Solution Chemistry of Macrocycles. Part 3.† Synthesis and Thermodynamics of Protonation of Some Tetra-azamacrocycles

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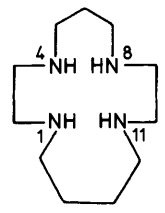
The synthesis of the tetra-aza-macrocycle 1,4,8,11-tetra-azacyclopentadecane is reported. The enthalpy and entropy contributions to the stepwise protonation of the three macrocycles, 1,4,8,11-tetra-azacyclopentadecane, 1,5,8,12-tetra-azacyclohexadecane, and 1,5,9,13-tetra-azacycloheptadecane, have been determined at 25 °C in 0.5M-KNO_3. A fully automatic potentiometric technique has been used to determine the basicity constants and a continuous titration calorimetric technique has been used to determine the corresponding enthalpy changes. The thermodynamic functions have been explained in terms of macrocyclic ring size and relative length of hydrocarbon chains between the nitrogen atoms. For large macrocycles the protonation behaviour is very similar to that of the corresponding open-chain tetramines.

THE unusual properties frequently conferred upon metal atoms when bound to poly-azamacrocycles and the possibility of many complexes containing these ligands serving as models for biologically important species, are only two of the many reasons justifying the interest shown toward the complexation properties of poly-azamacrocycles in the last few years.[1-6] In view of our systematic studies on the solution chemistry of these ligands [7,8] we have synthesized a further poly-azamacrocycle, 1,4,8,11-tetra-azacyclopentadecane (L^1). The thermodynamic quantities $\Delta H^\ominus$ and $\Delta S^\ominus$ for the protonation equilibria have been determined for this ligand and for 1,5,8,12-tetra-azacyclohexadecane (L^2) and 1,5,9,13-tetra-azacycloheptadecane (L^3). The basicity constants have been determined using potentiometric methods and the stepwise enthalpies of protonation have been measured by continuous titration calorimetry. The aim of this work was to clarify the mechanism of the protonation of these polyamines and to gauge the influence of the length of hydrocarbon chains between the amino-groups on the enthalpy and entropy of the protonation step.

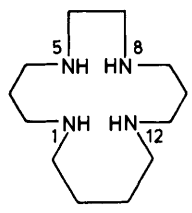
Comparison with other poly-azamacrocycles and with the corresponding linear tetra-amines has also been made.

EXPERIMENTAL

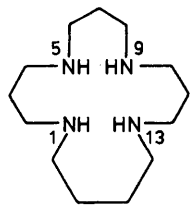
Preparation of Ligands.—1,4,8,11-*Tetra-azacyclopentadecane* (L^1). The tetratosyl derivative of (L^1), 1,4,8,11-tetrakis-(*p*-tolylsulphonyl)-1,4,8,11-tetra-azacyclopentadecane was obtained by adding dropwise to a solution (850 cm^3) of the disodium salt of *NN'N''N'''*-tetrakis(*p*-tolylsulphonyl)-1,4,8,11-tetra-azaundecane, a solution of *OO*-bis-(*p*-tolylsulphonyl)butane-1,4-diol in anhydrous DMF (500 cm^3). The mixture was refluxed for 1 h. The volume was reduced to 250 cm^3 by vacuum distillation and water (2 dm^3) was slowly added. The precipitate was filtered off, washed with water, and dried. The crude product was used without further purification, m.p. 279—281 °C (Found: C, 54.3; H, 6.5; N, 6.8. Calc. for $C_{39}H_{50}N_4O_8S_4$: C, 56.4; H, 6.0; N, 6.75%). I.r. spectra demonstrated that cyclization occurred since no bands in the N–H region (3 060—3 500 cm^{-1}) were observed. The free ligand (L^1) was obtained by hydrolysis of the tetratosylate with concentrated H_2SO_4 solution, following the procedure already described.[9] The crude free amine was purified as the tetrahydrochloride.



