Lanthanide(III)-catalysed Addition of Glycolate to Maleate. Investigation of Intermediates using Multinuclear Magnetic Resonance Spectroscopy

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The lanthanum(III)-catalysed addition of glycolate to maleate to yield carboxymethoxysuccinate(3−) (cmos) is described. It is shown that the reaction only proceeds above pH 6, indicating the formation of di-ionised glycolate as a pre-equilibrium for the rate-limiting step, *i.e.* the addition of the CH_2–O^- to the olefinic bond. Due to strong complexation of La^{III} by the product cmos, the reaction requires one La^{III} ion per two cmos formed. The inhibitory effects of non-reacting strong chelators such as ethylenediaminetetra-acetate, nitrilotriacetate, and 2,6-pyridinedicarboxylate indicate the formation of mixed-ligand complexes leading to the addition reaction. This has been confirmed by Gd^{III}-induced ^{13}C relaxation rate enhancements, and Dy^{III}-induced ^{17}O shift measurements.

The patented synthesis of carboxymethoxysuccinate(3−) (cmos) by addition of glycolate(1−) (ga) to maleate(2−) (male) in aqueous alkaline slurry (pH > 11) in the presence of Ca^{II} is an interesting example of homogeneous catalysis by hard cations.[1] It has been shown that this reaction is also applicable to various other α-OH, –NHR, and –SH substituted carboxylates with α,β-unsaturated dicarboxylates.[2] These reactions are, for instance, valuable for the preparation of metal ion sequestering agents.[3–6]

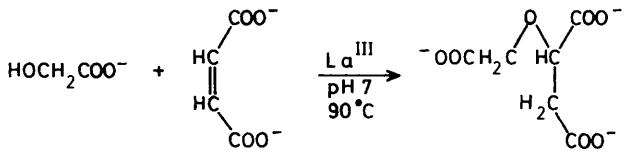
The lanthanide(III) cations (Ln^{III}) show a great chemical similarity with Ca^{II}: the ionic radii are comparable,[7] the interactions with organic ligands are largely of electrostatic nature,[8] the molecular structures of single crystals are similar to a large extent,[9] and often Ca^{II} and Ln^{III} are interchangeable in enzymes.[10–12] Consequently, paramagnetic Ln^{III} cations can act as a probe for the 'n.m.r. silent' Ca^{II} in multinuclear n.m.r. studies.[9,13] This in fact has been applied by us for structural investigations of various lanthanide complexes in solution.[9,14,15]

On the other hand, the difference in charge between Ca^{II} and Ln^{III} results in some important differences in the physical and chemical characteristics of these ions. For instance, the complexes of Ln^{III} cations have a relatively high stability[16] and Ln^{III}-co-ordinated alcohol groups have a relatively high acidity.[17] Therefore, we have investigated the applicability of Ln^{III} cations in the addition of glycolate to maleate. The paramagnetic properties of these cations were utilized for the detection and structure elucidation of mixed-ligand complexes formed prior to reaction.

So far, the use of Ln^{III} catalysis without changing the oxidation state of the cation is relatively scarce in the fast developing field of applications of Ln^{III} cations in organic synthesis.[18,19]

Experimental

Materials.—The $LnCl_3 \cdot xH_2O$ salts were purchased from Alfa Products. The Ln^{III} content was determined by ethylenediaminetetra-acetate titration with arsenazo I as the indicator. Glycolic acid (Hga) was obtained from Merck-Schuchardt. The other chemicals used were obtained from Aldrich. Dowex 50 W X8 50—100 mesh (H^+ form) was washed several times with demineralized water before use. The 10 μm Polygosil C18 column material was purchased from Macherey-Nagel (Düren, West Germany). The AG1-X8 (500—100 mesh) anion exchange material (Cl^- form) was purchased from Biorad.



ga male cmos

Kinetic Measurements.—A stock solution of glycolate (0.5 mol dm^{-3}) and maleate (0.5 mol dm^{-3}) in water was prepared by neutralization of the corresponding acids with NaOH. The reactions were carried out with 8 cm^3 of this stock solution, upon addition of the required amount of $LaCl_3 \cdot 6H_2O$, adjustment of the pH to the desired value with a dilute NaOH solution (0.5 mol dm^{-3}) and bringing the total volume to 10 cm^3 with water. The reaction mixture obtained (0.40 mol dm^{-3} in both glycolate and maleate) was heated at 363 K in a thermostatted reaction vessel with stirring. At suitable time intervals samples (100 mm^3) were taken, diluted with water (0.5 cm^3), acidified with Dowex H^+ (pH < 2), and analysed by h.p.l.c. The h.p.l.c. analyses were carried out using a Waters Assoc. M45 pump, a Rheodyne 7125 injection valve, a 4.6 × 300 mm 10 μm Polygosil C18 column, a Waters Assoc. R401 detector, and a Spectra-Physics SP4100 computing integrator. Water acidified with 0.01 mol dm^{-3} trifluoroacetic acid was used as the mobile phase at a flow rate of 1.0 cm^3 min^{-1}. The mobile phase was filtered and degassed by sonification *in vacuo* before use.

