Kinetics of the Reaction of Copper(II) with *meso*-5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetra-azacyclotetradecane

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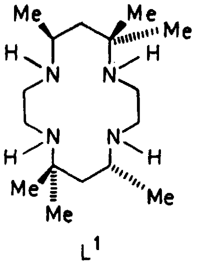
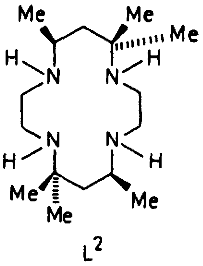
Copper(II) reacts with *meso*-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradecane (L^1) in aqueous solution (pH 4—6) to give $[CuL^1]^{2+}$ (blue) with $\lambda_{max.}$ 620 nm. At higher pH (*ca.* 9), $[CuL^1]^{2+}$ (blue) is slowly converted into $[CuL^1]^{2+}$ (violet) with $\lambda_{max.}$ 520 nm. The kinetics of formation of the blue complex have been studied at 25 °C and I = 0.1 mol dm^{-3} in both acetate and piperazine-*NN'*-bis(ethane-2-sulphonic acid) buffers. In the absence of acetate, Rate = $k_1[Cu^{2+}][HL^{1+}]$ but in acetate buffers Rate = $k_1[Cu^{2+}][HL^{1+}] + k_2[Cu(O_2CMe)][HL^{1+}] + k_3[Cu(O_2CMe)^+][H_2L^{1\,2+}]$, with $k_1 = 3.6 \times 10^3$ dm^3 mol^{-1} s^{-1}, $k_2 = 1.8 \times 10^4$ dm^3 mol^{-1} s^{-1}, and $k_3 = 1.5 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}. Possible mechanisms for the reaction are considered.

CABBINESS and Margerum [1] have studied the formation of the copper(II) complexes of *meso*-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradecane (L^1, tet*a*). In neutral or slightly acidic solution, Cu^{II} reacts with the ligand to give initially a blue complex $[CuL^1]^{2+}$ ($\lambda_{max.}$ 620 nm, ε 193 dm^3 mol^{-1} cm^{-1}) which is readily converted into the more thermodynamically stable violet isomer ($\lambda_{max.}$ 520 nm, ε 140 dm^3 mol^{-1} cm^{-1}) at higher pH. Similar behaviour is exhibited by the *rac* diastereoisomer (L^2, tet*b*).[1] The kinetics of formation of blue $[CuL^1]^{2+}$ and of the blue ⟶ violet conversion have been investigated by Kaden [2] using spectrophotometric and p*H-stat* techniques.

A crystal-structure determination of violet $[CuL^1][ClO_4]_2$ has recently been completed.[3] The violet complex has the *trans* [4] or cyclam structure (1) which



L^1



L^2

minimises proton–proton interactions in the chelate rings and is virtually free from torsional bond strain. The two perchlorate anions lie *trans* across the oxygen

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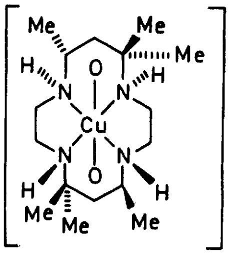
[1] D. K. Cabbiness and D. W. Margerum, *J. Amer. Chem. Soc.*, 1969, **91**, 6540; 1970, **92**, 2151.

[2] T. A. Kaden, *Helv. Chim. Acta*, 1971, **54**, 2307.

[3] R. M. Clay, P. Murray-Rust, and J. Murray-Rust, unpublished work.

