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Direct Evidence for Arylmethyl Ether Coordination of Sodium and Potassium Cations: An Electrospray Ionization Mass Spectrometry Study

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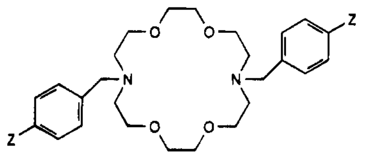
Abstract: Evidence is presented for complexation between sodium and potassium cation (1 mM) and the simple ethers dibenzyl ether, bis(*p*-methoxybenzyl) ether, bis(*p*-nitrobenzyl) ether, or bis(ferrocenylmethyl) ether (concentration 0.01−10 mM). Complexation was assessed by electrospray ionization mass spectrometry of chloroform−methanol solutions of the ethers and cations. Adducts of the type $[\text{ether}\cdot\text{cation}]^+$ and $[\text{ether}_2\cdot\text{cation}]^+$ were observed for each of the ethers along with $[CH_3OH\cdot\text{cation}\cdot\text{ether}]^+$. These species presumably arise from the chloroform−methanol solvent but $[CH_3OH\cdot\text{cation}\cdot\text{ether}]^+$ are never dominant. A clear correlation of adduct stability with ether donicity was observed and suggests that complexation between ethers and cations can be assessed quantitatively by this technique.

Alkali metal cations, especially sodium and potassium, in concert with the alkaline earth cations magnesium and calcium, are the predominant cations found in living systems. How they are bound, transported, and selected are issues of profound importance in biology.[1] The advent of crown ether chemistry[2] nearly thirty years ago afforded the possibility of forming stable complexes of these cations with uncharged donors and directly examining cation−donor group interactions. Much effort has been expended in order to understand in general the factors that control cation recognition and transport by macrocycles. The recent focus of interest within the biological community on the mechanisms by which transmembrane proteins regulate cation flux reinforces the need for understanding basic cation complexation and selectivity mechanisms.[1] Although this need is general, few studies of cation−ether complexation have been undertaken outside of crown ether chemistry because the individual ether−cation interactions are weak and therefore difficult to assess.[3]

One of the limitations that is faced in experimental assessments of cation complexation strengths and selectivities[4] is the solvent in which the system is studied. In the crown ether case, for example, it has been known for many years that the strength of cation complexation depends upon the solvent in which the reaction occurs.[5] Generally speaking, for the same crown and salt, the interaction between them is strongest in the least polar solvent although differing solubilities may make it troublesome to assess complexation by the same method with different cations in a broad range of solvent polarities.[6] Indeed, recent work has shown that anion dependence may be an issue as well.[7]

When studies are conducted in a single solvent or solvent mixture, it has been found that complexation strength follows ether donicity. Indeed, examples of crown ether systems that



obey the Hammett relationship have been reported.[8] In order to make such assessments, however, sufficient overall cation binding strength is required by the macrocycle for complexation measurements to be possible. As a result, the Lewis basicities of donor groups can normally be varied only at one or two of multiple donor sites before either binding strength falls below the range of the assessment technique or the structural variations so complicate synthetic access that the compounds become troublesome to obtain. For example, in the diaza-18-crown-6 system shown, the benzyl substituents on nitrogen were varied but the oxygen donors were unaltered.

During recent years, mass spectral techniques have proved useful in the assessment of cation−ligand interactions.[9] In particular, mass spectrometry has been used to evaluate crown-cation complexation in the absence of bulk solvent. The results of these inquiries have sometimes closely paralleled solution studies but at times other trends were apparent.[10] Most important, however, is that the mass spectral technique has permitted the assessment of cation binding interactions[11] in such complex binders as tris(crown ethers) that could not be evaluated

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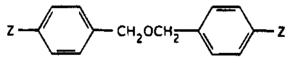
in other, more traditional ways.[12] The advent of mass spectral analytical methods in general and electrospray ionization mass spectrometry (ESI-MS) in particular[13] has proved to be useful in assessing complexation interactions. The FAB-MS and ESI-MS techniques are especially serviceable analytical tools for the evaluation of non-covalent interactions. Recent successes with these techniques include the study of non-covalent complexes,[14] aqueous solutions of metal salts,[15] charged clusters of amino acids,[16] peptide–metal ion interactions in solution,[17] bipyridyl amino acid–metal complexes,[18] alkali metal binding by valinomycin,[19] hydration of doubly protonated diamines,[20] and even the analysis of human erythrocyte plasma membrane phospholipids.[21]

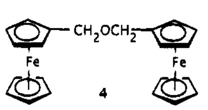
We report here the application of electrospray ionization mass spectrometry to study the interaction of sodium cation with four ethers (**1**–**4**) of the form $(Ar\text{-}CH_2)_2O$. In one case, the aryl residue is ferrocene which we have previously shown can directly interact with silver cation by using the iron atom as a donor group.[22] We describe here the use of the ESI-MS technique to give the first insight into the selective formation of sodium and potassium complexes of simple ethers.