The initial rate was determined by the tangent at $t = 0$ of the graph of the maleate conversion *versus* time.

N.M.R. Measurements.—All n.m.r. experiments were performed on a Nicolet NT-200 WB spectrometer at 298 K. The longitudinal ^{13}C relaxation rates were measured in D_2O containing 1.0 mol dm^{-3} of ligand and in the case of two ligands 1.0 mol dm^{-3} each. The pD was adjusted to 8 with a NaOD solution. A 12-mm sample tube containing 5.00 cm^3 of this solution was used for the measurements. The $Gd(NO_3)_3$ solution (18 mmol dm^{-3}) was added *via* a microsyringe. Six measurements at ρ values (molar ratio Gd^{III}:ligand) varying between 0 and 3 × 10^{-4} were carried out. The relaxation rates were obtained with an inversion recovery method [($90_x°$ $180_y°$ $90_x°$–τ–$90_x°$) pulse sequence]. The magnetization curves were fitted with a three parameter equation suggested by Levy and Peat[20] to correct for inhomogeneous H_1 fields which produce incomplete inversion by the 180° pulse. The relaxation rate

enhancements as a function of ρ were fitted with a linear function to obtain the induced relaxation rates ($1/T_1$) at ρ = 1. The intermolecular relaxation rate enhancement by Gd^{III} was neglected because of its low contribution in D_2O solutions.

The ^{17}O n.m.r. spectra of the water signal were recorded using 16-K data points and a spectral width of 20 kHz. A pulse duration of 30 μs (90° pulse) was followed by an acquisition time of 530 ms. Usually, about 200—400 transients were sufficient to obtain a good signal-to-noise ratio. The ^{17}O chemical shifts were measured with respect to the 27.13 MHz observe frequency. The ^2H signal of ^2H_2O was used for internal lock. The sample contained 0.35 mol dm^{-3} of ligand and in the case of two ligands 0.35 mol dm^{-3} each. The pD was adjusted with a NaOD solution. A 12-mm sample tube containing 5 cm^3 of this solution was used for the measurements. $DyCl_3 \cdot 6H_2O$ was added in portions varying between 10 and 20 mg. After addition the pD was readjusted by addition of NaOD. The Dy^{III} induced shifts *versus* the molar ratio Dy^{III}:water were fitted with a linear function to give the induced shift of water per added Dy^{III}.

Synthesis of Carboxymethoxysuccinate.—A solution of sodium glycolate (0.50 mol dm^{-3}), disodium maleate (0.50 mol dm^{-3}), and $LaCl_3$ (0.25 mol dm^{-3}) in water (0.05 dm^3) was prepared. The pH was adjusted to 7.5 with a dilute NaOH solution. The solution was heated at 363 K in a thermostatted vessel for 16 h. During the first 6 h the reaction proceeded in a clear solution. After standing overnight a slurry was present. After addition of water (150 cm^3) and Dowex H^+ (20 cm^3), the slurry was heated at 348 K to dissolve the precipitate. The solution obtained was cooled, neutralized with NaOH to pH 5, and then purified by anion exchange chromatography *via* a AG1-X8 anion exchange column (formate form). A gradient was applied from 0 to 2.0 mol dm^{-3} formic acid and the fractions obtained were analysed by h.p.l.c. and concentrated *in vacuo*. The concentrated solutions were coevaporated with water a few times to remove the formic acid. The remaining solution was neutralised with NaOH (1 mol dm^{-3}) and lyophilised. After drying *in vacuo* under P_2O_5, 4.45 g of $Na_3(cmos) \cdot 2.2H_2O$ were obtained (14.98 mmol, 60%). ^1H N.m.r. [D_2O, Bu^tOH reference (1.2 p.p.m.)]: δ, 4.03 (1 H, dd, $J_{3,4'}$ 9.16, $J_{3,4}$ 3.91, $C^3HC^4H_2$), 3.91 (1 H, d, $J_{1,1'}$ −15.0, $OOCC^1H_2O$), 3.80 (1 H, d, $J_{1,1'}$ −15.0, $OOCC^1H_2O$), 2.56 (1 H, dd, $J_{3,4}$ 3.91, $J_{4,4'}$ −14.9, $C^3HC^4H_2$), 2.43 (1 H, dd, $J_{3,4'}$ 9.16, $J_{4,4'}$ −14.9, $C^3HC^4H_2$).

