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Steric Effects in the Complexation Kinetics of Cyclic and Open-Chain Polyamines with Copper(II) in Basic Aqueous Media

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In order to investigate the effect of ligand cyclization upon complex formation rate constants, the kinetics of Cu(II) reacting with a series of open-chain and cyclic quadridentate polyamines have been examined at 25.0° using stopped-flow methods. These studies have been carried out in strongly basic aqueous media (0.1–2.0 M NaOH) to ensure the absence of ligand protonation. Under these conditions the copper is present as Cu(OH)₃⁻ and Cu(OH)₄²⁻ with Cu(OH)₃⁻ being the more reactive species. The comparative kinetic behavior of the most closely correlated open-chain and cyclic ligands (namely, 3,6,10,13-tetraazapentadecane (Et₂-2,3,2-tet) and 1,4,8,11-tetraazacyclotetradecane (cyclam)) indicates that ligand cyclization itself has only a relatively small influence upon the complex formation rate constants. Instead, the more significant kinetic effects arise from substitution at the nitrogen donor atoms of the open-chain ligands or on the alkyl backbone of the cyclic compounds. Jahn–Teller (tetragonal) inversion following the first-bond formation is proposed as the rate-determining step with Cu(OH)₃⁻. Second-bond formation is proposed as the rate-determining step for the Cu(OH)₄²⁻ reaction with the macrocyclic ligands and the more sterically hindered open-chain polyamines. Since in both cases the ligands are coordinated at the time of the rate-determining step, the reactions exhibit associative character.

Introduction

Recent studies on macrocyclic polyamine ligand kinetics have sought to examine the effects of the cyclic ligand structure upon metal complex formation rate constants, particularly as compared to corresponding open-chain polyamines.^{2–5} In studying the reaction of Ni(H₂O)₆²⁺ with the 14-membered saturated macrocycle 1,4,8,11-tetraazacyclotetradecane (cyclam, see Chart I), Kaden² reported that the mono-protonated and diprotonated ligand species exhibited formation rate constants which were approximately 30,000 times smaller than those observed for the corresponding species of the open-chain quadridentate polyamine 1,4,7,10-tetraazadecane (triethylenetetramine or trien).⁶ Kaden suggested that this difference reflected the loss in ligand flexibility brought about by cyclization.

As recently demonstrated, the electrostatic distance parameters encountered with protonated polyamine ligands differ from the distance of closest approach between the reactive centers in the precursor outer-sphere complex.⁷ Kaden failed to consider the magnification in such electrostatic effects exhibited in protonated cyclic ligands relative to corresponding open-chain species. It is apparent that the constraints of a cyclic structure decrease the distance between the protonated site(s) on the ligand and a metal ion approaching an unprotonated donor atom.

Of added importance is the recent evidence of enhanced steric and electrostatic effects in protonated open-chain polyamines as a result of intramolecular hydrogen bonding.^{8–10} This phenomenon is greatly exaggerated in cyclam by the tendency for such intramolecular hydrogen bonds to form within the ring.¹¹

To circumvent these ambiguities arising with protonated cyclic amine ligands, Cabiness and Margerum³ studied the kinetics of Cu(II) reacting with several substituted cyclam derivatives and related ligands in 0.5 M NaOH where the ligands are unprotonated neutral species and Cu(II) is present in the form of the soluble hydroxo species, Cu(OH)₃⁻ and Cu(OH)₄²⁻.¹² Under these conditions, the substituted cyclam ligands (including *meso*- and *rac*-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane: *tet-a* and *tet-b*, respectively) were found to react 10³–10⁴ times more slowly than the open-chain ligand 1,4,8,11-tetraazaundecane (2,3,2-tet) with which they were compared.

Recent studies on steric effects in complex formation reactions^{8,13,14} suggest that these observed differences between 2,3,2-tet and *tet-a* or *tet-b* reflect not only the effects attributable to cyclization but also (i) the steric effects resulting

from the six methyl groups on *tet-a* and *tet-b* and (ii) the greater reactivity of the primary nitrogen donor atoms in 2,3,2-tet relative to secondary nitrogen donor atoms⁸ as found in the cyclic ligands.

In the current investigation, we have attempted to establish the magnitude of the kinetic effects attributable to ligand cyclization. To accomplish this we have studied the kinetics of Cu(II) reacting with unprotonated cyclam and with 3,6,10,13-tetraazapentadecane (Et₂-2,3,2-tet) in strong NaOH solutions. Both ligands are unbranched and contain only secondary nitrogen donor atoms, the essential difference being that the former ligand is cyclic whereas the latter is open chain. For additional evaluation of the two types of steric effects presumed to influence the earlier conclusions, we have also (a) measured the kinetics of Cu(II) reacting with *meso*-5,12-dimethyl-1,4,8,11-tetraazacyclotetradecane (Me₂cyclam) (for comparison with cyclam and *tet-a*) and (b) studied the 2,3,2-tet reaction (for comparison with Et₂-2,3,2-tet). For the latter system, a more sophisticated mathematical treatment has been applied to the stopped-flow measurements to correct for errors normally inherent in utilizing this technique for very fast reactions.¹⁵ Finally, the reaction of Cu(II) with a highly substituted open-chain ligand, 3,9-diethyl-3,6,9-triazaundecane (1,1,7,7-tetraethyldiethylenetriamine or Etadien), has been studied under similar conditions to gauge the magnitude of large steric effects in the absence of ligand cyclization. All five ligands included in this investigation (as well as *tet-a*) are depicted in Chart I.

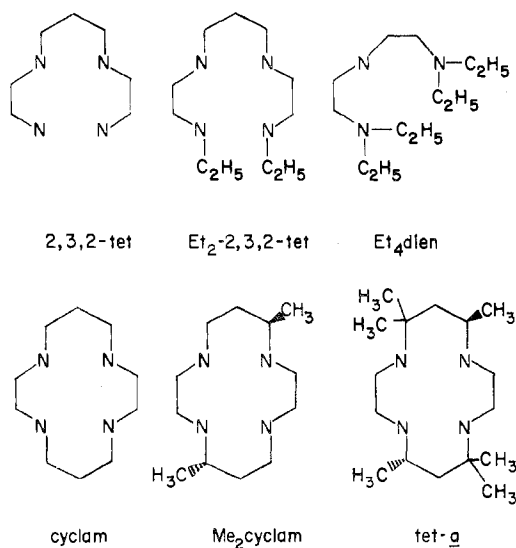
All five reactions have been studied as a function of NaOH concentration (at 25°) in an attempt to resolve the individual rate contributions of Cu(OH)₃⁻ and Cu(OH)₄²⁻. The resulting rate constant values, along with similar data from the earlier study on *tet-a*, yield a consistent trend reflecting the several types of steric effects inherent in these systems.

