

SYNTHESIS OF POLY(HYDROXY)CARBOXYLATES-PART II.
ADDITION OF POLYOLS TO MALEATE HOMOGENEOUSLY CATALYSED BY
MULTIVALENT METAL IONS.

Jeroen van Westrenen, Robin M. Roggen, Mattheus A. Hoefnagel, Joop A. Peters,
Antonius P.G. Kieboom and Herman van Bekkum.

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

(Received in UK 2 April 1990)

Abstract: A Michael-type addition reaction of polyhydroxylated compounds to maleate, homogeneously catalysed by multivalent metal ions, is described. The degree of O-alkylation in the product is strongly dependent upon the choice of the metal ion and upon the amount of catalyst used. The reactions are performed in the polyol as solvent, if necessary, with water as co-solvent.

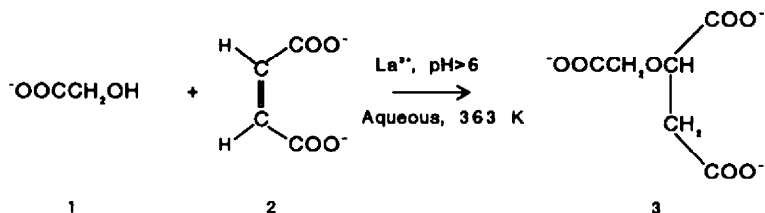
Introduction

Water soluble chelating agents have found widespread use in many fields of science and technology, varying from pharmaceuticals to galvanic industry to builders in detergents.¹ Environmental aspects such as biodegradability are important in the design of chelators. Therefore, carbohydrates and other oxygen containing derivatives may be interesting starting compounds in the synthesis of chelators.

Several Ca(II) and Mg(II) complexing systems have been developed on the basis of carbohydrate derivatives. Examples are the oxidation products of starch,^{2,3} the borate-glucarate system,⁴⁻⁶ in which two sugar acid entities are linked via borate generating an improved cation coordination site, and several low molecular weight carboxylate containing chelators.⁷⁻¹² The latter category includes trisodium carboxymethoxysuccinate (3), which is formed by the alkylation of glycolate (1) with maleate (2) promoted by a twofold excess of calcium hydroxide.⁸ This reaction is an interesting pathway towards some other oxygen containing ligands.⁹

Recently, the homogeneous La(III) catalysed alkylation reaction of 1 with 2 has shown to be a convenient way to synthesize 3 (Scheme I).¹³ A mechanistic study of this La(III)-catalysed reaction has revealed that the addition occurs in ternary La(III) complexes of 1 and 2. Aside from functioning as a template, the La(III) ion assists the ionisation of the α -hydroxyl group of 1.^{13,14} Product inhibition occurs because of the relatively high stabilities of the La(III) complexes of the product 3,¹⁵ and, in practice, limits the formation of 3 to two molecules per La(III) ion present,¹³ which corresponds to the maximum number of coordinated 3 ligands for the La(III) ion.¹⁶ The Ca(II) sequestering

ability of 3 is moderate compared to sodium triphosphate, but might be sufficient for combined use with zeolite NaA.^{17,18}



Scheme I

Polyols derived from carbohydrates are usually rather weak ligands for metal ions.¹⁹ Introduction of carboxylate groups leads to products with a much higher affinity for metal ions. Therefore, we have studied the alkylation reactions of polyols with 2 that results in O-alkyl carboxylates. Up to now, only an alkylation of glycerol with 2 promoted by an excess of calcium hydroxide in aqueous solutions has been described.¹² This reaction, however, leads to considerable amounts of the side products, due to addition of water to 2.

