Chiral Host-Guest Recognition in an Ion-Molecule Reaction

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Abstract: Chiral recognition is observed for a gas-phase host-guest system by using Fourier transform ion cyclotron resonance mass spectrometry to determine equilibrium constants for the transfer of (*R*)- or (*S*)-(1-naphthyl)-ethylammonium (NapEt$^+$) cation from (*S*,*S*)-dimethyldiketopyridino-18-crown-6 to unsubstituted 18-crown-6. The unsubstituted crown has substantially higher affinity for both guests than the chiral crown. The measured equilibrium constants are 130 ± 15 for *R*-NapEt$^+$, and 567 ± 68 for *S*-NapEt$^+$, yielding a difference of 4.2 ± 0.4 kJ mol^{-1} between the stabilities of the complexes of the two enantiomeric guests with the chiral host. Recognition is greater in the gas phase than in a previously reported experiment in methanol solution, which gave a stability difference of 2.3 kJ mol^{-1} between complexes of the two enantiomeric guests, but similar to that seen in CD_2Cl_2, 4.6 kJ mol^{-1}. Molecular mechanics calculations are in good agreement with the experimental findings.

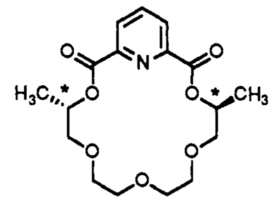
Introduction

The "handedness" of molecules and the reactivity which depends on this characteristic are of fundamental importance to organic and biochemistry. However, chiral recognition is rarely observed in gas-phase ion-molecule reactions. Herein we demonstrate and quantify chiral recognition for a gas-phase ion-molecule host-guest system, and compare the results with those obtained for the same system in solution and in molecular mechanics calculations.

Enantiomer-selective reactivity has been an important goal of mass spectrometrists seeking to extend the technique beyond the measurement of mass to the ability to also distinguish isomeric structures. In one elegant set of experiments,[1] the concentrations of proton-bound dimers of L- and D-dimethyl tartrate and L- and D-diisopropyl tartrate were measured as a function of time using Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR/MS). The equilibrium signals from the mixed enantiomer complexes were found to be about a factor of 3 less intense than those from homogeneous dimers, impying the L,D cluster is 2.7 kJ mol^{-1} less stable than the L,L or D,D clusters.

More recently, several groups have reported the use of fast atom bombardment mass spectrometry (FAB-MS) to examine chiral recognition.[2,3] In general, the experiments involved measurement of the relative intensities of adduct peaks arising from interactions between chiral molecules in a FAB ion source. In several cases, recognition was observed. However, conditions in the FAB source make it difficult to distinguish whether adduct formation took place in the gas phase or prior to desorption from the FAB matrix, so it is unclear whether the results reflect recognition in the gas phase or in solution.

Our experiments, which are part of a broad investigation of host-guest chemistry from a solvent-free perspective,[4-6] involve measurement of equilibrium constants for reactions involving transfer of the *R* and *S* enantiomers of α-(1-naphthyl)ethylammonium (NapEt$^+$) cation between (*S*,*S*)-dimethyldiketopyridino-18-crown-6 (*S*,*S*-**1**) and the achiral host 18-crown-6 (18C6) (reaction 1).



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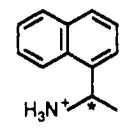

α-(1-naphthyl)ethylammonium (NapEt$^+$)

$$S,S\text{-}\mathbf{1}\cdot(R \text{ or } S)\text{-NapEt}^+ + 18\text{C6} \rightleftharpoons S,S\text{-}\mathbf{1} + 18\text{C6}\cdot(R \text{ or } S)\text{-NapEt}^+ \quad (1)$$

Experimental Section

FT-ICR/MS (Nicolet/Extrel FTMS-1000) was used to trap and monitor the ions of interest as a function of reaction time. The synthesis of *S*,*S*-**1** has been described.[7] The ligand 18C6 and the enantiomeric amines were purchased (Aldrich) and used as supplied. In a typical experiment, the two ligands and one of the amines were introduced into the instrument via temperature-controlled solid probes. Sufficient pressures of all materials except *S*,*S*-**1** were obtained at ambient temperatures, determined to be 50 °C at the trapping cell using a thermocouple. The probe holding *S*,*S*-**1** was warmed to 90 °C. Absolute pressures in the trapping cell were typically about 5-10 × 10^{-8} Torr. Ions were formed using 70-eV electron impact, and, after approximately 3 s reaction time, the only ions observed in the trapping cell were the complexes of NapEt$^+$ with the two host molecules. The time scale of these reactions is long enough that we can safely assume thermalization of the ions. Reaction 1 was monitored as a function of time until the *S*,*S*-**1**·NapEt$^+$/18C6·NapEt$^+$ ratio became constant.