[4] B. Bosnich, M. L. Tobe, and G. A. Webb, *Inorg. Chem.*, 1965, **4**, 1102; B. Bosnich, R. Mason, P. Pauling, G. B. Robertson, and M. L. Tobe, *Chem. Comm.*, 1965, 97.

with a Cu–O distance of 2.60 Å indicating significant bonding interactions. Crystallography[3] of the analogous blue complex is less advanced due to symmetry problems; however, the two perchlorate anions appear to lie *trans* across the copper(II) ion suggesting that the ligand is in a planar rather than a folded configuration. It appears likely that the blue species differs from the violet only in the configuration of a single chiral nitrogen centre. The kinetics of the blue ⟶ violet conversion follow a rate law,[2] Rate = $k[\mathrm{CuL^{1\,2+}}\text{ (blue)}][\mathrm{OH^-}]$, which lends support to this view. It is clear that the blue species is the kinetically controlled product while the violet is the thermodynamically controlled product.



(1); O = unidentate perchlorate

The tetra-azacyclotetradecanes react with metal ions 10^3—10^4 times more slowly than analogous open-chain tetra-amines for which the rate-determining step is formation of the first metal–nitrogen bond.[5] A number of explanations have been suggested to account for the slower reaction rates of the macrocycles: (*a*) multiple desolvation, such as accompanies the binding of metal ions in the more rigid porphyrin structures;[1] (*b*) a high-energy barrier to internal rotation, since some degree of ligand twisting or folding may be necessary to effect complex formation;[1,2,6] and (*c*) steric effects due to *N*-substitution.[7]

A number of recent papers have dealt with various aspects of the kinetics of incorporation of metal ions into macrocyclic ligands.[1,2,6,8-10] The present paper discusses the kinetics of formation of blue $[\mathrm{CuL^1}]^{2+}$ in the presence and absence of acetate ion. Kaden's work[2] had indicated that acetate ion had a significant effect on the kinetics.

EXPERIMENTAL

meso-5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetra-azacyclotetradecane dihydrate was prepared as previously described,[11] m.p. 146—147 °C (lit.,[11] 146—148 °C) (Found: C, 60.3; H, 12.4; N, 17.7. Calc. for $C_{16}H_{40}N_4O_2$: C, 60.0; H, 12.6; N, 17.5%).

Blue $[\mathrm{CuL^1}][\mathrm{ClO_4}]_2\cdot\mathrm{H_2O}$ was prepared as follows. Copper(II) acetate dihydrate (1.36 g, 6.2 mmol) was mixed with L^1 (0.2 g, 6.2 mmol) in water (30 cm³) and the mixture was stirred and heated on a water-bath for 15 min. Perchloric acid (2 cm³, 35%) was added and the solution was cooled in ice. The resulting blue crystals were filtered off, washed with cold ethanol, and dried *in vacuo* (Found: C, 34.1; H, 7.1; N, 10.3. Calc. for $C_{16}H_{38}Cl_2CuN_4O_9$: C, 34.0; H, 6.8; N, 9.9%).*

Piperazine-*NN'*-bis(ethane-2-sulphonic acid) (pipes) was purchased from B.D.H. Other chemicals were of AnalaR quality.

Potentiometric titration of a saturated solution of L^1 (8.5×10^{-4} mol dm⁻³) at 25 °C and $I = 0.1$ mol dm⁻³ (KCl) gave $\mathrm{p}K_3^{\mathrm{M}} = 10.30 \pm 0.05$ in good agreement with the value reported by Cabbiness and Margerum (10.4 ± 0.1).[1] The low solubility of the ligand prevented the determination of other protonation constants. A solvent-extraction procedure has given $\mathrm{p}K_4^{\mathrm{M}} = 12.6$, and $\mathrm{p}K_3^{\mathrm{M}}$ has been reported[1] as 10.4 at 25 °C and $I = 0.1$ mol dm⁻³. ($\mathrm{p}K^{\mathrm{M}}$ Values are mixed constants involving the hydrogen-ion activity and the concentrations of the other species.)

