of an intermediate with the metal ion normal to the ligand molecular plane, roughly above the central oxygen atom. This is approximately in agreement with conservation of hybridization at the central oxygen ligand. It is difficult to differentiate experimentally between the two mechanisms.

Conclusions

The exchange process of some closed-shell metal ions in the alterdentate radical ligands ninr and allr is a relatively fast intramolecular process. It represents an example for a molecular system in which a charged species can wander along a path of low potential energy without becoming detached from the parent structure. The presently investigated systems represent but the simplest situations, in which two symmetric minima exist on the energy hypersurface. Organized structures of higher complexity could extend the possibilities for such motion of ionic species considerably.

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Supplementary Material Available: Observed and simulated ESR spectra (Figures 14–44), most spectra used for the evaluation of the kinetic data, and the spectra of the rapidly exchanging complexes are given (28 pages). Ordering information is given on any current masthead page.

Nuclear Magnetic Resonance and Calorimetric Studies on the Solvation of Cryptand C221 and Its Na^+ and K^+ Complexes in Nonaqueous Solvents

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Abstract: Carbon-13 and proton NMR as well as calorimetric measurements were used to study interactions of cryptand C221 with Na^+ and K^+ ions and with organic solvent molecules in a variety of nonaqueous solvents. The NMR spectra of the two alkali complexes in solution are quite different, indicating that the ligand exists in different conformations (as it does in the crystalline state). The ^{13}C spectra of free ligands in different solvents fall into two groups, designated here as A and B. Class A spectra are similar to those of the K^+·C221 complex while class B spectra approximate that of the Na^+·C221 complex. In the former case the spectra are believed to indicate a significant solvent molecule–ligand interaction. Calorimetric measurements show that while C221 forms a more stable complex with Na^+ than with K^+, the enthalpy of complexation in the latter case is more negative but the K^+ complex is entropy destabilized. The Na^+/K^+ selectivity strongly depends on the solvent and is especially pronounced in nitromethane solutions.

A number of previously reported studies have clearly shown that the stabilities of macrocyclic complexes are very significantly affected by physicochemical properties of the solvent in which the reaction takes place.[3-5] The role of the solvent becomes even more evident when we consider separately the enthalpy and the entropy of complexation.[3]

It is obvious, of course, that the extent of the cation–solvent interaction can have a very significant influence on the thermodynamics of complexation reactions. Other factors, however, may play an equally prominent role; in particular, the role of solvent–ligand interactions in complex formation seems to be somewhat neglected, although Hinz and Margerum indicated some years ago[6,7] that such interactions can have an important influence on the overall complexation reaction.

Recent studies by several investigators have shown that in some solvents crown ethers strongly interact with solvent molecules. In fact, solid solutes of 18-crown-6 with acetonitrile,[8] acetamide,[9] and nitromethane[10] have been isolated and, in the latter case, the structure of the complex, $18C6\cdot(CH_3NO_2)_2$, has been determined by X-ray crystallography. Clearly such interactions must also exist, to a greater or lesser extent, in solutions and must modify the complexing abilities of the macrocycles; they may, for example, alter the conformation of the macrocyclic ligand, rendering it either less or more capable of complex formation.

It has been stated recently that solvent–cryptand and solvent–cryptate interactions are weak in comparison with the solvent–cation ones and moreover that the former do not vary significantly from solvent to solvent.[11] It should be noted, however, that direct calorimetric measurements of Abraham et al.[12] showed that the enthalpy of transfer of cryptand C222 from water to methanol is +13.9 kcal mol^{-1} while for 18C6 it is +13.6 kcal mol^{-1}. These results clearly indicate not only that the enthalpy of solvation of macrocyclic ligands can be very substantial but also that it can vary drastically with the solvent.

