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RATE AND EQUILIBRIUM OF ACCELERATED S_N-2 TYPE LIGAND EXCHANGE REACTION FOR MACROCYCLIC POLYAMINE-Cu^{++}

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A lot of macrocyclic compounds containing heteroatoms in their ring components have been synthesized[1] and their complex formation with metal ions has been studied.[2] Enormously large association constants observed in many examples, however, may involve some uncertainties in very "slow" reactions where the determination of equilibrium constants are based on such less satisfactory assumption as equilibrium attainment before titration.[2a] Some unusual binding properties reported in literatures might be due to these uncertainties.

Thus, the most important point to be ascertained for the determination of very large K is that the reaction in question attains to the equilibrium to satisfactory extent, since such limitation of the forward (complex formation, k_1) rate as the diffusion control make the reverse (complex dissociation, k_{-1}) rate extremely small and treatment of "slow" equilibrium is inevitable.

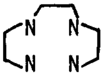
$$L_1 + M \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} L \cdot M \qquad (1)$$

$$K = k_1 / k_{-1} \gg 1 \qquad (2)$$

Now we wish to report that this is the very case for cyclic polyamine-Cu^{++} complexes and that the problem can be practically solved by enormous acceleration of the dissociation step of the complex through the S_N-2 type ligand exchange, making the equilibrium to be fast enough or, at least, accelerating the rate to be measurable. Very fast rates of the simple association of Cu^{++} with polyamines were measured with the stopped-flow and the rapid-scan UV technique, showing that the rates followed simple second order kinetics. Rate constants thus obtained (k_1) are listed in Table I, together with <u>equilibrium constants</u>,[3] independently observed. As expected, the simple dissociation constants estimated from these values and by use of eq. 2, are so small that the half-lives of the dissociation processes should lie between 5×10^7 to 1×10^{12} <u>years</u>!

Table I. Ligand-Metal Complex Formation

L	k_1 ($sec^{-1} \cdot M^{-1}$)[a]	log K[b]	k_{-1} (sec^{-1})[c]
II	1.31×10^5	20.5[d]	3.43×10^{-16}
III	1.70×10^5	25.0[d]	1.70×10^{-20}
IV	2.19×10^5	25.5[e]	5.73×10^{-21}
V	4.57×10^5	25.9[e]	5.75×10^{-21}
VI	5.33×10^5	20.7[f]	1.06×10^{-16}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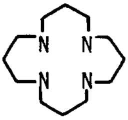
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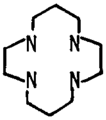
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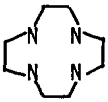
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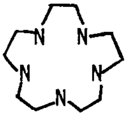
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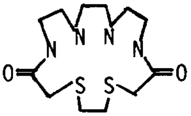

VI

[a] 0.5 N NaOH at 20°C. [b] 0.1 N NaOH at 20°C. [c] approximated value calculated from k_1 and K. [d] based on the reported log K value for I in 0.1 N NaOH at 20°C. [e] based on the log K for III determined above. [f] based on the log K for II determined above.

However, in the presence of another "good" ligand L_2, the Cu^{++} binding constant of which (reaction 3) is not extremely different from that of L_1, the reverse rate constant of the reaction 4, $k_{2,1}$, as well as the corresponding forward rate constant, $k_{1,2}$, was observed to be rapid enough to reach to <u>equilibrium</u> practically. As shown in Table II, the S_N-2 nature of the ligand exchange was ascertained by the rate measurement in different polyamine concentration.

Based on the assumption that both of the reactions 1 and 3 are in <u>real</u> equilibrium, apparent equilibrium constant observed for the S_N-2 type ligand exchange reaction 4, $K_{1,2}$, should also be expressed by eq. 5.

$$L_2 + M \overset{K_2}{\rightleftharpoons} L_2 \cdot M \qquad (3)$$

$$L_1\cdot M + L_2 \underset{k_{2,1}}{\overset{k_{1,2}}{\rightleftharpoons}} L_1 + L_2\cdot M \tag{4}$$

$$K_{1,2} = K_2 / K_1 \tag{5}$$

Table II. $I\cdot Cu^{++} + II \underset{k_{2,1}}{\overset{k_{1,2}}{\rightleftharpoons}} II\cdot Cu^{++} + I$

