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The Addition of Hydroxyl Compounds to Unsaturated Carboxylic Acids Homogeneously Catalysed by Lanthanide(III)

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Abstract: La(III) is a good catalyst for the addition of hydroxyl compounds to unsaturated carboxylic acids, yielding etherpolycarboxylates The La(III) can be applied as the chloride, the alkoxide, or the oxide In the latter case *in situ* conversion to the La(III) salt of the unsaturated carboxylic acid is required Lanthanum alkoxides, which combine the activation of the reactants by La(III) with a high basicity of the solution, give the highest addition reaction rates The addition of ethylene glycol to acetylenedicarboxylate yields the dioxolane **12** upon removal of La(III) ^{13}C and ^{17}O NMR prove that the production of this ketalised oxaloacetate proceeds *via* two intermediates, namely the monoadduct **10** and the diadduct **11**, of which the latter only exists as a La(III)-complex The addition of glycerol to **8** yields a mixture of two dioxolanes **15** and **16** in a molar ratio of about 2 5, which indicates that the cyclisation is thermodynamically controlled

INTRODUCTION

Etherpolycarboxylates are promising compounds for use as metal sequestrants They have excellent complexing abilities[1-3] and are in general readily biodegradable,[1] whereas the toxicity is low[4] Specific use can be in detergent formulations[5-7]

It has been shown that multivalent metal ions are useful catalysts in aqueous and alcoholic media for the synthesis of etherpolycarboxylates[8-10] Thus these compounds can be obtained by a Ca(II)-catalysed Michael-type addition[2] of alcohols to unsaturated carboxylic acids However, Ca(II) has a relatively low charge density so deprotonation of the hydroxyl group, which is necessary for the addition reaction, only occurs at high pH (above 10) We have found that these reactions can be performed under much milder conditions under the influence of Ln(III) ions, which have high coordination numbers (8 to 9 in aqueous medium[11-13]) and a relatively large charge density Therefore, deprotonation of coordinated hydroxyl groups occurs at neutral pH[8,14,15]

In the addition reaction the Ln(III) cation accelerates the reaction in two ways It functions as a template,[8,16] but more importantly, it activates both reactants Firstly, the electronic repulsion of the hydroxyl proton of the alcohol by the Ln(III) cation[14,15] enhances its acidity Secondly, the coordination of the carboxylate group of the unsaturated carboxylate causes an increase of the electrophilicity of the β-carbon atom Further advantages of Ln(III) ions are the fast exchangeability[17] of ligands and the almost purely electrostatic binding type[18] of the metal ligand

bonds which provides great flexibility to complex geometries Additional advantages of the use of Ln(III) ions are their paramagnetic properties,[17] which allow study of the complexes involved by spectroscopic methods, such as multinuclear NMR

Complexing molecules that have been synthesised with Ln(III) as template have usually also good sequestering abilities for Ca(II), because of the great chemical similarities between Ln(III) and Ca(II). ionic radii are comparable,[19] bonding of organic ligands is largely electrostatic,[18] and the molecular structures of single crystals are similar to a large extent.[20]

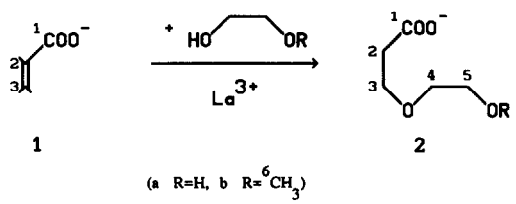
In the present paper we report the results of a study on the addition of ethylene glycol (EG), ethylene glycol monomethyl ether (EGMME), and glycerol (GL) to acrylic acid and acetylene mono- and di-carboxylic acid, catalysed by Ln(III) under mild reaction conditions Model reactions were studied, mechanistic aspects are discussed, and a comparison is made of some lanthanide catalyst systems

RESULTS AND DISCUSSION

Alkoxylations of Acrylate

When sodium acrylate (1) was dissolved (1 3 mol dm^{-3}) in EG and heated to 90 °C only 7 % of the addition product 3-(2-hydroxy-ethoxy)propionic acid (**2a**) was formed after 48 h (Scheme 1a, R=H) This reaction was accelerated substantially by addition of La(III)· in the presence of an equimolar amount of $LaCl_3.3H_2O$ the conversion towards **2a** was 60 % after 24 and almost complete after 48 h A small amount (less than 5 %) of the intermolecular esterification product of **2a** was obtained as a side-product

Previously it has been shown that $LaCl_3$ in EG is solvated by EG and that chloride ions are not in the first coordination sphere of La(III) [10] Coordination of EG by La(III) results in a substantial decrease of the pK_a of its hydroxy groups,[8,14,15] and consequently an acidic environment is reached under the conditions described above. Obviously, the concentration of the reactive species, deprotonated EG coordinated to La(III), can be further increased by an increase of the basicity of the reaction mixture. When one equivalent (La with respect to 1) La_2O_3 was used instead of $LaCl_3$ almost no catalytic effect was observed It appeared that the La_2O_3 did not dissolve, which suggests that no heterogeneous catalysis by La_2O_3 occurs However, when 1 is partly or completely added as the free acid, then indeed catalysis is observed, which can be explained by solubilisation of La_2O_3, after which



1 2

(a R=H, b R=$^{6}CH_3$)

Scheme 1

Table 1. Relative Activity of Some Lanthanum Catalyst Systems in the Addition Reaction of EG to Acrylate at 90 °C

catalyst	La(III) mol dm^{-3}	acrylic acid mol dm^{-3}	sodium acrylate mol dm^{-3}	relative initial rate[a]
-	-	-	1 0	1
1 0 M $LaCl_3$	1 0	-	1 0	17 2
0 5 M La_2O_3	1 0	-	1 0	2 0
0 05 M La_2O_3	0 1	0 1	0 9	23 8
0 25 M La_2O_3	0 5	0 5	0 5	54 0
0 5 M La_2O_3	1 0	1 0	-	68 3
1 5 M $KOCH_2CH_2OH$	-	-	1 0	186
0 5 M $La(OMe)(OiPr)_2$[b]	0 5	-	1 0	276

a absolute initial rate for the non-catalysed reaction 0 00167 mol dm^3 h^1

b containing 0 5 mol dm^{-3} THF

a slightly basic or neutral environment is reached Optimisation showed that the highest rates are obtained when an equimolar amount of acid is added relative to the amount of La(III) Selected conditions with their catalytic effects are described in Table 1