It should be noted that in the vast majority of cases where the enthalpy and the entropy of macrocyclic complex formation were determined in nonaqueous solvents, the complexes were found to be enthalpy stabilized but entropy destabilized.[13] The magnitudes of the entropy changes, however, very much depend on the nature of the solvent. The desolvation of the cation and/or the ligand

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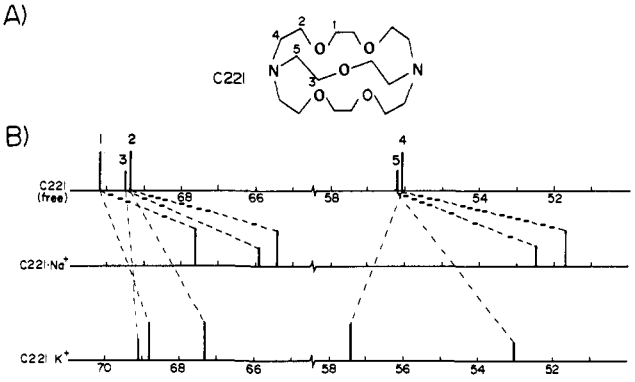

Figure 1. (A) Magnetically unequivalent carbon atoms of ligand C221; (B) ^{13}C spectra of free C221 and of its Na^+ and K^+ complexes in deuteriochloroform solutions.

during complex formation should result in an increase in the total entropy of the system due to an increase in the translational entropy (as is the case in chelation, at least in aqueous solutions[14]). It seems that with the macrocyclic complexes this effect is offset by a decrease in the conformational entropy of the ligand since the number of conformations available to it decreases upon complex formation.

It was of interest to us to investigate in some detail macrocyclic ligand–solvent interactions and to see to what extent such interactions influence the complexation of alkali cations. We selected cryptand C221 for the initial studies since (a) the ligand is fairly rigid by comparison with crown ethers and conformational changes should be more easily detected, (b) spectroscopic properties are favorable for the detection of conformational changes since the ligand has five carbon signals (Figure 1) and an ABXY proton NMR pattern, both of which are sensitive to conformational changes, and (c) the crystal structures of the $C221{\cdot}Na^+$ and $C221{\cdot}K^+$ complexes have been determined.[15] Consequently we investigated solutions of this ligand by ^{13}C and ^1H NMR in a variety of solvents so as to detect any specific solvent–ligand interactions. Thermodynamics of $Na^+{\cdot}C221$ and $K^+{\cdot}C221$ cryptate formation in some of those solvents were also determined in order to see if there is any correlation between the ligand–solvent and ligand–alkali ion interactions.

Experimental Section

Reagents. Cryptand 221 (C221, Merck) was dried under vacuum at 25 °C for 2 days. With the exception of nitromethane, solvents used for the calorimetric measurements were judged to be of sufficient purity for the measurements and were used as received. Nitromethane was dried and distilled before use. Solvents used for the NMR studies were purified by the techniques described below.

Nitromethane (Mallinckrodt or MCB), nitroethane (City Chemical Corp.), pyridine, tetramethylguanidine (Eastman), dimethylformamide (Mallinckrodt), dimethyl sulfoxide (Fisher), formamide (Fisher), acetonitrile (Mallinckrodt), 1,3-dioxolane (Aldrich), and dichloromethane (Drake Brothers) were refluxed over calcium hydride (under reduced pressure for the first seven solvents) for 12–24 h and then fractionally distilled. Toluene (Fisher) and 1-nitropropane (City Chemical Corp.) were refluxed over phosphrus pentoxide (Fisher) under reduced pressure for 3 h in a Bantamware apparatus and then fractionally distilled. The same procedure was used for anisole (Aldrich) except for the drying agent, which was barium oxide (Fisher). Methanol (Mallinckrodt) was refluxed over magnesium tunings and iodine for 12–24 h and then fractionally distilled. Acetone (Mallinckrodt) was purified in the same way, but with Drierite as the drying agent. The water content of solvents, except acetone, was checked by automatic Karl Fischer titration with an Aquatest II (Photovolt) and was found to be always below 100 ppm. The purity of solvents was also checked by ^{13}C NMR, and no detectable amount of impurities were found.