Results and Discussion

Kinetics.—The original procedure[1] for preparing cmos consisted of refluxing an aqueous slurry of maleic acid and glycolic acid (1.0 mol dm^{-3} each) with $Ca(OH)_2$ (1.8 mol dm^{-3}) at pH 11.4. We have now been able to perform this reaction with sodium glycolate and disodium maleate at lower pH (*ca.* 7—8) and 363 K in a homogeneous solution with 99% selectivity towards cmos formation by using lanthanum(III) trichloride (0.5 mol equivalent) (see Figure 1). Only trace amounts of malate and fumarate were formed by competitive H_2O addition to maleate.

The reaction rate appeared to be strongly dependent upon the pH at 5 < pH < 9 (Figure 2). No reaction was observed at pH <5, even after prolonged reaction times, whereas precipitation of La^{III} hydroxides occurred at pH >9.

The steep increase in reaction rate at pH >5 is in agreement with the reported dissociation constant of the CH_2OH group in Ln^{III}-co-ordinated glycolate.[17] In this pH range dissociation of water ligands occurs as well.[21] This strongly suggests that dissociation of the La^{III}-co-ordinated hydroxyl group of glycolate and/or co-ordinated water ligands are important in this reaction. The high selectivity towards ether formation

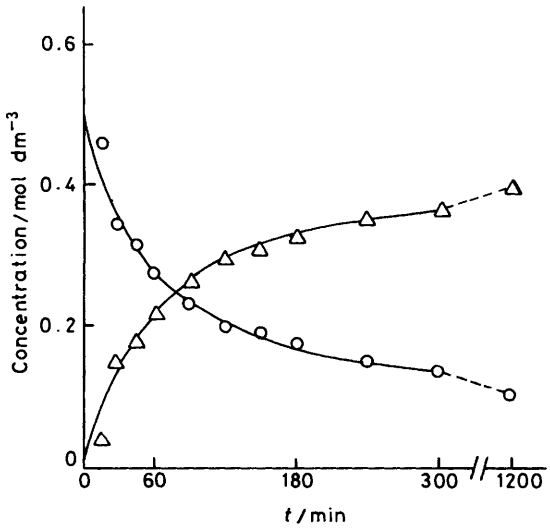


Figure 1. Addition of glycolate (0.5 mol dm^{-3}) to maleate (0.5 mol dm^{-3}) mediated by La^{III} (0.25 mol dm^{-3}) at pH 7.5 and T = 363 K. pH determined at 298 K: (○) maleate, (△) carboxymethoxysuccinate

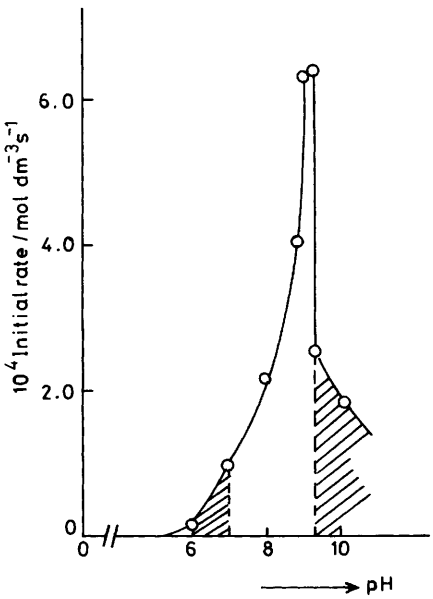


Figure 2. Initial reaction rate as function of pH. pH measured at 298 K. 1.0 mol dm^{-3} maleate, 1.2 mol dm^{-3} glycolate, and 0.2 mol dm^{-3} $LaCl_3$ in water at 363 K. (////) indicates precipitation

(99%), however, shows that ionisation of the CH_2OH group of La^{III}-co-ordinated glycolate is an essential factor in this reaction. The analogous dependence upon the pH of the reaction catalysed by Ca^{II}, where a steep increase occurs at pH 11, corresponds once again with the pK_a of the Ca^{II}-co-ordinated hydroxy group of glycolate and with the pK_a of Ca^{II}-co-ordinated water.[17b,21] Most probably, within the first co-ordination sphere an equilibrium between di-ionised glycolate and mono-ionised glycolate exists, coupled with a co-ordinated hydroxide–water equilibrium.

