Solution Chemistry of Macrocycles. Part 4.† Thermodynamics of Protonation and Complexation of several N_2S_2 Macrocycles

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The protonation of six N_2S_2 macrocycles L^1—L^6 and the open-chain ligand 2,13-dithia-6,9-diazatetradecane (L^7) as well as their complexation with Cu^{2+} have been studied by pH titrations, spectrophotometric titrations, and calorimetry at 25 °C and I = 0.5 mol dm^{-3} (KNO_3). The first protonation constant, $pK_{H,1}$, of these ligands is in the range of slightly acidified secondary aliphatic ammonium ions, whereas the second $pK_{H,2}$ is essentially determined by electrostatic factors. So the difference $pK_{H,1} - pK_{H,2}$ is larger for the *cis* than for the *trans* derivatives and decreases with ring size for both *cis* and *trans* compounds. The ligands give mononuclear species $[ML]^{2+}$ with stabilities of $10^{10.6}$—10^{16} dm^3 mol^{-1} for Cu^{2+} and $10^{7.8}$—$10^{9.1}$ dm^3 mol^{-1} for Ni^{2+}. In addition for the 12-membered ligands (L^1 and L^2) and the open-chain ligand L^7 partially hydrolysed species $[CuL(OH)]^+$ are also observed. The Cu^{2+} complex of 1,4-dithia-8,11-diazacyclotetradecane is more stable than that of the open-chain ligand L^7. This extra stability (macrocyclic effect) is due to both favourable enthalpic and entropic terms.

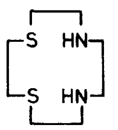
Metal complexes with tetra-azacycloalkanes have attracted the interest of many inorganic chemists because of their marked kinetic inertness,[1] high thermodynamic stability,[2] the possibility of stabilization of high oxidation states,[3] and the possibility for use as simple models for naturally occurring metal–macrocycle centres.[4] In comparison with complexes of analogous open-chain ligands, the macrocyclic complexes show an additional stability and this has been termed the 'macrocyclic effect'.[2] The thermodynamic nature of this effect has been discussed[5] and it has been shown that it is made up of different contributions, among which solvation of the macrocyclic ligand plays an important role.[6]

The protonation of tetra-aza macrocycles has also been carefully studied. There are two high and two low pK_H values,[7] clearly differing from those found in analogous open-chain tetra-amines. The protonation behaviour is similar to that of open-chain ligands only when the ring becomes large (17-membered).[8]

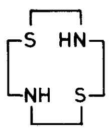
We have now measured the protonation and complexation of a series of N_2S_2 macrocycles (L^1—L^6) which differ in ring size and in the relative arrangement of their donor atoms. The *cis* or the *trans* arrangement of the heteroatoms in the macrocycles makes it possible to study hydrogen bonding between adjacent and distant amino-nitrogens, as well as to see whether the sequence of donors influences the stability of the metal complexes. In addition, one open-chain ligand, L^7, has also been studied for comparison. This study involves the determination of stability constants and the calorimetric measurement of ΔH° values.

Experimental

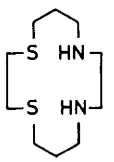
The macrocycles L^1—L^6 were synthesized as described previously.[9] All other reagents were of analytical grade and were used without further purification. The measurements were made at 25.0 ± 0.1 °C and I = 0.5 mol dm^{-3} (KNO_3).



