47. Metal Complexes of Pentadentate Macrocyclic Ligands Containing Oxygen and Nitrogen as Donor Atoms

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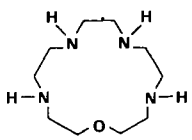
Four macrocyclic ligands have been synthesized: 1-oxa-4,7,10,13-tetraazacyclopentadecane (**1**), 1,4-dioxa-7,10,13-triazacyclopentadecane (**2**), 1,4-dioxa-7,11,14-triazacyclohexadecane (**3**), 1,4-dioxa-7,11,15-triazacycloheptadecane (**4**), one of them, **3**, for the first time. The protonation constants of the ligands and the stability constants of the complexes formed by the four ligands with some divalent first-series transition-metal ions, Cd^{2+} and Pb^{2+}, were determined by potentiometric methods, in aqueous solution, at 25° and $I = 0.10$M (KNO_3). The sequence of protonation of ligand **1** was studied by ^{1}H-NMR spectroscopy. The *Irving-Williams*' order of stability is obeyed for the complexes of all the ligands, and the metal complexes of **1** present the higher values of stability. A drop in the stability of all the metal complexes studied is observed when the metal complexes of **1** are compared with the corresponding complexes of **2**. The effect of the increase of the ring size of the macrocycle can be observed for metal complexes of the series of ligands **2–4**, where, in spite of the slight increase of the overall basicity of the ligands (20.28, 22.25, and 24.96 for **2**, **3**, and **4** respectively), small differences in stability are found for the corresponding complexes of **2** and **3**, but a significant drop occurs for all the metal complexes formed with the 17-membered ligand, specially for the larger metal ions like Mn^{2+} and Pb^{2+}.

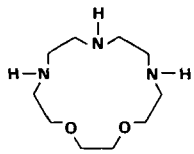
Introduction. – The ability to predict the selectivity of metal complexes is of great interest in many fields, as in analytical chemistry for the selective separation or determination of metals [1] [2], in medicine for the treatment of metal intoxications [3] or for imaging and therapy agents [4] [5]. In the last few decades, many works have been published on metal complexes using macrocyclic ligands, but, contrary to the conclusions of the first studies on this subject which suggested that metal ions were most strongly complexed in the case of closest match between the size of the metal ion and the cavity of the macrocycle (size-match selectivity) [6], the prediction of the selectivity is much more complicated, as many other factors are generally to be considered [7] [8]. It is known that even minor variations in the structure of the macrocycle may lead to considerable differences in the behavior of the metal complexes that cannot be anticipated.

Our aim is to understand the factors which control the selectivity of metal complexes formed by simple macrocyclic ligands. Although a very large volume of work has been published on tetraaza-macrocyclic ligands (especially the 14-membered ligands) [9], and some research has been made on metal complexation of pentaaza-macrocyclic ligands [10], much less information is available on ligands containing both oxygen and nitrogen as donor atoms, especially in the case of larger ring systems. In the present work, we have synthesized four potentially pentadentate ligands, **1–4**, and studied their stability with several divalent first-series transition-metal ions. We are mainly interested in studying the effect of the replacement of N-atoms by O-atoms in the macrocyclic ring and the

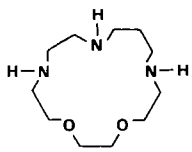
increase of the size of the cavity in the selectivity of the complexes. *Hancock et al.* [2] [11] have determined the stability constants of the complexes of Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} with ligands **1** and **2**. We extended those determinations to the complexes of Mn^{2+}, Fe^{2+}, and Co^{2+}, and also to the complexes of larger cavity size **3** and **4**.



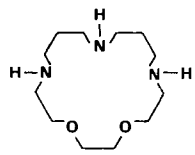
1 (1-Oxa-4,7,10,13-tetraazacyclopentadecane ([15]aneN$_4$O))



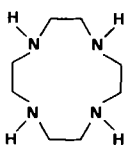
2 1,4-Dioxa-7,10,13-triazacyclopentadecane ([15]aneN$_3$O$_2$))



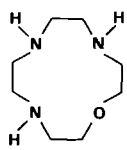
3 1,4-Dioxa-7,11,14-triazacyclohexadecane ([16]aneN$_3$O$_2$))



4 1,4-Dioxa-7,11,15-triazacycloheptadecane ([17]aneN$_3$O$_2$))



5 (1,4,7,10-Tetraazacyclododecane ([12]aneN$_4$; *cyclen*))



6 (1-Oxa-4,7,10-triazacyclododecane ([12]aneN$_3$O))

Experimental. – *Reagents.* *N*-(2-aminoethyl)propane-1,3-diamine (97%), bis(3-aminopropyl)amine (98%) were obtained from *Aldrich Chemical Co.*; diethyleneglycol and NaH from *Merck*; diethylenetriamine and triethyleneglycol from *BDH*. All of them were used as supplied without further purification. All the other chemicals used were of reagent-grade, and org. solvents were purified by standard methods [12].

