Further insight to selectivity issues in halide binding in a tiny octaazacryptand

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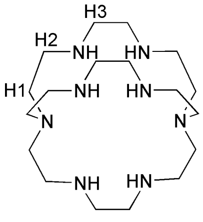
The crystal structure of the hexahydrochloride salt of the tiny azacryptand, 1,4,7,10,13,16,21,24-octaazabicyclo-[8.8.8]hexacosane, reveals a chloride ion inside the tiny bicyclic cavity; ^{1}H NMR studies indicate that while only fluoride binds strongly in the pH range 5.5–2.5, a dramatic increase in the affinity for chloride occurs at pH $\leqslant$ 2.5.

The crystal structure of the hexahydrochloride salt of the tiny azacryptand, 1,4,7,10,13,16,21,24-octaazabicyclo[8.8.8]hexacosane **1**, known as 'octaazacryptand', reveals a chloride ion unexpectedly inside the bicyclic cavity. While it was previously thought that the small cryptand was highly selective only for fluoride,[1–3] our crystallographic and NMR findings indicate that the pattern shifts from selectivity for fluoride at higher pH to high affinity for both fluoride and chloride under very acidic conditions (pH < 2.5). It is well known that **1** displays incredible affinity for fluoride ion, with log K_s values reported as 10.70[2] and 11.18[3] in aqueous solution under slightly different conditions. Molecular mechanics calculations also indicate that the cavity size is ideally suited to the fluoride ionic radius, with an increase in strain energy of 10.2 kcal mol^{-1} predicted for the projected increase in halide–nitrogen bond length in progressing from N···F to N···Cl.[3] As a result it has been speculated that because of its small cavity diameter (only 6.65 Å between bridgehead nitrogens in the fluoride structure) no other halide would be capable of binding inside the cavity.[2,3] Furthermore, potentiometric studies in aqueous media tended to confirm only weak binding for chloride (log K_s < 2).[2,3] We were thus amazed when the crystal structure revealed a chloride ion inside the bicyclic cavity, and decided to investigate further.



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The octaazacryptand **1** was synthesized using the previously reported procedure.[1] Crystals suitable for X-ray analysis were obtained by dissolving the free base **1** in methanol and adding concentrated HCl dropwise.† The precipitate, which formed immediately, was filtered off and redissolved in ethanol with a few drops of water. Colorless prisms were obtained at 0 °C after three days. Single crystal X-ray diffraction showed the crystals to be the hexahydrochloride salt with 2.75 water molecules of crystallization. A single chloride ion was found to reside inside the cavity (Fig. 1), while the remaining five were outside, as were the water molecules.

Not unexpectedly, the cavity is similar in size to that of the fluoride complex, although it is in fact somewhat smaller from end to end. In the chloride complex the apical N···N distance is 6.60 Å, compared to 6.65 Å in the fluoride complex.[1,2] (It should be noted that in a larger member of the series, 1,4,8,11,14,18,23,27-octaazabicyclo[9.9.9]nonacosane **2**, with propylene bridges between the two tren units, chloride also resides inside the cavity with an apical N···N separation a rather long 7.40 Å.[4]) The chloride in octaazacryptand **1** is held tightly, although not symmetrically, by a hydrogen bond network with the six amine nitrogens, with distances ranging from 2.99(1) to 3.18(1) Å. These hydrogen bonds are shorter than those observed in the aforementioned chloride structure in the larger **2**, for which the average chloride distance is 3.30 Å from the secondary amine nitrogens.[4] In **1**, the anion appears to be displaced toward one chain by virtue of the shorter interactions observed, 2.99(1) and 3.04(1) Å, and the distances of the chloride to the apical nitrogens are 3.27(1) and 3.32(1) Å.

Finding chloride in the cavity was unanticipated because of the previous studies that had clearly indicated low affinity of the cryptand for chloride. The selectivity ratio had, in fact, been noted as being exceedingly large (10^7) based on the ratio of the two binding constants.[3] However, these constants reflect binding at pH *ca.* 4, since the potentiometric techniques used are not accurate at low pH. We therefore decided to examine chemical shifts of the three independent carbon protons of **1** as a function of pH in the presence of chloride and fluoride, and in comparison with a 'control', the hexatosylate salt of **1**, to see whether we could observe binding of chloride at lower pH.