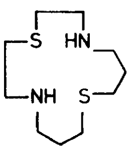
L^1



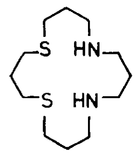
L^2



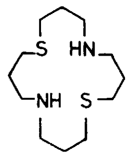
L^3



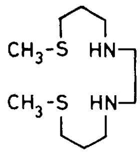
L^4



L^5



L^6



L^7

2,13-*Dithia*-6,9-*diazatetradecane* (L^7).—A solution of 3-methylthiopropylamine (5 g, 48 mmol)[10] and 1,2-dibromoethane (2.05 cm^3, 24 mmol) in absolute EtOH (50 cm^3) was refluxed for 4 d. After cooling to −18 °C, 1.7 g of $L^7 \cdot 2HBr$ were collected. An additional crop (400 mg) was obtained from the mother-liquor by partially evaporating the solvent (total yield 23%). Recrystallization from EtOH, 47% HBr, and a little water gave the pure compound, m.p. 232—233 °C. ^1H n.m.r. (D_2O): 1.6—2.1 (10 H, m + s, 2 CCH_2C + 2CH_3S), 2.5 (4 H, t, 2CH_2S), and 3.0—3.5 (8 H, t + s, 4CH_2N) (Found: C, 30.15; H, 6.55; Br, 39.90; N, 7.10. Calc. for $C_{10}H_{26}Br_2N_2S_2$: C, 30.15; H 6.60; Br, 40.15; N, 7.05%).

Potentiometric measurements were made using our fully automated pH-titration unit,[11] consisting of a Dolphin microprocessor with tape recorder (Microcorder ZE 601), a Metrohm E 655 digital burette, enabling addition of 10-µl aliquots, and a Metrohm E 600 digital pH-meter with a combined UX-electrode. The glass electrode was calibrated with two buffer solutions of pH 4 and 7 and checked daily by titrating a standard mixture of HNO_3 and CH_3CO_2H. The pK_H values of the ligands were determined by titrating 10 or 5 mmol dm^{-3} ligand dihydrochloride or dihydrobromide in 0.5 mol dm^{-3} KNO_3 with 0.4 mol dm^{-3} NaOH. The hydrolysis constants of the copper(II) complexes with L^1, L^2, and L^7 as well

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† Part 3 is ref. 8.

as the stability constants of those with L^2, L^4, L^5, L^6, and L^7 were obtained by titrating a mixture of 2×10^{-3} mol dm^{-3} ligand dihydrochloride and 1.8×10^{-3} or 0.9×10^{-3} mol dm^{-3} Cu^{2+}. In the case of L^5 and L^6, precipitation of $Cu(OH)_2$ occurred at pH > 8.

Potentiometric batch titrations were used to determine the stability of the nickel(II) complexes with L^1—L^4. Mixtures of 2×10^{-3} mol dm^{-3} ligand and 1.8×10^{-3} mol dm^{-3} Ni^{2+} in 0.5 mol dm^{-3} KNO_3 were titrated with NaOH to cover pH values ranging from 4 to 9. These solutions were kept for 3 d in a thermostat and the pH values were then measured. Each curve consisted of 10—12 titration points.

Spectrophotometric measurements were also necessary because of the high stability of the copper(II) complexes with L^1 and L^3. For L^1 a 3.2×10^{-4} mol dm^{-3} ligand solution in 0.5 mol dm^{-3} KNO_3 kept at constant pH (1.51, 1.71, or 1.87, respectively) was titrated with Cu^{2+} so that $[Cu^{2+}]$ varied from 0 to 2.5×10^{-3} mol dm^{-3} using the automatic titration set-up for a Cary 118C instrument as previously described.[12] The stability constant of the copper(II) complex with L^3 was determined by spectrophotometric batch titrations since the complex forms slowly at low pH. A solution of 1×10^{-3} mol dm^{-3} ligand and 0.9×10^{-3} mol dm^{-3} Cu^{2+} was mixed with different portions of NaOH so as to cover the range pH 0.5—3. The solutions were kept for 2 d in a thermostat so as to attain equilibrium and were then examined spectrophotometrically. The calculation of equilibrium constants from potentiometric measurements was done with the program TITFIT,[13] whereas the spectrophotometric measurements were evaluated with SPECFIT.[14]

The calorimetric measurements to determine the heats of protonation were done on a model 8700 LKB calorimeter, using the continuous-titration technique. The apparatus, the experimental procedure, and the computer programs necessary to determine the stepwise enthalpy of protonation have already been reported.[15] The heat of neutralization of water was determined by adding a NaOH solution to a HCl solution in the calorimetric vessel. The value found, 56.5 ± 0.1 kJ mol^{-1}, is in good agreement with the literature.[16] The experimental details of the calorimetric titrations are reported in Table 1.

