Dynamics of Crown and Lariat Ether Cation Complexation Assessed by ^{13}C NMR Relaxation Times

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Abstract: ^{13}C NMR longitudinal relaxation times (T_1s) have been determined for 15-crown-5, 18-crown-6, and several C- and N-pivot lariat ethers in the absence and presence of Na^+, K^+, and Ca^{2+} cations. The C-pivot compounds are 2-substituted 15-crown-5 derivatives as follows, in which Me = CH_3 and E = CH_2CH_2: **1**, CH_2O-*n*-Pr; **2**, CH_2OEOMe; **3**, $CH_2OC_6H_4$-2-OMe; **4**, $CH_2OC_6H_4$-4-OMe. The N-substituted monoaza-15-crown-5 derivatives are as follows: **5**, Me; **6**, *n*-Bu; **7**, EOMe; **8**, EOEOMe. The N-substituted monoaza-18-crown-6 derivatives are as follows: **9**, EOMe; **10**, EOEOMe. The relaxation time data are used to assess structural changes which accompany cation complexation, the degree of macroring vs. sidearm participation, and the effect of cation charge on the complexation process. In general, the C-pivot lariat ethers (**1-4**) appear to rely more strongly on the macroring for complexation of cations than do the N-pivot compounds (**7-10**) except when donor groups are absent from the sidearm (**5, 6**). For N-pivot lariat ethers **8** and **9**, the result of Ca^{2+} complexation is a rigid, cryptate-like structure in solution, suggesting that Ca^{2+} plays a very strong organizing role on the ligand structure.

The lariat ethers[1] have been designed as cation complexing agents which exhibit the dynamic properties[2] of simple monocyclic crown ethers and the three-dimensional binding character of the less dynamic cryptand[3] molecules. They are intermediate between these two species in that they are generally better binders[4] than simple crowns but poorer than cryptands. Although the lariat ethers were designed to be more dynamic than the cryptands, the physical evidence on this point has so far been scarce. In previous work[5] we have shown that the presumption of three dimensionality is a reasonable one. Studies of ammonium cation binding in MeOH solution[6] and a crystal structure study in the solid state[7] both confirm that the sidearm is involved intramolecularly with the ring-bound cation.

The purpose of the present study was to determine the extent of ring and sidearm involvement in the binding and to assess molecular dynamics both in the presence and absence of cations. We[8] and others[9] have shown that ^{13}C NMR relaxation times provide considerable information on ligand structural properties, binding strengths, and binding dynamics. This technique offers a convenient means for assessing specific binding (structural) interactions in different portions of a ligand molecule. This, in turn, gives inferential information on microstructural interactions in individual molecular complexes.

Experimental Section

15-Crown-5 was purchased (Aldrich) and 18-crown-6 was prepared as previously described.[10] Both were distilled prior to use. The lariat ethers **1-10** were prepared as previously described.[1,5]

Na^+, K^+, and Ca^{2+} perchlorate salts were purchased (Alfa) and dried in vacuo for 48 h prior to use. All solvents were spectral grade: 99.7% D_2O (Merck) and 99.8% $CDCl_3$ and CH_3OH (Aldrich). The solvents were vacuum transferred into the NMR sample tubes without additional purification. NMR samples consisted of 0.5 mL of solution in 5-mm o.d. tubes which were sealed under vacuum after careful degassing by at least 3 freeze-pump-thaw cycles. All glassware was washed with 0.01 M EDTA solution to remove paramagnetic impurities. Relaxation time experiments were performed in CH_3OH:D_2O (90:10) solutions 0.1-0.7 M in the appropriate ethers. No concentration dependence of T_1 values was detected within this concentration range. Stoichiometric amounts of metal perchlorate salts were utilized for the complexation studies. For most ligands studied here, the fraction found in the complexed form is essentially 100% under these conditions. Even the ligands with the smallest binding constants have complexed fractions well over 90%. Therefore, the possible error introduced by incomplete complex formation in the T_1 values is, at its most, comparable to the observed standard deviation of the measurements. $CDCl_3$ was used only in the few cases where complexes were quite insoluble in CH_3OH:D_2O.

