Ring-size Effects of Macrocyclic Ligands on Complex Stabilities. Mercury(II) Complexes of Twelve- to Fifteen-membered Cyclic Tetra-amines

By **Mutsuo Kodama**, Department of Chemistry, College of General Education, Hirosaki University, Bunkyo, Hirosaki, Japan
Eiichi Kimura,* Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine, Kasumi, Hiroshima, Japan

A polarographic method has been used to study the equilibria of complex formation of mercury(II) ion with linear and 12—15-membered cyclic tetra-amines: 1,4,7,10-tetra-azacyclododecane(L^1), 1,4,7,10-tetra-azacyclotridecane(L^2), 1,4,8,11-tetra-azacyclotetradecane(L^3), and 1,4,8,12-tetra-azacyclopentadecane(L^4). The stability constants are $10^{25.5}$, $10^{25.3}$, $10^{23.0}$, and $10^{23.7}$ (at 25 °C, $I = 0.20$ mol dm^{-3}) for the 1 : 1 complexes, respectively, indicating no special cavity selectivities. The constants are a little greater than those for related open-chain tetra-amines($10^{24.5}$ for 3,6-diazaoctane-1,8-diamine and $10^{22.1}$ for 3,7-diazanonane-1,9-diamine). Ligand cyclization in general causes mercury(II) complexes to undergo enthalpy loss which outweighs the normal compensation of the entropy terms, thus preventing an occurrence of the large macrocyclic effect seen for smaller metal ions. However, a unique macrocyclic ring-size effect towards Hg^{II} occurs with the 14-membered ring, where the large negative enthalpy contribution outweighs the unfavourable entropy effect, a trend opposite to those in other macrocyclic systems.

DEPENDING on the ring size, two thermodynamic contributions may account for the enhanced stabilities of complexes of macrocyclic ligands over the corresponding complexes of linear tetra-amines with several metal ions. Thus, the entropy term represents the sole or major contribution for the complexes of 1,4,7,10-tetra-azacyclododecane (L^1 or cyclen) [1,2] and 1,4,7,10-tetra-azacyclotridecane (L^2) [3,4] with Cu^{II}, whereas for the nickel(II) chelate of 1,4,8,11-tetra-azacyclotetradecane (L^3 or cyclam) [5,6] and the copper(II) chelate of 1,4,8,12-tetra-azacyclopentadecane (L^4) [7] the enthalpy term is the dominant parameter. However, such a characteristic ligand ring-size effect does not occur in the zinc(II) series, where a similarly favourable ΔS term is common with the 12—15-membered macrocycles.[8] The large positive ΔS values apparently result from the smaller loss of configurational entropy on co-ordination of the cyclic ligands. The large negative ΔH values may arise from the smaller extent of solvation of the cyclic ligand due to the steric hindrance,[5,6] although this interpretation may be subject to modification.[9]

We have now studied the stability of mercury(II) complexes with these macrocycles. Mercury(II) ion, unlike Cu^{II}, Ni^{II}, or Zn^{II}, is too big to lie in the N_4 cavities of these relatively small macrocycles. Hence, this system may provide another example of the macrocyclic effects on the metal complexation. We have also determined the stability constants for the related linear tetra-amines 3,6-diazaoctane-1,8-diamine(3NH-od, trien) and 3,7-diazanonane-1,9-diamine(3,7NH-nd, 2,3,2-tet) which serve as references. The present equilibrium study has employed a polarographic method to measure the half-wave potentials of the anodic waves due to the uncomplexed tetra-amines at a dropping mercury electrode (d.m.e.).

EXPERIMENTAL

Reagents.—The macrocyclic ligands L^1—L^4 were prepared by the method of Martin *et al.*[10] The first and second protonation constants (pK_1 and pK_2) ($I = 0.20$ mol dm^{-3}) are 10.7 and 9.7 for L^1,[2] 11.1 and 10.1 for L^2,[4] 11.5 and 10.2 for L^3,[4] and 11.2 and 10.1 for L^4.[7] The third and fourth protonation constants (pK_3 and pK_4) lie between 2 and 1 for any of the macrocycles. 3,6-Diazaoctane-1,8-diamine was separated as the tetrahydrochloride from the commercially available amine which was purified by the method of Jonassen and Strickland.[11] 3,7-Diazanonane-1,9-diamine was purified by twice recrystallizing (from 6 mol dm^{-3} HCl) its tetrahydrochloride which was prepared from the commercial amine (Eastman). Standard solutions of the tetra-amines were prepared by dissolving known amounts in redistilled water. All the other chemicals were of analytical reagent grade and were used without further purification. D,L-Valine used for buffering was recrystallized from its aqueous solution by adding concentrated HCl and ethyl alcohol.