Spectrophotometric kinetic measurements were made with a Gifford 2400S instrument. A strong charge-transfer band is exhibited by $[\mathrm{CuL^1}]^{2+}$ (blue) at 275 nm (ε *ca.* 10^4 dm³ mol⁻¹ cm⁻¹) and the complex-formation reaction was monitored at this wavelength. A number of runs were followed by pH-stat methods using instrumentation previously described.[12] Two protons are released per mol of L^1 on formation of $[\mathrm{CuL^1}]^{2+}$ (blue) [equation (1)]. In all cases the copper(II) concentration was at least 20 times that of the ligand so that pseudo-first-order conditions were fulfilled. Under the conditions of the measurements (pH 4—6) the blue ⟶ violet conversion was not observed since this only becomes important at higher pH (8—9).[2] Rate constants were obtained from linear plots of $\log(A_t - A_\infty)$ against time, except for slower reactions ($t_{\frac{1}{2}} > 100$ min) when Guggenheim plots were used. Potentiometric measurements were made with a Radiometer 26 pH meter.

$$\mathrm{Cu^{2+}} + [\mathrm{H_2L^1}]^{2+} \longrightarrow [\mathrm{CuL^1}]^{2+}\text{ (blue)} + 2\mathrm{H^+} \qquad (1)$$

RESULTS AND DISCUSSION

The protonation equilibria of L^1 can be represented as in (2)—(5). Cabbiness and Margerum[1] estimated the values $\mathrm{p}K_1 = 0$, $\mathrm{p}K_2 = 0.8$, $\mathrm{p}K_3 = 10.4$, and $\mathrm{p}K_4 = 12.6$. Our own potentiometric data give $\mathrm{p}K_3^{\mathrm{M}} = 10.30$ at $I = 0.1$ mol cm⁻³, in reasonable agreement.

$$[\mathrm{H_4L^1}]^{4+} \overset{K_1}{\rightleftharpoons} [\mathrm{H_3L^1}]^{3+} + \mathrm{H^+} \qquad (2)$$

$$[\mathrm{H_3L^1}]^{3+} \overset{K_2}{\rightleftharpoons} [\mathrm{H_2L^1}]^{2+} + \mathrm{H^+} \qquad (3)$$

$$[\mathrm{H_2L^1}]^{2+} \overset{K_3}{\rightleftharpoons} [\mathrm{HL^1}]^{+} + \mathrm{H^+} \qquad (4)$$

$$[\mathrm{HL^1}]^{+} \overset{K_4}{\rightleftharpoons} \mathrm{L^1} + \mathrm{H^+} \qquad (5)$$

The kinetics of the reaction between $\mathrm{Cu^{II}}$ and L^1 to give $[\mathrm{CuL^1}]^{2+}$ (blue) were studied at 25 °C and $I = 0.1$ mol dm⁻³ in (*a*) acetate buffers and (*b*) in the absence of acetate using pipes buffer or a pH-stat to maintain the

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* Prolonged drying gives the anhydrous complex.

[5] R. E. Shepard, G. M. Hodgson, and D. W. Margerum, *Inorg. Chem.*, 1971, **10**, 989.

[6] R. Buxtorf and T. A. Kaden, *Helv. Chim. Acta*, 1974, **57**, 1035.

[7] T. S. Turan and D. B. Rorabacher, *Inorg. Chem.*, 1972, **11**, 288.

[8] C. T. Lin, D. R. Rorabacher, G. R. Cayler, and D. W. Margerum, *Inorg. Chem.*, 1975, **14**, 919.

[9] T. A. Kaden, *Helv. Chim. Acta*, 1970, **53**, 617.

[10] L. Hertli and T. A. Kaden, *Helv. Chim. Acta*, 1974, **57**, 1328.

[11] R. W. Hay, G. A. Lawrance, and N. F. Curtis, *J.C.S. Perkin I*, 1975, 591.