The enthalpies of metal complex formation were determined by using a model 10700-2 LKB batch microcalorimeter. A full description of the apparatus, its calibration, and the calorimetric procedure have already been reported.[17,18] In a typical experiment an aqueous solution of Cu^{2+} and a solution of the neutralized ligand were mixed. Under the reaction conditions and employing the determined stability constants, the species present and their percentages at equilibrium before and after mixing were calculated by means of the DISPO computer program.[19] The only significant species present at equilibrium before and after mixing were the free non-protonated ligand and the complex $[CuL]^{2+}$, respectively. Blank experiments were carried out to correct for the enthalpy of dilution of the NaOH solution.

Table 1. Experimental details of the calorimetric measurements of the protonation reaction

	Initial quantities				
Titration	Ligand (mmol)	HCl (mmol)	Volume (cm^3)	NaOH added (mmol)	Rate (μmol s^{-1})
1	(L^1) 0.328	0.656	80.65	1.551	1.724
2	(L^1) 0.262	0.524	79.84	0.827	1.724
3	(L^2) 0.328	0.656	80.21	1.034	1.724
4	(L^2) 0.204	0.408	76.53	0.829	1.381
5	(L^3) 0.415	0.830	78.42	1.551	1.724
6	(L^5) 0.257	0.515	78.09	1.570	1.724
7	(L^5) 0.284	0.568	80.65	1.239	1.376
8	(L^6) 0.506	1.012	79.83	1.551	1.724
9	(L^7) 0.441	0.882	79.73	1.551	1.724
10	(L^7) 0.226	0.452	80.50	1.551	1.724

Results and Discussion

The protonation constants and the related thermodynamic properties for the macrocycles L^1—L^6 and for the open-chain ligand L^7 are reported in Table 2. The pK_H values for the first protonation step are typical for secondary amines, although the values for L^1, L^2, and L^4 are at the lowest limit. A similar trend is also observed in the $-\Delta H_1^{\circ}$ values, which are above 42 kJ mol^{-1} for the larger rings L^5 and L^6 and for the open-chain ligand L^7, but somewhat lower for L^1 and L^2. Both could be due to differences in solvation and/or conformation, which might depend on the ring size. The second protonation step ($pK_{H,2}$) clearly is determined by electrostatic effects and by the relative position of the two nitrogens to each other. So the $pK_{H,2}$ values are always lower for the *cis* than for the *trans* compounds of the same ring size and the larger the ring the smaller is the difference $pK_{H,1} - pK_{H,2}$. The enthalpies of protonation for the second step are similar to those of the first. In some cases (L^1 and L^2), however, $-\Delta H_2^{\circ}$ is larger than $-\Delta H_1^{\circ}$. This behaviour has been observed also for tetra-aza macrocycles.[7] Whether this is due to conformational changes during the different protonation steps is difficult to say. Both the overall basicity and exothermicity of the *trans* ligands are greater than those of the *cis* ligands. The entropy decreases on going from the first to the second step as expected when the degree of protonation increases.[20] In comparison with the tetra-aza macrocycles, which have two high and two low pK_H values, the values of the N_2S_2 macrocycles appear normal. This means that probably there are no internal hydrogen bonds which would stabilize one or the other protonated species.