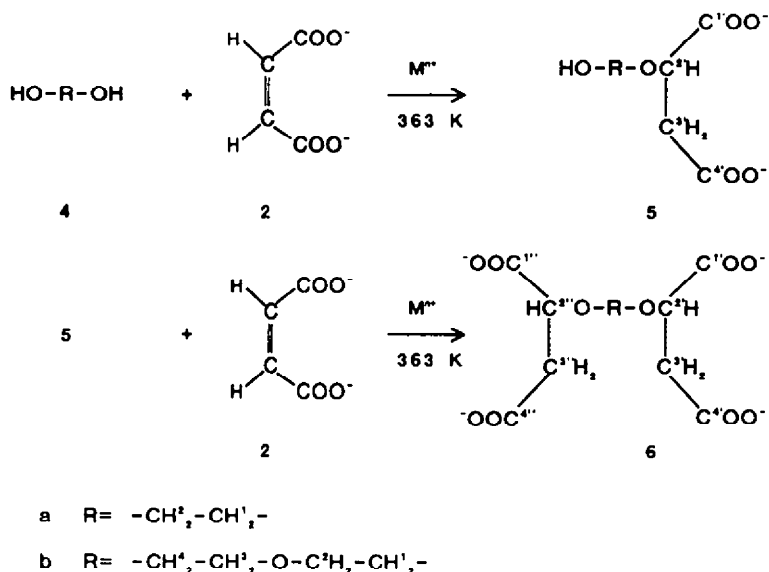
In this paper the La(III) catalysed O-alkylation of ethylene glycol (4a), diethylene glycol (4b), and glycerol (7) with 2 is described, whereby these polyols are used both as reactant and as solvent. In all cases mono-O and di-O,O'-alkyl products are obtained. Obviously, a consecutive reaction can occur in which the second hydroxyl group of the polyol is alkylated with 2. The extent to which such a consecutive reaction takes place will be shown to be highly dependent upon the multivalent cation used (lanthanides, group 13 and first row transition metal ions). For La(III) the dependence of the ratio of the mono-O to di-O,O'-alkylation upon the amount of catalyst added has been studied. In the presence of a small amount of water as a co-solvent the reaction also proceeds for extended polyols such as erythritol (14) and mannitol (17) using Al(III) as the catalyst. Small amounts of side products resulting from water addition are observed. The effects of water on the course of the alkylation reaction are studied in some detail. The synthesized compounds have been tested for their Ca(II) sequestering properties.

Results and discussion

La(III) promoted alkylation of di- and triols with maleate (2).

When a solution of sodium maleate (2) in ethylene glycol (4a) was heated at 363 K, only 4% conversion into the mono-O-alkylation product (5a, Scheme II) was observed after 33 h. Upon partial ionisation of ethylene glycol by addition of sodium, the reaction remained sluggish (Table I). In the presence of 3 mol% of $LaCl_3 \cdot 7H_2O$ (relative to 2), however, a dramatic improvement of the reaction rate was obtained. Now both the mono-O- (5a) and the di-O,O'-alkyl product of ethylene glycol (6a) were formed (Figure 1). No reaction

products from an addition of water to 2 were detected, although the hydrated metal salt was used as the catalyst.