The reaction rate decreases with time at constant pH, suggesting the reaction is inhibited by the product cmos (Figure 1). The inhibitory effect reaches its maximum when *ca.* 2 mol of cmos per mol La^{III} are formed. This is in accordance with the high stability constants of the La^{III}–cmos complexes compared

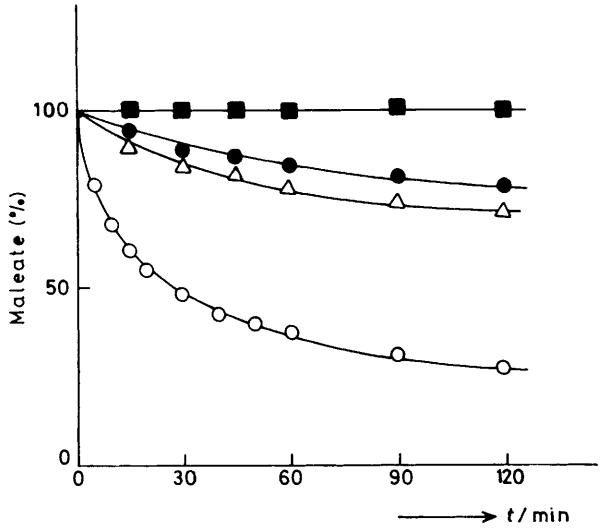


Figure 3. Effect of chelating agents on the maleate conversion rate. 0.40 mol dm^{-3} maleate, 0.40 mol dm^{-3} glycolate, 0.20 mol dm^{-3} $LaCl_3$, and 0.20 mol dm^{-3} edta (■), nta (●), or pydca (△) were used. (○) Without chelating agent; pH = 8 and T = 363 K

to those of the reactants* and with the fact that below a Ln^{III}:ligand molar ratio of 0.5 the complex $[Ln(cmos)_2(H_2O)]^{3-}$ predominates.[14] The inhibition by the latter complex suggests that ternary complexes of La^{III}, maleate, and glycolate play an important role in the addition reaction. In order to establish this, we have performed the synthesis of cmos in the presence of strongly chelating ligands, like ethylenediaminetetra-acetate(4−) (edta),[22,13] nitrilotriacetate(3−) (nta),[23-25] and 2,6-pyridinedicarboxylate(2−) (pydca)[26-28] which occupy six, four, and three ligand co-ordination sites of the La^{III} ion, respectively, at pH 8. The results shown in Figure 3 demonstrate the requirement of at least five 'free' ligand positions, indicating that the addition occurs in a complex in which both glycolate and maleate are co-ordinated.

Thus, the rate equation at a constant pH may be given by equation (1) in which $[La(male)_m(ga - H)_n]$ is the predomin-

$$d[cmos]/dt = k_0[La(male)_m(ga - H)_n] + k_1[La(cmos)(male)_x(ga - H)_y] \quad (1)$$

ating ternary complex between La^{III}, maleate, and glycolate (di-ionized, ga − H) and $[La(cmos)(male)_x(ga - H)_y]$ is the analogous one with a cmos ligand added.

Below 50% conversion, it may be assumed that the concentration of $[La(cmos)_2]^{3-}$ is negligible and that each cmos formed is bound to a La^{III} cation and, therefore, the mass balance can be given by equation (2). If [cmos] = x,

$$[La]_{tot} = [La(male)_m(ga - H)_n] + [La(cmos)(male)_x(ga - H)_y] \quad (2)$$

combination of (1) and (2) gives equation (3), where $c = k_1/k_0$.

$$dx/dt = k_0\{[La]_{tot} + x(c - 1)\} \quad (3)$$

Upon integration of equation (3) we obtain equation (4) where

* By comparison with the stability constants of La^{III}–citrate complexes the log K values of the 1:1 and 1:2 La–cmos complexes were estimated to be 8.0 and 4.0, respectively. For maleate log K_1 is 3.45 and for glycolate log K_1 is 2.18 at I = 1.0 mol dm^{-3}.[16]

Table 1. Influence of the La^{III} concentration on the reaction rate of cmos formation[a]

$[La^{III}]$/ mol dm^{-3}	k_1/k_0	10^4k_0/s^{-1}	[cmos][b]/ mol dm^{-3}
0.0726	0.095	6.42	0.095
0.0872	0.154	6.09	0.117
0.1120	0.200	5.71	0.160
0.1311	0.192	6.47	0.209
0.1471	0.175	7.06	0.229
0.1678	0.170	8.31	0.256

[a] 0.398 mol dm^{-3} maleate and 0.401 mol dm^{-3} glycolate at T = 363 K; pH 8 at 298 K. [b] After 2 h reaction.