Synthesis and Characterization of the Ligands. Compounds **1–4** were synthesized in two steps. In the first one, cyclization process, the cyclic compounds protected with *p*-toluenesulfonyl groups (Ts = tosyl) on the N-atoms were obtained, following a modified method of *Richman* and *Atkins* [13] [14]. In the second step, the protected groups were removed by a reductive alkaline cleavage (Na/Hg) in buffered MeOH solution [15–17].

The *N*-tetratosyl derivative of **1** was prepared by condensation of disodium salt of 3,6,*N*,*N*′-tetra(*p*-toluenesulfonyl)-3,6-diazaoctane-1,8-diamine (0.025 mol; 19.12 g) with 1-*O*,5-*O*-di(*p*-toluenesulfonyl)-3-oxapentane-1,5-diol (0.025 mol; 10.36 g), in 125 ml of dry DMF at 110° for 6 h. The disodium salt was obtained immediately before the reaction by addition of NaH (0.1 mol) in dry DMF (30 ml) to a soln. of 3,6,*N*,*N*′-tetra(*p*-toluenesulfonyl)-3,6-diazaoctane-1,8-diamine (0.025 mol) in DMF (125 ml), under N_2. The soln. of the 1-*O*,5-*O*-di(*p*-toluenesulfonyl)-3-oxapentane-1,5-diol was added slowly, dropwise, within 3 h. At the end of the reaction, the soln. was filtered off and concentrated to 1/10 of the initial volume and then slowly poured into crushed ice. The product then precipitated was washed with warm water (60°), 5M NaOH, and H_2O again. The pure tetratosylated cyclic amine was obtained after recrystallization from toluene/hexane. Yield 82.0%. ^{1}H-NMR ($CDCl_3$, TMS): 2.44 (*s*, 12 H); 3.28 (*s*, 4 H); 3.31 (*m*, 8 H); 3.57 (*t*, 4 H); 7.31 (*m*, 8 H); 7.69 (*m*, 8 H). The *N*-tosyl derivatives of **2–4** were synthesized by the same method, but using 1,*O*,8-*O*-di(*p*-toluenesulfonyl)-3,6-dioxaoctane-1,8-diol (0.025 mol, 11.5 g) instead of the 1-*O*,5-*O*-di(*p*-toluenesulfonyl)-3-oxapentane-1,5-diol and disodium salt of 3,*N*,*N*′-tri(*p*-toluenesulfonyl)-3-azapentane-1,5-diamine (0.025 mol, 14.2 g) for the derivative of **2**, of 3,*N*,*N*′-tri(*p*-toluenesulfonyl)-3-azahexane-1,6-diamine (0.025 mol, 14.5 g) for the derivative of **3**, and of 4,*N*,*N*′-tri(*p*-toluenesulfonyl)-4-

azaheptane-1,7-diamine (0.025 mol, 14.84 g) for the derivative of **4**, respectively, instead of the disodium salt of the 3,6,*N*,*N'*-tetra(*p*-toluenesulfonyl)-3,6-diazaoctane-1,8-diamine. Compound **2**·3Ts was recrystallized from CH_2Cl_2. Yield 78.4%. ^{1}H-NMR ($CDCl_3$): 2.40 (*s*, 3 H); 2.43 (*s*, 6 H); 3.25–3.29 (*m*, 8 H); 3.37 (*t*, 4 H); 3.48 (*s*, 4 H); 3.57 (*t*, 4 H); 7.32, 7.33 (*d*, 6 H); 7.70–7.82 (*m*, 6 H). Compound **3**·3Ts was recrystallized from toluene/hexane (yield: 71.5%). ^{1}H-NMR ($CDCl_3$): 1.96 (*q*, 2 H); 2.38, 2.39 (*d*, 9 H); 3.02 (*t*, 4 H); 3.08 (*t*, 4 H); 3.31 (*m*, 8 H); 3.50 (*s*, 4 H); 3.56 (*t*, 4 H); 7.28 (*m*, 6 H); 7.69 (*m*, 6 H). Compound **4**·3 Ts was recrystallized from CH_2Cl_2. Yield 78.5%. ^{1}H-NMR ($CDCl_3$): 1.95 (*q*, 4 H); 2.40 (*s*, 9 H); 3.11–3.24 (*m*, 12 H); 3.53 (*s*, 4 H); 3.60 (*t*, 4 H); 7.28 (*m*, 6 H); 7.66 (*m*, 6 H).