The deuterated solvents acetone-d_6 (Stohler Isotope Chemicals, SIC), methanol-d_4 (SIC or Aldrich Gold Label), chloroform-d (Aldrich Gold Label) and D_2O (SIC) were used as received.

Potassium and sodium thiocyanates (Prolabo) were dried for 24 h.

Calorimetric Measurements. Solutions of C221 and of the alkali salts were prepared by weight. The concentrations were 2×10^{-3} M for the ligand and 2×10^{-2} M for the salts. The same batch of a purified solvent was used for the preparation of the ligand and of the salt solutions.

The heats of complexation were measured at 25 ∓ 0.1 °C with an LKB 10700 flow microcalorimeter equipped with a recorder and a curve integrator and LKB 10200 and LKB 12000 peristatic pumps. The flow of the salt solutions was 2.5 times faster than the flow of the ligand solution. The quantity of the ligand consumed was derived from the determination of the exact flow rate (measured for each solvent) and the injection time of the ligand solution. The base line was fixed by the mixing of the salt solutions with the pure solvents. The heat of dilution of the ligand was considered to be negligible. The measurements were repeated at least three times and the reproducibility of the ΔH values was ∓0.1 kcal mol^{-1}.

Carbon-13 Measurements. Carbon-13 measurements at MSU were made either on a Varian CFT-20 spectrometer operating at a field of 18.68 kG and a frequency of 20.0 MHz or on a Bruker WM-250 spectrometer (58.7 kG and 62.9 MHz). The sample solutions were placed in a 8 mm o.d. NMR tube which was coaxially inserted in a 10 mm o.d. NMR tube containing acetone-d_6 as the lock. The methyl carbon peak of acetone-d_6 was used as the external reference. The chemical shifts were corrected for the differences in bulk magnetic susceptibilities between the sample solvent and acetone.

At the Le Bel Institute ^{13}C measurements were carried out on a Bruker WP-200 spectrometer, and a Varian XL-100 spectrometer was used for the relaxation measurements.

Proton NMR Measurements. Proton NMR measurements were carried out on a Bruker WM-250 spectrometer operating at a field strength of 58.72 kG and 250.00 MHz. The chemical shifts were referred to Me_4Si.

Selectivity Measurements. The Na^+/K^+ selectivity measurements were carried out with ^{13}C NMR. Since the species $Na^+{\cdot}C221$ and $K^+{\cdot}C221$ are in slow exchange in solvents such as methanol, nitromethane, and acetone, the concentrations of the complexed sodium and potassium ions were determined by integrating the ^{13}C lines of the cryptates (eq 1). The concentrations of the free alkali ions were obtained

$$\frac{K_{Na^+}}{K_{K^+}} = \frac{[Na^+{\cdot}C221][K^+]}{[K^+{\cdot}C221][Na^+]} \quad (1)$$

from the known total concentrations of the salts and of the cryptands.

Relaxation Times Measurements. Carbon-13 relaxation times were measured by the inversion–recovery pulse sequence 180°–τ–90°, with 12 to 14 values.[16] Experimental data were fitted to the three-parameter equation with the help of the KINFIT program.[17]

$$Mz = A + Be^{-\tau/T_1} \quad (2)$$

Results and Discussion

A. ^{13}C Chemical Shifts. As seen in Figure 1A, cryptand C221 has five different carbon-13 resonances. The resonances of the free ligand and of the Na^+ and K^+ complexes in deuteriochloroform solutions are shown schematically in Figure 1B. Assignments are given according to the numbering of carbon atoms in 1A. They are obvious for carbons 3, 4, and 5, but carbons 1 and 2 are assigned by measuring the satellite ^{13}C–^{13}C coupling patterns with the INADEQUATE pulse sequence.[18] In the satellite spectrum, carbons 2 and 4 form an AX system with $J = 43$ Hz whereas no satellite spectrum is obtained for carbon 1.