Small amounts (up to 20 %) of water did not interfere in these reactions $LaCl_3$ can be added in a hydrated form Larger reaction rates as in the reactions with La_2O_3 could be obtained with the potassium salt of deprotonated EG as the base in the absence of La(III) (see Table 1), but then strictly anhydrous conditions were required, analogous to literature reports[21] With lanthanum alkoxides an acceleration with a factor of 1 5 compared to the latter case was observed, which may be ascribed to the template effect and the activation of the terminal vinylic carbon atom of acrylate by La(III) However, it should be noted that these effects are partly counteracted by the decrease in nucleophilic strength of the deprotonated EG-molecules, due to coordination to La(III)

When the addition was performed with ethylene glycol monomethyl ether (EGMME) as the hydroxylic reagent (Scheme 1b, R=Me), only about 50 % conversion to **2b** was reached after 48 h at 90 °C in the presence of an equimolar amount of $LaCl_3$ $3H_2O$ This may be due to the low solubility of the La(III) compounds in the relatively apolar EGMME compared to EG, and to the fact that EGMME has only one hydroxyl group per molecule Better results were obtained when 0 5 equivalent $La(OMe)(OiPr)_2$ was used Then complete conversion was reached in about 20 h

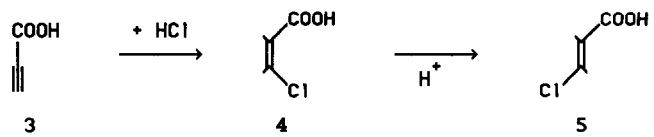
Alkoxylations of Propiolate and Acetylenedicarboxylate

Propiolic acid (**3**) and acetylenedicarboxylic acid (**8**) are known to undergo decarboxylation rapidly both in aqueous and in alcoholic solutions[22 27] However, heating of a 1 mol dm^3 aqueous solution of **3** in the presence of $LaCl_3$ (1 mol dm^{-3}) or HCl (2 mol dm^{-3}) resulted in rapid addition of HCl giving *cis*- (**4**) and *trans*-3- chloroacrylic acid (**5**, Scheme 2), in a molar ratio of about 9 1 The addition of HCl

to acetylenic acids has been reported in literature to be kinetically determined yielding the *anti*-adducts [28-30] In contrast with these literature data,[28] we observed isomerisation of **4** to the thermodynamically more stable compound **5** under strongly acidic conditions during the reaction (see Figure 1) It should be noted that coordination to La(III) plays a minor role under acidic conditions

Propiolic acid and an equimolar amount of $LaCl_3$ in EG yielded a mixture of the chlorides **4** and **5**, and the EG-ester of **4** (molar ratio. 7 1:2) after heating at 90 °C for 24 h Almost no decarboxylation was observed (less than 3 %[31]) and only traces of the EG-ester of **5** were detected Upon dissolution of **3** in EG in the absence of $LaCl_3$ or any other chloride-containing reagent, decarboxylation appeared to be the major reaction path However, in the present case three products were obtained in small amounts besides the dominant product, the EG-ester of **3**, 2-carboxymethoxy-1,3-dioxolane (**7**, see Scheme 3), together with its EG-ester, were detected.

The mentioned esterification could be prevented by the use of the sodium salt of **3** instead of the free acid. Dissolution in EG (1 mol dm^{-3}) and heating at 90 °C gave 95 % conversion of **3** to yield



3 4 5

Scheme 2

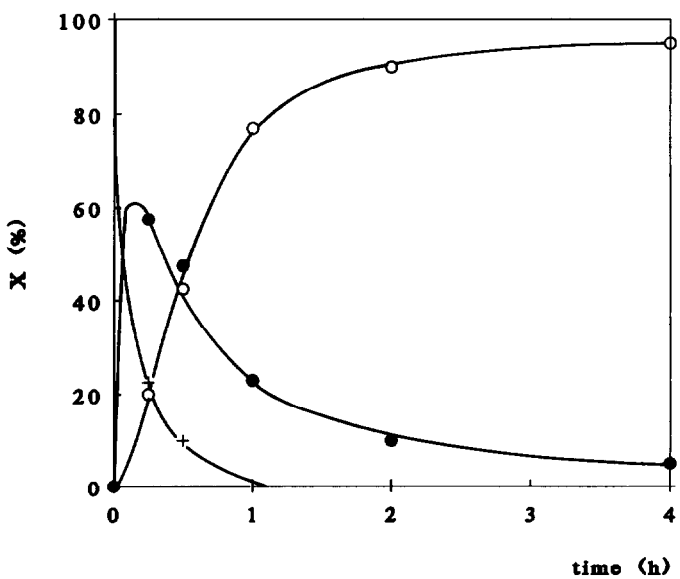
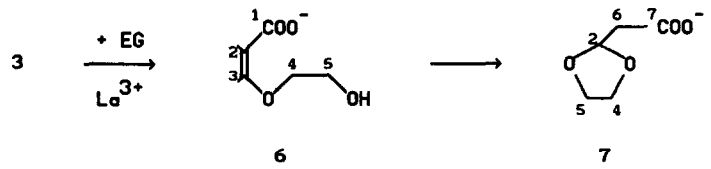
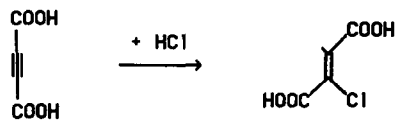


Figure 1. Product distribution of the hydrochlorination of **3** (1 mol dm^{-3}) and the consecutive isomerisation in strongly acidic (15 % w/w HCl) aqueous medium at 90 °C (+ **3**, • **4**, o **5**)