Apparatus and Experimental Procedures.—All the polarograms were obtained with a Yanagimoto P-8 pen-recording polarograph or a manual polarograph similar to that of Kolthoff and Lingane.[12] The polarographic dropping mercury electrode (d.m.e.) had the open-circuit characteristics $m = 0.917$ mg s^{-1} and $t_d = 4.80$ s in an air-free 0.10 mol dm^{-3} Na[ClO$_4$] solution at a column height of 45 cm at 25 °C. A saturated calomel electrode (s.c.e.) of large surface area was used as reference and was connected to the cell solution through a Hume and Harris salt bridge.[13] When an a.c. polarogram was recorded, a platinum-wire electrode with a large surface area was inserted into the electrolytic

---

[1] M. Kodama and E. Kimura, *J.C.S. Chem. Comm.*, 1975, 326.

[2] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 116.

[3] M. Kodama and E. Kimura, *J.C.S. Chem. Comm.*, 1975, 891.

[4] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 1720.

[5] F. P. Hinz and D. W. Margerum, *J. Amer. Chem. Soc.*, 1974, **96**, 4993.

[6] F. P. Hinz and D. W. Margerum, *Inorg. Chem.*, 1974, **13**, 2941.

[7] M. Kodama and E. Kimura, unpublished work.

[8] M. Kodama and E. Kimura, submitted for publication.

[9] T. E. Jones, L. L. Zimmer, L. L. Diaddario, D. B. Rorabacher, and L. A. Ochrymowycz, *J. Amer. Chem. Soc.*, 1975, **97**, 7163.

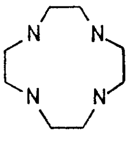
[10] L. Martin, L. J. DeHayes, L. J. Zompa, and D. H. Busch, *J. Amer. Chem. Soc.*, 1974, **96**, 4046.

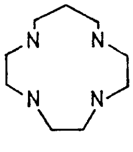
[11] H. B. Jonassen and G. T. Strickland, *J. Amer. Chem. Soc.*, 1958, **80**, 312.

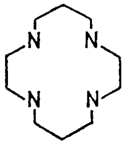
[12] I. M. Kolthoff and J. J. Lingane, 'Polarography,' Interscience, New York, 1952, vol. 1, p. 297.

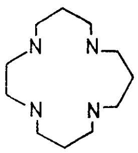
[13] D. N. Hume and W. E. Harris, *Ind. and Eng. Chem. Analyt. Edn.*, 1943, **15**, 465.

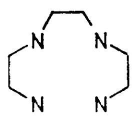
solution as a third electrode. It was terminated at the s.c.e. through a 200 μF capacitor in order to minimize the impedance of the cell.[14] The d.c. polarographic data given in this paper were corrected for the residual current and the ohmic drop of the cell circuit. The solution pH was measured with a glass-electrode pH meter (Hitachi–Horiba model F-7). A water-jacketed beaker-type cell with a rubber top, thermostatted to ±0.1 °C, was used for all the experiments. The ionic strength of the solution was adjusted to 0.20 mol dm^{-3} by adding an appropriate amount of Na[ClO$_4$]. The oxygen dissolved in the sample solution was removed by bubbling pure nitrogen gas through the solution for 15 min. All the other experimental procedures were given previously.[2] In order to maintain constant the solution pH, valinate buffer was used in this study ($8.80 < \mathrm{pH} < 10.00$).

