Lanthanide(III)-Catalyzed Synthesis of 2-(Carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane and Its Coordination to Lanthanide(III) and Calcium(II)

Jurriaan Huskens, Joop A. Peters,* and Herman van Bekkum

Laboratory of Organic Chemistry and Catalysis, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

Gregory R. Choppin*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306-3006

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The Michael-type addition of *l*-tartrate and acetylenedicarboxylate is performed using a lanthanide (Ln(III)) alkoxide catalyst. The thermodynamics of the complexation of the adduct 2-(carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane (L) with Ln(III) and Ca(II) is investigated using potentiometry and calorimetry. The curves of ΔH_{101} and ΔS_{101} for the 1:1 complexation *vs* the atomic number of Ln(III) are parallel with a change of slope between Eu(III) and Dy(III). Ln(III)-induced ^{17}O NMR shifts show that both LnL and LnL_2 constitute series with constant hydration numbers. Ln(III)-induced ^{1}H shifts suggest that no abrupt geometrical change occurs in the middle of the Ln(III) series. Comparison of the entropy data with literature values for other neutral oxygen donor ligands indicates that the change in the ΔS_{101} values at Eu–Dy is not due to a structural change of the coordination of L within LnL across the Ln(III) series, but may be attributed to a difference in the hydration of the aquo ions between the light and the heavy Ln(III). A complete assignment of the ^{13}C NMR resonances of L is offered from the CH-coupling data and the Nd(III)- and Gd(III)-induced ^{13}C longitudinal relaxation rate enhancements. The coordination of L in LnL is tetradentate *via* three carboxylate groups and one ether oxygen. The two carboxylate groups of highest pK_as are involved in coordination, as shown by ^{13}C NMR shifts. As one carboxylate group remains uncoordinated in LnL and LnL_2, the complex TmL_2 was tested as a ^{23}Na NMR shift reagent. However, its performance is moderate, due to a large Tm(III)–Na(I) distance, a low stability of LnL_2 with Na(I), and a small uptake of Na(I).

Introduction

Ether polycarboxylates are promising compounds for use as metal sequestrants. They have excellent complexing abilities[1–3] and are in general readily biodegradable,[7] whereas their toxicity is low.[4] The lanthanides (Ln(III)) constitute a series of hard Lewis acids with similar chemical behavior.[5] By virtue of their ionic bonding,[6] combined with their high charge density, high coordination numbers, and rapid ligand exchange,[5,7–9] the Ln(III) ions are rapidly gaining importance in homogeneous and heterogeneous catalysis and in coordination chemistry. Furthermore, the similarity with Ca(II)[6,10,11] makes Ln(III) a substitute for the NMR silent Ca(II) in coordination and biochemical studies. The diversity of the magnetic properties allows various analytical techniques for complex structure elucidation, especially multinuclear magnetic resonance.

In this paper, we report the synthesis of 2-(carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane (L) by a La(III)-catalyzed Michael-type addition of *l*-tartrate to acetylenedicarboxylate. This adduct is interesting from a coordination chemistry point of view, because of the presence of several coordinating groups which can not be involved in coordination simultaneously. It also has potential applications as a detergent builder[12–15] and mouthwash ingredient.[16] The thermodynamics of the coordination of the adduct to Ln(III) and Ca(II) has been investigated by potentiometry and calorimetry, while a multinuclear magnetic resonance study was performed to elucidate the structure of the complexes involved. The Ln(III) series were used as a probe for the behavior of Ca(II). The possibilities of L as a ligand for a ^{23}Na NMR shift reagent have been studied.

Experimental Section

Materials. Water used in the potentiometric and calorimetric titrations and the NMR measurements was demineralized. Lanthanum chloride was obtained as a mixed hydrate; the La(III) content was determined by complexometric titration with xylenol orange as the

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indicator.[17] The other lanthanum(III) chlorides were obtained as the hexahydrates and used as such. Calcium(II) chloride and sodium perchlorate were obtained as the dihydrates. 2-Propanol and toluene were dried on zeolite NaA. All chemicals were reagent grade.

Synthesis of 2-(Carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane. The catalyst La(OiPr)$_3$/iPrOH was prepared from hydrated LaCl$_3$, trimethyl orthoformate, iPrOH, and BuLi in hexane, according to a known procedure,[18,19] which yielded 140 mL of 0.14 M La(OiPr)$_3$·3LiCl/iPrOH. To 70 mL of this solution was added 50 mL of toluene, and the mixture was heated to 90 °C, thus evaporating about 50 mL of iPrOH. Dimethyl L-tartrate (**2**, 8.90 g, 50 mmol) and dimethyl acetylenedicarboxylate (**1**, 7.10 g, 50 mmol) were added, and the mixture was stirred for 24 h. The mixture, after cooling to room temperature, was poured into aqueous HCl (65 mL, 0.5 M) and the product extracted with diethyl ether (five portions of 50 mL). The combined ether layers were washed with saturated aqueous NaHCO$_3$ and dried with MgSO$_4$. After evaporation of the diethyl ether, a crude product was obtained (15 g), which contained the mixed tetraester **3** with MeOH and iPrOH, due to transesterification of part of the methyl groups with iPr groups, and a few percent of unreacted **2**. The product was purified by chromatography using a silica column, which was eluted with 3% (v/v) MeOH/CH$_2$Cl$_2$, yielding the pure mixed ester product **3** (12.2 g). This was hydrolyzed to **4** by aqueous NaOH during 15 h at 60 °C. The alcohols produced were removed by evaporation, followed by neutralization with DOWEX-H$^+$. Lyophilization gave the pure tetrasodium salt (**4**, 9.4 g, 50%). Anal. Calcd C$_8$H$_4$O$_{10}$Na$_4$.1.93H$_2$O: C, 24.84; H, 2.05. Found: C, 24.93; H, 2.06. ^{1}H NMR (D$_2$O, pD = 7): δ (ppm) 2.80, 2.84 (AB system, 2 H, H6ab, $^2J_{\mathrm{gem}} = -15.1$ Hz), 4.32, 4.34 (AB system, 2 H, H4/H5, $^3J_{\mathrm{H4H5}} = 8.0$ Hz). ^{13}C NMR (30% D$_2$O/H$_2$O, pH = 7): δ (ppm) 178.7 (t, C7, $^2J_{\mathrm{CH}} = 6.3$ Hz), 177.5 (d, C10, $^2J_{\mathrm{CH}} = 2.3$ Hz), 177.4 (d, C9, $^2J_{\mathrm{CH}} = 2.3$ Hz), 177.2 (t, C8, $^3J_{\mathrm{CH}} = 2.7$ Hz), 109.7 (t, C2, $^2J_{\mathrm{CH}} = 5.5$ Hz), 81.5 (dd, C5, $^1J_{\mathrm{CH}} = 153.9$ Hz, $^2J_{\mathrm{CH}} = 3.6$ Hz), 81.4 (dd, C4, $^1J_{\mathrm{CH}} = 153.7$ Hz, $^2J_{\mathrm{CH}} = 3.1$ Hz), 46.3 (t, C6, $^1J_{\mathrm{CH}} = 129.3$ Hz).