[12] R. W. Hay, L. J. Porter, and P. J. Morris, *Austral. J. Chem.*, 1966, **19**, 1197.

pH (Table). As the copper(II) concentration was in excess (>20 fold) over the ligand concentration, pseudo-first-order conditions were fulfilled and values of $k_{obs.}$ at constant pH are listed. In the pH range of the measurements the predominant ligand species (>99.9%) is $[H_2L^1]^{2+}$. At constant metal-ion concentration, values of $k_{obs.}$ increased as the pH increased suggesting that $[HL^1]^+$ is the reactive species with Cu^{II} and that the rate expression takes the form (6). In the range pH 5—6.3

$$\text{Rate} = k_1[Cu^{2+}][HL^{1+}] \qquad (6)$$

the total ligand concentration $[L^1]_T \sim [H_2L^{1\,2+}]$ so we obtain (7) and (8). Values of the function $k_{obs.}a_{H^+}/[Cu^{2+}]$ should be constant and equal to $k_1K_3^M$, as is found

$$k_{obs.}[L^1]_T = k_1[Cu^{2+}][HL^{1+}] \qquad (7)$$

$$k_{obs.} = \frac{k_1[Cu^{2+}][HL^{1+}]}{[H_2L^{1\,2+}]} = \frac{k_1K_3^M[Cu^{2+}]}{a_{H^+}} \qquad (8)$$

to be the case (Table). The average value of $k_1K_3^M$ is 1.8×10^{-7} s^{-1} and, since $K_3^M = 5 \times 10^{-11}$ mol dm^{-3}, k_1 is 3.6×10^3 dm^3 mol^{-1} s^{-1} at 25 °C and $I = 0.1$ mol dm^{-3}.

Rate constants for the reaction of copper(II) with L^1 at 25 °C and $I = 0.1$ mol dm^{-3} to give $[CuL^1]^{2+}$ (blue). Reactions monitored spectrophotometrically unless otherwise stated. Ligand concentration 2.7×10^{-5}—3.3×10^{-5} mol dm^{-3}

(*a*) In the absence of acetate [a]

pH	$10^6a_{H^+}$ / mol dm^{-3}	$10^3[Cu^{2+}]$ / mol dm^{-3}	$10^4k_{obs.}$ / s^{-1}	$10^7k_{obs.}a_{H^+}/[Cu^{2+}]$ / s^{-1}
4.900 [b]	12.59	9.48	1.36	1.81
5.000 [b]	10.0	9.48	1.68	1.77
5.100 [b]	7.94	9.48	2.13	1.78
5.200 [b]	6.31	9.48	2.91	1.93
5.300 [b]	5.01	9.48	3.39	1.79
5.400 [b]	3.98	9.48	4.31	1.81
5.500 [b]	3.16	9.48	5.28	1.76
5.640	2.29	5.00	3.71	1.70
5.945	1.14	2.50	3.91	1.77
6.200	0.631	1.49	4.43	1.87
6.220	0.602	1.01	3.07	1.83
6.270	0.537	0.503	1.72	1.84

(*b*) Acetate buffered [c]

pH	$10^5a_{H^+}$ / mol dm^{-3}	$10^3[MeCO_2^-]$ / mol dm^{-3}	$10^3[MeCO_2H]$ / mol dm^{-3}	$10^3[Cu(O_2CMe)^+]$ / mol dm^{-3}	$10^3[Cu^{2+}]$ / mol dm^{-3}	$10^4k_{obs.}$ / s^{-1}	$10^4k_{calc.}$[d] / s^{-1}
4.080	8.32	0.79	2.89	1.32	18.68	0.80	0.75
4.485	3.27	1.37	1.98	1.65	13.35	1.50	1.44
4.600	2.51	3.59	3.97	2.44	7.56	1.74	1.80
4.790	1.62	4.23	3.02	2.75	7.25	2.71	2.78
4.860	1.38	3.34	2.03	4.63	15.37	6.44	5.77
4.970	1.07	2.25	1.06	1.69	8.31	3.29	3.10
5.010	0.977	4.84	2.08	3.08	6.92	4.64	4.56
5.055	0.881	7.83	3.04	4.13	5.87	6.15	6.13
5.440	0.363	6.94	1.11	1.95	3.05	6.75	6.63

[a] Reactions buffered with 5×10^{-3} mol dm^{-3} pipes. [b] pH-Stat runs, ligand concentration 1.0×10^{-4} mol dm^{-3}. [c] The total copper(II) concentration, $[Cu^{2+}]_T = [Cu(O_2CMe)^+] + [Cu^{2+}]$. [d] Calculated using equation (14), see text.