The Ts groups were removed under reductive alkaline cleavage. In a typical reaction, **1** was obtained as follows: a mixture of the tosylated cyclic amine (2.0 g), anh. disodium phosphate (4.96 g), and 2% Na/Hg (96 g) in dry MeOH (40 ml) was rapidly stirred and heated to reflux for 21 h, under N_2. The Hg was then decanted from the slurry, the soln. filtered off, concentrated almost to dryness, and H_2O (20 ml) was added. The mixture was extracted with $CHCl_3$ (5 × 25 ml), the org. layer concentrated and then extracted with 5M HCl. The required cyclic amine was precipitated from the aq. layer with MeOH. Yield 70.0%. M.p. 254–256°. ^{1}H-NMR (D_2O, DSS): 3.09 (*s*, 4 H); 3.22 (*t*, 4 H); 3.29–3.34 (*m*, 8 H); 3.76 (*t*, 4 H). ^{13}C-NMR (D_2O, dioxane): 42.73; 43.19; 43.87; 46.50; 65.67. Anal. calc. for $C_{10}H_{28}Cl_4N_4O \cdot 2\,H_2O$: C 30.16, H 8.10, N 14.07; found: C 29.9, H 8.1, N 14.2.

Compound **2** was obtained by a similar procedure (yield: 55.3%). M.p. 264–266°. ^{1}H-NMR (D_2O, DSS): 3.32 (*t*, 4 H); 3.42 (*t*, 4 H); 3.45 (*t*, 4 H); 3.64 (*s*, 4 H); 3.76 (*t*, 4 H). ^{13}C-NMR (D_2O, dioxane): 42.73; 43.04; 45.90; 65.30; 69.86. Anal. calc. for $C_{10}H_{26}Cl_3N_3O_2$: C 36.76, H 8.02, N 12.8; found: C 36.6, H 8.1, N 12.7.

Compound **3** was also obtained by the same procedure, refluxing for 30 h. The impure detosylated cyclic amine obtained as a colorless oil was dissolved in a minimum amount of $CHCl_3$ and applied to a column of silica gel *60* for chromatography (35–70 mesh ASTM). The column was first eluted with a mixture $CHCl_3$/MeOH 1:1 and then with a mixture of MeOH/acetone/HCl (2M) 9:1.5:1. The aq. layer was concentrated and the pure cyclic amine precipitated from EtOH. Yield 59.0%. M.p. 232–233°. ^{1}H-NMR (D_2O, DSS): 2.14 (*q*, 2 H); 3.18–3.42 (*m*, 8 H); 3.50 (*q*, 4 H); 3.72 (*s*, 4 H); 3.80 (*q*, 4 H). ^{13}C-NMR (D_2O, dioxane): 21.19; 41.81; 42.31; 43.37 (*d*); 45.22; 46.27; 65.19; 65.46; 69.91 (*d*). Anal. calc. for $C_{11}H_{28}Cl_3N_3O_2 \cdot H_2O$: C 36.82, H 8.43, N 11.71; found: C 36.6, H 8.5, N 11.6.

Compound **4** was obtained and purified by the same method as **3**. Yield 65.5%. M.p. 243–245°. ^{1}H-NMR (D_2O, DSS): 2.08 (*q*, 4 H); 3.17 (*t*, 4 H); 3.20 (*t*, 4 H); 3.26 (*t*, 4 H); 3.64 (*s*, 4 H); 3.73 (*t*, 4 H). ^{13}C-NMR (D_2O, dioxane): 21.32; 42.89; 43.64; 46.13; 65.42; 69.98. Anal. calc. for $C_{12}H_{30}Cl_3N_3O_2 \cdot 2\,H_2O$: C 36.89, H 8.77, N 10.75; found: C 36.7, H 8.8, N 10.7.

Other Reagents and Standard Solutions. Metal nitrates of anal. grade were used and solns. prepared in demineralized water (obtained by a *Millipore/Milli-Q* system) and standardized with Na_2H_2EDTA [18]. Carbonate-free solns. of the titrant, KOH, were prepared by dilution of a commercial ampoule of *Titrisol* (*Merck*) with demineralized water under a stream of purified N_2. The solns. were standardized by titration with HCl and discarded when the concentration of carbonate reached 0.5% of the KOH present.

Potentiometric Equipment and Measurements. For potentiomeric titrations, *Orion 720* measuring instrument was used together with an *Orion 91-01* glass electrode, an *Orion 90-05* Ag/AgCl reference electrode, and a *Wilhelm*-type salt bridge containing 0.10M KNO_3 soln. Titration was carried out in a thermostated cell kept at 25.0 ± 0.1° by circulating water through the jacketed titration cell from a *Grant W6* thermostat, and the ionic strength of the solns. was kept at 0.10M with KNO_3. A stream of N_2 was bubbled through the titration soln. to remove atmospheric CO_2, and the solns. were stirred using a magnetic stirrer, as described in [19].