^{13}C NMR measurements were performed at 22.5 MHz on a JEOL FX90Q spectrometer equipped with quadrature phase detection system. Relaxation times (T_1s) were measured under proton-noise-decoupling conditions by the inversion-recovery technique. A waiting time (t_W) of at least five times the longest relaxation time was used in each case. Thirteen different pulse intervals, τ, were used for each individual measurement and chosen so that at least seven points were included for each T_1 calculation. Usually, 80-120 scans were necessary for each τ value in order to obtain a reasonable signal-to-noise ratio. On the average, each run required 12 h. In every case probe temperature was controlled to ±1 °C with a JEOL NM-VTA variable temperature controller. Unless otherwise specified, all spectra were recorded at 35 ± 1 °C. T_1 values were determined by a linear least-squares, two-parameter fit of the experimental data directly performed by the spectrometer computer.

A minimum of three runs were accumulated for each system. We estimate the standard deviation to be ±8% based on the values from all runs. The relaxation time of the CH_3OH resonance was used as internal standard. Values obtained ranged from 12.7 to 13.8 s, in good agreement with literature values.[12] Nuclear Overhauser enhancement (NOE)

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Table I. ^{13}C NMR Relaxation Times for Lariat Ethers and Their Complexes[a]

compd	K_s[b]	cation[c]	C-1	C-2	C-3	C-4	CH_3	C-α	other av[d]	range[e]	solvent
15-crown-5	NA	NA	NA	NA	NA	NA	NA	2.14	NA	NA	90% MeOH
	927	Na^+	NA	NA	NA	NA	NA	1.26 (41%)	NA	NA	90% MeOH
1	NA	NA	UAS	2.37	2.74	NA	4.25	1.40	0.95	0.77–1.02	90% MeOH
	692	Na^+	UAS	2.01 (15%)	2.60 (5%)	NA	4.47 (–5%)	1.00 (29%)	0.71 (25%)	0.56–1.14	90% MeOH
2	NA	NA	UAS	UAS	2.61	NA	9.06	1.72	1.46	1.07–1.80	90% MeOH
	669	Na^+	UAS	UAS	1.62 (38%)	NA	7.18 (21%)	0.99 (42%)	0.65 (55%)	0.39–0.66	90% MeOH
		Ca^{2+}	UAS	0.68 or	0.60	NA	3.64 (60%)	0.66 (62%)	0.42 (71%)	0.38–0.49	90% MeOH
3	NA	NA	UAS	19.1 or	16.9	NA	3.60	1.3	1.05	0.81–1.32	90% MeOH
	927	Na^+	UAS	13.6 or	11.3	NA	1.80 (50%)	0.70 (46%)	0.49 (53%)	0.42–0.67	90% MeOH
4	NA	NA	UAS	26.6 or	18.7	NA	4.30	1.20	0.91	0.64–1.13	90% MeOH
	364	Na^+	UAS	13.6 or	10.8	NA	4.60 (–7%)	0.70 (42%)	0.61 (33%)	0.49–0.79	90% MeOH
5	NA	NA	NA	NA	NA	NA	1.12	1.14	1.21	1.18–1.24	90% MeOH
	2455[f]	Na^+	NA	NA	NA	NA	1.20 (–7%)	1.02 (11%)	1.05 (13%)	0.98–1.11	90% MeOH
6	NA	NA	1.48	1.60	2.43	NA	2.98	1.63	1.47	1.43–1.54	90% MeOH
	414	Na^+	0.62 (58%)	0.93 (42%)	1.39 (43%)	NA	2.65 (11%)	0.47 (71%)	0.54 (63%)	0.51–0.56	90% MeOH
7	NA	NA	2.62	2.84	NA	NA	8.40	2.96	2.24	2.05–2.46	90% MeOH