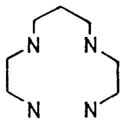

L^1


L^2


L^3


L^4


3,6NH-od


3,7NH-nd

RESULTS

In the valinate buffer solutions all the macrocyclic tetra-amines gave well defined anodic waves at the d.m.e. (a typical polarogram obtained for L^2 is presented in Figure 1). The limiting currents were proportional to the bulk concentration of the macrocycles and to the square root of the effective pressure on the d.m.e. Plots of $\log\,[i/(i_l - i)]$ against d.c. potential, E, invariably gave straight lines having reciprocal gradients of −28 to −33 mV over the entire pH range covered, which suggests a two-electron reversible oxidation. The reversible nature of the electrode reaction was also confirmed by the a.c. polarographic method.[15] The summit potentials were nearly equal to the corresponding d.c. half-wave potentials (see Figure 1), and the value indicating the degree of reversibility, $I_{ac}/i_d n t_d^{\frac{1}{2}}$, was nearly identical to that of the cathodic wave of Cd^{2+} in K[NO$_3$] solution. Here, I_{ac}, i_d, and n, respectively, denote the a.c. peak height, d.c. diffusion current, and number of electrons involved in the electrode reaction.

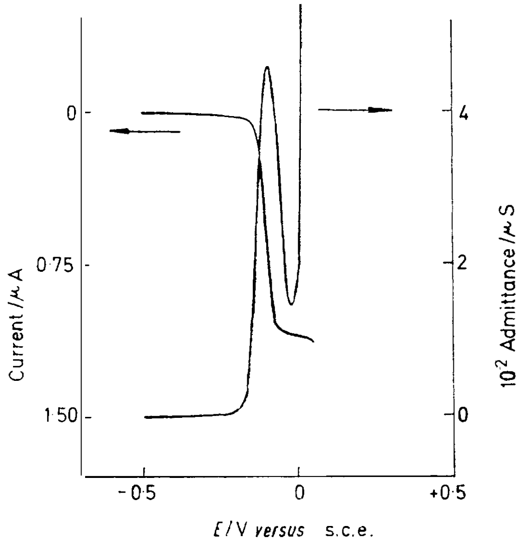


FIGURE 1 Polarogram of L^4. $[L^4] = 0.40 \times 10^{-3}$ mol dm^{-3}, [valine] = 0.05 mol dm^{-3}, pH 9.90, I = 0.20 mol dm^{-3}, 25 °C

TABLE 1

Effect of pH on the half-wave potentials at I = 0.20 mol dm^{-3} and 25 °C

System	pH	log $(\alpha_H)_L$	$E_{\frac{1}{2}}$ / V versus s.c.e.	$\Delta E_{\frac{1}{2}}$/mV obs.	calc.[a]
L^1 [b]	9.00	2.48	−0.129	16	15.7
	9.30	1.95	−0.145	0	0
	10.00	0.87	−0.175	−30	−32.0
L^2 [b]	8.92	3.38	−0.091	0	0
	9.27	2.72	−0.115	−24	−19.4
	9.72	1.92	−0.136	−45	−43.2
L^3 [b]	9.10	3.62	−0.023	34	32.8
	9.65	2.51	−0.057	0	0
	9.92	2.05	−0.071	−14	−14.4
L^4 [c]	8.80	3.72	--0.035	23	23.2
	9.20	2.94	−0.058	0	0
	10.00	1.57	−0.101	−43	−40.5

[a] Using equation (1). [b] Ligand concentration = 0.40×10^{-3} mol dm^{-3}, [valine] = 0.10 mol dm^{-3}. [c] Ligand concentration = 0.48×10^{-3} mol dm^{-3}, [valine] = 0.08 mol dm^{-3}.

The d.c. half-wave potential, $E_{\frac{1}{2}}$, was independent of the concentrations of the macrocycles as well as of the valinate, but shifted to a more negative value on increasing the solution pH according to relation (1) (Table 1), where $(\alpha_H)_L$

$$\frac{\Delta E_{\frac{1}{2}}}{\Delta \log(\alpha_H)_L} = -30 \text{ mV} \qquad (1)$$

is defined as $1 + K_1[H^+] + K_1K_2[H^+]^2 + K_1K_2K_3[H^+]^3 + K_1K_2K_3K_4[H^+]^4 \approx 1 + K_1[H^+] + K_1K_2[H^+]^2$ in the pH region under coverage [K_i is the equilibrium constant for $H_iL^{i+} \rightleftharpoons H_{i-1}L^{(i-1)+} + H^+$]. Combined with the fact that the valinate had little influence on $E_{\frac{1}{2}}$ and on the height of the anodic wave due to the uncomplexed macrocycle, the above findings indicate that only a 1 : 1 mercury(II)–macrocycle complex is formed in reaction (2). The half-wave potential

