# Complex Formation between 4,9-Diazadodecane-1,12-diamine (Spermine) and Copper(II) Ions and Protons in Aqueous Solution

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Equilibrium constants are reported for protonation of the linear tetra-amine 4,9-diazadodecane-1,12-diamine (4,9NH-ddd) and for formation of the complexes $[CuL]^{2+}$ and $[Cu(HL)]^{3+}$ (L = 4,9NH-ddd) at $I$ = 0·1M-NaCl and 25 °C. The bis(propane-1,3-diamine) complex, $[Cu(prd)_2]^{2+}$, and that formed by the title ligand are of similar stability; in this respect 4,9NH-ddd contrasts with the lower members of the homologous series of tetra-amines (3,6-diazaoctane-1,8-diamine and 3,7-diazanonane-1,9-diamine with respect to ethylenediamine, and 4,7-diazadecane-1,10-diamine and 4,8-diazaundecane-1,11-diamine with respect to prd) and displays a much reduced ' chelate effect.'

THERMODYNAMIC data have recently been reported for complex formation by members of the homologous series of tetra-amines $NH_2\cdot[CH_2]_x\cdot NH\cdot[CH_2]_y\cdot NH\cdot[CH_2]_x\cdot NH_2$ with protons and copper(II) ions.[1-6] We now report the first equilibrium-constant data for complexing by a linear tetra-amine, 4,9-diazadodecane-1,12-diamine (spermine), which has two amine groups separated by a tetramethylene chain and which gives complexes containing a seven-membered chelate ring. The effect of the long central tetramethylene chain is that stabilities of the proton and copper(II) complexes are comparable with those containing two isolated propane-1,3-diamine molecules.

## EXPERIMENTAL

*Materials.*—The ligand 4,9-diazadodecane-1,12-diamine (4,9NH-ddd) (puriss, Koch–Light) was purified as its tetra(hydrochloride) salt[7] (Found: C, 34·5; H, 8·7; N, 16·3. Calc. for $C_{10}H_{30}Cl_4N_4$: C, 34·5; H, 8·7; N, 16·1%). The copper(II) complex was prepared as follows. The ligand tetra(hydrochloride) salt (0·25 g, $7{\cdot}2 \times 10^{-4}$ mol) was dissolved in $H_2O$ (10 cm$^3$), and aqueous 1M-sodium hydroxide ($3{\cdot}6 \times 10^{-3}$ mol) was added followed by aqueous 0·3M-copper dichloride ($7{\cdot}2 \times 10^{-4}$ mol);† the solution was then filtered and solid sodium perchlorate (0·3 g) was added. Purple crystals of the product formed on cooling and were collected and washed sparingly with cold ethanol [Found: C, 26·1; H, $5{\cdot}8_5$. Calc. for $C_{10}H_{26}Cl_2CuN_4O_8$: C, $25{\cdot}8_5$; H, $5{\cdot}6_5$%. Equivalent weight (by acid titration), 114 (Calc., 116)]. Standard solutions of sodium hydroxide and copper dichloride were prepared as previously described.[5]

pH *Measurements.*—pH Data were obtained by potentio-

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† 1M = 1 mol dm$^{-3}$.

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metric titrations with the apparatus and the [H$^+$]-calibration method described.[8]