The e.m.f. of the cell is given by $E = E'^{\circ} + Q \log[H^+] + E_j$ and both E'° and Q were determined by titrating a soln. of known $[H^+]$ at the same ionic strength, using the acid p[H] range of the titration. The term p[H] is defined as $-\log[H^+]$. E_j, the liquid-junction potential, was found to be negligible in the experimental conditions used. The ionic product of water, $K_w = ([H^+][OH^-])$, was determined from data obtained in the alkaline range of the titration, considering E'° and Q valid for the entire p[H] range, and found equal to $10^{-13.78}$.

The potentiometric equilibrium measurements were made on 20.00 ml of ligand ($\sim 2.50 \times 10^{-3}$ M) diluted to a final volume of 30.00 ml, first in the absence of metal ions and then in the presence of each metal ion for which the $m_L : m_M$ ratio were 1:1 or 2:1. The E data were collected after additions of 0.025- or 0.050-ml increments of standard KOH soln.

Equilibration of ligands **1**–**4** with all the metal ions is fairly rapid and automatic titrations were possible.

Calculation of Equilibrium Constants. Protonation constants

$$K_i^H = \frac{[H_iL]}{[H_{i-1}L][H]^i}$$

were calculated by fitting the potentiometric data to the *Superquad* program [20]. The stability constants of the various species formed in the aq. soln. were also obtained from the experimental data with the aid of *Superquad* program. The inital computations were obtained in the form of overall stability constants or β values:

$$\beta = \frac{[M_m L_l H_h]}{[M]^m [L]^l [H]^h}$$

Differences between the various log β's provide the stepwise formation and protonation reaction constants. The species introduced were limited to those which can be justified by established principles of coordination chemistry.

A minimum of two titrations, performed by the automated system, for which the $m_L : m_M$ ratios were 1:1 and 2:1, was used.

The errors quoted are the standard deviations of the overall stability constants given directly by the program. For the stepwise formation and protonation constants, the standard deviations were determined by the normal propagation rules and in neither case do they represent the total experimental errors, but show the validity of the model and the experimental errors of the specific experiment considered.

NMR Studies. ^{1}H-NMR Spectra were recorded with a *Varian Unity 300* spectrometer. The adjustment in p[D] for the NMR titrations was performed with an *Orion 420A* instrument fitted with a combined *Ingold* microelectrode. The $-\log[H^+]$ was measured directly in the NMR tube, after the calibration of the microelectrode with buffered aq. solns., and the final p[D] calculated by the equation p[D] = p[H] + 0.40 [21]. Solns. of the ligands for the NMR measurements (~ 0.01M) were made up in D_2O, and the p[D] was adjusted by adding DCl or CO_2-free KOD. Sodium 3-(trimethylsilyl)propane-1-sulfonate (DSS) was used as an internal reference. ^{13}C-NMR spectra were recorded with the same spectrometer, and dioxane was used as internal reference.

Results and Discussion. – *Synthesis.* Ligand **3** was prepared for the first time in the present work. The other three ligands were synthesized before by different routes. The synthesis of ligand **1** was first performed by *Pelissard* and *Louis* [22] using a high-dilution procedure, by the condensation of triethylenetetraamine with 'diglycolyl dichloride' followed by the reduction of the amide with $LiAlH_4$ in THF. Later [23], the same ligand and also **2** were prepared, in a very small yield, by the aminolysis of appropriate dimethyl esters of α,ω-dicarboxylic acids with polyethylenepolyamine (12.1% for **1** and 32.0% for **2**). The tosyl derivatives of **1**, **2**, and **4** were prepared by *Rasshofer et al.* [24] and also by *Atkins et al.* [14] by a procedure similar to that used by us in the present work, but involving one step more, as the disodium salt of the *N*-tosyl-amine was isolated and purified before the cyclization reaction. We have obtained better yields for **1**·4Ts and almost similar ones for **2**·3Ts and **4**·3Ts. *Lukyanenko et al.* [25] [26] prepared **2** and **4** by the reaction of tri(sulfonamide) with appropriate dibromides in a two-phase system consisting of benzene or toluene and aqueous alkali hydroxide in the presence of quaternary ammonium salts, followed by a reductive cleavage with a mixture of HBr/AcOH and PhOH for the removal of the protecting groups and have claimed very good yields for the first step, although a low yield (30%) was obtained for **4** in the second step. *Hancock et al.* [11], after unsuccessful attempts to prepare **1** by published methods [14], have adopted a reaction of bis(2-iodoethyl) ether with the tetratosyl derivative of triethylenetetraamine, and for **2** have adopted the procedure of *Atkins* and *Richman* [14] followed in both cases by the reductive acid cleavage. We have tried the method of detosylation under acidic conditions [27] but, in our hands, very low yields were obtained, especially for the cyclic compounds with $-OCH_2CH_2O-$ moiety. However, the reaction under basic conditions with the Na/Hg has improved the yields.