The relative reactivities of Cu(OH)₃⁻, Cu(OH)₄²⁻, and Cu(H₂O)₆²⁺ lead to the postulate that the hydroxo complexes utilize an associative mechanism in their reactions with the polyamines and that first-bond formation is the rate-determining step for the less sterically hindered amines reacting with Cu(OH)₃⁻.

Experimental Section

Reagents. 2,3,2-tet (Eastman Organic Chemicals) was purified by vacuum distillation, the middle third of the distillate being collected (bp 91° (0.03 mm)). Et₂-2,3,2-tet was synthesized by the condensation of 2,3,2-tet with acetaldehyde followed by reduction of the double bonds with sodium borohydride in methanol. After removal of the methanol by steam bath distillation, the product was dissolved in water,

Chart I



extracted with ether, and dried under vacuum. Cyclam was synthesized from 2,3,2-tet and 1,3-dibromopropane as described by Tobe, *et al.*,¹¹ using a high-dilution apparatus.⁵ The final product was recrystallized from dioxane; mp 185–190° (lit. mp 173°¹¹ and 185°¹⁶). Me₂cyclam was synthesized and purified by the method of Kolinski and Korybut-Daszkiewicz.¹⁷ Et₄dien was obtained from Ames Laboratories and purified as Et₄dien·3HCl as previously described.¹⁸

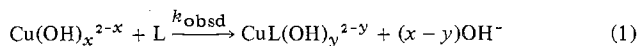
All ligand stock solutions were standardized either by potentiometric titration with standard acid solution or by spectrophotometric mole ratio plots with standard Cu(II) solution. Cu(ClO₄)₂·6H₂O was recrystallized from water and standardized by EDTA titration. NaClO₄ was recrystallized before use.

Kinetic Measurements. All reactions were studied using the stopped-flow technique. The reactions of Cu(II) with 2,3,2-tet, Et₂-2,3,2-tet, and cyclam were monitored at 263, 280, and 290 nm, respectively, using an Aminco-Morrow stopped-flow mixing device mounted on a Beckman DU-2 spectrophotometer with appropriate modifications as described elsewhere.¹⁹ The reactions with Me₂cyclam and Et₄dien were monitored at 270 and 290 nm, respectively, using a Durrum stopped-flow spectrophotometer interfaced to a Hewlett-Packard 2115A computer.²⁰ All reactions were carried out in strongly basic media containing between 0.1 and 2.0 M NaOH. Ionic strength was dependent upon the concentration of NaOH present in solution unless otherwise noted.

Spectral Measurements. A Cary 14 spectrophotometer with a thermostated cell compartment was used for equilibrium constant determinations with Et₄dien and copper.

Results

In the strongly basic media utilized, all ligands are essentially unprotonated,³ while Cu(II) exists as a mixture of soluble hydroxide species.¹² All reactions studied may therefore be represented by the general formulation in eq 1, where L



represents the free unprotonated ligand. In each system, the reactions were found to be first order with respect to each reactant (overall second order) and, except for Et₄dien, to proceed to completion according to the rate expression in eq 2, where [Cu]_T equals [Cu(OH)₃⁻] plus [Cu(OH)₄²⁻]. The

$$d[\text{CuL}]/dt = k_{\text{obsd}} [\text{Cu}]_{\text{T}} [\text{L}] \quad (2)$$

reactions with 2,3,2-tet, Et₂-2,3,2-tet, and cyclam were studied using equal reactant concentrations. For the more slowly reacting ligands, Me₂cyclam and Et₄dien, the kinetic studies were carried out under pseudo-first-order conditions by using at least a tenfold excess of ligand. With Me₂cyclam $k'_{\text{obsd}} = k_{\text{obsd}}[\text{L}]$, while with Et₄dien, which is first-order reversible, $k''_{\text{obsd}} = k_{\text{obsd}}[\text{L}] + k_d$ where k_d is the first-order dissociation rate constant at a specific hydroxide ion concentration.

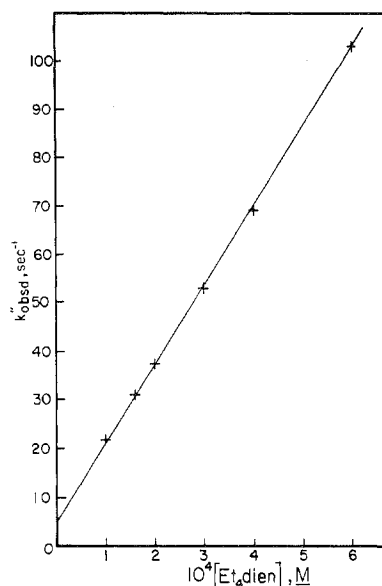


Figure 1. Observed first-order rate constants (k''_{obsd}) as a function of Et₄dien concentration for the reaction with Cu(II) ($(0.95\text{--}1.9) \times 10^{-5} \text{ M}$) in 0.10 M NaOH, $\mu = 0.5 \text{ M}$ (NaClO₄), 25.0°. The reaction is reversible first order and $k''_{\text{obsd}} = k_{\text{obsd}}[\text{Et}_4\text{dien}] + k_d$.