## RESULTS AND CALCULATIONS

Representative pH data from titrations of (*i*) NaOH against solutions of 4,9NH-ddd,4HCl, and NaCl ($I$ = 0·10M) and (*ii*) NaOH against solutions of 4,9NH-ddd,-4HCl, copper(II) chloride, NaCl, and HCl ($I$ = 0·10M) are deposited in Supplementary Publication No. SUP 21076 (3 pp.).* The pH against titre curve for the titration of NaOH against 4,9NH-ddd,4HCl solutions (1·5—2·4 × 10$^{-3}$M) showed no inflexions. Protonation constants were calculated from the derived $\bar{n}_H$(obs), pH data by use of the least-squares procedure previously described.[8] For each titration the constants were computed from 40 to 60 data points in the range $\bar{n}_H$ = 0·5—3·7; an $R$ factor[9] of *ca.* 0·2—0·45% was achieved and there were no systematic trends in the values of the residuals[10] $\bar{n}_H$(obs) − $\bar{n}_H$(calc).† The stepwise protonation constants are shown in Table 1. Calculations to determine the distribution curves for the protonated ligand species established that the concentration of $LH_3^{3+}$ is a maximum at pH 8·4 (59% of total ligand) and greater than 10% in the pH range 7·0—9·65; the respective figures for $LH_2^{2+}$ and $LH^+$ are 9·45 (66%) and 8·1—10·7 and 10·4 (55%) and 9·2—*ca.* 11·7.

TABLE 1

Equilibrium constants for stepwise protonation of tetra-amine ligands at 25 °C and $I$ = 0·10M

| Tetra-amine | log $K_1$ | log $K_2$ | log $K_3$ | log $K_4$ | Σ (log $K_i$) |
|---|---|---|---|---|---|
| 4,9NH-ddd [a] | 10·80 ± 0·01 | 10·02 ± 0·01 | 8·85 ± 0·01 | 7·96 ± 0·01 | 37·6 |
| 4,8NH-ud [b] | 10·45 | 9·82 | 8·54 | 7·22 | 36·0 |
| 4,7NH-dd [c] | 10·53 ± 0·02 | 9·77 ± 0·02 | 8·30 ± 0·02 | 5·59 ± 0·02 | 34·2 |
| $Me_6$-4,7NH-dd [d] | 11·09 ± 0·03 | 10·06 ± 0·02 | 7·61 ± 0·01 | 4·90 ± 0·01 | 33·7 |
| 3,7NH-nd [e] | 10·25 ± 0·02 | 9·50 ± 0·05 | 7·28 ± 0·02 | 6·02 ± 0·02 | 33·1 |
| 3,6NH-od [f] | 9·78 | 9·06 | 6·55 | 3·24 | 28·6 |

[a] This work, 0·10M-NaCl; mean ± standard deviation from four titrations. [b] Data from ref. 4, 0·10M-$NaNO_3$. [c] Data from ref. 5, 0·10M-NaCl. [d] Data from ref. 6, 0·10M-NaCl; $Me_6$-4,7NH-dd = 1,3,3,8,8,10-hexamethyl-4,7-diazadecane-1,10-diamine. [e] Data from ref. 3, 0·5M-KCl. [f] Data from ref. 1, 0·10M-KCl.

TABLE 2

Equilibrium constants for formation of copper complexes with linear tetra-amine ligands at 25 °C and $I$ = 0·10M

| | Tetra-amine | | | | |
|---|---|---|---|---|---|
| Reaction | 4,9NH-ddd [a] | 4,8NH-ud [b] | 4,7NH-dd [c] | 3,7NH-nd [d] | 3,6NH-od [e] |
| (1); log $K_1$ | 14·70 ± 0·07 | $17{\cdot}0_5$ ± 0·1 | 21·69 ± 0·08 | 23·9 ± 0·1 | 20·8 |
| (2); log $K_2$ | 9·99 ± 0·02 | | 14·69 ± 0·08 | | 13·8 |

[a] This work, 0·10M-NaCl; mean ± standard deviation from four titrations. [b] Data from ref. 4, 0·10M-$NaNO_3$. [c] Data from ref. 5, 0·10M-NaCl. [d] Data from ref. 3, 0·5M-KCl. [e] Data from ref. 2, 0·10M-HCl.

