

Macrocyclic chemistry without solvents: Gas phase reaction rates

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Abstract. Both size selection and macrocyclic effects are observed for crown ethers reacting with alkali metal cations in the absence of solvent species. The efficiencies of the radiatively-stabilized 1:1 ligand:metal complexation reactions scale directly with cation charge density, suggesting that ion-induced rearrangement of the ligand into a favorable binding conformation is more efficient for smaller cations. The 1:1 reaction efficiencies are also greater for the macrocycles than for the corresponding acyclic ligands, reflecting preorganization of the binding cavity in the case of the crowns. The efficiencies of the subsequent reactions of the 1:1 complexes to form 2:1 ligand:metal species are dominated by size effects: when the cations are small enough to enter the macrocycle cavity, reaction is very slow, but the reactions occur readily when the cations cannot enter the crown cavity. Acyclic ligands undergo the 2:1 complexation reaction much more slowly and less selectively than do the macrocycles, again evidencing macrocyclic effects in the absence of solvation.

INTRODUCTION

One of the most important insights provided by modern chemical science is the realization that molecular size and shape play crucial roles in determining reactivity (ref. 1). Crown ethers (ref. 2, 3) have long been recognized as simple model ligands which exhibit size-selective reactivity; in fact, the remarkable ability of crowns to selectively form complexes with alkali metal ions is believed to arise from the "fit" of the cation within the binding cavity of the crown (ref. 4, 5, 6, 7).

Crown-cation complexation in solution is a very complex process (ref. 8), involving at least partial desolvation of both the ligand and the metal ion, and inevitably influenced to some degree by the presence of an associated anion, especially in less polar solvents. Stability constants measured in solution (ref. 9, 10) therefore always reflect solvent and counterion effects, and do not directly measure the *intrinsic* interactions between the crown host and its cation guest. Hence the role of solvation in phenomena such as size-match selectivity and the macrocyclic effect is not completely understood and has not been probed by direct experiment. An obvious direct approach to examining *intrinsic* host-guest chemistry is to carry out the reactions in the gas phase (ref. 11, 12, 13, 14, 15, 16, 17), where complications arising from solvation and ion pairing are not present.

Two issues are of particular interest in this study. First, does the size dependence evident in solution stability constants persist in the gas phase? Size-specific reactivity arising from non-covalent interactions is rarely invoked to explain gas-phase ion-molecule chemistry, so a clear demonstration of its importance could be of great interest. Second, are there macrocyclic effects (ref. 18) in the absence of solvent? Both configurational entropy and differences in the solvation energies of cyclic and acyclic ligands (ref. 19, 20) are believed to contribute to the higher stability constants and greater selectivities of macrocyclic complexes relative to complexes of acyclic ligands in solution. In the gas phase, the second factor is

absent, so configurational entropy should play a greater role (ref. 20). Each of these issues has been discussed in preliminary communications (ref. 21, 22).

EXPERIMENTAL

Experiments were conducted using Fourier transform ion cyclotron resonance mass spectrometry (ref. 23), which is a well-established technique for ion-molecule studies. In brief, ions are generated and trapped electromagnetically inside a vacuum chamber with a base pressure of 10^{-9} Torr. The ions can easily be retained in the trap for periods of minutes, making studies of reactions with neutrals possible despite the low-pressure conditions.

This work employed a Nicolet (now Extrel) FTMS-1000 instrument specially modified for increased pumping speed and simultaneous introduction of two temperature-controlled probes into the vacuum chamber, to facilitate experiments with less-volatile compounds. Alkali metal cations were generated by desorbing alkali nitrates or chlorides from one of the probes using the focused output of an excimer-pumped dye laser. Volatile ligands such as 12-crown-4, triglyme, and 15-crown-5 were introduced into the chamber via precision variable leak valves, while less volatile ligands such as 18-crown-6 were usually placed on the probes. Pressures, in the range 5×10^{-8} - 5×10^{-7} Torr, were measured using a Bayard-Alpert ionization gauge calibrated by measuring the rate of self-chemical ionization of acetone (a reaction with a well-established rate constant) (ref. 24).

