119. Chloride Binding by Polyammonium Receptor Molecules: ^{35}Cl-NMR Studies

by **Mir Wais Hosseini, Jean-Pierre Kintzinger, Jean-Marie Lehn*,** and **Assou Zahidi**

Institut Le Bel, Université Louis Pasteur, 4, rue Blaise Pascal, F–67000 Strasbourg[1])

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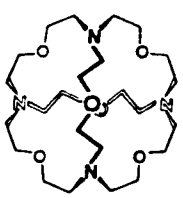
Binding of chloride anion by protonated polyamines was investigated by ^{35}Cl-NMR spectroscopy. The presence of protonated macro(poly)cyclic polyamines caused downfield shifts and significant line broadening of the ^{35}Cl-NMR signals. ^{35}Cl-NMR spectroscopy was used for complex-formation stoichiometry determination and revealed the formation of a binuclear chloride complex with the fully protonated ditopic hexaazamacrocyclic receptor **6**. ^{35}Cl-NMR spectroscopy was also applied in competition experiments between Cl- and SO_4^{2-} and demonstrated that the fully protonated macrocyclic hexaamine **4** forms a strong complex with SO_4^{-2} with 1:1 stoichiometry.

Introduction. – Anion coordination chemistry, the binding of anions by organic ligands has recently been recognized and developed as a new area of coordination chemistry [1] [2]. Macro(poly)cyclic polyamines, when protonated, bind a variety of organic as well as inorganic anions (for reviews see [2–4]). The potentiometric determination of the protonation constants of polyamines and the stability constants of complexes formed by their protonated forms with various anions requires the presence of a supporting electrolyte, typically Me_4NCl, so as to minimize the effect of the medium. Since protonated polyamines bind to some extent the anion of the supporting electrolyte,



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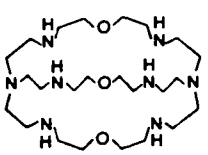

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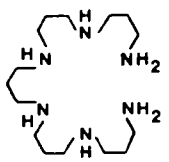

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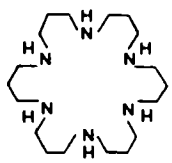

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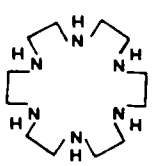

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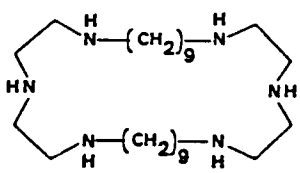

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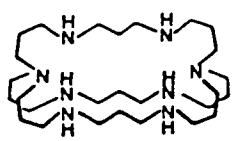

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the protonation constants as well as the stability constants obtained are apparent values and hold for the medium used.

Anion complexation may also be studied by direct observation of the bound species using NMR spectroscopy.

The fully protonated macrotricyclic receptor **1**-4H$^+$ [5] [6] and the macrobicyclic receptor **2**-6H$^+$ [7] [8] both form cryptate-inclusion complexes with Cl^- anion in solution as well as in the solid state. We previously studied the binding of Cl^- anion by macro-(poly)cyclic receptor molecules, like **1** and **2**, using ^{35}Cl-NMR spectroscopy [9]. We report here the ^{35}Cl-NMR study of Cl^- binding by protonated linear (**3**), macrocyclic (**4**–**6**), and macrobicyclic (**7**) polyamines [10].

Results. – The ^{35}Cl linewidths and chemical shifts of Cl^- bound to **1**-4H$^+$ and **2**-6H$^+$ [9] as well as the observed chemical shifts and linewidths of ^{35}Cl-NMR signals in the presence of protonated compounds **3**–**7** (L-nH$^+$, nCl$^-$) are given in the *Table*. In all cases low-field shifts and line broadening were observed for aqueous solutions of (L-nH$^+$, nCl$^-$; L = **3**–**7**) but the measured values varied considerably depending on the receptor studied and were very different from the reference values obtained for complexation of Cl^- by **1**-4H$^+$ and **2**-6H$^+$.

Table. *^{35}Cl-NMR Chemical Shifts (δ) and Linewidths (W) for Cl^- Binding by the Protonated Polyamines* **1**–**7**[a])

Ligands[b])	δ_{obs}[c]) [ppm]	W_{obs}[c]) [Hz]	δ_c[d])	W_c[d])
1-4H$^+$			52 ± 0.5	125 ± 10
2-6H$^+$			66 ± 6	2600 ± 300
3-6H$^+$[e])	2.9 ± 0.3	31 ± 3		
4-6H$^+$	6.1 ± 0.6	126 ± 13		
5-6H$^+$	14.5 ± 1	380 ± 40	69 ± 6	2100 ± 240
6-6H$^+$	4.6 ± 0.5	147 ± 15		
7-8H$^+$[e])	6.2 ± 0.5	600 ± 60	29 ± 4	4700 ± 480

[a]) In H_2O/D_2O 9: 1 at 25°; concentration range 0.01–0.025M.
[b]) Compounds **2**–**7** as their HCl salts.
[c]) δ_{obs}: observed chemical shifts with respect to 0.05M aq. NH_4Cl as external reference; W_{obs}: observed linewidth.
[d]) Chemical shifts and linewidths for complexed Cl^- anion, see text. *Eqns. 1* and *2* or [9].
[e]) At pH 3.3 adjusted with TsOH.

