Polyamine Complexes with Seven-membered Chelate Rings: Complex Formation of 3-Azaheptane-1,7-diamine, 4-Azaoctane-1,8-diamine (Spermidine), and 4,9-Diazadodecane-1,12-diamine (Spermine) with Copper(II) and Hydrogen Ions in Aqueous Solution †

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Equilibrium constants have been determined for protonation of the linear triamines 3-azaheptane-1,7-diamine (3NH-hd) and 4-azaoctane-1,8-diamine (4NH-od, spermidine) at $I = 0{\cdot}10$M (NaCl) and 25 °C. Enthalpy (calorimetric) and entropy data are reported for protonation of 4,9-diazadodecane-1,12-diamine (4,9NH-ddd, spermine). Equilibrium formation constants and spectrophotometric data are also given for the complexes $[CuL]^{2+}$, $[Cu(HL)]^{3+}$, $[Cu(OH)L]^{+}$ (L = 3NH-hd or 4NH-od), and $[Cu(HL)_2]^{4+}$ (L = 3NH-hd). The data are compared with those for analogous tri- and tetra-amines.

THERMODYNAMIC data have previously been reported for the formation of hydrogen and metal-ion complexes with homologous triamines $NH_2{\cdot}[CH_2]_x{\cdot}NH{\cdot}[CH_2]_y{\cdot}NH_2$ and some *N*-alkyl-substituted derivatives, *viz.* 3-azapentane-1,5-diamine (3NH-pd or 2,2-tri, $x = y = 2$)[1-3] and derivatives[4,5] and 3-azahexane-1,6-diamine (3NH-hxd or 2,3-tri)[6,7] and 4-azaheptane-1,7-diamine (4NH-hd or 3,3-tri)[8,9] and their derivatives.[10] We now report data for the homologous triamines 3-azaheptane-1,7-diamine (3NH-hd or 2,4-tri) and 4-azaoctane-1,8-diamine (4NH-od or 3,4-tri) which contain a tetramethylene linkage and which give metal complexes containing seven-membered

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chelate rings. Relative to the diamines ethylenediamine (en) and propane-1,3-diamine (pnd), the seven-membered chelate ring contributes only 10^2—10^3 l mol^{-1} to the formation constant for the copper complex compared with *ca.* $10^{4\cdot6}$—10^7 l mol^{-1} for a five- or six-membered ring.

EXPERIMENTAL

4-Azaoctane-1,8-diamine (4NH-od) (pure: Koch–Light) was purified as its tris(hydrochloride) salt[11] (Found: C, 33·0; H, 8·5; N, 16·7. Calc. for $C_7H_{22}Cl_3N_3$: C, 33·0; H, 8·7; N, 16·5%). 3-Azaheptane-1,7-diamine (3NH-hd) (purum; Fluka) was converted to its tris(hydrochloride) salt by dissolving the free base (2·5 g) in conc. HCl (25%)–ethanol (30 cm^3); the resulting solution was evaporated to a syrup and the solid product which separated on cooling was twice recrystallised from methanol by Soxhlet extraction (Found: C, 30·1; H, 8·3; N, 17·5. Calc. for $C_6H_{20}Cl_3N_3$: C, 29·9; H, 8·4; N, 17·5%). 4,9-Diazadodecane-1,12-diamine (4,9NH-ddd) was purified as its tetrakis(hydrochloride) salt as described previously.[12]

pH$^+$ *Measurements*.—pH$^+$ Data were obtained by potentiometric titrations with the apparatus and [H$^+$]-calibration method previously described.[13]

Calorimetric Measurements.—The calorimeter has already been described.[14] The accuracy of the system was checked by determining the enthalpy change for protonation of Tris(aq) with HCl; the mean and standard deviation of five measurements (measured heat change *ca.* 8 J) was $-47\cdot6 \pm 0\cdot3$ kJ mol^{-1} (lit., $-47\cdot48$ and $-47\cdot44$ kJ mol^{-1}).[15,16] For protonation of 4,9NH-ddd, solutions of the ligand (C_L *ca.* 2×10^{-3}—3×10^{-3}M, $\bar{n}_H$ *ca.* 0·0—0·5) * were titrated with HCl (*ca.* 1M).