1, Z = H

2, Z = OCH3

3, Z = NO2



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Results

Compounds Studied. Dibenzyl ether, (**1**) was obtained commercially. Bis(4-methoxybenzyl) ether, (**2**) was prepared by a somewhat unusual reaction. A 16:1 molar ratio of the alcohol, $CH_3OC_6H_4CH_2OH$, and dimethyl sulfoxide was heated at *ca.* 175 °C for 30 min. The ether, **2**, was isolated by chromatography in 76% yield.[23] Bis(4-nitrobenzyl) ether, (**3**) was prepared by standard sulfuric acid catalyzed dehydration of 4-nitrobenzyl alcohol to afford 22% of the product as a white solid.[24] Bis(ferrocenylmethyl) ether, (**4**) was isolated as a yellow solid from the reaction of ferrocenecarboxaldehyde with $NaBH_4$. We presume in the latter reaction that reduction of the aldehyde affords, at some stage, the very stable ferrocenylmethyl carbocation which is intercepted by a molecule of hydroxymethylferrocene or its anion. It should be noted that the latter compound has previously been prepared in a more traditional fashion by briefly shaking ferrocenylmethanol with HCl. The ferrocenylmethyl carbocation's stability permits this symmetrical ether synthesis reaction to be conducted at room temperature.[25]

Cation Complexation. Solutions were prepared of compounds **1**–**4** at concentrations from 0.01 to 10 mM in a chloroform–methanol (1:4 v/v) mixture. The solvent system was selected because it provided an appropriate combination of solubility for the ethers and for the salts. Either sodium or potassium chloride was added to make each solution 1 mM in salt.

The electrospray ionization (ESI) mass spectra were acquired on a triple quadrupole tandem mass spectrometer equipped with an electrospray interface. Details of the electrospray ion source have been reported previously[26] and additional information may be found in the Experimental Section. The temperature of N_2 drying gas was set at 100 °C and the gas was held at a constant pressure (25 psi) as it entered the electrospray chamber. Signal was averaged for a period of 4 min for each spectrum. Sample solutions (~25 °C) were infused directly into the ESI chamber by syringe pump (rate = 2 μL/min).

Electrospray ionization mass spectra were then acquired for each of the solutions.[27] Figures 1–4 show the spectra obtained for compounds **1**–**4** at [ether] = [NaCl] = 1 mM. In each case, the spectra reveal three major peaks. These correspond to (i) $[ether{\cdot}Na]^+$, (ii) $[ether{\cdot}Na{\cdot}CH_3OH]^+$, and (iii) $[ether_2{\cdot}Na]^+$.

Sodium Binding by Ethers. In Table 1 are shown the data[28] obtained for each of the four ethers (**1**–**4**) in the presence of either sodium or potassium cation. The concentration of each ether was varied as follows: 0.01 mM, 0.1 mM, 1.0 mM, and 10 mM. In each case, only three significant peaks were

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(28) A number of duplicate runs are included in Table 1 so that the quality of the data obtained can be evaluated. For the most part, experimental error is ≤±5%. The absence of an entry indicates that the experiment was not done for that ether at that concentration. The most significant variation in data is observed in two experiments conducted with **2** (1 mM) and K^+.

Table 1. Peak Intensity Data for ESI-MS Analyses of Ethers with Sodium and Potassium Cations[a]

ion[c]	0.01 mM[b]		0.1 mM[b]		1.0 mM[b]		10 mM[b]	
	$[LX]^+$	$[L_2X]^+$	$[LX]^+$	$[L_2X]^+$	$[LX]^+$	$[L_2X]^+$	$[LX]^+$	$[L_2X]^+$
			X = Na					
$(PhCH_2)_2O$ (**1**)	100	8.32	100	12.84	100	69.82	8.52	100
			100	11.25				
$(CH_3OC_6H_4CH_2)_2O$ (**2**)	100	37.91	71.39	100	42.84	100		
	100	37.60	71.09	100	45.49	100		
$(O_2NC_6H_4CH_2)_2O$ (**3**)	100	0	100	12.34	100	21.49	100	32.08
			100	9.48	100	19.71	100	35.38
$(C_{10}H_9FeCH_2)_2O$ (**4**)	100	42.85	48.83	100	20.25	100		
	100	35.85	54.85	100	19.51	100		
			X = K					
$(PhCH_2)_2O$ (**1**)			100	6.98	100	36.15	83.72	100
			100	8.53	100	38.79	75.86	100
$(CH_3OC_6H_4CH_2)_2O$ (**2**)	100	18.88	100	66.80	100	99.86	57.40	100
	100	16.24	100	63.83	85.53	100	46.44	100
$(O_2NC_6H_4CH_2)_2O$ (**3**)			100	19.45	100	28.41	100	33.07
			100	21.86	100	27.44	100	33.11
$(C_{10}H_9FeCH_2)_2O$ (**4**)			100	71.91	52.90	100	42.07	100
							33.97	100

[a] Solvent is 20% (v/v) chloroform in methanol. [b] Ether (designated L for ligand) concentration was varied; cation concentration was held at 1.0 mM. [c] The molecular weight observed corresponds to the structure of the ion shown.