6 7

Scheme 3



8 9

Scheme 4

about 10 % **7** in 24 h. The remainder of **3** was decarboxylated A similar situation was observed when 0 1 mol dm^{-3} $LaCl_3$ was applied, however, in the presence of an equimolar amount of $LaCl_3$ complete conversion of **3** occurred in about 15 h, yielding **7** (55 %) and **4** (45 %) Apparently, in the presence of La(III) alkoxylation is favored over decarboxylation The production of **4** is probably due to a higher acidity of the solution caused by the large amount of La(III) [17]

The formation of the chloride **4** could be prohibited by using La_2O_3 as the catalyst and adding **3** as the free acid Hardly any decarboxylation was observed and the only product obtained was **7** The reaction was already complete after 6 h So, the use of La_2O_3 has two advantages over $LaCl_3$ the reaction rate is higher and no chloride addition takes place

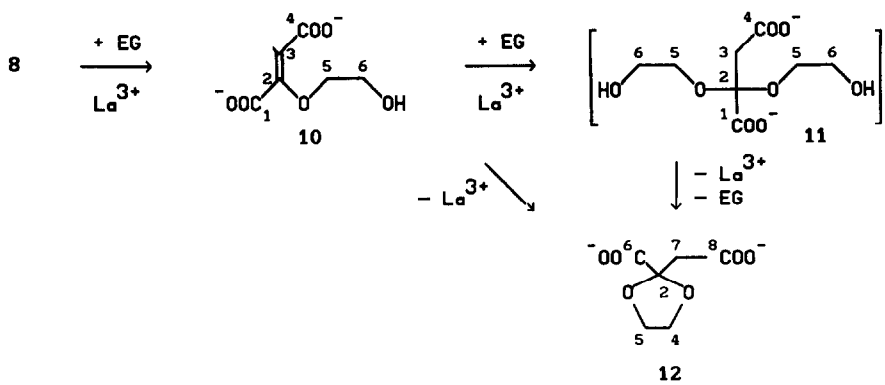
On the basis of a kinetic study Bowden and Price[28] have proposed a mechanism for the hydrochlorination of **3** in aqueous medium in which the carboxylic acid group is protonated after which chloride is added in a rate determining step giving a carbanion intermediate The final product is then formed by proton abstraction from the solvent Complexation of the carboxylate group of propiolate in EG with the La(III) cation has the same effect as protonation of the carboxylic acid group in the aqueous hydrochlorination the triple bond is activated for addition So we assume that the first step in the formation of **7** under neutral La(III)-catalysed conditions is in fact a Michael type *anti*-addition, yielding **6** (see Scheme 3) This intermediate product is then converted in a fast second step to the final product **7** The here described *anti*-addition is in correspondence with general views concerning additions to triple bonds [32,33]

With acetylenedicarboxylic acid (**8**) as the unsaturated carboxylic acid, either as the free acid or as the disodium salt in water, stepwise decarboxylation to **3** and acetylene was observed, which is in agreement with literature reports [22,25] Using a 1 mol dm^{-3} solution of **8** as the free acid in EG with 1 mol dm^{-3} $LaCl_3$ or 3 mol dm^{-3} NaCl rapid formation of chlorofumaric acid (**9**, Scheme 4) was observed Here, too, *anti*-addition takes place now yielding directly the thermodynamically more stable isomer,

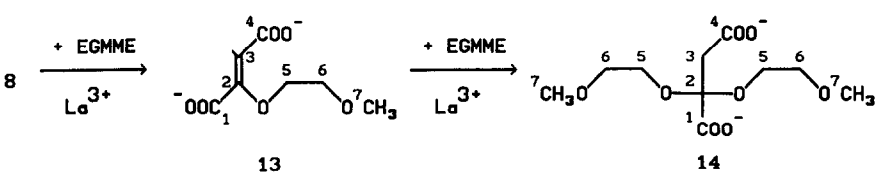
which reaction is already described in the early literature[29,34,35] The hydrochlorination was fast with respect to decarboxylation and water addition, so that only traces of **4**, which is the hydrochlorination product of **3**, and oxalacetic acid, which is the water addition product of **8**, were detected (together less than 1 %) Heating the free acid of **8** in EG in the absence of $LaCl_3$ resulted in partial esterification of the carboxylate groups and in decarboxylation (> 85 %)

Upon heating of the disodium salt of **8** in EG (1 mol dm^{-3}) again the cyclic adduct **7** was obtained, so the same product as was obtained from a similar reaction of the sodium salt of **3** and EG Apparently, **8** decarboxylates first to **3** which then forms the addition product **7** Similar results were obtained in the presence of small amounts of $LaCl_3$ However, with an equimolar amount of $LaCl_3$ a high yield (90 %) of 2-carboxy-2-carboxymethoxy-1,3-dioxolane (**12**, see Scheme 5) was formed after 10 h Side products, resulting from decarboxylation and hydrochlorination of **8**, were **7** (10 %) and traces of **9**, **4** and oxalacetic acid (together less than 1 %) By HPLC the intermediates (2-hydroxyethoxy)-fumaric acid (**10**) and **3** could be observed. The maximum amount of **10** (15 %) was present after 30 minutes (see Figure 2) By terminating the reaction at this time and work-up this intermediate could be isolated and identified by ^{13}C NMR. The intermediate **10** most likely is the fumarate derivative in line with the already described preferred *anti*-addition

When the addition of EGMME to **8** was performed with the use of $LaCl_3$ as the catalyst (see Scheme 6), a mixture was obtained of mono- (**13**) and diadduct (**14**) From the presence of the latter we conclude that also the addition of EG to **8** proceeds *via* the diadduct **11** (see Scheme 5) A further argument in



