Molecular Recognition. Selective Ammonium Cryptates of Synthetic Receptor Molecules Possessing a Tetrahedral Recognition Site

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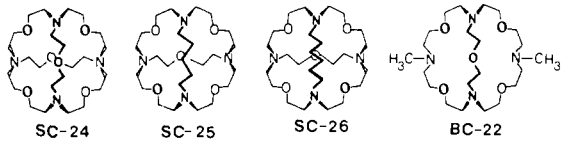
Abstract: The spherical macrotricyclic molecules **1–3** yield ammonium cryptates by inclusion of the NH_4^+ ion into the molecular cavity. Cryptand **1, SC-24**, forms by far the most stable and the most selective NH_4^+ complex known. The cation is expected to be bound by a tetrahedral array of N^+–H···N hydrogen bonds to the four nitrogen sites and by 12 electrostatic interactions (or bent hydrogen bonds) to the oxygens of the ligand. Such a structure agrees with both the high stability and the high selectivity of the [$NH_4^+ \subset$**SC-24**] cryptate. The cavity is probably somewhat too large and slightly flattened to accommodate the cation. The exchange of the cation is very slow. Comparison with the macrobicyclic analog **4, BC-22**, indicates the presence of a large cryptate effect on stability, selectivity, and kinetics of NH_4^+ binding. Comparison of **SC-24** and **SC-25** stresses the requirement for best fit in order to achieve optimal binding of NH_4^+. It is concluded that the cryptand **SC-24** is a molecular receptor possessing a tetrahedral recognition site of high structural and binding complementarity toward the tetrahedral substrate NH_4^+. It represents a state of the art illustration of the molecular engineering involved in abiotic receptor chemistry.

The design of synthetic receptor molecules has at least two aims: to understand the energetic and geometric factors which control molecular association and recognition by the manipulation of binding sites and structural units; to elaborate ligands which selectively bind a given set of substrates for use as complexing agents and/or transformation into molecular carriers and catalysts.[1] In addition, the ability to design artificial receptors also provides insight into the origin of molecular specificity in biological systems.

We describe here the remarkable binding properties of the spherical macrotricyclic cryptands **1–3** (**SC-24**, **SC-25**, **SC-26**[2])



1 2 3 4

toward the ammonium cation NH_4^+ and analyze the factors responsible for the highly selective recognition of this tetrahedral substrate, especially by the symmetrical receptor **SC-24**. The NH_4^+ cation is a substrate of particular interest; it represents the parent species of the substituted ammonium ions, whose complexation has been actively investigated in recent years,[1,3-5] and which plays also a very important role in biochemistry and biology.

Compounds **1–3** have been synthesized earlier and shown to form alkali and alkaline-earth complexes by inclusion of a cation into the molecular cavity, yielding *spherical cryptates*.[2] Their ability to bind a water molecule or halide anions when protonated has also been briefly described.[1,6] The macrobicyclic cryptand **4, BC-22**,[2] has been investigated here mainly for comparison purposes.

Results

1. Formation and Properties of the Ammonium Complexes of Cryptands 1–4. Addition of an insoluble ammonium salt NH_4X ($X = NO_3^-$, Cl^-, ClO_4^-) to solutions of **1–4** in CD_2Cl_2 is followed by the progressive disappearance of the original ^1H NMR spectrum and by the appearance of a new spectrum at slightly higher field (Figure 1; see Table I). At the same time, a triplet corresponding to the ammonium protons appears at low field. The same changes are also observed in other solvents like $CDCl_3$, $(CD_3)_2CO$, and CD_3OH. The ^{13}C NMR spectrum of the complex in methanol contains two signals at 53.8 (NCH_2) and 69.6 ppm (OCH_2) (from internal Me_4Si) as compared to 57.1 and 71.0 ppm, respectively, for the free cryptand. In the presence of excess ammonium iodide, a methanolic solution of **1** shows two ^{14}N NMR signals (Figure 1) whose chemical shifts both correspond to an NH_4^+ species.[7] In the absence of **1** only the unsplit resonance of free NH_4^+ is observed at −27.8 ppm. The quintuplet at δ −22.8 ppm results from N–H coupling ($J_{NH} = 52 \pm 1$ Hz) as shown by proton decoupling.

On cooling a solution of (**1**,$^{15}NH_4^+$) in CD_2Cl_2, the doublet of the ammonium protons broadens, giving at −95 °C very broad signals ($\Delta\nu_{1/2} \sim 70$ Hz) shifted slightly upfield to about 7.6 ppm. As this occurs, the CH_2O and CH_2N triplet resonances of the ligand split each into two ill-resolved bands as shown in Figure 2; this corresponds to the change from an AA′XX′ spectrum to a broadened ABCD type spectrum (or to a superposition of several such spectra) for the NCH_2CH_2O units. In the same temperature range, no broadening or shift is observable in the proton-decoupled ^{15}N NMR spectrum.

The ^1H NMR spectra indicate that addition of an ammonium salt to aqueous solutions of **1** or **2**, yields the same species as in CD_2Cl_2 solution (Table I). In H_2O solution, the NH_4^+ triplet is observed. Experiments at different pH values show that the ammonium complex of **1** is in slow exchange with either the free base or its diprotonated form. In contrast, only averaged spectra are obtained for both ligand and substrate, on progressive addition of an ammonium salt to aqueous solutions of the macrobicycle **4**; for an equimolecular amount of NH_4^+, the spectrum is neither that of the initial compound nor that of a partially protonated species. Since the stability of the (**4**,NH_4^+) complex is comparatively small (see below), uncomplexed ammonium cations exist in solution. The transprotonation reactions 1 and 2 occur; since

$$L + NH_4^+ \rightleftharpoons LH^+ + NH_3 \quad (1)$$

$$LH^+ + NH_4^+ \rightleftharpoons LH_2^{2+} + NH_3 \quad (2)$$

proton exchange is rapid on the NMR time scale, only average signals are observed for L, LH_1^+, LH_2^{2+}, and (L,NH_4^+).

Characteristic changes are also observed by IR spectroscopy (Figure 3). In the presence of NH_4ClO_4, one observes a change in the band shape of the CH stretching and bending modes of ligand **1** (CH_2Cl_2 solution) together with the appearance of new

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(7) "Nitrogen NMR"; Witanowski, M., Webb, G. A., Eds.; Plenum Press: London and New York, 1973.