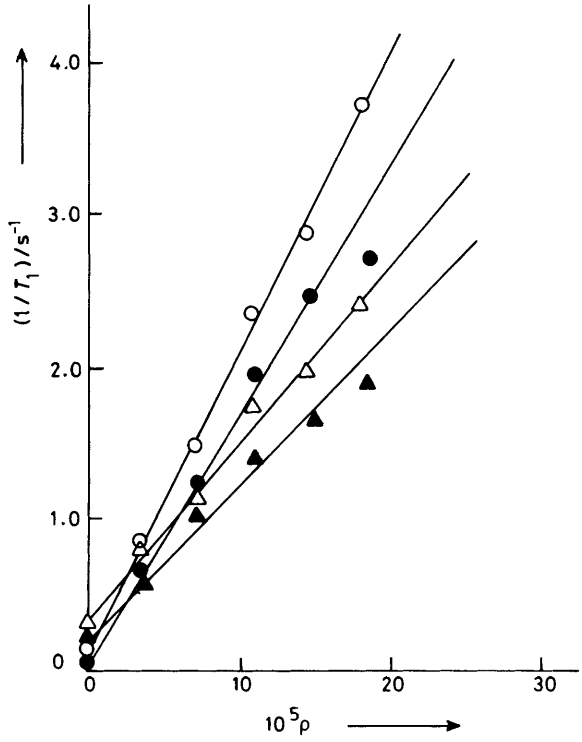


Figure 4. Gd^{III}-induced ^{13}C relaxation rate enhancement of glycolate [COO^- (●), CH_2OH (▲)] and of glycolate in a 1:1 mixture with maleate [COO^- (○), CH_2OH (△)] as a function of the Gd^{III} to glycolate ratio (ρ). Concentration of the ligand = 1.0 mol dm^{-3}, T = 298 K

$$[cmos]_t = \{[La]_{tot}/(c - 1)\}[e^{k_0t(c-1)} - 1] \quad (4)$$

$[cmos]_t$ is the concentration of cmos formed at time t.

Fitting the data from the experiments at various La^{III} concentrations with this function gives the k_0 and c ($=k_1/k_0$) values (see Table 1), which are rather independent of $[La]_{tot}$. We obtain an average value of k_0 of 7 × 10^{-4} s^{-1} and a shielding factor ($1/c$) of *ca.* 6.1 when one cmos ligand is present. This high shielding factor suggests that any cmos that is tetra- or tridentate to La^{III} gives rise to a large inhibition of the reaction.[14] The followed kinetic approach is rather rough, a more detailed kinetic investigation is in progress.

To establish that mixed-ligand complexes are involved in the reaction, we have used multinuclear n.m.r. spectroscopy at 298 K, under which condition no reaction occurs. We have selected Gd^{III}-induced relaxation rate enhancements and Dy^{III}-

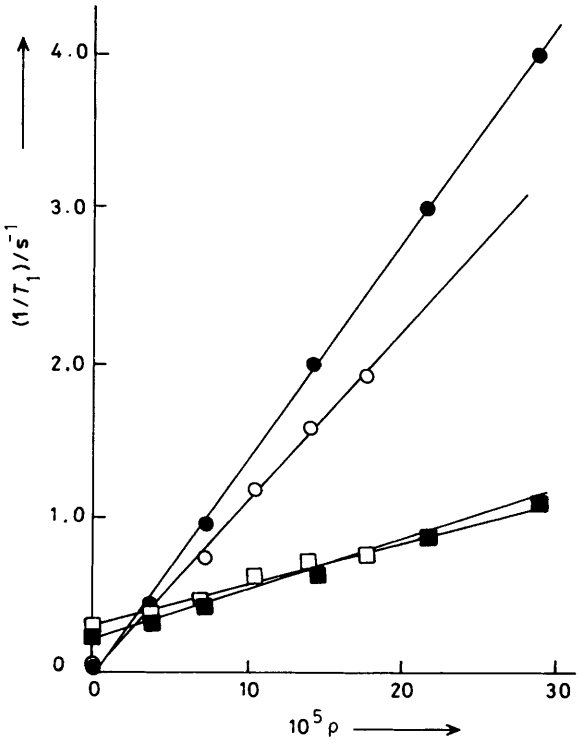


Figure 5. Gd^{III}-induced ^{13}C relaxation rate enhancement of maleate [COO^- (●), C=C (■)] and of maleate in a 1:1 mixture with glycolate [COO^- (○), C=C (□)] as a function of the Gd^{III} to maleate ratio (ρ). Concentration of the ligand = 1.0 mol dm^{-3}, T = 298 K

induced ^{17}O shifts to study the Ln^{III} co-ordination in these systems prior to reaction.[9,29] In all cases averaged spectra of the complexed and free ligands were obtained, due to fast ligand exchange on the n.m.r. time-scale. Gd^{III}-induced relaxation rate enhancements and Dy^{III}-induced ^{17}O shifts are both performed at low Ln^{III} to ligand ratios, comparable to that in the kinetic experiments.

Gd^{III}-*Induced* ^{13}C *Relaxation Rate Enhancements.*—The ^{13}C longitudinal relaxation rate enhancements,[30] $(1/T_1)_i$, of solutions in D_2O of glycolate (1.0 mol dm^{-3}), maleate (1.0 mol dm^{-3}), and of a solution containing both of these ligands (1.0 mol dm^{-3} each) were measured upon successive additions of small amounts of Gd^{III} ($\rho < 3.0 \times 10^{-4}$). In all cases a linear relationship between the relaxation rate enhancement and ρ was found (see Figures 4 and 5).

