# Solution Chemistry of Macrocycles. Part 1. Basicity Constants of 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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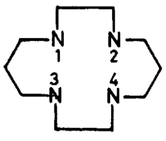
The four protonation constants of the macrocyclic tetra-amines 1,4,8,11-tetra-azacyclotetradecane ([14]ane$N_4$), 1,4,8,12-tetra-azacyclopentadecane ([15]ane$N_4$), and 1,4,8,11-tetramethyl-1,4,8,11-tetra-azacyclotetradecane ($Me_4$[14]ane$N_4$) have been determined in 0.5M-$KNO_3$ at 25 °C. Glass and silver/silver chloride electrodes were employed and the experimental e.m.f. values have been corrected for the liquid junction potential. The computer program MINIQUAD has been used for the calculation of the equilibrium constants. The values obtained are: [14]ane$N_4$, $\log K_1 = 11.59$, $\log K_2 = 10.62$, $\log K_3 = 1.61$, $\log K_4 = 2.42$; [15]ane$N_4$, $\log K_1 = 11.08$, $\log K_2 = 10.38$, $\log K_3 = 5.28$, $\log K_4 = 3.60$; $Me_4$[14]ane$N_4$, $\log K_1 = 9.70$, $\log K_2 = 9.31$, $\log K_3 = 3.09$, $\log K_4 = 2.64$. For the first two protonation steps the macrocyclic tetra-amines are more basic than the corresponding open-chain tetra-amines, even if the former exhibit a lower overall basicity.

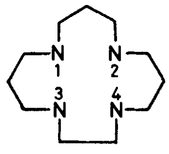
MANY papers in recent years have been concerned with reactions between metal ions and tetra-azacycloalkanes.[1-3] Particular attention has been paid to the kinetics of formation of the metal complexes and some thermodynamic parameters have been determined.[2-8] The high thermodynamic stability of the complexes in aqueous solution has been variously attributed to either an entropic or enthalpic effect or a combination of both.[3,5,7]

Very few values of protonation constants, obtained by different techniques, have been published.[3,5,9] Agreement is poor and frequently the values used for thermodynamic and kinetics measurements are unpublished results.[9]

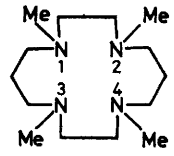
For our systematic study of the co-ordination capability of macrocyclic ligands we have investigated the protonation equilibria of 1,4,8,11-tetra-azacyclotetradecane ([14]ane$N_4$), 1,4,8,12-tetra-azacyclopentadecane ([15]ane$N_4$), and 1,4,8,11-tetramethyl-1,4,8,11-tetra-azacyclotetradecane ($Me_4$[14]ane$N_4$). The basicity constants have been determined using potentiometric methods.



[14]ane$N_4$



[15]ane$N_4$



$Me_4$[14]ane$N_4$

EXPERIMENTAL

*Ligands*.—[14]ane$N_4$ was supplied by Strem Chemicals and recrystallized twice from acetonitrile (Found: C, 60.15; H, 12.65; N, 28.1. Calc. for $C_{10}H_{24}N_4$: C, 59.95; H, 12.1; N, 27.95%).

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[1] B. Bosnich, C. K. Poon, and M. L. Tobe, *Inorg. Chem.*, 1965, **8**, 1102.

[2] D. K. Cabbiness and D. W. Margerum, *J. Amer. Chem. Soc.*, 1969, **91**, 6540.

[3] F. P. Hinz and D. W. Margerum, *Inorg. Chem.*, 1974, **13**, 2941.

[4] M. Kodama and E. Kimura, *J.C.S. Chem. Comm.*, 1975, 326.

[5] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 116.

[6] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 2341.

[7] A. Anichini, L. Fabbrizzi, and P. Paoletti, *Inorg. Chem. Acta*, 1977, **22**, L25.

[8] A. Anichini, L. Fabbrizzi, P. Paoletti, and R. M. Clay, *J.C.S. Chem. Comm.*, 1977, 244.

[9] K. H. Mayer, Dissertation, Munich, 1960.

$[15]aneN_4 \cdot 4HCl$. Gaseous hydrogen chloride was bubbled through an ether solution of $[15]aneN_4$ supplied by Strem Chemicals. The white crystals of $[15]aneN_4 \cdot 4HCl$ monohydrate were filtered off and washed with ether (Found: C, 35.55; H, 8.55; N, 14.95. Calc. for $C_{11}H_{32}Cl_4N_4O$: C, 35.0; H, 8.55; N, 14.8%).