Scheme 5



Scheme 6

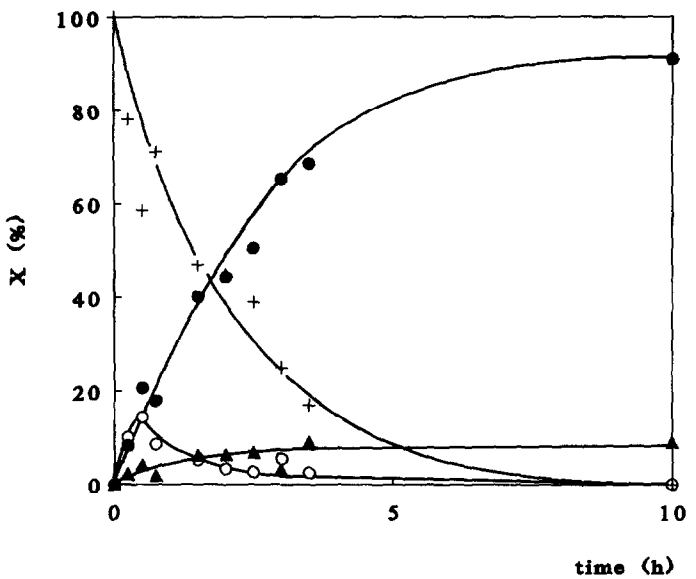


Figure 2. *Product distribution of the addition of EG to* **8** (1 mol dm^3) with use of an equimolar amount of $LaCl_3$ at 90 °C, analyses performed by HPLC after La-removal (+ **8**, o **10**, • **12**, ▲ **7**)

favor of this intermediate **11** is that it is a better complexing agent than the cyclic endproduct **12**, because of a larger number of coordination sites and greater flexibility So, the concerning transition state probably has a lower free enthalpy than that of the direct ring closure to **12**

Compound **11** could be examined with ^{13}C NMR in the crude reaction mixture of an addition reaction of EG to **8** in the presence of an equimolar amount of $LaCl_3$, which was diluted with 20 % (v/v) D_2O after 24 h Part of the spectrum is reproduced in Figure 3a showing signals belonging to the EG-units at 67 and at 61 ppm (EG 64 ppm (solvent)), which are assigned to C5 and C6 of compound **11**, respectively After removal of La(III), either by means of DOWEX-H^+ (Figure 3b) or by precipitation with sodium carbonate (Figure 3c), the large peak at 67 ppm was predominant, whereas the peak at 61 ppm was greatly reduced, which demonstrates that the diadduct **11** is converted into the cyclic adduct **12**

Further support for the occurrence of intermediate **11** was obtained by ^{17}O NMR of the reaction mixture of a Dy(III) catalysed reaction Figure 4 shows the ^{17}O NMR spectra of pure EG (Figure 4a), of 0 1 mol dm^{-3} $DyCl_3$ in EG (Figure 4b), and of a reaction mixture obtained from 0 1 mol dm^3 anhydrous $DyCl_3$ and 0 1 mol dm^{-3} dilithium salt of **8** in EG after 24 h (Figure 4c) Only one averaged ^{17}O signal is obtained in each case, showing that the exchange of ethylene glycol molecules between the complex and the bulk is fast on the NMR time scale Previously, it has been shown that by measurement of Dy(III)-induced ^{17}O shifts it is possible to determine the number of coordinated oxygen atoms of the solvent (here EG) per Dy(III) ion [10,20,36] Following this procedure it can be concluded from the ^{17}O NMR shift for EG in the reaction mixture (Figure 4c) that 22 % of the coordination sites of the Dy(III) ion are occupied by EG, and consequently 78 % by the reaction product The coordination number of

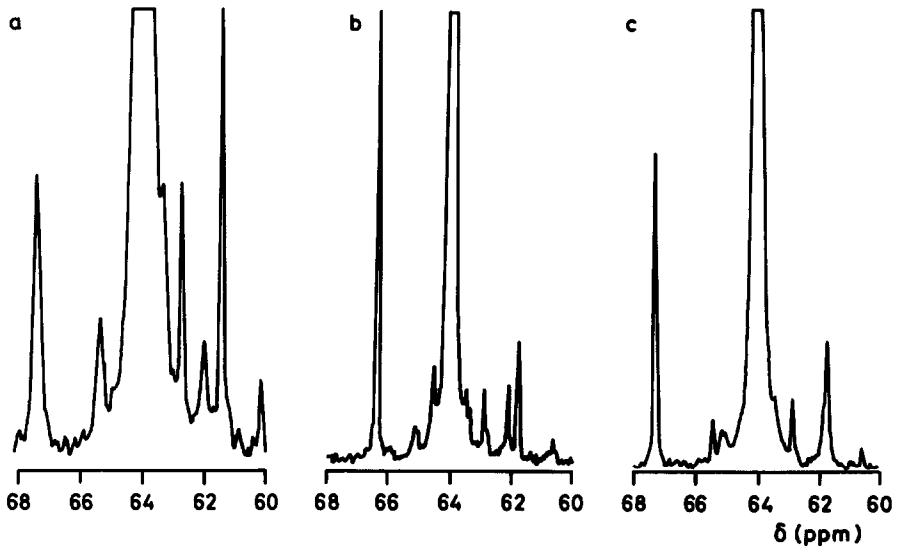


Figure 3. ^{13}C NMR spectra (100 MHz, 30 °C) of the reaction mixture after 24 h at 90 °C of the addition of EG to **8** (1 mol dm^{-3}) catalysed by an equimolar amount of $LaCl_3$ before (a) and after La-removal by DOWEX-H^+ (b) or Na_2CO_3 (c), showing the cyclisation of **11** to **12**

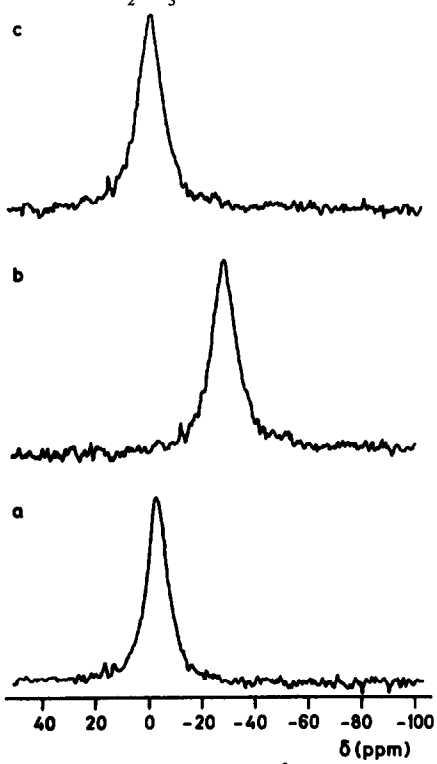


Figure 4. ^{17}O NMR spectra of pure EG (a), 0 1 mol dm^3 $DyCl_3$ in EG (b), and the reaction mixture after 24 h at 90 °C of the addition of EG to **8** (0 1 mol dm^{-3}) catalysed by 0 1 mol dm^{-3} $DyCl_3$ (c)