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Table I. 250-MHz Proton NMR Spectra of Ligands 1-4 and Their Ammonium Cryptates at 18 °C[a]

	1		2		3		4	
solvent	free	$+NH_4^+$	free	$+NH_4^+$	free	$+NH_4^+$	free	$+NH_4^+$
CD_2Cl_2	NCH_2		NCH_2		NCH_2		NCH_2	
	2.70 (24 H)	2.59 (24 H)	2.39 (4 H)	2.39 (4 H)	2.45 (4 H)	2.32 (4 H)	2.62 (8 H)	2.41 (4 H)
			2.51 (8 H)	2.52 (8 H)	2.57 (8 H)	2.60 (20 H)	2.68 (8 H)	2.61 (16 H)
			2.67 (12 H)	2.61 (12 H)	2.69 (12 H)		2.71 (4 H)	
	OCH_2		OCH_2		OCH_2		OCH_2	
	3.63 (24 H)	3.52 (24 H)	3.58 (20 H)	3.52 (20 H)	3.55 (20 H)	3.50 (20 H)	3.51 (8 H)	3.52 (20 H)
			$C\text{-}CH_2$		$C\text{-}CH_2$		3.55 (8 H)	
			1.46 (6 H)	1.22 (2 H)	1.45 (8 H)	1.47 (8 H)	3.58 (4 H)	
				1.50 (4 H)			NCH_3	
		NH_4^+		NH_4^+		NH_4^+	2.27 (6 H)	2.22 (6 H)
		6.77 (4 H)		6.90 (4 H)		7.00 (4 H)		7.20 (4 H)
H_2O	NCH_2		NCH_2				NCH_2	
	2.89 (24 H)	2.62 (24 H)	2.57 (4 H)	2.28 (4 H)			2.69 (4 H)	2.61 (8 H)
			2.73 (20 H)	2.40 (8 H)			2.61 (16 H)	2.53 (12 H)
				2.49 (12 H)				
	OCH_2		OCH_2				OCH_2	OCH_2
	3.69 (24 H)	3.58 (24 H)	3.55 (20 H)	3.46 (20 H)			3.49 (20 H)	3.49 (20 H)
			$C\text{-}CH_2$				NCH_3	NCH_3
			1.32 (2 H)	1.10 (2 H)			2.13 (6 H)	2.21 (6 H)
			1.42 (4 H)	1.38 (4 H)				
		NH_4^+		NH_4^+[b]				NH_4^+[b]
		6.97 (4 H)						

[a] Shifts in ppm downfield from Me_4Si or TMPS in CD_2Cl_2 and D_2O, respectively. Solution concentration is about 5×10^{-2} mol L^{-1} in ligand. For compounds 2, 3, 4 fortuitous chemical shift equivalence occurs sometimes for nonequivalent CH_2 groups or for diastereotopic hydrogen in CH_2 groups. For the resolved AA'XX' spectra arising from OCH_2CH_2N fragments, an average ^3J coupling constant of 5.5 Hz is measurable. The NH_4^+ protons give a broadened triplet with $J(^{14}N,H) = 52 \pm 0.5$ Hz. [b] No signal observed for the NH_4^+ protons.

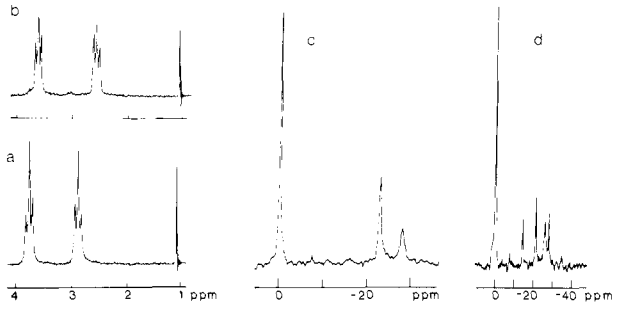

Figure 1. NMR spectra of the [$NH_4^+ \subset$**SC-24**] cryptate. Proton NMR spectra at 60 MHz in D_2O (a) of cryptand **1**, **SC-24**, at pH 12.7; (b) of the complex (**SC-24**,NH_4^+) at pH 9.4. Note the appearance of very small bumps at δ 3.0 and 3.65 ppm due to a trace of the diprotonated ligand **SC-24**,$2H^+$; the signal at about 1 ppm is due to internal *t*-BuOH (ref. TMPS). Nitrogen-14 NMR spectra of the (**SC-24**,NH_4^+) complex at 7.22 MHz in methanol solution in the presence of an excess of NH_4I; (c) with proton decoupling, (d) without proton decoupling. Note that the N,H coupling is observable for the complexed cation; the chemical shifts are given with respect to internal NMe_4Cl at 30 °C.

lines belonging to the ammonium species. The difference spectrum between (**1**,NH_4^+) and (**1**,ND_4^+) gives the shape of the NH stretching and bending modes.

Finally, X-ray analysis of the crystalline $\mathbf{1}/NH_4I/H_2O$ compound has already shown that it is a complex in which ammonium cation is included in the cavity of **1**.[8]

2. Determination of the Stability Constants. The stability constants of the NH_4^+ complexes of ligands **1**–**4** were determined by pH metric titration in the domain where only the mono- and diprotonated species need to be considered in addition to the complex. The following equilibria obtain:

$$L + NH_4^+ \rightleftharpoons (L,NH_4^+) \qquad K_s \qquad (3)$$

$$LH^+ \rightleftharpoons L + H^+ \qquad K_1 \qquad (4)$$

$$LH_2^{2+} \rightleftharpoons LH^+ + H^+ \qquad K_2 \qquad (5)$$

$$NH_4^+ \rightleftharpoons NH_3 + H^+ \qquad K_N \qquad (6)$$

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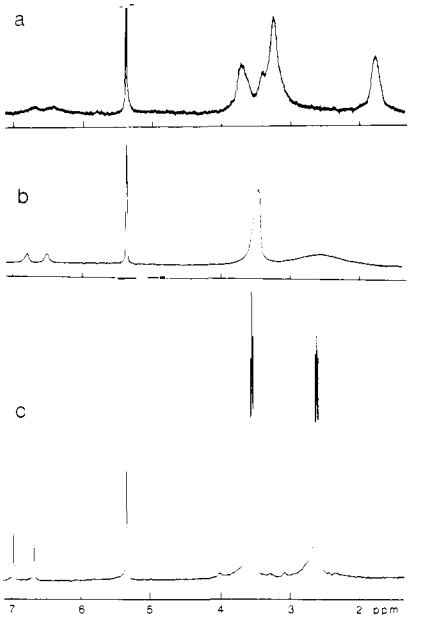

Figure 2. Temperature dependence of the 250-MHz ^1H NMR spectrum of the $^{15}NH_4NO_3$ cryptate of **SC-24** in CD_2Cl_2: (a) spectrum at −95 °C; (b) spectrum at −80 °C, showing the coalescence of the NCH_AH_B signals; (c) spectrum at 18 °C. The spectrum of the NCH_2CH_2O units is of ABCD type with $NCH_A \sim 1.75$ ppm, $NCH_B \sim OCH_C \sim 3.3$ ppm, $OCH_D \sim 3.7$ ppm (ref. Me_4Si).

