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Thermodynamic and structural aspects of manganese(II) complexes with polyaminopolycarboxylic ligands based upon 1,4,7,10-tetraazacyclododecane (cyclen). Crystal structure of dimeric $[MnL]_2·2CH_3OH$ containing the new ligand 1,4,7,10-tetraazacyclododecane-1,4-diacetate

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The formation of manganese(II) complexes with polyaminopolycarboxylic ligands based upon 1,4,7,10-tetraazacyclododecane (cyclen) has been studied in aqueous solution by means of potentiometric and microcalorimetric techniques affording log K, $\Delta H°$ and $T\Delta S°$ values for the complexation reactions. The ML complexes present high stability constants, due to both favourable enthalpic and entropic contributions; with the unique exception of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), the entropic term is prevalent. The new ligand 1,4-DO2A (1,4,7,10-tetraazacyclododecane-1,4-diacetic acid) forms a more stable complex than the 1,7-DO2A isomer.
The thermodynamic results are discussed in terms of ligand characteristics: number and type of donor atoms, overall charge, substituent location. The crystal structure of $[MnL]_2·2CH_3OH$ (H_2L = 1,4-DO2A), obtained by single crystal X-ray analysis, displays a centrosymmetric dimeric $[Mn_2L_2]$ unit in which each manganese atom is seven-coordinated by four nitrogen atoms of a cyclen macrocycle, one oxygen atom of each of the acetate groups linked to this macrocyclic unit, and one oxygen atom pertaining to an acetate group of the other cyclen molecule in the same dimeric unit and bridging the two metal centers. The resulting binuclear complex contains a doubly bridged bimetallic core with Mn · · · Mn distance of 3.537(1) Å.

Introduction

Many ligands based upon 1,4,7,10-tetraazacyclododecane (cyclen) and containing different types and numbers of pendant coordinating functionalities have been the subject of intense studies in the last few years, due to several successful applications of their metal complexes.[1] For instance, lanthanide complexes of such ligands have proved useful as magnetic resonance imaging (MRI) contrast agents,[2] NMR shift reagents,[3] *in vivo* temperature reporters,[4] and catalysts in RNA cleavage.[5]

The properties of these complexes are strictly connected with the nature and number of pendant groups. The acetic acid group (CH_2CO_2H) is probably the most exploited functionality, since cyclen-based ligands containing similar groups form metal complexes characterized by high thermodynamic stability and marked kinetic inertness towards dissociation, favoring their use for *in vivo* applications.[6] A typical example of similar complexes is the gadolinium(III) complex of DOTA (Fig. 1) which is presently in use as an MRI contrast agent with the brand name DOTAREM™. A prime contribution to the effectiveness of this complex as a contrast agent is given by the presence of a water molecule in the first coordination sphere of the metal ion, which is in rapid exchange with the bulk solvent, enhancing the relaxation of solvent protons.[1] Ligands containing a lower number of coordinating functionalities, such as DO3A and 1,7-DO2A (Fig. 1), forming gadolinium(III) complexes with greater numbers of water molecules in the first coordination sphere, were successively developed.[6l,7] Indeed, the lower denticity of the ligands increased the water protons relaxivity promoted by the gadolinium(III) complex, but also caused a marked loss of complex stability (thermodynamic stability).[6l]

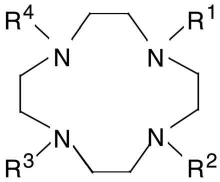

Fig. 1 Ligands discussed in this study: DOTA, R^1–R^4 = CH_2CO_2H; DO3A, R^1–R^3 = CH_2CO_2H, R^4 = H; HPDO3A, R^1–R^3 = CH_2CO_2H, R^4 = $CH_2CH(CH_3)OH$; 1,4-DO2A, R^1 = R^2 = CH_2CO_2H, R^3 = R^4 = H; 1,7-DO2A, R^1 = R^3 = CH_2CO_2H, R^2 = R^4 = H.

