Stability of Complexes of the Macrocycles 1,5,9,13-Tetraazacyclohexadecane and 1,4,7,11-Tetraazacyclotetradecane with Metal Ions. Effect of Large Hole Size and of Chelate Ring Sequence

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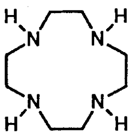
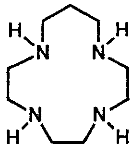
A glass-electrode study of the formation constants of [16]aneN_4 (1,5,9,13-tetraazacyclohexadecane) and isocyclam (1,4,7,11-tetraazacyclotetradecane) with several metal ions is reported. The formation constants, log K_1, for the complexes of [16]aneN_4 at 25 °C and in 0.1 mol dm^{-3} $NaNO_3$ are: Zn^{II}, 13.02; Cd^{II}, 12.65; Pb^{II}, 9.29. With isocyclam, log K_1 at 25 °C in 0.1 mol dm^{-3} $NaNO_3$ is: Zn^{II}, 15.44; Cd^{II}, 11.84; Pb^{II}, 10.86. A spectroscopic study of the copper(II) complex of isocyclam at 25 °C in 0.5 mol dm^{-3} $NaNO_3$ gave log K_1 as 27.3. The surprising result of the complexes of isocyclam being of almost identical stability to those of cyclam (1,4,8,11-tetraazacyclotetradecane) is discussed, as is the pattern of complex stability of the tetraaza macrocycles as a function of macrocyclic ring size.

Size-match selectivity[1] has been much used in rationalising the patterns of formation constants of complexes of macrocyclic ligands with metal ions. This is the idea that the metal will form its most stable complex with the member of a set of macrocycles where the match between the cavity in the macrocycle and the size of the metal ion is closest. In expectation of confirming this idea for the tetraaza macrocycles, we measured[2,3] the formation constants of some of the metal ions Cu^{II}, Ni^{II}, Zn^{II}, Cd^{II} and Pb^{II} with the ligands [12]aneN_4 through [15]aneN_4. The results obtained led to the realisation[2] that the macrocyclic cavity was not of great importance in controlling metal-ion size selectivity. The tetraaza macrocycles are too flexible for macrocyclic cavity size to be an important factor.[4] Several conformers of the macrocyclic complex occur, in some of which the metal ion is co-ordinated lying out of the plane of the macrocycle, and in this situation the factors controlling selectivity are the same as those in open-chain ligands, namely the size of the chelate ring.[4–7] This work did not include the formation constants for the ligand [16]aneN_4 (1,5,9,13-tetraazacyclohexadecane), which has the largest cavity of the tetraaza macrocycles if we limit chelate-ring size in the complexes to a maximum of six-membered. The best-fit M–N length for co-ordination to [16]aneN_4 has been calculated to be 2.38 Å by De Hayes and Busch[8] using molecular mechanics. The macrocycle [16]aneN_4 should therefore fit Cd^{II} almost exactly with its M–N bond lengths of 2.35 Å. It is thus of interest to see whether there is any sign that the larger metal ions Cd^{II} (octahedral ionic radius 0.95 Å[9]) and Pb^{II} (ionic radius 1.18 Å[9]) show any peak in stability with the larger cavity macrocycle.

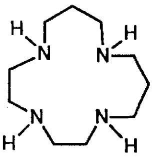
In order to obtain a more complete picture of complex stability of the tetraaza macrocycles with the above set of metal ions, it was decided to measure the formation constants of complexes of Pb^{II} and Cd^{II} with [16]aneN_4, to supplement those for Cu^{II},[10,11] Ni^{II}[10,12] and Zn^{II} (ref. 13) in the literature. The formation constant of the complex between Zn^{II} and [16]aneN_4 was also determined as a check on our potentiometric techniques. Isocyclam (1,4,7,11-tetraazacyclotetradecane) has been found to form complexes with Cu^{II} which appear, on the basis of the enthalpy of complex formation, to be less stable than those formed by cyclam (1,4,8,11-tetraazacyclotetradecane) itself.[14] This has been attributed[14] to the sequence of chelate-ring size in isocyclam complexes being such as to lead to greater steric strain in the M–N bonds and hence less stable complexes.