Titration of NaOH against 1 : 1 metal : ligand tetra(hydrochloride) salt solutions (*ca.* 1·0 × 10$^{-3}$M) led to precipitation of copper(II) hydroxide at pH *ca.* 6·2, at which point complex formation was just commencing. The problem of precipitation was avoided by (*i*) use of a seven- or ten-fold excess of ligand tetra(hydrochloride) ([Cu$^{2+}$] = 0·7 × 10$^{-3}$—0·9 × 10$^{-3}$M), (*ii*) use of more dilute solutions (3·4 × 10$^{-4}$M) of 1 : 1 stoicheiometry, and (*iii*) by titrating the dissolved complex [Cu(4,9NH-ddd)][$ClO_4$]$_2$ with standard acid. Unlike the reaction of many other polyamines with copper(II), complex formation did not commence until the pH was above that for the end-point ($\bar{n}_H$ 4·0) for the ligand-protonation curve (pH *ca.* 5—6). Use of conditions (*i*) and (*ii*) had the effect of lowering the pH of the buffer region in the titration and not only prevented formation of $Cu(OH)_2$ but, by employing low metal concentrations, minimised formation of hydrolysed copper(II) species $Cu_x(OH)_y$. With the exception of the region $\bar{n}_H$ *ca.* 4·0, all pH readings were stable (readability ±0·001 pH unit) and solutions at different pH set aside from these titrations showed no evidence of precipitation after 24 h. [Approximate calculations based on the equilibrium $2Cu^{2+} + 2H_2O \rightleftharpoons Cu_2(OH)_2 + 2H^+$ (log $K$ *ca.* −11·0) indicated that for 1 : 7 M : L titrations the percentage of total copper present as $Cu_2(OH)_2$ varied between *ca.* 0·1 and 0·6% and for the 1 : 1 titrations between *ca.* 0·1 and 1·5%.]

pH Data could not be satisfactorily interpreted in terms of only one complex [CuL]$^{2+}$. (Analysis in terms of one complex gave a value of log $K$ which decreased steadily from 15·09 at $\bar{n}$ = 0·25 to 14·59 at $\bar{n}$ = 0·83 for a 1 : 7 metal : ligand ratio.) Spectrophotometric measurements as a function of pH indicated a decrease in $\lambda_{max.}$ as the pH increased from 6·4 ($\lambda_{max.}$ 598 nm) to 7·9 (568 nm), which suggested formation of a protonated complex in the lower part of this pH range.[5] Spectrophotometric and pH measurements indicated that no hydroxo-species [CuL(OH)]$^+$ is formed. Stability constants for the formation of the complexes [equations (1) and (2)] were calculated using a non-linear least-squares procedure[5,8] minimising the term

$$Cu^{2+} + L \xrightleftharpoons{K_1} [CuL]^{2+} \qquad (1)$$

$$Cu^{2+} + HL^+ \xrightleftharpoons{K_2} [Cu(HL)]^{3+} \qquad (2)$$

$\Sigma[C_H(\text{obs}) - C_H(\text{calc})]^2$ where $C_H$ = total ionisable acid. For each titration the constants were computed from 25 to 32 data points; $R$ factors[9] of 0·4 and 1·8% respectively were obtained for data from 1 : 7 and 1 : 1 metal : ligand

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† $\bar{n}_H$ = average number of protons bound per ligand molecule.

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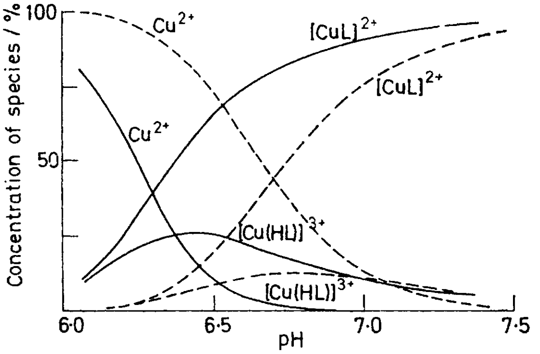
systems. There were no systematic trends in the least-squares residuals.[10] The equilibrium constants are shown in Table 2. Distribution curves for the species present throughout the titration are shown in the Figure. Physical parameters for the complex $[Cu(4,9NH\text{-}ddd)][ClO_4]_2$ were: solution absorption spectrum, $\lambda_{max.}$ 564 nm ($\varepsilon_{max.}$ 146 dm$^3$ mol$^{-1}$ cm$^{-1}$); powder e.s.r. spectrum, $g_{\parallel}$ 2·20, $g_{\perp}$ 2·04.