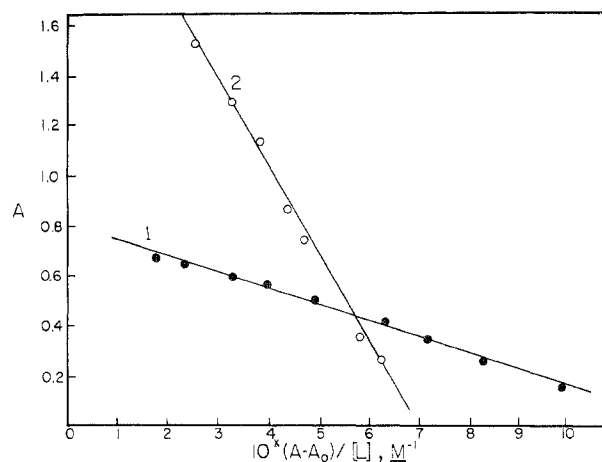


Figure 2. Spectrophotometric determination of the stability constant of Cu(II) with Et₄dien in NaOH at 25.0°. The absorbance (A) is plotted for two different abscissa values. Curve 1: 0.1 M NaOH ($\mu = 0.1 \text{ M}$), 5-cm cell path, the abscissa is $10^3(A - A_0)/[\text{L}]$. Curve 2: 0.5 M NaOH ($\mu = 0.5 \text{ M}$), 2-cm cell path, the abscissa is $10^2(A - A_0)/[\text{L}]$.

Thus a plot of k''_{obsd} vs. $[\text{L}]$ gives a straight line with slope k_{obsd} and intercept k_d as shown in Figure 1. The ratio k_{obsd}/k_d is equal to K , the stability constant of the complex, which was determined independently from spectrophotometric measurements. This equilibrium value of K was used to improve the fit of the kinetic data by fixing the ratio of k_{obsd} to k_d .

The stability constants for Cu(Et₄dien)(OH)⁺ were determined in 0.1 and 0.5 M NaOH by measuring the absorbance of solutions of a fixed total copper concentration but with varying total Et₄dien concentration, $[\text{L}]_{\text{T}}$. If A is the absorbance of the solution and A_0 that of the copper alone, a plot of A against $(A - A_0)/[\text{L}]$, where $[\text{L}] = [\text{L}]_{\text{T}} - [\text{CuL}]$, gives a straight line of slope $-1/K$, as shown in Figure 2. The values of $[\text{L}]$ were calculated by an iterative procedure in which an estimated value of K was used to calculate values of $[\text{L}]$ and then these were used to obtain a new value of K until the least-squares deviation in the plot of A vs. $(A - A_0)/[\text{L}]$ reached a minimum value. The measured values of K are $1.56 \times 10^4 \text{ M}^{-1}$ at 0.1 M NaOH and $2.84 \times 10^2 \text{ M}^{-1}$ at 0.5 M NaOH and 25.0°.

Modified Mathematical Treatment for Cu^{II}-2,3,2-tet. In the case of Cu(II) reacting with 2,3,2-tet at high pH, the formation rate was so great, even at the lowest detectable concentrations, that significant mixing-time errors and concentration inhomogeneities within the monitoring light path were encountered (slit-length error). These errors were circumvented by (a) utilizing the concept of "corrected" apparent starting concentrations and (b) treating the solution within the reaction cell as a series of "homogeneous" segments.¹⁵ For the situation in which the *initial reactant concentrations are stoichiometrically equivalent*, this treatment involves the use of the multiparameter expression

$$\frac{n(A_t - A_\infty)}{b\Delta\epsilon} = B_{10} \sum_{j=1}^n \{k_{\text{obsd}} B_{10} [t + (j-1)t_x/n] + 1\}^{-1} \quad (3)$$

where n represents an arbitrary number of "homogeneous" segments into which the stopped-flow cell is divided; A_t and A_∞ represent the measured absorbance at any time, t , and at infinite time, respectively; b represents the total length of the observation cell (b/n being the length of each homogeneous segment); $\Delta\epsilon$ represents the difference between the molar absorptivities of the reactants and of the products; B_{10} represents the "corrected" initial reactant concentration in the first cell segment at the arbitrarily selected starting time; k_{obsd} represents the observed second-order rate constant (eq 2); and t_x represents the time required to fill the observation cell during the flow period (thus specifying the difference in apparent reaction time of each successive "homogeneous" segment at the time the flow is stopped). The simultaneous solution of eq 3 for the values of k_{obsd} and B_{10} was then accomplished by an iterative technique as previously described.¹⁵ This approach is most useful for reactions where: $10/t_x \geq k_{\text{obsd}} B_{10} \geq 10^{-1}/t_x$.

As applied to the reaction of Cu(II) with 2,3,2-tet in this investigation, the following parameter values were used: $b = 1.00$ cm (Aminco stopped-flow cell), $n = 5$, $\Delta\epsilon = -3330 M^{-1} \text{cm}^{-1}$ (for $\lambda = 263$ nm), $t_x = 5.5$ msec (for 60 psi driving pressure). The t_x value was experimentally determined using a Biomation Model 802 transient recorder in the "pretrigger record" mode. It should be noted that this value of t_x differs markedly from the value of 3 msec (cited in the company literature) which was utilized in our initial data resolution (see ref 15; Note added in Proof). The use of the larger value for t_x results in a much more rapid convergence of eq 3 yielding k_{obsd} values which are about 30% smaller and *contain no apparent dependence on initial reactant concentrations*, even in 0.1 M NaOH medium where mixing errors are most prominent.

Although the use of eq 3 permits the selection of any arbitrary starting time (since the value of B_{10} is iterated from the data), we chose to utilize values of " t " based upon the assignment of $t = 0$ as the apparent triggering time of the oscilloscope. Interestingly, under our operating conditions this assignment generally resulted in iterated B_{10} values which were within 10% of the initial reactant concentrations as corrected for dilution upon mixing (*i.e.*, B_0). Whereas this agreement is presumed to be fortuitous, being dependent upon the mixing and triggering functions, kinetic runs in which B_{10} differed markedly from B_0 were rare and appeared to be accompanied by erroneous values of k_{obsd} .

The data thus obtained for the 2,3,2-tet reaction are tabulated in Table I. The observed rate constant values for the remaining four systems are tabulated in Tables II-V.