It is immediately obvious not only that the complexation results in substantial modifications of the ligand's spectrum but also that the spectra of the two cryptates are very much different. Figure 1B shows that the $Na^+{\cdot}C221$ resonances are all upfield from those of the $K^+{\cdot}C221$ cryptate and in the latter case carbon 4 and 5 become separated by about 4.4 ppm. This difference very probably reflects the different structures of the two cryptates in solution. Weiss et al.[15] have shown that in the solid state the conformations of the two complexes are quite distinct. In the case of the $Na^+{\cdot}C221$ complex the cation is in the center of the ligand cavity and the N····N distance is 4.94 Å. By contrast, the K^+ cation is located in the cavity of the 18-membered ring of the ligand and the N····N distance increases to 5.14 Å. Several torsion angles in the $Na^+{\cdot}C221$ and $K^+{\cdot}C221$ complexes are different, but the decrease in the cavity size for the Na^+ complex is mainly due to

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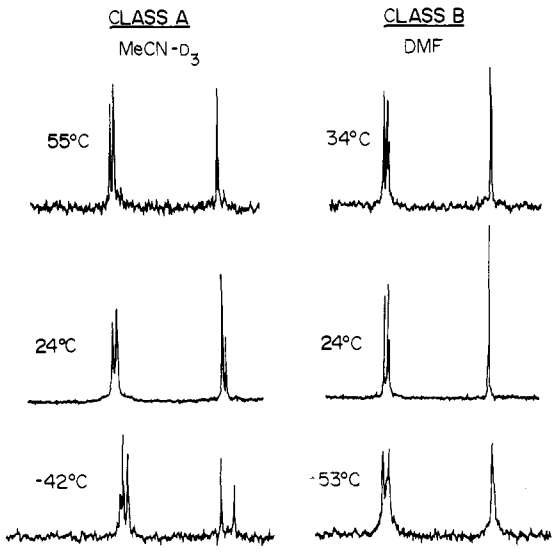

Figure 2. Typical carbon-13 NMR spectra of uncomplexed C221 in class A solvents and class B solvents.

a change in torsion angles for one O–C_2 and one C_2–C_4 bond followed by an interchange of the trans/gauche relationship relative to the N–C_4 bond. The overall high-field shift of the ^{13}C resonance lines in the Na^+·C221 complex compared to K^+·C221 must be due to an increase of γ-interactions in the C–O(N)–C–C fragments. The large separation of carbon 4 and 5 resonances for K^+·C221 (~4.4 ppm) as compared with that for Na^+·C221 (~0.5 ppm) must be principally due to the absence of γ-interactions in the "crown" N_2O_4 and, therefore, to the opening of that pair upon complexation. It would be reasonable to expect that the two complexes also have different structures in solution and that these differences will be reflected in the ^{13}C spectra of the complexed ligand.

Carbon-13 NMR spectra of the free ligand were measured in a number of different solvents and at different temperatures. The resonance frequencies were found to be independent of concentration in the 0.05–0.25 M range.

It became immediately obvious that the ^{13}C spectrum of the ligand is very much influenced by the medium and by the temperature. In general, the spectra can be separated into two quite distinct classes, which we will designate by "A" and "B". The A spectra, at room temperature or below, are very similar to that of the K^+·C221 complex. In particular there is a very definite separation of the C(4) and C(5) signals, which increases as the temperature is lowered. By contrast the B spectra resemble that of the Na^+·C221 complex and the C(4) and C(5) signals essentially are superimposed at all accessible temperatures. A typical example is shown in Figure 2 where the ^{13}C spectra of C221 in acetonitrile and dimethylformamide solutions are compared. The separation of the C(4) and C(5) resonances at different temperatures is shown in Table I. In all cases, in a given solvent, the measured T_1 values are equal for the different carbon sites of the free and the complexed ligand. The results indicate that the overall reorientation is dominant over the internal motion.