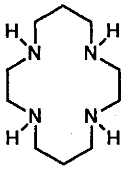
[12]aneN_4



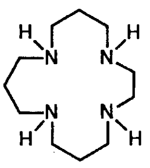
[13]aneN_4



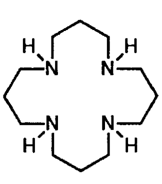
Isocyclam



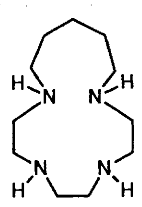
cyclam



[15]aneN_4



[16]aneN_4



[15]ane$N_4$8

There are little data, apart from a formation constant for Co^{II},[15] to confirm that metal ions in general form complexes with isocyclam which are less stable than those of cyclam. The formation constants of complexes of Cu^{II}, Zn^{II}, Cd^{II} and Pb^{II} with isocyclam are also reported here.

Experimental

The ligands isocyclam and [16]aneN_4 were synthesised by literature methods.[14,16,17] The rate of equilibration for the complexes of Pb^{II} and Cd^{II} was, as found[2] with cyclam itself, rapid, and straightforward glass-electrode potentiometry yielded the formation constants, which are reported in Table 1 in 0.1 mol dm^{-3} $NaNO_3$ at 25 °C. Zinc(II) equilibrated fairly slowly in titrations with isocyclam and [16]aneN_4, but not so slowly as to render conventional glass-electrode potentiometry

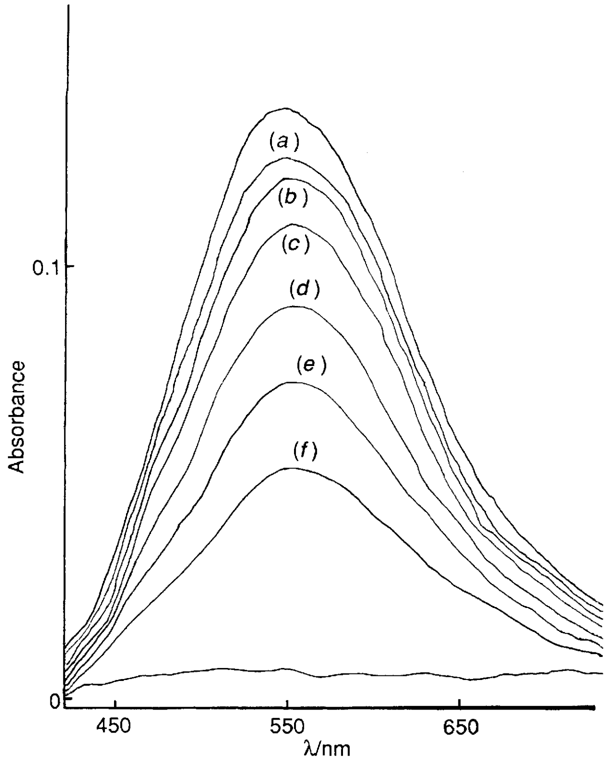


Fig. 1 Variation of the electronic spectra of solutions of 8.33 × 10^{-4} mol dm^{-3} Cu^{II} and 1.50 × 10^{-3} mol dm^{-3} isocylam with acid concentration, after equilibration for 6 weeks. The lowest trace is for Cu^{2+} with no ligand added and the uppermost is for the fully formed complex. The calculated pH for the other solutions is 1.510 (*a*), 1.301 (*b*), 1.000 (*c*), 0.824 (*d*), 0.699 (*e*) and 0.600 (*f*)