Assuming that all Gd^{III} added is bound and that the mean residence time of the ligand in a Gd^{III} complex is short with respect to the longitudinal relaxation time (T_1) of the ^{13}C nuclei of the ligand, the measured relaxation rate enhancement extrapolated to $\rho = 1$, $(1/T_1)_i$, can be related to the complex structure *via* equation (5), where i is the nucleus under study, k is

$$(1/T_1)_i = kn\tau_r/r_i^6 \quad (5)$$

a constant, n is the number of co-ordinated ligands, τ_r is the rotational correlation time, and r_i is the distance between the nucleus i and Gd^{III}. The ratios $R_{i/j}$ between relaxation rates of two nuclei i and j in a complex are intrinsic values of the Gd^{III}-co-ordinated ligand structure, equation (6).

$$R_{i/j} = (1/T_1)_i/(1/T_1)_j = r_i^{-6}/r_j^{-6} \quad (6)$$

The $R_{i/j}$ value for glycolate shows that it co-ordinates in a bidentate manner *via* the hydroxy and carboxylate group (Figure 4 and Table 2), which is in agreement with our previous investigations.[30] From the potentiometrically determined Gd^{III} association constants,[16] it can be calculated that 96% of the Gd^{III} is bound by three glycolate ligands within the ρ range used ($< 1.8 \times 10^{-4}$ at 1.00 mol dm^{-3} glycolate).* Previously, we have determined the structure of the 1:3 Gd^{III}–glycolate complex in solution.[15] Using that structure and equation (5) with $n = 3$ and the Stokes–Einstein relation, the molecular radius of the complex can be estimated to be *ca.* 4.7 Å, which is consistent with the proposed structure.

A $R_{i/j}$ value of 4.30 is obtained for maleate (Figure 5, Table 2). Using the crystal structure of Ca^{II}–maleate[36] as a model for the geometry of the Gd^{III} complex, $R_{i/j}$ values of 2.58 and 9.34 are obtained for the seven-membered chelate structure involving two co-ordinated carboxylates (in a monodentate fashion) and a chelate structure in which only one carboxylate is co-ordinated (in a bidentate fashion), respectively. Both modes of co-ordination are present in the *X*-ray structure. The experimental $R_{i/j} = 4.30$ from n.m.r., therefore, suggests the occurrence of both chelate structures at a low Gd^{III} to maleate ratio (ρ) of which the seven-membered chelate is slightly more abundant. In this concentration range the occurrence of binuclear complexes does not seem very likely. From the potentiometrically determined association constants,[16,37] it can be calculated that under the conditions applied, Gd^{III} is almost exclusively present as the 1:2 Gd^{III}–maleate complex.

In a 1:1 mixture of glycolate and maleate Gd^{III} enhances the longitudinal relaxation rates ($1/T_1$) of both glycolate and maleate (Figures 4 and 5, Table 3). From a comparison of these relaxation rates, extrapolated to a Gd^{III} to ligand (maleate or glycolate) ratio $\rho = 1$, with those from the experiments with the individual ligands described above, we conclude that here predominantly ternary Gd^{III} complexes with one maleate and two–three glycolates are present. It may be noted that without ternary complex formation the concentration of Gd^{III}-bound glycolate and Gd^{III}-bound maleate would be 1.0×10^{-4} and 2.9×10^{-4} mol dm^{-3}, respectively, under these conditions.

Table 2. ^{13}C Ratios of the Gd^{III}-induced longitudinal relaxation rate enhancements*

Ligand	$R_{COO^-/C=C}$	R_{COO^-/CH_2}
Maleate	4.3	
Glycolate		1.6
Maleate + glycolate	4.1	1.7

* For conditions see Figures 3 and 4.

Table 3. Gd^{III}-induced relaxation rate enhancements, 10^{-3} $(1/T_1)/s^{-1}$ *

	Maleate		Glycolate	
Ligand	COO^-	C=C	COO^-	CH_2OH
Maleate	14.1	3.28		
Glycolate			16.9	10.4
Maleate + glycolate	11.0	2.68	20.2	11.9

* For conditions see Figures 3 and 4. Values obtained by extrapolation to Gd^{III}:ligand ratio $\rho = 1$.

* From several studies it has been concluded that a 1:4 Ln–glycolate complex can be formed.[31–35] Because of random computational errors the stability constants β_4 are, however, not very reliable. We assume that under the conditions applied, the concentration of a 1:4 Ln–glycolate complex is negligible.