Discussion

Resolved Rate Constants. For each of the systems studied, the k_{obsd} values exhibit a distinct decreasing trend with increasing NaOH concentration. Since the ligands are not protonated under the conditions of this study, the observed

Table I. Observed Rate Constant Values for Copper(II) Reacting with 2,3,2-tet in Strongly Basic Solution at $25.0 \pm 0.4^\circ$ ($[\text{Cu}]_T = [\text{L}] = B_0$)

[NaOH], M	$10^5 B_0, M$	Iterated $10^5 B_{10}, M$	Iterated $10^{-6} k_{\text{obsd}},$ $M^{-1} \text{sec}^{-1}$	
0.10	1.0	0.8	7.0	
	1.0	0.9	10.8	
	1.5	1.5	9.5	
	2.5	2.5 ^a	13.0 ^a	
0.13	1.0	1.0	11.5	
	1.0	0.9	6.5	
0.20	1.5	1.5	5.9	
	2.0	2.0	5.5	
	3.0	3.0	6.1	
	10.0	10 ^a	6 ^a	
	0.30	1.0	1.1	5.2
		2.0	2.0	5.3
3.0		2.9	4.8	
0.50	1.0	1.15	4.3	
	2.0	2.5	5.0	
	3.0	3.0	4.9	
	10.0	9 ^a	4.1 ^a	
1.00	1.0	0.9	4.3	
	2.0	1.9	4.3	
	3.0	3.0	4.4	
	10.0	10	3.7	
1.50	1.0	0.75	5.0	
2.00	1.0	0.90	4.8	
With 0.80 M NaClO ₄ Added				
0.13	1.0	1.0	6.3	
0.20	1.0	1.0 ^a	4.0	
	1.5	1.3	3.9	
	2.0	1.9 ^a	4.2 ^a	
	3.0	2.5	4.2	
0.30	1.0	0.9	5.0	

^a These runs required more iterations to converge and yield less precise k_{obsd} values.

Table II. Observed Rate Constant Values for Copper(II) Reacting with Et₂-2,3,2-tet in Basic Solution at $25.0 \pm 0.4^\circ$ ($[\text{Cu}]_T = [\text{L}] = B_0$)

[NaOH], M	$10^5 B_0,$ M	$10^{-5} k_{\text{obsd}},^a$ $M^{-1} \text{sec}^{-1}$	[NaOH], M	$10^5 B_0,$ M	$10^{-5} k_{\text{obsd}},^a$ $M^{-1} \text{sec}^{-1}$
0.10	2.0	14.0	0.30	3.0	7.4
	3.0	14.0		5.0	7.3
0.13	2.0	13.0	0.40	7.0	7.7
	3.0	13.5		5.0	7.4
0.20	3.0	9.1		7.0	5.8
	5.0	8.9			

^a $d[\text{CuL}]/dt = k_{\text{obsd}}[\text{Cu}]_T[\text{L}]$.

Table III. Observed Rate Constant Values for Copper(II) Reacting with Cyclam in Basic Solution at $25.0 \pm 0.4^\circ$ ($[\text{Cu}]_T = [\text{L}] = B_0$)

[NaOH], M	$10^5 B_0,$ M	$10^{-5} k_{\text{obsd}},^a$ $M^{-1} \text{sec}^{-1}$	[NaOH], M	$10^5 B_0,$ M	$10^{-5} k_{\text{obsd}},^a$ $M^{-1} \text{sec}^{-1}$	
0.10	2.0	12.5	0.50	5.0	2.8	
	3.0	13.3			2.5 ^b	
0.20	3.0	6.1	1.00	3.0	1.7	
	5.0	6.5		7.0	1.8	
	7.0	6.9		5.0	1.6	
0.30	3.0	5.8	1.50	7.0	1.6	
	5.0	5.3		2.00	5.0	1.1
	7.0	4.6		7.0	1.1	

^a $d[\text{CuL}]/dt = k_{\text{obsd}}[\text{Cu}]_T[\text{L}]$. ^b Value listed includes data at six concentrations as determined by a previous investigator: R. B. Cruz, Ph.D. Dissertation, Wayne State University, 1972.

behavior can be attributed to the differing reactivities of $\text{Cu}(\text{OH})_3^-$ and $\text{Cu}(\text{OH})_4^{2-}$ according to the relationship in eq 4 (modified from eq 2). The equilibrium constant for the two copper species at infinite dilution is given in eq 5.¹² Using

Table IV. Observed Rate Constant Values for Copper(II) Reacting with Me₂cyclam in Basic Solution at 25.0 ± 0.1°, μ = 0.5 M (NaClO₄ + NaOH)

10 ⁶ [Cu] _T , M	10 ⁵ [L], M	[NaOH], M	k' obsd, sec ⁻¹	10 ⁻⁴ k obsd = k' obsd/[L], M ⁻¹ sec ⁻¹
5.6	8	0.1	18.2	22.8
5.6	12	0.1	29.0	24.2
5.6	16	0.1	35.4	22.1
11.2	20	0.1	42.5	21.3
11.2	24	0.1	51.7	21.5
11.2	28	0.1	59.2	21.1
11.2	40	0.1	88.5	22.1
5.6	8	0.5	5.25	6.56
5.6	12	0.5	7.8	6.50
11.2	20	0.5	13.2	6.60
5.6	24	0.5	17.1	7.13
11.2	32	0.5	23.7	7.40
11.2	40	0.5	27.0	6.75
11.2	60	0.5	43.0	7.17

Table V. Observed Rate Constant Values for Copper(II) Reacting with Et₄dien in Basic Solution at 25.0 ± 0.1°