Protonation Constants. The protonation constants of the ligands **1**–**4** studied in the present work and those obtained from the literature for the same ligands are summarized in *Table 1*. *Hancock et al.* [2] [11] have determined the protonation constants for ligands **1**

and **2** and have obtained similar values, the larger difference (0.22 log units) being found for the first constant of **2**, in spite of the different medium used in both works. All of these ligands present two high values of protonation constants. In the case of **2–4**, a low value is found for the third and last protonation constant, which increases with increasing size of the chains of hydrocarbons between contiguous N-atoms. As is usual for cyclic amines and also for acyclic ones, the first two N-atoms being protonated are those located at a longer distance (in macrocyclic compounds they are usually in opposite positions), to minimize the electrostatic repulsions between positive ammonium ions formed; the third protonation occurs at the N-atom located between two already protonated, and the repulsions of closely neighboring positive charges are more intense for shorter distances of the two centres, the corresponding constant being lower. So, the first two values of protonation constants are similar for the ligands **2–4**, but the third one increases slightly from **2** to **4** (2.30, 4.06, and 6.30 for **2**, **3**, and **4**, respectively, in log units). In the case of **1**, two basic constants and two acidic ones were found, one of them presenting a very low value. To understand the protonation scheme of this ligand, a ^{1}H-NMR spectroscopy titration was carried out. In *Fig. 1* is shown a spectrum of **1** at p[D] 1.77 and the titration curves for all the p[D] range for this ligand.

Table 1. *Protonation* (log K_i^H) *Constants of Ligands* **1–4** (T = 25.0°; I = 0.10M KNO_3)

Ligand	Equilibrium quotient [log units]			
	[HL]/[L][H]	[H_2L]/[HL][H]	[H_3L]/[H_2L][H]	[H_4L]/[H_3L][H]
[15]aneN_4O (**1**)	9.66(1)	8.77(2)	5.30(2)	1.2(1)
	9.56[a])	8.75[a])	5.31[a])	–
[15]aneN_3O_2 (**2**)	9.51(1)	8.47(1)	2.30(1)	–
	9.29[b])	8.50[b])	2.12[b])	
[16]aneN_3O_2 (**3**)	9.81(2)	8.38(4)	4.06(6)	–
[17]aneN_3O_2 (**4**)	10.07(5)	8.59(7)	6.30(8)	–

[a]) I = 0.1M $NaNO_3$ [11]. [b]) I = 0.1M $NaNO_3$ [2].

The spectra of **1** exhibit four resonances over almost the entire p[D] range, the resonances assigned to *b* and *c* overlap for p[D] values below 9.5 and *c* and *d* for values above 9.5. The assignment of the resonances was made by double-resonance experiments and also by taking into account the pattern of each absorption and the profile of the titration curve. Protons *a*, deshielded by the electronegative O-atom nearby, appear as a *triplet* at lower field. The assignment of the *triplet* corresponding to protons *b* was made by irradiation of the resonance of protons *a* at p[D] values 13.61, 11.92, 7.07, 3.52, 1.57, and 0.62. The *singlet* is readily assigned to the CH_2 protons *e* and the two *triplets* to CH_2 protons *c* and *d*. The assignment of protons *c* was made by the profile of the titration curve, as the signals of those protons are shifted downfield mainly by the protonation of the N^2-atoms, following the shift of protons *b*. The ^{1}H-NMR titration curves show the effect of the successive protonation of the various basic centres of the molecule; the first 2 equiv. of acid added to the basic form of the ligand (p[D] 13.5–8.0) spread out over the four N-atoms of the ligand, but the first equiv. of acid is more confined within the protonation of N^1-atoms and the second one within the N^2-atoms, as all the resonances shift downfield in this p[D] region, but resonance *a* and *b* shift more in the last part of the