Figure 3. Infrared difference spectra between the NH_4^+ and ND_4^+ cryptates of **SC-24** in CH_2Cl_2 solution: NH stretching (left) and bending (right) modes.

Computer analysis of the titration curves and knowledge of the protonation pK_a's allows the calculation of the stability constant

Table II. Stability Constants Log K_s and NH_4^+/K^+ Selectivity of the Complexes of the Spherical Cryptands 1 and 2 and of Selected Synthetic and Natural Ligands[a]

ligand	solvent	log K_s[b] for cation			selectivity
		NH_4^+	K^+	Rb^+	NH_4^+/K^+
1, **SC-24**	W	6.1 (0.2)	3.4[2] (0.2)	4.2[2] (0.2)	500
2, SC-25	W	4.3 (0.2)	2.5[2] (0.2)	3.3[2] (0.2)	63
4, **BC-22**	W	1.7 (0.2)	1.3 (0.4)	1.3[2] (0.4)	2.5
6[33]	W	1.23 (0.06)	2.03[c] (0.1)	1.56 (0.02)	0.16
7[34]	W	3.5 (0.1)	5.5 (0.2)		0.01
8[35]	M/W 9/1	4.8[d] (0.1)	3.8 (0.1)		11
nonactin[36]	M	4.4 (0.1)	4.15 (0.1)	4.15 (0.1)	1.7
trinactin[36]	M	5.3 (0.1)	4.95 (0.1)	4.9 (0.1)	2.3
valinomycin[38]	M	1.67	4.90	5.26	0.0006

[a] At 25 °C in aqueous (W) or methanolic (M) solution. [b] Error limits (±) are given in parentheses, as estimated for the present data or taken from the literature. [c] 6.10 in methanol.[34] [d] Stability constant for $CH_3-NH_3^+$.

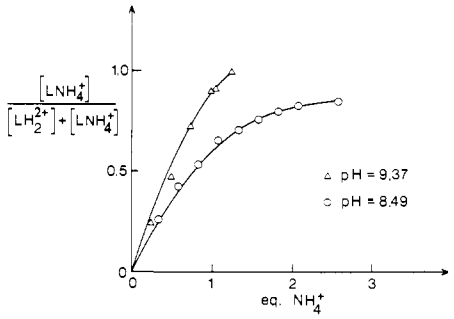

Figure 4. Determination of the stability constant of the $[NH_4^+ \subset$ **SC-24**] cryptate by competition with the diprotonated form of the ligand; plot of the complexed fraction of NH_4^+ against equivalents of NH_4NO_3 added to an aqueous solution of L = **SC-24** at two different pH values.

K_s. The following pK_1 and pK_2 values (±0.1) have been determined:[2] 10.9 and 9.65 for **2**; 10.4 and 8.3 for **3**; 10.4 and 8.3 for **4**. The special protonation properties of **1** (see, for instance, ref 1) will be described in another publication; for the present purpose it suffices to know the sum $pK_1 + pK_2 = 21$.

Since the species L,LH_2^{2+} and (L,NH_4^+) are in slow exchange on the ^1H NMR time scale (see below), integration of the different signals at a given pH allows also the calculation of K_s. For compound **1**, complete equilibrium curves in buffered solutions at pH 9.37 and 8.49 were measured (Figure 4); for compound **2** only one determination was made at pH 9. Agreement between the different measurements is satisfactory. The data are listed in Table II, together with some literature results on NH_4^+ complexation by other ligands.

3. Rates of Exchange of the Ammonium Cation. Depending on the pH of the solution, the $(\mathbf{1},NH_4^+)$ complex is in equilibrium with the free base **1** and NH_3 or with its diprotonated form $\mathbf{1},H_2^{2+}$ and NH_4^+. Separate NMR signals have been observed in aqueous solutions at 25 °C for **1**, for $(\mathbf{1},NH_4^+)$, and for $(\mathbf{1},H_2^{2+})$, indicating that exchange is slow. The rate of decomplexation of the cation has been determined over a wide range of pH values from the temperature dependence of the ^1H NMR signals of the ligand and of the species $^{14}NH_4^+$ and $^{15}NH_4^+$, or of the ^{14}N NMR signals of the free and complexed ammonium cations.

At pH values of 8 and 9.1, the coalescence of the NCH_2 ^1H NMR signals in a solution containing equimolecular amounts of $(\mathbf{1},NH_4^+)$ and $(\mathbf{1},H_2^{2+})$ occurs at 80 and 75 °C, respectively. From the chemical shift difference of 0.43 ppm (26 Hz at 60 MHz), the free energies of activation at the coalescence temperature $\Delta G^{\ddagger}_c$, may be calculated by means of the usual equations:[9] $\Delta G^{\ddagger}_{353} = 17.9$ kcal/mol at pH 8 and $\Delta G^{\ddagger}_{348} = 17.6$ kcal/mol at pH 9.1. At pH 11.6 $(\mathbf{1},H_2^{2+})$ is not observed in the spectrum and $(\mathbf{1},NH_4^+)$ is in equilibrium with the free base **1**,

$$(\mathbf{1},NH_4^+) + OH^- \rightleftharpoons \mathbf{1} + NH_3 + H_2O \qquad (7)$$

making the reasonable assumption that NH_3 exchange is fast. Coalescence of the NCH_2 signals ($\Delta\nu = 14$ Hz at 90 MHz) occurs at 50 °C giving $\Delta G^{\ddagger}_{323} = 16.7$ kcal/ml (pH 11.6).

Attempts to measure directly the exchange rate by ^{14}N NMR gave only a lower limit for $\Delta G^{\ddagger}$. At pH 8.7, the ^{14}N NMR signal due to the mixture of free ammonium cation and ammonia shifts to high field toward the signal of the complex as the temperature increases; only a limit $\Delta G^{\ddagger}(^{14}N) > 17$ kcal/mol may be calculated from the chemical shift difference at 25 °C.

At pH 10, the complex $(\mathbf{1},^{15}NH_4^+)$ shows a slightly broadened doublet ($\Delta\nu_{1/2} = 4$ Hz; $J_{^{15}N-H} = 72.5$ Hz; 22 °C; 250 MHz) for the ammonium protons. This broadening remains constant up to 32 °C but increases markedly when the solution is heated to 60 °C. The origin of the ambient temperature broadening will be discussed below; the further broadening at higher temperature ($\Delta\nu_{1/2} = 16$ Hz at 60 °C) allows the calculation of the exchange rate[9] of the ammonium protons, giving a free energy of activation $\Delta G^{\ddagger}_{333} \sim 17$ kcal/mol.

Discussion

1. Nature and Structure of the NH_4^+ Complexes. The spectral and analytical data described above indicate that ligands **1–4** form complexes with the ammonium cation.