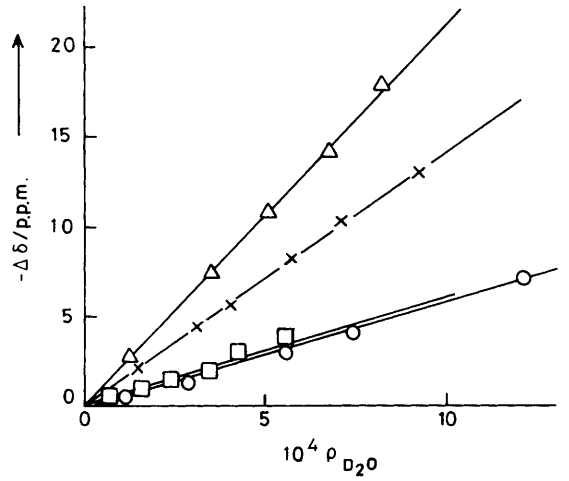


Figure 6. The Dy^{III}-induced ^{17}O chemical shift ($\Delta\delta$) of D_2O as a function of the Dy^{III}:D_2O ratio: ($\triangle$) without organic ligand, ($\times$) maleate (0.35 mol dm^{-3}), ($\square$) glycolate (0.35 mol dm^{-3}) (pD 6.5), and ($\bigcirc$) maleate + glycolate (0.35 mol dm^{-3} each); T = 298 K

Comparing these concentrations with those in the experiments with each of the ligands separately (5.2 and 3.6 × 10^{-4} mol dm^{-3}, respectively) a decrease in relaxation rate enhancement of all ligand nuclei should occur for both glycolate and maleate, when no ternary complexes are formed. The slightly higher $1/T_1$ value for glycolate in the mixed-ligand system (see Figures 3 and 4) may be the result of a τ_r value which is somewhat higher in the Gd^{III}–glycolate–maleate than in the Gd^{III}–glycolate complex. Analogously, the relative decrease of $1/T_1$ of the maleate ligand is in accordance with one maleate ligand bound in the mixed-ligand complexes.

The small variation in $R_{i/j}$ values in all experiments (Table 2) shows that the ligands are co-ordinated in the same way in the binary and ternary systems.

Dy^{III}-*Induced* ^{17}O *Shifts of* D_2O.—To establish the formation of mixed-ligand complexes of Ln^{III} ions with one maleate and two or three glycolates at low Ln^{III} to ligand ratios, we have determined the number of co-ordinated ligand oxygens with the use of Dy^{III}-induced ^{17}O shift measurements.[38] Indirectly, this can be done by determination of the number of co-ordinated waters in the first co-ordination sphere of the Dy^{III} cation. In the absence of other ligands nine D_2O ligands are co-ordinated in the first co-ordination sphere of Dy^{III}. The Dy^{III}-induced shifts are a linear function of the Dy^{III} to D_2O molar ratio (σ_{D_2O}) as shown in Figure 6.

From extrapolation to ρ_{D_2O} = 1:9 the shift contribution for each co-ordinated D_2O ligand was estimated to be 2 350 p.p.m. at 298 K. Previously, we have shown that this shift contribution is independent of the presence of other ligands.[38] Thus, the number of D_2O ligands in the first co-ordination sphere of a Dy^{III} complex can be calculated from extrapolation of the Dy^{III}-induced shift to ρ_{D_2O} = 1, followed by division by 2 350 p.p.m. The numbers of waters in the first co-ordination sphere estimated in this way are given in Table 4 for the various ligands.

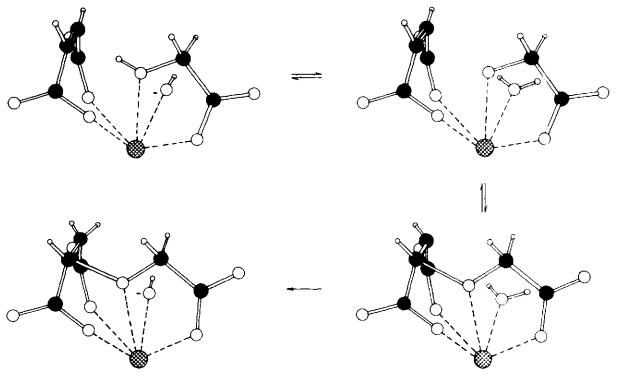
For glycolate, the number of co-ordinated waters is constant (2.6) throughout the pH range 4.6—6.5, although ionization of the α-OH group occurs in this range.[17] From the association constants of Dy^{III}–glycolate complexes[16,†] it can be calculated that under the conditions applied (0.0628 mol dm^{-3} Dy^{III} and 0.35 mol dm^{-3} glycolate) the average number of co-ordinated waters is 3.4, assuming that each glycolate expels two waters upon complexation. This value fits reasonably well with the experimentally found value of 2.6.

