A Thermodynamic and Kinetic Interpretation of the Macrocyclic Effect. Polarographic Studies on Copper(II) 1,4,7,10-Tetraazacyclododecane Complexation

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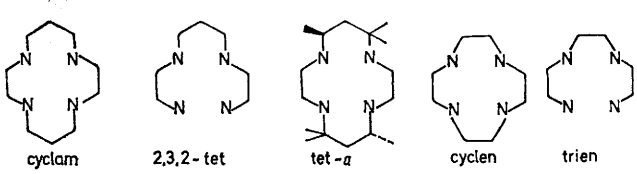
Summary Polarographic studies on Cu^{II}-1,4,7,10-tetraazacyclododecane (cyclen) complexation have shown that the thermodynamic and kinetic macrocyclic effect is evident despite the unfavourable steric constraints, and that the increased stability constant of Cu^{II}-cyclen compared to Cu^{II}-trien is accounted for solely by the entropy term.

SOME macrocyclic ligands form more stable complexes with metal ions than open-chain ligands having the same donor group; this is termed the macrocyclic effect or multiple



juxtapositional fixedness.[1-3] Recently Hinz and Margerum assigned a 10^6-fold increase in the stability constant of $Ni(cyclam)^{2+}$ compared to $Ni(2,3,2\text{-tet})^{2+}$ to a more favourable change in ΔH which overcomes a less favourable change in ΔS, and reasoned that the free macrocycle is less solvated due to steric hindrance and hence less enthalpic energy need be expended for desolvation before complexation.[1] We have investigated the competition between the macrocyclic effect and the destabilizing effect of severe steric constraints using the 12-membered macrocyclic tetramine, cyclen.[4] Our kinetic and equilibrium studies on the Cu^{II}-cyclen complex by the polarographic method[5] have given some significantly different results from those found earlier.

TABLE. Comparison of stability constants, enthalpy and entropy of formation of tetramine complexes at 25°.

Complex	log K_{ML}	ΔH /kcal mol^{-1}	ΔS /cal K^{-1} mol^{-1}
$Cu(cyclen)^{2+}$ [a]	24·8	−18·3	51·4
$Cu(trien)^{2+}$ [b]	20·0	−21·6	19·5
$Cu(2,3,2\text{-tet})^{2+}$ [b]	23·9	−27·7	16·5
$Ni(cyclam)^{2+}$ [c]	22·2	−31·0	−2
$Ni(trien)^{2+}$ [c]	13·8	−14·0	16·0
$Ni(2,3,2\text{-tet})^{2+}$ [c]	15·8	−19·4	7·2

[a] This work, $\mu = 0{\cdot}20$. ΔH and ΔS were determined from the temperature dependence (10—30°) of the equilibrium constants. [b] See R. Barbucci, L. Fabbrizzi, and P. Paoletti, *Co-ord. Chem. Rev.*, 1972, 8. [c] Ref. 1.

We have measured the formation constant of the 1:1 Cu^{II}-cyclen complex from the shifts of the half-wave

potential[6] at various hydrogen ion and cyclen concentrations for the electrode reaction,

$$Cu(cyclen)^{2+} + 2e^- + Hg \rightleftharpoons Cu(Hg) + cyclen.$$

The acetate ion employed for the buffer had practically no effect on the polarographic behaviour of the cyclen complex. We observed, unlike the case of tet *a*,[2] only a blue complex solution (λ_{max} 600 nm), which enabled the straightforward determination of the equilibrium constant. A comparison with the equilibrium constant for the non-cyclic tetramine, trien, shows that the macrocyclic effect in cyclen is evident despite the less exothermic enthalpy change (Table). The enhanced stability of $Cu(cyclen)^{2+}$ arises entirely from the favourable change in ΔS. The lower heat of formation of the cyclic complex may be due to several factors such as the steric constraints, and less co-ordinate bond energy in the change from two primary and two secondary (trien) to four secondary nitrogen atoms (cyclen),[7] (both endothermic), and less ligand solvation,[1] (exothermic). The favourable entropy contribution for cyclen can be explained by the pre-orientation before chelation due to steric requirements, and by the decreased complex solvation in the inner co-ordination sphere due to distorted geometry[8] as well as in the outer sphere due to the hydrophobic exterior. The contrast in the thermodynamic parameters between $Cu(cyclen)^{2+}$ and $Ni(cyclam)^{2+}$ does not seem fully accountable by the difference in the metal ion or the ligand ring size, and we are investigating this further.

In the macrocyclic structure the protonation of the nitrogens of cyclen, and of cyclam,[9] occurs in two stages, one weakly basic, and the other strongly basic; $pK_1 = 10{\cdot}7$, $pK_2 = 9{\cdot}7$, pK_3 and $pK_4 = 1{\cdot}5$—2 (determined potentiometrically). The reaction mechanism for the Cu^{II}-cyclen complex formation (Scheme) has been established from the plot of $(-\Delta i_d/\Delta t)_0(\alpha_H)_{cyclen}/[Cu^{II}]_{ap}\cdot[cyclen]_l\cdot[H^+]$ against $[H^+]$ which gave a straight line. The second-order rate constants, $k_1 = 10^{6.30}$ and $k_2 = 10^{-0.74}$ M^{-1} s^{-1} (25 °C), were determined from the intercept and slope. The equilibrium constants were calculated as $K_1 = 10^{17.2}$ and $K_2 = 10^{7.5}$.

$$\begin{array}{l} Cu(OAc)_2 \\ \uparrow\downarrow \qquad cyclenH^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Cu(cyclen)^{2+} + HOAc \qquad K_1 \\ Cu(OAc)^+ + \\ \uparrow\downarrow \qquad cyclenH_2^{2+} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Cu(cyclen)^{2+} + HOAc + H^+ \quad K_2 \\ Cu^{2+} \end{array}$$

SCHEME

As is the case for tet *a*,[2] the rate of complex formation is dramatically influenced by the protonation of the macrocyclic ligand. The effect of acetate anion on the reaction rate was checked by plotting $(-\Delta i_d/\Delta t)_0\cdot\beta_{Ac}/[Cu^{II}]_{ap}\cdot[cyclen]_l$ against $[OAc^-]$, which gave a straight line passing through the point of origin. The comparison of the calculated dissociation rate constants, $k_{-1} = 10^{-10.9}$ and $k_{-2} = 10^{-8.2}$ M^{-1} s^{-1}, with other linear polyamine ligands[10] supports the earlier finding[2b] that the kinetic macrocyclic effect occurs most notably in the dissociation step.

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