Dy(III) is assumed to be 8,[12] so the product occupies six sites Thus, before removal of the Ln(III) ion the product is obtained as the diadduct **11**, which has six donor sites, rather than the three donor sites, which should be expected for **12** In this way convincing evidence is obtained that the addition of EG to **8** proceeds *via* two intermediates, namely **10** and **11**, following the reaction path depicted in Figure 5

When the diadduct **11** is dissociated from the La(III)-cation by acidification or by precipitation of La(III) with carbonate, apparently an EG-molecule is expelled from the diadduct, forming the cyclic adduct **12** Acidification causes protonation of one of the ether oxygen atoms,[37] followed by departure of an EG-unit and resulting in an intramolecular ring closure In the case of work-up with carbonate a deprotonated hydroxyl group of an EG-unit attacks at the ketal carbon atom, resulting in an intramolecular concerted nucleophilic substitution, also leading to the cyclic endproduct **12**

Finally, an equimolar amount of **8** was added to a 1 mol dm^{-3} solution of $LaCl_3$ in glycerol (GL), followed by heating at 90 °C HPLC showed complete conversion of **8** after 10 h A mixture was obtained after work-up with Na_2CO_3, which consisted, according to NMR, of the two cyclic diastereomers **15** and **16** (see Scheme 7) of which one, further called A, was 2 5 times more abundant than the other (**B**) [38] Complete assignment of the proton signals was possible after a HETCOR-experiment NOESY and NOE-difference experiments gave no additional information Measurement of Gd(III)-induced ^{13}C relaxation rate enhancements showed two aspects (Table 2) Firstly, in both compounds A and B

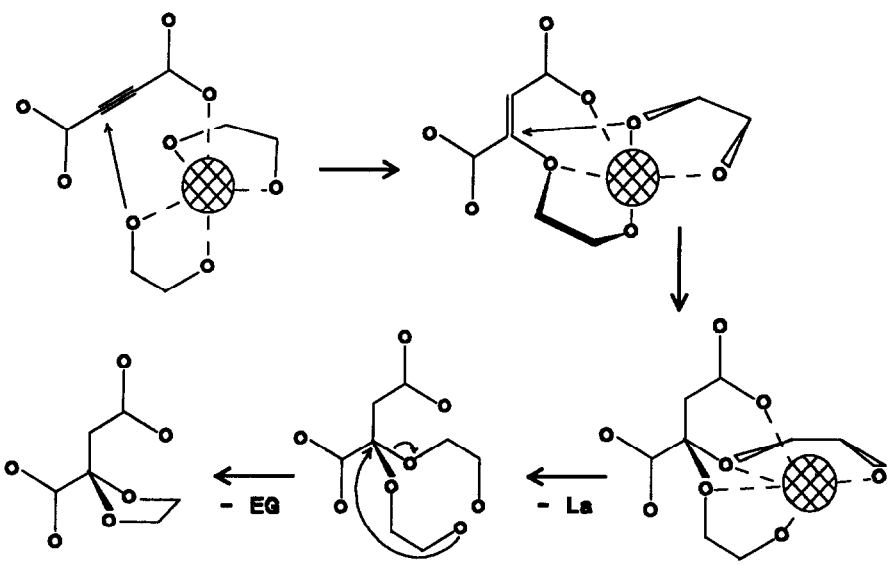
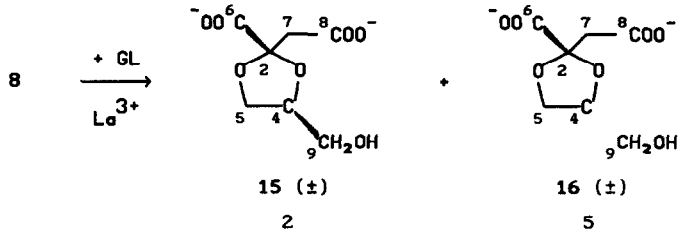


Figure 5. Mechanism of the Ln(III)-catalysed addition of EG to **8** proceeding *via* the two intermediates **10** and **11** and finally yielding the cyclic endproduct **12**



Scheme 7

Table 2. Gd(III)-Induced ^{13}C Relaxation Rate Enhancements (100 MHz, 30 °C) of **15** and **16** (2 mol dm^{-3})

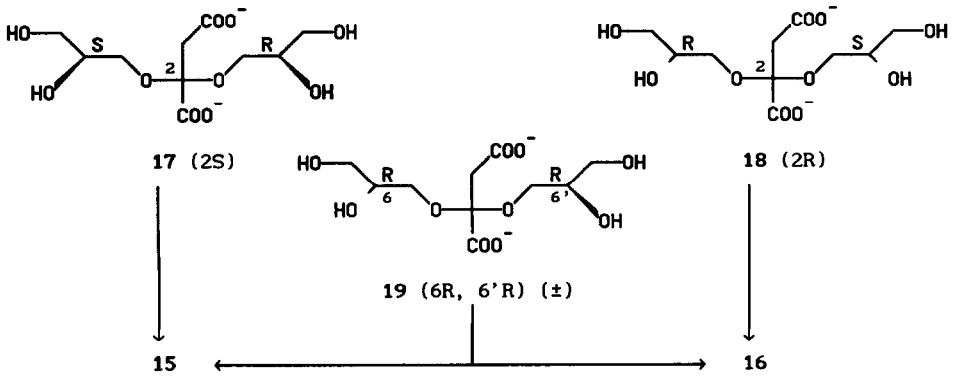
carbon atom	$1/T_1$ [a] (10^4 s^{-1})	
	A (16)	B (15)
C2	1 565	1 588
C4	0 627	0 910
C5	0 515	0 804
C6	5 286	5 310
C7	0 885	0 940
C8	2 499	2 450
C9	0 223	0 646

a values extrapolated to [Gd]/[ligand] = 1

Gd(III) is preferably coordinated by the carboxylate group of C6 together with one of the dioxolane oxygens, as shown by a twice as high relaxation rate enhancement for C6 as for C8 Secondly, a three times higher relaxation rate enhancement was observed for C9 of compound **B** than for C9 of **A** So, in **B** both C9 and C6 are at the same side of the five-membered ring, which leads to the conclusion that **B** is **15**, while **A** is **16**

