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Evaluation of Proton-binding Capabilities of Polyether and Pyridyl Ligands

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The competitive proton-binding abilities of a series of pyridyl and polyether ligands were examined by application of ligand-exchange and collisionally activated dissociation (CAD) methods. Many of the ligands of interest are multidentate, thus giving them enhanced capabilities for coordinating the proton, and they also may undergo a substantial loss of entropy, predominantly in rotational and vibrational modes of freedom, when binding a proton because the electrostatic interactions between donor atoms and the proton create a degree of organization of the ligand. The presence of dominant mixed-dimer complexes formed during the ligand-exchange reactions provides key evidence that multiple hydrogen-bond formation is operative for one or both ligands. Although CAD provides some insight into the factors which influence proton-binding strengths of the ligands in dimers, several general issues emerge when applying the CAD (i.e. the kinetic method) to estimate proton affinities of multidentate ligands. Owing to the severe impact of entropic effects upon dissociation of the dimers involving multidentate ligands, the ratio of product ions does not reflect the order of proton affinities of the ligands involved in the dimer. The CAD experiments give the order of gas-phase basicities at a higher temperature in which the entropy term is much more significant. This effect is especially significant when one of the ligands is floppy and multidentate and the other is rigid or monodentate. © **1998 John Wiley & Sons, Ltd.**

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KEYWORDS: ligand exchange; kinetic method; proton affinity; gas-phase basicity; polyether; pyridine

INTRODUCTION

The determination of the strength of binding interactions between organic molecules and cations or anions remains an ongoing challenge in gas-phase ion chemistry. The strengths of the binding interactions influence the mobility of the cation (or anion), affect the stability of the cationized organic molecule and influence its dissociation pathways. The elucidation of the binding interactions of large, multidentate molecules that may engage in cooperative interactions when binding a cation or even partially encapsulate a cation has become a growing area of interest, in part due to the development of ionization methods such as matrix-assisted laser desorption/ionization (MALDI), fast atom bombardment (FAB) and electrospray ionization (ESI) that can create ions of huge size.[1–4] Production of ions specifically by proton attachment remains the most common method of ionization, hence there are numerous ongoing studies of the determination of gas-phase basicities of organic molecules and the elucidation of structural factors that influence gas-phase basicities,[5–12] in both singly and multi-charged ions. An understanding of the role of multiple binding interactions is particularly important in the assessment of binding strengths of supramolecular complexes, such as the non-covalently bound complexes that have recently generated considerable interest in electrospray studies.[13–18]

Two of the most popular methods for evaluating gas-phase basicities are the bracketing method and the kinetic method.[19,20] For the bracketing method,[21,22] relative gas-phase basicities are determined by establishing the favored direction of proton transfer between base pairs. The guideline to differentiate an endoergic *vs.* exoergic reaction is typically defined at a proton transfer reaction efficiency of 10%.[23] The kinetic method involves the formation and dissociation of proton-bound dimers containing two bases of interest. The loosely bound dimer typically dissociates by cleavage across the proton bridge, resulting in the production of protonated bases. The base that constitutes the greater fragment ion abundance is presumed to have the greater gas-phase basicity. It is well recognized that the kinetic method can give misleading results for cases in which intramolecular hydrogen bonding of the bases may exist or in which large changes in net entropy occur upon dissociation of the dimer by competing pathways.[24–27]

Our group has undertaken a systematic evaluation of binding interactions of various types of gas-phase ions

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in order to develop methods for probing the strengths of binding interactions and to correlate the strengths of the interactions with structural factors of organic molecules.[28–33] We have predominantly focused our efforts on the examination of the binding interactions of specific classes of multidentate ligands with metal cations, the ammonium ion and the proton. In the present study, we turned our attention to the competitive proton-binding ability of two classes of multidentate ligands, polyethers and pyridyl molecules (Fig. 1). The competitive proton-binding abilities of these two classes provide an interesting case because the ligands are available with a range of uniform binding sites (from one to seven oxygen atoms in polyethers and from one to three nitrogen atoms in pyridyl molecules), their gas-phase basicities are either well known or can be determined from routine measurements and the degree of flexibility of the ligands varies. In addition, these multidentate ligands may undergo a substantial loss of entropy, predominantly in rotational and vibrational modes of freedom, when binding a proton because the electrostatic interactions between donor atoms and the proton create a degree of organization of the ligand. Although relatively simple molecules, the pyridyl and polyether ligands are excellent models of more complex biologically related receptor ligands that may participate in non-covalent binding interactions within supramolecular complexes.

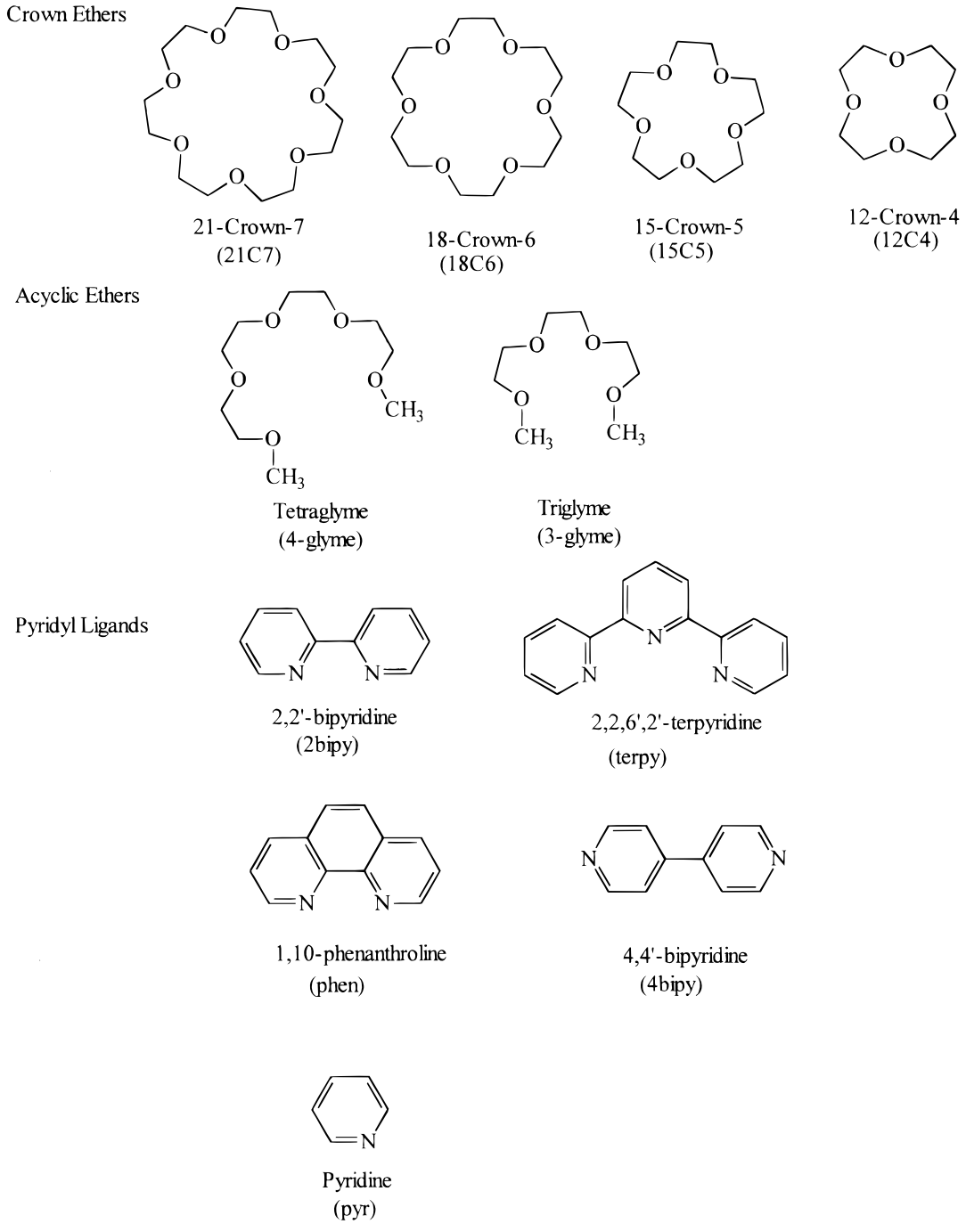

Figure 1. Structures of multidentate molecules.