By analogy with the inclusion of metal cations in macrobicyclic ligands[1,10] as well as in compounds **1–4**,[2] the ammonium complexes of the latter are also expected to be of the cryptate type. The physicochemical data agree with this formulation. It is confirmed by the crystal structure of $(\mathbf{1},NH_4^+)I^-,H_2O$,[8] where the N^+ atom is found at the center of a tetrahedron formed by the four nitrogen sites of the ligand oriented inside the cavity in the i_4 conformation.[2] The IR spectrum of **1** in $CDCl_3$ contains a satellite at 2190 cm^{-1} due to $N\cdots D—CCl_3$ hydrogen bonding of the solvent to outward oriented ligand nitrogen sites;[11] this band is absent in the spectrum of the $(\mathbf{1},NH_4^+)$ complex, indicating that the ligand in the complex also assumes the i_4 form in solution.

Among the four $N^+\cdots N$ distances measured in the crystal, one is shorter (3.05 Å) than the three other ones (3.15, 3.15, and 3.17 Å). An even greater dispersion is observed for the $N^+\cdots O$ distances which range from 3.00 to 3.28 Å. Strong $N—H^+\cdots N$ hydrogen bonds have appreciably shorter $N^+\cdots N$ distances (~2.92 Å).[12] All the $N^+\cdots O$ distances are longer than those found for the $N—H^+\cdots O$ hydrogen bonds present in the crystal structure of the NH_4^+ complexes of macrotetrolide antibiotics (2.83–2.93 Å)[13,14] and of 18-crown-6 (2.86–2.88 Å).[15] Thus the cavity of **1** appears

(9) $\Delta G^{\ddagger} = 4.57T[10.32 + \log(T/k)]$ kcal/mol; $k_c = 2.221\Delta\nu$ s^{-1}. k_c = rate at coalescence temperature T_c; $\Delta\nu$ = chemical shift difference in hertz. Rate $k = \pi B$; B = line broadening due to exchange below coalescence: Johnson, C. S. *Adv. Magn. Reson.* **1965**, *1*, 33–102. Binsch, G. *Top. Stereochem.* **1968**, *3*, 97–192. Lehn, J. M. *Top. Curr. Chem.* **1970**, *15*, 311–377. Anderson, J. E.; Lehn, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 81–87.

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to be somewhat too large for NH_4^+. Furthermore, the binding pattern of NH_4^+ is not clear since the hydrogens have not been located. In order to describe the complexes more precisely than just by their inclusion nature, several questions must be considered concerning the occurrence of transprotonation inside the cavity, the nature of the binding interactions, and the position and dynamics of the complexed cation.

The chemical shift, the multiplicity, the $^{14}N,H$ coupling constant, and the relatively small line width of the ^{14}N NMR signal of the complexed species in ($\mathbf{1},NH_4^+$) (Figure 1) correspond to an ammonium cation and not to NH_3, which would result from proton transfer from NH_4^+ to an endo oriented ligand nitrogen site in the cavity.[7] The complex is therefore an *ammonium cryptate* [$NH_4^+\subset$**SC-24**], **4**.

The transprotonation process (eq 8) should also affect the

$$[NH_4^+\subset\mathbf{SC\text{-}24}] \rightleftharpoons [NH_3\subset\mathbf{SC\text{-}24}\text{—}H^+] \qquad (8)$$

coupling pattern of the ^{14}N NMR spectrum (see Experimental Section). Since the multiplet splittings measured for NH_4^+ either in the ^{14}N (or ^{15}N) or in the ^1H spectra of the complex are equal within experimental error (±0.5 Hz), transprotonation is at most about 5%.

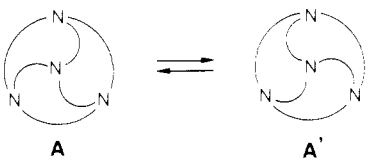
The N–H stretching mode in the IR spectrum of the ($\mathbf{1},NH_4^+$) complex (Figure 3) appears as a triplet at 3000 cm^{-1}, shifted from the value of 3200–3300 cm^{-1} corresponding to the weakly or non-hydrogen-bonded NH_4^+ cation in NH_4ClO_4.[16] The NH bending mode shows a fine structure which is absent in the low-temperature IR spectrum of the tetrahedral NH_4Cl[17a] but present in the deformed lattice of NH_4N_3.[17b]

In the proton-decoupled ^{14}N NMR spectrum of ($\mathbf{1},NH_4^+$) in water or in chloroform (Figure 1), the signal of the bound ammonium ion is broadened ($\Delta\nu_{1/2}$ = 7 Hz in water) with respect to free NH_4^+ ($\Delta\nu_{1/2}$ < 1 Hz). Measurement of the spin–lattice relaxation time gives $T_1 = T_2 = 45 \pm 5$ ms (in water) and $T_1 = T_2 = 140 \pm 10$ ms (in chloroform). The absence of a nuclear Overhauser effect between proton-decoupled and nondecoupled spectra indicates that ^{14}N relaxes mainly through the quadrupolar mechanism. The correlation times of the ligand and of the complex have been calculated from their ^{13}C relaxation times. As for sodium cryptates in methanol,[18] they decrease on complexation in both aqueous (from 130 to 90 ps) and chloroform solutions (from 56 to 33 ps). The rather broad deuterium triplet resonance of the ($\mathbf{1},ND_4^+$) complex ($\Delta\nu_{1/2} \sim 6$ Hz) indicates that the ammonium ion does not reorient rapidly (with respect to overall molecular motions) inside the cavity, so that the correlation time τ obtained from ^{13}C measurements is transferable to ^{14}N. Using $T_1(^{14}N)$ and $\tau(^{13}C)$ for the complex and eq 9,[19] a value of 80 ±

$$1/T_1(^{14}N) = \tfrac{3}{2}\pi^2\chi^2(^{14}N)\tau(^{13}C) \qquad (9)$$

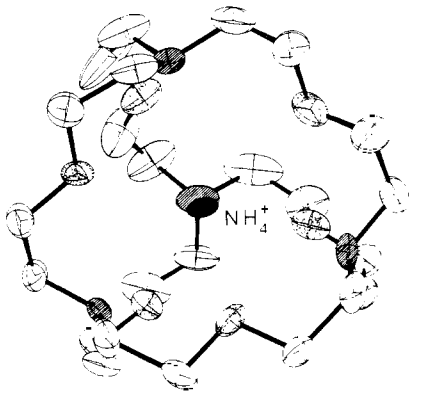
5 kHz is calculated for the nuclear quadrupole coupling constant $\chi(^{14}N)$ of the nitrogen of the complexed NH_4^+ cation. This value appears too high for such a symmetrical ion to result solely from an electric field gradient created by the dipoles surrounding it in the complex.[7] It may come from a nonsymmetrical complex and/or from a very small amount of transprotonation (eq 8). But, whatever the origin of this dissymmetry, an averaging process must be present, since at ambient temperature the NMR spectrum of the ($\mathbf{1},NH_4^+$) complex is that of a symmetrical species.