Compound **16** is the more abundant isomer, which can be explained thermodynamically the C8 carboxylate group in **16** can be turned away from the C^9H_2OH group and therefore gives less steric hindrance than the C6 carboxylate group with the C^9H_2OH group in **15** The question remains how the obtained relative amounts can be explained In Scheme 8 all possible diadducts are depicted It is assumed for steric and reactivity reasons that only primary hydroxyl groups of GL react[9] to form the mono- and diadducts Analogous to the reaction of **8** with EG, ring closure of the decomplexed diadduct gives the final cyclic endproducts **15** and **16** Also is assumed that no preference is made in the stereochemistry of the second attached GL-unit Then we can expect the formation of the diadducts **17** and **18**, which have both an internal plane of symmetry, and **19**, which is a pair of two enantiomers, in a

molar ratio of 1 1 2 (Scheme 8) Examination of the stereochemistry of these diadducts shows that cyclisation of **17** can only yield **15**, while **18** only yields **16** However, the racemic diadduct **19** can give both **15** and **16** So, from the molar ratio of the cyclic products **15** and **16**, which is 29 to 71, it can be deduced that **15** is almost exclusively formed by the cyclisation of **17**, while the diadduct **19** gives for more than 90 % cyclisation to **16** Therefore it is concluded that after decomplexation from Ln(III) the diadduct **19** forms the thermodynamically stable isomer **16**



Scheme 8

CONCLUSIONS

Ln(III) ions effectively promote the synthesis of etherpolycarboxylates from hydroxyl compounds and unsaturated carboxylic acids Different types of lanthanide catalyst systems have been compared, of which the oxides seem very promising for aqueous systems in which high reaction rates are required because of lability of the reactants Ln(III)-catalysed reactions are also attractive because the catalyst can be easily recovered by precipitation as the carbonate salt and subsequent conversion to chloride or oxide

Acetylene derivatives are shown to give diadducts, which are converted into cyclic ketals upon removal of the Ln(III) catalyst These compounds may find further use in organic synthesis For example, oxaloacetate is rapidly decarboxylating, especially in the presence of metal ions and therefore the protected oxaloacetate **12**, which seems very stable, may be a more attractive building block The dioxolanes **12**, **15**, and **16** can also be seen as model compounds for the addition product of dl-tartrate and **8**, which is a promising compound for use in mouth washes [39,40]

EXPERIMENTAL SECTION

General Procedures

Ethylene glycol (EG) was distilled *in vacuo* and dried over zeolite KA Ethylene glycol monomethyl ether (EGMME) was dried over zeolite KA The acids **1**, **3**, and **8** were obtained from Janssen Chimica The disodium and dilithium salts of **8** and the sodium salts of **3** and **1** were prepared by addition of the acid to the appropriate amount of dilute aqueous NaOH or LiOH while cooling with ice, followed by evaporation of the water *in vacuo* After drying *in vacuo* at 40 °C the anhydrous sodium salt of **1**, the dilithium salt of **8**, the sodium salt of **3**, and the dihydrated disodium salt of **8** were obtained The amounts of hydrated water were calculated from weight changes HPLC and ^{13}C NMR showed that no decarboxylation of **3** and **8** had occurred during this preparation

$LaCl_3$ was obtained from Janssen Chimica as the heptahydrate Drying in an oven at 40 °C *in vacuo* resulted in $LaCl_3\ 3H_2O$, as calculated by the decrease of the weight Dry La_2O_3 was obtained from Janssen Chimica $YbCl_3$ was obtained from Ventron as the hexahydrate Anhydrous solutions of lanthanum and ytterbium chloride in EG and GL were obtained by adding an equimolar amount of trimethyl orthoformate (obtained from Janssen Chimica) with respect to water to the alcoholic solution, followed by refluxing during 4 h Methanol and methyl formate were removed by evaporation at 75 °C / 20 mm Completeness of removal was checked by HPLC The lanthanide concentration was then determined by complexometric titration as described in the literature [41] $La(OMe)(OiPr)_2$ was synthesised according to a known procedure,[42] leaving a salt contaminated with LiCl Purification was achieved by recrystallisation from THF (freshly distilled from $LiAlH_4$), to yield $La(OMe)(OiPr)_2$ THF The relative amounts of methoxide, isopropoxide, and THF were determined by ^1H NMR The lanthanum concentration was determined by complexometric titration,[41] while the overall basicity was checked by reverse acid-base-titration with methyl orange as the indicator The results were in excellent agreement with the formula given

HPLC-analyses were performed using a Waters Assoc 590 pump, a Perkin-Elmer ISS-100 autosampler, a 7 8 mm / 300 mm Aminex ion exclusion HPX87H column, a Shodex RI SE-51 detector, a Shimadzu UV SPD-6A detector, and a Spectra-Physics SP4270 computing integrator ^{13}C NMR spectra were recorded at 50 3 MHz with a Nicolet NT-200 WB NMR spectrometer with D_2O/H_2O (20/80) as the solvent and t-butanol as internal standard (δ (ppm) 31 2 (methyl)) The multiplicities of the ^{13}C signals were established by Attached Proton Tests ^1H NMR spectra were recorded using a Varian VXR-400 S NMR spectrometer with D_2O as the solvent and t-butanol as internal standard (δ (ppm) 1 20 (methyl)) ^{17}O NMR spectra were recorded using a Varian VXR-400 S NMR spectrometer without using an internal standard Therefore, a correction for the change in the bulk magnetic susceptibility was applied to the chemical shifts as described in literature [10] Experimental data of the HETCOR experiment and the Gd(III)-induced ^{13}C relaxation rate enhancement measurements will be published elsewhere [43]