impractical, with equilibration times of the order of 30 min being required for each titration point. For Cu^{II} the rate of equilibration of the isocyclam complex was slow, and the formation constant was determined by an out-of-cell spectrophotometric approach similar to that used[2] for cyclam. A set of solutions containing in total 8.33 × 10^{-4} mol dm^{-3} Cu^{II}, 1.50 × 10^{-3} mol dm^{-3} isocyclam, total acid concentrations ranging from 6 × 10^{-3} up to 0.25 mol dm^{-3}, and sufficient $NaNO_3$ to keep the total ionic strength at 0.5 mol dm^{-3} was allowed to equilibrate in sealed volumetric flasks in a water-bath thermostatted to 25.0 °C. Electronic spectra of samples of the solutions were recorded after 1 week, 1 month and 6 weeks. The spectra of the solutions changed slightly from 1 week to 1 month, but the 1 month and 6 week spectra were virtually identical, and it was assumed that equilibrium had been reached. The band at 550 nm is due to the copper(II) complex with isocyclam,[14] and its intensity was used to calculate the formation constant together with the reported[10] protonation constants for isocyclam at an ionic strength of 0.5 mol dm^{-3}. In Fig. 1 is seen the variation of the electronic spectra of the solutions of Cu^{II} and isocyclam as a function of pH.

The protonation constants of isocyclam and [16]aneN_4 have been extensively reported in the literature, and the values have been critically evaluated.[19] Values of the protonation constants of [16]aneN_4 are available at ionic strengths I of 0.1[11] and 0.5 mol dm^{-3},[10,13] and are available for isocyclam at I = 0.1[15] and 0.5 mol dm^{-3}.[14] Since measurement of the first two protonation constants requires considerable effort because of the poorer electrode responses at these high pH values, it was decided to use the pK_a values critically selected by Martell and Smith[19] for the purposes of calculating formation constants. However, as part of the process of standardising the ligands by pH titration, the lower third and, in the case of [16]aneN_4, fourth pK_a values were measured at I = 0.1 mol dm^{-3}, and are reported here. As seen in Table 1, these are in reasonably good agreement with the reported values, except for the third pK_a value for isocyclam as compared with the value reported by Kodama and Kimura.[15] Since our value is in good agreement with that reported by Michaloni and Paoletti[13] at I = 0.5 mol dm^{-3}, we have used it in preference to the reported[15] value. The calculation of the formation constants from the glass-electrode potentiometric data was carried out with the program EQUILIBRIA,[20] using the protonation constants for isocyclam, pK_1 = 10.93, pK_2 = 9.86 and pK_3 = 4.01, and for [16]aneN_4, pK_1 = 10.64, pK_2 = 9.49, pK_3 = 7.06 and pK_4 = 5.30.

Table 1 Protonation and formation constants for [16]aneN_4 and isocyclam measured in this work, together with literature values for comparison[a]

Equilibrium[b]		log K	log K (literature)	
L = isocyclam	M	I = 0.1 mol dm^{-3}	I = 0.1	0.5 mol dm^{-3}
$H + L \rightleftharpoons HL$			10.93[c]	11.1[d]
$H + HL = H_2L$		9.86(2)	9.86[c]	10.04[d]
$H + H_2L = H_3L$		4.01(2)	3.20[c]	4.17[d]
$M + L = ML$	Cu^{II}	27.3(1)		
$M + L = ML$	Zn^{II}	15.44(4)		
$M + L = ML$	Cd^{II}	11.84(3)		
$M + L = ML$	Pb^{II}	10.86(3)		
$M + L = ML$	Co^{II}		10.9[e]	
L = [16]aneN_4				
$H + L = HL$			10.64[f]	10.70[g]
$HL + H = H_2L$			9.49[f]	9.65[g]
$H_2L + H = H_3L$		7.06(2)	6.77[f]	7.06[g]
$H_3L + H = H_4L$		5.30(2)	5.25[f]	5.54[g]
$M + L = ML$	Cu^{II}			20.92[h]
$M + L = ML$	Ni^{II}			13.23[i]
$M + L = ML$	Zn^{II}	13.02(6)		13.05[j]
$M + L = ML$	Cd^{II}	12.65(7)		
$M + L = ML$	Pb^{II}	9.29(8)		
$ML + OH = ML(OH)$	Pb^{II}	4.7(1)		

[a] At 25 °C. [b] For simplicity charges have been omitted, so that H is the proton, L the ligand, M the metal ion indicated and OH the hydroxide ion. [c] Ref. 15. [d] Ref. 14. [e] Ref. 15, I = 0.2 mol dm^{-3} and 35 °C. [f] Ref. 11. [g] Ref. 10 and 13. [h] Ref. 10. [i] Ref. 18. [j] Ref. 13.