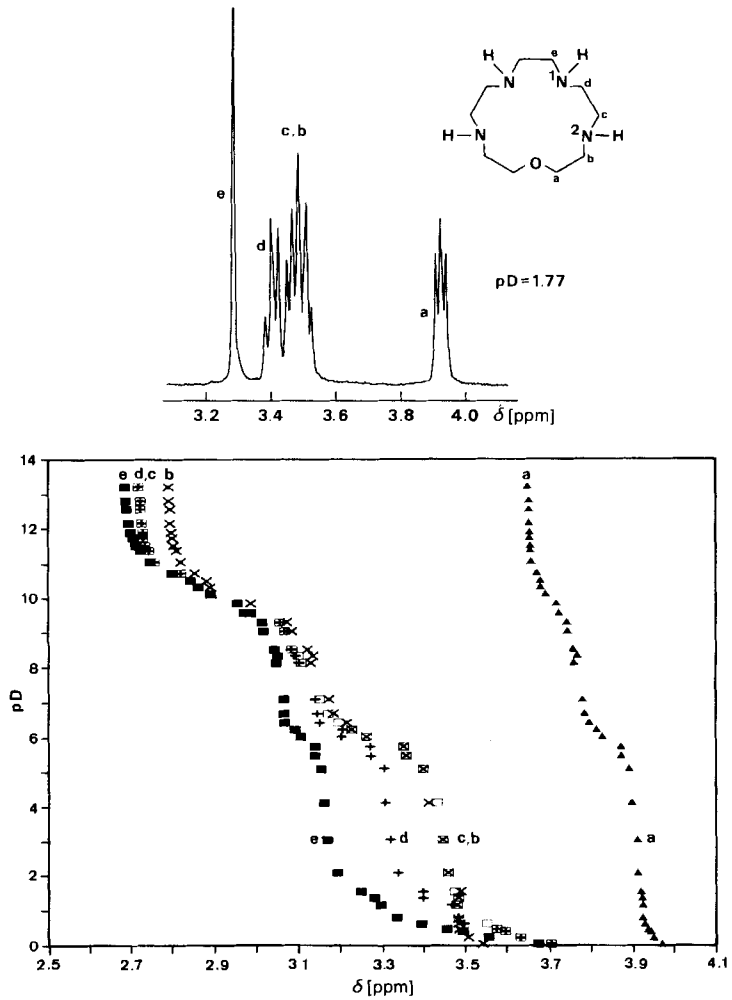


Fig. 1. *^{1}H-NMR Spectrum of ligand* **1** *at p[D] 1.77 and tritation curve p[D]* vs. δ [ppm]. ▲ :*a*, x:*b*, □ :*c*, + :*d*, ■ :e.

p[D] region. The third equiv. of acid added (p[D] 7.0–5.5) protonates mainly the N^2-centre, as resonances *a*, *b*, and *c* have the significant shift, although a smaller protonation occurs in the N^1-centre, as resonances *d* and *e* have a small shift downfield. The addition of one more equiv. of acid (p[D] < 3.0) causes mainly the shift of resonances *d* and *e* showing that the N^1-centre is protonated in larger extent. At p[D] values of *ca.* 0, the ligand is not completely protonated. The last protonation occurs at a centre at very short distance from others already protonated, and the strong repulsions then aroused in the molecule, where the motion is limited by the skeleton of the ring, renders the protonation difficult.

The ^{1}H-NMR titrations also allowed the determination of the protonation constants in D_2O. The values obtained are: $\log K_1(D) = 11.0(1)$, $\log K_2(D) = 9.8(2)$, $\log K_3(D) = 6.40(1)$, and $\log K_4(D) = 1.0(2)$. Those values are in agreement with the equation for

the correlation between the protonation constants determined in H_2O and D_2O obtained before [21]: $pK(D) = 0.11 + 1.10\ pK(H)$.

Stability Constants. The values of the stability constants for the complexes of the four ligands with some divalent first-series transition-metal ions, Cd^{2+} and Pb^{2+}, determined in aqueous solution and at $I = 0.10$M KNO_3, are shown in *Table 2*. In most cases, only 1:1 complexes are formed; but hydroxo complexes are also found with some metal ions. The stability constant of the complex of Fe^{2+} with **4** was impossible to determine, as, due to its low value, a precipitate is formed at the beginning of the titration. We have checked the possibility of formation of other species like protonated (MH_iL) or ML_2, but they do not appear to be formed under the conditions used, according to the results obtained by the *Superquad* program.

Table 2. *Stability Constants* (log *K*) *for the Metal Complexes of Ligands* **1**–**4** *with Several Divalent Metal Ions* ($T = 25.0°$; $I = 0.10$M KNO_3)

Metal Ion	Equilibrium quotient [log units]	[15]aneN$_4$O (**1**)	[15]aneN$_3$O$_2$ (**2**)	[16]aneN$_3$O$_2$ (**3**)	[17]aneN$_3$O$_2$ (**4**)
Mn^{2+}	[ML]/[M][L]	8.53(1)	6.63(1)	6.49(2)	3.42(7)
	[ML]/[MLOH][H]	–	–	–	–
Fe^{2+}	[ML]/[M][L]	10.34(1)	7.79(1)	6.73(3)	pp
	[ML]/[MLOH][H]	pp	9.1(1)	7.81(6)	
Co^{2+}	[ML]/[M][L]	12.72(1)	8.49(1)	7.85(2)	5.40(3)
	[ML]/[MLOH][H]	–	–	–	9.30(7)
Ni^{2+}	[ML]/[M][L]	14.76(2); 13.33[a])	9.26(1); 8.93[b])	10.28(1)	7.69(3)
	[ML]/[MLOH][H]	8.38(9)	–	–	–
Cu^{2+}	[ML]/[M][L]	20.34(9); 20.07[a])	15.72(1); 15.27[b])	14.72(1)	12.34(1)
	[ML]/[MLOH][H]	10.4(1)	8.87(2)	9.44(7)	10.16(5)
Zn^{2+}	[ML]/[M][L]	13.21(1); 13.11[a])	8.95(1); 8.85[b])	8.10(3)	7.09(1)
	[ML]/[MLOH][H]	–	–	8.66(9)	8.06(2)
Cd^{2+}	[ML]/[M][L]	13.41[a])	10.05[b])	11.02(1)	8.23(2)
	[ML]/[MLOH][H]	–	–	8.87(6)	10.15(9)
Pb^{2+}	[ML]/[M][L]	12.28[a])	10.07[b])	8.46(3)	7.39(5)
	[ML]/[MLOH][H]	–	–	–	8.7(1)