(L^1)



(L^2)



(L^3)

1,4,8,11-*Tetra-azacyclopentadecane–hydrogen chloride* (1/4)–*monohydrate* was obtained by bubbling gaseous hydrogen chloride through a solution of the ligand in diethyl ether. Crystals of this compound were filtered, washed with diethyl ether and recrystallized from ethanol (Found: C, 35.1; H, 8.2; N, 15.1; Cl, 37.6. $C_{11}H_{32}Cl_4N_4O$ requires C, 34.9; H, 8.5; N, 14.8; Cl, 37.5%). Ligands (L^2) and (L^3) were prepared according to the procedure reported by Kimura *et al.*[10] Elemental analysis for the hydrochloride derivatives gave the following results: 1,5,8,12-*tetra-azacyclohexadecane–hydrogen chloride* (1/4)–*monohydrate* (Found: C, 37.0; H, 8.6; N, 14.7; Cl, 36.3. $C_{12}H_{34}Cl_4N_4O$ requires C, 36.75; H, 8.7; N, 14.3; Cl, 36.15%); 1,5,9,13-*tetra-azacycloheptadecane–hydrogen chloride* (1/4)–*monohydrate* (Found: C, 38.4; H, 8.6; N, 13.8; Cl, 34.9. $C_{13}H_{36}Cl_4N_4O$ requires C, 38.45; H, 8.95; N, 13.8; Cl, 34.9%).

Materials.—All potentiometric and calorimetric measurements were carried out in 0.5 mol dm^{-3} KNO_3 as ionic medium, using commercial KNO_3 (C. Erba ACS grade) without further purification. Standardized, CO_2-free solu-

† Part 2, ref. 8.

tions of NaOH, used in the potentiometric and calorimetric titrations, were prepared according to the procedure already described.[11]

E.m.f. Measurements.—Potentiometric titrations were carried out using the following equipment: reaction vessel, 80 cm^3 capacity; water-thermostatted titration vessel maintained at 25 ± 0.1 °C; Mettler DV 70 mechanical stirrer; source of nitrogen presaturated with 0.5M-KNO_3 to pass over the surface of the titration solution. The titrant was delivered by a Mettler DV 10 piston burette graduated to 10^{-2} cm^3. The potentiometric measurements were made using an Orion 701-A digital pH–mV meter, an Orion 91–01 glass electrode, and an Ag–AgCl reference electrode kept in 3 mol dm^{-3} KCl solution. The reference electrode was connected to the titration cell by a Wilhelm bridge containing 0.5 mol dm^{-3} KNO_3 solution. The titration system was controlled by a Rockwell AIM 65 microprocessor programmed in BASIC to monitor, for each titration point, the e.m.f. values and the volume of titrant added. When the observed e.m.f. was constant within user-defined limits, the next volume of titrant was added automatically and the cycle repeated until the predefined total volume of titrant had been added. The experimental e.m.f. values were not corrected for the liquid junction potential [12] because this effect was negligible in the pH range investigated. The initial concentrations of the reagents and the pH-range explored for each titration are shown in Table 1.

TABLE 1

Experimental details of the e.m.f. measurements

	Initial concentrations (mmol)			
Curve	Ligand	HCl	pH Range	Data points
1	(L^1) 0.329	1.836	2.2—10.9	78
2	(L^1) 0.291	1.674	2.2—11.0	76
3	(L^2) 0.189	1.570	2.6—10.8	51
4	(L^2) 0.338	1.697	2.7—11.0	77
5	(L^3) 0.204	1.009	3.1—11.2	30
6	(L^3) 0.215	1.267	3.1—11.2	56
7	(L^3) 0.221	1.291	3.0—11.2	62

The MINIQUAD program [13] was used to process the data and calculate the basicity constants. Excellent agreement between the observed and calculated total concentrations of acid and ligand was obtained in the refinement of the basicity constants, by assuming a formula corresponding to L.4HCl. H_2O, for the hydrochlorides.

Calorimetric Measurements.—The enthalpies of protonation were determined with an LKB calorimeter model 8700, using the continuous titration technique. The apparatus, experimental procedure, and computer programs necessary to determine the stepwise enthalpy of protonation have already been reported.[14] The heat of ionization of water was determined by adding the NaOH solution to a HCl solution contained in the calorimetric vessel. The value found, 56.4 kJ mol^{-1}, was in good agreement with the literature value.[15] The experimental details of the calorimetric measurements are reported in Table 2.