Calculations. The calculations for the potentiometric and calorimetric titrations were performed using a spreadsheet program.[20,21] For each point of a potentiometric titration, the speciation and the stability constant were determined. The stability constants were used as verification in a speciation simulation, generating pH values. In all cases, good agreement between the calculated pH curve and the experimental one was observed. For evaluation of the calorimetric titrations, a simulation was performed to calculate the speciation. The same procedure was followed for calculation of the pHs, the speciation, and the simulated ^{13}C NMR shifts for the titration of Na$_4$L with HCl, as monitored by ^{13}C NMR (see Figure 3).

Potentiometry. The potentiometric titrations were conducted at 298 K in a jacketed vessel. Millivolt readings, obtained with a glass electrode, were converted into pH values using a calibration curve, which was determined from standard buffer solutions. The ionic strength was maintained constant at 0.1 M using NaClO$_4$. The protonation constants of L were determined by titration of 5.08 mM Na$_4$L with 0.100 M HCl. The stability constants of Ln(III) with L were determined by titration of 2.5 mM LnCl$_3$/0.500 mM HCl with 5.08 mM Na$_4$L. The stability constants of Ca(II) and Cd(II) with L were determined by titration of 5.0 mM CaCl$_2$ or Cd(ClO$_4$)$_2$/0.500 mM HCl with 5.08 mM Na$_4$L. Some of these titrations were repeated and always found to reproduce well. Each constant was calculated from at least 15 data points. All calculations were performed with a spreadsheet program as described above.[20,21]

Calorimetry. The calorimetric titrations were conducted at 298 K. The ionic strength was maintained constant at 0.1 M using NaClO$_4$. The calorimeter was calibrated using the protonation heat of acetate. The dilution heat was determined by titration of a solution of metal or ligand in 0.1 M NaClO$_4$ with 0.1 M NaClO$_4$. The protonation heats of L were determined by titration of 10.4 mM Na$_4$L with 0.100 M HCl. The complexation heats of Ln(III) with L were determined by titration of 5.0 mM LnCl$_3$ with 9.91 mM Na$_4$L/0.80 mM HCl. The complexation heats of Ca(II) with L were determined by titration of 10.0 mM CaCl$_2$ with 9.91 mM Na$_4$L/0.80 mM HCl. Some of these titrations were repeated and always found to reproduce well. All speciations were calculated with a spreadsheet program as described above.[20,21] The enthalpies were calculated by plotting the total evolved heat, Q_{tot} (corrected for the heat of dilution, and, when necessary, for the heat of protonation), *vs* the total number of moles formed of the species involved. ΔH_{101} is the inverse of the slope of such a plot (see Figure 1).

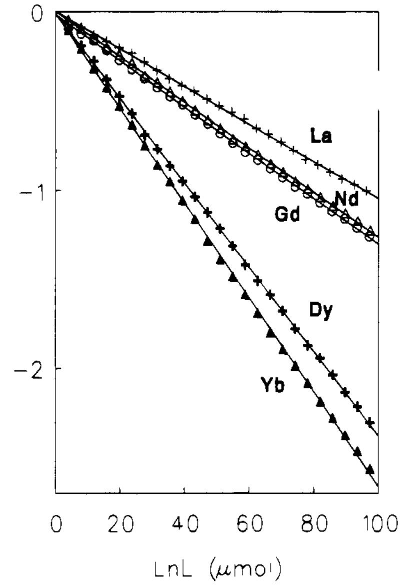

Figure 1. Total complexation heat (in J) *vs* the number of moles formed of LnL in the calorimetric titration of aqueous LnCl$_3$ with aqueous Na$_4$L at 298 K and $I = 0.1$ M (NaClO$_4$).

NMR Measurements. All measurements were performed on a Nicolet NT-200 WB (^{13}C, ^{17}O, ^{23}Na) or a Varian VXR-400 S NMR spectrometer (^{1}H, ^{13}C) at a temperature of 358 K, unless stated otherwise. The aqueous samples were measured in the presence of D$_2$O for locking.

The Ln(III)-induced ^{1}H NMR shift measurements were performed at 400 MHz, using 2-methyl-2-propanol as an internal standard. Samples were prepared by addition of Na$_4$L to a solution of about 20 mg LnCl$_3$ in 1 mL D$_2$O, providing for each Ln(III) three different ratios, $\varrho_{\mathrm{L}} = [\mathrm{Ln}]/[\mathrm{L}]$, of which one was about 0.8 and two were <0.5. Fast exchange on the NMR time scale was observed for La−Eu and Lu and slow exchange for Tb−Yb. Sm(III) was not used because of its extremely small induced shifts.

The ^{13}C−^{1}H-coupled spectrum of the free ligand and the NdL$_2$ complex were investigated at 100.6 and 50.3 MHz, respectively, using 2-methyl-2-propanol as an internal standard. The La(III)-induced ^{13}C shifts of the LaL$_2$ complex were measured at 100.6 MHz. These samples were prepared by the addition of various amounts of LnCl$_3$ to a solution of 70 mg Na$_4$L in 1 mL of D$_2$O. The Ln(III)-induced ^{13}C relaxation rate enhancements (REs) were determined at 50.3 MHz. The ^{13}C relaxation rates of the free ligand and the LaL$_2$ and NdL$_2$ complexes were measured at a ligand concentration of 0.4 M, with $\varrho_{\mathrm{L}} = 0$, 0.487, and 0.462, respectively, using the inversion recovery pulse sequence. The relaxation times were calculated with the aid of a nonlinear least squares three-parameter curve fitting routine.[22] For the GdL$_2$ complex, the REs were determined by addition of 12.1 mM GdCl$_3$/D$_2$O to 0.4 M Na$_4$L, providing ϱ_{L} values of 0−0.0003. The ^{13}C NMR shifts of L *vs* pH were determined at 50.3 MHz using 2-methyl-2-propanol as an internal standard. Samples were prepared by the addition of 12 M

