Chelate-ring Sequence and Enthalpy of Formation of Copper(II) Complexes with Tetra-aza Macrocycles

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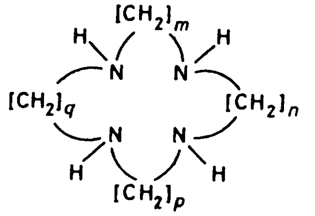
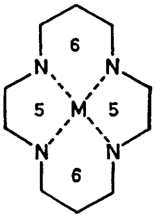
The direct calorimetric determination of the enthalpy of formation of copper(II) complexes with three tetra-aza macrocyclic ligands of different ring size has been made at 25 °C. The enthalpy of formation for complex of 1,4,7,10-tetra-azacyclotridecane is intermediate between those of 1,4,7,10-tetra-azacyclododecane and 1,4,8,11-tetra-azacyclotetradecane (cyclam). The calorimetric results show that the 14-membered macrocycle 1,4,7,11-tetra-azacyclotetradecane(isocyclam) incorporates Cu^{II} ion less exothermically than its more symmetric isomer cyclam and the proposed explanation is the formation of weaker in-plane Cu–N interactions. The introduction of a pyridine ring into the macrocyclic framework further reduces the heat of complexation.

THERE are two main reasons why the solution behaviour of tetra-aza macrocyclic 3*d* metal complexes is of interest from a thermodynamic standpoint: (*i*) their exceedingly higher stability with respect to corresponding complexes with open-chain ligands [the so-called macrocyclic effect[1]: the 14-membered 1,4,8,11-tetra-azacyclotetradecane (L^3 or cyclam) gives 3*d* metal complexes which are several orders of magnitude more stable than those of the corresponding open-chain analogue 3,7-diazanonane-1,9-diamine (2,3,2-tet)];[2,3] (*ii*) the great influence of the size of the macrocyclic hole upon metal complex stability.[4] As regards (*i*), after temperature-dependent equilibrium studies had led to conflicting conclusions, the design of a new calorimetric experiment[5] in this laboratory allowed a definitive assessment of the enthalpy and entropy contributions to the extra stability of macrocyclic complexes (both of them being remarkably more favourable than for complexes of open-chain ligands). Concerning (*ii*), we have demonstrated that the 14-membered macrocycle, cyclam, gives more exothermic complexation with copper(II) ion than the smaller L^1 and larger L^4 macrocycles.

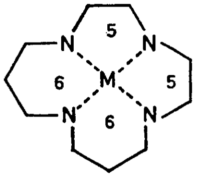


L^1 $m = n = p = q = 2$
L^2 $m = n = p = 2;\ q = 3$
L^3or cyclam $m = p = 2;\ n = q = 3$
L^4 $m = 2;\ n = p = q = 3$

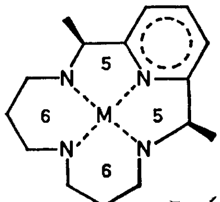
The present calorimetric study on the copper(II) complex of L^2 allows one to fully consider how progressive macrocycle expansion affects the enthalpy of complex formation in the series of 12- to 15-membered ligands. It should be noted that cyclam (L^3), which on complexation gives a series of alternating five- and six-membered chelate rings (sequence: 5,6,5,6), is not the only representative of the 14-membered ligands: we have now synthesized the isomeric ligand (L^5), which forms a different series of chelate rings (sequence: 5,5,6,6): it has been called isocyclam. Thermochemical investigation of isocyclam complexation provides the unique opportunity of evaluating how different in-plane sequential arrangements of nitrogen atoms affect the energy of the metal–donor atom interaction, for macrocycles having approximately the same size. Finally, we also wanted to investigate the reaction of copper(II) with Busch's macrocycle L^6. This is a ligand similar to isocyclam, with the same chelate ring sequence. However, the presence of a sp^2 hybridized pyridine, rather than a sp^3 amine, nitrogen atom, as well as increased rigidity due to the introduction of an aromatic ring into the cyclic framework, are expected to modify the energy of the metal–ligand interactions. Preliminary results of this work have been reported previously.[6]



L^3



L^5



L^6

EXPERIMENTAL

Ligands.—The ligands L^2 and isocyclam (L^5) were synthesized through condensation of the appropriate tosylated segments in basic solution, according to the method described by Richman and Atkins.[7] Experimental details have been reported elsewhere.[8] The ligand L^6 was obtained through nickel(II)-assisted reaction of diacetylpyridine (Aldrich, Europe) and dipropylenetriamine

(Fluka, Purum), according to the procedure of Karn and Busch.[9] The unsaturated co-ordinated macrocycle was hydrogenated with $Na[BH_4]$ in methanol. *Meso* and *rac* diasteroisomers were separated *via* oxalate reactions,[9] and the free ligand was extracted in chloroform, after destruction of the complex by alkaline cyanide solutions.