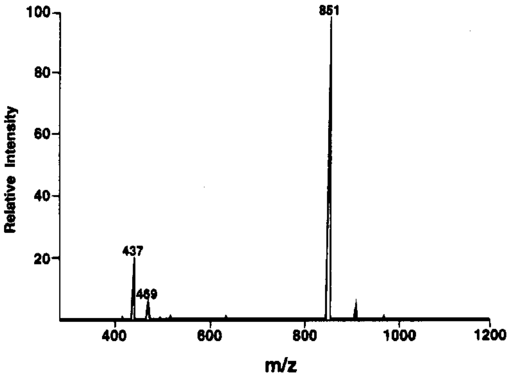

Figure 1. ESI-MS spectrum of bis(ferrocenylmethyl) ether (**4**) in 1:4 (v/v) $CHCl_3-CH_3OH$ containing NaCl.

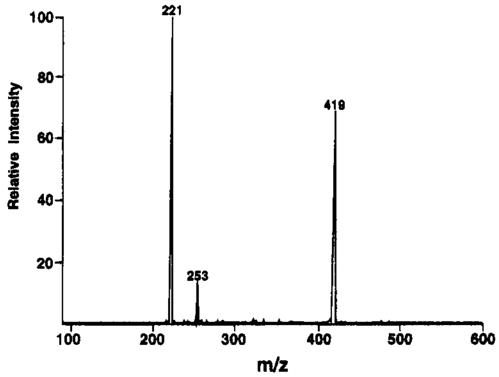

Figure 2. ESI-MS spectrum of dibenzyl ether (**1**) in 1:4 (v/v) $CHCl_3-CH_3OH$ containing NaCl.

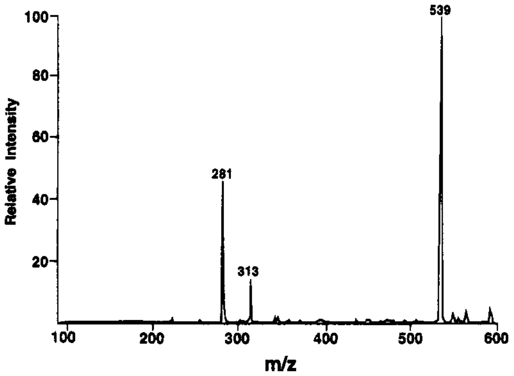

Figure 3. ESI-MS spectrum of bis(4-methoxybenzyl) ether (**2**) in 1:4 (v/v) $CHCl_3-CH_3OH$ containing NaCl.

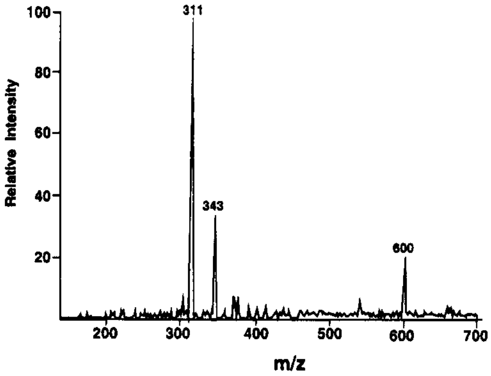

Figure 4. ESI-MS spectrum of bis(4-nitrobenzyl) ether (**3**) in 1:4 (v/v) $CHCl_3-CH_3OH$ containing NaCl.

observed. These were [ether•Na]$^+$, [ether•CH_3OH•Na]$^+$, and [ether$_2$•Na]$^+$. In all cases, either [ether•Na]$^+$ or [ether$_2$•Na]$^+$ was the base peak. The intensity of [ether•CH_3OH•Na]$^+$ did not exceed the intensities of the [ether•Na]$^+$ or [ether$_2$•Na]$^+$ peaks in any case.

The first set of experiments was conducted on samples in which the concentration of ethers **1**–**4** was 0.01 mM in each case and [Na$^+$] was maintained at 1.0 mM. In this group of experiments, the ether (referred to hereinafter as **L** for ligand) was present in solution in only 1/100 the concentration of Na$^+$. In all cases, [**L**•Na]$^+$ was the base peak. The amount of dimer [**L**$_2$•Na]$^+$ formed from each ether varied in the order of its electron richness, *i.e.* **4** ≥ **2** >**1** > **3**. For the most electron poor ether (weakest donor), no simple ether complex ([**3**•Na]$^+$) was observed.