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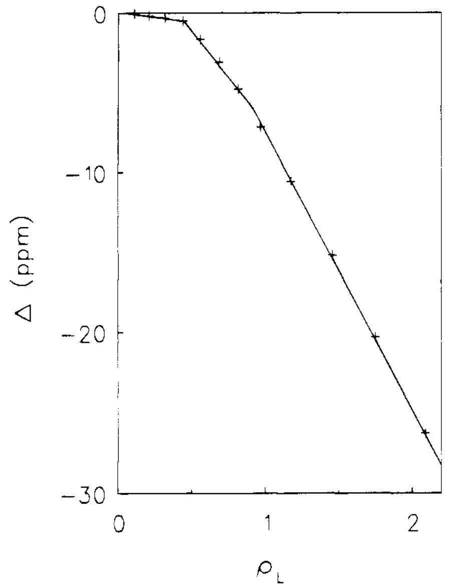


Figure 2. Dy(III)-induced ^{17}O NMR shift of solvent water *vs* ϱ_L (=[Dy]/[L]), measured at 27.1 MHz and 358 K.

aqueous HCl to a solution of Na_4L (0.3 M) in 30% D_2O/H_2O. The measured pHs were somewhat lower (0.2–0.5) than calculated from the speciation, probably due to a decrease of the pK_as at this ionic strength (1–3 M).

The Ln(III)-induced ^{17}O water shift measurements were conducted at 27.1 MHz, using D_2O as an external standard. Samples were prepared by addition of Na_4L to a solution of about 50 mg of $LnCl_3$ in 6 mL of D_2O, providing for each Ln(III) $\varrho_L = 0.4$ and 0.8. From the former, the number of coordinated water molecules for the LnL_2 complexes were obtained. For the LnL complexes, N_w was derived from the sample with $\varrho_L = 0.8$ and the ^{17}O shift for the LnL_2 complexes. With Dy(III), a series of measurements was performed at $\varrho_L = 0–2$ (Figure 2).

The TmL_2-induced ^{23}Na NMR shifts were conducted at 52.9 MHz, using aqueous Na_4L as an external standard. Samples were prepared by the addition of $TmCl_3$ to a solution of Na_4L (0.2 M) in 30% D_2O/H_2O, providing several ϱ_L values <0.5. The observed ^{23}Na shifts followed a linear relationship with ϱ_L.

Results

Synthesis of 2-(Carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane. There is a patent[15] on the synthesis of 2-(carboxymethyl)-2,4,5-tricarboxy-1,3-dioxolane by the addition of dimethyl acetylenedicarboxylate (**1**) and diethyl *d*-tartrate, using NaOMe/THF as the catalyst, and subsequent hydrolysis with NaOH to yield 20% of the desired product, but no further details are supplied.

We used two pathways to synthesize 2-(carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3–dioxolane: (i) the La(III)-catalyzed Michael-type addition of the free acids of **1** and l-tartrate (**2**) in water at pH 7, analogous to syntheses of etherpolycarboxylates described previously,[23] and (ii) the reaction of the dimethyl esters of **1** and **2**, catalyzed by $La(OiPr)_3$/toluene (see Scheme 1). The first route yielded directly the adduct **4** but only in low yield (20%), due to decarboxylation of **1**.[23] Separation of unreacted **2** from **4** could be achieved only by cation exchange column chromatography. Therefore, we have synthesized **4** by an alternative route *via* its tetramethyl ester (**3**), which could be prepared by a similar addition using the methyl esters of **1** and **2** as starting materials and $La(OiPr)_3$ as the catalyst[18,19] (Scheme 1). The latter catalyst combines a high Lewis acidity with a high basicity. The conversion of **2** was much higher (80%) with complete selectivity to **3**, and purification was achieved by extraction and subsequent column chromatography with silicagel (isolated yield 50%). No product loss occurred in the extra hydrolysis step of **3** to **4**.

Table 1. Thermodynamic Parameters of the Complexation of L (**4**); $T = 298$ K and $I = 0.1$ M ($NaClO_4$)[c]

(a) Acid

species	log β_{0n1}[a]	ΔG_{0n1}[b]	ΔH_{0n1}[b]	ΔS_{0n1}[c]
HL	5.70 ± 0.02	−32.5 ± 0.1	2.4 ± 0.1	117 ± 1
H_2L	9.87 ± 0.05	−56.3 ± 0.3	4.6 ± 0.1	204 ± 1
H_3L	12.8 ± 0.1	−73.0 ± 0.6	5.8 ± 0.3	264 ± 2
H_4L	15.1 ± 0.3	−86.1 ± 1.7	6.2 ± 2.0	310 ± 5

(b) Metal Complexes

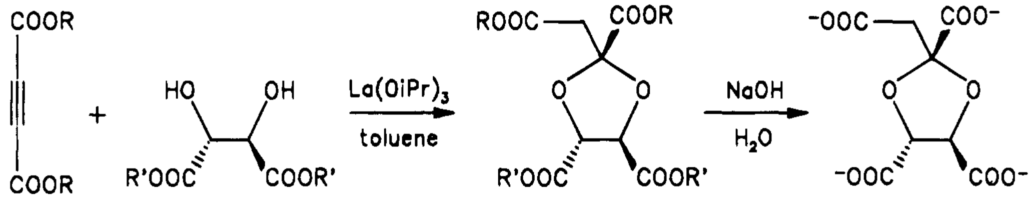
species	log β_{101}[a]	ΔG_{101}[b]	ΔH_{101}[b]	ΔS_{101}[c]	log β_{102}[a]
LaL	6.21 ± 0.10	−35.4 ± 0.6	10.5 ± 0.3	154 ± 2	10.0 ± 0.2
NdL	6.26 ± 0.10	−35.7 ± 0.6	12.7 ± 0.3	162 ± 2	10.0 ± 0.2
GdL	6.13 ± 0.10	−35.0 ± 0.6	12.9 ± 0.3	161 ± 2	10.0 ± 0.2
DyL	6.28 ± 0.10	−35.8 ± 0.6	23.7 ± 0.3	200 ± 2	10.4 ± 0.2
YbL	6.20 ± 0.10	−35.4 ± 0.6	26.5 ± 0.3	208 ± 2	10.1 ± 0.2
CaL	4.02 ± 0.10	−22.9 ± 0.6	−2.8 ± 0.3	67 ± 2	

[a] $\beta_{mna} = [M_mH_nL_a]/[M]^m[H]^n[L]^a$. [b] In kJ/mol. [c] In J/(mol K). Standard deviations given were obtained from single titrations.