It was also observed that, at least in the case of lanthanides, 1,7-DO2A is more sensitive to changes in the cation size, displaying a much greater increase in complex stability with decreasing cation size than DOTA and DO3A, probably because of the more pronounced steric hindrance or electrostatic repulsion between the acetate pendant groups in the complexes of the last two ligands.[6l]

In this light it seemed interesting to know to what extent the relative position of the two acetate groups in DO2A might affect the ligational properties of the ligand. For this purpose we consider here the 1,4-DO2A ligand (Fig. 1), a new DO2A isomer bearing the acetate groups on vicinal ligand nitrogens, and compare its coordination properties towards Mn^{II}, in aqueous solution, with those presented by 1,7-DO2A and other similar ligands based upon cyclen, such as DOTA, DO3A and

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HPDO3A (Fig. 1). The choice of Mn^{II} was determined by the recent interest demonstrated towards this metal ion for the preparation of MRI contrast agents[8] and by the fact that it is a transition metal ion that, due to its electronic structure, is particularly sensitive to the presence of negatively charged oxygen donors in the ligands. In this paper we report the results of potentiometric and microcalorimetric studies on the complexation of Mn^{II} by 1,4-DO2A, 1,7-DO2A, DOTA, DO3A and HPDO3A ligands in solution, affording the first set of thermodynamic data (log K, $\Delta H°$, $T\Delta S°$) for these types of complexation reaction, along with the crystal structure of the binuclear complex $[MnL]_2\cdot 2CH_3OH$ (H_2L = 1,4-DO2A).

Experimental

Materials

The compounds DOTA,[9] DO3A, HPDO3A,[6c] 1,4-DO2A[10] and 1,7-DO2A[11] were synthesized as described. All these ligands were obtained in neutral form (number of acidic protons equal to the number of carboxylate groups), the different samples containing different amounts of crystallization water. All samples were characterized by means of elemental analysis, including determination of crystallization water by Karl Fischer's method, mass spectroscopy (ESI), ^1H and ^{13}C NMR, and HPLC, which verified the stoichiometry and purity.

$[MnL]_2\cdot 2CH_3OH$ (H_2L = 1,4-DO2A)

Equimolar amounts of H_2L (0.1 mmol) and $MnCl_2$ (0.1 mmol) were reacted in boiling water (20 cm^3) at pH 6.8 for a few min. The white solid separated on cooling was filtered off, washed with cold water and recrystallised from methanol to obtain crystals of $[MnL]_2\cdot 2CH_3OH$ suitable for X-ray analysis. Yield 73%. The stoichiometry of the compound was determined by X-ray analysis and successively confirmed by elemental analysis.

Crystal structure analysis for $[MnL]_2\cdot 2CH_3OH$ (H_2L = 1,4-DO2A)

Cell parameters were determined from the setting angles of 25 reflections, measured on a Siemens P4 automatic diffractometer with Mo-Kα radiation (λ 0.71068 Å), by using a colourless crystal of the compound. Intensities were collected, on the same diffractometer, by using graphite-monochromated Mo-Kα radiation and the θ–2θ technique. Three standard reflections were measured periodically to check the stability of the crystal and of the diffractometer. A total of 2958 reflections was collected of which 2361 had $I > 2\sigma(I)$.

Intensities were corrected for Lorentz and polarization effects and an absorption correction was applied once the structure was solved by using the Walker and Stuart method.[12] The structure was solved by direct methods, using the SIR 97 program,[13] and subsequently refined by full-matrix least squares with SHELXL 93.[14] Table 1 collects crystallographic refinement data. All the hydrogen atoms were introduced in calculated position and their coordinates refined in agreement with those of the linked atoms, with the exception of those linked to N1 and N2 which were located in ΔF Fourier syntheses and individually refined with an individual isotropic thermal parameter. The remaining hydrogen atoms were refined with an overall isotropic thermal parameter. Carbon, oxygen, nitrogen and manganese atoms were refined anisotropically. Atomic scattering factors and anomalous dispersion corrections for all the atoms were taken from ref. 15. Geometrical calculations were performed by PARST 93[16] and molecular plots were produced by the ORTEP program.[17]

CCDC reference number 153198.