The series of ^{1}H NMR spectra indicate very little change in chemical shift as a function of pH for the tosylate salt,‡ but significant changes for the fluoride salt over the entire range investigated, and for the chloride salt only at pH values lower than 2.5. These shifts are clearly evident in the plots of the

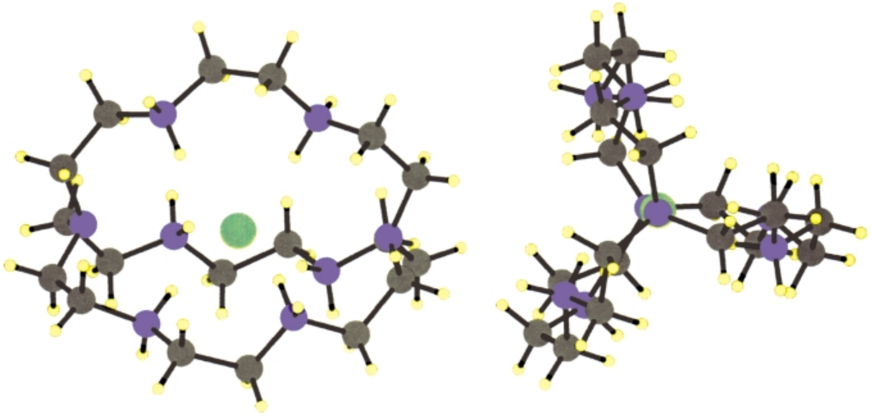

Fig. 1 Perspective views of the octaazacryptand **1** encapsulating chloride.

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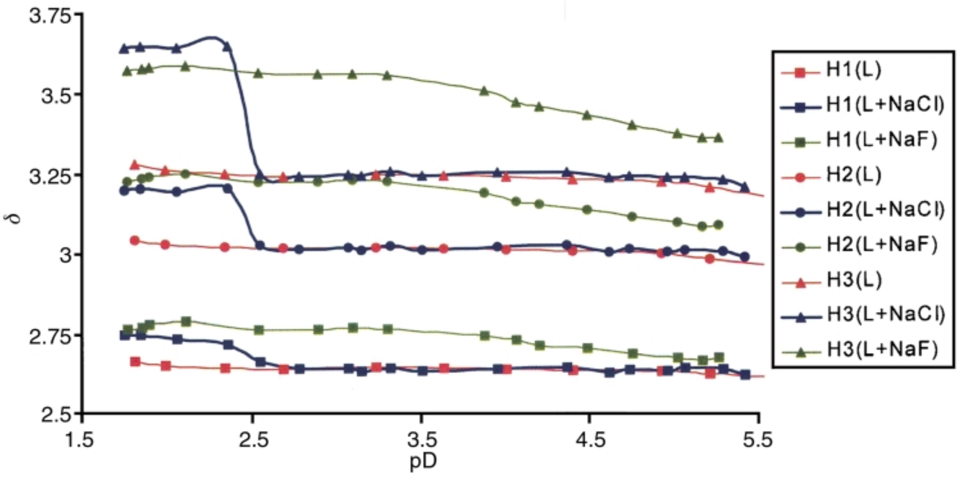

Fig. 2 Chemical shifts of the three independent protons of the octaazacryptand as a function of pH (L = **1**·8TsOH): (■) H1, (●) H2, (▲) H3.

chemical shift pattern for the three independent protons of **1** for the three samples as a function of pH (Fig. 2). The chloride and fluoride NMR findings are very similar to the previously reported results.[3]§ In the earlier publication, however, the changes in the NMR spectra as a function of pH using KCl as supporting electrolyte were attributed to changes in ligand conformation upon protonation, certainly a reasonable assumption, given the earlier potentiometric results indicating only weak binding for chloride.[3] Now that the crystallographic data indicate encapsulation of the chloride, these changes can be attributed to a dramatic enhancement of the binding of chloride below pH 2.5. This conclusion is further confirmed by comparison with chemical shifts for the 'control', the bulky tosylate salt of **1**, which shows little change as a function of pH.