It seems to us that the A spectra indicate a specific solvent–ligand interactions where a part of the solvent molecule (e.g., OH, NH, or CH_3) penetrates into the cavity of the ligand, forms hydrogen bonds with some (or all) heteroatoms of the latter, and forces it into an "open face" configuration similar to the one observed for the K^+·C221 complex. The comparison of the two classes of solvents indicates that in the A case the solvents are capable of hydrogen bonding and that in some cases, as pointed out above,[8-10] they do form hydrogen-bonded adducts with crown ethers.

B. ^{13}C Relaxation Times. Carbon-13 relaxation times were measured for the free ligand as well as for Na^+ and K^+ complexes in some of the type A and type B solvents. The results are shown in Table II.

It is seen that in all solvents the spin–lattice relaxation time of the potassium complex is smaller than that of the sodium complex. In the former case, therefore, the bound ligand must have a higher rigidity.

Table I. C(4) and C(5) Separation in ^{13}C Spectra of Cryptand C221

solvent	t, °C	$\delta_4-\delta_5$	solvent	t, °C	$\delta_4-\delta_5$
A Solvents			B Solvents		
formamide	34	2.32	dimethylformamide	−53	0.0
water	30	2.00	tetrahydrofuran	−88	0.0
nitromethane	−20	1.78	1,3-dioxolane	−93	0.0
nitroethane	−70	1.49	pyridine	−39	0.0
nitropropane	−80	1.26	tetramethylguanidine	−25	0.0
acetonitrile	24	0.47	acetone	−90	0.0
acetonitrile	−42	1.64	toluene	−80	0.0
methanol	−43	0.92	anisole	−37	0.0
methanol	−80	1.70	methyl acetate	34	0.0
ethanol	−84	1.15			
dichloromethane	−42	1.06			

Table II. Carbon Relaxation Times

	C221		C221·NaSCN		C221·KSCN	
solvent	T_1, s[a]	τ, ps[b]	T_1, s[a]	τ, ps[b]	T_1, s[a]	τ, ps[b]
D_2O	0.4	57	0.75	30	0.65	35
CD_3OD	1.3	17	1.9	12	1.4	16
CD_3CN	1.9	12	2.2	10	1.9	12
CD_3NO_2	0.8	28	0.95	24	0.9	23
$(CD_3)_2CO$	2.5	9	1.9	12	1.5	15
$CDCl_3$	1.2	19	0.9	25	0.6	38

[a] Relaxation times of different CH_2's are equal to within 10%. Average values are given above. [b] Correlation times are calculated on the basis of dipole-dipole relaxation mechanisms with d_{CH} = 1.085 Å.

In a noninteracting (B) medium, such as $(CD_3)_2CO$ or when the external hydrogen bond is formed ($CDCl_3$), the correlation time varies in the order $\tau_{free} < \tau_{Na^+\cdot C221} < \tau_{K^+\cdot C221}$, which indicates that the free ligand is more mobile than the cryptates. On the other hand, in solvents which give the A ^{13}C spectra of the free ligand we have $\tau_{free} \geq \tau_{Na^+\cdot C221} \sim \tau_{K^+\cdot C221}$.

These results are consistent with the hypothesis that in the latter cases there is the formation of a solvent–C221 complex which restricts the ligand's mobility.

C. Proton NMR Studies. In the proton NMR spectra of Na^+·C221 and of K^+·C221, the hydrogen atoms α to nitrogen belonging to the N_2O_4 face are diastereotopic and form an ABXY system with the neighboring OCH_2 whereas the NCH_2CH_2O protons of the short chain form an AA'XX' system. In this spectral region, the main difference between the two spectra is the value of the diastereotopy (0.075 ppm for Na·C221 and 0.295 ppm for K^+·C221). A more fundamental difference is observed for the proton NMR of C221 in different solvents. For noninteracting solvents of class B (acetone, pyridine, THF, DMF) the NCH_2 protons of the N_2O_4 face are equivalent in the whole temperature range whereas an increasing diastereotopy appears for solutions in interacting solvents of class A (CH_3CN, CH_3NO_2, CH_3OH) as the temperature decreases (Figure 3). Since these hydrogens are diastereotopic by nature, these experiments show that the conformational diastereotopy is more important than the intrinsic diastereotopy.[20] Neglecting then the intrinsic diastereotopy and considering the different conformations along the C_4–C_2 bond for the two invertomers at the nitrogen site (Figure 4), it is readily apparent that H_1 and H_2 are equivalent when the pairs of forms I and V, II and IV, and III and VI can be considered as equally populated enantiotopic pairs.