See http://www.rsc.org/suppdata/dt/b0/b009242h/ for crystallographic data in CIF or other electronic format.

Potentiometric measurements

All pH-metric measurements (pH = −log [H^+]) employed for the determination of both protonation and manganese(II) complexation constants were carried out in 0.10 mol dm^{-3} Me_4NCl solutions at 298.1 ± 0.1 K, by using equipment and methodology previously described.[18] The combined Ingold 405 S7/120 electrode was calibrated as a hydrogen concentration probe by titrating known amounts of HCl with CO_2-free Me_4NOH solutions and determining the equivalence point by Gran's method[19] which allows one to determine the standard potential $E°$ and the ionic product of water ($pK_w = 13.83(1)$ at 298.1 K in 0.10 mol dm^{-3} Me_4NCl). All solutions were degassed and kept under an argon atmosphere. At least three measurements (about 100 data points each) were performed for each system in the pH range 2.5–11.0. In all experiments the ligand concentration [L] was varied in the range 5×10^{-4}–5×10^{-3} mol dm^{-3}. In the complexation experiments $[Mn^{II}] = 0.8[L]$. The computer program HYPERQUAD[20] was used to calculate the equilibrium constants from emf data. The protonation constants of DOTA, DO3A and HPDO3A used in the calculation of complexation constants were reported in a previous paper.[6m]

Microcalorimetric measurements

The enthalpies of ligand protonation and metal ion complexation were determined in 0.10 mol dm^{-3} Me_4NCl solution by means of an automated system composed of a Thermometric AB thermal activity monitor (model 2277) equipped with a perfusion-titration device and a Hamilton Pump (model Microlab M) coupled with a 0.250 cm^3 gas-tight Hamilton syringe (model 1750 LT). The microcalorimeter was checked by determining the enthalpy of reaction of strong base (Me_4NOH) with strong acid (HCl) solutions. The value obtained, −13.55(5) kcal mol^{-1}, was in agreement with the literature value.[21] Further checks were performed by determining the enthalpies of protonation of ethylenediamine.

Protonation enthalpies were determined by addition of a Me_4NOH solution (0.15 mol dm^{-3}, addition volumes 15 μl) to acidic solutions of the ligands (5×10^{-3} mol dm^{-3}, 1.5 cm^3). Two different procedures were adopted to determine the complexation enthalpies: (*i*) titration with Me_4NOH solution of acidic solutions of the ligands (5×10^{-3} mol dm^{-3}) containing the metal ion ($[Mn^{II}] = 0.8[L]$); (*ii*) titration with manganese(II) solution of ligand solutions at appropriate pH values. Calorimetric data deriving from both kinds of measurements were merged to obtain the complexation enthalpies. Calculations were performed by means of the AAAL program.[22] At least three titrations (about 120 data points) were performed for each system. The protonation enthalpies of DOTA, DO3A, and HPDO3A employed in the calculations were reported previously.[6m]

Results and discussion

Crystal structure of $[MnL]_2\cdot 2CH_3OH$

The structure of the compound consists of centrosymmetric dimeric $[Mn_2L_2]$ units in which each manganese atom is seven-coordinated (Fig. 2). The seven donors are the four nitrogen atoms of a cyclen macrocycle (N1, N2, N3, N4), one oxygen atom (O1, O3) of each acetate group linked to this macrocyclic unit, and one oxygen atom (O1′) pertaining to an acetate group of the other cyclen molecule in the same dimeric unit and bridging the two metal centers. The resulting binuclear complex contains a doubly bridged bimetallic core with Mn ··· Mn distance of 3.537(1) Å.