When the ether concentration was increased 10-fold from 0.01 to 0.1 mM ([Na$^+$] held constant at 1.0 mM), a different, but related, profile was observed. The base peak in the case of the two strongest donors, bis(ferrocenylmethyl) ether, (**4**) and bis(*p*-methoxybenzyl) ether, (**2**) corresponded to [ether$_2$•Na]$^+$. For the weaker donors, *i.e.*, dibenzyl ether (**1**) and bis(*p*-nitrobenzyl) ether (**3**), [ether•Na]$^+$ was the base peak. It is interesting to note the intensities of the peaks in this case. Since [ether•Na]$^+$ was the base peak for **1** and **3**, the intensity order for this complex is **1** (100%) = **3** > **2** > **4**. The peak intensities for $[ether_2{\cdot}Na]^+$ decreased in the following order: **2** (100%) = **4** > **1** ≈ **3**.

When the concentrations of ether and Na^+ were equal (both 1.0 mM), a trend similar to that described above was observed. Again, for poorer donors **1** and **3**, $[ether{\cdot}Na]^+$ was the base peak and the intensity order for $[ether{\cdot}Na]^+$ was found to be **1** (100%) = **3** > **2** > **4**. Note that the exact peak intensities for the complexes of **2** and **4** differed somewhat from the values observed in the previous experiment. The peak intensities for $[ether_2{\cdot}Na]^+$ decreased in the following order: **2** (100%) = **4** > **1** > **3**. Indeed, the intensity of the $[\mathbf{1}_2{\cdot}Na]^+$ ion was about 70% of that observed for the $[\mathbf{1}{\cdot}Na]^+$ ion. The intensity ratio for the $[L_2{\cdot}Na]^+$ peaks for compounds **1** and **3** was about 3.5:1.

The data set obtained when the concentration of ether:Na^+ was 10:1 is too limited to discern any significant trend. It should be noted, however, that for dibenzyl ether (**1**), the monomer:dimer ratios are essentially inverted from the situation when only 0.01 mM ether was present.

Potassium Binding by Ethers. The experiments recorded in this section of Table 1 were conducted exactly as described above except that KCl replaced NaCl. As above, ether concentration was varied over the range 0.01−10 mM while the KCl concentration was held constant at 1.0 mM.

The data set for 0.01 mM ether in the potassium case is limited to bis(*p*-methoxybenzyl) ether, (**2**). As in the sodium case, $[L{\cdot}K]^+$ is the base peak and the ion corresponding to $[L_2{\cdot}K]^+$ is only about one-fifth as intense. In the sodium case, the dimer ion is about one-third as intense as the monomer base peak.

When the ether concentration is 0.1 mM, the base peak corresponds to $[L{\cdot}K]^+$ in all cases. The dimer ($[L_2{\cdot}K]^+$) peak intensities decrease in the order **2** ≈ **4** > **3** > **1**. Although the intensity values for **3** are about twice that of **1**, both are low. If they are considered to be similar, then the trends in both the sodium and potassium cation cases are similar at this ether concentration.

When the potassium and ether concentrations are both 1 mM, the monomer ion ($[L{\cdot}K]^+$) dominated in the cases of the weaker donors (**1**, **3**) as was the case for Na^+. In contrast to the sodium case, however, about equal amounts of monomer and dimer were observed for bis(*p*-methoxybenzyl) ether (**2**). As in the sodium case, $[(FcCH_2)_2O{\cdot}K{\cdot}O(CH_2Fc)_2]^+$ was the preferred ion by about 2:1 over monomer.

Comparisons at 10 mM ether concentration between the sodium and potassium cases are rendered difficult by the relative lack of data for the former case. Nevertheless, we note that monomer predominates and there is an almost identical monomer/dimer ratio for bis(*p*-nitrobenzyl) ether (**3**). For the other ethers, dimer is the base peak.

An experiment was also conducted in which a mixture of compounds **1**, **2**, and **3** (each 1 mM) was dissolved in 20% (v/v) $CHCl_3-CH_3OH$ along with 1 mM NaCl. In the mass range 150−750, only five peaks were observed which had intensities >20%. These were observed at *m/z* values (rounded to whole numbers) of 221, 281, 419, 479, and 539. The peaks at 221 and 281 correspond to monomer peaks $[L{\cdot}Na]^+$ for dibenzyl (**1**) and bis(*p*-methoxybenzyl) ethers (**2**). The peaks observed at *m/z* values of 419 and 539 are assigned as the corresponding dimer peaks $[L_2{\cdot}Na]^+$. The peak at *m/z* = 479 corresponds to $[(C_6H_5CH_2)_2O{\cdot}Na{\cdot}O(CH_2C_6H_4OCH_3)_2]^+$. None of the major peaks appear to derive from the nitro-substituted ether. Note also that the ferrocenyl system, expected to be the strongest donor, was not included in this experiment.