A typical experimental sequence (Figure 1) begins with a "quench" event to remove all ions from the cell, followed by a laser shot to generate alkali metal cations. After a suitable delay (a few hundred milliseconds to a few seconds) to allow ion-molecule "synthesis" reactions, unwanted ions (such as the products whose formation rates are to be measured) are ejected from the trapping cell, leaving only the reactants of interest. After a variable reaction delay (of a few milliseconds to a few minutes), reaction products and the remaining reactants are monitored. Systematic variation of the reaction delay in these experimental sequences allows ion-molecule reactions to be followed as a function of time. All ion signal intensities were normalized to the most intense mass peak in each spectrum, and analyzed using pseudo-first-order kinetics.

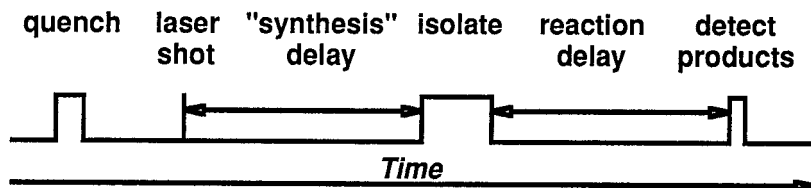


Fig. 1. Sequence of events in a Fourier transform ion cyclotron resonance mass spectrometry experiment to probe the kinetics of ion-macrocylic molecule reactions. Events are not drawn to scale.

Rate constants for 2-4 metals were determined simultaneously in each experiment, ensuring that the metals were subjected to identical ligand pressures. The largest likely source of error in the rate constant measurements is in the pressure determinations, but even if those are afflicted by relatively large systematic errors, the *relative* magnitudes of the rate constants are estimated to be correct within $\pm 10\%$.

All of the ligands were obtained from Aldrich. All were used as supplied, except for repetitive freeze-pump-thaw cycling for compounds used with the leak valves.

RESULTS AND DISCUSSION

All the ligands examined were observed to form 1:1 alkali metal complexes. These are clearly gas-phase reactions, since the ligands and metals were introduced separately with no

opportunity for reaction except as gaseous species. It is somewhat surprising that these reactions are observed so readily, since they are exothermic processes with no third body present to carry off the energy released. Collisions with neutrals at these pressures are too infrequent to account for stabilization of the complexes, so these reactions are most likely stabilized by emitting the excess energy as infrared photons (ref. 25, 26). This type of radiative stabilization has been invoked before to explain the stabilities of 1:1 complexes between singly-charged transition metal ions and tribenzocyclotriyne in the gas phase (ref. 27), and polyethers, with multiple C-O bonds, would appear to be especially effective (ref. 28) at radiative cooling.

The 1:1 complexation reactions were followed as a function of time and rate constants were determined as described above. The rate constants were converted to relative reaction efficiencies by dividing each by the corresponding collision rate constant calculated using LGS theory (ref. 29). The efficiency data reflect the fraction of ion-molecule encounters which result in successful complex formation. Relative efficiencies determined for the reactions of Na^+ , K^+ , Rb^+ , and Cs^+ with 12-crown-4 and 15-crown-5, as well as with the analogous acyclic molecules triglyme and tetraglyme, are presented in Figure 2 as a function of $1/R^3$, where R is the ionic radius of the alkali metal from x-ray crystallographic measurements (ref. 30). Linear least-squares fits to the data yield functions which have intercepts within experimental error of zero on the reaction efficiency axis, and whose slopes reflect the relative degree of dependence of the complexation rates for each ligand on the charge density of the metal.

From Figure 2 it is immediately apparent that 1:1 complexation does not occur on every collision; if that were the case, efficiency would not increase with increasing charge density. It is interesting that the more charge-dense cations yield the highest efficiencies. This appears to be a general phenomenon, since we observe the same general trends of increasing efficiency with increasing charge density in 1:1 complexation involving other ligands such as *p*-*tert*-butylcalix[4]arene (ref. 31) and valinomycin (ref. 32). The efficiencies are not controlled by the efficiency of radiative cooling, since in that case the *less* exothermic reactions involving the less charge-dense cations would be expected to be the *most* efficient. Speculating on the origin of this effect, it seems likely that the more charge-dense cations are more effective at inducing the orientation of the dipoles of the ligand for optimal cation binding than are the more diffuse metal ions. Examination of additional systems, particularly as the flexibility of the ligand is systematically varied, should shed further light on this question.