In acetate buffer solutions the function $k_{obs.}a_{H^+}/[Cu^{2+}]$ is not constant but increases as the total acetate concentration increases. The copper(II) ion will be present as Cu^{2+} and as $[Cu(O_2CMe)]^+$. The association of Cu^{II} with acetate ions can be represented by the equilibrium $Cu^{2+} + [MeCO_2]^- \rightleftharpoons [Cu(O_2CMe)]^+$ with $K_{Cu(O_2CMe)} = [Cu(O_2CMe)^+]/[Cu^{2+}][MeCO_2^-]$. Literature values of $K_{Cu(O_2CMe)}$ lie within the range [13] 60—120 dm^3 mol^{-1}. The concentrations of the various acetate species were obtained from the pH and the total acetate and copper concentrations using an average value of $K_{Cu(O_2CMe)} = 90$ dm^3 mol^{-1} and a value of $K^M_{MeCO_2H} = 2.27 \times 10^{-5}$ mol dm^{-3} at 25 °C and $I = 0.1$ mol dm^{-3}. Formation of $[Cu(O_2CMe)_2]$ was not significant under the conditions of the experiments.

If the rate expression takes the form (9) then (10) can

$$\text{Rate} = k_1[Cu^{2+}][HL^{1+}] + k_2[Cu(O_2CMe)^+][HL^{1\,+}] \qquad (9)$$

$$k_{obs.}[H_2L^{1\,2+}] = k_1[Cu^{2+}][HL^{1+}] + k_2[Cu(O_2CMe)^+][HL^{1\,+}] \qquad (10)$$

$$k_{obs.}a_{H^+}/[Cu^{2+}] = k_1K_3^M + k_2K_3^MK_{Cu(O_2CMe)}[MeCO_2] \qquad (11)$$

be written and it can readily be shown that (11) is applicable. Plots of the left-hand side of equation (11) against the 'free' acetate concentration should be linear of gradient $k_2K_3^MK_{Cu(O_2CMe)}$ and intercept $k_1K_3^M$. Such plots showed considerable scatter, but provide a rough estimate of $k_2 = 2 \times 10^4$ dm^3 mol^{-1} s^{-1}.

Much better agreement with the experimental data is given by the three-term rate expression (12). In this case,

$$\text{Rate} = k_1[Cu^{2+}][HL^{1+}] + k_2[Cu(O_2CMe)^+][HL^{1+}] + k_3[Cu(O_2CMe)^+][H_2L^{1\,2+}] \qquad (12)$$

equation (13) can be written which can be simplified to (14) where $k_1' = k_1K_3^M$, $k_2' = k_2K_3^MK_{Cu(O_2CMe)}$, and