Our specific objectives were aimed at comparing the proton-binding strengths of pyridyl and polyether molecules by examination of competitive proton-transfer experiments and dissociation of mixed proton-bound dimers. The possibility that the larger polyethers can more fully encapsulate a proton and retard proton transfer to another ligand was evaluated, along with consideration of the importance of entropic effects that may significantly influence the dissociation of proton-bound dimers. In addition, a direct comparison of the bracketing method and the kinetic method was undertaken to seek discrepancies that might occur in the determination of relative proton affinities by these two different methods.

EXPERIMENTAL

All experiments were performed by ion trap mass spectrometry (ITMS) using a Finnigan instrument operated in the mass-selective instability scan mode.[34] Liquid samples were introduced into the ion trap by means of precision leak valves and the solid samples were admitted using a heated direct insertion probe. The pressure of each sample was about 1×10^{-6} Torr (1 Torr = 133.3 Pa). After the introduction of the samples, helium was admitted at about 1 mTorr. All experiments were performed at a trap temperature of 120 °C.

Typical experiments were performed with the following steps. A short electron ionization (EI) pulse (10 ms) was used to evaluate the relative amount of each reactant to avoid dependence on potentially misleading partial pressure readings. All EI fragments from one reactant were co-added so the overall intensity could be compared with the other reactant. Ligand concentrations were also verified by proton-transfer reactions from protonated dimethyl ether to the ligand in a short chemical ionization period. The estimated concentrations of the ligands were similar by both methods. In either case, it is difficult to establish confidently equal concentrations of any pair of ligands because one ligand must always be added after the first one, and thus our efforts were focused on establishing a reproducible procedure that may suffer from some systematic, albeit minimized, errors. Since the ionization cross-sections for each ligand differ, experiments were also undertaken in which the concentration of each ligand (as determined by the spectral intensity) was raised and lowered to see if there was a significant change in the trends for the results. For pairs of ligands in which the cross-sections should differ most dramatically (i.e. 18-crown-6 and pyridine), the product distributions from the ligand-exchange reactions changed by up to 10%, but reversals in the observed trends were not observed.

After ionization of the reactants, a 100–1000 ms reaction time was allowed for self-chemical ionization to occur. For the ligand-exchange experiments, after this reaction time, the apex isolation method was used to isolate one of the reactant ions of interest. After the isolation step, an additional 300–1000 ms reaction time was given to allow proton-transfer reactions to take place. This sequence was also run in the reverse direction for further evaluation of the proton-transfer efficiency. If proton-bound heterodimers incorporating the two reactants formed during the reaction period, then the dimer was isolated and low-amplitude collisional activation was used to dissociate the dimers. The typical tickle voltage for activation was between 200 and 1000 mV p–p applied for 10 ms using a q_z value of 0.3.

The polyethers and pyridyl molecules including triglyme, tetraglyme, 12-crown-4, 15-crown-5, 18-crown-6, 1,10-phenanthroline, 4,4′-bipyridine and 2,2′,2,6-terpyridine were purchased from Aldrich Chemical (Milwaukee, WI, USA), 2,2′-bipyridine from Sigma (St. Louis, MO, USA) and 21-crown-7 from Parish Chemical (Orem, UT, USA). All chemicals were used without further purification.

DISCUSSION

Gas-phase basicities

The proton affinities and gas-phase basicities of all of the polyethers except 21-crown-7 have been previously characterized, and the proton affinities are known to range from 226.5 kcal mol^{-1} (1 kcal = 4.184 kJ) for triglyme to 231.4 kcal mol^{-1} for 18-crown-6[5,35,36] (Table 1). In the present study, the gas-phase basicity of 21-crown-7 was estimated to fall in the range 225–230 kcal mol^{-1} based on bracketing experiments. As previous studies in this area have noted, a fairly uniform correlation between the number of oxygen atoms and basicities is observed. Two independent studies have found that acyclic ethers possess greater gas-phase basicities than those of crown analogs.[35,36] The less favorable dipole orientation in 12-crown-4 and 15-crown-5 results in a net lower stabilization of the proton than in their acyclic counterparts, in which the greater flexibility of the polyether backbone allows optimization of the oxygen dipole orientation.[35] The acyclic polyethers suffer a greater decrease in entropy when binding the proton than do the analogous crown ethers because of the degree of organization that must occur to coordinate the proton optimally, and this decrease in entropy partially offsets the gain in enthalpy, thus making the net gas-phase basicities of the crown ethers and glymes similar.

The proton affinities and gas-phase basicities of the pyridyl ligands used in this study other than pyridine have not been previously established. In order to understand quantitatively the difference in the binding behavior between polyether and pyridyl ligands, the basicities of the pyridyl ligands were obtained. In the present

Table 1. Gas-phase basicities of polyethers[5]

Polyether	Gas-phase basicity (kcal mol^{-1})	Proton affinity (kcal mol^{-1})
Triglyme[a]	213.5	226.5
Tetraglyme[a]	214.7	228.0
12-Crown-4[a]	212.8	221.6
15-Crown-5[a]	215.0	225.6
18-Crown-6[a]	217.6	231.4
21-Crown-7[b]	228 ± 3	N/A

[a] From Ref. 5.
[b] This work.

study, the gas-phase basicities of the pyridyl ligands including 2,2′-bipyridine, 4,4′-bipyridine, 1,10-phenanthroline and 2,2,6′,2-terpyridine were anchored by ligand-exchange experiments with reference compounds of known gas-phase basicities, as listed in Fig. 2. The gas-phase basicities for these pyridyl ligands range from 2,2,6′,2-terpyridine which has a gas-phase basicity just below that of *N*,*N*-tetramethyl-1,8-diaminonaphthalene (238.8 kcal mol^{-1}),[5] to pyridine (214.7 kcal mol^{-1}).[5] The observed order of gas-phase basicities agrees well with a previous study in which the relationship between basicities and polarizabilities of the pyridyl ligands was found.[28] 4,4′-Bipyridine possesses a gas-phase basicity more similar to that of pyridine than its positional isomer 2,2′-bipyridine. This result stems from the fact that the nitrogen binding sites of 4,4′-bipyridine are located on the ring at positions *para* to each other, which prevents both nitrogen atoms from bridging the proton at the same time. The polydentate pyridyl ligands have higher gas-phase basicities than all of the polyethers except 21-crown-7. This result is not surprising because the greater basicities of nitrogen-containing compounds relative to oxygen-containing compounds are well documented.[5]