$Me_4[14]aneN_4 \cdot 4HCl$ was prepared according to the method described above, using as starting material $Me[14]aneN_4$ supplied by Strem Chemicals (Found: C, 41.25; H, 9.3; N, 13.75. Calc. for $C_{14}H_{36}Cl_4N_4$: C, 41.8; H, 9.0; N, 13.95%).

*Other Reagents.*—0.5M-$CO_2$-free solutions of sodium hydroxide were prepared, stored, and standardized as described elsewhere.[10] 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 e.m.f. measurements.

*E.m.f. Measurements.*—The potentiometric titrations were carried out using an Orion 91–01 glass electrode, a silver/silver chloride electrode and a salt bridge containing 0.5M-potassium nitrate solution. The titration vessel was a seven-necked 150-ml flask. The entire cell was thermostatted at 25.0 ± 0.1 °C. A stream of nitrogen, presaturated with water vapour by bubbling it through a 0.5M-potassium nitrate solution, was passed over the surface of the solution. For the titrations, the sodium hydroxide solution was dispensed from a Metrohm Multidosimat piston burette graduated in hundredths of a millilitre. The experimental values of the e.m.f., in the strongly acidic region, have been corrected for the liquid junction potential following the procedure reported by Bates.[11] The corrections terms, for converting e.m.f. values into hydrogen ion concentrations have been determined before each measurement by titration of strong acid with a strong base.

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 (mM) | | | | |
|---|---|---|---|---|---|
| Curve | Ligand | | HCl | pH-Range | Data points |
| 1 | $[14]aneN_4$ | 0.333 | 2.156 | 1.9—10.9 | 33 |
| 2 | $[14]aneN_4$ | 0.328 | 2.155 | 1.9—10.8 | 36 |
| 3 | $[14]aneN_4$ | 1.384 | 7.001 | 1.7—11.3 | 76 |
| 4 | $[14]aneN_4$ | 0.396 | 2.148 | 2.0—10.7 | 35 |
| 5 | $[15]aneN_4$ | 0.613 | 4.065 | 2.1—10.7 | 52 |
| 6 | $[15]aneN_4$ | 0.548 | 3.266 | 2.3—11.2 | 51 |
| 7 | $Me_4[14]aneN_4$ | 0.317 | 2.344 | 1.9—10.9 | 51 |
| 8 | $Me_4[14]aneN_4$ | 0.672 | 3.759 | 2.0—10.3 | 68 |

*Calculations and Results.*—The computer program MINIQUAD [12] was used to calculate the protonation constants. The stepwise equilibrium constants for the ligands investigated and the relative standard deviations, obtained by the previously described procedure,[10] are shown in Table 2.

TABLE 2

Basicity constants of $[14]aneN_4$, $[15]aneN_4$, and $Me_4[14]aneN_4$ with their standard deviations at 25.0 °C and $\mu = 0.5$M ($KNO_3$)

| | Ligands | | |
|---|---|---|---|
| Log $K$ | $[14]aneN_4$ | $[15]aneN_4$ | $Me_4[14]aneN_4$ |
| log $K_1$ | 11.585 ± 0.005 | 11.081 ± 0.005 | 9.701 ± 0.003 |
| log $K_2$ | 10.624 ± 0.004 | 10.381 ± 0.005 | 9.314 ± 0.004 |
| log $K_3$ | 1.611 ± 0.011 | 5.279 ± 0.006 | 3.094 ± 0.005 |
| log $K_4$ | 2.415 ± 0.011 | 3.602 ± 0.014 | 2.635 ± 0.005 |
| log $\beta_4$ | 26.235 ± 0.004 | 30.343 ± 0.009 | 24.744 ± 0.004 |

DISCUSSION

Different sets of values of the stepwise protonation constants of $[14]aneN_4$ have been reported.[3,9] The agreement between them is very poor. The large differences between our values and literature values cannot be explained by the different conditions of temperature and ionic medium employed. For the amines $[15]aneN_4$ and $Me_4[14]aneN_4$ no values of protonation constants have been reported until now. All the cyclic amines investigated exhibit high basicity in the first two steps and rather low basicity in the last two steps. Accordingly the pH-jump in the titration curves is very sharp (Figure 1) and the diprotonated species is present over a large pH range (Figure 2).