Two additional experiments deserve mention. 1,4-Dinitrobenzene, bis(4-nitrobenzyl) ether, and sodium chloride were dissolved in 20% chloroform in methanol to form a solution having concentrations of 1 mM in each species. The ESI-MS spectrum obtained from said solution showed only peaks which were associated with bis(4-nitrobenzyl) ether, and no peak attributable to 1,4-dinitrobenzene was observed. A similar experiment was done using 1,4-dimethoxybenzene and bis(4-methoxybenzyl) ether. No ion that appeared to contain 1,4-dimethoxybenzene was detected.

Table 2. Relative Intensity Ratios $[(ether)_2 + Na]^+/[ether + Na^+]$ vs Monomer Concentration[a]

	[ether] (mM) in 20% (v/v) $CHCl_3$/MeOH			
	0.01	0.1	1	10
$(C_5H_5FeC_5H_4-CH_2)_2O$ (**4**)	0.51	2.51	6.52	
$(p\text{-}CH_3O-C_6H_4-CH_2)_2O$ (**2**)	0.44	1.62	2.61	
$(C_6H_5CH_2)_2O$ (**1**)	0.09	0.14	0.79	13.33
$(p\text{-}O_2N-C_6H_4-CH_2)_2O$(**3**)	0	0.12	0.23	0.38

[a] $[Na^+]$ = 1 mM; data are corrected for isotope composition.

The relative intensity values have been calculated for $[ether_2{\cdot}Na]^+/[ether{\cdot}Na]^+$ and are set forth in Table 2.

Discussion

Several things are clear from the results. No sodium or potassium complexes of the type $[(CH_3OH)_n{\cdot}M]^+$ were observed in any spectrum under the current experimental conditions although mixed ions of the composition $[ether{\cdot}Na{\cdot}CH_3OH]^+$ were apparent. This seems remarkable at first since the concentration of methanol is many-fold that of any ether at any concentration surveyed. The absence of multiple methanol adducts may simply be due to the fact that volatile solvent is stripped off as the sample enters the probe. If a significant amount of methanol remains, such ions might be absent anyway because the stabilization provided by multiple hydrogen bonds could prevent the vaporization of such an ion from what would be essentially a bulk methanol phase.

The most general observation that can be made is that the appearance of sodium or potassium complexes appears to parallel the donicities of the ethers. Each of the four ethers has more than one donor site. The aromatic rings could, in principle, serve as donors for Na^+ and K^+.[29] In the present context, we expect this to be a weak interaction relative to the Lewis basic donor interactions of oxygen. The nitro group oxygens are also notably weak donors.[30] As noted above, ferrocenyl iron can serve as a donor but strong interaction was observed for silver rather than either Na^+ or K^+.[22] This leaves only 4-bis(methoxybenzyl) ether. The issue in this case is which of the two oxygens will serve as donor to the cation. The CH_3-OAr oxygen will be sp^2 hybridized and less basic that the $ArCH_2OCH_2Ar$ oxygen. Moreover, the aromatic ring hinders access to the oxygen whereas the dialkyl ether oxygen is more accessible.

One way to assess electron richness or Lewis basicity is by using the Hammett equation. The Hammett constants (σ_p) for *p*-nitro, *p*-hydrogen, and *p*-methoxy are +0.78, 0, and −0.27, respectively. To our knowledge, no Hammett constant is available for ferrocene, but the latter is known to undergo Friedel−Crafts acylation approximately 10^6-fold faster than benzene.[31] Considering compounds **1**−**3**, the nitro-substituted ether should be a poorer donor than dibenzyl ether and the

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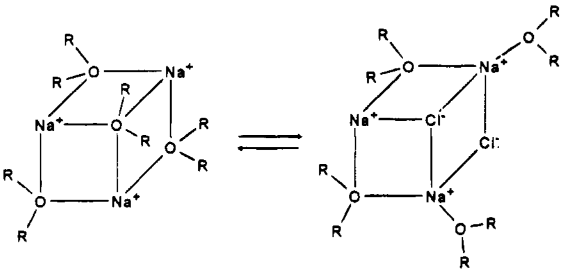

Figure 5. Postulated cubic aggregate of sodium cations and ether molecules.

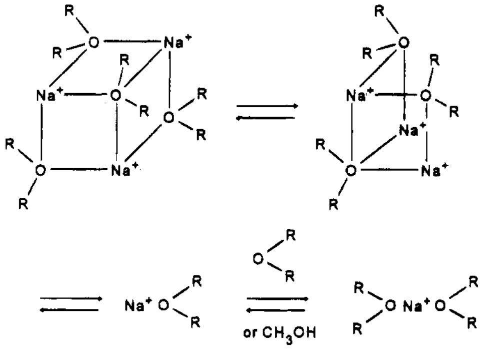

Figure 6. Postulated fragmentation of Na$^+$•ether aggregates.