Equilibrium constants *K* were measured by application of eq 2. The

$$K = I_{18\text{C6}\cdot\text{NapEt}^+}P_{S,S\text{-}1}/I_{S,S\text{-}1\cdot\text{NapEt}^+}P_{18\text{C6}} \quad (2)$$

reactant and product ion intensities at equilibrium, $I_{18\text{C6}\cdot\text{NapEt}^+}$ and $I_{S,S\text{-}1\cdot\text{NapEt}^+}$, were read directly from the mass spectra.

Determination of *K* also requires accurate measurement of the relative pressures of neutral *S*,*S*-**1** and 18C6, $P_{S,S\text{-}1}$ and $P_{18\text{C6}}$, in the FTICR trapping cell. For volatile materials, this is normally done using some sort of ionization gauge. However, ionization gauge techniques are difficult to apply for the relatively involatile *S*,*S*-**1**, since it is likely to condense between the trapping cell and the gauge tube. Therefore, we employ an alternate method to measure the pressure ratio within the

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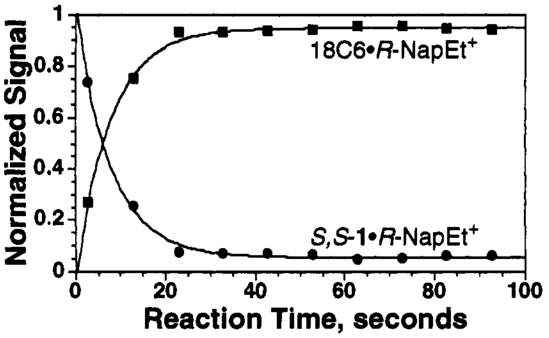

Figure 1. Signal intensity as a function of time for the reaction S,S-**1**·(R- or S)-NapEt$^+$ + 18C6 $\rightleftharpoons$ S,S-**1** + 18C6·(R- or S)-NapEt$^+$. $P_{18C6}/P_{S,S\text{-}1} = 7$, determined using initial H$^+$-attachment rates. The lines are exponential fits to the experimental data.

Table I. Mean Equilibrium Constants, K, with Standard Deviations, Measured for Transfer of S- or R-NapEt$^+$ from S,S-**1** to 18C6 in the Gas Phase[a]

guest	K	log K	ΔG, kJ mol^{-1}
S-NapEt$^+$	567 ± 68	2.75 ± 0.05	−18.4 ± 0.3
R-NapEt$^+$	130 ± 15	2.11 ± 0.05	−14.2 ± 0.3

[a] ΔG values derived assuming a cell temperature of 350 K.

trapping cell. The rates of all ion–molecule reactions are, of course, strongly dependent on the pressure of the neutral reactant. Thus, we might expect rate measurements to be a sensitive means of pressure determination, particularly for highly efficient reactions where the reaction rates approach the collision rates.

Since exothermic proton transfer generally occurs with efficiencies of 90% or greater,[8] and since crown ethers are known to have high proton affinities,[9,10] measurement of the relative rates of proton attachment to the two crowns should yield an accurate determination of their relative pressures. These measurements assume that the efficiency of proton attachment for the two ligands is similar. The assumption is unlikely to introduce large errors since 18C6 and S,S-**1** are structurally very similar, suggesting their proton attachment kinetics should also be alike. It is important to note that only the attachment *efficiencies* need be similar; the proton affinities of the two ligands need not be the same. Overall, we expect the ratios determined using this method to be within about ±10% of the true value. The equilibrium results depend on the *ratio* of the pressures of the two ligands being compared, so absolute pressures need not be determined. For observation of equilibrium, $P_{S,S\text{-}1}/P_{18C6}$ ratios of about 10:1 were typically used.

Results and Discussion

The results of a typical experiment are shown in Figure 1. Ejection of either equilibrium product ion results (after suitable delay) in reestablishment of the same reactant/product ratio, verifying the existence of true equilibrium conditions. Mean equilibrium constants, K, for reaction 1 involving the two enantiomeric guests, as well as the ΔG values derived from them using an estimated cell temperature of 350 K, are given in Table I. We note that the cell is not in thermal equilibrium, since S,S-**1** molecules are desorbed from a heated probe, and the S,S-**1** "temperature" is therefore somewhat between ambient and the 90 °C probe temperature. However, we expect the temperature dependence of the difference between the log K values involving the two enantiomeric guests is not large. Temperature effects will be probed in future work.

18C6 has a considerably higher intrinsic affinity for both guests than does S,S-**1**. This is interesting since 18C6 lacks the capability of favorable π-stacking interactions present in S,S-**1**. Rather, the result probably reflects the greater flexibility of 18C6 which enables it to more easily adopt conformations favorable for binding the guest. Conformational flexibility arguments have been invoked previously[11] to explain why replacement of the methyl groups of S,S-**1** by hydrogen atoms results in a large increase in affinity for NH$_4^+$.