Distribution curves for the $Cu^{2+}$–4,9NH-ddd system: (——), for a 1 : 7 metal : ligand ratio; (— — —), for a 1 : 1 metal : ligand ratio. Percentages relative to total metal concentration

DISCUSSION

*Protonation*.—For the protonation of an amine nitrogen atom in the presence of a charged (ammonium) or dipolar (amino) centre elsewhere in the molecule, the free-energy change becomes more negative as the distance of the charge or dipole from the protonation site increases. For linear tetra-amines, $NH_2\cdot[CH_2]_x\cdot NH\cdot[CH_2]_y\cdot NH\cdot[CH_2]_x\cdot NH_2$, with methylene chains of varying length joining the four nitrogen atoms, the predicted basicity sequences [for log $K_i$ and $\sum_i$ log $K_i$ ($i$ = 1—4)] are 4,9NH-ddd > 4,8NH-ud > 4,7NH-dd > 3,7NH-nd > 3,6NH-od (where 4,9NH-ddd is the amine with $x = 3$ and $y = 4$).* The available data for these amines (Table 1) show that the predicted sequences are observed (log $K_1$ for 4,8NH-ud is the exception).

The sequence of sites for protonation on an individual polyamine cannot be unambiguously predicted because of the similar basicity for primary and secondary amine groups[11] (compare ethylenediamine[12] and *NN'*-dimethylethylenediamine[13]). Analyses of entropy and enthalpy changes for polyamine protonation suggest that the first and second protonation steps involve the addition of protons to both primary and secondary amine nitrogen atoms to yield tautomers in equilibrium;[1,5,14] thus the diammonium cation for 4,9NH-ddd would have in equilibrium two tautomers, protonated on N(1), N(12) and N(1), N(9). To a much greater extent than for the other linked tetra-amines, 4,9NH-ddd, with a longer central methylene linkage, behaves like two isolated diamine residues in its protonation reaction. This is evident from the fact that log $K_1 \sim$ log $K_2 \sim$ log $K_1$ (prd) (10·72[15]) and log $K_3 \sim$ log $K_4 \sim$ log $K_2$ (prd) (8·98[15]). This is related to the diminishing transmission of polar effects with increasing length of the (central) methylene linkages.[16,17]

*Copper Complexes*.—The ligand 4,9NH-ddd forms the least-stable complex, [CuL], of the linear tetra-amines listed in Table 2 although it has the highest basicity ($\sum_{i=1}^{4}$ log $K_i$). Earlier studies on copper complexes of linear tetra-amines[3,5,18] concluded that complexes display an enhanced stability when the ligand involves an alternating sequence of five- and six-membered chelate rings, and pointed to the lower stability of complexes of 4,8NH-ud and 3,6NH-od, *e.g.* the observed log $K_{CuL^{2+}}$ sequence is 3,7NH-nd > 4,7NH-dd > 3,6NH-od > 4,8NH-ud (> 4,9NH-ddd). This sequence has been discussed on the basis of (*i*) cumulative ring strain[5,18,19] in complexed 4,8NH-ud and 3,6NH-od for which each ring is unable to adopt respectively the favoured chair and *gauche* conformations, and (*ii*) the apparently strain-free ring conformations adopted by 4,7NH-dd and 3,7NH-nd.[5,18] Such a rationale is not able to account for the low stability of the ion $[Cu(4,9NH\text{-}ddd)]^{2+}$ for which models indicate that the favoured chair and twist-chair[20] conformations can be adopted by the six-membered and seven-membered chelate rings respectively.