Thermodynamics of the Complexation of 2-(Carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane with Ln(III). The constants of the protonation and metal complexation with **4** were determined by potentiometry at 298 K and ionic strength, $I = 0.1$ M, and are collected in Table 1. For the Ln(III) ions, the complexes ML and ML_2 were observed ($[Ln]_{tot} = 1–2.5$ mM); even at higher concentrations (10 mM), no ML_3 was detected. For Ca(II), which was used to check the potential of **4** as a metal ion sequestering agent, only formation of ML was observed in the concentration range used ($[M]_{tot} = 3–5$ mM).

The protonation and the complexation heats were determined by calorimetry, and the results are listed also in Table 1. The calculation of the enthalpies was preceded by a simulation of the titration,[20] using the stability constants, in order to obtain the speciation. The total evolved heat, Q_{tot}, was plotted *vs* the number of moles formed of the species involved, and the enthalpy was obtained from the slope. For the Ln(III) ions, these plots are shown in Figure 1. The entropy changes were derived from the free energies, calculated from the stability

Scheme 1



1 **2** **3** **4**

$R = R' = CH_3$

Table 2. Ln(III)-Induced ^{1}H and ^{17}O NMR Shifts[a] for LnL and LnL_2 (T = 358 K)

Ln	LnL					LnL_2				
	H4,H5		H6a,H6b		H_2O[b]	H4,H5		H6a,H6b		H_2O[b]
La	0.4	−0.1	0.3	0.1	583	0.4	−0.1	0.3	0.1	140
Ce	4.0	−0.3	−1.1	0.3	782	6.3	2.4	4.4	2.8	313
Pr	9.6	1.4	2.2	0.3	1478	11.5	4.1	5.5	2.4	397
Nd	2.8	−0.4	−1.2	0.3	1869	4.7	2.6	3.1	1.6	462
Eu	3.1	2.1	−1.8	0.8	−2705	−5.8	−4.1	0.9	−0.6	−320
Tb					−10674	83.2	12.9	47.2	1.2	−1187
Dy	56.4	34.1	−59.6	−13.6	−10314	98.2	−2.3	37.5	−3.8	−895
Ho					−6518	45.2	8.2	29.8	−0.8	−556
Er	−12.9	−11.9	−8.1	5.7	−4488	−31.8	−0.3	−6.1	3.2	−3
Tm					−2221	−68.2	−19.7	−36.2	1.7	43
Yb	−19.1	−14.8	11.0	−3.4	−335	−22.1	−1.4	−7.9	9.1	277
Lu	0.4	−0.1	0.3	0.2	497	0.4	−0.1	0.3	0.2	282

[a] In ppm; the ionic strength was not controlled. [b] ±2%; $\varrho_w = [Ln]/[H_2O] = 1$.

constants, and the enthalpies. The resulting thermodynamic parameters are included in Table 1.

The five Ln(III) ions selected are representative of the complete lanthanide series. Table 1 shows that the values of ΔS_{101} and of ΔH_{101} can be divided into two separate series for the light (La−Gd) and heavy Ln(III) (Dy−Yb), respectively. The compensation effect[5] between ΔS_{101} and ΔH_{101} results in similar values of ΔG_{101} across the whole Ln(III) series. We performed a multinuclear magnetic resonance study to investigate the coordinating behavior of L and to see whether the observed break in the Ln(III) series for the entropy and enthalpy data is due to a structural difference in the LnL complexes between the light and heavy Ln(III) ions.

Multinuclear NMR Study of the Coordination of 2-(Carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane to Ln(III). The Ln(III)-induced NMR shift (LIS) of a ligand nucleus i is, in general, described by eq 1, in which Δ is the observed chemical shift, and Δ_d, Δ_c, and Δ_p are the diamagnetic, contact, and pseudocontact contributions, respectively.[11]

$$\Delta_i = \Delta_{d,i} + \Delta_{c,i} + \Delta_{p,i} \qquad (1)$$

$$\Delta_i' = \Delta_i - \Delta_{d,i} = \Delta_{c,i} + \Delta_{p,i} = F_i\langle S_z\rangle + G_iC^D \qquad (2)$$

According to eq 2, Δ_i', which is the paramagnetic contribution to the LIS, is composed of two Ln(III)-dependent parameters, $\langle S_z\rangle$ and C^D, and two nucleus-dependent parameters, F and G.[24,25] F is related to the electron-nuclear hyperfine coupling constant and G to the crystal field coefficients and the location of the ligand nuclei with respect to the principal axes of the magnetic susceptibility tensor. Values for $\langle S_z\rangle$ and C^D are listed in the literature.[24−28] Values for C^D have been calculated using the first term (T^{-2}) of an infinite series,[25] while there are also data available on the second term (T^{-3}).[29] When Δ is measured for all Ln(III) ions, F and G can be evaluated, assuming that no geometrical change occurs across the Ln(III) series with respect to the complexation of the ligand.[30] When the complex geometry does change, different sets of F and G values are obtained for the light and heavy Ln(III). This can be visualized by plotting the data according to either one of the two linearized forms of eq 2, given in eqs 3a and 3b.[31] Equation 3a is preferably

$$\Delta_i'/C^D = F_i(\langle S_z\rangle/C^D) + G_i \qquad (3a)$$

$$\Delta_i'/\langle S_z\rangle = F_i + G_i(C^D/\langle S_z\rangle) \qquad (3b)$$

used for nuclei with large contact contributions and eq 3b for nuclei with large pseudocontact contributions. The contact contribution, described by F, is usually only large for nuclei directly coordinated to the Ln(III) ion, and diminishes rapidly when the number of bonds between the Ln(III) ion and the nuclei increases.

The number of water molecules present in the first coordination sphere of LnL and LnL_2 was investigated by Ln(III) induced ^{17}O shift measurements. The contact contribution to the LIS of a Ln(III)-bound ^{17}O nucleus is almost independent of the nature of the ligand in question as well as of other ligands coordinated to the same metal ion.[32] Therefore, these shifts are useful for the determination of the hydration numbers. The exchange between bound and bulk water is fast on the NMR time scale. Accordingly, the observed LIS represents a concentration weighted average of the shifts of the individual species in solution. In Figure 2, the curve of the ^{17}O resonance of the solvent water (δ) *vs* the ratio $\varrho_L = [Dy]/[L]$ is shown. A significant break occurs at $\varrho_L = 0.5$, which indicates the formation of DyL_2 as the highest complex. Also, a small change in slope at $\varrho_L = 1.0$ can be observed, which is due to differences in coordination number of Dy(III) between the aquo ion and the Dy(III) complexes.