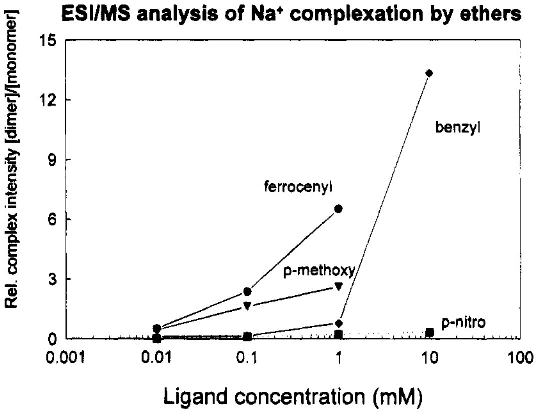

Figure 7. Graph of Table 2 data set.

methoxy-substituted system should be stronger. Bis(ferrocenylmethyl) ether should be the best donor of the four giving an overall donicity order of **4** > **2** > **1** > **3**.

In order to evaluate the observed spectra in relation to the dynamics of the system, a number of equilibria must be considered. The mixture of chloroform and methanol is relatively nonpolar and the ion pairs are almost certainly clustered in solution. Aggregates of cations, anions, the ether ($ArCH_2OCH_2Ar$), and chloride anions are all likely and likely in all proportions. An example of the possibilities is shown in Figure 5. In this figure is represented two arbitrary aggregated systems,[32] each based upon the cubic geometry known for sodium chloride and surmised for aggregated bases.[33] It is now known, in part from the work of Williard and co-workers,[34] that structurally well-defined aggregates of the type suggested here exist in the solid state and that these structures correlate well with observations made in solution-phase studies.

In the case of a tetrameric, cubic aggregate containing four cations and four counterions such as *tert*-butoxide, the base would normally be neutral and therefore invisible to the ESI-MS technique. In the present case the cations may be solvated by ethers, methanol, or chloride but can be neutralized only by the latter.

In Figure 6 is shown a hypothetical, symmetrical aggregate (at the left) which may dissociate by loss of a Na$^+$ adduct. Such a complex may take many forms. Statistically, the most likely aggregate is $(CH_3OH)_n$•Na$^+$•Cl$^-$, but because it is neutral overall, it will not be detected by mass spectrometry. Sodium methoxide is also overall neutral and undetectable by this method although its formation is unlikely in this dilute, neutral, and poorly ionizing solution. A sodium or potassium complex containing several methanol molecules also seems quite likely but it is not detected in these experiments. In contrast, $[Na(EtOAc)_n]^+$ ions were apparent when a solution of NaCl in 1% EtOAc–MeOH was analyzed. This suggests that the absence of $[Na(CH_3OH)_n]^+$ peaks is due simply to solvent stripping during the ionization process. A chemical, rather than physical, explanation is that the complex $Na^+(CH_3OH)_n$ contains *n* hydrogen bonds, each of which must be broken for the ion to be released from the bulk phase. In water or methanol, these hydrogen bonds are expected to have energies of 3–5 kcal/mol. Breaking six of them would require an energy of at least 18 kcal/mol. None of the figures shows the mass region corresponding to $[(CH_3OH)_2{\cdot}Na]^+$ (m/z = 87) but the ion was not observed in any spectrum. Likewise, no significant (clearly discernible from baseline noise) ion could be detected at m/z = 215, the molecular weight corresponding to $[(CH_3OH)_6{\cdot}Na]^+$.

In attempting to decide whether the predominant equilibrium being detected is dissociation of the aggregate in solution or its release into the gas phase, the question must be asked whether there is any clear trend apparent in the results disclosed here. In each case, the three ions noted above, *i.e.* [ether•Na]$^+$, [ether•Na•CH$_3$OH]$^+$, and [ether$_2$•Na]$^+$, are observed in differing amounts. The ratio of dimer to monomer for the sodium complexes at all ether concentrations is in the order **4** > **2** > **1** > **3** (Figure 7). The "electron richness" of the substituent R on $(RCH_2)_2O$ decreases in the same order. Thus, the amount of [ether$_2$•Na]$^+$ observed and its relative intensity compared to [ether•Na]$^+$ correlate with the donicity of R.

If the clusters of cations and anions exist in solution, it is expected that those ethers which are most effective at solvating either sodium or potassium cation would be most successful at dislodging the cation from the aggregate. Sodium and potassium cations both bear a single positive charge but their diameters are ≈2.0 and 2.6 Å, respectively. The former is thus more charge dense and requires greater solvation for stabilization. We note that when potassium rather than sodium was studied, the dominant ion at [ether] = 0.1 mM was ROR•K$^+$.