The NMR spectrum of the octatosylate salt of the ligand at pD 2.0[5] is shown in Fig. 3A, and changes in the spectra, as aliquots of NaCl are added to obtain a final molar ratio of 1 : 1 of **1** with chloride, are shown in Fig. 3B–E. The signal at δ 2.36 is assigned to the methyl protons of the tosylate anion, and the triplet at δ *ca*. 2.9 is an impurity from the TPS reference.§ As chloride is added, the signals broaden and shift, which can be attributed to chloride binding in the cavity. At pD = 4.0, however, in the presence of 1 equivalent of NaCl, the spectrum mirrors that observed for the tosylate salt at pD 2.0 without chloride (Fig. 3F).

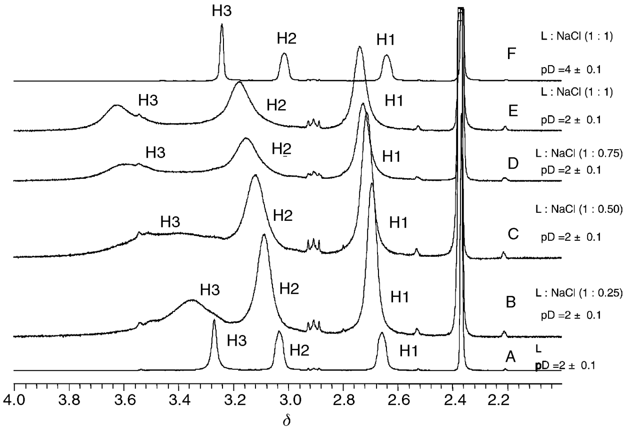

Fig. 3 ^{1}H NMR spectra of L (**1**·8Ts): A, L at pD = 2.0; B, L + 0.25 eq. NaCl at pD 2.0; C, L + 0.50 eq. NaCl at pD 2.0; D, L + 0.75 eq. NaCl at pD 2.0; E, L + 1.0 eq. NaCl at pD 2.0; F, L + 1.0 eq. NaCl at pD 4.0.

In summary, an unanticipated change in the selectivity pattern has been uncovered for a small azacryptand noted for its selectivity for fluoride. These findings provide new evidence that selectivity patterns can change dramatically as a function of pH and are also a reminder of the inherent flexibility of these systems that is sometimes overlooked.

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Notes and references

† *Crystal structure data*: $C_{18}H_{54}N_8Cl_6O_{2.75}$, M_w = 639.39, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 12.143(7), b = 21.64(1), c = 11.97(3) Å, V = 3144(5) Å^3, D_c = 1.351 g cm^{-3}, Z = 4. Single crystal X-ray structure analysis was carried out on a crystal of dimensions 0.20 × 0.10 × 0.20 mm using a Rigaku AFC5R diffractometer with graphite-monchromated Cu-Kα (λ = 1.54178 Å) radiation at 23 °C. Data collection to a $2\theta_{max}$ of 120.1° gave 2679 unique reflections. The structure was solved according to previously reported methods (G. Papoyan, K. Gu, J. Wiórkiewicz-Kuczera and K. Bowman-James, *J. Am. Chem. Soc.*, 1996, **118**, 1354). The asymmetric unit included three water molecules, one of which had an occupancy factor of 0.75. Some of the hydrogen atoms were found on difference maps; however, most of the hydrogens were placed in calculated positions and were included in subsequent calculations but not refined. Refinement included 316 parameters on 1630 reflections for which $I > 1.0\sigma(I)$, to give R = 0.064 and R_w = 0.059, and GOF = 1.57. CCDC 182/1794. See http://www.rsc.org/suppdata/cc/b0/b004167j/ for crystallographic files in .cif format.

‡ $H_8L\cdot 8Ts$ was prepared by reacting **1** with a five-fold excess of *p*-toluenesulfonic acid in ethanol. The oily layer, which was separated by the addition of diethyl ether, was collected and diluted with methanol and *n*-hexane. The white microcrystalline product, formed on sudden cooling of the solution in an acetone/dry ice mixture, was filtered off and washed with diethyl ether.

§ ^{1}H NMR spectra were recorded on a Bruker AM400 spectrometer at 400 MHz and chemical shifts were recorded in ppm. TPS (3-(trimethylsilyl)-propionic acid sodium salt) in deuterium oxide was used as an external reference in a capillary tube. All spectra were recorded at room temperature, and the concentration of the ligand (**1**·8Ts) was 0.01 mol dm^{-3} in D_2O. The pH was adjusted with a concentrated solution of TsOH or NaOH in D_2O.

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