RESULTS AND CALCULATIONS

Representative pH data for titration of NaOH against solutions of (*i*) 3NH-hd,3HCl and NaCl, and (*ii*) 4NH-od,3HCl and NaCl at $I = 0\cdot10$M are deposited in Supplementary Publication No. SUP 21046 (9 pp.).† For titration of 3NH-hd,3HCl the pH against titre curve showed a single well defined inflexion (end point) after the addition of one equivalent of alkali ($\bar{n}_H$ 2·0), whereas the curve for 4NH-od,3HCl showed no inflexions as was the case for 4,9NH-ddd,4HCl.[12] The stepwise protonation constants in Table 1 were computed from derived $\bar{n}_H$(obs), pH data by use of the least-squares procedure previously described.[13] Each calculation used 32—46 data points in the range $\bar{n}_H$ = 0·4—2·8; an *R* factor[17] of *ca.* 0·1—0·5% was achieved and there were no systematic trends in the residuals[18] $\bar{n}_H$(obs) − $\bar{n}_H$(calc).

Data for the enthalpimetric titration of HCl against solutions of 4,9NH-ddd, HCl, and NaCl ($I = 0\cdot10$M) are deposited in SUP 21046. The stepwise enthalpy changes for ligand protonation were determined from 24 data points (four titrations) using calculation procedures outlined previously;[14] ΔH_i values are given in Table 2 and are compared with those for homologous tetra-amines.

TABLE 1

Equilibrium constants for stepwise protonation of triamine ligands at 25 °C and $I = 0\cdot10$M

Triamine	log K_1	log K_2	log K_3
3NH-hd [a]	10·65 ± 0·02	9·42 ± 0·01	6·71 ± 0·01
4NH-od [a]	10·89 ± 0·05	9·81 ± 0·02	8·34 ± 0·03
3NH-hxd [b]	10·44	9·36	6·37
3NH-pd [c]	9·79	8·98	4·25
4NH-hd [d]	10·65	9·57	7·72

[a] This work, 0·10M-NaCl; mean ± standard deviation from four titrations. [b] Ref. 7, 0·5M-KNO_3. [c] Ref. 3, 0·10M-KCl. [d] Ref. 8, 0·10M-KCl.

For the titration of NaOH against a solution of 3NH-hd,3HCl ($2\cdot36 \times 10^{-3}$M), copper(II) chloride ($1\cdot958 \times 10^{-3}$M), HCl, and NaCl ($I = 0\cdot10$M) the pH against titre curve showed a marked inflexion (*ca.* pH 7·0—8·4) after the addition of three equivalents of alkali, followed by a second buffered region. Data at pH <7 could not be satisfactorily interpreted in terms of a single complex [CuL]$^{2+}$. Spectrophotometric measurements as a function of pH indicated a decrease in $\lambda_{max.}$ as the pH increased from 5·6 ($\lambda_{max.}$ 676 nm) to 7·0 (613 nm) to 10·2 (590 nm), which suggested formation of a protonated complex [Cu(HL)]$^{3+}$ in the lower pH range (two N-donor atoms co-ordinated), complete formation of [CuL]$^{2+}$ (three N atoms co-ordinated) at pH 7 ($\varepsilon_{max.}$ 61·3 l mol^{-1} cm^{-1}), and formation of [Cu(OH)L]$^+$ at pH >8·7.

TABLE 2

Thermodynamic functions for stepwise protonation of tetra-amine ligands at 25 °C and $I = 0\cdot10$M

n	logK_n	$\frac{-\Delta G}{\text{kJ mol}^{-1}}$	$\frac{-\Delta H}{\text{kJ mol}^{-1}}$	$\frac{\Delta S}{\text{J K}^{-1}\text{ mol}^{-1}}$
	4,7-Diazadecane-1,10-diamine (4,7NH-dd) [a]			
1	10·53	60·1	51·7	28·3
2	9·77	55·8	51·8	13·3
3	8·30	47·4	43·2	14·1
4	5·59	31·9	34·2	−7·6
	34·2			
	4,8-Diazaundecane-1,11-diamine (4,8NH-ud) [b]			
1	10·45	59·7	51·0	28·9
2	9·82	56·1	52·2	13·4
3	8·54	48·7	48·7	0·0
4	7·22	41·2	45·5	−14·6
	36·0			
	4,9-Diazadodecane-1,12-diamine(4,9NH-ddd) [c,d]			
1	10·80 ± 0·01	61·63 ± 0·06	55·0 ± 1·0	22 ± 3
2	10·02 ± 0·01	57·18 ± 0·06	52·0 ± 0·7	17 ± 3
3	8·85 ± 0·01	50·51 ± 0·06	52·0 ± 0·6	−5 ± 2
4	7·96 ± 0·01	45·42 ± 0·06	47·9 ± 0·6	−8·5 ± 2·5
	37·6			

[a] Ref. 14. [b] R. Barbucci, L. Fabbrizzi, P. Paoletti, and A. Vacca, *J.C.S. Dalton*, 1972, 740. [c] Ref. 12. [d] This work.