Scheme II

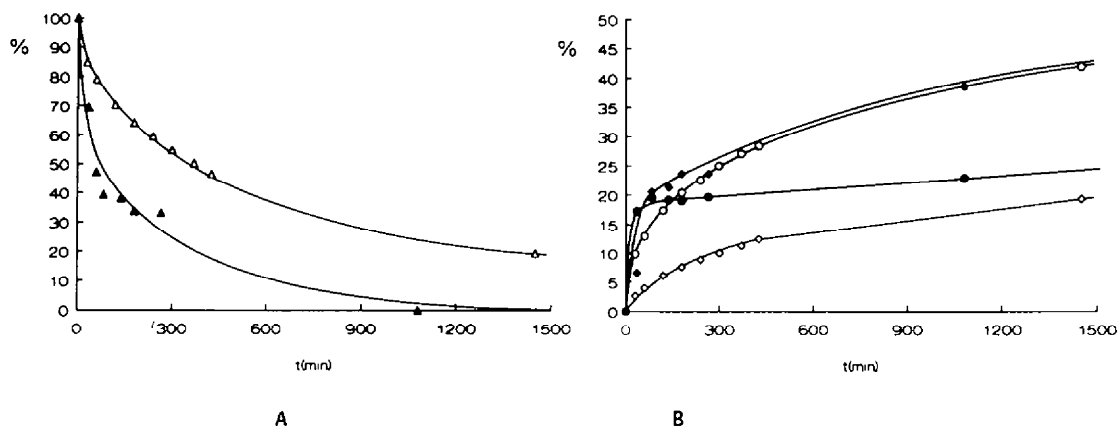


Figure 1A and 1B. The formation of mono-O- and di-O,O'-alkyl products (5a and 6a) by alkylation of ethylene glycol (4a) with Li₂maleate (2, 17.5 mmol) catalysed by LaCl₃ in 15 ml ethylene glycol at 363 K. Fig. 1A: conversion of 2 using 0.5 mmol LaCl₃(Δ) and 12.6 mmol LaCl₃(▲), respectively. Fig. 1B: the formation of 5a (○), and 6a (◇) with 0.5 mmol La(III) and the formation of 5a (●), and 6a (◆) with 12.6 mmol La(III).

We assume that the mechanism of this reaction is analogous to that of the previously studied alkylation of glycolate (1) with 2 (Scheme I).¹³ Thus the rate determining step is most likely a nucleophilic attack of a coordinated alcoholate group of 4a on 2 in a ternary complex of La(III)-2-4a. The La(III) ion, probably, functions as template and it increases the acidity of bound ethylene glycol (4a). This reaction showed appreciably less product inhibition than that between 1 and 2 in aqueous medium, where the reaction rate was negligible after the formation of 2 moles of 3 per La(III) ion.¹³ Apparently the starting compounds (2 and 4a) are able to compete with the products 5a and 6a for La(III) coordination. The structures of the various complexes present in the reaction mixture are currently under study.²⁰

The La(III) catalysed reaction is reversible. This could be demonstrated by heating pure 5a in a solution of LaCl₃ in ethylene glycol (4a). After 48 h 5% of 6a and a small amount of 2 (<1%) were present in the reaction mixture, and after 140 h the amount of 6a was increased to 15%. Apparently, the equilibrium is reached very slowly, which implies that, under the usual reaction conditions, the ratio of the mono-0- and di-0,0'-alkylated diol (5a and 6a) is determined kinetically.

In the reaction product 6a the meso form was slightly more abundant than the racemic form (molar ratio 3/2), which probably reflects differences in steric strain in the concerning intermediate complexes.

The reaction can be directed towards the di-0,0'-alkyl product by increasing the amount of catalyst (Figure 1B). Obviously, in this way the concentration of the intermediate La(III) complex for the consecutive reaction step (La(III)-2-5a) increases and consequently that reaction (5a-6a) is enhanced.

The La(III) catalysed 0-alkylation of diethylene glycol (4b) with 2 is in many respects analogous (Figure 2), yielding mono-0- and di-0,0'-alkyl products (5b, 6b respectively).

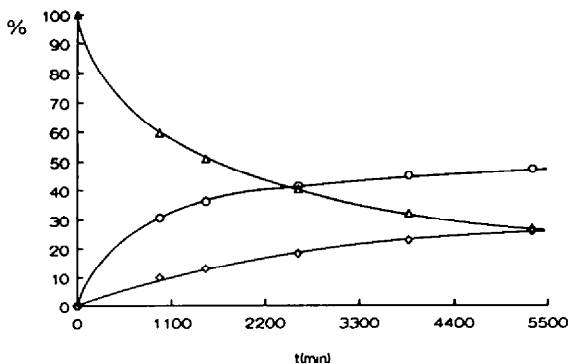
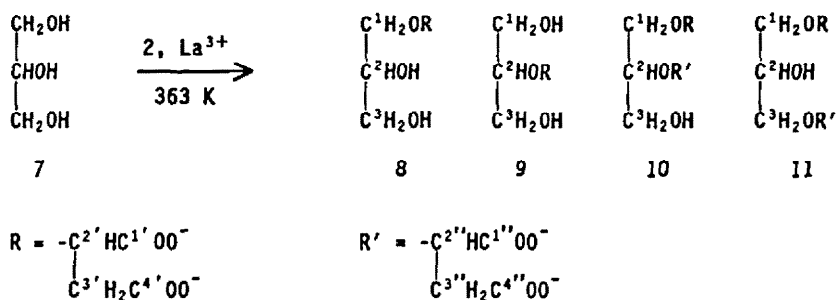


Figure 2. The formation of mono-0- and di-0,0'-alkyl products 5b (○) and 6b (◇) by alkylation of diethylene glycol (4b, 30 ml) with Li₂maleate (2, 30 mmol, Δ) catalysed by LaCl₃ (1 mmol) in 4b at 363 K.