TABLE 2

Experimental details of the calorimetric measurements

	Initial quantities (mmol)				
Titration	Ligand	HCl	Initial volume (cm^3)	NaOH added (mmol)	Rate (μmol s^{-1})
1	(L^1) 0.118	0.731	77.30	0.796	1.658
2	(L^1) 0.222	1.232	77.82	1.492	1.658
3	(L^2) 0.211	1.104	74.91	1.195	1.660
4	(L^2) 0.067	0.456	75.92	0.995	1.660
5	(L^3) 0.210	1.097	75.91	1.195	1.660
6	(L^3) 0.244	1.320	74.48	1.494	1.660

RESULTS AND DISCUSSION

Table 3 reports the thermodynamic functions $\Delta H^\ominus$ and $T\Delta S^\ominus$ for the protonation of the macrocycles (L^1)—(L^3). The same functions for the similar macrocycles 1,4,8,12-tetra-azacyclopentadecane (L^4) and 1,5,9,13-tetra-azacyclohexadecane (L^5), are reported for comparison.[7,8,16,17]

The largest macrocycle (L^3) exhibits a higher overall basicity than either (L^2) or (L^1), due to the increased length of the hydrocarbon chains. This trend is clearly shown in the Figure where the overall basicity of some tetra-azamacrocycles is plotted against the total number of atoms in the macrocyclic ring (atomicity). It should be noted that for macrocycles having the same atomicity,

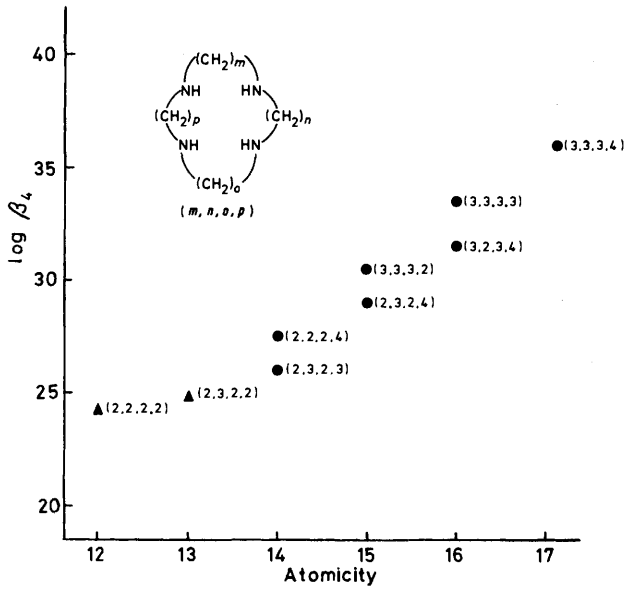


FIGURE Overall basicity ($\log\beta_4$) of some tetra-azamacrocycles plotted against the overall number of atoms in the macrocyclic ring (atomicity). Values for ▲ are from ref. 16 and are the highest values in the estimated range, the true value is likely to be several log units lower

the overall basicity is influenced by the relative sequence of hydrocarbon chains between the nitrogen atoms in such a way that a less regular arrangement lowers the overall basicity. Only in the case of the fourteen-membered macrocycle 1,4,7,11 tetra-azacyclotetradecane (cyclam) is this not true but it has often been pointed out that cyclam behaves in a quite exceptional way.[2,7,18,19] In all three macrocycles investigated in this work the first two basicity constants are much higher than the last two, making the diprotonated species the most important over a large pH range. This behaviour can be easily rationalized because the second proton can always add to a nitrogen atom far from the one to which the first proton is already bound. As a result the interaction between the protonated nitrogens is small and the

first two basicity constants are similar. Since the addition of the third and fourth protons must be to a nitrogen atom adjacent to protonated nitrogen, the interaction between the protonated nitrogens increases dramatically; as a result the third and fourth protonation constants are strongly influenced by the ring size and the relative length of hydrocarbon bridges between the nitrogen atoms. For the smaller ligand (L^1) there is a dramatic decrease in the basicity constant between the second and the third steps (6.5 log units) of protonation indicating that the addition of the third and fourth protons to the ligand (L^1) to form a tetraprotonated species is much less favoured than the addition of the first two protons. For ligands (L^2) and (L^3), with larger ring sizes than (L^1), the decrease of the basicity constant between the second and third steps is much smaller.