$[I\cdot Cu^{++}]_0$	$[II]_0$	$k_{obs1,2}$[a] (sec^{-1})	$k_{1,2}$[a] $(sec^{-1}\cdot M^{-1})$
1.0×10^{-4}M	1.3×10^{-3}M	3.38×10^{-3}	2.60
5.0×10^{-5}M	2.5×10^{-3}M	6.40×10^{-3}	2.56
5.0×10^{-5}M	4.0×10^{-3}M	1.12×10^{-2}	2.81
$[II\cdot Cu^{++}]_0$	$[I]_0$	$k_{obs2,1}$[a] (sec^{-1})	$k_{2,1}$[a] $(sec^{-1}\cdot M^{-1})$
1.0×10^{-4}M	1.3×10^{-3}M	2.73×10^{-4}	2.10×10^{-1}
5.0×10^{-5}M	2.5×10^{-3}M	4.93×10^{-4}	1.97×10^{-1}
5.0×10^{-5}M	4.0×10^{-3}M	7.95×10^{-4}	1.99×10^{-1}

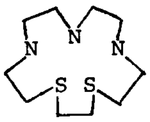
[a] 0.1 N NaOH at 20°C.

Thus, a certain (unknown) equilibrium constant, K_2, can be determined on the basis of a given (known) equilibrium constant, K_1 and observed constant, $K_{1,2}$. When a real equilibrium (not too large) constant is determined, any other equilibrium constant can be determined in a stepwise fassion. As shown in Table III the apparent equilibrium constant, $K_{1,2}$, $(=k_{1,2}/k_{2,1})$ can also be estimated from rate constants $k_{1,2}$ and $k_{2,1}$ where direct determination of $K_{i,j}$ is difficult.

Table III. Ligand Exchange Reaction

L_1	L_2	$k_{1,2}$[a] $(sec^{-1}\cdot M^{-1})$	$k_{2,1}$[a] $(sec^{-1}\cdot M^{-1})$	$k_{1,2}/k_{2,1}$	$K_{1,2}$[b]
VII	II	5.94	4.67	1.27	2.52
VIII	II	4.26	0.385	11.1	15.0
II	VI	3.14	1.46	2.15	1.45

[a] 0.1 N NaOH at 20°C. [b] from direct determination.



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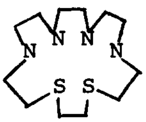

VIII

Thus, very large dissociation constants via eq. 6 where the determination should start from the most reliable equilibrium constant, K_1.

$$K_n = \frac{K_n}{K_{n-1}} \cdot \frac{K_{n-1}}{K_{n-2}} \cdot\cdot\cdot\cdot\cdot \frac{K_3}{K_2} \cdot \frac{K_2}{K_1} \cdot K_1$$

$$= K_{n-1,n} \cdot K_{n-2,n-1} \cdot\cdot\cdot\cdot\cdot K_{2,3} \cdot K_{1,2} \cdot K_1 = K_1 \cdot \prod_{i=1}^{n-1} K_{i,i+1} \qquad (6a)$$

$$= K_1 \cdot \prod_{i=1}^{n-1} \frac{k_{i,i+1}}{k_{i+1,i}} \qquad (6b)$$

The authors have experienced slight deviations from the relationship of eq. 5 in a few examples involving (7), and the nature of this peculiar deviation

$$\mathrm{I} + \mathrm{II} \cdot Cu^{++} \rightleftharpoons \mathrm{I} \cdot Cu^{++} + \mathrm{II} \qquad (7)$$

has not yet been clarified. However, since the deviation was not serious, the determination of equilibrium constants via eq. 6b seems to be still much safer than the direct determination of a never-equilibrated system.

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3. First, we have obtained the log K value of $\mathrm{II} \cdot Cu^{++}$, $\mathrm{III} \cdot Cu^{++}$ based on the reported value of $\mathrm{I} \cdot Cu^{++}$,[2a] then using these values we obtained the other log K's.