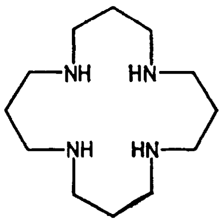
Enthalpic and Entropic Contributions in the Reactions of Hydrogen, Copper(II), and Nickel(II) Ions with the Macrocycle 1,5,9,13-Tetra-azacyclohexadecane

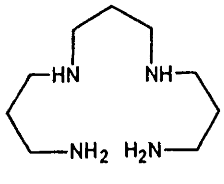
By **Elisabetta Gallori, Emilio Martini, Mauro Micheloni, and Piero Paoletti,*** Istituto di Chimica Generale ed Inorganica, Università di Firenze, and Laboratorio C.N.R., Via J. Nardi 39, 50132 Florence, Italy

Enthalpies of protonation of 1,5,9,13-tetra-azacyclohexadecane (L^1) have been determined by a continuous-titration calorimetric technique and the corresponding entropy values obtained by combination with the free-energy data. The stepwise enthalpies are all very similar, and are interpreted in terms of the ability of the amino-groups to behave independently of each other towards protons. The stability constants of the complexes $[CuL^1]^{2+}$ and $[Cu(HL^1)]^{3+}$ have been determined by potentiometry at 25 °C in 0.5 mol dm^{-3} $K[NO_3]$. The enthalpies of formation of the copper(II) and nickel(II) complexes of L^1 have been determined by batch microcalorimetry, and are discussed in terms of the unfavourable free-ligand conformation and the presence of hindered chelate rings in the complexes. Finally the stability of the $[CuL^1]^{2+}$ complex is compared with that of the corresponding complex with the acyclic ligand 4,8-diazaundecane-1,11-diamine; the greater stability of the former complex is attributed to a very favourable entropy term and to a slightly favourable enthalpy term.

THERE has been intense interest during the last few years in the reactions between metal ions and tetra-aza-cycloalkanes,[1] partly attributed to the fact that the complexes formed can be regarded as simple models for naturally occurring structures found in proteins.[2] The greater thermodynamic stability of macrocyclic complexes in aqueous solution compared with those of analogous acyclic tetramines has been extensively studied and variously attributed to either an entropic or enthalpic effect or a combination of both.[3-7] As part of our systematic study of tetra-azamacrocycles we have investigated the reaction between 1,5,9,13-tetra-aza-cyclohexadecane (L^1) and H^+, Cu^{2+}, and Ni^{2+}. The basicity constants of L^1 under the same experimental conditions have already been reported.[8] The stability constants of the complexes $[CuL^1]^{2+}$ and $[Cu(HL^1)]^{3+}$ have been determined by potentiometry. Two different calorimetric procedures, based on titration calorimetry and batch microcalorimetry, were used to determine the enthalpy of protonation of the ligand and that of formation of the metal complexes, respectively. The results are compared with those obtained with smaller tetra-azamacrocycles[5,9] and with the open-chain analogue 4,8-diazaundecane-1,11-diamine (L^2).[10] Recently, the synthesis and crystal structure of the title compound (L^1) have been reported.[11]



L^1



L^2

EXPERIMENTAL

Reagents.—The compound 1,5,9,13-tetra-azacyclohexadecane (L^1) was prepared following the procedure already described,[11] and was recrystallized from acetonitrile and sublimed twice. The purity of the white crystals obtained was checked by differential scanning calorimetry (d.s.c.) (Found: C, 63.2; H, 12.1; N, 24.4. Calc. for $C_{12}H_{28}N_4$: C, 63.1; H, 12.35; N, 24.55%). The complex $[NiL^1][ClO_4]_2$ was prepared by mixing equimolecular solutions of $Ni[ClO_4]_2 \cdot 6H_2O$ and ligand in hot ethanol (Found: C, 29.6; H, 5.8; N, 11.7. Calc. for $C_{12}H_{28}Cl_2N_4NiO_8$: C, 29.65; H, 5.80; N, 11.55%).