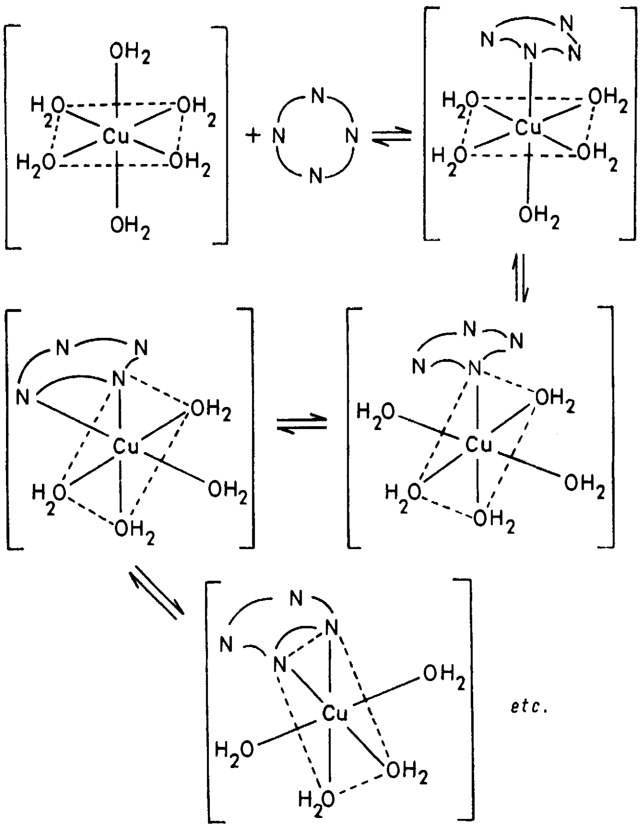
$$k_{obs.}a_{H^+}/[Cu^{2+}] = k_1K_3^M + k_2K_3^MK_{Cu(O_2CMe)}[MeCO_2^-] + k_3K^M_{MeCO_2H}K_{Cu(O_2CMe)}[MeCO_2H] \qquad (13)$$

$$k_{obs.}a_{H^+}/[Cu^{2+}] = k_1' + k_2'[MeCO_2^-] + k_3'[MeCO_2H] \qquad (14)$$

[13] L. G. Sillén and A. E. Martell, 'Stability Constants of Metal-Ion Complexes, *Chem. Soc. Special Publ.*, The Chemical Society, London, 1964, no. 17.

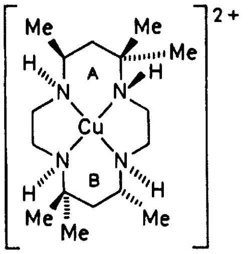
$k_3' = k_3K^{M}_{MeCO_2H}K_{Cu(O_2CMe)}$. The best fit to the experimental data is given by $k_1 = 3.6 \times 10^3$ dm^3 mol^{-1} s^{-1}, $k_2 = 1.8 \times 10^4$ dm^3 mol^{-1} s^{-1}, and $k_3 = 1.5 \times 10^{-2}$ dm^3 mol^{-1} s^{-1} (Table). In the run at pH 4.08 the k_1 term contributes *ca.* 54%, the k_2 term *ca.* 20%, and the k_3 term *ca.* 26% to the overall reaction.

The k_2 term could be due to the reaction of $[Cu(O_2CMe)]^+$ with $[HL^1]^+$, general-acid catalysis of the reaction of Cu^{2+} with L^1 $\{Cu^{2+} + MeCO_2H + L^1 \longrightarrow [CuL^1]^{2+}$ (blue)$\}$, or to general-base catalysis of the reaction of Cu^{2+} with $[HL^1]^+$ $\{Cu^{2+} + [MeCO_2]^- + [HL^1]^+ \longrightarrow [CuL^1]^{2+}$ (blue)$\}$. Paths involving general-acid catalysis appear unlikely, the third path being more mechanistically appropriate. In the kinetic runs using pipes buffer no buffer effects were observed with a two-fold variation in the pipes concentration. This buffer does not complex significantly with metal ions and, since it is a stronger base than acetate (pK_2^{M} 6.73), catalysis by this buffer would be expected if the reaction was subject to general-base catalysis. The present results suggest that the k_2 term is due to the reaction of $[Cu(O_2CMe)]^+$ with $[HL^1]^+$. (It should be noted that these arguments do not exclude $[MeCO_2]^-$ acting as a general-base catalyst in the co-ordination sphere of the metal ion.) Similar considerations also apply to the k_3 term which we believe to be due to the reaction of $[Cu(O_2CMe)]^+$ with $[H_2L^1]^{2+}$, rather than the kinetically equivalent processes of $MeCO_2H$ acting as a general acid in the reaction of Cu^{2+} with $[HL^1]^+$ or $[MeCO_2]^-$ acting as a general-base catalyst in the reaction of Cu^{2+} with $[H_2L^1]^{2+}$.