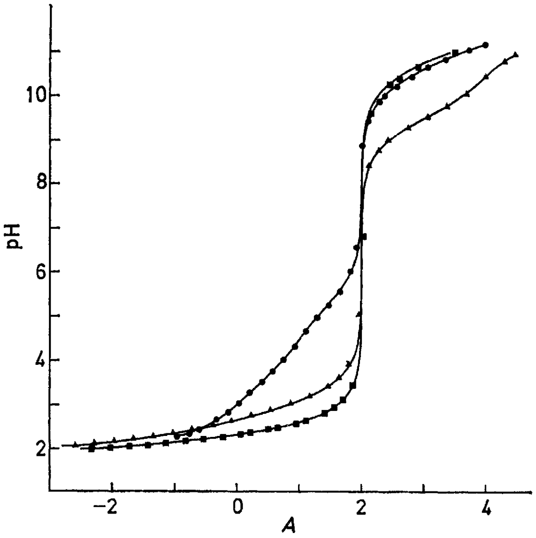

FIGURE 1 Titration curves of: $[14]aneN_4$ –■–■–■ data taken from curve 1 in Table 1, $[15]aneN_4$ –●–●–● data taken from curve 6 in Table 1, and $Me_4[14]aneN_4$ _▲_▲_▲ data taken from curve 7 in Table 1. $A = (n_{OH} - n_H/n_L) + 4$

The cyclic polyamines $[14]aneN_4$ and $[15]aneN_4$ are more basic than the linear open-chain tetra-amines in the first two steps; in fact in the series 2,2,2-tet, 2,3,2-tet, 3,2,3-tet, 3,3,3-tet † the values of log $K_1$ range from 9.95 [13] to 10.67 [14] and log $K_2$ from 9.31 [13] to 9.98.[14]

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* Listing of the computer output containing the experimental data is deposited as a Supplementary publication, SUP No. 22271 (5 pp.). See Notice to Authors No. 7, *J.C.S. Perkin II*, 1977, Index issue.

† Linear aliphatic tetra-amines 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.

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

[11] R. G. Bates, 'Determination of pH,' Wiley–Interscience, New York, 2nd edn., 1973, p. 261.

[12] A. Sabatini, A. Vacca, and P. Gans, *Talanta*, 1974, 21, 53.

[13] G. Schwarzenbach, *Helv. Chim. Acta*, 1950, **33**, 974; L. Sacconi, P. Paoletti, and M. Ciampolini, *J. Chem. Soc.*, 1961, 5115.

[14] P. Teyssie, G. Anderegg, and G. Schwarzenbach, *Bull. Soc. chim. belges*, 1962, **71**, 177; R. Barbucci, L. Fabbrizzi, and P. Paoletti, *J.C.S. Dalton*, 1972, 745.

For the $Me_4[14]aneN_4$ a similar comparison cannot be made because no data are available for the basicity constants of a linear tetra-amine containing only tertiary amino-groups. In any case, $Me_4[14]aneN_4$ is more basic in the first two steps of protonation than both *NNN'N'*-tetramethylethylenediamine ($\log K_1 = 9.29$, $\log K_2 = 6.13$)[15] and 1,1',4,7,10,13,13'-heptamethyl-1,4,7,10,13-penta-azatridecane ($\log K_1 = 9.42$ and $\log K_2 = 8.74$).[16]

Considering the first step of protonation of $[14]aneN_4$ and $[15]aneN_4$, the ' longer ' amine $[15]aneN_4$ should be more basic than $[14]aneN_4$; the opposite result (Table 2) can be partially explained by considering the statistical factor, the free amine $[14]aneN_4$ contains four nitrogen atoms in identical environments to which the first proton can add, making the $\log K_1$ greater by a term which is $\log 4 = 0.6$, while in the case of $[15]aneN_4$ there are two pairs of nitrogen atoms in identical environments and the statistical factor is lower.