The reaction rate was somewhat lower than that of the previous reaction, which is probably caused by the higher denticity of 4b versus 4a resulting in a lower amount of ionised hydroxyl groups coordinated per La(III) ion. Once again increase of the amount of La(III) favoured the formation of the di-0,0'-alkyl product (6b).²¹ No diastereomeric preference was observed in this case.

When the alkylation reaction was performed with glycerol (7) as the starting hydroxy compound, more complex reaction mixtures consisting of all possible mono-0- and di-0,0'-alkyl products resulted (Scheme III).



Scheme III

With 3 mol% La(III) as the catalyst, the ratio of 1-0-(8) and 2-0-alkylated glycerol (9) was 2.5, whereas the di-0,0'-alkyl products consisted predominantly of 1,3-di-0,0'-alkylated glycerol (11) (Figure 3). This shows that a small preference exists for reaction at the primary hydroxyl groups. With 42 mol% of La(III),²² again more di-0,0'-alkyl product was obtained (ratio mono/di = 1.2/1), but now with about equal amounts of the two possible isomers 10 and 11. Moreover, the ratio 8/9 was 5/1.

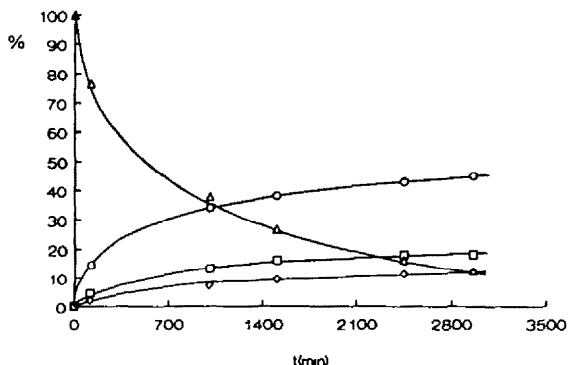


Figure 3. The formation of mono-0- and di-0,0'-alkyl products by alkylation of glycerol (7, 30 ml) with Li_2 maleate (2, 30 mmol, Δ) catalysed by LaCl_3 (1 mmol) in 7 at 363 K. 8 (\circ), 9 (\square), and a mixture of 10 and 11 (\diamond) (see Scheme III).

Apparently, the route via 9 to 10 gains importance upon increasing the amount of La(III), probably as a result of the increase of the concentration of the ternary complex La(III)-9-2.

The effect of the choice of the metal ion on the rate and the selectivity of the alkylation of ethylene glycol (4a) with maleate (2).

The effect of various metal ions on the course of the alkylation reaction was studied at 363 K using 3 mol% of catalyst. Though hydrated metal chlorides were applied, products originating from the addition of water to 2 were not detected. The compositions of the product mixtures obtained after 33 h of reaction are given in Table I.

Table I. -The influence of various metal ions on the alkylation of 4a by 2 at 363 K.^a

M ⁿ⁺	Conversion of maleate (2) after 33 h (%)	Molar ratio 5a/6a		Conversion of maleate (2) after 33 h (%)	Molar ratio 5a/6a
-	4	>100	Zn(II)	53	5.5
Na(OCH ₂ CH ₂ OH) ^b	14	>100	Al(III)	62	>100
La(III)	83	2.2	Al(III), NaOCH ₂ CH ₂ OH ^b	63	>100
Nd(III)	94	2.9	Ga(III)	20	>100
Eu(III)	95	3.7	In(III)	54	>100
Ho(III)	96	5.7	Ca(II) ^d	5	>100
Yb(III)	95	7.0	Ba(II) ^d	6	>100
Fe(II) ^c	35	>100	Fe(III) ^c	39	>100
Co(II) ^c	64	2.2	Zr(IV)	46	>100
Ni(II) ^c	80	0.8	Ti(IV)	85	>100
Cu(II) ^c	20	20.8	Ti(OiPr) ₄	94	>100

