Solution Chemistry of Macrocycles. Part 2.[1] Enthalpic and Entropic Contributions to the Proton Basicity of Cyclic Tetra-amine Ligands: 1,4,8,11-Tetra-azacyclotetradecane, 1,4,8,12-Tetra-azacyclopentadecane, and 1,4,8,11-Tetramethyl-1,4,8,11-tetra-azacyclotetradecane

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The enthalpy changes of stepwise protonation of the cyclic tetra-amines: 1,4,8,11-tetra-azacyclotetradecane, [14]aneN$_4$, 1,4,8,12-tetra-azacyclopentadecane, [15]aneN$_4$, and 1,4,8,11-tetramethyl-1,4,8,11-tetra-azacyclotetradecane, Me$_4$[14]aneN$_4$, have been determined at 25 °C in 0.5M-KNO$_3$ by calorimetry using the continuous titration procedure. Through a combination of the values of the enthalpy changes with the corresponding free-energy changes, reported elsewhere, the entropies of protonation have been obtained. In order to explain these thermodynamic functions two factors, which are not involved in the case of open-chain polyamines, are to be taken into account: (i) the presence of internal hydrogen bonds of the type N–H · · · N and (ii) conformational rearrangements of the macrocyclic ring due to the nitrogen inversion, the lone pairs being directed either towards the inside or the outside of the ring.

IN a previous study we have determined the successive protonation constants of the title cyclic tetra-amines.[1] The first two constants are greater than those of the corresponding linear tetra-amines while the third and fourth are smaller. The hypothesis has previously been proposed that this different behaviour can be rationalised on account of the ability of the ions H_2L^{2+}, in the cyclic tetra-amines to form internal hydrogen bonds.[1] This type of hydrogen bonding cannot occur in the linear tetra-amine, which will instead be bonded to the solvent. The X-ray crystal structure of H_2[14]aneN$_4$(ClO$_4$)$_2$ [2] has revealed the presence of internal bonds of the type N–H · · · N. In order to clarify the mechanism of the protonation of these polyamines, we have measured the stepwise enthalpies of protonation by continuous titration calorimetry and have deduced the respective entropies. The values are compared with those of the corresponding linear tetra-amine.

EXPERIMENTAL

Ligands.—[14]aneN$_4$, was supplied by Strem Chemicals and recrystallized twice from acetonitrile (Found: C, 60.1; H, 12.6; N, 28.4. Calc. for $C_{10}H_{24}N_4$: C, 60.0; H, 12.0; N, 28.0%).

[15]aneN$_4$·4HCl. Gaseous hydrogen chloride was bubbled through an ether solution of [15]aneN$_4$ supplied by Strem Chemicals. The white crystals of [15]aneN$_4$·4HCl·H$_2$O were filtered off and washed with ether (Found: C, 35.6; H, 8.6; N, 15.0. Calc. for $C_{11}H_{32}Cl_4N_4O$: C, 35.0; H, 8.5; N, 14.8%).

Me$_4$[14]aneN$_4$·4HCl, was prepared according to the method described above, using as starting material Me$_4$-[14]aneN$_4$ supplied by Strem Chemicals (Found: C, 41.2; H, 9.3; N, 13.7. Calc. for $C_{14}H_{36}N_4Cl_4$: C, 41.8; H, 9.0; N, 13.9%).

Other Reagents. 0.5M-CO$_2$-free solutions of sodium hydroxide were prepared, stored, and standardized as described elsewhere.[3] 0.5M-Potassium nitrate stock solutions were prepared from potassium nitrate (C. Erba, A. C. S. grade) without further purification and used as the ionic medium for calorimetric measurements.