[a]) $I = 0.1$M $NaNO_3$ [11]. [b]) $I = 0.1$M $NaNO_3$ [2].

Hancock et al. [2] [11] have also determined the stability constants for some metal complexes of ligands **1** and **2**, working under almost identical operative conditions (same temperature and the same ionic strength, although maintained with a different medium ($NaNO_3$)), and those values are also indicated in *Table 2* for comparison. Agreement is, in general, satisfactory for the constants of the complexes formed with ligand **2**, where the differences are practically explained by the lower value of the first protonation constant for the ligand obtained by those authors. However, a poor agreement is found for the Ni^{2+} complex of **1**, where a difference of 1.43 log units is noted between our value and that of *Hancock et al.* As any remarkable difference was pointed out for the protonation constants of the ligand (*cf. Table 1*), and such a difference in the value of the stability constant obtained by both laboratories could not be explained by the differences in the medium, the inconsistency can probably be a result of the low kinetics of formation of this complex. In our case, *ca.* 15–30 min were necessary for the stabilization of each point of the titration.

The *Irving-Williams'* order of stability, which largely reflects ligand dipole/metal ion electrostatic effects and crystal-field effects, is obeyed for the complexes of all the ligands, and the maximum values of stabilities are found for the Cu^{II} complexes. The metal complexes of ligand **1** have the higher values of stability constants of those listed in *Table 2*, in accordance with the larger number of N-atoms of the ligand.

When the behavior of the metal complexes of **1** is compared with the corresponding complexes of **2**, both ligands having the same number of atoms in the ring and the same relative position of the donor atoms, but one N-atom of **1** is replaced by an O-atom in the ring of **2**, a drop in the stability of all the metal complexes studied is observed. The differences in the values of stability constants are larger for Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} (of 4.23 to 5.5 log units) and lower for the complexes of Mn^{2+}, Fe^{2+}, Cd^{2+}, and Pb^{2+} (1.9, 2.55, 3.36, and 2.21 log units, respectively). The lower differences for these last metal ions can be derived from the fact that those metal ions have lower affinity for N-atoms, as they tend to behave more like alkaline-earth-metal ions in their complexes. However, the differences in the values of stability constants of the complexes of **1** and **2** are less pronounced than expected. In fact, the overall basicity of **1** is 4.65 log units higher than that of ligand **2**, and it was found in the comparison of macrocyclic ligands of the same overall basicities that the replacement of one N- by an O-atom usually leads to differences in stability of their complexes (formed with divalent metal ions) of 4 or more log units [19] [28]. The relatively low stability of the metal complexes of **1** can be emphasized when their values are compared with those of the corresponding metal complexes of **5** (*cf. Fig. 2*, the stability constants for the complexes of **5** were taken from the literature and compiled in [29]). In spite of the lower basicity of **5** (1.5 to 2 log units depending on the authors), the stability constants of its metal complexes are higher than those of corresponding complexes of **1**, the larger differences having been observed for the Zn^{2+} and Pb^{2+} complexes. The match between the size of the cavity of the macrocycle and the ionic radius of the metal ion is not relevant for those series of complexes, as the Pb^{2+} complex of **5** (which has only 12 atoms in the ring) is more stable than the corresponding complex of **1**, meaning that larger metal ions prefer the smaller rings. This fact was already observed for other complexes and studied in a theoretical basis by *Hancock* and coworkers [8] [30–32]. These authors have attributed it to a more elastic structure adopted by the complexes involving macrocyclic ligands with smaller cavity sizes, like **5**, which is much more tolerant to change in metal-ion size [8] [30–32]. In fact, the metal ion does not enter the cavity of the small macrocycles and is responding to the geometrical requirements for the coordination out of the plane of the donor atoms. Based on spectroscopic data (electronic and ESR spectroscopy), *Blinn* and coworkers [33] suggested a square-pyramidal structure for the Cu^{2+} complex of **5**, $[Cu(\mathbf{5})(NO_3)_2]$. The structure of this complex was solved later by X-ray crystallography, and it was found that the Cu^{2+} is in a square-pyramidal environment, the Cu being 0.5 Å above the plane containing the four N-atoms of the macrocycle [34]. *Kimura* and coworkers [35] reported, based on electronic, magnetic circular dichroism, and ESR spectroscopy, that the Cu^{2+} complex of **1** has a square-pyramidal geometry with the O-atom of the macrocyclic ligand binding to Cu^{2+} at apical position. So, if this structure are correctly postulated, it seems possible that the Cu^{II} complexes of both ligands have a similar set of donor atoms and adopt a similar coordination geometry. The smaller stability constant of the Cu complex of **1**, and also of the other metal complexes, can be interpreted as a less favorable enthalpy changes (less