The number of coordinated water molecules (N_w) in all complexes LnL and LnL_2 was examined by measuring the ^{17}O water shift (δ_i) of an aqueous solution of LnL and of LnL_2. The slopes of the curves of δ_i *vs* $\varrho_w = [Ln]/[H_2O]$ give $N_w\Delta_i$ of LnL_2 for $\varrho_L = 0-0.5$ and of LnL for $\varrho_L = 0.5-1$, respectively (see Table 2). The $N_w\Delta_i$ data could be fitted well in a multiple regression analysis[33] of eq 2 with a single value for N_wF (LnL, −332 ± 10; LnL_2, −38 ± 3)[34] and for N_wG (LnL, 8 ± 4; LnL_2, 2 ± 1) for the whole Ln(III) series. From the excellent correlation for the N_wF values and from the fact that division of these data into two sets for the light and the heavy Ln(III) subseries does not lead to an improvement of the correlation, it can be concluded that no change of N_w occurs

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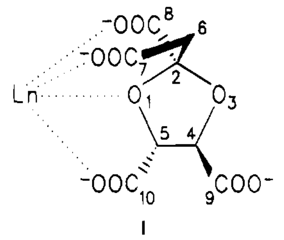
across the Ln(III) series for both LnL and LnL_2. Previously,[35] we have shown that a coordinated water molecule has an F value of −70, at 346 K. Since *F* is linearly related to T^{-1},[24] $F = -68$ at 358 K. Then, the average number of coordinated water molecules for LnL and for LnL_2 can be calculated to be 4.9 and 0.6, respectively. Usually, Ln(III) ions show nine-coordination in this type of complexes. Therefore, these data suggest that L is bound in a tetradentate fashion in all complexes.

We also determined the Ln(III)-induced ^1H shifts of L. It appeared that exchange was fast on the NMR time scale only for the light Ln(III) ions and for Lu(III). In these cases, the bound shifts, $\delta_{LnL2,i}$, of H4/H5 and H6a/b (structure **I**) were obtained from measurements of the chemical shifts at various molar ratios [Ln]/[L] ($= \varrho_L < 0.5$). Under these conditions, there is an equilibrium between LnL_2 and uncomplexed L since the stability constants are relatively high (see Table 1). The Ln(III)-induced bound shift $\Delta_{LnL2,i}$ can be calculated by eq 4,



I

$$\Delta_{LnL2,i} = (\delta_{Ln,i} - \delta_i)/2\varrho_L \qquad (\varrho_L = 0-0.5) \qquad (4)$$

in which $\delta_{Ln,i}$ and δ_i are the chemical shifts of nucleus *i* in the presence and absence of Ln, respectively. For the complexes LnL, the bound shift $\Delta_{LnL,i}$ was determined similarly from $\delta_{Ln,i}$ using eq 5 at $\varrho_L = 0.8$, where an equilibrium between LnL_2

$$\Delta_{LnL,i} = ((\delta_{Ln,i} - \delta_i) - (2 - 2\varrho_L)\Delta_{LnL2,i})/(2\varrho_L - 1) \qquad (\varrho_L = 0.5-1) \qquad (5)$$

and LnL exists. Correlation according to eq 2 can be visualized by plotting $\Delta'/\langle S_z\rangle$ *vs* $C^D/\langle S_z\rangle$ (eq 3b), because the contact contribution is generally relatively small for ^1H nuclei.[31] For the heavy paramagnetic Ln(III) ions, the exchange between free and complexed ligand was slow on the NMR time scale. The assignments of the complex ^1H resonances was accomplished by plotting the $\Delta'/\langle S_z\rangle$ values *vs* $C^D/\langle S_z\rangle$, as mentioned above, and comparing with the results for the light Ln(III) ions. The bound shifts are given in Table 2.

In plots of $\Delta'/\langle S_z\rangle$ *vs* $C^D/\langle S_z\rangle$ for the LnL_2 complexes, rather poor fits were obtained for all ^1H nuclei. Multiple linear regression analysis of the ^1H NMR shift data using eq 2 showed no improvement of the correlation upon division of the Ln(III) series into the light and heavy Ln(III) subseries. This suggests the absence of a major structural difference, such as a change of binding mode, between the complexes of these subseries around the middle of the Ln(III) series, where a clear and abrupt break was observed in the ΔH_{101} and ΔS_{101} values. The poor fit may be ascribed to the flexibility of the ligand L, which may lead to conformational changes in L upon change of the ionic radius of the Ln(III) ion across the Ln(III) series.

The same procedure was followed for the LnL complexes. Here, as already mentioned, the ^1H shifts induced by the light Ln(III) ions were obtained from the LnL/LnL_2 equilibrium, and are, therefore, less accurate. Furthermore, the solubility of the LnL complexes is low (<0.01 M at 358 K), with an inverse temperature relationship. As a result, we were not able to determine the induced shifts for all Ln(III) ions. Plots of $\Delta'/\langle S_z\rangle$ *vs* $C^D/\langle S_z\rangle$ (eq 3b) were analogous to the plots as described above for the LnL_2 complexes, also suggesting the absence of a major structural break in the middle of the Ln(III) series.

The geometry of L in LnL_2 was studied by measurement of Nd(III)-induced ^{13}C longitudinal relaxation rate enhancements. The relaxation rate enhancement, RE, of a nucleus *i* of a ligand coordinated to Ln(III) can be calculated from the longitudinal relaxation times, T_1, according to eq 6, provided that the T_1

$$n\varrho_L \mathrm{RE}_i = (1/T_1)_i - (1/T_1)_{0,i} \qquad (6)$$

values are significantly greater than the mean residence time of the ligand in the first coordination sphere of the metal ion.[36−38] In eq 6, $(1/T_1)_i$ and $(1/T_1)_{0,i}$ are the longitudinal relaxation rates in the presence and absence of Ln(III), respectively, *n* is the number of ligands present in the complex, and ϱ_L is the metal-to-ligand ratio. Geometrical information can be obtained from the difference in relaxation rate caused by complexation to Nd(III) and La(III), with the use of eq 7.

$$\mathrm{RE}_i^{\mathrm{Nd}} - \mathrm{RE}_i^{\mathrm{La}} = C/r_i^6 \qquad (7)$$

Here, r_i is the distance between the Ln(III) center and the nucleus under investigation, *i*, and *C* is a nucleus dependent constant, which is given by eq 8, where $\mu_0/4\pi$ is the magnetic permeability

$$C = (4/3)(\mu_0/4\pi)^2\mu^2\gamma^2\beta^2T_{1e} \qquad (8)$$

of a vacuum, μ is the effective magnetic moment of Nd(III), δ is the magnetogyric ratio, β is the Bohr magneton, and T_{1e} is the longitudinal electron spin relaxation time. Equation 8 can be deduced from the Solomon-Bloembergen equation.[39,40] For Nd(III), T_{1e} is dominating the correlation time (τ_c) and then $\omega_I^2\tau_c^2 \ll 1$ and $\omega_S^2\tau_c^2 \ll 1$. T_{1e} (1.15×10^{-13} s for the Nd(III) aquo ion) is shown to be rather independent of the ligation of the Ln(III) cation.[41,42] Therefore, for ^{13}C, the value of *C* is estimated to be 8.08×10^3 Å^6 s^{-1}.