Complexes.—Copper(II) complexes of the above ligands were prepared as perchlorates by mixing equimolar amounts of ligand and copper(II) perchlorate in ethanol. Elemental analysis of these compounds gave satisfactory agreement with calculated values.

Calorimetric Measurements.—In aqueous solutions of the macrocycles, which are very strong bases, the main species present is the diprotonated form $[H_2L]^{2+}$; the presence of two proximate positive charges causes the insertion of the metal ion into the ligand cavity to be very slow. This problem can be avoided by working in strongly alkaline solution where the macrocycle is uncharged: we therefore studied macrocycle complexation in 1 mol dm^{-3} Na[OH]. Owing to the low solubility (*ca.* 1.5×10^{-4} mol dm^{-3}) of Cu^{II} ion at pH 14, the heat effect of reaction (1) (Table 1) is small, but it can be accurately monitored by a microcalorimetric apparatus. The enthalpy change can be related to that in neutral solution through appropriate dilution experiments (Table 1).

TABLE 1

Enthalpies of formation, $\Delta H^{\ominus}$(aq)/kcal mol^{-1}, of copper(II) complexes with tetra-aza macrocycles, in aqueous solution at 25 °C. The values are calculated from the following cycle

$$\begin{tikzcd}
Cu^{2+}\,(1\ \mathrm{mol\ dm^{-3}\ Na[OH]}) & + & L(1\ \mathrm{mol\ dm^{-3}\ Na[OH]}) \arrow[r, "\Delta H^{\ominus}_1"] & {[CuL]^{2+}}\,(1\ \mathrm{mol\ dm^{-3}\ Na[OH]}) \arrow[d, "\Delta H^{\ominus}_2"] \\
Cu^{2+}(aq) \arrow[u, "\Delta H^{\ominus}_{3}{}^{a}"'] & + & L(aq) \arrow[u, "\Delta H^{\ominus}_{4}{}^{b}"'] \arrow[r, "\Delta H^{\ominus}(aq)"] & {[CuL]^{2+}(aq)}
\end{tikzcd}$$

$$\Delta H^{\ominus}(aq) = \Delta H^{\ominus}_1 + \Delta H^{\ominus}_2 + \Delta H^{\ominus}_3 + \Delta H^{\ominus}_4$$

L	$\Delta H^{\ominus}_1$	$\Delta H^{\ominus}_2$	$\Delta H^{\ominus}$(aq)
L^2	-15.13 ± 0.08	0.38 ± 0.06	-25.6 ± 0.1
L^5, Isocyclam	-17.71 ± 0.06	0.85 ± 0.06	-27.8 ± 0.1
L^6	-13.14 ± 0.06	0.17 ± 0.05	-23.9 ± 0.1

[a] $\Delta H^{\ominus}_3 = -10.9$ kcal mol^{-1}, evaluated as described in ref. 5. [b] Process assumed athermic, see ref. 5.

Calorimetric studies were carried out with a 10700-1 LKB flow microcalorimeter, equipped with a Keithley model 150B microvolt Ammeter. Solutions were injected in the calorimeter by high-precision electronic burettes (Mettler model DV 10) equipped with 50-cm^3 glass cylinders (Mettler model DV-105). The flow rate from each burette was varied by a resistance box and ranged from 4.2 to 6.8 μl s^{-1}. In a typical experiment on reaction (1), a solution of Cu^{II} (1.5×10^{-4} mol dm^{-3}) in 1 mol dm^{-3} Na[OH] (burette A) and a solution of the ligand, or its hydrochloride (1.6×10^{-4} mol dm^{-3}), in 1 mol dm^{-3} Na[OH] (burette B) were injected in the flow apparatus: the flow rates were changed in such a way to have a metal to ligand ratio ranging from 1 to 1.8 : 1. The heat flow per number of moles of Cu^{II} was found to be constant, demonstrating that only the $[Cu(macrocycle)]^{2+}$ complex was formed in the range investigated. The heat effect of reaction (2) was measured from reactions of a neutral solution of a preformed $[Cu(macrocycle)]^{2+}$ complex and solutions of Na[OH] of increasing concentrations: the heat effect did not change with increasing sodium hydroxide concentration. The heat effect for reaction (3) was evaluated previously.[5] The transfer of L from 1 mol dm^{-3} Na[OH] to neutral solution (4) was assumed to be athermic, as previously discussed.[5] Calorimetric responses for reactions (1) and (2) are reported in Table 1.