Other Reagents.—Carbon dioxide-free solutions of 0.5 mol dm^{-3} Na[OH], used for e.m.f. measurements, were prepared, stored, and standardized as described elsewhere.[12] A 0.5 mol dm^{-3} potassium nitrate stock solution was prepared from potassium nitrate (C. Erba, ACS grade) without further purification and used as the ionic medium for potentiometric and calorimetric measurements. Stock solutions containing Cu^{II} and Ni^{II} were prepared from solid salts (C. Erba, ACS grade) and standardized by standard gravimetric methods.

E.M.F. Measurements.—The potentiometric measurements were carried out using an Orion model 801 potentiometer, equipped with an Orion model 91-01 glass electrode, a silver–silver chloride electrode, and a salt bridge containing 0.5 mol dm^{-3} potassium nitrate solution. The titration vessel was a seven-necked flask (150 cm^3), thermostatted at 25.0 ± 0.1 °C. A stream of nitrogen, presaturated with water vapour by bubbling it through a 0.5 mol dm^{-3} $K[NO_3]$ solution, was passed over the surface of the solution. For the determination of the equilibrium constants of the Cu^{II}-L^1 system, the cell was filled with 0.5 mol dm^{-3} $K[NO_3]$ (*ca.* 100 cm^3) and various quantities of copper(II) chloride, ligand, and hydrochloric acid; the Na[OH] solution was dispensed from a Metrohm Multidosimat piston burette graduated to 0.01 cm^3. Equilibrium was reached almost instantaneously in the second part of the titration curve; a few minutes were necessary for equilibrium to be attained at the beginning of the titration in the acid region. The experimental values of the e.m.f. have not been corrected for the liquid-junction potential.

The computer program MINIQUAD[13] was used to calculate the equilibrium constants. The criteria adopted in the procedure for selecting the species formed at equilibrium have already been reported.[13-15]

Calorimetric Procedure.—Continuous titration techniques were used to obtain the enthalpies of protonation of L^1. An LKB model 8700 calorimeter was employed, the output voltages of the unbalanced Wheatstone bridge being automatically recorded every 20 s by a Solartron model A. 200 digital voltmeter and a Printina Gay alphanumeric printer. Electrical calibrations were performed both before and after the reaction. The heats of protonation were obtained by introducing the titrant (Na[OH]) into the calorimeter, which contained a solution of the amine in an excess of HCl, at a constant flow rate by means of a specially modified Braun syringe. The same experiment, but with only HCl present, gave a value for the enthalpy of formation of water of 13.54 kcal mol^{-1}.[*] Numerical analysis of the data was handled by means of a computer program,[16] and the enthalpies of protonation of L^1 with their standard deviations are reported in Table 1.

Batch technique. Because the reactions between the nickel ion and tetra-azamacrocycles are too slow to be directly monitored by calorimetry we chose to examine the decomposition of the $[NiL^1]^{2+}$ complex by excess of Na[CN] in strong alkaline solution, *i.e.* $[NiL_n]^{2+} + 4CN^- \rightarrow [Ni(CN)_4]^{2-} + nL$ (where $L = L^1$, $n = 1$). For $L = H_2O$, $n = 6$, the $\Delta H^\ominus$ value has already been reported.[6] An LKB model 10700-2 batch microcalorimeter was used, and a full description of this apparatus, its calibration and its mode of operation for slow reactions has already been reported.[6] In a typical experiment, the solution of the nickel complex (0.005 mol dm^{-3}, 0.4 cm^3) was introduced by weight into one side of the calorimetric cell; the Na[OH]–Na[CN] solution (0.9 mol dm^{-3} Na[OH], 0.1 mol dm^{-3} Na[CN]) (2.30 cm^3) was introduced into the other side using a precision pipette (Pipetman). The calorimeter was allowed to equilibrate overnight until a steady baseline was obtained in the desired sensitivity range and the reaction was then started by mixing the reactants. The reaction was considered to be complete when no further heat effect could be detected, the reaction time being typically 40—45 min. Furthermore, to confirm that the reaction was complete, and that equilibrium had been established, the concentration of $[Ni(CN)_4]^{2-}$ in the reaction mixture was determined spectrophotometrically as soon as the thermal measurements were complete, using the absorption band at 268 nm ($\varepsilon = 1.21 \times 10^4$ dm^3 mol^{-1} cm^{-1}).