Reaction products were purified by anion exchange column chromatography eluted with aqueous formic acid or ammonium formate as eluents, applied as a gradient from 0 to 1 mol dm^3 Formic acid was obtained from Merck and ammonium formate from BDH The anion exchange column material AG1X8 (chloride form) was obtained from BioRad and converted to the formate form by treatment with 1 mol dm^3 ammonium formate, in total applying 20 equivalents DOWEX-H^+ was obtained from Janssen Chimica

DOWEX-NH_4^+ was obtained by treatment of DOWEX-H^+ with 1 mol dm^{-3} aqueous ammonium chloride, in total applying 10 equivalents

Standard Reaction Procedure

Unless stated otherwise $LaCl_3\,3H_2O$ was added to 15 ml solvent, which is generally also the hydroxyl reactant, after which the reaction mixture was heated to 90 °C Then the unsaturated carboxylic acid (as the free acid or as the sodium salt) was added and the reaction mixture was stirred during several hours The reaction was monitored by HPLC

Hereafter the reaction mixture was cooled to room temperature and 25 ml demineralised water was added La(III) was removed by either a twofold use of a large excess of DOWEX-H^+ or DOWEX-NH_4^+ followed by filtration, or by precipitation as its carbonate with Na_2CO_3 followed by centrifugation If necessary the solution was neutralised with aqueous NaOH Purification of the reaction product was achieved by anion exchange column chromatography with aqueous ammonium formate or sodium hydrogen carbonate as eluent after which the appropriate fractions were concentrated and lyophilised Then the obtained ammonium salt was converted to the sodium or potassium salt by consecutive treatment with DOWEX-H^+ and neutralisation with aqueous NaOH or KOH, respectively, followed by lyophilisation

*3-(2-Hydroxyethoxy)propionic acid (***2a***)* The standard procedure was followed using 20 mL 1 mol dm^3 $LaCl_3$ in EG (dried with trimethyl orthoformate) and 1 88 g of **1** (20 mmol, sodium salt) The reaction mixture was a white suspension The reaction was stopped after 47 h, after which HPLC showed complete conversion of **1** to **2a**. Traces of a second product were detected La(III) was removed by DOWEX-H^+ Purification[44] gave 1 24 g (36 %) of the potassium salt of **2a** ^{13}C NMR (**2a**, pH=1) δ (ppm) 177 9 (s, C1), 73 1 (t, C4), 67 6 (t, C3), 61 9 (t, C5), 36 0 (t, C2) ^{13}C NMR (pH=10) δ (ppm) 181 9 (s, C1), 72 9 (t, C4), 69 3 (t, C3), 62 0 (t, C5), 39 2 (t, C2)

*3-(2-Methoxyethoxy)propionic acid (***2b***)* The standard procedure was followed using 6 1 mmol (1 76 g) La(OMe)($OiPr$)$_2$ THF, 15 mL EGMME, and 1 15 g of **1** (12 2 mmol, sodium salt) The mixture was a yellow suspension, which turned brown during reaction The reaction was stopped after 24 h, HPLC showing complete conversion to **2b** Purification[44] gave 1 78 g (52 %) sodium salt of **2b** ^{13}C NMR (pH=1) δ (ppm) 177 4 (s, C1), 72 3, 70 7 (t, C4, t, C5), 67 5 (t, C3), 59 4 (q, C6), 35 8 (t, C2)

*2-Carboxymethyl-1,3-dioxolane (***7***)* The standard procedure was followed using 10 0 mmol (3 26 g) La_2O_3, 20 mL EG and 20 mmol (1 40 g) of **3** (free acid) The reaction mixture was a suspension, which slowly turned brown HPLC showed complete conversion to **7** in 6 h, after which the reaction was stopped La(III) was removed by precipitation with Na_2CO_3 After purification[44] 0 70 g (23 %) sodium salt of **7** was obtained ^{1}H NMR δ (ppm) 5 24 (t, 1 H, H2), 4 01, 3 93 (m, m, 4 H, H4, H5), 2 76 (d, 2 H, H6), J_{26}= 4 8 Hz ^{13}C NMR (pH=2) δ (ppm) 175 1 (s, C7), 101 9 (d, C2), 66 3 (t, C4, C5), 40 4 (t, C6) ^{13}C NMR (pH=7) δ (ppm) 178 5 (s, C7), 103 2 (d, C2), 66 0 (t, C4, C5), 43 2 (t, C6)

*(2-Hydroxyethoxy)fumaric acid (***10***)* The standard procedure was followed using 20 mmol (6 0 g) $LaCl_3\,3H_2O$, 15 mL EG and 20 mmol (3 24 g) dilithium salt of **8** The $LaCl_3\,3H_2O$ was dissolved before adding **8**, after which a suspension was obtained HPLC showed that the maximum amount of **10** was reached after 30 min At that time 15 % of **10**, accompanied by 45 % of **8** and 40 % of **12** was present Then the reaction was stopped by cooling and removal of La(III) using DOWEX-NH_4^+ The DOWEX was filtered off and the clear solution was concentrated *in vacuo* to 15 mL Isolation of **10** was achieved by anion exchange

column chromatography with aqueous formic acid as the eluent After removal of water and formic acid by lyophilisation 0.38 g **10** (as the free acid), contaminated with 20 % of **12** was obtained Further purification was not attempted ^{1}H NMR (pH=8) δ (ppm) 6.07 (s, 1 H, H3), 4 64, 4 39 (m, m, 4 H, H5, H6). ^{13}C NMR (pH=8) δ (ppm) 175.7, 172 3 (s, s, C1, C4), 155 0 (s, C2), 114 4 (d, C3), 73 9 (t, C5), 61 9 (t, C6).