^aLi₂maleate (17.5 mmol) was added to a solution of metal chloride (0.5 mmol) dissolved in 4a (15 ml) (Ref. 34). ^bSodium 2-hydroxyethanolate, formed by dissolving sodium (Na(O)). The disodium salt of 2 was used. ^cColour changes were observed during the reaction: Fe(II) (yellow to orange), Co(II) (purple to light purple), Ni(II) (green), Cu(II) (blue to yellow-green), Fe(III) (dark-yellow). ^dA white precipitate was present during the reaction.

Several lanthanide ions (Ln(III)) were included in this study, because these ions constitute a unique series with very similar chemical properties. The binding of Ln(III) ions to ligands is of a predominant electrostatic character, and consequently the geometry

and the stability of Ln(III) complexes is determined almost exclusively by steric factors. With all Ln(III) ions both mono-O- and di-O,O'-alkyl products (5a and 6a) were obtained. The ratio of these products decreases with the ionic radius (Figure 4). At the same time the initial reaction rate also decreases (Figure 4). Thus upon decrease of the ionic radius, the rate of the alkylation of 4a with 2 increases, whereas that of the consecutive step (5a→6a) decreases. The increase of the reaction rate upon decrease of the ionic radius can be explained by a decrease of the pKa of coordinated ethylene glycol (4a) as a result of the increasing charge density (z/r^2) of the metal ion.¹⁴ This implies that the concentration of the reactive complex (Ln(III)-(2-hydroxyethanolate)-2)²³ and thus the reaction rate increases going from La(III) to Yb(III). The same should hold for the consecutive reaction step (5a→6a), but there this effect is apparently counteracted by the increase of the steric strain on the stability of the intermediate complex upon a decrease of the ionic radius. This rationalization is supported by similar trends observed in the stability constants of the Ln(III) complexes of 5a and 6a.²⁰ The former increase with decreasing ionic radius, whereas those of the more bulky 6a decrease in that order.

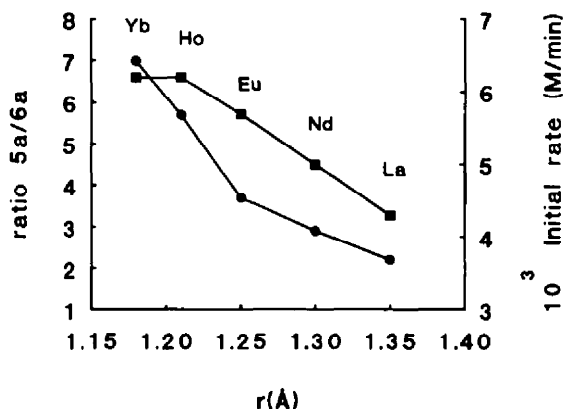


Figure 4. Left: The molar ratio 5a/6a after 33 hrs of reaction as a function the Ln(III) ion used (●). Right: Initial rate of the conversion of 2 as a function of the Ln(III) ion used as catalyst (■). Reaction conditions: see Table I.

Multivalent metal ions with a small ionic radius, such as Ti(IV) and Al(III) gave, as should be anticipated from the results mentioned above, exclusively mono-O-alkyl product (5a). The reaction with $Ti(OiPr)_4$ was somewhat faster than that with $TiCl_4$, as a result of the enhanced ionisation of Ti(IV) coordinated ethylene glycol by virtue of the higher basicity of isopropoxide relative to chloride. Small amounts of two side products were formed (5%): a lactone of 5a and an ester of ethylene glycol (4a) and 6a. These side

products could easily be removed by hydrolysis in aqueous solution at high pH.

An almost linear relationship exists between the conversion of **2** and the effective charge density (as defined by Brown *et al.*)²⁴ of the metal ion used as catalyst. This supports the idea that the extent of ionisation of the coordinated hydroxyl group of ethylene glycol (**4a**) plays an important role in the reaction.