Selected bond distances and angles are in Table 2. The Mn–N bond distances, which range from 2.310(5) to 2.449(5) Å, and the Mn–O bond distances, which are between 2.163(4) and 2.265(4) Å, are comparable to those usually found in seven-

Table 1 Crystal data and structure refinement for $[MnL]_2 \cdot CH_3OH$ (H_2L = 1,4-DO2A)

Empirical formula	$C_{26}H_{52}Mn_2N_8O_{10}$
M	746.64
T/K	293
Crystal symmetry	Monoclinic
Space group	$P2_1/c$
a/Å	8.869(1)
b/Å	12.965(2)
c/Å	14.165(2)
β/°	96.01(1)
V/Å^3	1619.8(4)
Z	2
μ/mm^{-1}	0.85
$R\ [I > 2\sigma(I)]$	0.0778
$wR2$	0.2104

Table 2 Selected bond lengths (Å) and angles (°) for the coordination sphere of the $[MnL]_2 \cdot CH_3OH$ (H_2L = 1,4-DO2A)

Mn(1)–O(3)	2.163(4)	Mn(1)–N(2)	2.341(5)
Mn(1)–O(1)′	2.238(4)	Mn(1)–N(3)	2.357(4)
Mn(1)–O(1)	2.265(4)	Mn(1)–N(4)	2.449(5)
Mn(1)–N(1)	2.310(5)		
O(3)–Mn(1)–O(1)′	85.5(2)	O(1)′–Mn(1)–N(3)	142.2(2)
O(3)–Mn(1)–O(1)	83.7(2)	O(1)–Mn(1)–N(3)	70.77(14)
O(1)′–Mn(1)–O(1)	76.5(2)	N(1)–Mn(1)–N(3)	117.9(2)
O(3)–Mn(1)–N(1)	111.4(2)	N(2)–Mn(1)–N(3)	75.1(2)
O(1)′–Mn(1)–N(1)	86.5(2)	O(3)–Mn(1)–N(4)	72.1(2)
O(1)–Mn(1)–N(1)	156.4(2)	O(1)′–Mn(1)–N(4)	142.40(14)
O(3)–Mn(1)–N(2)	168.7(2)	O(1)–Mn(1)–N(4)	128.4(2)
O(1)′–Mn(1)–N(2)	85.4(2)	N(1)–Mn(1)–N(4)	74.8(2)
O(1)–Mn(1)–N(2)	87.6(2)	N(2)–Mn(1)–N(4)	119.2(2)
N(1)–Mn(1)–N(2)	74.8(2)	N(3)–Mn(1)–N(4)	74.9(2)
O(3)–Mn(1)–N(3)	108.6(2)		

′ $-x + 1, -y, -z + 1$.

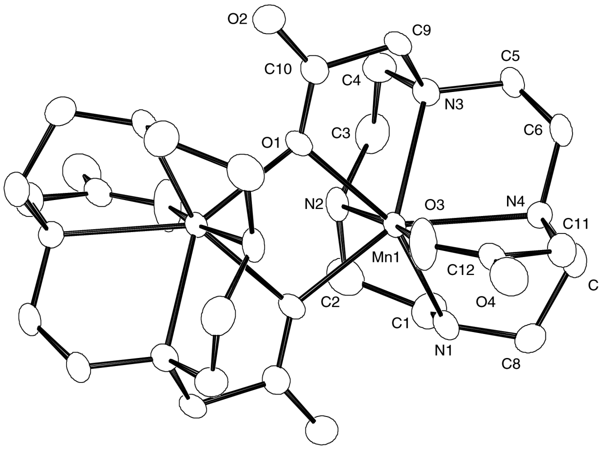

Fig. 2 ORTEP[17] view of $[MnL]_2 \cdot 2CH_3OH$.