*2-Carboxy-2-carboxymethyl-1,3-dioxolane (**12**)* The standard procedure was followed using 20 mL 1 mol dm^{-3} $LaCl_3$ in EG and 20 mmol (3 88 g) dihydrated disodium salt of **8** After 6 h HPLC showed complete conversion of **8** and **10** to the dioxolanes **12** and **7** (90 and 10 % respectively) and traces of **9**, **4**, and oxalacetic acid La(III) was removed by precipitation with Na_2CO_3 and the precipitated $La_2(CO_3)_3$ was filtered off. The clear filtrate was concentrated *in vacuo* to 15 mL and added to 50 mL ethanol upon which the crude product precipitated The precipitate was dissolved in 10 mL water and the precipitation procedure was repeated The product was further purified by anion exchange column chromatography and lyophilisation,[44] resulting in 0 55 g (13 %) of disodium salt of **12** ^{1}H NMR δ (ppm) 4 07 (m, 4 H, H4, H5), 3 03 (s, 2 H, H7) ^{13}C NMR (pH=1) δ (ppm) 174 0, 173 7 (s, s, C6, C8), 105 4 (s, C2), 67 4 (t, C4, C5), 42 2 (t, C7) ^{13}C NMR (pH=8) δ (ppm) 178 6, 178 1 (s, s, C6, C8), 108 1 (s, C2), 66 5 (t; C4, C5), 45 2 (t, C7)

*(2-Methoxyethoxy)fumaric acid (**13**) and 2,2-bis(2-methoxyethoxy)succinic acid (**14**)* The standard procedure was followed using 20 mmol (6 0 g) $LaCl_3\ 3H_2O$, 15 mL EGMME and 20 mmol (3 16 g) disodium salt of **8** $LaCl_3\ 3H_2O$ was completely dissolved before **8** was added, after which a suspension was obtained which turned brown during the reaction After 26 h HPLC showed 80 % conversion of **8** to **13**, **14**, and **9** (8, 80 and 12 % respectively) and traces of **3** and **4** The reaction was stopped and La(III) was removed by DOWEX-H$^+$ Purification[44] gave a fraction of 0 47 g **14** (diammonium salt, 1 6 mmol, 9 %) and a fraction of 1 40 g containing a mixture of about equal amounts of the diammonium salts of **13** and **9** Compound **13** was not further purified, while **14** was converted to its sodium form ^{13}C NMR (**13**, pH=9) δ (ppm) 174 5, 171 9 (s, s, C1, C4), 156 5 (s, C2), 110 7 (d, C3), 72 5, 71 3 (t, t, C5, C6), 59 5 (q, C7) ^{1}H NMR (**14**) δ (ppm) 3 69, 3 48 (t, t, 8 H, H5, H6), 3 34 (s, 6 H, H7), 2 82 (s, 2 H, H3) ^{13}C NMR (**14**, pH=9) δ (ppm) 177 3, 175 9 (s, s, C1, C4), 102 6 (s, C2), 72 7 (t, C6), 62 2 (t, C5), 59 5 (q, C7), 44 0 (t, C3)

*2-Carboxy-2-carboxymethyl-4-hydroxymethyl-1,3-dioxolane ((2R,4S)(2S,4R)) **15**, ((2R,4R)(2S,4S)) **16**)* The standard procedure was followed using 20 mL 1 mol dm^{-3} $LaCl_3$ in glycerol (GL) and 20 mmol (3 88 g) dihydrated disodium salt of **8** After 10 h HPLC showed complete conversion of **8** The reaction mixture was cooled, 30 mL water was added and La(III) was removed by precipitation as the carbonate salt The product, which NMR showed to be a mixture of **15** and **16** in a molar ratio of 2 5, was precipitated in 200 mL ethanol The precipitate was centrifuged off and dissolved in 10 mL water Further purification[44] was performed as described in the standard reaction procedure yielding 1 10 g (23 %) of a mixture of the disodium salts of **15** and **16**, still in a molar ratio of 2 5 ^{1}H NMR (**15**) δ (ppm) 4 56 (m, 1 H, H4), 4 43, (dd, 1 H, H5, $J_{55'}$=-8 54 Hz, J_{45}=6 44 Hz), 3 97 (dd, 1 H, H5', $J_{55'}$=-8 54 Hz, J_{45}=3 90 Hz), 3 93 (dd, 1 H, H9, $J_{99'}$=-12 08 Hz, J_{49}=8 16 Hz), 3 85 (dd, 1 H, H9', $J_{99'}$=-12 08 Hz, $J_{49'}$=5 69 Hz), 3 00 (AB, 2 H, H7, Δδ=14 8 Hz, $J_{77'}$=-14 2 Hz) ^{13}C NMR (**15**, pH=8) δ (ppm) 178 3 (s, C6), 178 0 (s, C8), 108 5 (s, C2), 78 9 (d, C4), 67 9 (t, C5), 62 2 (t, C9), 45 1 (t, C7) ^{1}H NMR (**16**) δ (ppm) 4 55 (m, 1 H, H4), 4 23, (dd, 1 H, H5, $J_{55'}$=-8 38 Hz, J_{45}=7 08 Hz), 4 09 (dd,

1 H, H5', $J_{55'}$=-8 38 Hz, $J_{45'}$=5 37 Hz), 3.97 (dd, 1 H, H9, $J_{99'}$=-12 24 Hz, J_{49}=3 43 Hz), 3 81 (dd, 1 H, H9', $J_{99'}$=-12 24 Hz, $J_{49'}$=5 16 Hz), 3.03 (AB, 2 H, H7, $\Delta\delta$=15 9 Hz, $J_{77'}$=-14 4 Hz) ^{13}C NMR (**16**, pH=8) δ (ppm) 178 2 (s, C6), 178.0 (s, C8), 108 5 (s, C2), 77 9 (d, C4), 67 5 (t, C5), 63 4 (t, C9), 45 1 (t, C7)

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