	4587	Na^+	2.35 (10%)	2.65 (7%)	NA	NA	7.87 (6%)	2.17 (27%)	2.21 (1%)	2.16–2.34	90% MeOH
8	NA	NA	1.07	UAS	UAS	2.96	9.79	0.99	1.46	1.21–1.74	90% MeOH
	14630	Na^+	1.17 (–9%)	UAS	UAS	1.68 (43%)	7.19 (27%)	1.18 (–19%)	1.34 (8%)	1.18–1.65	90% MeOH
	11481[f]	Ca^{2+}	0.41 (62%)	UAS	UAS	UAS	2.81 (71%)	0.42 (58%)	0.43 (71%)	0.41–0.44	90% MeOH
18-crown-6	NA	NA	NA	NA	NA	NA	NA	1.28	NA	NA	90% MeOH
	NA	NA	NA	NA	NA	NA	NA	1.56	NA	NA	$CDCl_3$
	4378	Na^+	NA	NA	NA	NA	NA	1.10 (14%)	NA	NA	90% MeOH
		Na^+	NA	NA	NA	NA	NA	0.82 (47%)	NA	NA	$CDCl_3$
	278000	K^+	NA	NA	NA	NA	NA	1.33 (–4%)	NA	NA	90% MeOH
		K^+	NA	NA	NA	NA	NA	0.54 (65%)	NA	NA	$CDCl_3$
9	NA	NA	1.22	2.09	NA	NA	5.89	0.88	1.18	1.10–1.27	90% MeOH
	15635	Na^+	0.73 (40%)	0.80 (62%)	NA	NA	4.18 (29%)	0.66 (25%)	0.76 (36%)	0.74–0.77	90% MeOH
	21877[f]	Ca^{2+}	0.45 (63%)	UAS	NA	NA	2.77	0.38 (57%)	0.41 (65%)	0.40–0.44	90% MeOH
		NA	0.70	UAS	NA	NA	4.24	0.96	0.96	0.86–1.01	$CDCl_3$
		Na^+	0.88 (–26%)	UAS	NA	NA	3.41 (20%)	0.84 (13%)	0.84 (12%)	0.81–0.89	$CDCl_3$
		K^+	0.81 (–16%)	UAS	NA	NA	4.12 (3%)	0.62 (35%)	0.63 (34%)	0.56–0.74	$CDCl_3$
10	NA	NA	1.01	UAS	UAS	UAS	8.22	0.72	1.36	1.06–1.48	90% MeOH
	8410	Na^+	0.92 (9%)	UAS	UAS	UAS	6.91 (16%)	0.80 (–11%)	0.88 (35%)	0.83–0.94	90% MeOH
	230020	K^+	0.77 (24%)	UAS	UAS	UAS	4.82 (41%)	0.66 (8%)	0.72 (47%)	0.58–0.86	90% MeOH

[a] All T_1 values are in seconds; NA means "not applicable", UAS means "unassigned", and values in parentheses are the percentage decrease in the T_1 value when the ligand is complexed by the indicated cation. [b] K_s is the equilibrium stability (binding) constant, determined in 90% MeOH:H_2O, v/v. [c] As the perchlorate salt. [d] Average of all other T_1 values determined. [e] Inclusive range of average T_1 values; see footnote *d* above. [f] Binding constant values are for anhydrous methanol rather than 90% methanol and were determined as described in ref 12.

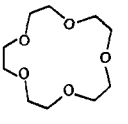
factors were measured in each case and are those expected for a predominantly dipole–dipole relaxation technique (2.8–3.0). The only exceptions were T_1s for the CH_3 carbons, which exhibited NOE values in the range 2.1–2.6 due to spin rotational contributions. ^{23}Na NMR spectra were obtained with the same spectrometer operating at 23.71 MHz. Spectral windows between 1000 and 5000 Hz were used, and pulse delays of 0.5 were utilized between consecutive pulse-accumulation sequences. In cases where line widths exceeded 2000 Hz, spectral windows of 10 000 Hz were used. Samples contained 2:1 $[Na^+]$/ligand ratios in order to have approximately equal concentrations of complexed and free sodium cation.