Calorimetric Measurements.—An LKB 8700 calorimeter was used. The output voltages of the unbalanced Wheatstone Bridge were recorded every 20 s using a Solartron Digital Voltmeter (A200). Electrical calibrations were performed both before and after the reaction. The enthalpies of protonation were obtained using the continuous titration calorimetric method;[4] the titrant (NaOH) was introduced into the calorimeter, containing a solution of the amine in an excess of HCl, at constant velocity by a Mettler DV 10 piston automatic burette. Tables of heat output as a function of volume of titrant added are available as supplementary material. The same experiment, but with only HCl present, gave a value for the enthalpy of formation of H$_2$O of 13.5 kcal mol^{-1}, in good agreement with the accepted value.[5] Numerical analysis of the data was handled by means of the computer program [6] and enthalpies of protonation together with standard deviations are reported in Table 1.

DISCUSSION

In order to interpret correctly the thermodynamic functions associated with the protonation of amines,

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[1] Part 1, M. Micheloni, A. Sabatini, and P. Paoletti, *J.C.S. Perkin II*, 1978, 828.

[2] C. Nave and M. R. Truter, *J. Chem. Soc.*, 1974, 2351.

[3] M. Micheloni, A. Sabatini, and A. Vacca, *Inorg. Chim. Acta*, 1977, **25**, 41.

[4] A. Sabatini and A. Vacca, to be published.

[5] J. D. Hale, R. M. Izatt, and J. J. Christensen, *J. Phys. Chem.*, 1963, **67**, 2605; C. E. Vanderzee and J. A. Swanson, *ibid.*, p. 2608; L. Fabbrizzi, R. Barbucci, and P. Paoletti, *J.C.S. Dalton*, 1972, 1529.

[6] R. Barbucci, L. Fabbrizzi, P. Paoletti, and A. Vacca, *J.C.S. Dalton*, 1973, 1763.

some important terms need to be considered. In aqueous solution the amine nitrogens are bonded to one molecule of H_2O through a hydrogen bond of the type $N \cdots\cdots H{-}OH$ [7] (Table 2). During the protonation, the $O{-}H^+$ bond of the hydrated hydrogen ion ($H_9O_4^+$) is broken and an $N{-}H^+$ bond is formed in a process which overall is strongly exothermic (Table 2). At the same time, however, the molecule of water bonded to the amine nitrogen is released, as are the molecules of water previously associated with the H^+ ion; both these processes are responsible for a positive contribution to $\Delta H°$ of protonation but an increase in the entropy due to the increased disorder. The protonated amine ion so formed bonds, ultimately, through hydrogen bonds of the type $N{-}H \cdots O{-}H$ to as many H_2O molecules as there are H-atoms bound to nitrogen. The significance of this latter process, which is exothermic and produces a diminution in entropy [8] will diminish in the order primary > secondary > tertiary nitrogen atoms.

TABLE 1

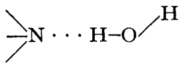
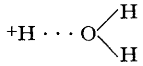
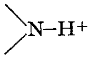
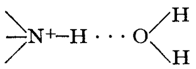
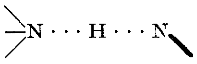
Thermodynamic quantities of stepwise protonation of cyclic tetra-amines in aqueous solution at 25 °C in 0.5M-KNO_3

	Step	[14]aneN_4	[15]aneN_4	Me_4[14]aneN_4
$-\Delta G°$/kcal mol^{-1}	1	15.80(1) [a]	15.11(1)	13.23(1)
	2	14.49(1)	14.16(1)	12.70(1)
	3	2.20(2)	7.20(1)	4.22(1)
	4	3.29(2)	4.91(2)	3.59(1)
$-\Delta H°$/kcal mol^{-1}	1	12.3(2)	10.8(1)	5.1(2)
	2	12.76(8)	12.3(1)	10.3(2)
	3	2.8(5)	7.22(5)	3.6(2)
	4	7.7(7)	7.71(6)	6.9(4)
$\Delta S°$/cal mol^{-1} K^{-1}	1	11.7(6)	14.4(5)	27.4(6)
	S	5.8(3)	6.3(3)	8.1(5)
	3	−2(2)	−0.1(2)	2.1(7)
	4	−15(2)	−9.4(2)	−11(1)

[a] Values in parentheses are standard deviations on the last significant figure.