Ultraviolet spectral measurements were made on a Varian Cary 17 spectrophotometer equipped with 1 mm path length quartz cells. In all measurements the concentration of $[Ni(CN)_4]^{2-}$ was, within experimental error, equal to the equilibrium value expected. Correction for the enthalpy of dilution of the Na[OH]–Na[CN] solution was made by introducing this solution (2.3 cm^3) into one side of the cell and pure water (0.4 cm^3) into the other.

The same apparatus was used to determine the enthalpy of formation of the $[CuL^1]^{2+}$ complex. The direct reaction between Cu^{2+} and L^1 is fast; the heat involved was measured by mixing an aqueous solution of Cu^{2+} with a solution of the ligand containing Na[OH] in excess. Under the reaction conditions used in the calorimeter, and employing the determined stability constants, the species present and their percentages at equilibrium before and after mixing were calculated by means of the DISPOL[17] computer program. The only significant species present at equilibrium before and after mixing were the free non-protonated ligand and the complex $[CuL^1]^{2+}$ respectively. A correction for the enthalpy of dilution of the Na[OH]–L^1 solution was made for each measurement, following the procedure previously described.

RESULTS AND DISCUSSION

Protonation.—In Table 1 are reported the thermodynamic functions $\Delta H^\ominus$ and $T\Delta S^\ominus$ for the protonation of the ligand L^1 determined at 25 °C in 0.5 mol dm^{-3} $K[NO_3]$. The same parameters for the smaller macrocycles 1,4,8,11-tetra-azacyclotetradecane (L^3) and 1,4,8,12-tetra-azacyclopentadecane (L^4), together with those of the corresponding open-chain analogue L^2, are given for comparison. The macrocycle L^1 exhibits a higher overall basicity than the smaller L^3 and L^4,[18] due to the increased size of the hydrocarbon chain. On the other hand the macrocycle L^1 shows a lower overall basicity than the corresponding open-chain tetramine L^2.[10]

TABLE 1

Thermodynamic quantities of stepwise protonation of L^1 and of some cyclic and acylic tetramines in aqueous solution, at 25 °C in 0.5 mol dm^{-3} $K[NO_3]$

	Step	L^3 [a]	L^4 [a]	L^1	L^2 [b]
log K	1	11.585(5) [c]	11.081(5)	10.85(2) [d]	10.45
	2	10.624(4)	10.381(5)	9.80(2) [d]	9.82
	3	1.61(1)	5.279(6)	7.21(2) [d]	8.54
	4	2.42(1)	3.60(1)	5.69(3) [d]	7.22
log β_4		26.24	30.34	33.55 [d]	36.04
$-\Delta H^\ominus$/kcal mol^{-1}	1	12.3(2)	10.8(1)	10.04(8) [e]	12.20
	2	12.8(1)	12.3(1)	10.7(1) [e]	12.47
	3	2.8(5)	7.22(5)	10.27(8) [e]	11.65
	4	7.7(7)	7.71(6)	10.56(8) [e]	10.88
$T\Delta S^\ominus$/kcal mol^{-1}	1	3.5(2)	4.3(1)	4.8(1)	2.1
	2	1.7(1)	1.9(1)	2.7(1)	1.0
	3	−0.6(1)	0.0(1)	−0.4(1)	0.0
	4	−4.5(1)	−2.8(1)	−2.8(1)	−1.0

[a] Values from refs. 19 and 20. [b] Values from ref. 10. [c] Values in parentheses are standard deviations in the last significant figure. [d] Values of basicity constants were taken from ref. 8. [e] This work.

As far as the protonation enthalpies of L^1 are concerned, the following observations can be made: (*a*) in the first two steps the reaction is less exothermic than that for L^3 in which the first two protons are involved in forming two hydrogen bonds across the inside of the macrocyclic ring[19] with a consequent negative contribution to $\Delta H^\ominus$; (*b*) the enthalpies of the first step for L^1 and L^4 are similar, 10.04 and 10.8 kcal mol^{-1} respectively (protonation of a nitrogen in an *exo* configuration was suggested[19] in the case of L^4 to explain the latter value); (*c*) the stepwise protonation enthalpies of L^1 are all very similar (see Table 1), there being no significant difference between the second and third enthalpies of protonation in sharp contrast with those for smaller macrocycles.[19] We conclude that in the case of L^1 no internal hydrogen bonds are formed in any protonated species. The free amine in solution has all its nitrogens in a configuration in which the lone pairs point in different directions and are able to act independently of each other. It is interesting to note that the first two protonation steps of L^1, involving secondary amino-groups, are less exothermic than the corresponding steps of L^2 where primary amino-groups are protonated first.[20]

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[*] Throughout this paper: 1 cal = 4.184 J.