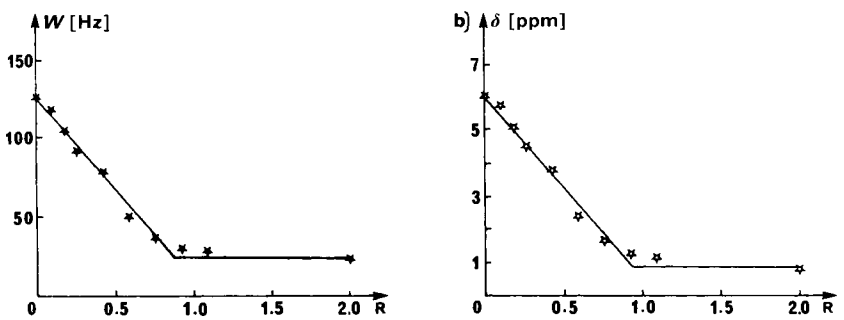

Fig. 1. *^{35}Cl Linewidths (W) and chemical shifts (δ) of the ^{35}Cl-NMR signal of Cl^- in the presence of* **4** *as a function of increasing Na_2SO_4/***4** *ratio R, in D_2O/H_2O 1:9* (0.02M (**4**-6 H$^+$, 6 Cl^-), pH 3.3, 20°)

^{35}Cl-NMR spectroscopy was used for stoichiometry determination either in competition experiments between Cl^- and SO_4^{2-} in the case of compound **4** (by addition of increasing amounts of Na_2SO_4 to a 0.02M solution of **4**-6HCl in D_2O/H_2O 1:9 at pH 3.3, 20°; *Fig. 1*) or between Cl^- and paratoluenesulfonate (TsO^-) in the case of compound **6** (by addition of **6**-6TsOH to a 0.03M solution of NaCl in MeOH/D_2O 6:4 at pH 3.0, 20°; *Fig. 2*). The effect of pH of the solution on the ^{35}Cl-NMR signal of Cl^- anion in the presence of the linear hexaamine **3** and of the macrobicyclic compound **7** as their 6 HCl and 8 HCl salts, respectively, is illustrated in *Fig. 3*.

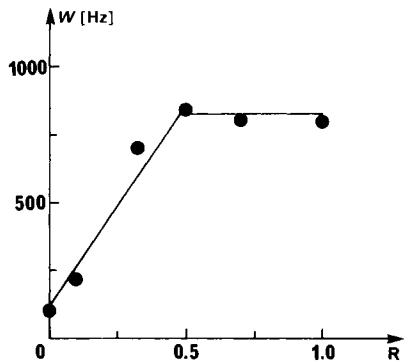

Fig. 2. *Observed ^{35}Cl linewidths (W) of the ^{35}Cl-NMR signal of Cl^- in the presence of* (**6**-6 H^+, 6 TsO^-) *as a function of increasing* **6**/*NaCl ratio R, in MeOH/D_2O 6:4* (0.03M NaCl, pH 3.0, 20°)

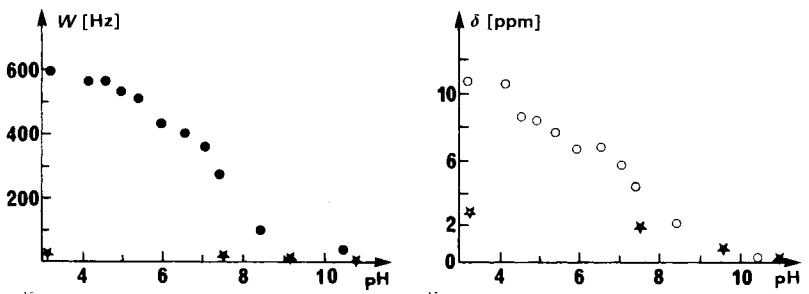

Fig. 3. *Observed ^{35}Cl linewidths (W) and chemical shifts (δ) of the ^{35}Cl-NMR of Cl^- in the presence of* **3** (★, ☆) *and* **7** (●, ○) *as a function of pH, in D_2O/H_2O 1:9* (0.01M (**3**-6 H^+, 6 Cl^-); 0.01M (**7**-8 H^+, 8 Cl^-), 20°)