The value of K for S-NapEt$^+$ is greater than that for R-NapEt$^+$ by more than a factor of 4, corresponding to the S,S-**1**·R-NapEt$^+$ complex being 4.2 ± 0.4 kJ mol^{-1} more stable than the S,S-**1**·S-NapEt$^+$ complex. We take this difference in K values to be a direct measure of the degree of chiral recognition displayed. Thus, this system exhibits considerable recognition, which is easily measured using FT-ICR/MS techniques. Racemization does not occur upon ionization, as happens in some of the tartrate clusters,[1] since the chiral center is distinct from the charge center in NapEt$^+$.

Based on X-ray crystallographic studies,[11] the host–guest interaction in this system arises primarily from hydrogen bonding involving the heteroatoms of the host, and secondarily from π–π interactions between the pyridine moiety of the host and the naphthalene π-system of the guest. Unfavorable steric interactions are believed to destabilize the S,S-**1**·S-NapEt$^+$ complex relative to the S,S-**1**·R-NapEt$^+$ complex.

The S,S-**1**–NapEt$^+$ system also exhibits chiral recognition in condensed media. When crystals were formed from 1 equiv of S,S-**1** mixed with 2 equiv of racemic NapEt$^+$, NMR analysis found the resulting complexes contained 68% of the R enantiomer and 32% of the S enantiomer of NapEt$^+$.[11] From the difference between the complex formation constants measured in methanol[11] using titration calorimetry, it can be determined that the R-NapEt$^+$ complex is 2.3 kJ mol^{-1} more stable than that of S-NapEt$^+$ with S,S-**1**, qualitatively in excellent agreement with the gas-phase result. Similarly, a value for the differences in free energies of activation for complex dissociation, $\Delta\Delta G^{\ddagger}$, measured in CD$_2Cl_2$,[11] of 4.6 kJ mol^{-1}, is essentially identical with the gas-phase stability difference.

Comparison of the solution results with the gas-phase value of 4.2 ± 0.4 kJ mol^{-1} suggests that solvation *disfavors* recognition. The degree of recognition in methanol is clearly less than that in the gas phase, while weak solvation in CD$_2$Cl$_2$ gave results within experimental error of those seen in the absence of solvent. It is unclear precisely why solvation in methanol should make such a difference, although it is conceivable that the small differences in the shapes of the two complexes might result in different degrees of solvation. The π-stacking interactions will certainly be different, and probably weaker, in solution than in the gas phase. To the extent that recognition is dependent on the π-stacking, this might account for the difference. In general, it is reasonable to expect that solvation of the *chiral* host and guest by an *achiral* solvent should decrease the strength of the interactions between the two chiral species, thus decreasing the degree of recognition in condensed media relative to the gas phase.

The gas-phase results are of particular value because they can be compared with the predictions of theory. Molecular mechanics methods[12] are frequently used to compare the structures and energetics of host–guest systems. The energies obtained from such calculations include those from the host–guest interactions and from the "strain" in the molecules involved. The absolute values depend on the force field used, but differences between values for different conformations are generally believed to be fairly accurate estimates of the relative enthalpies of the conformations.[12]

The experimental results yield differences between the *free energies* for the complexes of S,S-**1** with the two enantiomeric guests, and comparison with theory requires that the theoretical enthalpy differences be converted to free energies. Lacking

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detailed information on the vibrational and rotational energies of the complexes, this is difficult to do, but at least crude estimates can be made by noting that, in methanol, approximately equal contributions to recognition come from enthalpy and entropy.[11] If we assume that the same is true for the calculated gas-phase complexes, then we might expect agreement between the gas-phase experimental difference of 4.2 ± 0.4 kJ mol^{-1} and *twice* the enthalpy differences obtained from molecular mechanics.

The calculations correctly predict the chiral binding preferences of NapEt$^+$ by *S*,*S*-**1**. In a thorough search of configuration space, a value of 2.9 kJ mol^{-1} was obtained for the difference in free energies of activation for complex dissociation ($\Delta\Delta G^{\ddagger}$).[13] This study apparently assumed that entropic effects are small and equated the calculated enthalpies with free energies. Our own much more limited calculations, using the MM+ version of MM2[12,14] implemented in the HyperChem program, give a difference of 1.8 kJ mol^{-1} between the lowest-energy conformations found for each enantiomer, although our search of configuration space may not have been sufficiently thorough to locate the global minima. Doubling this value to include estimated entropic contributions gives a difference of 3.6 kJ mol^{-1}, in close agreement with the experimental result. In general, molecular mechanics appears to do a reasonable job of predicting the relative thermochemistry of the *R*- and *S*-NapEt$^+$ complexes. Temperature-dependent equilibrium experiments now underway should provide a more stringent test, since these experiments will provide enthalpy data which are directly comparable with the results of the calculations.

In summary, ion–molecule reactivity using chiral reagents can be used to probe chirality in the gas phase. It is now feasible, in principle, to distinguish enantiomeric structures using mass spectrometric methods. FT-ICR/MS is a powerful new tool for the study of molecular recognition under solvent-free conditions. Solvation has a small but measurable masking effect on the extent of recognition. Finally, the description of this system using molecular mechanics yields a qualitatively and quantitatively reasonable estimate of the degree of chiral recognition.

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