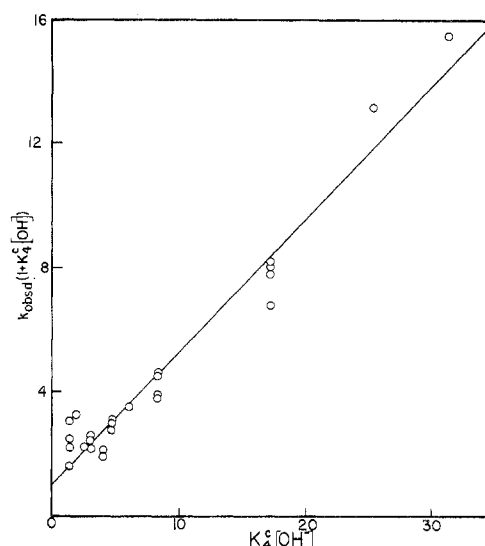
10 ⁶ [Cu] _T , M	10 ⁴ [L], M	[NaOH], M	k'' obsd, sec ⁻¹	k _d , sec ⁻¹	10 ⁻⁴ k obsd = (k'' obsd - k _d)/[L]
8	0.8	0.1	20.6	9.8	13.5
10	1.0	0.1	25.9	9.8	16.1
20	2.0	0.1	40.5	9.8	15.4
20	2.8	0.1	55.2	9.8	16.2
20	3.0	0.1	61.2	9.8	17.1
20	4.0	0.1	72.2	9.8	15.6
20	6.0	0.1	104.4	9.8	15.8
9.5	1.0	0.1 ^a	21.8	5.3	16.5
9.5	1.6	0.1 ^a	31.2	5.3	16.2
19	2.0	0.1 ^a	37.3	5.3	16.0
19	2.8	0.1 ^a	52.9	5.3	17.0
19	4.0	0.1 ^a	69.1	5.3	16.0
19	6.0	0.1 ^a	103.1	5.3	16.3
30	6	0.5	160.4	138.5	3.65
30	8	0.5	167.9	138.5	3.68
30	10	0.5	182.2	138.5	4.37
30	12	0.5	187.7	138.5	4.10
30	14	0.5	195.1	138.5	4.04

^a 0.4 M NaClO₄ added to obtain μ = 0.5 M.**Table VI.** Concentration Equilibrium Constants for Tetrahydroxocuprate(II) Used at Various NaOH Concentrations

[NaOH], M	γ _{NaOH} ^a	K ₄ ^{c, b} , M ⁻¹	[NaOH], M	γ _{NaOH} ^a	K ₄ ^{c, b} , M ⁻¹
0.1	0.766	13.4	0.7	0.681	16.9
0.2	0.727	14.9	0.8	0.679	17.0
0.3	0.708	15.7	0.9	0.678	17.1
0.4	0.697	16.2	1.0	0.678	17.1 ^d
0.5	0.690	16.5 ^c	1.5	0.683	16.8
0.6	0.685	16.8	2.0	0.707	15.7

^a H. S. Harned and J. C. Hecker, *J. Amer. Chem. Soc.*, **55**, 4838 (1933). ^b K₄^c = [Cu(OH)₄²⁻]/[Cu(OH)₃⁻][OH⁻]. ^c This value also was used for solutions containing 0.40 M NaClO₄ plus 0.10 M NaOH. ^d This value also was used for solutions containing 0.80 M NaClO₄ plus 0.13–0.30 M NaOH.**Table VII.** Resolved Formation Rate Constants for Hydroxocuprate(II) Species Reacting with Unprotonated Cyclic and Open-Chain Polyamines at 25°

Ligand	k ^L _{Cu(OH)₃} , M ⁻¹ sec ⁻¹	k ^L _{Cu(OH)₄} , M ⁻¹ sec ⁻¹	k ^L _{Cu(OH)₃} / k ^L _{Cu(OH)₄}	Remarks
2,3,2-tet	(1.0 ± 0.7) × 10 ⁷	(4.3 ± 0.2) × 10 ⁶	2.4	Open; primary N's
Et ₂ -2,3,2-tet	(3.0 ± 0.3) × 10 ⁶	(2.9 ± 0.6) × 10 ⁵	10	Open; secondary N's
Cyclam	(2.7 ± 0.4) × 10 ⁶	(3.8 ± 0.9) × 10 ⁴	72	Cyclic; unsubst
Me ₂ cyclam	5.6 × 10 ⁵	0.9 × 10 ⁴	60	Cyclic; subst
tet-a ^a	~10 ⁴	<10 ²	>10 ²	Cyclic; highly subst
Et ₄ dien	4.0 × 10 ⁵	<10 ³	>400	Open; tertiary N's and one secondary N

^a Reference 4.**Figure 3.** Plot of eq 6 to resolve the rate constants for the reaction of Cu(OH)₃⁻ and Cu(OH)₄²⁻ with 2,3,2-tet.

$$k_{\text{obsd}}[\text{Cu}]_{\text{T}}[\text{L}] = k^{\text{L}}_{\text{Cu(OH)}_3}[\text{Cu(OH)}_3^-][\text{L}] + k^{\text{L}}_{\text{Cu(OH)}_4}[\text{Cu(OH)}_4^{2-}][\text{L}] \quad (4)$$

$$K_4 = \frac{a_{\text{Cu(OH)}_4^{2-}}}{a_{\text{Cu(OH)}_3^-}a_{\text{OH}^-}} = 7.86 \quad (5)$$

the treatment of McDowell and Johnston¹² it can be shown that the concentration equilibrium constant, K_4^c equals $K_4/\gamma_{\text{NaOH}}^2$, where γ_{NaOH} is the mean activity coefficient for this electrolyte. The resulting K_4^c values are listed in Table VI and were used to solve for the concentrations of Cu(OH)₃⁻ and Cu(OH)₄²⁻ at each NaOH concentration. The individual rate constants were then obtained from eq 6. [In a few instances the concentrations of Cu(II) at the specified NaOH molarity exceed the solubility reported by McDowell and Johnston. However, their solutions required days to come to equilibrium with solid CuO. We find that in the absence of the solid phase these copper solutions are stable for relatively long periods (hours) but freshly prepared solutions were always used.] A plot of eq 6 for the kinetic data obtained with

$$k_{\text{obsd}}(1 + K_4^c[\text{OH}^-]) = k^{\text{L}}_{\text{Cu(OH)}_3} + k^{\text{L}}_{\text{Cu(OH)}_4}K_4^c[\text{OH}^-] \quad (6)$$

2,3,2-tet is shown in Figure 3.

The resulting resolved rate constant values (with standard deviations) for the five ligand systems included in this work are listed in Table VII along with corresponding values reported⁴ for tet-a.

Mechanistic Interpretation. As preliminary observations on the resolved rate constants in Table VII, the following are particularly noteworthy.