Discussion. – In the case of Cl^- binding by the macrocyclic compound **1**, a slow exchange process was observed [9]. In all systems studied here (L, nH^+, nCl^-; L = **3**–**7**), the Cl^- anions were in fast exchange between the complexed and the solvated state. The observed chemical shifts (δ_{obs}) as well as the linewidths (W_{obs}) are, therefore, given by *Eqns. 1* and *2*

$$\delta_{obs} = x\delta_c + (1 - x)\,\delta_s \quad (1)$$

$$W_{obs} = xW_c + (1 - x)\,W_s \quad (2)$$

where δ_c, δ_s, and W_c, W_s are the chemical shifts and linewidths of complexed and solvated chloride anion, respectively, x is the fraction of complexed chloride.

Solvation of Chloride. Extensive ^{35}Cl-NMR studies of various electrolytes containing Cl^- as the counteranion at different concentrations give extrapolated values of $\delta_s = 0$ ppm and $W_s = 8$ Hz for aqueous chloride solution at infinite dilution [11]. For aqueous solutions of NH_4Cl, in the concentration range between 0.001 to 0.1M, the linewidth was almost constant and equal to 14 Hz, whereas for NMe_4Cl solutions, in the same concentration range, it increased linearly from 14 to 22 Hz. The solvated Cl^- anion signal, in a solution containing 0.02M (**1**-4 H^+, Cl^-) complex was lowfield-shifted by *ca.* 1 ppm with a linewidth of 44 Hz [9]. These observations indicate that even at 10^{-2} M concentration, alkylammonium cations perturb the solvation sphere of Cl^- anion in H_2O and cause lowfield shifts and line broadening.

The fully protonated form of compound **3** (**3**-6 H^+), which may be considered as an open-chain analogue of **4**, caused slight downfield shift and line broadening of the ^{35}Cl signal (see the *Table*). pH-metric-tritration experiments showed that the protonation constants of **3** were almost the same in the presence of either 0.1M NMe_4Cl or TsONa, indicating that the protonated linear hexaamine **3** does probably not form stable complexes with either the Cl^- or TsO^- anion, since one would not expect both anions to form complexes of similar stabilities [12]. The ^{35}Cl chemical shifts and linewidths observed for the aqueous solution of (**3**-6 H^+, 6 Cl^-) could, therefore, be considered as representative values for solvated Cl^- in the presence of protonated polyamines. This assumption was further confirmed by the fact that shifts and linewidths decreased from 2.91 ppm and 31 Hz at pH 3.3 to 0.3 ppm and 19 Hz at pH 10.8, respectively *(Fig. 3)*.

Complexed Fraction. Since the stability constant for Cl^- binding by **5**-4 H^+ is 104 $l \cdot mol^{-1}$ [13], the fraction of complexed Cl^- is nearly equal to 1:6 for a 0.02M solution of the 6 HCl salt of **5** which exists as **5**-4 H^+ at the pH of the solution (2.5). Considering the δ and W values observed for (**3**-6 H^+, 6 Cl^-) as chemical shift (2.9 ppm) and linewidth (31 Hz) of solvated Cl^- in this type of medium, one calculates using *Eqns. 1* and *2* a chemical shift of 69 ppm and a linewidth of 2100 Hz for Cl^- bound to **5**-4 H^+. Since the stability constant for Cl^- binding by **7**-8 H^+ is 251 $l \cdot mol^{-1}$ [14], the fraction of complexed Cl^- is equal to $\sim 1/8$ for a 0.025M solution of the 8 HCl salt of **7** at pH 3.3 where the **7**-8 H^+ form is the dominant species ($\geq 95\%$). One obtains $\delta_c = 29$ ppm and $W_c = 4700$ Hz for the complexation of Cl^- by **7**-8 H^+.

Binding of Cl^- by the protonated macrocycle **4** has been demonstrated by pH-metric titration experiments using either NMe_4Cl or TsONa as supporting electrolytes [12]. This wals also confirmed by ^{35}Cl-NMR study. The observed chemical shifts and line broadenings lie between those induced by **3**-6 H^+, which does not form a stable complex with Cl^-, and by **5**-4 H^+, which binds Cl^- rather strongly. The differences between the values observed for (**4**-6 H^+, 6 Cl^-) and (**3**-6 H^+, 6 Cl^-) (3.2 ppm and 95 Hz) are due to the complexation contributions $x\delta_c$ and xW_c which cannot be further interpreted since neither x nor δ_c and W_c have been determined in this case. The same holds for (**6**-6 H^+, 6 Cl^-). Nevertheless, since both effects are significant, ^{35}Cl-NMR does reveal that binding occurs.

