conductance. Using this assumption and the Ostwald dilution law, we calculate[8] an equilibrium constant of $3.9 \times 10^{-3}$ for the reaction

$$Ni(Benzo\text{-}15\text{-}P_4)CN^+ \rightleftarrows Ni(Benzo\text{-}15\text{-}P_4)^{2+} + CN^-$$

The fact that only the cyanide ion is capable of entering the axial site of this complex is indicative of the strong ligand field strength of this macrocycle,[9] and thus these macrocycles have some similarity to the phthalocyanines.[4]

The effect of ring size on ligand field strength of macrocyclic ligands has been amply demonstrated.[10] It has been concluded in the case of the nitrogen macrocycles that the 14-membered ring is probably a very tight fit while the 15-membered example may be very close to ideal when high-spin nickel(II) is the encapsulated metal. The same types of arguments can be used in the present situation to conclude that the 15-membered phosphorus macrocycle is a very tight fit for the larger high-spin nickel(II), and thus, when encapsulated by Benzo-15-$P_4$, the nickel(II) ion prefers to remain in the smaller, low-spin configuration. Whether this explanation or the well-known back-bonding capabilities of ligating phosphine moieties are dominating the coordination chemistry of these macrocyclic phosphines will have to await further studies of variously sized phosphorus macrocycles.[2,3]

**Registry No.** $Ni(Benzo\text{-}15\text{-}P_4)(BF_4)_2$, 68024-58-8; $Ni(Benzo\text{-}15\text{-}P_4)Cl_2$, 65296-99-3; $Ni(Benzo\text{-}15\text{-}P_4)(NCS)_2$, 68024-59-9; $Ni(Benzo\text{-}15\text{-}P_4)(CN)(BF_4)$, 68024-61-3; 1,4,8,11-tetraphenyl-1,4,8,11-tetraphosphaundecane, 65201-65-2; $\alpha,\alpha'$-dibromo-*o*-xylene, 91-13-4; $C_{31}H_{36}P_4NiCl_2$, 65296-98-2.

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# Kinetics of Macrocyclic Tetraamine Reactions with Copper(II) Triglycine


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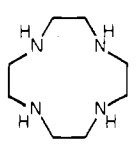
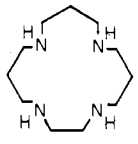
In order to explore the biological application of macrocyclic tetraamines, we have investigated kinetics of the replacement of triglycine by $L^1$ and $L^2$ on copper(II) ions, as shown by (1)

$$Cu(H_{-2}trigly)^- + L \rightarrow (CuL)^{2+} + trigly \qquad (1)$$

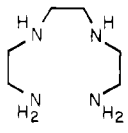
which represents the most fundamental reaction of copper transfer from copper-binding peptides. Reaction 1 is thermodynamically and kinetically very favorable with a linear tetraamine homologue $L^3$ (ref 2) which is used as a therapeutic agent to remove excess copper from the body in the treatment of Wilson's disease. Our previous studies showed the copper complexes of $L^1$ (ref 3) and $L^2$ (ref 4) to be far more stable than that of $L^3$, suggesting equilibrium 1 to be shifted more in favor of the copper transfer with the macrocycles. The kinetic aspects of reaction 1 thus drew our attention.



$L^1$
1,4,7,10-tetraazacyclododecane



$L^2$
1,4,8,12-tetraazacyclopentadecane



$L^3$
3,6-diazaoctane-1,8-diamine

Reaction 1 is also of interest from a mechanistic point of view. The replacement by $L^3$ occurs almost via a nucleophilic mechanism, wherein dissociation of triglycine in the rate-determining step is caused by the direct attack of the nitrogens of $L^3$. The restricted flexibility and steric hindrance of macrocycles might render the nucleophilic pathway unfeasible. The use of the two extreme macrocyclic tetraamines, the most rigid $L^1$ and the least rigid $L^2$ among the well-investigated 12- and 15-membered tetraamines,[3-6] may help identifying the reaction mechanism. This work constitutes a series of the investigations of macrocyclic polyamine replacement reactions.[7,8]

## Experimental Section

The macrocyclic tetraamines $L^1$ and $L^2$ were prepared as described before.[3,4] The mixed protonation constants used, log $K_1$ and log $K_2$, respectively, were 10.70 and 9.70 for $L_1$ and 11.20 and 10.10 for $L^2$.[3,4] The values of log $K_3$ and log $K_4$ are less than 2 for both, and the kinetic contributions of the tri- and tetraprotonated species were negligible in the borate buffer conditions used. Triglycine was obtained commercially. Copper–triglycine solution was prepared by mixing a stock solution of copper nitrate (standardized against EDTA) and triglycine (2% molar excess) in borate buffers (sodium borate–boric acid). Constant ionic strength was maintained at 0.2 M by adjusting with $NaClO_4$. All the work was at 25.0 ± 0.1 °C. The data associated with protonation constants are based on pH readings.

