

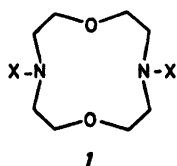
4,10-Bis(2-hydroxyethyl)-1,7-dioxo-4,10-diazacyclododecane. A Strong Calcium-binding Ligand

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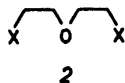
During the last three years several research groups have described macrocyclic ligands containing side chains with additional donor groups. These have been prepared either to study enantioselective complexation of ammonium salts,¹ to catalyse the thiolysis of amino acid ester salts^{2,3} or to change the stability of their complexes as compared to the parent compounds.^{4,5}

We now report the use of neutral *N*-hydroxyethyl groups to modify the binding properties of a macrocyclic ligand. The particularly good geometric fit of the twelve-membered ring for coordination to sodium^{6,7} and calcium,⁸ as manifested in several 12-crown-4 complexes,

a: X = CH₂CH₂OH

b: X = Tos

c: X = H

a: X = NH₂

b: X = NHTos

c: X = OTos

made us choose 1,7-dioxo-4,10-diazacyclododecane *1c*⁹ as the parent compound. Using Richman and Atkins' method, the disodium salt of *N,N'*-ditosyl-2,2'-diaminodiethyl ether *2b* and diethylene glycol ditosylate *2c* were condensed in DMF to yield 4,10-di-*p*-toluenesulfonyl-1,7-dioxo-4,10-diazacyclododecane *1b*¹⁰. Acid hydrolysis removed the tosyl protecting groups and the secondary amine *1c* was isolated in 88 % yield. Hydroxyethylation with ethylene oxide in aqueous methanol at 0 °C gave 41 % of the title compound *1a*.

The addition of increasing amounts of lithium and sodium perchlorate to a solution of ligand *1a* in methanol displaced the ¹³C NMR chemical shifts of all carbon atoms upfield. These displacements are larger for the ring carbons than for the carbon atoms in the side chain, reflecting a change of the ring conformation upon complex formation.^{11,12} Evaluation of titration curves for the ring carbons (see Fig. 1) by an iterative least-squares procedure^{13,14} gave the complexation constants and the limiting chemical shifts δ_c of the complexes (see Table 1). The parent secondary diamine *1c* showed only very

Table 1. Complexation constants for *1a* from analysis of ¹³C NMR titration curves.

Salt	Resonance	δ_c (Hz)	$\Delta\delta$ (Hz)	log <i>K</i>
LiClO ₄	CH ₂ O	593.5	41.0	2.8
	CH ₂ N	366.1	53.2	2.5
NaClO ₄	CH ₂ O	594.3	39.6	3.4
	CH ₂ N	375.4	43.3	3.2

small shift differences with these salts, and the complexation constants were estimated to be < 1.

Since the accuracy of this method is limited for constants *K* > 1000, the binding properties of ligand *1a* were also examined by pH-metric titrations in methanol-water (9:1). These results are summarized in Table 2.

The introduction of two hydroxyethyl side chains is thus indeed found to increase considerably the complex stabilities. This is presumably a consequence of the additional binding sites,¹⁵ but also the weaker solvation of tertiary as compared with secondary amine functions in the free ligand, may contribute to the favourable binding.¹⁶ The stability of the Ca²⁺ complex is similar to that of cryptates,¹⁷ but the Ca²⁺/Na⁺ selectivity is different. Cryptand [2.1.1], which has the same number of donor atoms as the hydroxyethylated ligand *1a*, shows an Na⁺ preference of 55, whereas ligand *1a* has a Ca²⁺/Na⁺ selectivity of 2000 and forms the most stable Ca²⁺ complex known for uncharged monocyclic ligands.

In less polar solvents, where ion pairing occurs to a great extent, the hydroxyethyl groups may play a stabilizing role by forming hydrogen bonds to the anion. Thus one can well envisage using ligand *1a* to extract calcium salts from water into nonpolar organic solvents.

Experimental. The melting points are uncorrected. IR spectra were recorded on a Jasco IRA-1 spectrophotometer and NMR spectra on a Varian A 60A or a Jeol JNM-FX60 Fourier Transform NMR spectrometer. MS data were obtained on an A.E.I. MS 902 spectrometer. The elemental analysis was carried out at Mikro-analytisches Laboratorium Ilse Beetz, 8640 Kronach, West-Germany.

Table 2. Complexation constants from analysis of pH titration curves.