Proton-transfer reactions of polyether and pyridyl ligands

Although the gas-phase basicities of the polyether and pyridyl ligands have been quantitated (see the previous section), an examination of the proton-transfer reactions, relative efficiencies and formation of proton-bound dimers may give further insight into some of the structural factors which mediate the proton-binding strengths of more complex multidentate ligands. In addition, anomalous results from the proton-transfer reactions of these multidentate ligands may forecast similar problems or discrepancies with larger biological

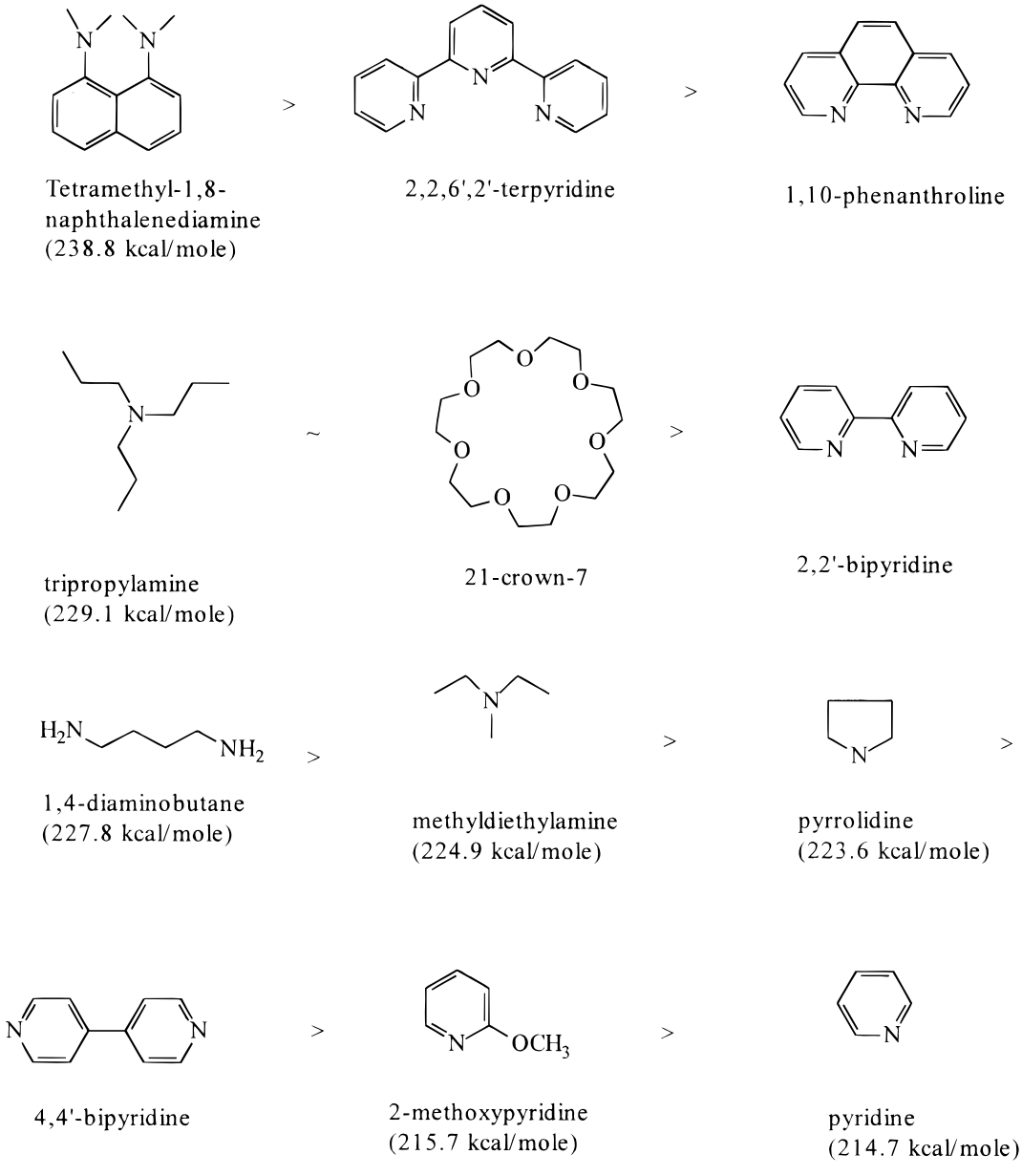

Figure 2. Gas-phase basicities of pyridyl ligands and 21-crown-7.

ligands. In these experiments, one polyether and one pyridyl ligand were admitted at similar concentrations to the trap. A short period was allowed for self-protonation, then each protonated ligand was isolated and allowed to undergo proton transfer with the other neutral ligands.

An example is shown in Fig. 3 for the proton-transfer reactions between 18-crown-6 and 2,2,6′,2′-terpyridine. As shown, protonated 2,2,6′,2′-terpyridine undergoes no deprotonation by 18-crown-6, but protonated 18-crown-6 undergoes extensive deprotonation by 2,2,6′,2′-terpyridine. A reaction time of 300 ms was selected because it represents a shorter period than that required to reach equilibrium, so the observed distribution of products reflects how fast and efficiently the proton-transfer reactions and formation of dimers occur, given that the pressures of ligands are controlled so that approximately equal numbers of collisions occur for each experiment. Since it is difficult to control the pressures precisely, the product distributions in Table 2 were used only to assess general trends.

The results of the experiments are given in Table 2. For example, the first entry shows the proton-transfer reactions between 2,2,6′,2′-terpyridine and 12-crown-4. For the first reaction, protonated 2,2,6′,2′-terpyridine was isolated and allowed to react with 12-crown-4. After 300 ms, no proton transfer to 12-crown-4 was observed. For the second reaction, protonated 12-crown-4 was isolated and allowed to react with 2,2,6′,2′-terpyridine. After 300 ms, the product distribution showed that 10% of the products remained as protonated 12-crown-4 and 90% of the products were protonated 2,2,6′,2′-terpyridine.

As the data show, three different outcomes are possible in these types of exchange reactions: (i) if the protonated ligand has a much higher basicity, then little or no exchange will take place, and the ion current of the first protonated ligand remains constant throughout the experiment; (ii) if the neutral ligand has a much higher basicity than does the initial protonated ligand, then most or all of the protons will migrate from the protonated ligand to the other neutral ligand by the end of the reaction period; (iii) if the neutral and the protonated ligand have similar basicities and the proton is not fully solvated by a single ligand, then a proton-bound dimer forms during the reaction time.

Reactions involving monodentate pyridyl ligands. The results of experiments involving the protonated 4,4′-bipyridine or protonated pyridine ligands with the polyethers are qualitatively similar. When either the [pyridine + H^+] or [4,4′-bipyridine + H^+] ions are isolated, the formation of mixed dimers, i.e. [pyridyl ligand + H^+ + polyether], is observed for reactions with each of the polyethers. This observation suggests that the proton attached to pyridine or 4,4′-bipyridine is accessible to 'solvation' by the neutral polyether molecules, resulting in the formation of complexes that are more thermodynamically stable than the simple protonated pyridyl ligands and in which the proton is more optimally coordinated in the gas phase. For reactions of protonated pyridine or protonated 4,4′-bipyridine with