It is also evident from the slopes in the plots of Figure 2 that the reaction efficiencies are greater for the cyclic ligands than for the corresponding acyclic glymes, and that the dependence of reaction efficiency on metal cation charge density is also greater for the macrocycles than for the glymes. Both phenomena probably arise from the more favorable

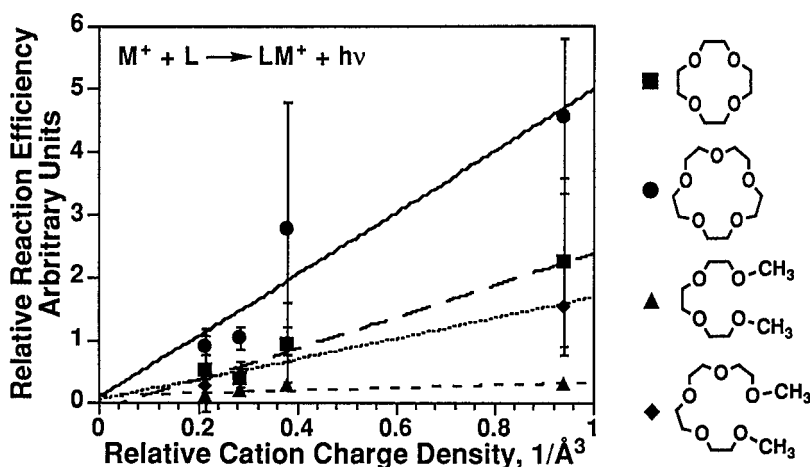


Fig. 2. Reaction efficiencies for 1:1 ligand:metal complexation as a function of relative cation charge density (expressed as R^{-3} , where R is the ionic radius of the metal). Error bars represent one standard deviation. Lines are linear least-squares fits to the data points for each ligand.

binding orientation of the donor atoms imposed by the macroring, making this another manifestation of the macrocyclic effect. The greater dependence on charge density of the efficiencies for the macrocycles lends credence to the idea that the more charge-dense metals are better able to influence the orientation of the ligand dipoles to promote binding.

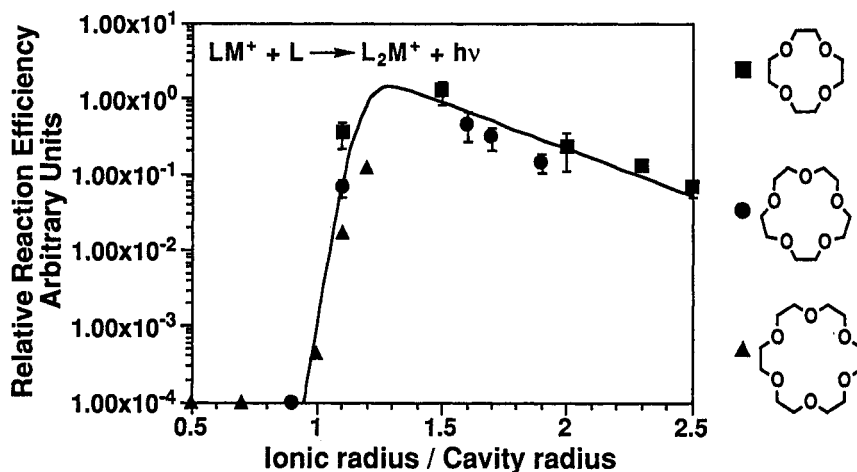


Fig. 3. Relative reaction efficiencies for 2:1 ligand:metal complex formation, plotted as a function of the ratio of metal ionic radius to ligand cavity radius. Error bars represent one standard deviation.