Results and Discussion

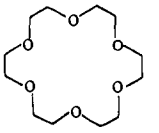
^{13}C NMR relaxation time measurements, determined at 22.5 MHz in either 90% CH_3OH:D_2O or $CDCl_3$, are reported in Table I. Individual carbon assignments were made on the basis of chemical shifts. In a few cases, assignments were made on the basis of relaxation times. Although many of the sidearm carbon atoms could be assigned unequivocally, ring carbon atoms were generally grouped together and are expressed in Table I by the average and range of their relaxation times. The difference between T_1 values before and after interaction with the designated cations is expressed as the percent by which the relaxation time dropped.

Relaxation Times for Uncomplexed Ligands. The relaxation times for any given molecule depend upon molecular mobility (tumbling) and specific motion determined by the internal degrees of freedom of the molecule. Although it is impossible to distinguish these two aspects of T_1, inferences about the relative motions can be drawn from a careful comparison of rings vs. sidearms in the same system or sidearms vs. sidearms in closely related systems.

If one assumes that the solvation of 15-crown-5 and 18-crown-6 by either MeOH:D_2O or $CDCl_3$ is similar, then the relaxation times should reflect differences in their overall mobilities. Since



15-Crown-5

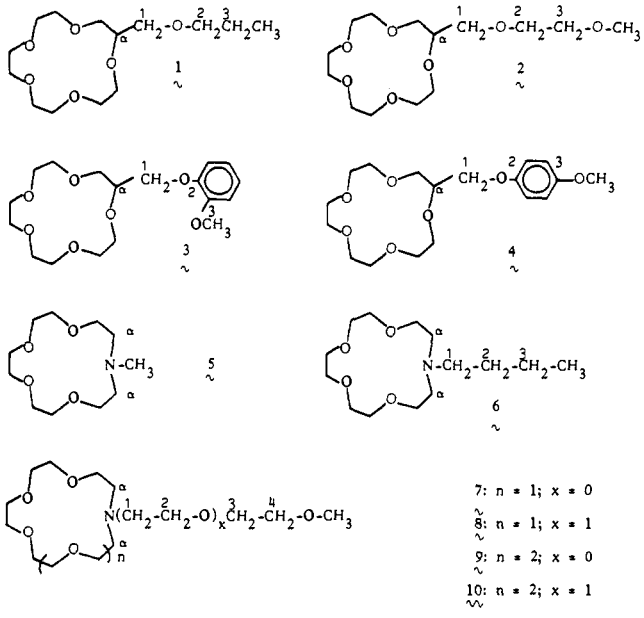


18-Crown-6

18-crown-6 is larger than 15-crown-5, its motion is expected to be somewhat slower than that for the smaller macrocycle. If the molecular mobility is lower, then the relaxation time for the 12-carbons in this system should be shorter than for the smaller macroring. Indeed, T_1 for 18-crown-6 is 1.28 s compared to 2.14 s for 15-crown-5.

In $CDCl_3$ solution, the molecular mobilities are expected to be higher than in MeOH:D_2O because of the higher viscosity of the latter and the ability to hydrogen bond. The T_1 value observed for 18-crown-6 is 1.56 s in $CDCl_3$ compared to 1.28 s in MeOH:D_2O. This is true for all the C- and N-pivot lariat ethers surveyed, with the exception of **9**, which may be due to ring-bound water (sterically compatible with 18-membered macrorings) hydrogen bonding the sidearm and making the entire structure more compact. This effect should also be observed with **10** (data not available) as was the case in our previously reported ammonium ion binding studies.[6]