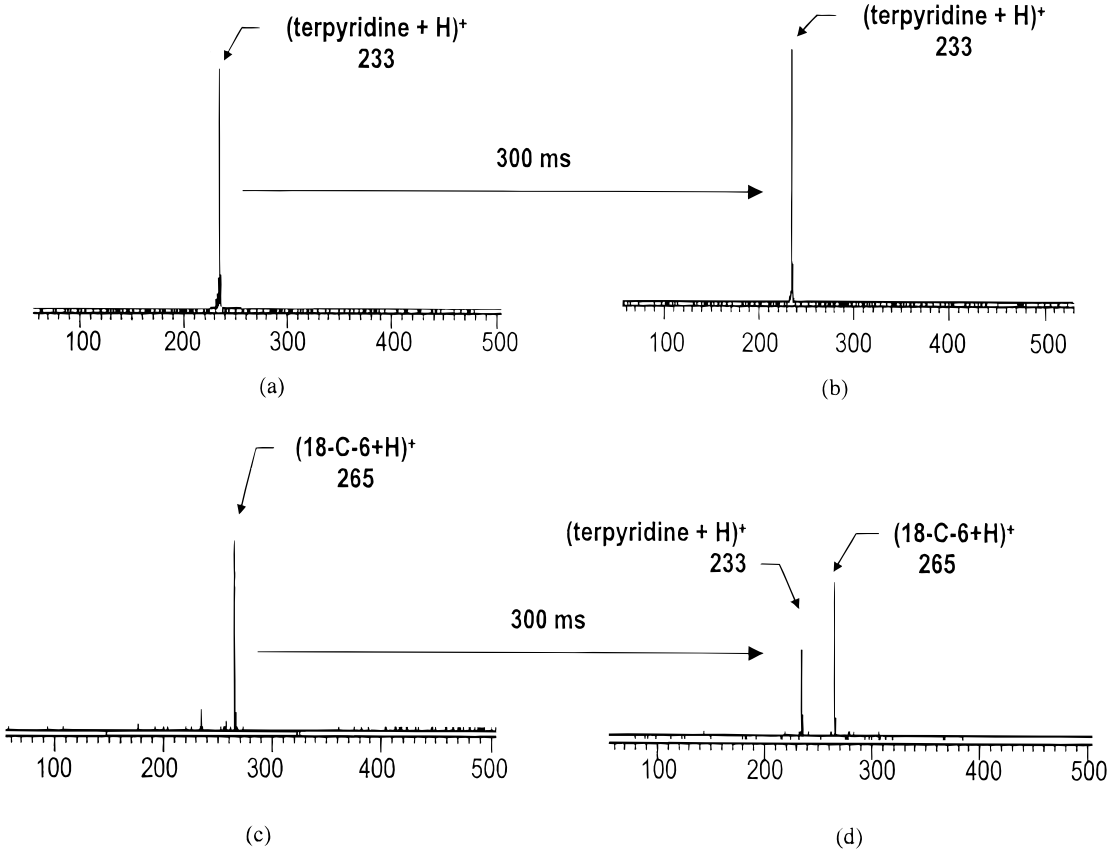

Figure 3. Proton transfer reaction between 2,2,6′,2′-terpyridine and 18-crown-6.

Table 2. Ligand-exchange reactions of protonated ligands: product distributions (%)[a]

		Reaction 1			Reaction 2		
Ligand 1	Ligand 2	PyrH$^+$	PolyH$^+$	DimH$^+$	PolyH$^+$	PyrH$^+$	DimH$^+$
2,2,6′,2-Terpyridine	12-Crown-4	100	0	0	10	90	0
	Triglyme	100	0	0	30	70	0
	15-Crown-5	100	0	0	60	40	0
	Tetraglyme	100	0	0	65	35	0
	18-Crown-6	100	0	0	70	30	0
	21-Crown-7	100	0	0	90	10	0
1,10-Phenanthroline	12-Crown-4	100	0	0	15	85	0
	Triglyme	100	0	0	30	70	0
	15-Crown-5	100	0	0	65	35	0
	Tetraglyme	100	0	0	80	30	0
	18-Crown-6	70	0	30	80	15	5
	21-Crown-7	50	5	45	60	20	20
2,2′-Bipyridine	12-Crown-4	100	0	0	40	60	0
	Triglyme	100	0	0	50	50	0
	15-Crown-5	100	0	0	65	35	0
	Tetraglyme	95	5	0	70	30	0
	18-Crown-6	70	0	30	70	25	5
	21-Crown-7	70	10	20	75	20	10
4,4′-Bipyridine	12-Crown-4	75	5	20	85	10	5
	Triglyme	45	0	55	60	15	25
	15-Crown-5	50	5	45	85	5	10
	Tetraglyme	50	5	45	85	5	10
	18-Crown-6	25	5	70	70	0	30
	21-Crown-7	20	10	70	90	0	10
Pyridine	12-Crown-4	30	0	70	5	35	60
	Triglyme	30	0	70	5	30	65
	15-Crown-5	75	5	25	20	0	80
	Tetraglyme	0	2	98	5	0	95
	18-Crown-6	0	5	95	30	0	70
	21-Crown-7	0	15	85	50	0	50

[a] For reaction 1, the protonated pyridyl ligand (ligand 1) was isolated and allowed to react for 300 ms with an equal concentration of ligand 1 and ligand 2. For reaction 2, the protonated polyether (ligand 2) was isolated and allowed to react for 300 ms with an equal concentration of ligand 1 and ligand 2. The three columns under reaction 1 show the relative percentages of [pyridyl + H$^+$], [polyether + H$^+$] and [pyridyl + H$^+$ + polyether]. The three columns under reaction 2 show the relative percentages of [polyether + H$^+$], [pyridyl + H$^+$] and [pyridyl + H$^+$ + polyether]. The standard deviations are ±5%.

15-crown-5, 18-crown-6, 21-crown-7 or tetraglyme, relatively little direct proton transfer to the polyethers occurs, even for the polyethers with much greater gas-phase basicities (21-crown-7, 18-crown-6) than pyridine and 4,4′-bipyridine. Instead of proton transfer, the formation of the proton-bound heterodimer is the dominant process. For the ligand-exchange reactions between protonated pyridine or protonated 4,4′-bipyridine and 18-crown-6 or 21-crown-7, the exothermicities of these proton transfer reactions are at least $\sim$ 3–8 kcal mol^{-1}, suggesting that the proton transfers might be expected to proceed efficiently. The preference for the formation of proton-bound dimers over proton transfer suggests that the great floppiness of the crown ethers facilitates radiative cooling of the proton-bridged intermediates, thus releasing the excess energy of the proton transfer process and stabilizing the proton-bridged complex.

In contrast to the similar results observed for reactions of either protonated pyridine or protonated 4,4′-bipyridine ligands with neutral polyethers, the results for the reverse reactions involving each protonated polyether with neutral pyridine or 4,4′-bipyridine are considerably different. When each [polyether + H$^+$] ion is isolated, reactions with 4,4′-bipyridine are relatively slow and generate only a minor amount of mixed dimer complexes, i.e. [4,4′-bipyridine + H$^+$ + polyether], whereas reactions of each protonated polyether with pyridine lead once again to the dominant formation of mixed dimer complexes, [pyridine + H$^+$ + polyether]. This contrast in the reactions involving the two types of monodentate pyridyl ligands probably reflects their ability to approach the solvated proton when it is partially or fully shielded by a flexible multidentate polyether ligand. Pyridine is much less bulky than 4,4′-bipyridine, hence it has greater accessibility to approach the solvated proton and attach to it. Although the intrinsic proton affinity and gas-phase basicity of 4,4′-bipyridine are slightly greater than those of pyridine (+1 kcal mol^{-1}), 4,4′-bipyridine is a bulkier ligand, and we therefore speculate that it has reduced accessibility to approach the solvated proton–polyether complex.