Kinetic runs were followed spectrophotometrically by measuring the increase in absorbance at the wavelengths sensitive to the formation of CuL, 630 nm for $L^1$ and 645 nm for $L^2$, on a Union Giken stopped-flow instrument with a 2-cm cell path. The second-order (unequal concentrations) plots and the initial-slope method gave practically the same observed rate constants $k_{obsd}$. Typical data by the second-order plots are shown in Table I.

## Results and Discussion

In the pH range of 8.2–9.6 used,[9] the copper–triglycine complex exists mostly in the form of $Cu(H_{-2}trigly)^-$,[10] the macrocyclic tetraamines in diprotonated form $(H_2L)^{2+}$, and the macrocyclic complexes in $(CuL)^{2+}$.[3,4] The log of the conditional equilibrium constants for (1) at pH 9 are estimated at 11 and 9.8, respectively, for $L^1$ and $L^2$ from the available constants.[3,4,10] Experimentally, the spectra of the product solutions corresponded to those of $(CuL)^{2+}$ and showed no evidence of mixed complexes.

The transfer of $Cu^{II}$ from triglycine to the macrocyclic tetraamines by the reaction 1 is much slower than to the linear homologue $L^3$: the half-lives are ca. 1 s ($L^1$) and 2 s ($L^2$) as against 0.1 ms (calculated value for $L^3$ using the data in ref 2) at the concentrations given in the caption to Figure 1 and pH 9. The exchange reactions were first order in $[Cu(H_{-2}trigly)]$ and first order in $[L]_{tot}$. The small pH dependence of the $k_{obsd}$ indicates that the reactive forms of L are mainly


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**Table I.** Typical Rate Data for the Reaction of Macrocyclic Tetraamines with $Cu(H_{-2}trigly)^-$ at $I = 0.2$ M and 25 °C

| $10^3 \times$ [Cu($H_{-2}$-trigly)], M | $10^3 \times [L]_{tot}$, M | $10^3 \times$ [borate], M | pH | $k_{obsd}$, $M^{-1}$ $s^{-1}$ |
|---|---|---|---|---|
| | | $L^1$ | | |
| 2.0 | 2.5 | 48.8 | 8.90 | 260 |
| 2.0 | 5.0 | 48.8 | 8.90 | 260 |
| 4.0 | 5.0 | 48.8 | 8.90 | 250 |
| 4.0 | 20 | 48.8 | 8.90 | 250 |
| 8.0 | 20 | 48.8 | 8.90 | 260 |
| 4.0 | 5.0 | 97.6 | 8.90 | 260 |
| 4.0 | 5.0 | 48.8 | 8.20 | 270 |
| | | | 8.43 | 260 |
| | | | 9.21 | 240 |
| | | | 9.62 | 220 |
| | | $L^2$ | | |
| 2.0 | 2.5 | 48.8 | 8.90 | 140 |
| 2.0 | 5.0 | 48.8 | 8.90 | 140 |
| 4.0 | 5.0 | 48.8 | 8.90 | 150 |
| 4.0 | 20 | 48.8 | 8.90 | 140 |
| 8.0 | 20 | 48.8 | 8.90 | 140 |
| 4.0 | 5.0 | 24.4 | 8.90 | 140 |
| 4.0 | 5.0 | 97.6 | 8.90 | 140 |
| 4.0 | 5.0 | 48.8 | 8.20 | 140 |
| | | | 8.43 | 140 |
| | | | 9.21 | 160 |
| | | | 9.62 | 170 |

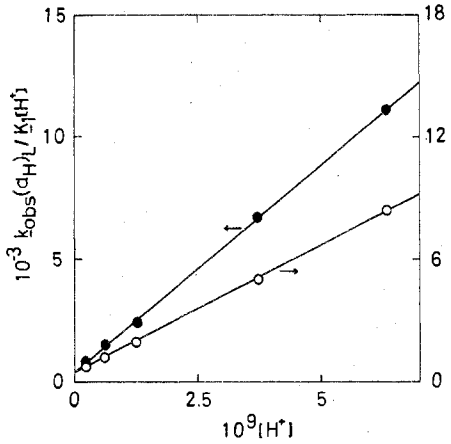


**Figure 1.** Plots of eq 2 for $L^1$ (○) and for $L^2$ (●) at $[Cu(H_{-2}trigly)] = 4.0 \times 10^{-3}$ M, $[L]_{tot} = 5.0 \times 10^{-3}$ M, [borate] = $48.8 \times 10^{-3}$ M, $I = 0.2$ M, and 25 °C.