Table 3 Thermodynamic data for protonation of 1,7-DO2A (H_2L) and 1,4-DO2A (H_2L), determined in 0.1 mol dm^{-3} Me_4NCl at 298.1 ± 0.1 K

	log *K*	−Δ*H*°/ kcal mol^{-1}	*T*Δ*S*°/ kcal mol^{-1}
1,7-DO2A			
$L + H \rightleftharpoons HL$[a]	11.29(2)[b]	10.7(1)	4.7(1)
$HL + H \rightleftharpoons H_2L$	9.84(1)	10.0(1)	3.4(1)
$H_2L + H \rightleftharpoons H_3L$	3.97(1)	1.2(1)	4.2(1)
$H_3L + H \rightleftharpoons H_4L$	2.59(5)	2.8(1)	0.7(1)
1,4-DO2A			
$L + H \rightleftharpoons HL$	11.07(2)	9.11(9)	6.0(1)
$HL + H \rightleftharpoons H_2L$	9.76(1)	10.00(8)	3.31(9)
$H_2L + H \rightleftharpoons H_3L$	3.84(1)	1.87(9)	3.37(9)
$H_3L + H \rightleftharpoons H_4L$	1.75(5)	0.2(1)	2.2(1)

[a] Charges omitted. [b] Values in parentheses are standard deviations in the last significant figure.

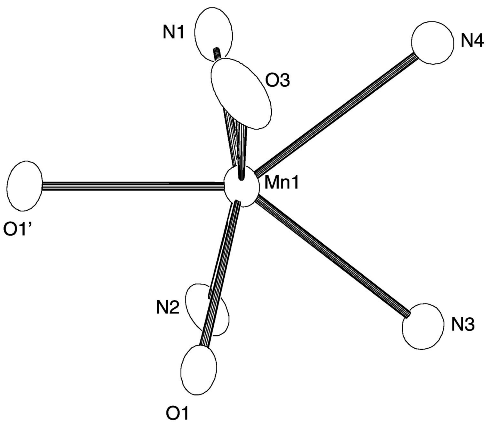

Fig. 3 Coordination polyhedron of Mn^{II} in $[MnL]_2 \cdot 2CH_3OH$.

coordinated manganese(II) complexes with N or O atoms as donors.

The coordination geometry of the manganese complex can be described as a distorted monocapped trigonal prism (C_s) where the oxygen O1′ is the capping atom of the N1N2O1O3 face (Fig. 3). The two triangular faces are nearly parallel, forming an angle of 1.8(2)°. Concerning the square faces of the prism, we note that the atoms N1N2N3N4 are well in a plane with a maximum deviation from the mean plane of 0.005(5) Å, while the other two planes appear to be a little more irregular, the maximum deviation being observed for the N3N4O1O3 plane (0.168(5) Å). It is worth noting that the manganese atom Mn1 is closer to the capped N1N2O1O3 plane than to the N3N4O1O3 and N1N2N3N4 ones, the distances being 0.2509(8), 1.1504(8) and 1.2075(8) Å, respectively. A search performed at the Cambridge Structural Database (V.5.1.6)[23] on Mn^{II} seven-coordinated by nitrogen and/or oxygen atoms evidences rather few structures, of which only eight have a four nitrogen and three oxygen coordination environment.[24] Although the monocapped trigonal prismatic disposition of the ligands around the Mn^{II} has been observed in manganese complexes with nitrogens and oxygens as donors,[25] we know of only one example of a binuclear complex having both metal ions surrounded by this kind of coordination sphere.[26]

Hydrogen-bond interactions are observed between the hydrogen atom bound to N1 (H1N) and the oxygen atom O2′ (2.12(7) Å), and between that bound to N2 (H2N) and O3′ (2.33(6) Å).

The tetraaza ring assumes a [3333] C corners conformation, which is the most common for this type of ligand,[27] namely a square conformation having three bonds between bends (corners), with carbon atoms occupying these corners.

Protonation of 1,7-DO2A and 1,4-DO2A

Table 3 lists the thermodynamic parameters (log *K*, Δ*H*°, *T*Δ*S*°) determined in this work for the protonation of 1,7-DO2A and 1,4-DO2A in 0.10 mol dm^{-3} Me_4NCl at 298.1 ± 0.1 K. In a recent paper we reported analogous data for DOTA, DO3A and HPDO3A.[6m] The protonation constants obtained for 1,7-DO2A are in good agreement with previously reported values determined under similar experimental conditions.[6l,n] Both ligands, in their fully deprotonated forms (L), contain six basic sites of which only four undergo protonation in the investigated pH region (2.5–11.0). Sherry and co-workers studied the microscopic protonation sequence of 1,7-DO2A by means of ^1H NMR/pH titrations showing that the first two protonations occur almost exclusively at the secondary nitrogens, despite the