Reactions involving multidentate pyridyl ligands. The proton-transfer reactions between the multidentate pyridyl ligands 1,10-phenanthroline, 2,2′-bipyridine and 2,2,6′,2-terpyridine and the polyethers also show some general

similarities. 2,2′-Bipyridine, 1,10-phenanthroline and 2,2,6′,2-terpyridine all have substantially higher gas-phase basicities than any of the polyethers except 21-crown-7, and this difference is clearly reflected in the proton transfer reactions. When the [1,10-phenanthroline + H^+] or [2,2′-bipyridine + H^+] or [2,2,6′,2-terpyridine + H^+] complexes are isolated, there is little if any proton transfer to any of the polyethers and there is little formation of proton-bound dimers, except for the reactions involving 18-crown-6 or 21-crown-7 (see Table 2). Therefore, in most cases, the higher basicities of the multidentate pyridyl ligands are clearly illustrated by the ligand-exchange reactions. When the protonated, 1,10-phenanthroline or 2,2′-bipyridine ligands are allowed to react with 21-crown-7, transfer of the proton to 21-crown-7 occurs to a minor extent because the gas-phase basicity of 21-crown-7 is within a few kcal mol^{-1} of those of both 1,10-phenanthroline and 2,2′-bipyridine. There is also a modest amount of formation of mixed dimer complexes between each of the two bidentate pyridyl ligands (i.e. 2,2′-bipyridine and 1,10-phenanthroline) and 18-crown-6 or 21-crown-7, the largest polyethers with the greatest gas-phase basicities. Thus, 18-crown-6 and 21-crown-7 are both sufficiently large, flexible and polarizable to provide some degree of competitive solvation of the proton when it is already attached to 1,10-phenanthroline or 2,2′-bipyridine. Conversely, the proton is so strongly bound in protonated 2,2,6′,2′-terpyridine that neither proton transfer nor formation of proton-bound dimers is observed for reactions with any of the polyethers. The other polyethers, including triglyme, tetraglyme, 15-crown-5 and 12-crown-4, have proton-binding strengths that are insufficient relative to the proton-binding abilities of the multidentate pyridyl ligands to allow competitive solvation of the proton.

The reverse experiments involve isolation of the protonated polyethers and subsequent reactions with the neutral multidentate pyridyl ligands. When each of the [polyether + H^+] ions is isolated, the proton transfers to 1,10-phenanthroline, 2,2′-bipyridine or 2,2,6′,2-terpyridine to some extent. The extent of the proton transfer generally scales with the intrinsic gas-phase basicity of each polyether, such that the proton extraction from the [21-crown-7 + H^+] complex is considerably slower than that from the [18-crown-6 + H^+] complex and so on, thus resulting in increased formation of protonated pyridyl ligands as the gas-phase basicity of the polyether decreases. For the majority of the proton transfer reactions involving the smaller polyethers, formation of mixed dimer complexes is not observed, suggesting that the proton-transfer reactions are sufficiently exothermic that stabilization of the proton-bound dimer is not possible on the time-scale of the experiment. For the reactions involving [18-crown-6 + H]$^+$, some mixed dimer formation is observed only during the reactions with 2,2′-bipyridine, the ligand which has the lowest gas-phase basicity of the three multidentate pyridyl ligands. For the reactions involving [21-crown-7 + H^+], some mixed dimer formation is observed during the reactions with 1,10-phenanthroline or 2,2′-bipyridine, but not with 2,2,6′,2′-terpyridine. The gas-phase basicity of 21-crown-7 is within 2–4 kcal mol^{-1} of those of both 2,2′-bipyridine and 1,10-phenanthroline, resulting in proton-transfer reactions that are only slightly exothermic and thus allowing stabilization of the intermediate proton-bound heterodimer by collisional deactivation or radiative cooling during the reaction period. The formation of proton-bound dimers is not unexpected when the two ligands have reasonably similar intrinsic basicities, as is the case for 21-crown-7 and 2,2′-bipyridine or 21-crown-7 and 1,10-phenanthroline. However, the gas-phase basicity of 18-crown-6 is ~6–7 kcal mol^{-1} less than that of 2,2′-bipyridine, meaning that the proton transfer reaction to 2,2′-bipyridine is predicted to be exothermic. The fact that mixed dimer formation, rather than only efficient proton transfer, is observed suggests that the floppiness of 18-crown-6 and its intrinsic flexibility in coordinating the proton promotes stabilization of the [18-crown-6 + H^+ + 2,2′-bipyridine] intermediate for a sufficiently long period that collisional and radiative cooling of the complex can occur, thus allowing disposal of the excess energy. This process would allow the survival of the heterodimer complex. [18-crown-6 + H^+ + 2,2′-bipyridine]. A similar phenomenon may enhance the efficiency of dimer formation for the reactions involving 21-crown-7 and 1,10-phenanthroline or 21-crown-7 and 2,2′-bipyridine.

Relative rates of proton-transfer reactions. Within the series of polyethers, the reactivity of the [polyether + H]$^+$ complexes towards deprotonation by the pyridyl ligands generally scales with the relative gas-phase basicity of the polyether. As the number of oxygen donor atoms increases and as the flexibility of the polyether increases, the rate of the deprotonation reactions decreases. For example, in the standard 300 ms reaction interval, the amount of protonated 2,2′-bipyridine that is generated upon reaction of 2,2′-bipyridine with each protonated polyether runs from 25% for 21-crown-7 and 18-crown-6 to 30–35% for tetraglyme and 15-crown-5 to 50–60% for triglyme and 12-crown-4. Although the table only shows the product distributions for one time window, the trend clearly shows that deprotonation of the smaller protonated polyethers occurs faster than that of the larger protonated polyethers, thus reflecting the intrinsic proton-solvating strength of each polyether.

Formation of proton-bound heterodimers. Although complete proton-transfer reactions such as those described for the reactions involving 2,2,6′,2-terpyridine and the polyethers are by far the most common reactions observed in the ligand-exchange experiments, the cases where heterodimer formation occur are especially interesting. As noted in Table 2, there are numerous examples where heterodimer formation is observed, and in some case it is the dominant process. Heterodimers are frequently formed even when the polyether has a substantially lower gas-phase basicity than the pyridyl ligand, as noted in the cases of 12-crown-4 and 4,4′-bipyridine ($\Delta GB \approx 3$ kcal mol^{-1}), triglyme and 4,4′-bipyridine ($\Delta GB \approx 3$ kcal mol^{-1}), 18-crown-6 and 1,10-phenanthroline ($\Delta GB \approx 12$ kcal mol^{-1}) and 18-crown-6 and 2,2′-bipyridine ($\Delta GB \approx 7$ kcal mol^{-1}), or when the pyridyl ligand has a lower gas-phase basicity than the polyether: pyridine and 18-crown-6 ($\Delta GB \approx 3$ kcal

Table 3. CAD results for [pyridyl + H^+ + polyether] complexes: fragment ion percentages

Proton-bound dimer	[Pyridyl + H^+]	[Polyether + H^+]
[1,10-Phenanthroline + H^+ + 18-crown-6]	100	0
[1,10-Phenanthroline + H^+ + 21-crown-7]	95	5
[2,2′-Bipyridine + H^+ + 18-crown-6]	100	0
[2,2′-Bipyridine + H^+ + 21-crown-7]	95	5
[4,4′-Bipyridine + H^+ + 12-crown-4]	100	0
[4,4′-Bipyridine + H^+ + triglyme]	100	0
[4,4′-Bipyridine + H^+ + 15-crown-5]	95	5
[4,4′-Bipyridine + H^+ + tetraglyme]	100	0
[4,4′-Bipyridine + H^+ + 18-crown-6]	75	25
[4,4′-Bipyridine + H^+ + 21-crown-7]	40	60
[Pyridine + H^+ + 12-crown-4]	90	10
[Pyridine + H^+ + triglyme]	100	0
[Pyridine + H^+ + 15-crown-5]	80	20
[Pyridine + H^+ + tetraglyme]	75	25
[Pyridine + H^+ + 18-crown-6]	70	30
[Pyridine + H^+ + 21-crown-7]	25	75[a]

[a] Summation of intact protonated 21-crown-7 and its fragment ions at *m/z* 133, 177 and 221.

mol^{-1}), pyridine and 21-crown-7 ($\Delta GB \approx 13$ kcal mol^{-1}) and 4,4′-bipyridine and 21-crown-7 ($\Delta GB \approx 12$ kcal mol). In most cases in which the $\Delta GB \geqslant 3$ kcal mol^{-1}, mixed dimer complexes are not observed unless one of the larger polyethers is involved.