Notwithstanding their relatively small ionic radius Ni(II), Co(II), and Zn(II)²⁵ gave all rise to the formation of **6a**, whereas Fe(II) and Cu(II) gave **5a** exclusively. The relative initial rate of the conversion of **2** and the percentages of **6a** in the reaction products versus the metal ion are shown in Figure 5. Molecular models and a crystal structure of the related Co(ethylenediamine)₂(**2**) ternary complex²⁶ show that in an octahedral rearrangement of the ligands around the transition metal ion, the ionised hydroxyl group of **4a** or **5a** is located in an ideal position for attack on the olefinic bond of **2** (Scheme IV).

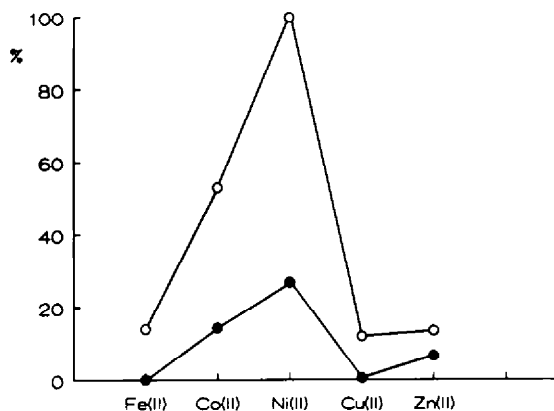
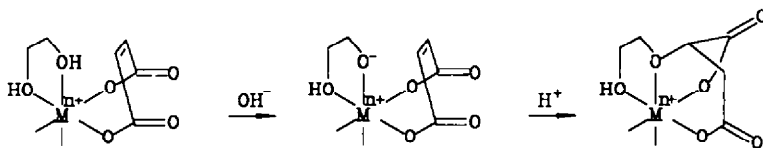


Figure 5. Relative initial rate of the conversion of **2** (○) and the percentage of **6a** formed after 33 h (●), as function of the divalent first row transition metal ions used as catalyst. Reaction conditions: see Table I.



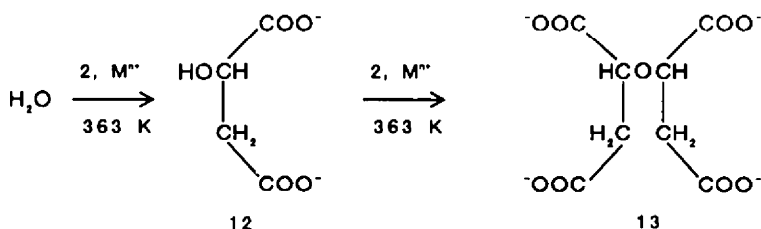
Scheme IV

The graphs (Figure 5) are in agreement with the Irving and Williams order of the stability constants within the series Fe(II), Co(II), Ni(II), Cu(II), and Zn(II),²⁷ except

for Cu(II). An analogous behaviour is observed for the third stability constants of transition metal ion-ethylenediamine complexes.²⁸ There the value of Cu(II) also is exceptionally small. This is explained by the Jahn-Teller effect, which causes a tetrahedral distortion of the octahedron; in this case probably by elongation of the axial bonds. This will result in a destabilization of octahedral ternary complexes involved prior to the formation of 5a and 6a, and consequently in a reduction of the concerned reaction rates.

The effect of the water on La(III) promoted alkylation reactions.

In the experiments described up to now, always hydrated metal salts were used as the catalysts. No addition products from water to maleate (2) were detected. When the La(III) catalysed reaction was performed in water as the solvent, however, substantial amounts of these products emerged. A precipitate was formed in the aqueous reaction mixture containing 4a (0.8 M), and 2 (0.2 M) at pH 8.0,²⁹ which slowly dissolved over 48 h. HPLC and ¹³C NMR analysis showed 83% conversion of 2 into 5a (29%), 6a (31%); fumarate (5%), and the water addition products malate (12, 23%) and oxydibutanedioate (13, 12%) (Scheme V). The ratio of the products originating from addition of 4a to those from addition of water was 1.7/1, whereas the molar ratio of these two reactants was 0.84/54. This selectivity may be explained by the somewhat higher affinity of 4a for La(III), which probably carries on in the corresponding intermediate complexes.