DISCUSSION

12 to 15-Membered Macrocycles.—It must first be noted that the enthalpy change for the formation of aqueous $[CuL^2]^{2+}$ is remarkable different from that obtained from the temperature dependence of the reduction polarographic half-wave potential to copper amalgam in acetate buffer.[10] Discrepancies between the calorimetric and temperature-dependent data were also found with the L^1 system.[4,10] We believe that the direct microcalorimetric method employed in this and previous works [4,5] is the most appropriate for determining the enthalpy of formation of tetra-aza macrocyclic complexes in aqueous solution, whereas the indirect method employed by other workers involves several sources of error such as the choice of a narrow range of temperature, the drawing of the van't Hoff straight line through only three points, interference from ligand protonation and its temperature dependence, and incomplete reversibility of the electrode process.

It is seen (Table 2) that L^2 reacts less exothermically with copper(II) ion than its higher homologues L^3 (cyclam) and L^4.[5] It has been already proposed [5] that the enthalpy of metal tetra-aza macrocyclic complexes

TABLE 2

Enthalpies of formation (kcal mol^{-1}) of copper(II) complexes with tetra-aza macrocycles in aqueous solution at 25 °C

	$-\Delta H^{\ominus}$		
Macrocycle	calorimetric	non-calorimetric [a]	$\nu(d\text{–}d)$ [b]/cm^{-1}
L^1	22.7 [c]	18.3 [d]	16 810 [c]
L^2	25.6 [e]	29.2 [d]	18 310 [e]
L^3, Cyclam	32.4 [c]	30.4 [d]	19 900
L^4	26.5 [c]	26.5 [d]	17 610 [e]
L^5, Isocyclam	27.8 [e]		18 180 [e]
L^6	23.9 [e]		

[a] Enthalpic values obtained from the temperature dependence of log$K$, polarographically or potentiometrically determined. [b] For the maximum of the absorption band. [c] Ref. 5. [d] Ref. 3 and reference therein. [e] This work.

can be reasonably interpreted in terms of a more or less favourable matching between the size of the metal ion to be incorporated and the amplitude of the ligand cavity. This latter parameter has been evaluated by Busch and his co-workers [11] through conformational arguments and is usually expressed by the ' ideal M–N distance,' *i.e.* the bond distance for a virtual cation dropped in the macrocycle ' relaxed ' to its coplanar arrangement of minimum strain energy. The extent of the exothermicity of copper(II) complexation reflects the extent of agreement of the ' ideal ' M–N distance with the ' experimental ' Cu–N bond distance obtained from *X*-ray analysis of tetragonal copper(II) complexes with polyamines (2.02—2.07 Å).[12] In this connection L^3 gives the most exothermic complexation since it has the appropriate minimized strain aperture (ideal M–N 2.07 Å) [11] to incorporate Cu^{II} ion and to establish the strongest Cu–N co-ordinate bonds. This is also shown by the highest energy shown for the visible *d–d* band, which is an approximate measure of the intensity of Cu–N in-plane interactions.[13]

The ligand L^4 (ideal distance M–N 2.22 Å) [11] seems too large to adequately encircle copper(II) ion in a strain-free configuration. A recent crystallographic study [14] on $[CuL^4][ClO_4]_2$ has shown that the Cu–N distance in this complex is that expected (mean 2.03 Å) for a normal copper(II) polyamine complex, but the decreased size of the macrocyclic hole involves serious sterical contraints in the ligand framework. This is expected to decrease the heat evolved during metal co-ordination.

On the other hand, L^1 has too small a cavity (ideal M–N 1.82 Å) [11] to co-ordinate copper(II). *X*-Ray analysis [15] on $[CuL^1(NO_3)][NO_3]$ has shown that Cu^{II} is removed 0.4 Å above the N_4 plane to give a square-pyramidal chromophore. A similar stereochemistry has been deduced also for the solvated complex, from electronic and e.s.r. spectra.[16] There is no doubt that raising of the Cu^{II} ion above the plane of nitrogen atoms must reduce the energy of Cu–N interactions, and is reflected in a relatively small enthalpy change.

No structural data are available for the $[CuL^2]^{2+}$ complex; the 13-membered ligand has a small cavity size (ideal M–N 1.92 Å) [11] for chelation of Cu^{II} in a coplanar strain-free fashion. It is probable that some raising of the cation out of the N_4 plane occurs also with this complex. This arrangement would account for the heat effect which is smaller than for the perfectly sized cyclam, but also than for L^4 which gives a constrained coplanar co-ordination.