$(H_2L)^{2+}$ with a small contribution from $(HL)^+$. This was determined graphically (see Figure 1)[11] using

$$k_{obsd}(\alpha_H)_L = k_H[H^+]K_1 + k_{2H}[H^+]^2K_1K_2 \quad (2)$$

where

$$(\alpha_H)_L = [L]_{tot}/[L] = [H^+]K_1 + [H^+]^2K_1K_2 \quad (3)$$

The resolved rate constants are listed in Table II in comparison with the relevant values for $L_3$.

Almost comparable values of $k_H$ and $k_{2H}$ and very little dependence of the $k_{iH}$ values on the macrocyclic ring size well characterize the present replacement reaction. These facts have not been encountered before[3-8] and are not compatible with the macrocyclic tetraamines acting as good nucleophiles. In the nucleophilic mechanism the relative reactivity of protonated tetraamines would be $(HL)^+ >> (H_2L)^{2+}$ (as found with $L^3$),[2] and the $k_{iH}$ values for more flexible $L^2$ would be greater than those for less flexible $L^1$. The nucleophilic

**Table II.** Comparison of Rate Constants for Tetraamine Species Reaction with $Cu(H_{-2}trigly)^-$

| tetraamine | reacting species | $k_{iH}$, $M^{-1}$ $s^{-1}$ |
|---|---|---|
| $L^1$ [a] | $(HL)^+$ | $(2.5 \pm 0.3) \times 10^2$ |
| | $(H_2L)^{2+}$ | $(2.7 \pm 0.3) \times 10^2$ |
| $L^2$ [a] | $(HL)^+$ | $(3 \pm 1) \times 10^2$ |
| | $(H_2L)^{2+}$ | $(1.4 \pm 0.1) \times 10^2$ |
| $L^3$ [b] | L | $1.1 \times 10^7$ |
| | $(HL)^+$ | $5.1 \times 10^6$ |
| | $(H_2L)^{2+}$ | $1.2 \times 10^5$ |

[a] This work; at $I = 0.2$ M and 25 °C. [b] Reference 2; at $I = 0.1$ M and 25 °C. The data are based on hydrogen ion concentrations.

behavior of macrocyclic tetraamines is well illustrated in the exchange reactions of $Cu(EDTA)^{2-}$: the rate constants for unprotonated L, $(HL)^+$, and $(H_2L)^{2+}$, respectively, are 31, 17, and $7.4 \times 10^{-3}$ $M^{-1}$ $s^{-1}$ for the 13-membered homologue 1,4,7,10-tetraazacyclotridecane and 250, 40, and $3.4 \times 10^{-2}$ $M^{-1}$ $s^{-1}$ for $L^2$.[7] Comparing $Cu(H_{-2}trigly)^-$ to $Cu(EDTA)^{2-}$, we find ratios of the rate constants for mono- and diprotonated $L^2$ are 7.5 and 4100, to be compared with 145 and 570 for the corresponding $L^3$. An unusual increase in the reactivity of the diprotonated macrocyclic species indicates a significant role of the protons in the replacement of triglycine. We interpret these facts as follows.

The replacement probably starts with a nitrogen coordination at the site initially occupied by the carboxylate, as proposed for the $L^3$ reaction.[2] The succeeding chelation mechanism may differ greatly between the protonated linear and macrocyclic ligands. The second nitrogen on the flexible $L^3$ can immediately attack and labilize the dissociation of a copper–imide bond. The protons located near the reaction center will not pose a serious problem, since they can be readily transferred intramolecularly to other basic sites.[12] The chelation would proceed to completion without much trouble. On the other hand, the macrocyclic $L^1$ and $L^2$ must overcome steric as well as proton-transfer difficulties[12] (if the nucleophilic pathway is chosen) in the second and the following Cu–N bond formations. The protonated (especially diprotonated) macrocycles would find a solution in a proton-transfer pathway wherein they release the protons to basic copper–imide bonds to give more labile coordination which permits rearrangement to a copper–triglycine complex sterically more favorable for the macrocycle chelation. In the replacement of EDTA, there is not such a proton acceptor, so the macrocyclic tetraamines while being bothered with the protons have to drive off the EDTA by nucleophilic attack.

**Registry No.** $Cu(H_{-2}trigly)^-$, 34803-37-7; $L^1$, 294-90-6; $L^2$, 15439-16-4.

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(9) At higher pH, the kinetic data were too complex to be resolved.
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(11) We repeated the experiments three times. It was always found that the $k_{obsd}$ values are pH dependent (though small) beyond experimental errors and that the intercepts in Figure 1 were finite, from which we assessed the $k_H$ values.
(12) These notions would be supported by the fact that the third and fourth protonation constants of $L^3$ are much higher (see, e.g., ref 2) than those of $L^1$ and $L^2$.