Scheme V

Synthesis of di-0,0'-alkyl tetracarboxylates by a two-step synthesis using two different metal ions.

In the synthesis of the di-0,0'-alkyl product 6a in 4a as the solvent promoted by a stoichiometric amount of La(III) a maximum conversion of about 80% was obtained (Fig. 1B). Higher La(III) concentrations did not increase this conversion. As these products are of major importance because of their Ca(II) and Mg(II) sequestration (see below) a procedure was developed for easy access to high yields of di-0,0'-alkylated polyol compounds. For 6a, the intermediate 5a could be synthesized in a high yield with Ti(OiPr)₄ as the catalyst in 4a as the solvent. After isolation of 5a by precipitation it was employed in the second reaction step, using water as the sole solvent and La(III) as the catalyst.

Before adding La(III), TiO_2 was filtered off. Optimal results were obtained with a molar ratio of La/5a/2 of 1/1/1 (pH 8 at 298 K). After 18 h at 363 K, the conversion of 5a to 6a was 93%. No sideproducts from reaction with water were observed (Scheme V). Apparently, the higher affinity for La(III) of 5a and 3 withholds water from reacting, which was already observed in the synthesis of 3.¹³ During the reaction a precipitate is formed, which turns out to be 1:1 complex of La(III) and 6a, and therefore, the purification of 6a from the starting compounds is very simple. An isolated yield of 82% was obtained. This two-step procedure may also be very useful for the O-alkylation of a polyhydroxylated compound with two different α,β -unsaturated dicarboxylates.

Extension of the scope of reaction to longer chain polyols.

Upon extending the scope of the reaction to longer chain polyols water has to be used as a co-solvent. Al(III) was taken as the metal ion because this metal ion has been shown to give rise to selective mono-O-alkylation in the reactions with simple polyols. A model reaction with 2.5 mol% Al(III) (relative to 2) in ethylene glycol and water as co-solvent (3:2 v/v), was performed at various pH values (Figure 6). The reaction rate was very low up to pH 11, at which pH a steep increase is observed. At this pH the formation of aluminate esters of polyols is very likely.¹⁴ Some water addition to 2 had also occurred (< 7%).

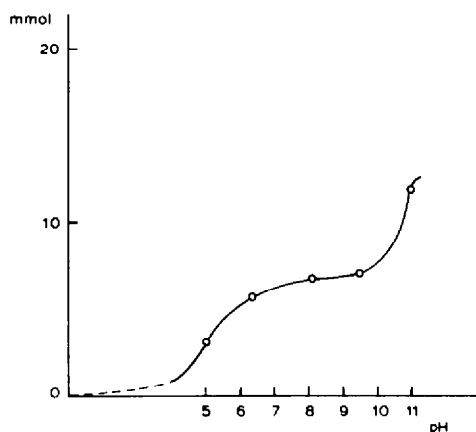
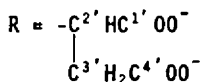
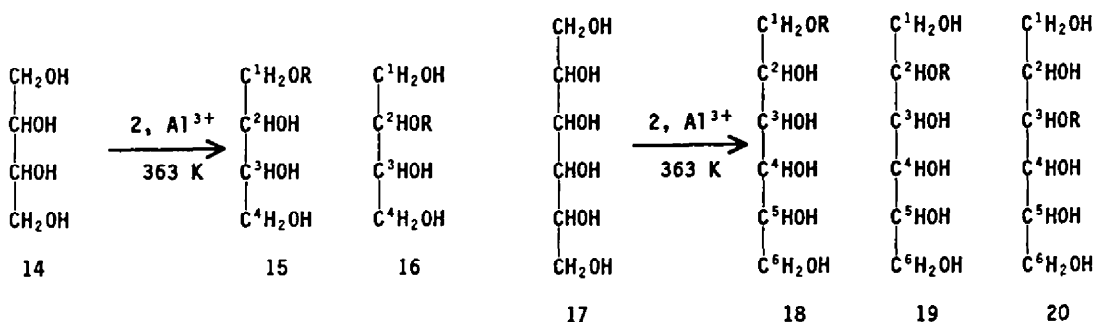