14-Membered Macrocycles.—The different sequence of fused chelate rings (5,5,6,6) in the isocyclam complex causes a dramatic decrease of the enthalpy of formation in water with respect to the 5,6,5,6 sequenced cyclam complex (see Table 2). Furthermore $[CuL^5]^{2+}$ absorbs visible light at a lower energy than its 14-membered isomeric form, suggesting that the less pronounced exothermicity reflects the formation of weaker co-ordinative Cu–N interactions. The different behaviour cannot be obviously explained in terms of the size of the macrocyclic cavity, which must be approximately the same for the two ligands. The two most strained six-membered chelate rings, probably in their preferred chair configuration, in complexed cyclam are *trans* to each other, minimizing their steric repulsions. Steric repulsions must be much greater in co-ordinated isocyclam, where the two six-membered chelate rings are adjacent. This situation could induce some distortion in the macrocyclic framework in the form of displacement of the nitrogen atoms from co-ordination sites preferred by copper(II) ion and/or of a less favourable orientation of their lone pairs. A less symmetric arrangement of the donor atoms in $[CuL^5]^{2+}$, with respect to the cyclam analogue, is also indicated by the considerably larger molar absorption coefficient of the visible band (172 compared with 100 $dm^3\ mol^{-1}\ cm^{-1}$).

Comparison of $[CuL^5]^{2+}$ and $[CuL^6]^{2+}$ complexes which present the same sequence of chelate rings (5,5,6,6) should allow an evaluation of how substitution of an amine group by a pyridine nitrogen atom affects the enthalpy of formation. In fact, L^6 also contains two methyl groups on the aliphatic backbone, but it has been demonstrated by calorimetric studies on copper(II) complexes with *C*-alkyl-substituted ethylenediamines [17] that the presence of groups on the aliphatic chain of the ligand does not affect the enthalpy of complexation.

Insertion of the pyridine ring in the 5,5,6,6 macrocyclic framework involves a decrease of the heat effect of 4 kcal mol^{-1}.* Noticeably smaller differences are observed when simple pyridine (py) and amine complexes (en = ethylenediamine) of copper(II) are compared {*e.g.* $[Cu(NH_3)]^{2+}$, $\Delta H^{\ominus} = -5$; $[Cu(py)]^{2+}$, $\Delta H^{\ominus} = -4$; $[Cu(en)]^{2+}$, $\frac{1}{2}\Delta H^{\ominus} = -6$; $[Cu(py)_2]^{2+}$, $\frac{1}{2}\Delta H^{\ominus} = -4$ kcal mol^{-1}}.[18] Also, when the pyridine nitrogen is inserted in an open-chain multidentate ligand the heat of complexation to copper(II) is only 1—2 kcal mol^{-1} per nitrogen atom lower than the chelating homologue containing all amine groups.[19] Insertion of the pyridine ring in the cyclic framework induces further steric constraints and further reduces the ligand flexibility; as a consequence, the nitrogen atoms of L^6 can be forced into an unnatural co-ordinative arrangement (deviations from the square or unfavourable orientation of donor atoms). This would lead to the formation of weaker and less exothermic Cu–N bonds.

The Enthalpy Macrocyclic Effect.—It is well known that a cyclic structure of the ligand enhances some metal complex properties with respect to the open-chain analogues. Some of these properties are: (*i*) the thermodynamic solution stability ($\Delta G^{\ominus}$ of formation); [1] (*ii*) inertness towards destruction; [20] (*iii*) spectroscopic *Dq* value; [21,22] (*iv*) ease of achievement of higher metal ion oxidation state (less positive $E^{\ominus}$).[23,24]

As regards the enthalpy of complexation, a macrocyclic effect is also noted, in that cyclam reacts more exothermically with copper(II) than the acyclic tetramine 2,3,2-tet ($\Delta H^{\ominus} = -27.7$ kcal mol^{-1}).[25] However,

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* Throughout this paper: 1 cal = 4.184 J.

among macrocycles, the heat effect is approximately the same for isocyclam and smaller for other ligands.

The more exothermic formation of $[\mathrm{Cu(cyclam)}]^{2+}$ with respect to $[\mathrm{Cu(2,3,2\text{-}tet)}]^{2+}$ depends upon the fact that cyclam is perfectly orientated before co-ordination, whereas with the open-chain tetramine, energy has to be expended in folding in order to dispose the donor atoms at the corners of the co-ordination square. The different exothermicity of complexation for cyclic and acyclic ligands was previously ascribed to the different hydration of unco-ordinated ligands.[26] Subsequent studies[22] demonstrated that these conclusions were based on inaccurate results. With tetra-aza macrocycles, when an extremely favourable pre-orientation is not present, owing to a less favourable sequencing of nitrogen atoms (isocyclam) or unsuitable size, the energy saving due to the cyclization is outbalanced by the formation of weaker and less exothermic Cu–N bonds with respect to the open-chain ligand 2,3,2-tet giving a 5,6,5 chelate-ring sequence.

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