$$Hg + H_iL^{i+} \rightleftharpoons [HgL]^{2+} + iH^+ + 2e^- \qquad (2)$$

is then expressed as in (3). The diffusion coefficients of the

$$(E_{\frac{1}{2}})_{HgL} = E_{Hg}^{\ominus} + 0.0296[\log f_{Hg^{2+}} - \log K_{HgL} + \log (\alpha_H)_L] + 0.0296 \log(k_L/k_{HgL}) \qquad (3)$$

mercury(II) complex, k_{HgL}, and of the various forms of H_iL^{i+}, k_L, are assumed equal for approximation.[16] In

---

[14] D. Breyer, F. Gutmann, and S. Hacobian, *Austral. J. Sci. Res.*, 1951, **A4**, 595.

[15] M. Senda, M. Senda, and I. Tachi, *J. Electrochem. Soc. Japan*, 1959, **27**, 83; M. Kodama and M. Abe, *Nippon Kagaku Zasshi*, 1962, **83**, 679.

[16] M. Kodama and A. Kimura, *Bull. Chem. Soc. Japan*, 1967, **40**, 1639.

equation (3), $E_{Hg}^{\ominus}$ is the ordinary standard potential [17] and K_{HgL} is defined as $[HgL^{2+}]/[Hg^{2+}][L]$.

According to Reilley *et al.*,[18] an ethylenediaminetetra-acetate anion, edta^{4-}, similarly gives a single well defined anodic wave at a d.m.e. with the half-wave potential expressed in the same form as (3). Hence, the difference in $E_{\frac{1}{2}}$ between edta^{4-} (L′) and the macrocycle systems, $\Delta E_{\frac{1}{2}}$, is as in (4). With the aid of equation (4), log K_{HgL} values were

$$\begin{aligned}\Delta E_{\frac{1}{2}} &= (E_{\frac{1}{2}})_{HgL'} - (E_{\frac{1}{2}})_{HgL} \\ &= 0.0296[\log K_{HgL} - \log K_{HgL'} - \\ &\qquad \log(\alpha_H)_L + \log(\alpha_H)_{L'}] \quad (4)\end{aligned}$$

determined. Here, the reported [19] $K_{HgL'}$ and dissociation constants of H_4edta (at $I = 0.10$ mol dm^{-3}) [20] were corrected to $I = 0.20$ mol dm^{-3} by using the activity coefficients of the ions derived from the Davies relation.[21] The half-wave potential of the edta system, $(E_{\frac{1}{2}})_{HgL'}$, used for the calculation was 0.050 V *versus* the s.c.e., a value measured in an acetate buffer at pH 5.75.[18] The stability constants, K_{HgL}, thus estimated are listed in Table 2. The stability constants measured at several temperatures (15—35 °C) gave thermodynamic parameters (Figure 2) which are summarized in Table 2.

TABLE 2

Comparison of stability constants and enthalpy and entropy of formation of mercury(II) tetra-amine complexes at $I = 0.20$ mol dm^{-3} and 25 °C

Tetra-amine	log H_{HgL} *	$-\Delta H$ * kcal mol^{-1}	ΔS * cal K^{-1} mol^{-1}
3,6NH-od	24.5 ± 0.3	30.2 ± 0.5	10.8 ± 3
3,7NH-nd	22.1 ± 0.3	27.4 ± 0.5	9.1 ± 3
L^1	25.5 ± 0.3	23.6 ± 0.5	37.7 ± 3
L^2	25.3 ± 0.3	24.7 ± 0.5	33.3 ± 3
L^3	23.0 ± 0.3	32.9 ± 0.5	−4.9 ± 3
L^4	23.7 ± 0.3	24.7 ± 0.5	25.5 ± 3

* Uncertainties are the standard deviations.