As far as the entropy contribution is concerned it should be noted that $T\Delta S^\ominus$ decreases regularly, as expected when the degree of protonation of the polyamines increases.[21]

Copper Complexes.—Thermodynamic parameters of copper(II) complexes with L^1 are reported in Table 2, together with $\Delta H^\ominus$ and $T\Delta S^\ominus$ values of the equivalent complex with the acyclic ligand L^2, in which the chelate rings are present in the same alternating ring sequence (6,6,6). The macrocyclic complex is more stable than the acyclic counterpart, due almost entirely to a favourable entropy term (see Table 2), which arises from the fact that the macrocyclic ligand, before co-ordination, is already rigid and preorientated, unlike its acyclic counterpart, and will therefore not lose as much configurational entropy after co-ordination. With respect to the enthalpy contributions, it can be seen that L^1 reacts only slightly more exothermically with the copper(II) ion than does L^2 (0.5 kcal mol^{-1}). If we compare the formation enthalpy of $[CuL^1]^{2+}$ with those of complexes of the smaller macrocycles,[5] we obtain the sequence: $L^3 > L^5 > L^4 > L^6 > L^1$, where L^5 = 1,4,7,10-tetra-azatridecane and L^6 = 1,3,6,9-tetra-azadodecane.

TABLE 2

Thermodynamic parameters,[a] $\Delta H^\ominus$ and $T\Delta S^\ominus$, of formation of copper(II) complexes with ligands L^1 and L^2

Reaction	log *k*	$-\Delta H^\ominus$ kcal mol^{-1}	$T\Delta S^\ominus$ kcal mol^{-1}	Ref.
$Cu^{2+} + L^1 \longrightarrow [CuL^1]^{2+}$	20.92(1)	20.0(3)	8.5(1)	*b*
$Cu^{2+} + H^+ + L^1 \longrightarrow [Cu(HL^1)]^{3+}$	23.48(5)			*b*
$Cu^{2+} + L^2 \longrightarrow [CuL^2]^{2+}$	17.08	19.45(5)	3.8(2)	10
$[CuL^2]^{2+} + L^1 \longrightarrow [CuL^1]^{2+} + L^2$	3.84	0.55	4.7	*c*

[a] Values in parentheses are the standard deviations in the last significant figure. [b] This work. [c] Thermodynamic contributions to the macrocyclic effect.

The complex with L^3 which exhibits the highest enthalpy possesses a good match between ion size and macrocyclic hole with alternating five- and six-membered chelate rings, an arrangement which has previously been found to favour large exothermic enthalpies of formation in complexes of acyclic tetra-amines.[21] The reasons for the lower $\Delta H^\ominus$ values for copper(II) complexes of L^4, L^5, and L^6 have already been discussed.[5] In the case of $[CuL^1]^{2+}$, because L^1 is the largest tetra-azamacrocycle, the match between the size of the metal ion and the macrocyclic hole will be poor and this reduces the in-plane Cu–N interactions, which is reflected spectroscopically in the low value of 10 Dq^{xy} (16 600 cm^{-1}). It must be emphasized that in the structure of solid L^1 the four nitrogens atoms are in a square-planar arrangement with the hydrogen atoms on adjacent nitrogen atoms in *trans* positions;[11] thus for the free ligand to be co-ordinated to metal ions it must reorientate its lone pairs on the nitrogen atoms. This conformational rearrangement is, to some extent, endothermic and will make the overall complexation process less energetically favourable. The unfavourable free-ligand configuration together with the presence in the complex of four hindered six-membered chelate rings produces a net decrease in $\Delta H^\ominus$ of complex formation. Recently, decreases in formation enthalpies of complexes of polyamine ligands due to cumulative ring strain have been reported.[22] In conclusion, the low value of $\Delta H^\ominus$ for formation of $[CuL^1]^{2+}$ can be explained by the contemporaneous effects of many unfavourable contributions: unfavourable free-ligand conformation, a mismatch of the metal-ion size and macrocyclic hole, and hindered six-membered chelate rings.