1. All resolved formation rate constants are well below the

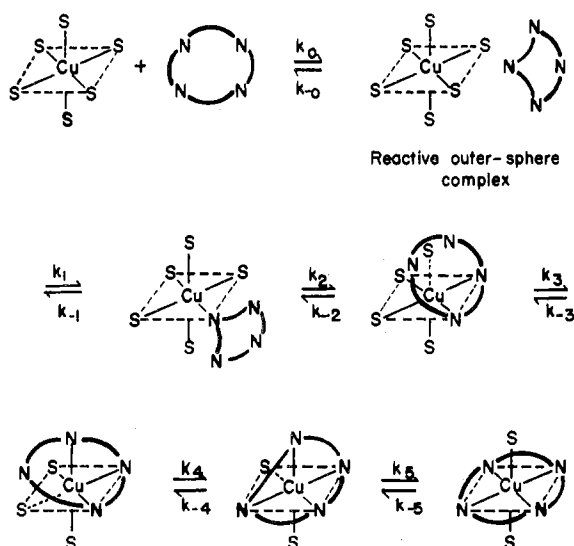


Figure 4. Schematic representation of the stepwise complexation of Cu(II) by a quadridentate polyamine (shown here as a cyclic species). Although Cu(II) is shown as bonded to six donor atoms at all times (where S represents either OH⁻ or H₂O), no significance is attached to the resulting tetragonal structure prior to the point where two nitrogen donor atoms are bonded in the inner sphere. For the sake of simplicity, Jahn-Teller inversions have been omitted. The structures with two and three nitrogen donor atoms bonded to copper severely crowd the solvent molecule shown by dashed lines to the metal ion. The coordination number of copper may be 4 or 5 rather than 6 in any of the complexes.

diffusion-limiting value and are smaller than the corresponding rate constants reported for Cu(H₂O)₆²⁺ reacting with neutral unidentate ligands.

2. The rate constants for Cu(OH)₃⁻ are consistently larger than those for Cu(OH)₄²⁻ with the difference increasing dramatically for the cyclic ligands and the highly substituted open-chain ligand Et₄dien.

3. Almost no difference is observed in the rate constants obtained for Cu(OH)₃⁻ reacting with the unsubstituted cyclic ligand cyclam and its corresponding open-chain analog Et₂-2,3,2-tet.

The implications of these observations are examined in detail below.

Although there is no direct evidence concerning the geometries of Cu(OH)₃⁻ and Cu(OH)₄²⁻, structural data for nearly 100 copper complexes have been interpreted to indicate that essentially all species of this type are distorted octahedra: tetragonal, square pyramidal, or square planar.²¹ For the latter two geometries, the species along the z axis, one or both of which are formally nonbonded, are still considered to influence the overall bonding and the electronic properties of the copper(II) complex, even when these species are not traditional donors.²¹ This suggests that axial interactions cannot be completely disregarded, particularly in aqueous solution where water molecules are readily available as potential z-axis donors.

Based on the cumulative evidence, Cu(OH)₃⁻ and Cu(OH)₄²⁻ may be assumed to have tetragonal geometries with the hydroxides preferentially occupying equatorial sites. For the purposes of visualization, therefore, we have represented in Figure 4 a stepwise mechanism for substitution by a flexible quadridentate cyclic polyamine on tetragonal Cu(II), where the individual identities of the coordinated OH⁻ and H₂O groups are not initially specified.

Comparison to Aquocopper(II) Kinetics. For the corresponding tetragonal aquocopper(II) species, ligand substitution kinetics have previously been shown to be consistent with a dissociative mechanism in which the rate-determining step is at the point of first coordinate bond formation at an axial site,

followed by rapid Jahn-Teller inversion to place the substituted ligand in the equatorial plane²² (this two-step process being combined into a single step in Figure 4, represented by the rate constant k_1). Anomalous rate behavior is frequently observed with polyamine reactions as a result of (i) the internal conjugate base (ICB) effect^{8,22,23} (leading to enhanced formation rate constants) or (ii) a shift in the rate-determining step to the point of proton loss in the case of highly protonated polyamine species (leading to depressed formation rate constants). [The ICB effect is postulated to arise from hydrogen-bond formation between a coordinated water molecule and the lone electron pair of one amine group when a second amine group is available to replace another coordinated water molecule. This leads to larger formation rate constants for diamines and polyamines.]

In the current study with hydroxocuprate(II) species as the reactants, the outer-sphere hydrogen-bonding required to promote an ICB effect²³ is not feasible for the inner-sphere hydroxide ligands and is unlikely for any remaining inner-sphere water molecules since the strength of the copper-water bonds should be weakened by the coordinated hydroxides making them much less acidic. Furthermore, under the conditions of this study the ligands are unprotonated so that proton loss is not involved. Thus, the anomalous influences which dominate the kinetic behavior of the aquocopper(II)-polyamine reactions²² should not be a factor in the current work.

The lability of axial water molecules would be expected to increase in the order Cu(H₂O)₆²⁺ << Cu(OH)₃(H₂O)₃⁻ < Cu(OH)₄(H₂O)₂²⁻ as a result of electrostatic effects and the presumed influence of the coordinated hydroxide ligands upon the extent of tetragonal distortion (as evidenced by the increasing tetragonality in the series Cu(H₂O)₆²⁺ << Cu(OH)₂ < CuO²¹). Since the apparent rate constant for axial solvent exchange on Cu(H₂O)₆²⁺ at 25° is approximately 2 × 10⁹ sec⁻¹,²² this implies that the corresponding value for the hydroxocuprate(II) species might approach or exceed the rate constant for the dissociation of the outer-sphere complex, k_{-6} , which previously has been estimated to be about 2 × 10¹⁰ sec⁻¹ (at 25°) for neutral ligand species.²² Under these circumstances, the formation reactions would become diffusion controlled with anticipated second-order rate constant values of about 6 × 10⁹ M⁻¹ sec⁻¹ (25°).²² Such behavior appears to be exhibited by Cu(H₂O)₆²⁺ in its reaction with ethylenediamine where, as a result of the ICB effect, a 25° formation rate constant of 4 × 10⁹ M⁻¹ sec⁻¹ has been reported,²⁴ which we have suggested represents the diffusion-limiting rate within experimental error.²²