Copper(II) *Complexes.*—The stability constants and the thermodynamic parameters of the copper(II) complexes with the cyclic ligands L^1—L^6 and the open-chain ligand L^7 are given in Table 3. For all ligands the formation of $[ML]^{2+}$ was observed [equation (1)]. Additionally the 12-membered macrocycles L^1

$$M^{2+} + L \rightleftharpoons [ML]^{2+};\ K_{ML} = [ML^{2+}]/[M^{2+}][L] \quad (1)$$

Table 2. Protonation constants and thermodynamic properties of ligands L^1—L^7 at 25 °C and $I = 0.5$ mol dm^{-3} (KNO_3)[a]

Ligand	Step	log K_H	$-\Delta G^{\circ}$/ kJ mol^{-1}	$-\Delta H^{\circ}$/ kJ mol^{-1}	ΔS°/ J K^{-1} mol^{-1}
L^1	1	9.13(1)	52.09(4)	33.9(2)	61.1(8)
	2	5.04(1)	28.74(4)	38.1(2)	−31.4(8)
L^2	1	9.24(1)	52.72(4)	40.0(2)	42.7(8)
	2	6.26(1)	35.73(4)	42.1(2)	−21.3(8)
L^3	1	9.77(2)	55.77(4)	40.5(2)	51.5(12)
	2	5.72(1)	32.64(8)	35.8(2)	−10.5(8)
L^4	1	9.25(2)			
	2	7.95(1)			
L^5	1	10.49(2)	59.87(12)	46.1(2)	46.0(8)
	2	7.74(1)	44.14(4)	44.9(2)	−2.5(8)
L^6	1	9.95(1)	56.78(4)	50.5(3)	20.9(8)
	2	9.09(2)	51.88(12)	47.0(2)	16.3(12)
L^7	1	9.74(2)	55.61(8)	43.2(1)	41.8(4)
	2	6.89(1)	39.33(4)	42.8(1)	−11.7(4)

[a] Values in parentheses, here and in Tables 3 and 4, are the standard deviations in the last significant figure.

Table 3. Stability constants and thermodynamic parameters for the complexation of Cu^{2+} with ligands L^1—L^7 at 25 °C and I = 0.5 mol dm^{-3} (KNO_3)

Ligand	log K_{CuL}	$-\Delta G^{\circ}$/ kJ mol^{-1}	$-\Delta H^{\circ}$/ kJ mol^{-1}	ΔS°/ J K^{-1} mol^{-1}	log $K_{CuL(OH)}$
L^1	14.21(2)	81.09(8)	59.4(8)	72.8(29)	2.79(3)
L^2	12.02(2)	68.62(12)	39.8(4)	96.6(12)	4.76(2)
L^3	15.96(3)	91.09(16)	66.1(8)	83.7(29)	*a*
L^4	13.14(2)	74.98(12)	58.2(8)	56.5(29)	*a*
L^5	10.56(2)				*b*
L^6	10.60(2)				*b*
L^7	11.41(2)	65.10(12)	57.7(4)	24.7(13)	3.67(2)

[a] No $[ML(OH)]^+$ formation up to pH 11. [b] Precipitation of $Cu(OH)_2$ at pH > 9.

and L^2 and the open-chain ligand L^7 give a hydroxo-species [equation (2)] at higher pH.

$$[ML]^{2+} + OH^- \rightleftharpoons [ML(OH)]^+;\ K_{ML(OH)} = [ML(OH)^+]/[ML^{2+}][OH^-] \quad (2)$$