The temperature-dependent ^1H NMR spectral changes (Figure 2) must arise from a rate process between two forms of the ($\mathbf{1},NH_4^+$) complex in which the CH_2 protons are nonequivalent. They may be explained by the presence of a *conformational twisting* process of the type represented schematically by A ⇌ A′, an exchange between two conformations of **SC-24** in which the cryptand is twisted around the axis of one bridgehead nitrogen and probably somewhat flattened along the same axis; this process is accompanied by rotations around the C–C bonds in the bridges and the twisting exchanges from one nitrogen site to another. The free energy of activation $\Delta G^\ddagger$ for this process, calculated[9] from the coalescence of the NCH_AH_B signals ($\Delta\nu \sim 390$ Hz), is about 8.5 kcal/mol at the coalescence temperature (about 193 K; Figure 2b). Similar conformational motions have been observed earlier for torsions around the bridgehead axis of macrobicyclic cryptands, with free energies of activation of 9–10 kcal/mol at about 180–200 K.[20]



A A′

As pictured in structure B,[8b] when viewed along an N···NH_4^+ axis, the ligand in the crystal structure of [$NH_4^+\subset$**SC-24**] has an overall twisted shape strikingly similar to that represented schematically by A, thus adding weight to the occurrence of the A ⇌ A′ process. Finally, low-temperature ^1H NMR studies of the [$Cs^+\subset$**SC-24**] cryptate give spectral changes resembling those shown in Figure 2, indicating that the same type of conformational process is occurring.[20c]



B

This discussion of the *spectroscopic properties* of the cryptate [$NH_4^+\subset$**SC-24**] leads to the following conclusions.

(a) The environment of the ammonium nitrogen is not a perfect but a deformed tetrahedron (^{14}N NMR and IR spectroscopy).

(b) At room temperature, fast exchange of the distortion gives ^1H and ^{13}C NMR spectra which correspond to effective tetrahedral symmetry; at low temperature the exchange process is slowed down and the ^1H NMR spectrum becomes nonsymmetrical, but the ^{15}N (^1H decoupled) spectrum is unchanged.

(c) The ammonium ion does not rotate in the cavity (^2D NMR spectroscopy), indicating tight dynamic coupling between receptor and substrate (*isodynamic* cryptate).[21]

In the *gas phase*[22,23] NH_4^+ is more strongly solvated by NH_3 than by H_2O, the enthalpy of formation being 24.8 kcal/mol for

(15) Nagano, D.; Kobayashi, A.; Sasaki, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 790–793.
(16) Bellamy, L. J. "The Infra-red Spectra of Complex Molecules"; Chapman and Hall: London, 1975; p 389. Miller, F. A.; Wilkins, C. H. *Anal. Chem.* **1952**, *24*, 1253–1294.
(17) (a) Wagner, E. L.; Hornig, D. F. *J. Chem. Phys.* **1959**, *18*, 296–304. (b) Dows, D. A.; Whittle, E.; Pimentel, G. C. *Ibid.* **1955**, *23*, 1475–1479.
(18) Kintzinger, J. P.; Lehn, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 3313–3314.
(19) Kintzinger, J. P.; Lehn, J. M. *Helv. Chim. Acta* **1975**, *58*, 905–917.
(20) (a) Dietrich, B.; Lehn, J. M.; Sauvage, J. P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629–1645. (b) Cheney, J.; Kintzinger, J. P.; Lehn, J. M. *Nouv. J. Chim.* **1978**, *2*, 411–418. The particularly large difference in chemical shift between the geminal NCH_AH_B protons (Figure 2) is indicative of a rotameric conformation in which the nitrogen lone pair is oriented trans to one H and gauche to the other one; a more complete study of conformational processes in various cryptands and cryptates, and of the use of NCH_AH_B signals as probes in such processes, is under way: (c) Kintzinger, J. P.; Lehn, J. M., work in progress.
(21) Behr, J. P.; Lehn, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 1743–1747. Kintzinger, J. P.; Kotzyba-Hibert, F.; Lehn, J. M.; Pagelot, A.; Saigo, K. *J. Chem. Soc., Chem. Commun.* **1981**, 833–836.
(22) Hogg, A. M.; Kebarle, P. *J. Chem. Phys.* **1965**, *43*, 449–456.
(23) Payzant, J. F.; Cunningham, A. J.; Kebarle, P. *Can. J. Chem.* **1973**, *51*, 3242–3249.

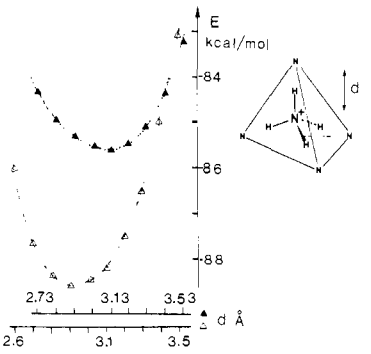
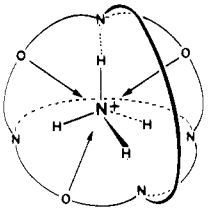


Figure 5. Computed total energy of the system formed by NH_4^+ and $4NH_3$ molecules oriented along the four N^+–H axes as a function of distance d when NH_4^+ moves along a C_3 axis of: (▲) a regular tetrahedron of the four NH_3 groups equidistant by 5.11 Å; (△) a flattened tetrahedron having one NH_3 at a distance of 5.01 Å from the three others equidistant by 5.11 Å (STO-3G computations[26]).

(NH_4^+,NH_3) and 17.3 kcal/mol for (NH_4^+,H_2O). Furthermore, four molecules of NH_3 are taken up first, giving (NH_4^+,$4NH_3$) ($\Delta H°$ = 68.6 kcal/mol) which then forms a second solvation shell preferentially with water. Ab initio[24] and semiempirical[25] computations indicate that: (1) in the addition compound (NH_4^+,L), binding of L along an N^+–H bond axis is much more favorable than interaction along the bisector of an H–N^+–N angle for both L = NH_3 or H_2O; (2) NH_4^+ has higher affinity for NH_3 than for H_2O (i.e., the H_3N^+–H···NH_3 hydrogen bond is stronger than the H_3N^+–H···OH_2 one); (3) the tetraammoniate of NH_4^+ is more stable than the tetrahydrate and its structure is symmetrical with the four NH_3 molecules approaching along the axes of the NH_4^+ tetrahedron; an interaction energy of 113 kcal/mol is computed for (NH_4^+,$4NH_3$) at the optimal equilibrium distance (2.7 Å).[24]

We have performed a series of calculations[26] on a model system in which an NH_4^+ ion moves along a C_3 axis of a tetrahedron of four NH_3 molecules oriented along the N^+–H bond axes, with N···N edges fixed at 5.11 Å. The most stable position of the ammonium ion is at the center of the cavity (stabilization of 85.6 kcal/mol; N^+–H···N = 3.13 Å). When the tetrahedron is slightly flattened, with one NH_3 at N···N = 5.01 Å from the three others equidistant by 5.11 Å (as in the X-ray structure of (1,NH_4^+)),[8] a more stable position is found (88.6 kcal/mol) when one N^+–H···N distance is equal to 2.9 Å and the three others are 3.16 Å (Figure 5). At this position, the barrier to rotation along the C_3 axis is 23 kcal/mol.