The most striking examples of dominant dimer formation are those that involve the bidentate pyridyl ligands (1,10-phenanthroline, 2,2′-bipyridine) with 18-crown-6 or 21-crown-7. Despite the relative large difference in the gas-phase basicities of 18-crown-6 or 21-crown-7 and the bidentate pyridyl ligands ($\Delta GB \leqslant 7$–13 kcal mol^{-1}), the existence of heterodimer complexes may occur because the large crown ether ligands are such flexible, polarizable ligands that the proton-transfer processes are slowed. Because of their flexibility in orienting the bond dipoles of their ether groups, the large polyethers can stick to the [pyridyl ligand + H^+] complexes for a sufficient amount of time that the intermediate [pyridyl ligand + H^+ + crown ether] complexes undergo radiative or collisional relaxation, thus stabilizing the otherwise energetic complexes. The sizes and flexibilities of 18-crown-6 and 21-crown-7 clearly play a particularly critical role because the smaller polyethers, such as 12-crown-4 and triglyme, can only form mixed dimers when the difference in gas-phase basicities of the polyether and pyridyl ligand is $\leqslant 3$ kcal mol^{-1}, suggesting more restrictions in the ability to stabilize the transient proton-bound heterodimer complexes. The great polarizabilities and flexibilities of 18-crown-6 and 21-crown-7 enhance their capability for long-range persistent electrostatic interactions with the proton.

In addition to the dependence on the difference in gas-phase basicities of the two ligands on the predominance of dimer formation, there is also a significant distinction for the cases involving the 4,4′-bipyridine and polyether reactions depending on whether the initial reactant is [4,4′-bipyridine + H^+] or [polyether + H^+]. When the initial reactant is [4,4′-bipyridine + H^+], attachment of a polyether ligand to form a stable heterodimer is rapid, whereas when the initial reactant is [polyether + H^+], attachment of 4,4′-bipyridine is substantially less efficient. This difference in dimerization behavior probably reflects the degree of access to the proton when it is coordinated to the monodentate 4,4′-bipyridine ligand and approached by a floppy, polarizable polyether molecule compared with when the proton is coordinated by a floppy, multidentate polyether and approached by a bulky monodentate 4,4′-bipyridine molecule. The two cases clearly cannot be easily rationalized by a simple quantitative assessment of the relative gas-phase basicities of the ligands. When the proton is attached to 4,4′-bipyridine, it is bonded via a single interaction with one nitrogen atom, meaning that the proton is fully accessible from its opposite side and a polyether can approach unhindered. When the proton is initially attached to the polyether, it is probably coordinated via a couple of hydrogen-bonding interactions in addition to other persistent electrostatic (solvating) interactions involving the free oxygen dipoles. For the larger crown ethers, including 15-crown-5, 18-crown-6 and 21-crown-7, and the flexible acyclic ethers, including triglyme and tetraglyme, the proton may be partially or fully encapsulated, thus severely reducing the accessibility of 4,4′-bipyridine. For these latter cases, formation of proton-bound dimers with 4,4′-bipyridine is quenched.

Summary of proton-transfer reactions. The proton-transfer reactions generally reflect the relative gas-phase basicities of the ligands involved in the reaction; however, the reactions are slow for the multidentate ligands even when the difference in gas-phase basicities of the two ligands is substantial. Monitoring the formation of dominant proton-bound heterodimers during the proton-transfer reactions gives an insight into the occurrence of multiple coordinating interactions. Although the presence of dominant heterodimer complexes does not unambiguously indicate which ligand has a greater proton-binding capability, it provides evi-

dence that multiple hydrogen-bond formation is operative. Even when proton-bound heterodimer formation is dominant, the small amounts of direct proton transfer that occur between the pyridyl and polyether ligands still allow accurate assessment of the relative order of gas-phase basicities.

Collisionally activated dissociation of proton-bound dimers. Dissociation of proton-bound heterodimers gives information about the relative gas-phase basicities of the two molecules involved in the dimer at a significantly higher temperature obtained by energizing the dimer. At this higher, albeit poorly defined, temperature, the entropy term of the gas-phase basicity may play a substantial role,[24–27] especially for the dimers involving multidentate ligands. As noted in the ligand-exchange experiments, stable proton-bound heterodimers are typically formed as the difference in gas-phase basicities of the polyether and pyridyl ligands is not greater than 3 kcal mol^{-1}. In some special cases, heterodimers are formed even when the difference in gas-phase basicities is greater than 10 kcal mol^{-1}. For example, proton-bound dimers involving pyridine or 4,4′-bipyridine and each of the polyethers were consistently observed. Conversely, proton-bound dimers involving 2,2′,6,2-terpyridine and any of the polyethers were never observed. Proton-bound dimers involving, 1,10-phenanthroline or 2,2′-bipyridine were only observed with 21-crown-7 and 18-crown-6, and these dimers were of relatively low abundance. As mentioned earlier, one reason why dimers are observed for these latter cases may stem from the presence of multiple electrostatic interactions that slow the exothermic proton-transfer reactions between the ligands and allow time for collisional or radiative relaxation of the energized proton-bound intermediate.

Each proton-bound dimer was subjected to low-energy collisionally activated dissociation (CAD) and the fragment ion distributions are reported in Table 3. An example is shown in Fig. 4 for the dissociation of the [15-crown-5 + H^+ + 4,4′-bipyridine] dimer. In this example, loss of the 15-crown-5 molecule as a neutral species is dominant. For the dimers incorporating 4,4′-bipyridine and each of the polyethers except 21-crown-7, the dominant pathway involves loss of the polyether ligand. Two factors may contribute to this fragmentation behavior. First, dissociation of the dimer via loss of the polyether results in a substantial gain in entropy due to the increase in the rotational and vibrational degrees of freedom of the neutral polyether as the electrostatic interactions between the proton and oxygen atoms are broken. There is no corresponding significant increase in entropy when the 4,4′-bipyridine molecule is released as a neutral because it acts as a monodentate ligand. Second, the intrinsically large proton binding strength of the polyethers may be perturbed when sharing the proton with another ligand. Hence, the natural ability of the polyether to encapsulate or surround the proton is impeded when the proton is hooked to another bulky ligand, such as 4,4′-bipyridine.