Protonated Copper Complexes.—The monoprotonated species $[Cu(HL^1)]^{3+}$ has been found and its stability constant measured potentiometrically at 25 °C in 0.5 mol dm^{-3} potassium nitrate (see Table 2). A monoprotonated complex was also found with L^4 and the stability constant determined polarographically.[23] Similar complexes have not been found for macrocycles having smaller ring sizes. The relative easy access of one proton to one of the nitrogen atoms in the complex $[CuL^1]^{2+}$ (log $K = 2.7$) is probably due to the conformational strain of the ligand, which contains hindered six-membered chelate rings, thereby resulting in a weaker Cu–N in-plane interaction and at the same time making a nitrogen lone pair available for the protonation. The stability constants for the reaction $[CuL]^{2+} + H^+ \longrightarrow [Cu(HL)]^{3+}$, even when obtained by different techniques under different experimental conditions, are significantly different, *cf.* log $K = 2.71$ for $L = L^1$ and log $K = 5.52$ when $L = L^4$. It is more interesting to compare the stability constants of the reactions between copper ion and the monoprotonated ligands (HL), $Cu^{2+} + HL^+ \longrightarrow [Cu(HL)]^{3+}$; thus log $K = 12.77$ for $L = L^1$ and log $K = 14.84$ for $L = L^4$. These results can be rationalized in terms of the less favourable configuration of monoprotonated L^1, in which three unprotonated nitrogens must be correctly orientated before co-ordination. This makes the equilibrium constant smaller than that for monoprotonated L^4 where the unprotonated nitrogens are already in the required orientation. Unfortunately, no final conclusions can be drawn since neither enthalpy nor entropy contributions are known.

Nickel(II) *Complexes.*—Nickel(II) complexes of macrocyclic ligands exist in aqueous solution as mixtures of the high-spin (octahedral) and low-spin (square-planar) forms: $[NiL(OH_2)_2]^{2+}$ (high-spin, blue) $\longrightarrow [NiL]^{2+}$ (low-spin, yellow) + $2H_2O$. In the case of the ligand L^1 the amount of the low-spin form, under our experimental conditions, is completely negligible. The enthalpy of formation of the octahedral $[NiL^1]^{2+}$ form is reported in Table 3 together with the formation enthalpies of high-spin nickel(II) complexes with smaller macrocycles.[6,9] The overall trend observed is the same as that in the copper series with $[NiL^3]^{2+}$ and $[NiL^1]^{2+}$ having the largest and smallest enthalpies of formation respectively.

TABLE 3

Enthalpies[a] of formation in aqueous solution at 25 °C of (high-spin octahedral) nickel(II) complexes with tetra-azamacrocycles

Complex	$-\Delta H^{\ominus}$/kcal mol^{-1}	Ref.
$[Ni[12]aneN_4]^{2+}$, $[NiL_6]^{2+}$	11.9(3)	9
$[Ni[13]aneN_4]^{2+}$, $[NiL^5]^{2+}$	20.0(3)	9
$[Ni[14]aneN_4]^{2+}$, $[NiL^3]^{2+}$	24.1(2)	6
$[Ni[15]aneN_4]^{2+}$, $[NiL^4]^{2+}$	17.9(3)	9
$[Ni[16]aneN_4]^{2+}$, $[NiL^1]^{2+}$	9.7(2)	*b*

[a] Values in parentheses are the errors in the last significant figure. [b] This work.

The extremely low enthalpy of formation of $[NiL^1]^{2+}$, 9.7 kcal mol^{-1}, may be compared with the value of 24.1 kcal mol^{-1} found for $[NiL^3]^{2+}$ and cannot be explained in terms of a mismatch of the size of the metal ion and the macrocyclic cavity. The unfavourable conformation of the free ligand L^1 and the ring strain present in the complex $[NiL^1]^{2+}$ are therefore implicated.

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