In conclusion, the structural, spectral, and computational results on the [NH_4^+⊂**SC-24**] *spherical cryptate* **5** are compatible with



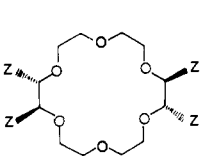
5

a structure in which (1) the NH_4^+ cation is bound inside the cavity of the spherical cryptand in its i_4 form, in a tetrahedral array of linear N^+–H···N hydrogen bonds with the four bridgehead nitrogen sites (the arrangement is reminiscent of the (NH_4^+,$4NH_3$) species); (2) the bridgehead nitrogen sites are arranged at the corners of a tetrahedron, somewhat flattened along one axis (as indicated by the crystal structure[8]), giving a binding pattern with one shorter and three longer hydrogen bonds; (3) the flattening exchanges between the four corners, the process being accompanied by a twisting motion A ⇌ A′ and rotations in the $NCH_2CH_2OCH_2$-CH_2N bridges; (4) the binding pattern is completed by a set of 12 electrostatic interactions between the partial charge on the NH_4^+ hydrogens and the six ether oxygens, located at the corners of an octahedron and fitting into the six H–N^+–H angles; they may be considered to form 12 weaker, bent N^+–H···O hydrogen bonds.[27-29]

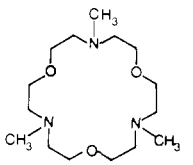
2. Stability and Selectivity of the Spherical NH_4^+ Cryptates. The ammonium cation is usually compared with the monovalent alkali cations and has been assigned an ionic radius of 1.43 Å, a size intermediate between K^+ (1.33 Å) and Rb^+ (1.49 Å).[30] The strong and selective binding of NH_4^+ relative to K^+ or Rb^+ is thus an especially interesting problem of molecular recognition. Table II gives the stability constants for the complexation of these cations by selected natural and synthetic macrocycles[31-38] in addition to the present receptor molecules **1**, **2**, and **4**.

Inspection of the data listed in Table II clearly shows that the spherical cryptand **SC-24** binds the NH_4^+ cation *far more strongly and far more selectively* than any other known complexing agent.

(a) The *stability* constant of 10^6 in aqueous solution for [NH_4^+⊂**SC-24**] is larger than that of the NH_4^+ complex of [18]-crown-6, **6**,[33] by a factor of about 10^5. It is even higher than



6, Z = H
7, Z = Co_2^-



8

that of the NH_4^+ complex of the chiral tetracarboxylate macrocyclic receptor **7**, which forms the most stable macrocyclic complexes known and binds both K^+ and NH_4^+ more strongly than either the parent **6** or valinomycin by at least two to three powers of 10.[34] One may estimate K_s of [NH_4^+⊂**SC-24**] to be about 10^3–10^4 times greater in methanol than in water,[1a] i.e., in the 10^9–10^{10} range. This is higher by factors of about 10^5 than the stabilities of the NH_4^+ complexes of the macrotetrolides (nonactin, monactin, dinactin, trinactin) which form the strongest NH_4^+ complexes of known natural macrocyclic ligands.[36,37]

(b) The binding *selectivity* NH_4^+/K^+ of about 500 displayed by **SC-24** is higher by a factor of about 250 than that of the most selective natural ligands, the macrotetrolides.[36] Since the [18]-N_3O_3 macrocycle **8** binds $CH_3NH_3^+$ better than K^+,[35] it may be

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(26) Ab initio STO-3G computations: Hehre, W. J.; Lathan, W. A.; Ditchfield, R.; Newton, M. D.; Pople, J. A. Program GAUSSIAN 70; *QCPE* No. 236, University of Indiana, Bloomington, Ind. Bond lengths N–H = 1.043 and 1.025 Å for NH_4^+ and NH_3, respectively. We thank Dr. G. Wipff for his help in performing these computations.
(27) In the NH_4^+ and R–NH_3^+ cations the positive charge is located on the hydrogen atoms as shown by both theoretical[24,28] and experimental[29] results.
(28) Kollman, P. *J. Am. Chem. Soc.* **1977**, *99*, 4875–4894. Lehn, J. M.; Wipff, G., unpublished computations.
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(31) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600–606.
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(34) Behr, J. P.; Lehn, J. M.; Vierling, P. *J. Chem. Soc., Chem. Commun.* **1976**, 621–623.
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(36) Chock, P. B.; Eggers, F.; Eigen, M.; Winkler, R. *Biophys. Chem.* **1977**, *6*, 239–251.
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expected to complex NH_4^+ preferentially to K^+, with a selectivity larger than that of the macrotetrolides, but still appreciably lower than for **SC-24**. In contrast, the macrocycles **6** and **7**, and especially valinomycin,[38] complex K^+ much more strongly than NH_4^+. The selectivity change from valinomycin to **SC-24** thus covers a range of about 10^6.

(c) Comparing **SC-24** to **SC-25**, it is seen that the replacement of just one oxygen by a CH_2 group markedly decreases the stability of the complexes and even more the NH_4^+/K^+ selectivity (Table II). This may arise from the lower symmetry of **SC-25** and its resulting lower complementarity to the NH_4^+ substrate, in addition to the decrease in electrostatic interaction.

(d) The macrobicycle **BC-22** has lost almost completely the complexation ability and the selectivity of **SC-24**. This dramatic effect results from the removal of just one bridge in **SC-24**, i.e., from a decrease in cyclic order from the tricyclic to the bicyclic ring system. It demonstrates the importance of the spherical macrotricyclic structure in achieving the remarkable binding properties of **SC-24**.