From the data in Table VII, we note that the rate constant for Cu(OH)₃⁻ reacting with the open-chain polyamine 2,3,2-tet is 400-fold smaller than the diffusion limit. Moreover, taking into account statistical and steric factors, one may estimate from the measured rate constant value for Cu(H₂O)₆²⁺ reacting with NH₃ at 25° (where $k_{CuNH_3} = 2 \times 10^8$ M⁻¹ sec⁻¹)²⁵ that the reaction rate constant for Cu(H₂O)₆²⁺ reacting with 2,3,2-tet would be about 8 × 10⁷ M⁻¹ sec⁻¹ in the absence of ICB effects.²⁶ This is a factor of 8 larger than the value obtained for Cu(OH)₃⁻ and a factor of 20 larger than that for Cu(OH)₄²⁻. Thus we are forced to conclude that *simple axial H₂O dissociation cannot be the rate-determining step* in the hydroxocuprate(II) complex formation reactions and, therefore, there must exist a significant degree of association with the incoming nucleophile at the point of the rate-determining step.

Rate-Determining Step. The actual position of the rate-determining step is an important consideration in comparing the reactivities of multidentate ligands with metal centers.²⁷ In the present work the fact that Cu(OH)₄²⁻ appears as a

reactant indicates that the rate-determining step occurs prior to the formation of the third coordinate bond to the incoming polyamine ligand. Otherwise, in order for $\text{Cu}(\text{OH})_4^{2-}$ to retain its identity, it would be necessary at some point to invoke a coordination number greater than 6 for $\text{Cu}(\text{II})$ which is extremely unlikely. Therefore, all the resolved rate constants in Table VII must involve first or second coordinate bond formation, or associated inner-sphere rearrangements, as the rate-determining step.

If all the formation rate constants involved the second-bond formation as the rate-determining step, there would be no apparent reason for the ratio of $k^{\text{I-Cu}}(\text{OH})_3^-/k^{\text{I-Cu}}(\text{OH})_4^{2-}$ to vary from 2.4 to >400 for the various ligands. The variation of this ratio strongly suggests that for 2,3,2-tet both $\text{Cu}(\text{OH})_3^-$ and $\text{Cu}(\text{OH})_4^{2-}$ involve first-bond formation, or an associated process, as the rate-determining step while with the macrocyclic ligands and Et4dien the rate-determining step shifts from first- to second-bond formation as the reactant changes from $\text{Cu}(\text{OH})_3^-$ to $\text{Cu}(\text{OH})_4^{2-}$.

The proposition that the rate-determining step lies close to the point of first-bond formation for $\text{Cu}(\text{OH})_3^-$ is consistent with the relative rate constants for this metal ion species reacting with the various ligands. Thus, the ratio of rate constants for 2,3,2-tet:Et2-2,3,2-tet:cyclam:Et4dien is 1:0.30:0.27:0.04 reflecting the relative reactivities of the donor atoms, *i.e.*, primary $>$ secondary \gg tertiary. In a previous paper⁸ we estimated that primary amine groups should be about 10–50 times more reactive than secondary amine groups. Subsequent evidence^{7,9} indicates that this factor is slightly too large due to the influence of intramolecular hydrogen bonding in the monoprotonated diamines which were utilized in its evaluation. If, in fact, a primary amine were considered to be 8 times more reactive than a secondary amine then, after making statistical corrections for the number of primary and secondary amines in each ligand, the corresponding predicted ratio of rate constants for first-bond formation is 1:0.22:0.22:0.055 which is in very good agreement with the experimental ratio cited above considering the precision of the rate constants. The rate constants for Me2cyclam and tet-*a* are consistent with the anticipated effects of ring substitution although no quantitative correlation can be generated at this time.

Proposed Detailed Mechanisms. How can the conclusion that first-bond formation is rate-determining for $\text{Cu}(\text{OH})_3^-$ be reconciled with the earlier conclusion that simple axial water loss from this species is not the rate-determining step? An obvious possibility is that substitution of the first nitrogen into the equatorial plane represents the rate-limiting process. Whereas direct substitution from the outer-sphere into the equatorial site originally occupied by a water molecule is a conceivable alternative, the facile substitution available at the axial sites suggests that axial substitution occurs initially, followed either by Jahn–Teller inversion or by a classical square-planar substitution pathway in which the nitrogen donor atom swings into the plane defined by the three hydroxide ligands. Since the hydroxide ligands are readily interconverted with water molecules, the inversion pathway appears particularly attractive. As represented in Figure 5 (which is an expanded version of the k_1 and k_2 steps from Figure 4), k_{1b} , the rate constant for Jahn–Teller inversion, is the suggested rate-determining step. Whereas previous evidence suggests that this step is generally rapid,²² the energy required to extend a coordinated OH group to an axial position is apparently sufficiently large that $k_{1b} < k_{-1a}$, the latter rate constant being exceptionally large due to the lability of the axial Cu–N bond when three OH groups are coordinated within the plane. This is consistent with esr evidence that Jahn–Teller inversion rates are diminished when the inner coordination sphere is inho-

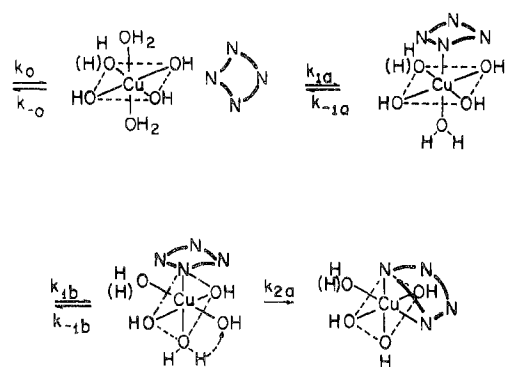


Figure 5. Detailed mechanism possible for the first two coordinate bond formation steps for $\text{Cu}(\text{OH})_3^-$ (or $\text{Cu}(\text{OH})_4^{2-}$) reacting with a quadridentate polyamine showing sequential bonding and Jahn–Teller (tetragonal) inversion steps. For $\text{Cu}(\text{OH})_3^-$ the proposed rate-determining step is k_{1b} , an inversion step which puts the nitrogen donor into a “planar” position. For $\text{Cu}(\text{OH})_4^{2-}$ the rate-determining step tends to shift to the chelate ring formation (the k_{2a} step).

mogeneous.²⁸ After the Cu–N bond is incorporated into the newly defined equatorial plane, solvent-assisted transfer of a proton from the recently “equatorialized” water to the “axialized” OH group could restore three hydroxides to the plane, thereby generating a stable species for subsequent substitution steps.