SCHEME Broken lines define the equatorial plane

In the absence of acetate no reaction was observed between Cu^{2+} and $[H_2L^1]^{2+}$, although $[H_2L^1]^{2+}$ is the major ligand species in the pH range of the measurements. The structure of the macrocycle causes the two protons of $[H_2L^1]^{2+}$ to be in closer proximity than would occur in an open-chain tetra-amine. It has been suggested [1] that the relatively high value of pK_3^{M} (10.3) is due to strong intramolecular hydrogen bonding in the diprotonated ligand which compensates for electrostatic repulsion between the two protons. The reaction between a rather stable diprotonated ligand species and the dipositive copper(II) ion would not be favoured on electrostatic grounds. The observation of a reaction of $[Cu(O_2CMe)]^+$ with $[H_2L^1]^{2+}$ could be due to the reduced charge on the metal ion. Electrostatic repulsion between the ions may also account for the five-fold difference in the reaction rates of Cu^{2+} and $[Cu(O_2CMe)]^+$ with the monoprotonated ligand. The relatively slow rates observed with the present ligand are in marked contrast to those observed for the reaction of Cu^{2+} with non-cyclic polyamines. For example, with 3,6,9-triazaundecane-1,11-diamine (L^3) the various protonated forms $[H_2L^3]^{2+}$, $[H_3L^3]^{3+}$, and $[H_4L^3]^{4+}$ all react with Cu^{2+} with resolved rate constants of 4.2×10^7, 1.6×10^5, and 1.4×10^4 dm^3 mol^{-1} s^{-1} respectively.[5] In this case the inclusion of acetate as a buffer also increases the reaction rates.



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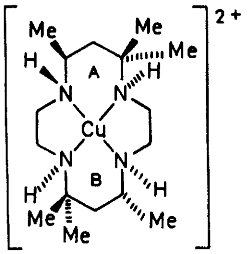

(3)

Mechanistic Considerations.—In tetragonal aquacopper(II) species, ligand-substitution kinetics are consistent with a dissociative mechanism in which the rate-determining step occurs at the point of formation of the first co-ordinate bond at an axial site. This step is followed by rapid Jahn–Teller inversion to place the substituted ligand in the equatorial plane (Scheme). It has been suggested that one important effect of ligand cyclisation is to make second-bond formation more difficult and possibly rate determining.[8]

Crystallographic work on blue $[CuL^1][ClO_4]_2$ suggests that the ligand is planar and does not adopt a folded configuration around the metal ion.[3] If the complex differs from the violet species only in the configuration of a single chiral nitrogen centre, then due to the symmetry elements of the molecule only two structures (2) and (3) can occur. Both structures have a twist-boat conformation for ring A and a chair conformation for ring B. Potentiometric measurements [2] show that blue

$$[CuL^1(OH_2)_2]^{2+} \text{ (blue)} \rightleftharpoons [CuL^1(OH)(OH_2)]^+ \text{ (blue)} + H^+ \quad (15)$$

$[CuL^1]^{2+}$ has a pK_a of 6.6 indicating that at least one, and probably two, water molecules occupy the axial positions [equation (15)]. The reported [2] rate expression for the blue ⟶ violet conversion is Rate = $k[CuL^1(OH)(OH_2)^+\text{-(blue)}][OH^-]$ with $k = 1.2 \times 10^3$ dm^3 mol^{-1} s^{-1} at 50 °C and $I = 0.5$ mol dm^{-3}. It has not been established whether the conversion involves a contribution from copper-bound hydroxide ion in an intramolecular reaction.

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