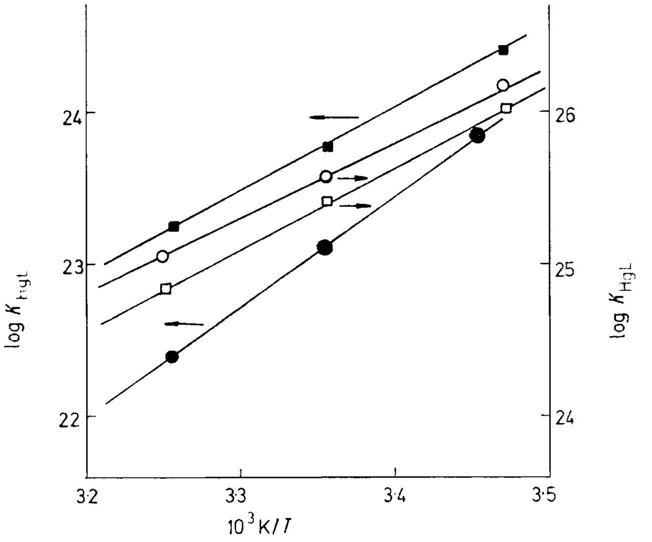


FIGURE 2 Temperature dependence of stability constants (K_{HgL}) for complexes of macrocyclic tetra-amines: (○), L^1; (□), L^2; (●), L^3; (■), L^4

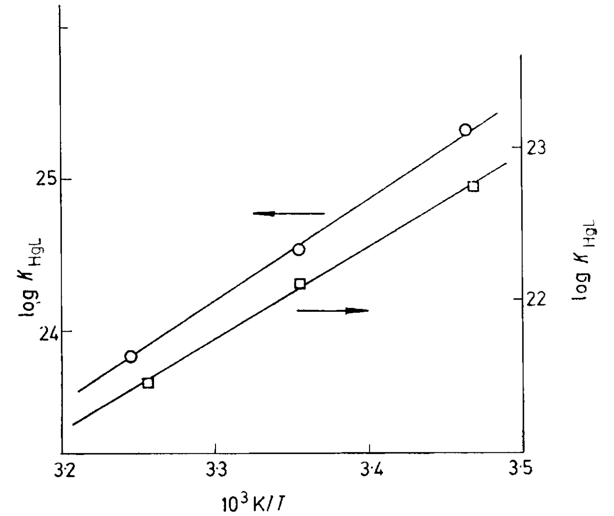


FIGURE 3 Temperature dependence of stability constants (K_{HgL}) for complexes of open-chain tetra-amines: (○), 3,6NH-od; (□), 3,7NH-nd

Stability constants and thermodynamic functions for the open-chain tetra-amines (Figure 3) were determined in an identical manner. The value log K_{HgL} = 24.5 for 3,6NH-od obtained by the present method is in satisfactory agreement with Reilley's value of 25.0 (at $I = 0.10$ mol dm^{-3}).[22] These results are included in Table 2.

DISCUSSION

The stability constants for the 1 : 1 complexes of Hg^{II} with 12—15-membered cyclic tetra-amines are not significantly greater than those for the corresponding open-chain analogues.* This is in contrast to the cases with smaller metal ions, Cu^{II} (ionic radius,[19] 0.72 Å),[1-4,23] Ni^{II} (0.69 Å),[5,6] or Zn^{II} (0.74 Å),[8] where 10^3—10^7-fold stability enhancements (' macrocyclic effect ') [23,24] prevail. One may thus infer that the occurrence of the macrocyclic effect is limited for large metal ions such as Hg^{II} (1.10 Å) which are hardly encircled by the macrocycle tetra-amine rings.[10] However, this does not seem to be generalized, as shown in a separate experiment on Pb^{II} which has an even larger ionic size (1.20 Å) where a 1 : 1 complex of L^1 exhibits a normal 10^5-fold macrocyclic effect.[25] Another feature with the present

---

* Although 3,7NH-nd normally forms more stable complexes than 3,6NH-od with smaller metal ions (P. Paoletti, L. Fabbrizzi, and R. Barbucci, *J.C.S. Dalton*, 1973, 1763), the situation is reversed with Hg^{II}. A referee suggests incomplete amine substitution for reaction of the former ligand.