As expected, for all of the lariats having aliphatic sidearms, side chain carbon mobility increases as the distance from the macroring increases. In the case of **6**, for example, T_1 values for C-1, C-2, C-3, and CH_3 are 1.48, 1.60, 2.43, and 2.98 s, re-



spectively. Furthermore, the methyl groups most remote from the pivot point (**7** vs. **8**; **9** vs. **10**) are the most mobile. Although the methyl terminus is more mobile as the side chain lengthens, this is coupled to a corresponding decrease in overall molecular mobility reflected in decreasing C-1 values for the same systems. The increased conformational mobility conferred on a chain by oxygen compared to carbon (sidearms of **6** vs. **7**) is reflected in a large increase in both CH_3 mobility and T_1. Finally, average ring carbon T_1s are higher for the N-pivot (**5–8**) than for the C-pivot (**1–4**) molecules. We do not have an explanation for the relatively high mobilities of the ring carbons in **2** and **7** which seem unusual for their respective series but which do not contradict the trend.

Relaxation Times for Na^+ Complexes. The affinity of the ligands in this study for a given cation was assessed by measuring the equilibrium binding (stability) constant (K_s) for the reaction between ligand and salt as shown in eq 1. These constants were

$$\text{ligand} + \text{cation} \overset{K_s}{\rightleftharpoons} \text{complex} \qquad (1)$$

determined as previously described for Na^+, K^+, and Ca^{2+} by ion-selective electrode methods in anhydrous MeOH solution.[13] Some values are also available in other solvents[1,4,5,14] including those in which the T_1 values were determined, but we include here only the MeOH values for consistency. Generally, K_s values determined in less polar solvents will be higher than those determined in more polar solvents.[15]

As previously reported,[8a] carbon-pivot lariat ether systems exhibit strong ring participation in cation binding. This is evident for **2** and is especially so for **1** where the single heteroatom in the sidearm is not properly disposed for interaction with ring-bound cation. The importance of the correct geometric disposition of sidearm heteroatoms is apparent in compounds **3** and **4**. When the methyl group is *para* (**4**), the attached oxygen is not involved in binding and the methyl group mobility remains high. In contrast, the interaction of the *o*-methoxy oxygen with the ring-bound cation leads to a methyl-carbon mobility for Na^+-**3** which is 50% less than that for **4**. Furthermore, this is clearly consistent with the independently determined stability constants (see Table I).

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Table II. ^{23}Na NMR Line Width Measurements

	^{23}Na line width ($\Delta\nu_{1/2}$), Hz			
temp, °C	**2**	**5**	**6**	**7**
+25	96	30	104	58
0	202	40	175	87
−25	587	80	370	190
−50	~2500	200	1240	490
−75	>2500	nd[a]	nd	~1300

[a] nd = not determined.

The nitrogen-pivot lariat ethers are expected to be more mobile structures than the corresponding C-pivot compounds since carbon cannot invert whereas nitrogen can do so rapidly. This flexibility is retained even in the cation complexes as we have previously reported.[8a] When no heteroatom is available in the N-pivot sidearm (**5**, **6**), all of the solvation must be provided by the ring donor groups and the high level of mobility is reduced considerably. Note that for **6**, all of the non-methyl carbon atoms are drastically reduced in mobility. In this respect, the C-pivot molecules and the N-pivot structures which lack sidearm donor groups are quite similar in that most, if not all, of the cation binding results from interactions between the cation and macroring.

A comparison of **5** and **6** is especially interesting since these two N-pivot structures lack sidearm donors but differ considerably in their mobilities when Na^+ complexed due to differences in sidearm lengths. Whereas the behavior of **6** parallels the C-pivot structures (e.g., **2**), *N*-methylmonoaza-15-crown-5 (**5**) is unusual. When Na^+ complexed, neither the ring nor the methyl carbon mobility is appreciably affected. This may reflect relatively higher dynamics for cation entry and egress due to reduced steric demands. If so, this should be apparent from ^{23}Na NMR studies. These are shown in Table II.