Because cation concentration was held constant throughout the study, the effect of ether variation can be assessed directly. We have noted above (*see* Results) the order of peak intensities for each cation at different ether concentrations. The calculated relative intensity ratios for $[L_2{\cdot}Na]^+/[L{\cdot}Na]^+$ at each ether concentration are summarized in Table 2 (see above). The data are plotted in Figure 7.

At all ether concentrations, the dimer:monomer ratios are observed to be in the order **4** > **2** > **1** > **3**. Thus, the dominant

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(31) Acetylation of ferrocene in methylene chloride at 0 °C occurs at a rate 3.3 × 10^6 faster than benzene: Rosenblum, M. *Chemistry of the Iron Group Metallocenes*; Wiley: New York, 1965; p 63.

(32) For an analogous structure, see: Schmidbaur, H.; Schier, A.; Schubert, U. *Chem. Ber.* **1983**, *116*, 1938.

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ion for the bis(ferrocenylmethyl) ether–cation adducts is dimer at 0.1 and 1 mM ether concentration. When [cation]/[ether] = 100, the monomer adduct predominates for **4** and, indeed, for all of the ethers surveyed. For bis(nitrobenzyl) ether, the monomer adduct predominated at all ether concentrations up to 10 mM.

It occurred to us that the formation of the monomer adduct in the nitrobenzyl case might simply result from this ether's very poor binding ability (Lewis base donicity). We thus measured the ion currents for the four ions. The values observed (ion counts $\times 10^{-7}$) and those estimated (by measurement of peak heights relative to a peak in the same spectrum of known ion current) from the spectra, given in parentheses, are as follows: **1**, monomer 10.4, dimer (7.2); **2**, monomer (2.6), dimer 5.66; **3**, monomer, 1.20, dimer (0.23); and **4**, monomer (1.6), dimer 7.71. Dibenzyl ether gives an unusually large ion current compared to the other ethers. As expected, however, the number of ions observed was lower for bis(nitrobenzyl) ether than for the other ethers. Thus, the formation of the monomer in that case is probably due to the fact that the monomeric ether is too poor a donor to compete with the solution aggregate. It is also possible that the aggregate in this case is unstable in the gas phase and dissociates.

Because the ion currents were determined in individual experiments there is the possibility that the values obtained are not directly comparable. We therefore prepared a solution containing 1 mM each of **1**–**3** and 1 mM of Na$^+$ [bis(ferrocenylmethyl) ether was absent]. As expected, no ion of relative intensity >20% suggested the presence of bis(nitrobenzyl) ether. The order of intensity for the dimeric ions was bis(*p*-methoxybenzyl) ether (**2**) > dibenzyl ether (**1**).

It was also anticipated that when equimolar **1** and **2** were present, a peak of the type *m/z* = 479 corresponding to $[\mathbf{1}\cdot\mathrm{Na}\cdot\mathbf{2}]^+$ would be apparent. Such a peak was, indeed, observed.

Inferences Drawn from Spectra Concerning the Solution Phase. The question of whether the electrospray ionization mass spectra reported here reflect solution behavior is a significant one. Indeed, whether the ESI-MS approach can generally give useful information about non-covalent complexes is of import to those involved in supramolecular chemistry. In recent work, Wang and Cole[35] report a "disparity between solution-phase equilibria and charge state distributions in positive-ion" ESI-MS. In this work, spectra of the peptides bradykinin and gramicidin S were obtained by the ESI-MS method from solutions held at different pH values. Alpin *et al.* have reported ESI-MS studies of porcine pancreatic elastase (PPE) in the presence of tetrapeptide inhibitors.[36] They state that based upon their results, "either PPE is very structurally nonspecific in terms of binding or the observation of these complexes by ESI MS does not *fully* reflect structurally specific binding in dilute solution". In the latter case, the expectation of structurally specific binding by the enzyme in solution is a reasonable inference but it remains undefined for the series of short peptides studied.

In contrast to these results, Wilson and Wu[19] have studied alkali metal complexation by valinomycin, a dodecadepsipeptide that selects K$^+$ *in vivo.* The ESI-MS method for similar cations was in accord with solution findings, a fact noted previously by Cheng *et al.*[15] In the present case, the ethers have a single, accessible oxygen donor site. The binding of these ethers to both sodium and potassium cations can be correlated to the time-honored Hammett equation. It seems unreasonable to think that the correlation would occur in the gas phase but not in the solution phase. The more reasonable conlcusion is that like the other relatively simple complexation process noted above, there is good agreement between solution phase chemistry and the gas phase spectra.

Conclusion

We have presented here gas phase evidence for aggregates (adducts) between simple ethers and Na$^+$ or K$^+$. We believe that the gas phase adducts represent fragments of more complex aggregates that exist in the relatively nonpolar chloroform–methanol solution studied. The stabilities of the complexes parallel the donicities of the oxygens in $\mathrm{ArCH_2OCH_2Ar}$. Such an effect is expected but is not, to our knowledge, previously documented. The correlation of the mass spectra to the Hammett equation strongly suggests (1) that the mass spectra clearly reflect the solution phase where such relationships were originally established, and (2) the ESI-MS technique may be used for closely related and perhaps relatively simple systems to probe solution chemistry and the formation of non-covalent complexation.