Results and Discussion

In Table 1 are seen the formation constants reported here for complexes of isocyclam and [16]aneN_4, together with the available literature values. In Table 2 are shown formation constants for complexes of the set of tetraaza macrocycles [12]aneN_4 through [16]aneN_4, plus isocyclam, which we have selected as the best currently available.

Fig. 2 shows how the stability of the complexes of the tetraaza macrocycles varies as a function of macrocyclic ring size for each metal ion. This is represented as the change in complex stability, Δ log K, which is log K_1 for the complex of the particular tetraaza macrocycle, minus log K_1 for the [12]aneN_4 complex, for each metal ion. This allows one to compare readily the way each metal ion responds to change in macrocyclic ring size. As has been contended previously,[2-7] the overall stability pattern for the tetraaza macrocycles from [12]aneN_4 through [16]aneN_4 does not accord with the idea of a size-match selectivity. The pattern in Fig. 2 is dependent on metal-ion size, with the points for the cyclam complexes occupying a pivotal position. As the metal ion becomes smaller, so the increase in log K_1 from the [12]aneN_4 to the cyclam value becomes steeper. It is steepest for the low-spin Ni^{II}, peaking strongly at the cyclam point, even though a careful evaluation of crystallographic data[26] shows that the low-spin Ni^{II} would fit best from the bond length point of view into [13]aneN_4 rather than cyclam. With Zn^{II} there is a gradual decrease in complex stability as the size of

Table 2 Compilation of formation constants for complexes of the set of tetraaza macrocycles [12]aneN_4 through [16]aneN_4, plus isocyclam[a]

		log K_1						
M	I/mol dm^{-3}	[12]aneN_4	[13]aneN_4	[14]aneN_4	[15]aneN_4	[16]aneN_4	Isocyclam	Ref.
Cu^{II}	0.1			27.2				21
	0.2				24.4			22
	0.5	23.29	24.36	26.5		20.92	27.3	2, 10*b*
Ni^{II}	0.1	14.0	17.90	20.0				3, 23
(S = 0)	0.5				16			3
Ni^{II}	0.1	16.4	17.08	19.6				3, 23
(S = 1)	0.5				18.38	13.23		18
Co^{II}	0.2[c]	13.8	14.28	12.71			10.9	15
Zn^{II}	0.1					13.02	15.44	*b*
	0.2	16.2	15.6	15.5	15.0			24
	0.5		15.74	15.34	15.35	13.05		13
Cd^{II}	0.1		12.71	11.23	12.10	12.65	11.84	2, 25*b*
	0.2	14.3						24
Pb^{II}	0.1		13.48	10.83	10.12	9.29	10.86	2, 25*b*
	0.2	15.9						24

[a] At 25 °C. [b] This work. [c] At 35 °C.