The stabilities of the copper(II) complexes increase from the 12- to the 14- and decrease to the 16-membered ligands for the *cis* as well as for the *trans* compounds. A similar trend has already been observed for tetra-aza macrocycles.[17,18] In addition the complexes with L^1 and L^3 are more stable than the corresponding *trans* ligands (L^2 and L^4). This is mainly due to the well known high stability of a five-membered chelate ring with two nitrogens. For the six-membered chelate ring with L^5 and L^6 no difference between the stabilities of the *cis* and *trans* arrangements are found (Table 3). Comparison of the thermodynamic data of the copper(II) complexes with L^3 and with the corresponding open-chain ligand L^7 gives the value for the 'macrocyclic effect.' The effect is large with $\Delta \log K = 4.55$ and is mainly due to the entropic term ($T\Delta S^{\circ} = 17.6$ kJ mol^{-1}), only partially to the enthalpic term ($-\Delta H^{\circ} = 8.4$ kJ mol^{-1}). Similarly, comparison of the values for $[CuL^1]^{2+}$ (Table 3) and those of the corresponding complex with 3,6-dithiaoctane-1,8-diamine (log $K_{CuL} = 10.911$, $-\Delta H^{\circ} = 67.9$ kJ mol^{-1}, and $\Delta S^{\circ} = -18.9$ J K^{-1} mol^{-1})[21] indicates that it is practically only the entropy term which is responsible for the macrocyclic effect with $\Delta \log K_{CuL} = 4.3$. In these cases, as also for tetra-azacycloalkanes,[22] the cyclization mainly influences the entropy. The entropy values for the formation of the macrocyclic copper(II) complexes (Table 3) are all between 56 and 97 J K^{-1} mol^{-1}, although the structures of the complexes of the 12- and 14-membered macrocycles are probably different,[9] the first ones being five-co-ordinated whereas the other ones are tetragonally distorted octahedral. This is also indicated by the fact that $[CuL^1]^{2+}$ and $[CuL^2]^{2+}$ hydrolyse to $[CuL(OH)]^+$, whereas the complexes with L^3 and L^4 do not. The hydrolysis is accompanied by a shift in the absorption maximum from 622 to 660 nm and from 620 to 687 nm, for L^1 and L^2 respectively.

Table 4. Stability constants [25 °C, I = 0.5 mol dm^{-3} (KNO_3)] and absorption spectra for the nickel(II) complexes with ligands L^1—L^4

		$\lambda_{max.}$/nm (ε/dm^3 mol^{-1} cm^{-1})		
Ligand	log K_{NiL}	$^3A_{2g} \rightarrow {}^3T_{1g}(P)$	$^3A_{2g} \rightarrow {}^3T_{1g}(F)$	$^3A_{2g} \rightarrow {}^3T_{2g}$
L^1	7.80(3)	370(49)	580(35)	>800
L^2	9.07(3)	360(66)	567(28)	>800
L^3	8.91(3)	353(53)	567(24)[a]	>800
L^4	8.32(4)	375(32)	585(17)[b]	>800

[a] Additional band at 443 nm (20 dm^3 mol^{-1} cm^{-1}). [b] Shoulder at 625 nm.

Nickel(II) *Complexes*.—The stability constants and the absorption spectra of the nickel(II) complexes are given in Table 4. First we note that the larger macrocycles L^5 and L^6 do not form complexes with Ni^{2+} in aqueous solution. They are too weak and hydrolyse to $Ni(OH)_2$. The other macrocycles L^1—L^4 give complexes with stabilities of $10^{7.8}$—$10^{9.1}$ dm^3 mol^{-1}. When compared to those of N_4 macrocycles they are relatively weak and no large discrimination is found when the ring size is varied. The absorption spectra of all the nickel(II) complexes are typical of octahedral geometry, indicating that solvent is probably involved in co-ordination. The ligand field of the N_2S_2 macrocycles is too weak to give the low-spin square-planar form found with many N_4 macrocycles. However, in the case of L^3 a weak band at 443 nm could be due to the presence of a small quantity of the square-planar form. For the nickel(II) complexes of the 14-membered ligands the stability of the *cis* isomer is higher than that of the *trans* and the explanation is similar to that proposed for the copper(II) complexes. On the other hand for the 12-membered ligands the *trans* macrocycle L^2 gives a more stable complex than L^1. With the paucity of data available, it can only be hypothesized that for the complex with the 12-membered ligand the Ni^{2+} does not sit in the cavity of the macrocycle, but the ligand folds to give a *cis*-octahedral structure.[23] Thus it would seem that the folding of the macrocycle with the *trans*-N_2S_2 arrangement could take place more readily than that with the *cis*-N_2S_2 arrangement.

Acknowledgements

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