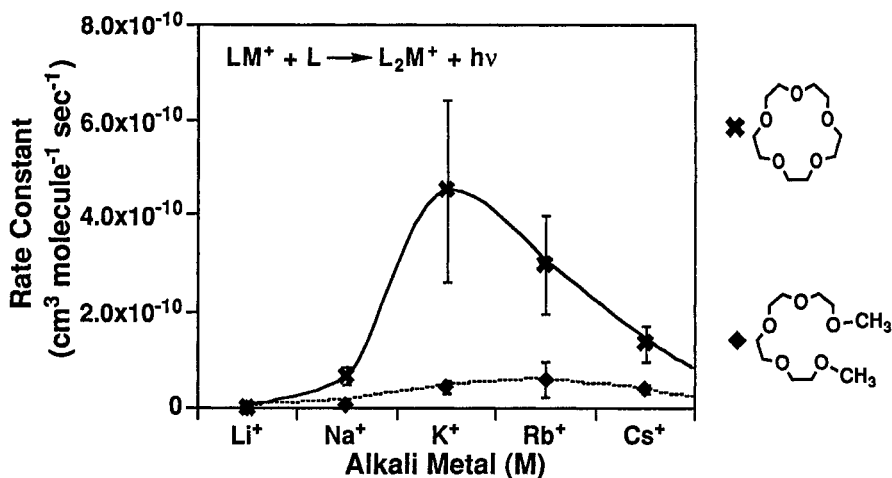


Fig. 4. Rate constants for formation of 2:1 ligand:metal complexes of 15-crown-5 and tetraglyme with alkali metal cations. Error bars represent one standard deviation.

Many of the 1:1 complexes were observed to undergo reaction with an additional ligand to form 2:1 ligand:metal complexes in the gas phase. Relative reaction efficiencies for Li^+ , Na^+ , K^+ , Rb^+ , and Cs^+ 1:1 complexes of 12-crown-4, 15-crown-5, and 18-crown-6 reacting with a second ligand to form homogeneous 2:1 complexes are given in Figure 3 as a function of the ratio of ionic radius to average crown cavity radius (ref. 33). The data points lying on the 1.00×10^{-4} relative efficiency line are upper limits, since 2:1 complexation was not observed in those cases.

Size-selective kinetics are dramatically apparent in the 2:1 reactions (ref. 21). When the cations are small enough to enter the cavity of the initially-attached crown, as is the case for Li^+ with 15-crown-5, and for Li^+ and Na^+ with 18-crown-6, attachment of a second ligand is too

slow to measure. This is most likely because access to the cation is blocked by the first ligand, making it sterically unavailable for attaching a second ligand. When the ratio of ionic radius to cavity size reaches 1 (18-crown-6/K⁺), the reaction is barely detected, then efficiencies increase abruptly as the ratio increases. The maximum reaction efficiency occurs at a ratio value in the range 1.2-1.5, while efficiency decreases at higher values of the ratio. We speculate that the decrease arises from charge density effects similar to those seen in the 1:1 reactions.

Macrocyclic effects are also evident in the 2:1 complexation reactions (ref. 22). Rate constants measured for 15-crown-5 and tetraglyme are compared in Figure 4. The (15-crown-5)₂M⁺ complexes form more rapidly, and with greater cation specificity, than those involving tetraglyme. The acyclic ligand is better able to encapsulate the cation than the macrocycle, which is constrained by its cyclic covalent backbone. Hence, the cation in the 1:1 crown complex is more accessible to attack by the second ligand than is that in the 1:1 glyme complex. Similar behavior is observed when 12-crown-4 and triglyme are compared.

It is noteworthy that size-dependent 2:1 complexation kinetics are observed even for the acyclic ligands. The fastest rate constants for triglyme and tetraglyme are observed in each case for the next larger metal than is seen for 12-crown-4 and 15-crown-5. This is consistent with greater flexibility in the acyclic ligands than in the macrocycles, enabling them to "wrap" larger cations than can the crowns. Thus, a pre-defined binding cavity is not a necessary condition for cation size selection in 2:1 complexation, but it does enhance the selection process.

SUMMARY

The application of gas-phase ion-molecule techniques to macrocyclic chemistry offers great promise as a means of probing the underlying interactions which govern the recognition of a host for particular guests. Solvation and counterion effects are completely eliminated in these experiments, but both macrocyclic effects and size-selective reactivity patterns are still observed. A number of macrocyclic effects are evident in the reaction kinetics. For 1:1 complexation, the cyclic ligands react more rapidly, and with efficiencies more strongly dependent on metal charge density, than do their acyclic counterparts. Cyclization also influences the ability of the metal-ligand complex to add a second ligand: acyclic ligands are more effective at blocking the approach and subsequent binding of a second ligand than are the cyclic ligands, and this is reflected in the reaction efficiencies for formation of 2:1 ligand:metal species.

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