In the case of $\text{Cu}(\text{OH})_4^{2-}$, a similar sequence of events can be postulated. In the Jahn–Teller inversion step, however, two hydroxide bonds must be elongated, a process which would presumably be reflected in a smaller value of k_{1b} while the value of k_{-1b} , involving the reelongation of the Cu–N bond, could be correspondingly enhanced. This would greatly improve the chances that $k_{-1b} > k_{2a}$ resulting in a shift of the rate-determining step to the point of second-bond formation.

The postulated change in the rate-determining step from first-bond ($k_{-1b} < k_{2a}$) to second-bond ($k_{-1b} > k_{2a}$) formation for the $\text{Cu}(\text{OH})_4^{2-}$ reactions for cyclic compared to open-chain ligands suggests that one important effect of cyclization is to make second-bond formation more difficult (*i.e.*, decrease k_{2a}). This is similar to the conclusion reported earlier with Ni(II)–diamine reactions wherein increased alkyl substitution on the ligand decreases the rate constant for the second-bond formation to the point where this step may become rate determining.⁸ (The same effect is apparent for Et4dien in the current study.) Furthermore, in the case of the cyclic ligands, bonding of the second donor atom crowds one of the remaining inner-sphere ligands, thereby enhancing the steric difficulties associated with this step.

Third-bond formation of a 14-membered macrocyclic ligand should crowd the metal solvation to an even greater extent than second-bond formation. Models show that it is difficult to maintain a coordination number of 6 with three amine groups and three solvent (or OH^-) groups. Were it not for the fact that the copper–amine bonds are quite stable, the barrier to third-bond formation might make it rate determining. However, when several amine groups are coordinated, it is possible to change the coordination around the metal and have a stable complex. Thus with tet-*b* (the racemic isomer of tet-*a*) the structure of a stable five-coordinate trigonal-bipyramidal copper complex has been shown with four nitrogens bonded and chloride or other ligands in one of the trigonal-planar positions.²⁹ Reactions corresponding to the k_5 step in Figure 4 have been studied in detail for $\text{Cu}(\text{tet-}a)^{2+}$ and $\text{Cu}(\text{tet-}b)^{2+}$ and are readily observed as blue-to-red interconversions of the complexes.³⁰

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Registry No. Cu(OH)₃⁻, 12443-58-2; Cu(OH)₄²⁻, 17949-75-6; 2,3,2-tet, 4741-99-5; Et₂-2,3,2-tet, 54020-32-5; cyclam, 295-37-4; meso-Me₂ cyclam, 41076-15-7; Et₄ dien, 123-12-6.

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Metal Ion Catalyzed Racemization and α -Proton Exchange of N,N-Dicarboxymethyl-D-phenylglycine

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The base-catalyzed racemization of N,N-dicarboxymethyl-D-phenylglycine Cm₂-D-Phgly³⁻, (-O₂CCH₂)₂NCH(Ph)CO₂⁻, has been studied in the absence and presence of metal ions in aqueous solution at 60.0°. Within experimental error, the rates of racemization and α -proton exchange with D₂O are the same both for the free Cm₂-D-Phgly³⁻ and for its complexes. The rates of racemization were observed to follow a rate law dominated by a term which was first order in OH⁻ concentration. This behavior together with the exchange results suggests a mechanism in which rate-determining α -proton removal by OH⁻ is followed by rapid reprotonation of the resulting symmetric carbanion intermediate. The predominant species present in solution and their decreasing rates of inversion are as follows: Pb(Cm₂-D-Phgly)⁻, $3.08 \times 10^{-2} >$ Cu(Cm₂-D-Phgly)(OH)²⁻, $2.31 \times 10^{-2} >$ Ni(Cm₂-D-Phgly)⁻, $2.01 \times 10^{-2} >>$ Zn(Cm₂-D-Phgly)(OH)²⁻, $0.381 \times 10^{-2} >>>$ Cm₂-D-Phgly³⁻, $5.8 \times 10^{-6} M^{-1} sec^{-1}$. When bound to these metal ions, the ligand undergoes racemization at rates up to 5000 times faster than observed for the free Cm₂-D-Phgly³⁻. The abilities of these metal ions to accelerate this racemization are compared with their activities in promoting the hydrolysis of amino acid esters.

Optically active amino acids have been observed to racemize in aqueous solution only at high temperatures (>100°).^{1,2} When coordinated to the inert metal ions Co(III)³⁻⁵ and Pt(II),⁶ however, they undergo racemization under much milder conditions (35–40°). In contrast to the detailed racemization studies of cobalt(III)-amino acid complexes, little has been reported on the effect of labile metal ions on amino acid racemization. Gillard and Phipps⁷ reported that alanine in the complex Cu(L-Ala)₂ racemizes in less than 12 hr at an unspecified temperature at pH values equal to or greater than 12. Also they noted that racemization occurred more slowly than α -proton exchange with D₂O, suggesting that protonation of the carbanion intermediate was stereoselective. Our attempts to repeat these studies were thwarted by precipitation of a Cu(II) complex as OH⁻ was added to bring the pH to

12. An earlier report⁸ indicated that only a trace of L-Ala racemized in a solution containing Cu(II) or Al(III) at 100° and pH 9.7. This result together with our precipitation difficulties suggests that Gillard and Phipps' results may be incorrect.

Studies^{9,10} of amino acids in the absence of metal ions at 60° in nonaqueous solvents showed that D-phenylglycine racemized more rapidly than other common amino acids. Rates of racemization and α -proton exchange were the same. Although the rates of racemization were substantially slower in water solvent (studied at 115°),¹¹ it appeared to us that D-phenylglycine may be sufficiently reactive for study of its racemization under mild conditions in the presence of labile metal ions. To simplify equilibria involving the metal ions and the amino acid, D-phenylglycine was converted to N,N-di-