^{23}Na NMR line widths are usually controlled by the quadrupolar contribution to the overall relaxation rate. It is known that the relaxation rate via this mechanism is inversely proportional to the absolute temperature.[16] Additional line broadening may result if one or more chemical exchange processes are present in the system. The faster the exchange mechanism, the smaller will be the line-broadening contribution.

The data for ^{23}Na line widths as a function of temperature are presented in Table II, when complexed by ligands **2**, **5**, **6**, and **7**. In all cases, decreasing the temperature increased the line width, as expected. This increase in $\Delta\nu_{1/2}$ is not very pronounced in the cases of **5** and **7**, where it approximately follows the expected inverse relationship with temperature. This indicates that the contribution to the line width due to chemical exchange is, qualitatively at least, negligible. This is not the case for ligands **2** and **6** where the observed inverse temperature line width dependence far exceeds the predicted one.[16] Therefore, it can be qualitatively concluded that fast ^{23}Na exchange remains, even at low temperatures, for ligands **5** and **7**, while slower exchange occurs for **2** and **6**. Thus carbon-pivot lariat ether **2** forms a more rigid complex with Na^+ than its nitrogen-pivot analogue, **7**. Similarly, the long hydrocarbon sidearm in **6** results in the formation of a more rigid complex than that with **5** (sidearm = methyl). This is a reflection of the reduced nitrogen inversion rate in the former case.

Nitrogen-pivot lariat ethers whose sidearms contain donor groups remain highly dynamic even when complexed by Na^+.[8a] This is due, in part, to cooperativity between both ring and sidearm in cation complexation. In addition, it appears that the cation may reside slightly below the macroring plane allowing the speed of entry and egress to be maximized. This structural situation is clear from the KI·**9** X-ray crystal structure.[7] Extrapolation of solid-state structural data for **9** to the present case may be tenuous since the solution behavior of Na^+-complexed **9** differs between $CDCl_3$ and MeOH:D_2O. The Na^+ complex of **9** in MeOH:D_2O shows a pronounced reduction in sidearm and ring mobility. This

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is not the case in $CDCl_3$ where flexibility is clearly maintained by both structural subunits. As noted above, this probably reflects the affinity of 18-membered rings for hydrogen-bonding water.

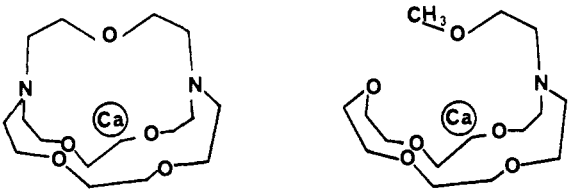
Relaxation Times for K^+ Complexes. The effect of cation changes on ligand relaxation times is clearly solvent dependent. In 18-crown-6, for example, the average relaxation times decrease on going from the free ligand to the K^+ complex in $CDCl_3$ (1.56 s free, 0.82 s for the Na^+ complex, and 0.54 s when complexed to K^+). This is the expected behavior if specific ligand solvation interactions are unimportant, due to increased cation–ligand interactions expected when going from sodium to potassium. This monotonic decrease is not observed in 90% MeOH where cation complexation is accompanied by substantial ligand desolvation.

The behavior noted above is exactly paralleled by the ring carbon atoms of **9** in $CDCl_3$ where the average value for the free ligand (0.96 s) decreases upon Na^+ complexation to 0.84 s and further diminishes to 0.63 s when K^+ is present.