	Li ⁺	Na ⁺	K ⁺	Ca ²⁺
Diaza-crown <i>1a</i>	2.4	3.6	2.0	6.9
Cryptand [2.1.1] ¹⁷	7.6	6.1	2.3	4.3

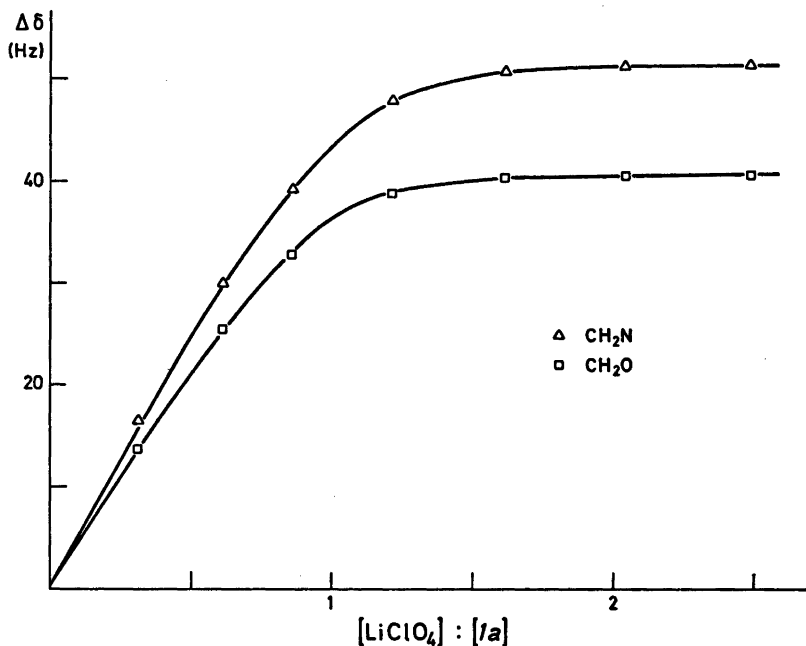


Fig. 1. ^{13}C NMR chemical shifts of the ring carbon atoms of *1a* $\Delta\delta$ vs. relative LiClO_4 concentration. Similar curves were obtained with NaClO_4 (cf. Table 1).

Starting materials. Standard methods were used to prepare diethylene glycol ditosylate *2c*¹⁸ and *N,N'*-ditosyl-2,2'-diaminodiethyl ether *2b*¹⁹ from 2,2'-diaminodiethyl ether *2a*.⁹

4,10-Ditosyl-1,7-dioxo-4,10-diazacyclododecane 1b. The general procedure of Richman and Atkins¹⁰ was used under the following specified conditions. The disodium salt of disulfonamide *2b* was crystallized in 95% yield from abs. ethanol containing a 10% excess of sodium ethoxide. This salt (36.9 g, 0.08 mol) and diethylene glycol ditosylate *2c* (33.5 g, 0.08 mol) were dissolved in dry DMF (400 ml), and the solution was stirred at 100°C during 12 h. After cooling and addition of water (2500 ml) the crude cyclic ditosyl compound *1b* was recrystallized from ethanol (1500 ml); yield, 33.4 g (87%), m.p. 204–206°C (Lit.: 203–204°C).¹⁰ MS, *m/e* (% rel. int.) 327 (63.0, M-Tos), 155 (27.0, Tos), 91 (100.0, C₂H₅). ^1H NMR (DMSO-*d*₆/acetone-*d*₆ (1:1)): δ 2.43 (6H, s, CH₃), 3.24 (8H, t, $J=5.0$ Hz, CH₂N), 3.73 (8H, t, $J=5.0$ Hz, CH₂O), 7.62 (8H, AA'BB'-system, aromatic protons).

1,7-Dioxo-4,10-diazacyclododecane 1c. The cyclic ditosyl compound *1b* (33.3 g, 0.07 mol) in H₂SO₄ (80 ml, 80%) was stirred at 100°C during 26 h. After cooling to 0°C the solution was first diluted with HCl (80 ml, 6 N), then with acetone (1000 ml). At -20°C the dihydrochloride of *1c* crystallized; yield, 15.0 g (88%),

m.p. 240–245°C. ^1H NMR (D₂O): δ 3.38 (half of AA'BB'-system, CH₂N), 3.88 (half of AA'BB'-system, CH₂O).