In contrast to the observed preferential loss of the polyether ligand for the heterodimers described above, the [4,4′-bipyridine + H^+ + 21-crown-7] complex exhibits a different dissociation behavior. For CAD of the [4,4′-bipyridine + H^+ + 21-crown-7] dimer, loss of 4,4′-bipyridine is the dominant pathway. In this latter case, the proton affinity of 21-crown-7 is estimated to be $\sim$ 12 kcal mol^{-1} greater than that of 4,4′-bipyridine, thus giving 21-crown-7 a sufficiently great proton-binding strength in the dimer to overcome any entropic losses.

Entropic factors. The influence of entropic factors on CAD results has been addressed recently.[24–27] In an extensive investigation of the alkali metal ion affinities of a series of DNA and RNA nucleobases in the gas

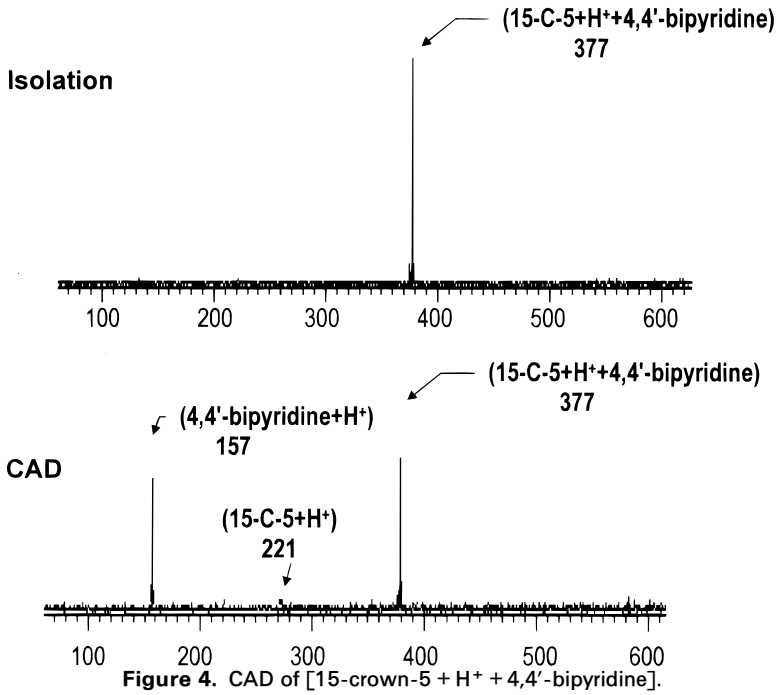

Figure 4. CAD of [15-crown-5 + H^+ + 4,4′-bipyridine].

phase as reflected by dissociation of metal-bound heterodimers, Cerda and Wesdemiotis[26] reported that rotational entropy changes during fragmentation of the heterodimers played a critical role in determining the preferred dissociation pathways. Any fragmentation pathway which resulted in an increase in rotational freedom of the products was more enhanced relative to others that did not result in an increase in rotational freedom. Thus, pathways that released multi-site coordination interactions were especially favored.[26] Although the present study does not involve metal chelation interactions, one can imagine that the coordination of the proton may incorporate numerous electrostatic solvating interactions involving the bond dipoles of the free ether groups of the polyether, thus severely limiting the rotational and vibrational degrees of freedom of the polyether ligand. In contrast, the nitrogen atoms of a monodentate pyridyl ligand such as 4,4′-bipyridine cannot interact simultaneously with the proton, so no losses of rotational freedom are incurred when it binds the proton. Upon dissociation of a proton-bound heterodimer such as [polyether + H^+ + 4,4′-bipyridine], cleavage of the electrostatic bonds between the proton and the polyether leads to a large gain in the rotational and vibrational degrees of freedom of the polyether, so there is a substantial increase in entropy for this pathway. This entropic gain would create a natural enhancement of this fragmentation route. The combination of this factor (gain in entropy) along with the high proton affinity of 4,4′-bipyridine and the restricted proton-binding capability of the polyethers in the dimer complexes promotes the dissociation of the proton-bound heterodimers by loss of the polyether ligand.

A similar rationalization may be used to explain the CAD results for the proton-bound heterodimers containing pyridine and the polyethers. For example, the [pyridine + H^+ + 18-crown-6] dimers predominantly dissociate via elimination of the polyether molecule despite the fact that the proton affinity of pyridine is ~ 9 kcal mol^{-1} *less* than that of 18-crown-6.[5] The loss of the polyether molecule as a neutral species allows a gain in rotational and vibrational freedom as the electrostatic interactions between the ether dipoles and proton are broken. In addition, the intrinsic proton binding strength of 18-crown-6 may be partially impeded by the attachment of the proton to the pyridine ligand in the dimer complex. Thus, for the dissociation of the [18-crown-6 + H^+ + pyridine] dimer, the distribution of [pyridine + H^+] and [18-crown-6 + H^+] ions does not accurately reflect the proton affinities of the ligands because of the more dominant entropic influences. For the [pyridine + H^+ + 21-crown-7] dimer, the elimination of pyridine is the dominant loss. The proton affinity of pyridine is estimated to be at least 12 kcal mol^{-1} less than that of 21-crown-7, so at this point the tremendous difference in intrinsic proton-binding strengths of the two ligands appears to play the dominant role in the dissociation kinetics.

CAD of heterodimers incorporating two multidentate ligands. The [18-crown-6 + H^+ + 2,2′-bipyridine], [18-crown-6 + H^+ + 1,10-phenanthroline], [21-crown-7 + H^+ + 2,2′-bipyridine] and [21-crown-7 + H^+ + 1,10-phenanthroline] dimers are interesting cases because each ligand is multidentate. Substantial rotational restrictions are expected when 2,2′-bipyridine, but not 1,10-phenanthroline, is bound to the proton, and both rotational and vibrational restrictions occur when the polyethers bind to the proton. For each of these heterodimers, the CAD spectra indicate that the elimination of the neutral polyether ligand is the favored process, and the proton predominantly remains associated with the pyridyl ligand. The entropic factors associated with the complexation of the proton by the polyether must play a larger role in influencing the favored dissociation pathways because the presence of 2,2′-bipyridine or 1,10-phenanthroline does not create a significant difference despite the fact that 1,10-phenanthroline is a rigid bidentate molecule whereas the two pyridine rings of 2,2-dipyridine have rotational freedom. 2,2′-Bipyridine and 1,10-phenanthroline both have intrinsic proton-binding capabilities that are estimated to be 5–11 kcal mol^{-1} higher than that of 18-crown-6, so it is not surprising that these pyridyl ligands demonstrate a greater ability to retain the proton during the dissociation of the dimers, even if entropic factors are also operative.

An interesting comparison is the case in which the gas-phase basicity of the polyether is known to be greater than that of the bidentate pyridyl ligand at the lower temperature of the ligand-exchange experiment. The gas-phase basicity of 21-crown-7 is estimated to be 2–4 kcal mol^{-1} greater than that of 2,2′-bipyridine based on the previous ligand-exchange experiments. In this case, CAD of the [12-crown-7 + H^+ + 2,2′-bipyridine] dimer still yields predominantly protonated 2,2′-bipyridine (95%) and only a minor amount of protonated 21-crown-7 ($\sim 5\%$). When binding to the proton in the heterodimer, the large, floppy 21-crown-7 ligand must undergo extensive organization to maximize its dipole interactions with the proton. Thus, the release of numerous rotational and vibrational degrees of freedom occurs upon loss of the 21-crown-7 ligand relative to loss of 2,2′-bipyridine. The temperature of the dimers attained in the CAD experiments is higher than the temperature of the protonated molecules in the ligand-exchange reactions, thus giving the entropy term greater significance and creating the observed reversal in the proton-binding properties of the ligands.