(e) Finally, in view of the highly connected structure of **SC-24**, delineating a well-enclosed cavity of defined size (of about 1.6 Å radius[2]), this cryptand should be able to realize a close to *total recognition* of NH_4^+ with respect to substituted ammonium salts, which are expected to be unable to enter the cavity. Primary ammonium cations $R-NH_3^+$ might be able to anchor the $-NH_3^+$ group into one of the four [18]-N_3O_3 faces of the **SC-24** tricycle, since the corresponding macrocycle **8** forms stable $R-NH_3^+$ complexes.[35] However, such anchoring should be rendered more difficult in **1** than in **8** by the locking of the N sites in the polycyclic structure. When about 1 equiv of $CH_3NH_3BF_4$ is added to a solution of **SC-24** in CD_3CN, the NMR spectrum at −40 °C is markedly affected; it indicates the formation of a slowly exchanging complex in which the ligand does not retain its symmetry; the signals observed agree with the fixation of a $CH_3NH_3^+$ cation on one [18]-N_3O_3 face (of type **8**[35]) of the cryptand; in view of the cavity size it is very probable that complexation is external, with the CH_3 group situated outside the molecular cavity. On the other hand, ^1H NMR indicates that progressive addition of *t*-Bu-NH_3^+ to a methanolic solution of **1** causes only ligand protonation by proton transfer from the substrate. The NH_4^+/RNH_3^+ structural recognition factor is therefore very high.

3. Effective pK_a of Bound NH_4^+ in the [$NH_4^+\subset$SC-24] Cryptate. The protonation equilibrium of the NH_4^+ cryptate of **1** is:

$$[NH_4^+\subset\text{SC-24}] \rightleftharpoons [NH_3\subset\text{SC-24}] + H^+ \qquad (10)$$

The NH_3 cryptate has probably low stability and dissociates rapidly. Attempts to observe this complex in a solution of **1** in benzene saturated with ammonia were unsuccessful. One may define an apparent acidity constant of the NH_4^+ cryptate by:

$$(L,NH_4^+) \rightleftharpoons L + NH_3 + H^+ \qquad (11)$$

$$K_{app} = [L][NH_3][H^+]/[(L,NH_4^+)] = K_N/K_s \qquad (12)$$

where K_s and K_N are defined by eq 3 and 6, respectively. One calculates an apparent pK_a for [$NH_4^+\subset$**SC-24**] of pK_{app} = 15.3. That our assumption is essentially correct is verified by following the deprotonation of (**1**,NH_4^+) at very high pH. At pH greater than 13, equilibrium (eq 11) is rapid on the ^1H NMR time scale, and only average signals between the complex and the free ligand are observed. At pH 13.8 the chemical shifts indicate that the ratio [(**1**,NH_4^+)]/[**1**] is equal to about 3. From the calculated concentration of free NH_4^+ at this pH, one obtains log K_s = 6 for the ammonium cryptate of **SC-24**, in agreement with the value determined above.

The very high pK_{app} of this complex means that the NH_4^+ cation is stabilized enough in the bound state to remain more than 50% protonated even in 10 M base. It is also a clear indication of how much tight binding in receptor–substrate associations of chemical as well as biological nature may affect the properties of ionizable groups. In enzyme active sites, local environment may greatly affect the pK_a of functional groups; in acetoacetate decarboxylase, the pK_a of the active site lysine ammonium group is lowered to 6.0 by a proximal positive charge, a pK_a shift of 4.7 from the value in aqueous solution.[39] In [$NH_4^+\subset$**SC-24**] the shift is even larger and in the opposite direction ($\Delta pK_a \sim 6$). Large pK_a shifts may thus arise in either the substrate or the receptor site on formation of the complex; a potential consequence of special interest is the activation of reactive groups in molecular catalysts on substrate binding.[40]

4. Kinetics of NH_4^+ Exchange. Since the activation energies calculated from the temperature dependence of the NMR signals of the ligand **SC-24** are nearly constant in the pH range 8–11.5, and since the same values are obtained from the nitrogen and hydrogen resonances of the ammonium ion, one can conclude that the observed rate process is exchange of the NH_4^+ cation and that the rate-limiting step in the decomplexation process is the exit of the ammonium ion out of the cavity. The energy barrier to NH_4^+ exchange (~17–17.5 kcal/mol) is very high, higher than that found for the Rb^+ cation, which forms the most stable alkali cation complex.[2] The exchange rate is also several orders of magnitude slower than the rates of dissociation of the macrotetrolide NH_4^+ complexes ($\sim 5 \times 10^4$ s^{-1}).[36] This very large hindrance to cation exchange may be ascribed to two main factors: the resistance of the triply connected faces of the macrotricyclic cryptand to deformation and the hindrance to stepwise cation solvation in the transition state as the cation slips through a face of the structure.

At high pH bimolecular decomplexation involving the hydroxide ion participates increasingly. It is only above pH 13 that exchange between [$NH_4^+\subset$**SC-24**] and the free base becomes fast, as shown by the coalescence of their ^1H NMR signals into averaged resonances. The observation at lower pH of an NH_4^+ proton signal in this cryptate, separate from the solvent water signal, indicates very slow proton exchange between the complexed NH_4^+ and external water. Thus, the cation inside the cavity is very efficiently shielded by the macrotricyclic structure from approach of hydroxide ions or water molecules through the 18-membered faces. Very large retardation of proton exchange has also been observed for macrobicyclic molecules and especially for the proton cryptates of the very tight [1.1.1] cryptand.[20b,41]

The very slow exchange rates of both the NH_4^+ cation and of its protons may thus be ascribed to the cryptate nature of the NH_4^+ complex of **SC-24**.

5. Spherical Macrotricyclic Cryptands: Receptor Molecules with a Tetrahedral Recognition Site. The unique features of cryptand **SC-24**—very strong binding of the NH_4^+ ion, very high NH_4^+/K^+ selectivity, very slow exchange of the cation—indicate that it is an *optimal receptor molecule* for NH_4^+.

From the *structural* point of view, the nature of the [$NH_4^+\subset$**SC-24**] cryptate has been described above. The intramolecular cavity of **SC-24** is of *size* compatible with the NH_4^+ substrate, although it appears to be slightly too large.

From the *energetic* point of view, the very high stability and NH_4^+/K^+ selectivity of the [$NH_4^+\subset$**SC-24**] cryptate rests not only on the arrangement of the binding sites but also on their nature, i.e., on the intermolecular interactions involved. The experimental[22,23] and theoretical[24,25] results mentioned above indicate a strong preference of NH_4^+ for binding NH_3 with respect to H_2O. On the other hand, the gas-phase solvation of the larger alkali cations is of similar strength for H_2O and NH_3, the binding enthalpies being −16.9 kcal/mol for (K^+,H_2O) and −17.8 kcal/mol for (K^+,NH_3).[42]

One may infer that for the [$NH_4^+\subset$**SC-24**] cryptate (1) the high stability arises from the geometrically optimal arrays of four

(39) Kokesh, F. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1971**, *93*, 7270–7274.
(40) Lehn, J. M.; Sirlin, C. *J. Chem. Soc., Chem. Commun.* **1978**, 949–951.
(41) Cheney, J.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 487–488. Smith, P. B.; Dye, J. L.; Cheney, J.; Lehn, J. M. *J. Am. Chem. Soc.* **1981**, *103*, 6044–6048.
(42) Davidson, W. R.; Kebarle, P. *J. Am. Chem. Soc.* **1976**, *98*, 6133–6138, and references therein.

strong N^+–H···N hydrogen bonds in a tetrahedral arrangement, and of the interactions with the octahedron of six ether oxygens which complete the binding shell; (2) the high NH_4^+/K^+ selectivity probably results from the stronger N^+–H···N interaction, as compared with K^+···N, and from a cavity size definitely too large for K^+.[2] The hindrance to solvation of any inside directed nitrogen binding site, due to the cryptand nature of **SC-24**, may also contribute to the strong and selective binding of NH_4^+.