4,10-Bis(2-hydroxyethyl)-1,7-dioxo-4,10-diazacyclododecane 1a. The dihydrochloride of *1c* (2.0 g, 8.1 mmol) was dissolved in water (10 ml) and the pH adjusted to 8–9 with aqueous NaOH (5%). The solution was diluted with water (10 ml) and methanol (40 ml) and cooled to 0°C. A solution of ethylene oxide (1.8 g, 40 mmol) in methanol (10 ml), which had previously been cooled with dry ice, was added and stirred at room temperature during 22 h. Water was then added and the solution extracted with CHCl₃ (4 × 50 ml). The organic phase was dried (MgSO₄) and the solvent evaporated. The remaining oily hydroxyethyl derivative *1a* was crystallized as the hygroscopic dihydrochloride salt from abs. ethanol (15 ml) containing a few drops of conc. HCl; yield, 1.1 g (41%), m.p. 219–222°C. Anal. Found: C 41.94, H 8.62. Calc. for C₁₂H₂₂N₂O₄Cl₂ · 5% H₂O: C 41.87, H 8.49 (weight of sample increased during weighing). ^1H NMR (D₂O): 3.50 (t, $J=7.0$ Hz, CH₂N (side chain)), 3.6 (half of AA'BB'-system, CH₂N (ring)), 3.9 (half of AA'BB'-system, CH₂O (r)), 3.99 (t, $J=7.0$ Hz, CH₂O (s)). The dihydrochloride of *1a* (1.10 g, 3.3 mmol) in water (5 ml) was adsorbed on a column containing the basic ion exchanging resin IRA-40(OH) and the diamine *1a* was eluted with water (300 ml). The

water was distilled off and the last traces were removed by azeotropic distillation with benzene (2 × 50 ml). After drying over P₂O₅ the yield of the free base *Ia* was 0.69 g (93 %). MS, *m/e* (% rel. int.) 262 (9.7, M), 244 (4.6, M - H₂O), 231 (13.5, M - CH₂OH). IR (film): 3280 (s, broad) cm⁻¹. ¹H NMR (CDCl₃): δ 2.68 (12H, complex, CH₂N), 3.54 (12H, complex, CH₂O), 4.68 (2H, s, OH). ¹³C NMR (15 MHz, CDCl₃): δ 60.4 (CH₂O (ring)), 59.5 (CH₂N (side chain)), 57.8 (CH₂O (s)), 54.8 (CH₂N (r)).

NMR measurements. The ligand solutions in methanol (1.50 ml) were 0.1–0.2 M. The ¹³C NMR chemical shifts δ were measured after each addition of solid perchlorate salt (TMS as internal standard). The accuracy of the δ determinations was ± 0.15 Hz. The temperature was held at 30 ± 1 °C. Using the 1:1 stoichiometry observed for Li⁺ and Na⁺, the data from the titration curves were analysed with a computer program based on Creswell and Allreds method.^{13,14} The error limits are about ± 0.2 for log *K* smaller than 3, but increase rapidly for higher values of log *K*.

pH-metric measurements.^{17,20} The solvent was in all cases methanol – water (9:1). An automatic titration apparatus (TACUSSEL, units TT100, TT200 and TT300) was used. The reference electrode was connected with an ionic bridge containing 0.1 M NMe₄Br. The measuring electrode was a TACUSSEL electrode for aqueous solutions, which had been conditioned during several days in the solvent used. To determine the protonation constants of the ligand, solutions (4.0 ml) containing the doubly protonated ligand (0.005 M) and NMe₄Br (0.1 M) were titrated with NMe₄OH (0.110 M): p*K*₁ = 6.8 ± 0.1, p*K*₂ = 10.0 ± 0.1 at 25 °C. The complexation constants were determined by titration of solutions (4.0 ml) containing the completely protonated ligand (0.005 M), the salt to be complexed (0.01 or 0.02 M) and NMe₄Br (0.1 M). The stoichiometry and the stability constants of the complexes were obtained by a computer analysis of the data from the titration curves (program SCO 75²¹). The error limits are about ± 0.2 for log *K* ~ 4 and about ± 0.3 for log *K* ~ 7. Further experimental details have been described elsewhere.²⁰

Acknowledgement: We thank Prof. J.-M. Lehn for the opportunity to carry out the pH-metric titrations in his laboratory.

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Received August 24, 1979.