For Na^+ and K^+ cryptates, according to the X-ray structure, one should expect that only forms I and II are present in solution, giving them an averaged ABXY pattern for the NCH_2CH_2O fragment of the N_2O_4 crown face. For C221 in noninteracting

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Table III. Thermodynamic Parameters for the Complexation of Na^+ and K^+ Ions by C221 at 25 °C

solvent	D		Na^+·C221	K^+·C221	$\Delta(Na^+-K^+)$	K_{Na^+}/K_{K^+}
H_2O	78.4	$\Delta G°$[a,b]	−7.2	−5.4	−1.8	(21)[e]
		$\Delta H°$[b]	−5.3	−6.8	+1.5	
		$T\Delta S°$	1.9	−1.4	+3.3	
MeOH	32.7	$\Delta G°$[c]	−13.1	−11.6	−1.5	15 ± 2
		$\Delta H°$	−9.4	−12.2	+2.8	
		$T\Delta S°$	+3.7	−0.6	+4.3	
MeCN	37.5	$\Delta G°$[c]	⩽−15.3	−12.9	⩽−2.4	
		$\Delta H°$	−10.4	−11.4	+1.0	
		$T\Delta S°$	⩽+4.9	+1.5	⩽+3.4	
$MeNO_2$	35.87[d]	$\Delta G°$			−3.6	400 ± 200
		$\Delta H°$	−16.7	−12.2	−4.5	
		$T\Delta S°$			−0.9	
Me_2CO	20.7	$\Delta G°$			−2.6	90 ± 10
		$\Delta H°$	−11.5	−12.6	+1.1	
		$T\Delta S°$			+3.7	
DMF	36.7	$\Delta G°$[c]	−10.8	−9.0	−1.8	(21)[e]
		$\Delta H°$	−8.5	−9.5	+1.0	
		$T\Delta S°$	+2.3	−0.5	+2.8	

[a] Values in kcal mol^{-1}. [b] Reference 19. [c] Reference 5. [d] At 30 °C. [e] Calculated.

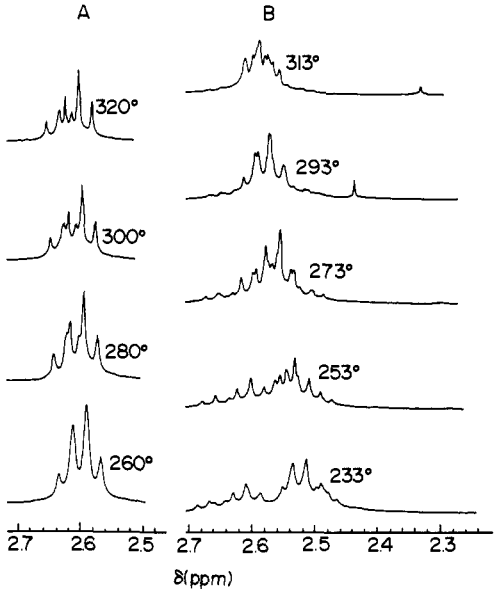

Figure 3. Proton magnetic resonance spectrum of the NCH_2 protons of C221: (A) dimethylformamide solution; (B) acetonitrile solution.