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* C_L = Total concentration of the ligand; $\bar{n}_H$ = average number of protons bound per ligand molecule.

† For details see Notice to Authors, No. 7, *J.C.S. Dalton*, 1973, Index issue (items less than 10 pp. are supplied as full-size copies).

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Stability constants for formation of the complexes in equations (1) and (2) were calculated from 27 data points in the

$$Cu^{2+} + L \overset{K_1}{\rightleftharpoons} [CuL]^{2+} \tag{1}$$

$$Cu^{2+} + HL^{+} \overset{K_2}{\rightleftharpoons} [Cu(HL)]^{3+} \tag{2}$$

pH range 4·7—7·0 using a non-linear least-squares procedure[13,14] which minimised the term $\Sigma[C_H(\text{obs}) - C_H(\text{calc})]^2$, where C_H is the total ionisable acid. An R factor of 0·5% was achieved. At pH >8·7, $[Cu(OH)L^+]$ was calculated from $[Cu(OH)L^+] = -\{(C_H)_i - NaOH - [H^+] + [OH^-] - \sum_i [H_iL]\}$, whence $K_{OH} = [Cu(OH)L^+]/[OH^-]\{C_M - [Cu(OH)L^+]\}$. The constant K_{OH} was calculated for each data point and an average value determined from data for which $0{\cdot}2 < \{[Cu(OH)L^+]/C_M\} < 0{\cdot}8$.

Table 3

Equilibrium constants (log K) for formation of copper(II) complexes with linear triamine ligands at 25 °C and $I = 0{\cdot}10$M

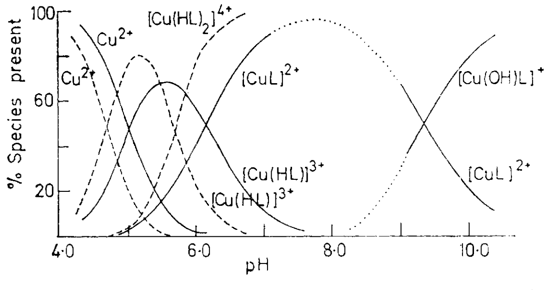
	Triamine				
Reaction	3NH-hd [a]	4NH-od [b]	3NH-hxd [c]	3NH-pd [d]	4NH-hd [e]
$Cu^{2+} + L \rightleftharpoons [CuL]^{2+}$ (log K_1)	13·44 ± 0·02	11·61 ± 0·02	16·60	15·80	14·20
$Cu^{2+} + HL^+ \rightleftharpoons [Cu(HL)]^{3+}$ (log K_2)	8·94 ± 0·02 (8·97 ± 0·01)	6·83 ± 0·1	9·02		
$[Cu(HL)]^{3+} + HL^+ \rightleftharpoons [Cu(HL)_2]^{4+}$ (log K_3)	(7·16 ± 0·02)				
$[CuL]^{2+} + OH^- \rightleftharpoons [Cu(OH)L]^+$ (log K_{OH})	4·42 ± 0·03	4·48 ± 0·05	4·72	4·50 [c]	4·1
$[CuL]^{2+} + L \rightleftharpoons [CuL_2]^{2+}$			3·28	5·21	

[a] This work, 0·10M-NaCl; average of two titrations, $C_M : C_L = 1 : 1{\cdot}2$. Results in parentheses from two titrations with $C_M : C_L = 1 : 4$. [b] This work, 0·10M-NaCl; average from two titrations, $C_M : C_L = 1 : 8$. [c] Ref. 7, 0·5M-KNO_3. [d] Ref. 2, 0·1M-KCl. [e] Ref. 8, 0·1M-KCl.