As far as the fourth protonation constant is concerned, ligand (L^3) exhibits the highest log K_4 value (6.30 log units) demonstrating that the introduction of the fourth proton is easier for the largest macrocycle than that for macrocycles (L^2) (log K_4 3.96) and (L^1) (log K_4 3.41). It is interesting to note that the value of log K_4 found for ligand (L^3) is comparable with those of many non-cyclic saturated tetramines; for the series 2,3,2-tet, 3,2,3-tet, 3,3,3-tet, and 3,4,3-tet * the values of log K_4 are 6.02, 5.82, 7.22, and 7.96, respectively.[20]

Let us now consider the enthalpies and entropies of protonation of the three macrocycles (L^1)—(L^3) (see Table 3). For ligand (L^1) both enthalpy and entropy contributions to the stepwise protonation reactions are very similar to those found for the related ligand (L^4).[8] In the proposed mechanism of protonation the first step involves the protonation of one nitrogen atom in an *exo*-configuration without formation of an internal hydrogen bond and the nitrogen atom involved may be one of the two bridged by the tetramethylene chain both of which are probably in an *exo*-configuration. The second step, which is also the most exothermic ($-\Delta H^\ominus$ 51.5 kJ mol^{-1}), can be explained by the formation of an internal hydrogen bond bridging the two nitrogens at the ends of the trimethylene chain. The addition of the third proton to the ligand (L^1) which will involve the nitrogen atom at the other end of the tetramethylene chain is less exothermic than the addition of the fourth proton. This behaviour can be explained by the increased concentration of positive charge in the triprotonated species without inversion of all the nitrogens. In the fourth protonation step the inversion of all the nitrogens occurs with consequent strong hydration which leads to a negative contribution to $\Delta H^\ominus$ and a decrease in $\Delta S^\ominus$.[8] For the sixteen-membered macrocycle (L^2) the first three stepwise protonation enthalpies are very similar (see Table 3) and there is not a significant difference between the second and third enthalpies of protonation in contrast with those for smaller macrocycles.[8] Similar behaviour has been explained for ligand (L^5) by the ability of the lone electron pairs on the nitrogen atoms to point in different directions (*exo*-configuration) and thus to act independently of each other. Only the last protonation step of (L^2) is less exothermic than the other three. This behaviour, which was not observed for ligand (L^5), can be explained in terms of the repulsion between the positive charges on the nitrogens linked by the ethylene bridge. For macrocycle (L^3) the stepwise protonation enthalpies are all very similar, indicating that for large macrocycles the nitrogen atoms can act independently of each other towards protons. We can say in conclusion that for tetra-azamacrocycles having hydrocarbon chains with more than two carbon atoms in each chain, the protonation behaviour is very similar to that of the corresponding open-chain tetramines. As far as the entropy contributions are concerned it should be noted that for the three macrocycles studied, $T\Delta S^\ominus$ decreases regularly as expected when the degree of protonation increases.[21]

TABLE 3

Thermodynamic quantities of stepwise protonation of macrocycles in aqueous solution, at 25 °C in 0.5 mol dm^{-3} KNO_3

	step	(L^1)	(L^2)	(L^3)	(L^4) [a]	(L^5) [b]
log K	1	11.04(1)	10.73(1)	11.20(1)	11.08	10.85
	2	10.47(1)	9.85(1)	10.13(1)	10.38	9.80
	3	3.98(1)	6.83(1)	7.96(3)	5.28	7.21
	4	3.41(1)	3.96(1)	6.30(4)	3.60	5.69
log β_4		28.90	31.37	35.59	30.34	33.55
$-\Delta H^\ominus$/kJ mol^{-1}	1	46.4(8)	46.4(4)	43.5(4)	45.2	41.8
	2	51.5(8)	47.7(4)	46.4(4)	51.5	44.8
	3	27.2(4)	42.7(4)	45.6(8)	30.1	43.1
	4	30.5(4)	33.5(8)	45.6(8)	32.2	44.4
$T\Delta S^\ominus$/kJ mol^{-1}	1	16.7(8)	14.6(4)	20.5(4)	18.0	20.1
	2	8.4(8)	8.4(4)	11.3(4)	7.9	11.3
	3	−4.6(4)	−3.8(4)	0.0(8)	0.0	−1.7
	4	−10.9(4)	−10.9(4)	−9.6(8)	−11.7	−11.7

[a] Values from refs. 7 and 8. [b] Values from refs. 16 and 17. [c] Values in parentheses are the errors in the last significant figure.

* Linear aliphatic tetramines of the type $H_2N(CH_2)_lNH(CH_2)_mNH(CH_2)_nNH_2$ may be denoted by the symbol *l,m,n*-tet.

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