In Table 3, the ^{13}C $(1/T_1)_i$ values of L in the free ligand form and in the complexes LnL_2 (Ln = La, Nd) are presented. The distances, r_i, were calculated from these results using eqs 6−8. As can be seen in Table 3, three carboxylate groups are involved in coordination, all at about the same distance to Ln(III), while one carboxylate remains uncoordinated. The distances obtained are in good agreement with those measured in a structural (Dreiding) model in which the carboxylate groups of C7, C8, and C10, and the ether oxygen O1 are bound to the Ln(III) ion (see structure **I**). This tetradentate coordination is in accordance with the results of the ^{17}O NMR measurements, which indicate that the LnL_2 complexes have one water molecule in the first coordination sphere. The total coordination number of Ln(III) is nine as is commonly observed in such complexes. The assignment of the ^{13}C signals was confirmed by the multiplicity of the carboxylate signals: two carboxylate resonances of the three with high RE showed a triplet CH-coupling in the NdL_2 complex. This suggests that the remaining signal with low RE is due to C9/C10.

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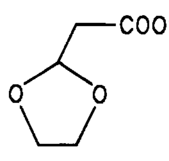
Table 3. Relaxation Rates and Diamagnetic La(III)-Induced Shifts of ^{13}C and the Ln$-^{13}C$ Internuclear Distances, r_i, for LnL_2 ($T = 358$ K)

i	Δ_i[a]	(1/T_1) (s^{-1})			m[b]	r_i^{exp}(Å)[c]	r_i^{mod} (Å)[d]
		L	LaL_2	NdL_2			
C2	−0.45	0.09	0.07	6.60	t	3.23	3.4
C4	0.83	0.87	1.14	1.65	dd	4.95	4.8
C5	−1.51	1.16	1.11	4.25	dd	3.65	3.6
C6	−1.20	2.58	2.23	4.28	t	3.92	3.9
C7	−1.58	0.07	0.09	4.54	t	3.45	3.2
C8	0.48	0.05	0.06	7.31	t	3.18	3.3
C9	−2.42	0.06	0.07	0.60	d	4.91	5.5
C10	0.09	0.07	0.02	7.31	d	3.42	3.5
H4							5.0
H5							3.5
H6							4.3, 4.9
ϱ_L	0.49	0.49	0.46				

[a] In ppm; given with free L (pH = 7) as an external standard. [b] Multiplicity. [c] Calculated from eq 7. [d] Measured from the Dreiding model.

The assignment of the ^{13}C signals in the spectrum of the free ligand was less straightforward. CH-couplings divided the four carboxylates in C7/C8 (triplets; 6.3 and 2.7 Hz) and C9/C10 (doublets; both 2.3 Hz). For the assignment of C9−C10 and C4−C5, we used Gd(III)-induced ^{13}C longitudinal relaxation rate enhancements, analogous to the procedure described for Nd(III). Only very low ϱ_L values ($<10^{-3}$) were needed, because Gd(III) is an extremely good relaxation agent. So, this procedure yields Ln(III)-induced REs, while the ^{13}C spectrum does not differ from the free ligand spectrum. Discrimination between C9 and C10 was possible due to the difference in their distance to the Ln(III) center, leading to a larger RE for C10. Analogously, C4 and C5 could be assigned. Discrimination between C7 ($\delta = 178.6$; $^2J_{CH} = 6.3$ Hz) and C8 ($\delta = 177.1$; $^2J_{CH} = 2.7$ Hz) was made by comparison of the CH-coupling constants with the corresponding one (7.3 Hz) in the Michael-type adduct of ethylene glycol and acetylenemonocarboxylate, **5**.[23] C7 shows the highest chemical shift, while there is no electron-withdrawing O atom attached to the neighboring C6 atom. This assignment is in accordance with the generally observed higher chemical shift values for RCH_2COO^- compared to $RCH(OR')COO^-$.



5

The diamagnetic La(III)-induced ^{13}C NMR shifts of L in LnL_2 are listed in Table 3. For carbon atoms of coordinating carboxylate groups, usually a positive shift is observed.[43] It can be seen that the lowest (negative) value for a carboxylate group is obtained for the noncoordinating C9. However, it is remarkable that also the coordinating carboxylate group C7 shows a negative diamagnetic shift, perhaps due to a rotation around C2−C6 upon complexation with Ln(III).

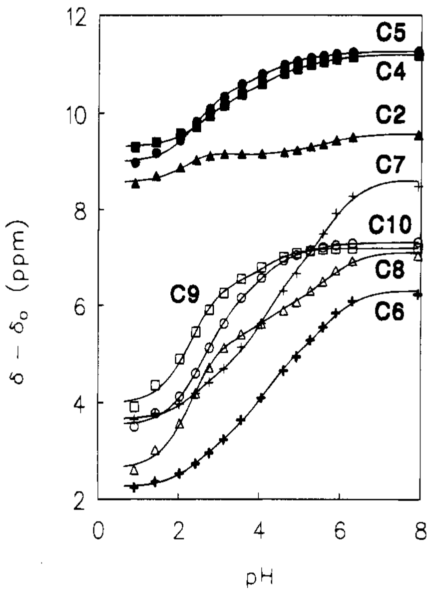


Figure 3. ^{13}C NMR shifts of L (measured at 50.3 MHz) *vs* pH in the titration of Na_4L with HCl at 298 K: C2, $\delta_0 = 100$; C4, C5, $\delta_0 = 70$; C6, $\delta_0 = 40$; C7−C10, $\delta_0 = 170$.

Table 4. ^{13}C NMR Shifts[a], δ_n of Nucleus i in H_nL, As Obtained by Multiple Regression Analysis of the Data of the Titration of Na_4L with HCl

i	δ_0	δ_1	δ_2	δ_3	δ_4
C2	109.59	109.24	109.09	109.38	108.57
C4	81.20	80.97	80.37	79.86	79.32
C5	81.27	81.13	80.56	80.16	78.99
C6	46.30	45.04	43.44	42.86	42.25
C7	178.60	176.76	174.84	174.37	173.67
C8	177.11	176.07	175.33	175.04	172.62
C9	177.21	177.20	176.47	176.23	173.97
C10	177.34	177.18	176.21	174.88	173.54

[a] Given in ppm; ±0.10.