†As on p. 2726.

Table 4. Number of co-ordinated waters in $Dy^{III}(D_2O)_x$(ligand) complexes as determined from Dy^{III}-induced ^{17}O n.m.r. chemical shifts*

Organic ligand	pD	10^{-4} Induced shift/ p.p.m.	Number of co-ordinated waters
None	4.5	2.12	9
Maleate	6.5	1.42	6.0
Glycolate	6.5	0.61	2.6
Glycolate	5.6	0.59	2.5
Glycolate	4.5	0.62	2.6
Maleate + glycolate	6.5	0.58	2.5

* For conditions see Figure 5.



Scheme.

Analogously, it can be calculated that in the Dy^{III}–maleate system, a 1:2 Dy^{III}–maleate complex with six bound waters predominates. The Gd^{III}-induced relaxation rate enhancements have shown that maleate is bound in two fashions: as a seven-membered chelate with two carboxylate oxygens co-ordinated and bidentate co-ordination *via* a single carboxylate group. The average number of six waters in the first co-ordination sphere might be explained by expulsion of two waters from the first co-ordination sphere of Dy^{III} upon co-ordination of the seven-membered chelate and only one water upon co-ordination in the other (sterically less demanding) fashion.

In the glycolate–maleate (molar ratio 1:1) mixed-ligand system the Dy^{III}-induced water shifts indicate that the average number of co-ordinated waters is 2.5. If the occurrence of mixed complexes were negligible the number of waters co-ordinated in the Dy^{III}–maleate–glycolate system can be calculated to be 5.7. This substantial deviation once again confirms mixed-ligand complex formation with predominance of complexes with two or three bound glycolate ligands and one bound maleate.

Reaction Mechanism.—The n.m.r. data show that the La^{III}-catalysed addition of glycolate to maleate occurs *via* a mixed-ligand complex of the lanthanum ion. The chelate structure in which the maleate is co-ordinated in a bidentate manner to form the seven-membered chelate most likely is the reactive form. In this complex structure the olefinic carbons are in close proximity to the ionised hydroxyl group of glycolate. So, the La^{III} cation is not only responsible for the glycolate hydroxyl ionisation, but also functions as a template (Scheme).

Because of the large angles of both carboxylate groups with the plane C(1),C(2),C(3),C(4) in the crystal structure of Ca^{II}–maleate (27.9 and 91.7°)[36] and in other crystal structures of maleate salts[39] there is probably hardly any π-bond conjugation of the olefinic carbons with one of the carboxylate

groups, neither in the initial state nor in the transition state of the glycolate–maleate addition reaction. Concomitant proton transfer from water in the first or second co-ordination sphere towards the developing carbanion, therefore, has to be an important factor in this Michael-type reaction.

The importance of mixed-ligand complexes is recently demonstrated by Sargeson and co-workers,[40] for the addition of ethylenediamine or glycine to maleate mediated by Co^{III}. The *X*-ray structure of the mixed complex between ethylenediamine and maleate shows a close proximity of the $-NH_2$ group to the olefinic carbon atoms of maleate (3.15 and 3.14 Å in the case of ethylenediamine).

It may be noted that the pH-dependent reaction rate originates from an equilibrium between an ionised water ligand and ionisation of the La^{III}-co-ordinated α-OH group of glycolate (Scheme). The addition reaction in the presence of Ca^{II} requires more alkaline conditions (pH > 11)[1] due to the lower electrostatic interaction of Ca^{II} with respect to La^{III}.

Another aspect of this reaction may be stabilization of the transition state *via* co-ordination to La^{III}. The relatively high association constant of cmos with respect to that of the ternary La^{III}–glycolate–maleate complexes is expected to be a driving force in the reaction. Most likely, the transition state is cmos-like according to the late transition state in the Hammond–Curtis principle.

The biological counterpart of the addition of glycolate to maleate is the enzymic hydration in the citric cycle, as catalysed by aconitase[41,42] and maleate hydratase.[43] There iron–sulphur clusters are responsible for the catalytic activity. Under physiological conditions the iron-bound water ligands are ionised. In this respect, with La^{III} cations we are able to mimic this kind of addition and, even more importantly, we are able to extend the reaction to more complex hydroxyl-containing systems.

Acknowledgements

This investigation was carried out under the auspices of the Netherlands Foundation for Chemical Research (S.O.N.) with support from the Netherlands Organisation for the Advancement of Pure Research (Z.W.O.). Thanks are due to Mr. A Sinnema for performing some of the n.m.r. analyses and to Dr. F. van Rantwijk and Mr. E. P. Sedlick for assistance with the h.p.l.c. analyses.

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Received 17*th November* 1987; *Paper* 7/2036