Table 4 Thermodynamic data for manganese(II) complexation with DOTA, DO3A, HPDO3A, 1,7-DO2A and 1,4-DO2A, determined in 0.1 mol dm^{-3} Me_4NCl at 298.1 ± 0.1 K. $\Delta H°$ and $T\Delta S°$ in kcal mol^{-1}

	DOTA (H_4L)			DO3A (H_3L)		
	log *K*	$-\Delta H°$	$T\Delta S°$	log *K*	$-\Delta H°$	$T\Delta S°$
Mn + L $\rightleftharpoons$ MnL[a]	19.89(2)[b]	15.8(3)	11.3(3)	19.40(1)	8.8(1)	17.6(1)
MnL + H $\rightleftharpoons$ Mn(HL)	4.26(2)	4.4(1)	1.4(1)	3.13(3)	2.1(2)	2.2(2)
Mn(HL) + H $\rightleftharpoons$ Mn(H_2L)	2.99(5)	0.7(2)	3.4(2)			
MnL + 2H $\rightleftharpoons$ Mn(H_2L)	7.25(5)	5.1(2)	4.8(2)			
	HPDO3A (H_3L)			1,7-DO2A (H_2L)		
	log *K*	$-\Delta H°$	$T\Delta S°$	log *K*	$-\Delta H°$	$T\Delta S°$
Mn + L $\rightleftharpoons$ MnL	17.89(2)	7.9(2)	16.5(2)	14.54(1)	5.6(1)	14.2(1)
MnL + H $\rightleftharpoons$ Mn(HL)	5.07(4)	6.0(2)	0.9(2)	4.25(5)	7.7(3)	−1.8(3)
Mn(HL) + H $\rightleftharpoons$ Mn(H_2L)				4.45(8)	8.1(3)	−2.0(3)
MnL + 2H $\rightleftharpoons$ Mn(H_2L)				8.70(8)	15.7(3)	−3.8(3)
MnL + OH $\rightleftharpoons$ MnL(OH)				2.50(3)	0.4(2)	3.0(2)
	1,4-DO2A (H_2L)					
	log *K*	$-\Delta H°$	$T\Delta S°$			
Mn + L $\rightleftharpoons$ MnL	16.13(2)	7.9(2)	14.1(2)			
MnL + H $\rightleftharpoons$ Mn(HL)						
Mn(HL) + H $\rightleftharpoons$ Mn(H_2L)						
MnL + 2H $\rightleftharpoons$ Mn(H_2L)	8.31(3)	10.0(1)	1.3(1)			
MnL + OH $\rightleftharpoons$ MnL(OH)	2.49(7)	0.2(1)	3.1(1)			

[a] Charges omitted. [b] Values in parentheses are standard deviations in the last significant figure.

fact that the acetate groups are capable of assisting protonation at the tertiary nitrogens by hydrogen bonding, while the next two occur almost exclusively at the carboxylate groups.[6l]

The calorimetric results (Table 3) we have obtained for protonation of 1,7-DO2A are in quite good agreement with this sequence. We have shown in previous papers dealing with similar ligands that protonation of amine groups is markedly exothermic, while that of acetate groups is almost athermic.[6m] Accordingly, the enthalpy changes determined for the first two protonations of 1,7-DO2A are typical of amine protonation[28] while the reduced exothermic contributions to the third and fourth protonation steps support a principal involvement of carboxylate groups. A very similar thermodynamic behaviour is displayed by 1,4-DO2A upon protonation, the unique remarkable difference being observed in the fourth protonation step. Actually, the basicity of this ligand is significantly lower than that of 1,7-DO2A at this protonation stage, and is accompanied by a lower enthalpic contribution, suggesting a lower participation of amine groups in the stabilization of the tetraprotonated species. Accordingly, the more favourable entropic contribution observed for this protonation step of 1,4-DO2A could be ascribed to the formation of a weaker intramolecular hydrogen bond network which locks the molecule in a less rigid conformation.