The importance of such generalized "lock and key" fit is clearly illustrated by the marked decrease in complex stability and selectivity found for **SC-25**, where a minor structural change lowers the degree of complementarity.

The several orders of magnitude higher complex stability and selectivity observed for **SC-24** with respect to **BC-22**, as well as the very slow cation and proton exchange rates, point to the presence of a very large "*spherical cryptate effect*", already observed for metal cation complexation.[2] It stresses again the importance of high connectivity and high cyclic order (i.e., high topology index[1a]) in the design of receptor molecules capable of strong and selective substrate binding, i.e., of high molecular recognition.

In conclusion, the spherical cryptand **SC-24** is a receptor molecule providing a *tetrahedral recognition site* and displaying *high receptor–substrate complementarity* toward the tetrahedral substrate NH_4^+ with respect to both geometrical and energetical features. It represents a state-of-the-art illustration of the *molecular engineering* involved in achieving the goal of *abiotic receptor chemistry*: the design of synthetic receptor molecules, by correct manipulation of geometrical (receptor structure) and energetical (binding sites, intermolecular interactions) features so as to achieve high receptor–substrate complementarity.

Experimental Section

The NMR spectra have been measured on the following spectrometers: Varian A-60 (^{1}H at 60 MHz), Bruker WH90 (^{1}H at 90 MHz, ^{15}N at 9.12 MHz at 13.82, Varian XL-100 (^{1}H at 100 MHz; ^{13}C at 25.14 MHz; ^{14}N at 7.2 MHz), and Cameca THN 250 (^{1}H at 250 MHz). The chemical shifts are given in ppm downfield from the ^{1}H or ^{13}C signals of internal tetramethylsilane. The ^{14}N shifts are given with respect to the tetramethylammonium cation. The electronic spectra are recorded on a Cary 118-C spectrophotometer and the IR spectra are obtained on a Perkin-Elmer 597 spectrometer in CaF_2 cells. The computations have been done with the Univac 1100 computer of the Centre de Calcul du Groupe de Laboratoires de Strasbourg-Cronenbourg.

1. Stability Constant Determinations. (a) pH Metric Measurements. For these measurements, an automatic titration unit Tacussel was used.[2] To avoid interferences from complexable cations and anions, the calomel reference electrode was in contact with the solution through a ionic bridge containing 0.1 mol/L of NMe_4NO_3. The pH was measured with a glass electrode Metrohm EA 109 in a thermostated cell at 25 °C. Stock solutions containing NMe_4NO_3 (0.1 M) and the ligand (2×10^{-3} M) with 5 equiv of nitric acid were prepared. Solutions containing 0.5 mL of stock solution and 3.5 mL of aqueous NMe_4NO_3 (0.1 M) or 0.5 mL of stock solution, 0.4 mL of ammonium salt solution (0.1 M), and 3.1 mL of aqueous NMe_4NO_3 (0.1 M) were back titrated with NMe_4OH (0.1 mol/L). The solution of tetramethylammonium hydroxide was freshly prepared from crystalline $NMe_4OH \cdot 5H_2O$ (Fluka). The titration curves were analyzed with the aid of the SCO 77 program[43] in order to extract the pK_a's of the ligands and the stability constants of the complex.

(b) NMR Measurements. Buffered solutions at pH 9.37 and 8.49 respectively were prepared from 4-aminopyridine (Fluka) or 4-aminomethylpyridine (Fluka) dissolved in water (2 M) and adjusted with HNO_3 (1 M). Ligand **1** was added (concentration 6.82×10^{-2} M) to these buffers, and, after each volumetric addition of an NH_4NO_3 solution, the relative intensity of the ^{1}H NMR signals corresponding to the complex (**1**,NH_4^+) and to the deprotonated ligand (**1**-$2H^+$) were measured (see Figure 4). Considering the protonation and the complexation equilibria 3–6, the equilibrium constant K_s is defined by:

$$K_s = [H^+]^2[(\mathbf{1},NH_4^+)]/K_1K_2[(\mathbf{1}\text{-}H_2^{2+})][NH_4^+] \qquad (13)$$

K_s is calculated by fitting this equation to the experimental curves (Figure 4) using the program KINFIT.[44]

2. Exchange Rate Measurements. Exchange rates were measured from the coalescence of the NMR signals in solutions containing equimolecular concentration of the ammonium complex and of the free ligand or its diprotonated analogue. Neglecting the spin–spin coupling, the rate at coalescence temperature was calculated by the usual procedure (see ref 9). The pH of the solution was determined spectrophotometrically with the help of added indicators (cresolphthalein or tropeolin O) or was measured with a pH meter directly after recording a spectrum.

3. Nitrogen NMR Spectra Simulation. If one considers an internal proton jump of type (**8**), the H-coupled nitrogen NMR spectrum is an average between a quintuplet and a quadruplet. In a fast-exchange situation the average spectrum is a symmetrical quintuplet of unequal splitting, since J(N,H) is different in NH_4^+ and in NH_3; furthermore, the splitting in the proton spectrum should also be different from those in the nitrogen spectrum.[45] Since the observed ^{14}N spectrum of the (**1**,NH_4^+) complex (Figure 1) displays equal splittings, which are also equal to the splittings in the proton spectrum within experimental error, one may estimate that there is less than 5% transprotonation (**8**) in this complex, if any.

Registry No. 1, 56698-26-1; **1** NH_4^+, 80515-41-9; **2**, 61136-92-3; **2** NH_4^+, 80515-42-0; **3**, 78648-22-3; **3** NH_4^+, 80515-43-1; **4**, 61136-93-4; **4** NH_4^+, 80532-11-2; **4** K^+, 80559-47-3.

(43) Sayce, I. G. *Talanta* **1968**, *145*, 1397–1411. Program adapted by P. Vitali.

(44) Dye, J. L.; Nicely, V. A. *J. Chem. Educ.* **1971**, *48*, 443–448.

(45) The simulated ^{14}N spectra may be obtained from the authors on request. They have been computed with the program ECHANG. We thank Professor J. J. Delpuech for a copy of this program, which is described in Delpuech, J. J.; Peguy, A.; Rubini, P.; Steinmetz, J. *Nouv. J. Chim.* **1977**, *1*, 133–139.