effective interaction of the metal ion with the donor atoms of ligand) or/and smaller entropy changes for the complexes of this ligand when compared with those of **5** (a greater loss of its configurational entropy as the ligand is more flexible). Unfortunately, there are no values of the thermodynamic functions (enthalpy and entropy changes) in the literature for this kind of complexes to confirm this conclusion.

The effect of the increase of the ring size of the macrocycle can be observed for metal complexes of the series of ligands **2**–**4**. In this series, one and two propylene moieties replace ethylene chains of ligand **2** to form a 16- and a 17-membered ligands, maintaining the same set of donor atoms. In spite of the slight increase of the overall basicity of the

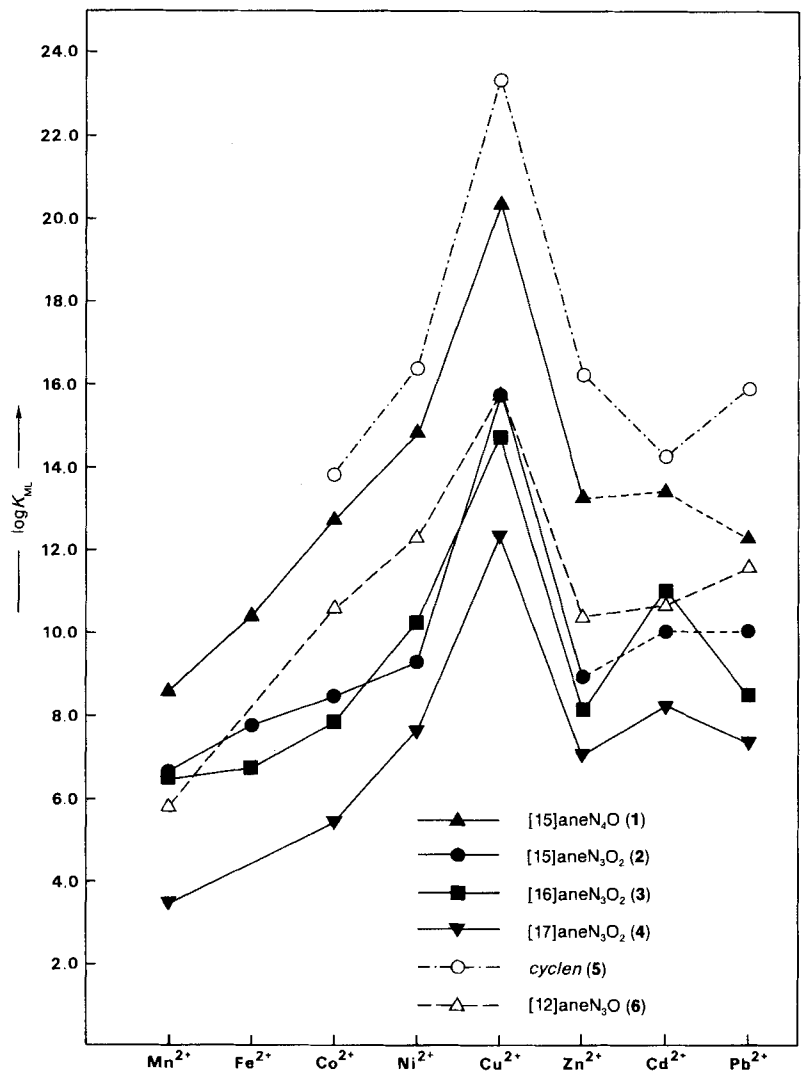


Fig. 2. *Variation of the stability constants* (log K_{ML}) *of the metal complexes of the ligands* **1**–**6** *with the atomic number of the metal ion*

ligands (20.28, 22.25, and 24.96 for **2**, **3**, and **4**, respectively), little differences in stability are found for the corresponding complexes of **2** and **3**; even the Ni^{2+} and the Cd^{2+} complexes of **3** are slightly more stable than those of **2**, but a significant drop is observed for all the metal complexes formed with the 17-membered ligand, especially for the larger metal ions like Mn^{2+} and Pb^{2+}. Again, it can be observed that the metal complexes formed with smaller ligands, like **6**, shown in *Fig. 2* [28], are more stable (except for the Mn^{2+} complex) than the complexes formed with the larger ligands having N_3O_2 as donor atoms, studied in this work.

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