For the titration of NaOH with solutions containing a 4 : 1 ratio of 3NH-hd,3HCl : Cu^{2+} ($C_M = 1{\cdot}63 \times 10^{-3}$M) the pH against titre curve showed a minor inflexion after addition of two equivalents of alkali (pH 5·2), corresponding to formation of the complex $[Cu(HL)]^{3+}$, and a marked inflexion (pH 7·5—8·6) after addition of a further four equivalents of alkali. At pH 5·3, $\lambda_{max.} = 667$ nm indicative of a two-co-ordinate species such as $[Cu(HL)]^{3+}$. At pH 7·5 and 10·0, $\lambda_{max.} = 565$ nm indicative of a four-co-ordinate species such as $[Cu(HL)_2]^{4+}$ ($\varepsilon_{max.}$ 95·6 l mol^{-1} cm^{-1}). A single isosbestic point occurred between pH 5·3 and 7·5. The end-point at pH 7·5—8·6 was rationalised in terms of four equivalents of alkali per mole of copper $\{[Cu(HL)_2]^{4+}$ formed$\}$ plus one equivalent of alkali for each mole of excess of ligand. (The end-point for the titration $H_3L^{3+} + OH^- \longrightarrow H_2L^{2+} + H_2O$ was observed at pH 7·5—9·0.) Equilibrium constants K_2 and K_3 $\{= [Cu(HL)_2{}^{4+}]/[Cu(HL)^{3+}][HL^+]\}$ were determined from these data by non-linear least-squares analysis; an R factor of 0·3% was achieved from 32 data points. The value obtained for K_2 agreed with that obtained from titration on a 1·2 : 1 L : M solution. There was no spectrophotometric or potentiometric evidence for formation of the complex $[Cu(OH)L]^+$ in this solution.

Titration of 1 : 1 solutions of 4NH-od,3HCl and copper(II) ions with NaOH led to precipitation of copper(II) hydroxide. No precipitation occurred in titration of an 8 : 1 solution. A small inflexion occurred after addition of three equivalents of alkali per mole of copper(II) (pH 6·9), corresponding to formation of the complex $[CuL]^{2+}$; this was followed by a buffered region arising from deprotonation of excess of ligand. Results of spectrophotometric measurements ($\lambda_{max.}$ 650, 625, 625, 605, and 592 nm at pH 6·5, 7·2, 8·0, 9·3, and 10·4 respectively) were consistent with formation of the complex $[Cu(HL)]^{3+}$ followed by $[CuL]^{2+}$ ($\lambda_{max.}$ 625 nm, ε 100 l mol^{-1} cm^{-1}) at pH values up to 6·9 and then formation of $[Cu(OH)L]^+$ at pH >9. The equilibrium constants K_1 and K_2 were determined from a non-linear least-squares analysis on data in the pH range 5·8—7·5; R factors of 0·2 and 0·3% were achieved from 28 data points. The constant K_{OH} was determined from titration of HCl with a buffered solution containing the complex $[Cu(OH)L]^+$ ($C_M = 1{\cdot}01 \times 10^{-3}$, $C_L = 2{\cdot}04 \times 10^{-3}$, and $C_{OH} = 9{\cdot}08 \times 10^{-4}$M); solutions were stable from pH 10·7 to 7·3 at which precipitation of copper(II) hydroxide occurred.

For titrations of metal–ligand solutions representative data are deposited in SUP 21046. Equilibrium constants are given in Table 3 and compared with those for homologous triamines. Distribution curves for the metal–ligand species present throughout 3NH-hd titrations are given in the Figure.



Distribution curves for the Cu^{2+}–3NH-hd system: (——), Cu^{2+} : L ratio 1 : 1·2; (– – – –), Cu^{2+} : L ratio 1 : 4. Percentages of the species present are relative to the total metal-ion concentration

