects of the

substituents, likely interfering with the ability of the system to form strong hydrogen bonds as noted above.

Finally, the sensitivity of the equilibrium constants to the degree of branching and the location of the branch point also suggests that the onaji site is preferentially populated, at least for the less bulky guest cations. Only the onaji site involves the possibility of steric interference between the host cyclohexano rings and the substituent of the guest. In fact, the hydrogen bond donor-acceptor distances for the hantai site are only slightly larger than those calculated for the unsubstituted 18C6 host, while the distances increase by about 0.1 Å for bulky guests bound in the onaji site (Table IV). Finally, the experimental results indicate that the free energy change in transferring the guest from 18C6 to *cis-syn-cis*-DC18C6 is nearly 7 kJ mol^{-1} less favorable for *tert*-butylammonium ion than for NH_4^+. For the anti isomer, with only one interfering cyclohexano substituent, this same difference is only about 5 kJ mol^{-1}. If the guest were bound in the hantai site, it would be very difficult to account for these results.

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References

1. R. B. Sharma, A. T. Blades, and P. Kebarle: *J. Am. Chem. Soc.* **106**, 510-516 (1984).
2. R. B. Sharma and P. Kebarle: *J. Am. Chem. Soc.* **106**, 3913-3916 (1984).
3. M. Meot-Ner: *J. Am. Chem. Soc.* **105**, 4906-4911 (1983).
4. M. Meot-Ner: *J. Am. Chem. Soc.* **105**, 4912-4915 (1983).
5. C. C. Liou and J. S. Brodbelt: *J. Am. Chem. Soc.* **114**, 6761-6764 (1992).
6. H.-F. Wu and J. S. Brodbelt: *J. Am. Soc. Mass Spectrom.* **4**, 718-722 (1993).
7. C. C. Liou, H.-F. Wu, and J. S. Brodbelt: *J. Am. Soc. Mass Spectrom.* **5**, 260-273 (1994).
8. D. Gehin, P. A. Kollman, and G. Wipff: *J. Am. Chem. Soc.* **111**, 3011-3023 (1989).
9. H. Zhang, I.-H. Chu, S. Leming, and D. V. Dearden: *J. Am. Chem. Soc.* **113**, 7415-7417 (1991).
10. H. Zhang and D. V. Dearden: *J. Am. Chem. Soc.* **114**, 2754-2755 (1992).
11. D. V. Dearden, H. Zhang, I.-H. Chu, P. Wong, and Q. Chen: *Pure Appl. Chem.* **65**, 423-428 (1993).
12. I.-H. Chu, D. V. Dearden, J. S. Bradshaw, P. Huszthy, and R. M. Izatt: *J. Am. Chem. Soc.* **115**, 4318-4320 (1993).
13. I. H. Chu, H. Zhang, and D. V. Dearden: *J. Am. Chem. Soc.* **115**, 5736-5744 (1993).
14. P. S. H. Wong, B. J. Antonio, and D. V. Dearden: *J. Am. Soc. Mass Spectrom.* **5**, 632-637 (1994).
15. I.-H. Chu and D. V. Dearden: *J. Am. Chem. Soc.* **117**, 8197-8203 (1995).
16. Q. Chen, K. Cannell, J. Nicoll, and D. V. Dearden: *J. Am. Chem. Soc.* **118**, 6335-6344 (1996).
17. P. S. H. Wong, X. Yu, and D. V. Dearden: *Inorg. Chim. Acta* **246**, 1-7 (1996).
18. J. S. Brodbelt and D. V. Dearden: in J. E. D. Davies and J. A. Ripmeester (eds.), *Physical Methods in Supramolecular Chemistry*, Comprehensive Supramolecular Chemistry, Vol. 8, Pergamon, Oxford (1996), pp. 567-591.

19. D. V. Dearden, C. Dejsupa, Y. Liang, J. S. Bradshaw, and R. M. Izatt: *J. Am. Chem. Soc.* **119**, 353-359 (1997).
20. J. J. P. Stewart: *J. Comput. Chem.* **10**, 209-220 (1989).
21. J. J. P. Stewart: *J. Comput. Chem.* **10**, 221-264 (1989).
22. Positive Ion Energetics Database, 1990, NIST, Gaithersburg, MD.
23. H. K. Frensdorff: *J. Am. Chem. Soc.* **93**, 600-606 (1971).
24. A. G. Marshall: *Acc. Chem. Res.* **18**, 316-322 (1985).
25. L. Chen, T.-C. L. Wang, T. L. Ricca, and A. G. Marshall: *Anal. Chem.* **59**, 449-454 (1987).
26. M. Dobler: *Ionophores and Their Structures*, Wiley, New York (1981).
27. R. M. Izatt, K. Pawlak, J. S. Bradshaw, and R. L. Bruening: *Chem. Rev.* **91**, 1721-2085 (1991).
28. K. J. Miller and J. A. Savchik: *J. Am. Chem. Soc.* **101**, 7206-7213 (1979).
29. K. J. Miller: *J. Am. Chem. Soc.* **112**, 8533-8542 (1990).
30. W. P. Kraemer and G. H. F. Diercksen: *Chem. Phys. Lett.* **5**, 463-465 (1970).
31. K. Hirao, M. Sano, and S. Yamabe: *Chem. Phys. Lett.* **87**, 181-185 (1982).