Relaxation Times for Ca^{2+} Complexes. When Ca^{2+} is bound by **2**, **8**, or **9**, a dramatic decrease in the mobilities of all carbons is observed. Sidearm relaxation times and therefore mobilities are reduced less in **2** relative to the ring carbons than in **8** and **9**. In the latter two compounds, all secondary carbon relaxation time values fall to approximately 0.40 s. This fact is especially intriguing since the carbon relaxation times differ considerably in free **8** and **9** as might be expected since they have different ring sizes and different sidearms. A similarity of **2** with **8** might have been anticipated because these compounds have the same ring sizes, although they differ in pivot atoms and sidearm lengths. The similarity of **8** and **9** when bound by Ca^{2+} is reminiscent of the similarity in binding constants observed with **8** and **9** when binding Na^+ which is isosteric to Ca^{2+}. In fact, the Ca^{2+} binding constants for **8** and **9** differ by less than 50% from each other (see Table I).

The reduction of all non-methyl carbon T_1 values to 0.40 s in N-pivot compounds **8** and **9** when bound to Ca^{2+} suggests that the motion of these complexes is isotropic. This is similar to the observation for cryptands and their complexes (cryptates) which exhibit essentially isotropic reorientational motion.[8b] All carbon atoms have T_1 values which are very close, indicative of molecular isotropicity and near-spherical symmetry. Apparently, Ca^{2+}, whose charge-to-size (Q/r) ratio is larger than that for Na^+, strongly organizes the ligand structure and its solvation shell. It is important to note that such isotropic motion is never attained throughout the C-pivot systems, although some of the ring carbons reduce in their mobilities to this same value. That the motion of such complexes is isotropic and that mobility is reduced to the level reflected by a relaxation time of 0.40 s is confirmed by the recent report of this same value for the $Ca^{2+}ClO_4^-$ complex in H_2O of ionizable EDTA.[17] For Na^+, whose Q/r ratio is lower, the T_1 values are also reduced, but not as much. The similarity in T_1 values for Ca^{2+}-bound **8**, **9**, and EDTA is certainly striking, especially considering how different these compounds are.

For the nitrogen-pivot lariat ethers studied here, the result of Ca^{2+} complexation is the formation of a rigid, cryptate-like structure in solution. The analogy is represented by the structures shown below.



cryptate-like structure (right) in analogy to the known structure for the sodium cation complex of cryptand [2.2.1]

Summary

From the results presented in this paper, it is clear that T_1 measurements are of considerable utility in assessing structural changes which accompany cation complexation, the degree of macroring vs. sidearm participation, and the effect of cation charge on the complexation process. For the N-pivot lariat ethers, the result of Ca^{2+} complexation is a rigid, cryptate-like structure in solution, suggesting that Ca^{2+} plays a very strong organizing role on the ligand structure.

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Registry No. **1**, 84130-85-8; **1**·$NaClO_4$, 91129-36-1; **2**, 76719-78-3; **2**·$NaClO_4$, 91129-37-2; **2**·$Ca(ClO_4)_2$, 91129-55-4; **3**, 76719-75-0; **3**·$NaClO_4$, 91129-39-4; **4**, 76719-76-1; **4**·$NaClO_4$, 91129-41-8; **5**, 69978-46-7; **5**·$NaClO_4$, 91129-43-0; **6**, 69978-48-9; **6**·$NaClO_4$, 91129-44-1; **7**, 79402-94-1; **7**·$NaClO_4$, 91129-45-2; **8**, 79402-96-3; **8**·$NaClO_4$, 91129-46-3; **8**·$Ca(ClO_4)_2$, 91129-57-6; **9**, 79402-95-2; **9**·$NaClO_4$, 91129-47-4; **9**·$KClO_4$, 91129-51-0; **9**·$Ca(ClO_4)$, 91129-59-8; **10**, 80755-63-1; **10**·$NaClO_4$, 91129-49-6; **10**·$KClO_4$, 91129-53-2; 15-crown-5·$NaClO_4$, 74060-74-5; 18-crown-6·$NaClO_4$, 74060-75-6; 18-crown-6·$KClO_4$, 74060-76-7; Na, 7440-23-5; 15-crown-5, 33100-27-5; 18-crown-6, 17455-13-9.