Manganese(II) complexation

The thermodynamic parameters (log *K*, $\Delta H°$, $T\Delta S°$) determined in 0.10 mol dm^{-3} Me_4NCl aqueous solution, at 298.1 ± 0.1 K, for the formation of manganese(II) complexes with the ligands studied in this work are listed in Table 4. Under our experimental conditions (excess of ligand) only 1 : 1 metal to ligand complexes were found. The stability constants obtained for the MnL and Mn(HL) complexes with DOTA are in quite good agreement with previous values obtained by Delgado and co-workers[29] under similar experimental conditions, although the fitting of our potentiometric titrations performed by means of the computer program HYPERQUAD[20] allowed the identification of a diprotonated species in acidic solution and the determination of its stability constant. No stability constants were found in the literature for manganese(II) complexes with the other ligands.

All these ligands form very stable MnL species. In acidic solution these complexes undergo protonation: DO3A and HPDO3A form only monoprotonated species, while diprotonated ones are also formed by DOTA, 1,4-DO2A, and 1,7-DO2A. In the case of 1,4-DO2A we were not able to distinguish the binding of the two protons as separated protonation processes and, consequently, only the equilibrium constant for the simultaneous addition of two H^+ ions to the complex was determined (Table 4). 1,4-DO2A and 1,7-DO2A also form hydroxylated complexes in alkaline solution. Such behaviour can be rationalized by considering the ability of Mn^{II} to form seven-coordinated complexes. From this point of view, DOTA, DO3A, and HPDO3A contain enough donor atoms to fulfil the coordination environment of Mn^{II}, while in MnL complexes of 1,4-DO2A and 1,7-DO2A seven-coordination is completed with a water molecule. Deprotonation of this water molecule, facilitated by metal coordination, gives rise to hydroxylated MnL(OH) complexes. Consistent with the number of donor atoms in the ligands, DOTA, DO3A, and HPDO3A form more stable MnL complexes than 1,4-DO2A and 1,7-DO2A.

Also the overall ligand charge is expected to contribute to the stability of the MnL complexes and, actually, the expected trend of binding ability (DOTA > DO3A, HPDO3A > 1,4-DO2A, 1,7-DO2A) is observed, although the difference in stability between complexes with equally charged ligands (1,4-DO2A, 1,7-DO2A) may be greater than for complexes with differently charged ones (DOTA, DO3A). This means that ligand organization in the complex, or ligand preorganization before complexation, play an important role in determining complex stability. In particular, when complexes of transition metal ions with high coordination numbers are considered, we would expect that also the presence of bulky substituents in the ligand may affect complex stability. Functionalization of the secondary nitrogen of DO3A by insertion of a 2-hydroxypropyl group, to obtain HPDO3A, gives rise to a stability loss of about 1.5 log *K* units (Table 4) for the relevant seven-coordinated MnL complexes, but very similar stability constants were found for other transition metal ions, such as Cu^{II} and Zn^{II}, forming complexes with lower coordination numbers.[30]

A similar difference in stability of MnL complexes is observed for 1,4-DO2A and 1,7-DO2A, the latter ligand forming the weaker species (Table 4). Both ligands have the same set of donor atoms, although they differ in the location of the acetate groups, and are expected to form seven-coordinated manganese(II) complexes in aqueous solution. Structural differences between these complexes probably explain the difference in stability, but unfortunately we were not able to obtain structural information for both of them. The structure of the 1,4-DO2A (H_2L) complex in solution should be similar to that displayed by the MnL unit in the solid $[Mn_2L_2]\cdot 2CH_3OH$ compound (Fig. 2), the bridging oxygen atoms pertaining to the symmetry related ligand molecule being replaced by a water molecule, but no structural details are available for the 1,7-DO2A complex, in spite of the great efforts devoted to the preparation of good crystals for its X-ray analysis.