In order to obtain insight into the stepwise protonation of the ligand L, we determined the ^{13}C NMR shifts as a function of the pH. Interpretation of the NMR titration curves (Figure 3) requires knowledge of the speciation, because several protonated forms exist simultaneously. For this ligand, the pK_as have similar values; therefore for the general formula H_nL, the n protons are not necessarily localized on specific carboxylate groups. Furthermore, intramolecular hydrogen bridging may occur. We dissected the ^{13}C NMR shifts for the contribution from each protonated form, using a multiple linear regression analysis of eq 9, where, $\delta_{obs,i}$ is the observed chemical shift for

$$\delta_{obs,i} = \sum x_n \delta_{n,i} \tag{9}$$

nucleus i, x_n is the mole fraction of H_nL, and $\delta_{n,i}$ is the chemical shift of H_nL. The optimized values for $\delta_{n,i}$ are listed in Table 4, while the solid curves in Figure 3 were calculated from eq 9 and the optimized $\delta_{n,i}$ values.

As can be seen in Table 4, protonation of L to HL leads to a shift of the ^{13}C resonance of the carboxylate carbon C7, accompanied by a somewhat smaller shift of C6, suggesting that the carboxylate group C7 has the highest pK_a (5.7). This is to be expected because C7 is the only carboxylate carbon that has no electron-withdrawing oxygen atom at the α-carbon atom. However, relatively small shifts for C8 and C2 suggest that there is some degree of hydrogen bridging between C7 and C8. Most likely, this hydrogen bridge is removed upon formation of H_2L from HL, expressed in a further decrease of the chemical shift of C7 and C6. Here, all three remaining carboxylate resonances show a decrease of the chemical shift, C10 somewhat larger than C8 and C9. Therefore, we assign the second pK_a (4.2) to C10. Probably, the larger distance between C7 and C10 compared to C7−C9 leads to a smaller influence of the already protonated C7 on the proton affinity of C10. The proton on C10 shows some hydrogen bridging

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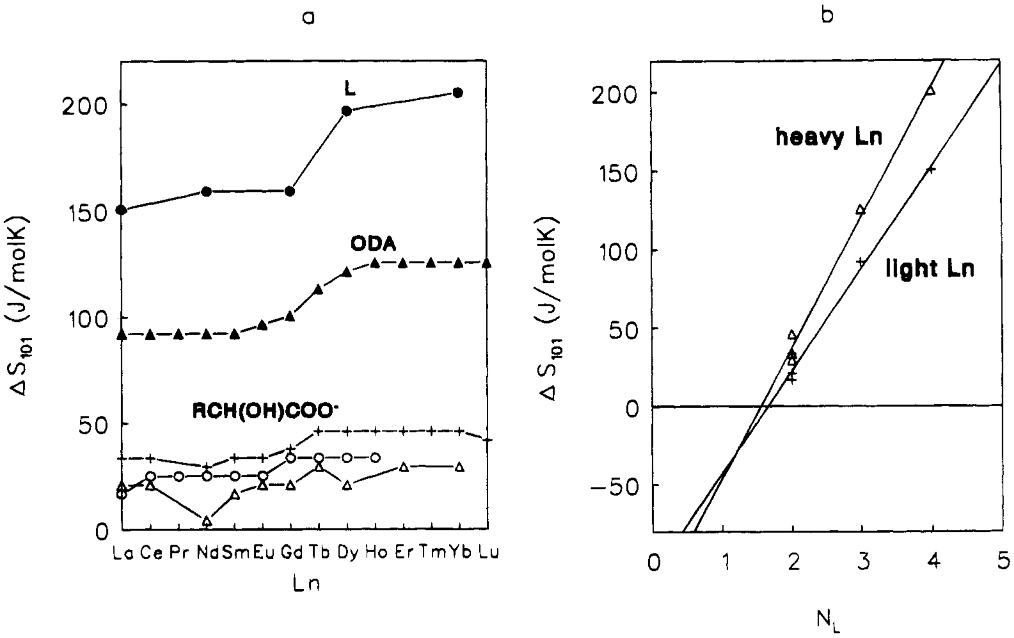

Figure 4. ΔS_{101} (at 298 K) (a) *vs* Ln(III) ($RCH(OH)COO^-$, R = H (+), CH_3 (△), Ph (○), ODA, and L) and (b) *vs* N_L (light Ln(III) (+), heavy Ln(III) (△); $N_L = 2$; $RCH(OH)COO^-$, $N_L = 3$, ODA; $N_L = 4$, L).

with C8 and C9, as suggested by the relatively small shifts of the latter. Comparison with two model compounds, L-tartrate (pK_as: 4.0 and 2.8)[44] for the backbone C9–C4–C5–C10 and malate (pK_as: 4.7 and 3.2) for C8–C2–C6–C1, confirms the assignment of pK_{a4} (HL to L) and pK_{a3} (H_2L to HL). Assignment of the remaining pK_as (2.9 and 2.3) is ambiguous because both C8 and C9 only show a large shift difference upon formation of H_4L. However, the formation of H_4L also has a large effect on C2. So, we suggest that this protonation involves the C8 carboxylate. This leaves C9 as the carboxylate group which is protonated upon the formation H_3L from H_2L. It is important, however, that the two carboxylates, C7 and C10, with the highest proton, and therefore metal, affinities are involved in the coordination to Ln(III).