A comparison of polyamine complex stabilities based only on log $K_{CuL^{2+}}$ overlooks the different basicities of the ligands. We submit that the relative stabilities of different chelate-ring systems are better gauged from log $K'$ for reaction (3), where log $K' = \sum_{i=1}^{4}$ (log $K_i$) − log $K_{CuL^{2+}}$. For the listed tetra-amines the sequence of log $K'$ values is 4,9NH-ddd (22·9) > 4,8NH-ud (19·0) > 4,7NH-dd (12·5) > 3,7NH-nd (9·2) > 3,6NH-od (8·5), indicating that maximum chelate-ring stability results for linked five-membered chelate rings as in 3,6NH-od, and that stability decreases with an increase in chelate-ring size, as is the case for simple diamines. A rationale for this observation is that for the free amine 3,6NH-od the adjacent nitrogen atoms are held at a separation

$$[CuL]^{2+} + 4H^+ \rightleftharpoons Cu^{2+} + LH_4^{4+} \qquad (3)$$

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* 4,8NH-ud = 4,8-Diazaundecane-1,11-diamine, 4,7NH-dd = 4,7-diazadecane-1,10-diamine, 3,7NH-nd = 3,7-diazanonane-1,9-diamine, and 3,6NH-od = 3,6-diazaoctane-1,8-diamine.

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similar to that adopted on co-ordination to a metal ion, whereas for larger chelate rings to effect chelation the polar amine groups must first be brought closer together, and the imposed interaction between these groups contributes an endothermic energy term to the complexing reaction. (This rationale accounts for the fact that ethylenediamine complexes are more stable than prd complexes, despite the greater basicity of the latter ligand.)

The ligand 4,9NH-ddd, with the central amine groups separated by four methylene groups, appears to represent an extreme case, in that log $K'$ is approximately equal to log $K'$ for the reaction involving two molecules of prd [equation (4)], where log $K' = 22{\cdot}5$.[15] This indicates, as

$$[\mathrm{CuL_2}]^{2+} + 4\mathrm{H}^+ \rightleftharpoons \mathrm{Cu}^{2+} + 2\mathrm{LH_2}^{2+} \qquad (4)$$

confirmed by log $K_i$ data, that in the free ligand 4,9NH-ddd there is negligible transmission of polar or inductive effects between N(4) and N(9). This contrasts with 3,6NH-od and ethylenediamine[12,19] for which log $K'$ is 8·5 and 14·5 respectively; 3,6NH-od gives the most stable complexes despite the effect of cumulative ring strain.

The log $K_2$ value for the protonated complex $[\mathrm{Cu(HL)}]^{3+}$ (L = 4,9NH-ddd) is similar to log $K_1$ for $[\mathrm{Cu(prd)}]^{2+}$, 9·77.[15] If it can be assumed that protonation of the co-ordinated ligand takes place on a terminal nitrogen atom, this indicates that the seven-membered chelate ring makes negligible contribution to the complexing tendency of 4,9NH-ddd. This result agrees with the observation that 'copper(II) and nickel(II) complexes of butane-1,4-diamine are so weak in aqueous solution that their stability constants cannot be measured.'[21]

It is of interest to note that protonated complexes $[\mathrm{Cu(HL)}]^{3+}$ have not been reported for 4,8NH-ud or 3,7NH-nd even though in each case homologous tetra-amines with smaller values of log $K'$ do give protonated complexes. One may infer that the complexes have not been observed rather than they do not exist.

We acknowledge helpful discussions with Dr. D. A. House and Professor N. F. Curtis, and the assistance of Dr. P. G. Hodgson with the e.s.r. spectrum. A single-crystal X-ray structure analysis of the complex $[\mathrm{Cu(4,9NH\text{-}ddd)}][\mathrm{ClO_4}]_2$ is in progress.

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