Competition Experiments. The protonated compound **4** also binds strongly SO_4^{2-} anion ($\log K_s = 4.05$, for (**4**-6 H^+, SO_4^{2-})) [14]. For the computation of the data obtained by pH-metric titration experiments, a 1:1 stoichiometry for SO_4^{2-} binding by protonated **4** was assumed. ^{35}Cl-NMR showed that addition of sulfate to a solution containing (**4**-6 H^+, 6 Cl^-) resulted in release of Cl^- which caused an upfield shift and a significant sharpening

of the signal. The titration of (**4**-6 H^+, 6 Cl^-) by SO_4^{2-} anion showed unambiguously that the complex formed with SO_4^{2-} is indeed strong and has a 1:1 stoichiometry. Plots of both the observed chemical shifts (δ_{obs}) and linewidths (W_{obs}) *vs.* SO_4^{2-} concentration are given in *Fig. 1*.

Stoichiometry of Chloride Binding. The ditopic hexaamine **6** possessing two diethylenetriamine binding subunits binds selectively dicarboxylate anions when protonated, forming mononuclear dihapto complexes and displaying linear molecular recognition [15].

The presence of protonated **6** induced downfield shifts and line broadening of the ^{35}Cl-NMR signal in H_2O/D_2O as well as in $MeOH/D_2O$ solutions. The titration of 0.03M solution of Cl^- by **6** fully protonated by 2,4,6-trimethylbenzenesulfonic acid in $MeOH/D_2O$ 6:4 has been followed by ^{35}Cl-NMR spectroscopy. The plot of the ^{35}Cl signal linewidth *vs.* the equivalents of macrocycle (**6**-6 H^+, 6 TsO^-) added *(Fig. 2)* gives clear evidence for the formation of a dinuclear chloride complex. The formation of such a complex has been proposed in the case of a large diazamacrobicycle [16].

Effect of pH on Chloride Binding. Protonated forms of the macrobicyclic compound **7** bind Cl^- in aqueous solution with log K_s values ranging from 2.4 for (**7**-8 H^+, Cl^-) to 1.5 for (**7**-5 H^+, Cl^-) complexes [14]. The effect of **7** on the ^{35}Cl-NMR signal was studied at different pH values. Plots of the observed chemical shifts and of the linewidths of the ^{35}Cl signal *vs.* the pH of the solution are given in *Fig. 3*. Starting at pH 3.3, where the receptor is fully protonated (**7**-8 H^+) and increasing the pH, the number of protonated amino groups in the macrobicycle decreases and the Cl^- binding ability of **7** drops very markedly. The effect of pH on the NMR signal of Cl^- anion correlates quite well with the ability of **7** in its different protonated forms to bind Cl^-. Indeed, the largest chemical shift difference and line broadening are observed for the fully protonated **7** at pH 3.3, whereas at pH 10.5, where the compound **7** is roughly monoprotonated and does not bind Cl^-, the shift of the ^{35}Cl signal with respect to free Cl^- drops to zero and its linewidth to the residual value of *ca.* 30 Hz.

Conclusion. – ^{35}Cl-NMR spectroscopy allows the direct observation of Cl^- binding by synthetic receptor molecules. The chemical shifts and the linewidths differences between the solvated Cl^- anion and the one complexed by the polyammonium ligands **1**–**7** are pronounced and may be used in competition experiments for the determination of the complexation stoichiometry and for an estimation of relative stabilities of the complexes formed with different anions. Since the linewidths are determined by nuclear quadrupolar effects, their analysis may, in principle, also yield information about the geometrical and electrical features of the binding site as well as about the dynamical properties of the complexes.

Experimental Part

The synthesis of *4,8,12,16-tetraazanonadecane-1,19-diamine* (**3**) [12], *1,5,9,13,17,21-hexaazacyclotetraicosane* (**4**) [12], *1,4,7,17,20,23-hexaazacyclodotriacontane* (**6**) [15], and *1,5,9,13,17,21,28,32-octaazabicyclo[11.11.11]-pentatriacontane* (**7**) [17] has been described previously. Compound **5** is commercially available as its trisulfate salt and was converted into its 6 HCl salt using an anion-exchange column *(Dowex 1 × 8)* followed by addition of conc. HCl. ^{35}Cl-NMR spectra were recorded at 19.6 MHz on a *Bruker WP-200-SY* spectrometer (20000 scans, $AQ = 0.819$ s) in a 10-mm tube containing typically 10^{-2}–$2.5 10^{-2}$ M of the HCl salts of **3**–**7** in 2 ml of D_2O/H_2O 1:9 or $MeOH/D_2O$ 6:4. Chemical shifts (δ) are given in ppm with respect to 0.05M aq. NH_4Cl as external reference. The pH of the soln. was adjusted to the desired value by addition of conc. NaOH or TsOH and was not corrected.

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