Experimental Section

^{1}H-NMR spectra were recorded on a Gemini 300 MHz or Varian 500 MHz NMR spectrometer in $\mathrm{CDCl_3}$ solvents and chemical shifts are reported in ppm (δ) downfield from internal $\mathrm{(CH_3)_4Si}$. Melting points were determined on a Thomas Hoover apparatus in open capillaries and are uncorrected. Thin layer chromatographic (TLC) analyses were performed on aluminum oxide 60 F-254 neutral (Type E) with a 0.2 mm layer thickness or on silica gel 60 F-254 with a 0.2 mm layer thickness. Flash chromatography columns were packed with silica gel, Merck grade 9385, 230–400 mesh 60 Å.

All reactions were conducted under dry $\mathrm{N_2}$ unless otherwise noted. All reagents were the best grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and are reported as percents.

ESI mass spectra were acquired on a triple quadrupole tandem mass spectrometer (Finnigan MAT TSQ 700, San Jose, CA) equipped with an electrospray interface (Analytica of Branford, Branford, CT). The detector of the instrument is an off-axis continuous dynode electron multiplier operable from −400 to −3000 V, with a variable post-acceleration/conversion dynode voltage from −3 to −20 kV for detection of positive ions. The electrospray ion source and its functional parts have been described in detail.[37] For all experiments, both the electrospray needle and the skimmer were operated at ground potential, whereas the electrospray chamber (i.e., cylindrical electrode) and metalized entrance of the glass capillary were operated at −3.5 kV. A +90 V potential was applied to the metalized exit of the glass capillary. A separate +175 V potential was placed on the tube lens for acquisition of the positive ions. The temperature of nitrogen drying gas as it entered the electrospray chamber was set at 100 °C and the drying gas was held at a constant pressure of 25 psi. A 4-min period of signal averaging was employed for each spectrum. Chloroform (20%) in methanol (v/v) was used as solvent in all experiments. Sample solution was infused directly into the ESI chamber with a syringe pump at a flow rate of 2 μL/min. All the sample solution was prepared and then kept at room temperature (~25 °C). The concentration of sodium chloride or potassium chloride in all sample solutions was 1 mM.

1,4-Dimethoxybenzene, 1,4-dinitrobenzene, and dibenzyl ether (1) were purchased from Aldrich Chemical Co.

Synthesis of Bis(4-methoxybenzyl) Ether (2). 4-Methoxybenzyl alcohol (4.0 g, 0.029 mol) and dimethyl sulfoxide (142 mg, 1.82 mmol, molar ratio 16:1) were heated in an open vessel to *ca.* 175 °C and

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stirred for 0.5 h. The reaction mixture was chromatographed on silica gel (flash, CH_2Cl_2) to afford a white solid which was distilled under reduced pressure to give **2** (2.86 g, 76%) as a white solid, mp 38−40 °C (lit.[23] mp 38−38.7 °C). ^{1}H-NMR: 3.81 (s, 6H); 4.46 (s, 4H); 6.89 (d, 4H); 7.29 (d, 4H).

Synthesis of Bis(4-nitrobenzyl) Ether (3). Concentrated H_2SO_4 (2 mL) was added to *p*-nitrobenzyl alcohol (8.3 g, 54.2 mmol) in benzene (50 mL). The solution was heated under reflux for 4 h. After cooling, the solution was washed with water until the wash water was neutral to pH paper. The benzene was evaporated and the residue was dissolved in a minimum of CH_2Cl_2 and chromatographed over silica gel (flash, 1:5 (v/v) EtOAc−hexanes). The fractions containing the product were evaporated to afford **3** (1.72 g, 22%) as a white solid, mp 96.5−97.5 °C (lit.[24] mp 97−98 °C). ^{1}H-NMR: 4.72 (s, 4H), 7.55 (d, 4H), 8.24 (d, 4H). Anal. Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.12; H, 4.24; N, 9.67.

Synthesis of Bis(ferrocenylmethyl) Ether (4). Ferrocenecarboxaldehyde (10.0 g, 46.7 mol) was reduced with sodium borohydride (1.77 g, 46.7 mol) in MeOH (100 mL). The crude product, which contained both ferrocenemethanol and bis(ferrocenylmethyl) ether, was recrystallized twice from methanol to afford a yellow solid, mp 130−132 °C (lit.[25] mp 130−131 °C). ^{1}NMR ($CDCl_3$): 4.12 (s, 10H), 4.14 (t, 4H), 4.23 (t, 4H), 4.27 (s, 4H).

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