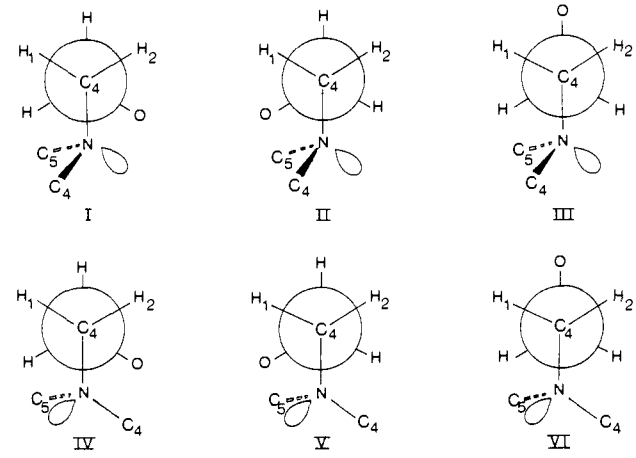

Figure 4. Different conformations along the C_2–C_4 axis of cryptand C221.

solvents, the equivalence of H_1 and H_2 is indicating that $P_I = P_V$; $P_{II} = P_{IV}$; $P_{III} = P_{VI}$. In interacting solvents, class A, one of these equalities is not satisfied any more indicating that the interaction between the solvent and the ligand is strong enough to modify significantly the distribution of conformers and/or invertomers.

D. Thermodynamic Studies. Enthalpies of complexation for the Na^+ and K^+ complexes with C221 were determined in six solvents and are shown in Table III. Whenever possible, these values have been combined with the literature values of the corresponding free energies of complexation so as to obtain the respective entropies of complexation.

It is interesting to note that nearly in all solvents (except $MeNO_2$) the enthalpy of complexation is larger for the potassium ion than for sodium. However, while the sodium complex is entropy stabilized ($\Delta S° > 0$), the potassium complex is entropy destabilized ($\Delta S° < 0$). The only exception seems to be in the acetonitrile solutions where both complexes appear to be entropy stabilized but the sodium cryptate much more so than the potassium one. The net effect of enthalpy and entropy contributions is to make the sodium complex more stable in all the solvents we examined.

It is seen that the selectivity is strongly dependent on the solvent, being, for example, much higher in nitromethan than in other solvents. If we include calculated K_{Na^+}/K_{K^+} ratios for the aqueous and DMF solutions, the Na^+/K^+ selectivity order of the solvents becomes $MeNO_2 > Me_2CO > H_2O \approx DMF > MeOH$.

The fact that solvents strongly influence complexation selectivities has been amply illustrated in studies of the alkali complexes of crown ethers. In fact, in some cases a change in the solvent can actually result in a selectivity reversal. For example, the K_{Na^+}/K_{Li^+} ratio for the diaza-18C6 complexes is 0.67 in acetone but 4900 in pyridine.[21] Hofmanova et al.[22] have also shown that in the case of 3,3-dimethyldibenzo-18C6 the K_{K^+}/K_{Tl^+} ratio is 0.63 in acetonitrile and 16 in methanol.

At this time, however, there is not enough information on alkali ion complexation by C221 in the B-class solvents to compare quantitatively the thermodynamics of complexation in the two classes of solvents. This work is in progress in our laboratories.

In summary, the results clearly indicate that in certain solvents which we class as A there is a specific solvent–C221 interaction that affects the configuration of the free ligand and undoubtedly influences its complexation ability toward alkali metal and other cations. It is evident, therefore, that the mechanism and the kinetics of macrocyclic complex formation in various solvents are strongly influenced not only by cation–solvent but, at least in certain media, by ligand–solvent interactions. Unfortunately quantitative information on the nature and the thermodynamics of ligand-solvent interactions is extremely meager at this time.

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Registry No. $MeNO_2$, 75-52-5; MeCN, 75-05-8; MeOH, 67-56-1; C221, 31364-42-8; formamide, 75-12-7; nitroethane, 79-24-3; nitropropane, 25322-01-4; ethanol, 64-17-5; dichloromethane, 75-09-2.

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