DISCUSSION

Protonation.—Equilibrium data for protonation of 4,9NH-ddd have been discussed previously.[12] The data in Table 2 indicate, as expected on the basis of increased chain length, that protonation of 4,9NH-ddd is considerably more exothermic than for 4,8-diazaundecane-1,11-diamine (4,8NH-ud or 3,3,3-tet) or 4,7-diazadecane-1,10-diamine (4,7NH-dd or 3,2,3-tet). The entropy for the initial protonation of 4,9NH-ddd, ΔS_1, is considerably lower than that for the other listed polyamines and 3,6-diazaoctane-1,8-diamine (3,6NH-od or 2,2,2-tet) (32·7 J K^{-1} mol^{-1}). Whereas the other values are intermediate to those for protonation of primary amines (*e.g.* en, 23·8 J K^{-1} mol^{-1}) and secondary amines (*e.g.* piperazine, 43·1 J K^{-1} mol^{-1}), and suggest that protonation in the first stepwise process involves tautomeric distribution of protons over both primary and secondary nitrogen atoms, the value for 4,9NH-ddd is similar to that for en suggesting that initial protonation is essentially on a terminal nitrogen atom. This is supported by the magnitude of ΔH_1 which is the same as that for the first protonation of pnd (55·2 kJ mol^{-1}).[19] We infer from these two observations, from the similarity of the other ΔH_i values to ΔH_1 and ΔH_2 for pnd, and from the equilibrium constants,[12] that, in contrast to 4,7NH-dd and 4,8NH-ud, the polyamine 4,9NH-ddd has protonation properties approaching those of two isolated diamine molecules, and prior to the initial protonation experiences negligible transmission of inductive effects[20] *via* the central tetramethylene linkage. Other factors which are pertinent to the magnitudes of ΔH_i and ΔS_i for protonation of tetra-amines have been discussed previously.[14]

Data for protonation of the triamines (Table 1) show, both for log K_i and for Σ_i log K_i (i = 1—3), the basicity sequences 3NH-hxd < 4NH-hd < 4NH-od and 3NH-pd < 3NH-hxd < 3NH-hd; these arise from the fact that, for protonation of an amine nitrogen in the presence of a charged (ammonium) or dipolar(amino) centre elsewhere in the molecule, ΔG becomes more negative as the distance between the charge or dipole and the protonation site increases.

Copper Complexes.—The data (Table 3) for formation of complexes $[CuL]^{2+}$ (log K_1) can be used to estimate the contribution of a five-, six-, or seven-membered chelate ring to the stability of a polyamine complex. Given that the formation constants for $[Cu(en)]^{2+}$ and $[Cu(prd)]^{2+}$ are log K_1 = 10·5 and 9·6 respectively, it is seen that addition of a five-, six-, or seven-membered chelate ring to these basic units adds respectively 5·3—7·0, 4·6—6·1, and 2·0—3·0 to log K_1 for formation of the complex; *i.e.* seven-membered chelate rings are the least stable of those considered, although the ligands containing them are the most basic. This deduction cannot be made quantitatively from a consideration of the simple diamines because the stability of the complex [Cu(butane-1,4-diamine)]$^{2+}$ cannot be measured in aqueous solution.[21]

From the marked stability of $[Cu(3NH\text{-}hxd)]^{2+}$, it has been deduced[7] that a sequence of linked five- and six-membered chelate rings in a ligand enhances the stability of a complex. However such a comparison of relative stabilities of different chelate-ring systems should not overlook the different basicities of the ligands,[12] *e.g.* a comparison could be based on log K' for reaction (3),

$$[CuL]^{2+} + 3H^+ \rightleftharpoons Cu^{2+} + H_3L^{3+} \qquad (3)$$

where $\log K' = \sum_i (\log K_i) - \log K_{CuL}$. For the listed triamines the sequence of log K' values is 4NH-od (17·4) > 4NH-hd (13·7) ~ 3NH-hd (13·3) > 3NH-hxd (9·6) > 3NH-pd (7·2), indicating that in a polyamine, as in a simple diamine, five-membered chelate rings give more stable complexes than six- and seven-membered rings. A rationale has been presented for this observation.[12]

The data in Table 3 show that each triamine forms a different set of simple and protonated complexes with copper(II). Four factors have been considered relevant to the formation of protonated complexes.[7] The unique tendency for 3NH-hd to form protonated complexes $\{[Cu(HL)]^{3+}$ and $[Cu(HL)_2]^{4+}\}$ arises from (*i*) the high stability of the retained five-membered chelate rings, (*ii*) the basicity of the terminal nitrogen atom, $\cdot[CH_2]_4\cdot$-NH_2, and (*iii*) the low stability of the seven-membered chelate ring which is broken in reaction (4). For the triamines 3NH-hd, 4NH-od, and 3NH-hxd values of

$$[CuL]^{2+} + H^+ \rightleftharpoons [Cu(HL)]^{3+}; \ \log K_{HL} \qquad (4)$$

log K_{HL} are 6·15, 6·11, and 2·86 respectively, a sequence which is in accord with (*ii*) and (*iii*) above.

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