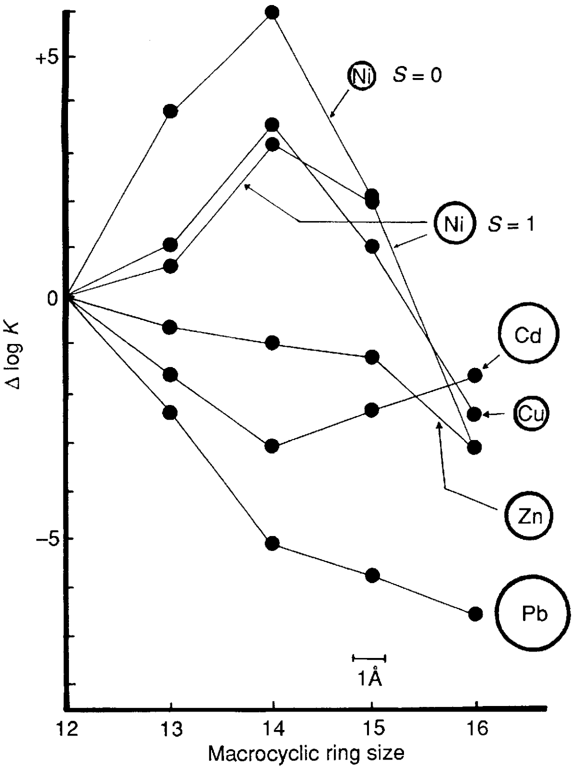


Fig. 2 Variation of complex stability as a function of macrocyclic ring size for a variety of metal ions with the tetraaza macrocycles [12]aneN_4 through [16]aneN_4. The variation has been represented as the change in complex stability, Δ log K, relative to log K_1 for the complex with [12]aneN_4 for each metal ion; formation constants from Table 2. The metal ions are shown inside circles of radius proportional to their ionic radii[9] (octahedral radii except for Cu^{II}, for which the square-planar radius is used)

the macrocyclic ring increases, with no peak in stability at [15]aneN_4, which should fit it best from the bond length point of view. The larger metal ions Cd^{II} and Pb^{II} show a strong decrease in complex stability from [12]aneN_4 to cyclam, which in the case of Pb^{II} persists even up to [16]aneN_4. This behaviour fits extremely well the proposal[2–7] that what is really controlling complex stability in the [12]aneN_4 to [14]aneN_4 part of the diagram is the size of the chelate rings formed in the complexes. The six-membered chelate rings accommodate small metal ions better, and large metal ions fit better into five-membered chelate rings. The point of interest here is what is happening to complex stability when macrocyclic ring size increases beyond 14-membered in the region cyclam to [16]aneN_4. The drop in complex stability for the smaller metal ions probably relates to steric crowding problems. It is no steeper[27] than the drop observed for the non-macrocyclic analogues with increasing chain length, and so one can plead no special effect of the macrocyclic ring. Cadmium(II) is of special interest in that it alone shows an increase in complex stability from [14]aneN_4 to [16]aneN_4. This might possibly reflect an influence of macrocyclic hole size, in that Cd^{II} should fit best into [16]aneN_4. However, it has been noted[28] that with open-chain polyamines, and with the series of tetraaza macrocycles which form three five-membered chelate rings plus one chelate ring which varies monotonically in size from five- ([12]aneN_4) up to eight-membered ([15]ane$N_4$8), Cd^{II} shows a much smaller drop in complex stability with increase in chelate ring size than do other metal ions. This may relate to the tendency of Cd^{II} to form a smaller tetrahedral ion, which would co-ordinate better to the six-membered chelate rings. What one might be seeing in series of complexes of Cd^{II} where chelate ring size is greatly increased, or the numbers of larger chelate rings are increased, is a progressive change from octahedral to tetrahedral co-ordination.

The results for log K_1 for the isocyclam complexes in Table 2 are rather surprising. For all of the metal ions, except Co^{II},[15] the formation constants of the isocyclam complexes are virtually identical to those of the cyclam complexes. This suggests, contrary to what has generally been believed, that the ring sequence in isocyclam does not have an unfavourable effect on the stability of its complexes. This is probably not too surprising for the complexes of Cd^{II} and Pb^{II} which are large and must lie well outside the macrocyclic ring, with more ionic M–L bonding, and Zn^{II} is rather flexible in its bonding arrangements, readily forming trigonal-bipyramidal, octahedral or tetrahedral complexes. However, the result is a little surprising for Cu^{II}. Preliminary studies using molecular mechanics calculations suggest that the lowest-energy conformer (a $++--$ conformer[4]) found for $[Cu(isocyclam)]^{2+}$ is some 8 kJ mol^{-1} higher in strain energy than the lowest-energy conformer for $[Cu(cyclam)]^{2+}$. This is not a great difference in energy, and possibly further work will show that even lower-energy conformers of the isocyclam complex exist, thus accounting for the small effect of altering the ring sequence in isocyclam on complex stability as compared to cyclam.

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