Summary of CAD results. In general, the CAD results provide one way of gauging the extent of entropic effects when generating large, loosely bound complexes and also allow examination of how the proton-binding strengths of ligands are modified when the ligands are bound in supramolecular structures. Although CAD can provide some insight into the factors which influence the proton-binding strengths of ligands in dimers, several general issues emerge when using CAD (i.e. the kinetic method) to estimate directly the relative proton affinities of polydentate ligands. Owing to the severe impact of entropic effects upon dissociation of the dimers, the ratio of product ions does not reflect the order of proton affinities of the ligands involved in the dimer. This effect is especially significant when one of the ligands is floppy and multidentate whereas the other is rigid or monodentate. For example, the elimination of the polyether ligand from proton-bound complexes involving pyridine or 4,4′-bipyridine releases

a great deal of the rotational and vibrational restrictions created by the large degree of organization of the polyether during its electrostatic solvation of the proton. The loss of the polyether is highly favored owing to the concomitant gain in entropy.

Comparison of proton transfer and metal complexation reactions

As mentioned in the Introduction, we have already completed an extensive study of the ligand-exchange and CAD reactions of polyether and pyridyl complexes.[33] Because this study involved the same ligands but a different type of cation, comparison of the general trends observed for the two types of systems allows an assessment of whether the factors that influence proton-binding affinities also influence metal-binding strengths in the same way. For example, the ligand-exchange reactions involving the polyethers and pyridyl ligands show that the orders of metal-binding affinities and proton-binding strengths do not agree. The order of metal-binding affinities is 2,2,6′,2-terpyridine > 18-crown-6 > tetraglyme > 15-crown-5 ≈ triglyme > 2,2′-bipyridine > 12-crown-4 > diglyme ≥ 4,4′-dipyridine > monoglyme and the order of gas-phase basicities is 2,2,6′,2-terpyridine > 2,2′-bipyridine > 18-crown-6 > tetraglyme > 15-crown-5 > 4,4′-bipyridine > triglyme > 12-crown-4 > diglyme > monoglyme. The most notable differences occur with the relative placement of 2,2′-bipyridine and 4,4′-bipyridine. 4,4′-Bipyridine and 2,2′-bipyridine have greater proton-binding strengths relative to their corresponding metal-binding strengths.

In cases which allowed comparison of the CAD spectra of the analogous metal-bound and proton-bound heterodimer complexes, the favored fragmentation pathways of the dimer complexes were strikingly different. For example, the [18-crown-6 + H^+ + 2,2′-bipyridine] complexes dissociate exclusively by loss of 18-crown-6, whereas the [18-crown-6 + M^+ + 2,2′-bipyridine) (where M is Co, Ni or Cu) dissociate exclusively by loss of 2,2′-bipyridine. The [12-crown-4 + H^+ + 4,4′-bipyridine] complexes dissociate by loss of 12-crown-4, whereas the [12-crown-4 + M^+ + 4,4′-bipyridine] complexes dissociate by elimination of 4,4′-bipyridine. In all comparable cases, loss of the neutral *polyether* moiety occurs for the proton-bound heterodimers, but loss of the neutral *pyridyl* ligand occurs for the metal-bound heterodimers. These contrasting CAD results confirm that the kinetically favored fragmentation pathway for the metal complexes is opposite to that for the protonated complexes.

Most of the differences in the behaviors between the proton-transfer results and the metal complexation results can be rationalized based on the difference in size, charge density and coordination symmetries of the cations. Because the monopositive metal ions are larger and less charge dense than the proton, each individual binding interaction between a donor atom of a pyridyl or polyether ligand and the metal ion is weaker and the metal–ligand bonds are longer than for the protonated complexes, factors which reduce the overall influence of ligand–ligand repulsions in the metal complexes, increase the degree of accessibility to the metal ion when it is bound by only a single ligand and favor certain binding geometries that involve multiple electrostatic interactions with polydentate ligands. Protons are small with high charge densities, and favor coordination by formation of proton bridges (i.e. two interactions between the proton and two donor sites) or single strong bonds with highly basic sites such as nitrogen atoms. These different binding characteristics lead to protonated complexes that favor the more rigid, nitrogen donor ligands and metal complexes that favor the more flexible polyethers that may be better able to adopt the most favorable orientation of multiple ether bond dipoles. For example, the two highly basic nitrogen atoms of 2,2′-bipyridine can cooperatively bind a proton, resulting in an exceptionally stable complex that is not readily deprotonated by any multidentate oxygen-containing ligand. In contrast, 2,2′-bipyridine can still cooperatively bind a metal ion, but the larger size of the metal cation relative to the proton allows greater accessibility to the [2,2′-bipyridine + M^+] complex for displacement of 2,2′-bipyridine by a flexible tetradentate or pentadentate ligand, such as triglyme, 15-crown-5 or 18-crown-6. A similar rationalization explains the differences in proton-binding and metal-binding affinities of 4,4-bipyridine. 4,4-Bipyridine can bind the proton to one of its highly basic nitrogen atoms, forming a complex that cannot be deprotonated by triglyme or 12-crown-4. In contrast, the [4,4′-bipyridine + M^+] complex contains only one nitrogen–metal bond, and the metal cation remains highly accessible to more favorable coordination by the flexible multidentate polyethers such as triglyme or 12-crown-4.

CONCLUSIONS

Ligand-exchange reactions and CAD experiments provide a qualitative insight into the influence of entropic factors on proton-binding strengths of multidentate ligands. Despite the relative large difference in the proton affinities and gas-phase basicities of some of the larger polyethers (i.e. 18-crown-6 and 21-crown-7) and the bidentate pyridyl ligands (i.e. 1,10-phenanthroline and 2,2′-bipyridine), the formation of mixed dimer complexes occurs because the large crown either ligands are such flexible, polarizable ligands that the exothermic proton transfer processes are slowed. Because of their flexibility in orienting the bond dipoles of their ether groups, the large polyethers can stick to the [pyridyl ligand + H^+] complexes for a sufficient amount of time that the intermediate [pyridyl ligand + H^+ + crown ether] complexes undergo radiative or collisional relaxation, thus stabilizing the otherwise energetic complexes. The sizes and flexibilities of 18-crown-6 and 21-crown-7 clearly play an essential role because the smaller polyethers, such as 12-crown-4 and triglyme, can only form mixed dimers when the difference in gas-phase basicities of the polyether and pyridyl ligand is $\leqslant 3$ kcal mol^{-1}, suggesting more restrictions in the ability to stabilize the proton-bound heterodimer complexes. The great polarizabilities and flexibilities of 18-

crown-6 and 21-crown-7 enhance their capability for long-range persistent and mobile electrostatic interactions with the proton. The CAD results provide one way of gauging the extent of entropic effects when generating large, loosely bound complexes and also allows examination of how the proton-binding strengths of ligands are modified when the ligands are bound in supramolecular structures. Owing to the severe impact of entropic effects upon dissociation of the dimers involving any multidentate ligand, the ratio of product ions does not reflect the order of intrinsic proton affinities of the ligands involved in the dimer. This concern is especially significant when one of the ligands is floppy and multidentate while the other is rigid or monodentate. The loss of the polyether is highly favored owing to the concomitant gain in entropy as rotational and vibrational degrees of freedom are released. In large non-covalently bound supramolecular complexes, entropic effects may likewise dominate the fragmentation behavior, and thus interpretation of dissociation patterns to predict accurately binding sites or binding affinities should be assisted by the use of auxiliary techniques such as ligand-exchange reactions.

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