Because one carboxylate group (C9) is not involved in Ln(III) complexation, we tested the complex TmL_2 as an NMR shift reagent for ^{23}Na, which is of importance for biochemical studies. The ^{23}Na NMR shift of a solution of Na_4L was monitored at increasing amounts of $TmCl_3$. The ^{23}Na shift increased linearly with the amount of Tm(III), leading to a $\Delta = 0.72$ ppm at $\varrho_L = 0.42$. When it is assumed that the TmL_2 complex binds two Na(I) ions, a bound ^{23}Na shift of only 3.4 ppm is calculated, which is small compared to e.g. $Tm(PPP)_2$ (61 ppm; PPP = tripolyphosphate).[35]

Discussion

Thermodynamics of the Complexation of 2-(Carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane with Ln(III). The Ln(III)-induced ^{17}O NMR shifts showed that both the LnL and LnL_2 complexes constitute series with constant hydration numbers. Furthermore, the Ln(III)-induced ^1H NMR shifts suggest the absence of an abrupt structural break in the middle of the Ln(III) series for both the LnL and LnL_2 complexes. We observed, however, a marked discontinuity in the values of ΔH_{101} and ΔS_{101} for the formation of LnL between Gd(III) and Dy(III). The entropy data were compared with values[44] obtained for other Ln(III) complexes with ligands that also contain neutral oxygen donors, namely $RCH(OH)COO^-$ (R = H, CH_3, Ph) and ODA (oxydiacetate: $O(CH_2COO^-)_2$) (see Figure 4a). Three important factors can be observed from these plots: (i) the occurrence of a break across the Ln(III) series is generally observed and is always at about the same position (between Eu(III) and Dy(III)); (ii) the effect is more pronounced for ligands with a higher denticity; (iii) ΔS_{101} is a measure for the denticity, N_L, of a ligand.[45–47] The slope of ΔS_{101} *vs* N_L (Figure 4b) is dependent on the position of the Ln(III) ion in the Ln(III) series: for the light Ln(III) the slope is about 67 J/(mol K) and for the heavy Ln(III) about 84 J/(mol K). This difference might be explained by a larger disturbance of the hydrational (outer) sphere for the heavy Ln(III) ions, due to their smaller ionic radii.[47]

In Figure 4b, the lines for the light and heavy Ln(III) intersect at $N_L = 1$. The rationale for this is that at $N_L = 1$ the incoming ligand replaces only one water molecule, so the number of species in the complexation equilibrium is equal for the left- and right-hand side. In an analogous plot for aminopolycarboxylate ligands the lines also dissect at $N_L = 1$. There at $N_L = 1$, $\Delta S_{101} = 0$, whereas in our case the dissection occurs at $\Delta S_{101} = -35$ J/(mol K). So, this low ΔS_{101} occurs for a ligand with a neutral oxygen donor site at $N_L = 1$ (which is the case for an alcohol or an ether) and might be due to participation of the neutral oxygen atom in hydrogen bridging within the complex.

Figure 4a shows that ΔS_{101} is about 160 J/(mol K) for Ln = La–Gd and about 200 J/(mol K) for Dy–Yb, which indicates that L is bound in a tetradentate fashion (cf. Figure 4a) both for the light and heavy Ln(III). This is in agreement with the ^{17}O NMR and the RE data, and further supported by the lack of formation of LnL_3. It can be concluded that the observed discontinuity in the entropy data is not due to structural differences in the coordinating behavior of L in LnL, but that it is a generally observed phenomenon. The break may arise from the difference in the number of coordinated water molecules between the light ($N_w = 9$) and the heavy ($N_w = 8$)

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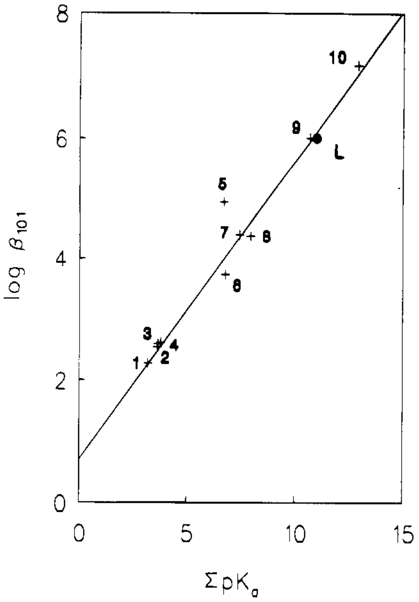

Figure 5. Plot of log β_{101} *vs* ΣpK_a for the LaL complexes of several neutral oxygen donor ligands at 298 K and $I = 0.1$ M;[44] mandelate (**1**), glycolate (**2**), lactate (**3**), 2-hydroxy-2-methylpropionate (**4**), oxydiacetate (**5**), *dl*-tartrate (**6**), *meso*-tartrate (**7**), malate (**8**), carboxymethoxysuccinate (**9**), citrate (**10**).

Ln(III) aquo ions. Also, orientation of water molecules in the second coordination sphere may be of importance: these water molecules seem to be coordinated more strongly to the heavy than to light Ln(III).[47] Upon coordination of a ligand, ΔS_{101} will be larger in the former case.

Ligands with neutral oxygen donors usually show a linear relationship between log β for formation of the Ln(III) complex and ΣpK_a.[48] For these compounds, the slope of this line is somewhat larger than for (poly)carboxylates lacking neutral oxygen donor sites.[45,48] From Figure 5, it can be seen that, for Ln = La, log $\beta = 6$ corresponds to $\Sigma pK_a = 12$, which is exactly the sum of the pK_as of the carboxylate groups (C7, C8, and C10) of L that are involved in coordination.

Geometry of 2-(Carboxymethyl)-2,4-(*R*),5-(*R*)-tricarboxy-1,3-dioxolane in LnL, LnL_2, and CaL. The ligand L coordinates in a tetradentate fashion to Ln(III), as found by Ln(III)-induced ^{17}O shift and Nd(III)-induced ^{13}C RE measurements. The assignment of the ^{13}C resonances of the free ligand was accomplished by the comparison of Nd(III)- and Gd(III)-induced REs.

As mentioned before, one carboxylate group (C9) is not involved in coordination to Ln(III). We assume that the low solubility of the LnL complexes, as observed during the ^{1}H NMR shift measurements at 358 K, is due to the formation of polynuclear complexes by coordination of the C9 carboxylate to another Ln(III) center.[49] The complex TmL_2 shows poor ^{23}Na NMR shift reagent abilities, which may be due to the large Tm(III)-Na(I) distance (about 7 Å) compared to $Tm(PPP)_2$ (5.7 Å),[35] the low coordination number for Na(I) (probably 2) compared to $Tm(PPP)_2$ (uptake up to 7 Na(I) ions),[35] and the low H^+ (pK_a = 2.9) and, therefore, Na(I) affinity of the C9 carboxylate group. The pK_a of C9 will be even lower in LnL_2 than in L, because of the presence of Ln(III).

Probably, L binds to Ca(II) in a tetradentate fashion too, for Ca(II) resembles the coordinating properties of Ln(III): the ionic radii,[10] the electrostatic bonding type,[6] the coordination numbers, and single crystal structures[11] are comparable. These features enhance the use of Ln(III) as a model for analysis of complexes of the NMR-silent Ca(II).

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(49) It is assumed that the formation of polynuclear complexes does not affect the potentiometric and calorimetric titrations because of the much lower concentrations applied in these measurements.