TABLE 2

Tabular summary of the principal events which occur during the protonation of cyclic amines and their influence on $\Delta H°$ and $\Delta S°$

	Contribution [a] to	
Event	$\Delta H°$	$\Delta S°$
H-bond breaking (dehydration)		
	+	+
H-bond breaking (in $H_9O_4^+$ ion)		
	+	+
Formation of bond due to protonation		
	Strongly −	≃
Formation of H-bond with H_2O after protonation		
	−	−
Formation of internal H-bond		
	−	−
Inversion of nitrogen and consequent strong hydration		
	−	Strongly −

[a] The symbols +, −, and ≃ have been used to mean positive, negative and negligible contributions respectively.

What has been discussed so far is pertinent to any molecule containing an amino nitrogen. In the case of cyclic amines, it is necessary to consider together with these effects the formation of internal hydrogen-bonded bridges of the type $N{-}H \cdots N$,[2] and the possibility of nitrogen inversion, the lone pairs being directed either towards the inside or the outside of the ring. Hydrogen bonds of the type $N{-}H \cdots N$ are stronger than those of the type $N{-}H \cdots O$ [9] and therefore the formation of an internal bridge should result in a negative contribution to $\Delta H°$; the entropy will decrease because of the rigidity of the bridged system. The inversion of the nitrogen atoms (lone-pairs going from the inside to the outside of the ring) is favoured both by protonation and repulsions towards groups of the same charge present on the inside of the ring. As a consequence of such an inversion, there is strong hydration of the polar group surrounded by solvent and, consequently, a favourable enthalpy term which compensates for the energy expended in breaking the internal hydrogen bonds and the inversion of the ring.

What has been discussed so far is summarised in Table 2. Let us now consider the protonation of the three cyclic amines. In the free amines with the [14]aneN_4 skeleton the lone-pairs of the nitrogens are pointing towards the inside of the ring, whilst in [15]aneN_4 at least one of the nitrogens would be inverted (see Figure) explaining the increased interaction with the solvent and consequently much greater solubility. In the first protonation step of [15]aneN_4 it is this particular nitrogen which is protonated, with an associated enthalpy similar to that of a linear amine (*e.g.* *NN′*-diethylethylenediamine, $-\Delta H°_1 = 10.87$ kcal mol^{-1}).[10] In [14]aneN_4, the first proton is involved in forming a hydrogen bond across the inside of the ring with a consequent negative contribution to $\Delta H°$ and decrease in the entropy due to the increase in rigidity of the system. For the methyl derivative, the proton will be on the inside but, given the presence of the methyls, the monoprotonated species will be very dehydrated with positive contribution to $\Delta H°$ and increase in $\Delta S°$ ($-\Delta H°_1 = 7.40$ and $\Delta S°_1 = 17.6$ for *NNN′N′*-tetramethylethylenediamine).[11] The second step in the protonation of both [14]aneN_4 and [15]aneN_4 is similar in all respects to the

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[7] M. T. Emerson, E. Grunwald, H. Kaplan, and R. A. Kromhout, *J. Amer. Chem. Soc.*, 1960, **82**, 6307.