As observed above, the formation of the DOTA complex displays some thermodynamic peculiarity, the enthalpic contribution being predominant in determining the complex stability. Actually, the complexation enthalpy is particularly high, while the complexation entropy is lower. This feature seems to be indicative of a stronger interaction (favourable enthalpic contribution) of DOTA with Mn^{II} leading to a more strained complex (unfavourable entropic contribution) in which the uncoordinated carboxylate group might be constrained to stay in proximity of the metal ion, contributing with its negative charge to enhance complex stability.

Useful information regarding the formation of manganese(II) complexes with these ligands is given by the enthalpic and entropic contributions to the complexation reactions. As can be seen from Table 4, both enthalpy and entropy changes promote the formation of MnL complexes, although the entropic terms are largely predominant, except for the DOTA complex. Entropically driven reactions are typical of complexation processes in which charge neutralization plays a major role. In such cases the release of solvent molecules from the reacting, charged species is the principal driving force for complexation. On the other hand, the unfavourable enthalpic contribution accompanying the desolvation process cancels out the favourable contribution deriving from metal to ligand interaction.

Actually, Mn^{II} forms rather weak complexes with polyamine ligands, since it does not take advantage of ligand field stabilization effects because of its d^5 electronic configuration, but the stability of its complexes is considerably enhanced by insertion of charged groups in the ligands which give rise to largely favourable entropic contributions.[31] From this point of view, the greater stability of 1,4-DO2A complex of Mn^{II}, with respect to that of 1,7-DO2A should be mostly due to a stronger interaction of the metal ion with the amine nitrogens, since it is exclusively determined by a favourable enthalpic term (Table 4). Consequently, it seems reasonable to believe that the principal effect of moving the acetate groups from the 1,7 to 1,4 positions in DO2A consists in a strengthening of the interaction of Mn^{II} with the cyclen ligand skeleton.

An important result of this calorimetric study consists in the determination of the enthalpy changes for the complex protonation reactions, since their values can furnish interesting information about the donor atoms being protonated. As observed above for the "free" ligands, protonation of amine groups is a markedly exothermic reaction, while protonation of acetate groups is almost athermic. On this basis we are confident of the fact that, at least for MnL complexes with HPDO3A, 1,4-DO2A and 1,7-DO2A, that protonation occurs at the amine nitrogens. These protonation reactions are evidently exothermic ($\Delta H^\circ < 0$), in spite of the fact that the favourable enthalpic contribution due to nitrogen protonation is partially compensated by the unfavourable contribution deriving from cleavage of the metal–nitrogen bond occurring upon complex protonation. On the other hand it seems reasonable to assume that carboxylate groups are the principal recipients of H^+ ions in the second protonation of the DOTA complex, as well as in the unique protonation stage of the DO3A complex. Unfortunately, a confident interpretation of the first protonation stage of the former is not possible, because the relevant enthalpy change is not so favourable clearly to justify protonation of an amine nitrogen, and it is too favourable to be ascribed to the protonation of a carboxylate group. Nevertheless, we must consider that protonation of the DOTA complex represents a separate case, with respect to the other complexes, because it contains a surplus of donor atoms to achieve seven-coordination, including four charged carboxylate groups, and consequently protonation is not expected to promote a decrease of the coordination number. For instance, protonation of an amine nitrogen should cause a change from a N_4O_3 to N_3O_4 set of donor atoms in the coordination environment of Mn^{II}. A similar situation could be consistent with the thermodynamic parameters observed for protonation of the DOTA complex.

As far as 1,4-DO2A and 1,7-DO2A complexes are concerned, it is interesting that the enthalpy change for the protonation of the latter complex, $MnL + 2H \rightleftharpoons Mn(H_2L,)$ is considerably more favourable than that determined for protonation of the former (Table 4). This finding is a further confirmation of the fact that the lower stability of the complex with 1,7-DO2A is due to a weaker interaction of the ligand amine nitrogens with the metal ion, since the enthalpic cost due to cleavage of the metal–nitrogen bonds is lower for this complex.

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