[17] W. M. Latimer, ' Oxidation Potentials,' Prentice–Hall, Englewood Cliffs, New Jersey, 1959, p. 179.

[18] C. N. Reilley, W. G. Scribner, and C. Temple, *Analyt. Chem.*, 1956, **28**, 450.

[19] D. L. Wright, J. H. Holloway, and C. N. Reilley, *Analyt. Chem.*, 1965, **37**, 884.

[20] T. A. Bohigran and A. E. Martell, U.S. Atomic Energy Commission Contract No. AT(30–1)–1823, Progress Report, 1960.

[21] J. N. Butler, ' Ionic Equilibrium,' Addison–Wesley, Reading, Massachusetts, 1964, p. 437.

[22] C. N. Reilley and R. W. Schmid, *J. Elisha Mitchell Sci. Soc.*, 1957, **73**, 279.

[23] D. K. Cabbiness and D. W. Margerum, *J. Amer. Chem. Soc.*, 1969, **91**, 6540.

[24] For reviews, see D. H. Busch, F. Karmery, V. Goedken, V. Katovic, A. C. Melnyk, C. R. Sperati, and N. Tokel, *Adv. Chem. Ser.*, 1971, **100**, 44; J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, 1974, **74**, 351; L. F. Lindoy, *Chem. Soc. Rev.*, 1975, 421.

[25] M. Kodama and E. Kimura, unpublished work.

mercury(II) complexes is that the stabilities vary little with the ligand ring size as found for the zinc(II) series,[8] which are to be compared with the copper(II) series; *e.g.* the complex of L^2 is 10^4 times more stable than that of L^1.[1-4]

A comparison of the thermodynamic parameters for the stability constants permits further insight. The apparent similarity in K_{HgL} for the macrocyclic and for the open-chain systems results from a combination of less favourable ΔH and of more favourable ΔS for the former (except for L^3). The positive values of ΔS for the mercury(II) macrocycles are not unusual compared with ΔS values for other metal-ion systems characteristic of ligand cyclization.[1-4,8] It is the enthalpy term that prevents Hg^{II} from enjoying a normal macrocyclic effect; the enthalpy loss on ligand cyclization in Cu^{II} and Zn^{II} is only a few kcal mol^{-1},[1-4,8] while in Hg^{II} this term is much bigger, outweighing the normal compensation by the entropy term. The remarkably low heat of reaction with the large metal ion * may be attributed to unusual conformational strain or incomplete chelation due to the steric constraint.

In the reactions between Hg^{II} and the 12—15-membered macrocycles, ΔH does not appreciably change while ΔS slightly decreases as the ring opens (except for L^3). A similar trend is noted for the zinc(II) system; almost invariably ΔH is *ca.* −8 kcal mol^{-1} and ΔS slowly decreases from 47 cal K^{-1} mol^{-1} for L^1 to 41 cal K^{-1} mol^{-1} for L^4.[8]

Among the macrocyclic tetra-amines reacting with Hg^{II}, the 14-membered ligand is unique; its ΔH and ΔS values deviate abruptly from the smooth trends in the series, although the overall free-energy change is similar. This is of interest in view of the normal behaviour of L^3 towards Zn^{II} like the other macrocyclic tetra-amines.[8] Meanwhile, a greater trend towards larger $-\Delta H$ and smaller ΔS relative to the linear ligands was reported for the $[Ni^{II}L^3]$ complex.[5,6] No matter what causes $[Hg^{II}L^3]$ to have such special thermodynamic functions, it should not be the ‘ ligand-solvation effect,’ an explanation advanced for the nickel(II) complex.[5,6,26] It seems inconceivable that this effect operates specifically on L^3 but not on L^2 or L^4. Some as yet unidentified properties attached to the ^{3} structure may be responsible, which we are currently investigating.

[6/629 *Received, 2nd April,* 1976]

---

* For $[Pb^{II}L^1]$ the enthalpy loss is 2 kcal mol^{-1}, which is more than offset by an unusually high ΔS term (51 cal K^{-1} mol^{-1}), resulting in the 10^5-fold macrocyclic effect;[25] 1 cal = 4.184 J.

[26] G. F. Smith and D. W. Margerum, *J.C.S. Chem. Comm.*, 1975, 807.