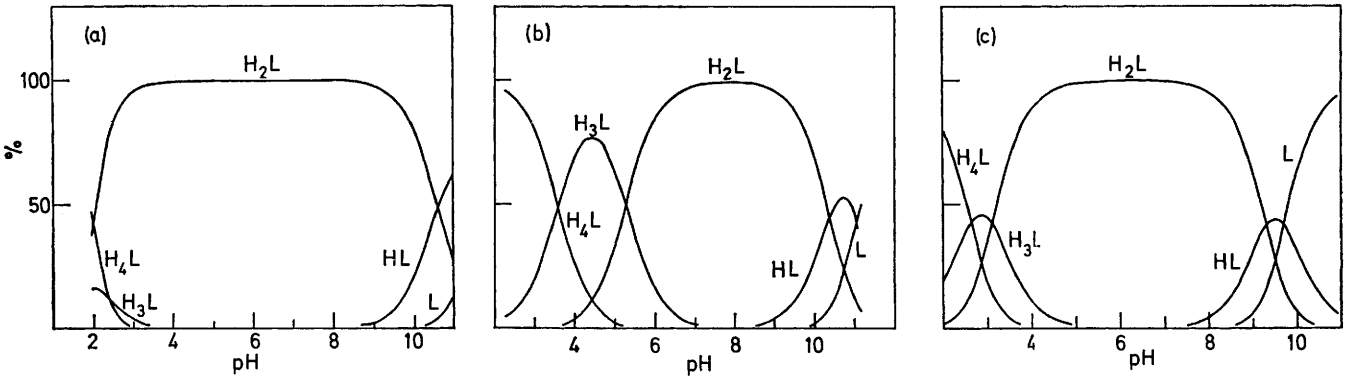

FIGURE 2 Distribution diagrams for the system: $H^+$–cyclic tetra-amines: (a) $H^+$–$[14]aneN_4$, the percentages have been calculated from the data of curve 1 in Table 1; (b) $H^+$–$[15]aneN_4$, the percentages have been calculated from the data of curve 6 in Table 1; (c) $H^+$–$Me_4[14]aneN_4$, the percentages have been calculated from the data of curve 7 in Table 1

In $[15]aneN_4$ the nitrogens 1 and 2 are expected to be the most basic and the first hydrogen ion will be added to one of these nitrogens, the second proton will bind the furthest nitrogen, 3 or 4, in order to minimize the electrical repulsion.

Nave *et al.* have reported the structure of the dihydroperchlorate of $[14]aneN_4$.[17] In this structure the hydrogen ions bound to the nitrogens in position 1,4 form hydrogen bonds with nitrogens in position 2,3 producing six-membered rings. Because of the cyclic nature of this amine, it is likely that the hydrogen bonds are retained in solution, giving an extra stability to the diprotonated species. In the two successive protonation steps such a system of hydrogen bonds will be broken. Since the value of $\log K_3$ is very low and even lower than $\log K_4$, it is reasonable to assume that the collapse of the structure occurs mainly at the third step.

In the case of $[15]aneN_4$ structural data are not available, but if we look at the diminution between $\log K_2$ and $\log K_3$ it appears reasonable to suppose that the slightly increased ring size prevents significant formation of intramolecular hydrogen bonds in the diprotonated form of $[15]aneN_4$.

Finally it is interesting to note that the overall basicity of $[15]aneN_4$ is higher than that of $[14]aneN_4$, due to the increasing size of the hydrocarbon chain, going from $[14]aneN_4$ to $[15]aneN_4$.

Except for $\log K_3$, all the values of stepwise protonation constants of $Me_4[14]aneN_4$ are lower than the corresponding values for $[14]aneN_4$, in accord with the fact that tertiary amino-groups are less basic than secondary amino-groups. The result, $\log K_3$ of $Me_4[14]aneN_4$ greater than $\log K_3$ of $[14]aneN_4$, can be explained by considering that the presence of the methyl groups on the nitrogen atoms strongly reduces the formation of hydrogen bonds in the diprotonated species. Consequently the introduction of the third proton in $Me_4[14]aneN_4$ is not as critical as in $[14]aneN_4$.

*Conclusions.*—In the first two steps of protonation the cyclic tetra-amines are more basic than the corresponding open-chain tetra-amines. This has to be attributed to the formation of intracation hydrogen bonds $N \cdots H\text{-}N^+$ for the macrocycle, whilst for the open-chain tetramines the protonated nitrogen atoms prefer to bind water molecules through hydrogen bridges $O \cdots H\text{-}N^+$.

On the other hand, the macrocycles exhibit a lower overall basicity than the corresponding open-chain tetra-amines. This is due to the electrostatic repulsion among positive charges which are constrained at a shorter distance by the rigid structure of the macrocyclic tetracation.

We thank Professor A. Vacca for helpful discussion.

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

[16] A. Vacca, *Ricerca Sci.*, 1966, **36**, 1363.

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