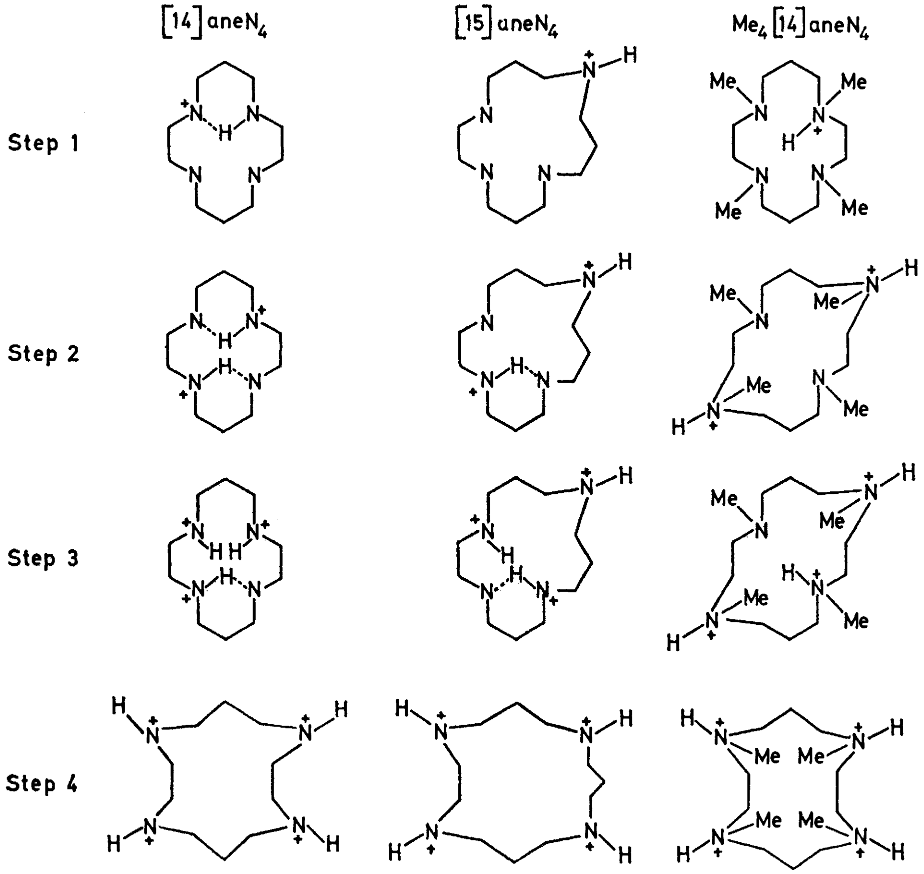
[8] P. Paoletti, L. Fabbrizzi, and R. Barbucci, 'Conference of Thermodynamique Biologiques,' S.C.F., Marseille, 1973.

[9] G. C. Pimentel and A. L. McClelland,' The Hydrogen Bond,' Reinholds, 1960.

[10] C. Bianchini, L. Fabbrizzi, and P. Paoletti, *J.C.S. Dalton*, 1975, 1036.

[11] P. Paoletti, R. Barbucci, A. Dei, and A. Vacca, *J. Chem. Soc.* (*A*), 1971, 310.

first step for [14]aneN_4, the enthalpies and entropies being similar. For Me_4[14]aneN_4, where internal hydrogen bonds do not exist, but the inversion of two protonated nitrogens towards the inside, with the consequent strong hydration leads to a negative contribution to $\Delta H°$ but decrease in $\Delta S°$.



A schematic representation of possible processes of protonation in cyclic amines. The ring conformation of the free amines is considered to be equal to that of the monoprotonated species

In the third protonation step of [14]aneN_4 a hydrogen bond has been broken without nitrogen inversion, with a consequent concentration of positive charge and thus a strong positive contribution to $\Delta H°$. In [15]aneN_4, no hydrogen bond is broken and the dramatic variation in $\Delta H°$, evident in [14]aneN_4, is not seen. For Me_4[14]aneN_4 the situation is similar to the first step with the nitrogen lone pairs pointing inwards and with the proton strongly shielded. In the final protonation step the inversion of all the nitrogens is completed for all three amines, together with the breaking of a hydrogen bond in [14]aneN_4 and [15]aneN_4. $\Delta H°$ for these two ligands is similar. For Me_4[14]aneN_4 the fourth step is similar to the second with a big positive contribution to $\Delta H°$ and a large fall in $\Delta S°$.

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