Figure 6. The formation of the mono-O-alkyl product 5a in a reaction mixture containing ethylene glycol (15 ml), Na_2 maleate (40 mmol), water as a co-solvent (10 ml) and AlCl_3 (1 mmol) as the catalyst after 140 h at 363 K. The pH of the reaction mixture was adjusted in the aqueous solution at 298 K before the addition of 4a.

Performing the reaction at this pH with meso-erythritol (14) resulted in the formation of the 1-O-alkyl product (15, 16%) and the 2-O-alkyl product (16, 4%) (Scheme VI).³⁰ Mannitol (17) resulted in the formation of all possible mono-O-alkyl compounds, in which

the 1-O-alkyl compound (18) was more abundant than both the 2-O- and 3-O-alkyl compounds (19 and 20, respectively) (Scheme VI).³⁰ Of the latter two components, the 3-O-alkylated compound was predominant. Probably, as a result of steric effects, a rather high selectivity for O-alkylation of the terminal positions exists.



Scheme VI

Measurements of the complexation of Ca(II) by the ligands synthesized.

In order to get an impression about the metal sequestering ability of the ligands synthesized, the Ca(II) complexation was studied by means of Ca(II) selective electrode measurements.

Table II. -Stability constants of Ca(II) complexes.

Ligand	LogK _{Ca} ^a
5a	2.4
6a	5.1
5b	2.7
6b	5.2
8	2.4
9	2.3
10/11 ^c	4.4
3	4.3
13	5.8 ^b
12	2.66 ^d

^a I=0.02, 298 K, pH 10 (Ref. 35). ^b Ref. 7. ^c Predominately 11. ^d I=0, 298 K (Ref. 31).

The values of $\log K_{Ca}$ obtained show that particularly the di-O-alkylated products (6a, 6b, 10, 11) have good Ca(II) chelating properties. These compounds meet the requirement of being able to bind Ca(II) as much as sodium triphosphate, and, therefore, they are potential substitutes for this compound in detergents.

Conclusions

The metal ion catalysed O-alkylation of polyol compounds with 2 is a convenient way to synthesize hydroxyethercarboxylates which may serve as sequestering agents. The product distribution is strongly dependent on the choice of metal ion catalyst. Mono-O-alkyl products are selectively obtained using catalytic amounts of Al(III) and Ti(IV) in an excess of the polyol as the solvent. Al(III) in combination with a small amount of water as the co-solvent can be applied when using solid high molecular weight polyols as starting compounds. The selectivity for a particular hydroxyl group of the polyol is low, although, some preference exists for the primary hydroxyls. The better Ca(II) complexing di-O, O'-alkyl products can be prepared in a high yield by a second alkylation with 2, with a stoichiometric amount of La(III) as promoter and with water as the solvent. Alternatively, Ni(II) at low molar ratio of metal ion/2 can be used in a one step procedure to give high amounts of di-O, O'-alkyl products.

Experimental part

Materials and Methods.

The HPLC analyses were carried out using a Waters Assoc. M45 pump, a Rheodyne 7125 injection valve, an Aminex HPX 87H column (200x9 mm) at 333 K, a Waters Assoc. R401 detector, and a Spectra-Physics SP4100 Computing integrator. An aqueous solution of 0.01 M trifluoroacetic acid was used as the mobile phase at a flow rate of 0.6 ml/min. The mobile phase was filtered and degassed by sonification in vacuo before use. At certain time intervals samples (100 μ l) were taken from the reaction mixture. The reactions were quenched by adding 1.0 M trifluoroacetic acid (500 μ l). The products were characterized by ^1H and ^{13}C NMR spectroscopy, combined with A(ttached) P(roton) T(est). The NMR experiments were performed on a Nicolet NT-200 WB spectrometer at 298 K or on a Varian VXR-400 S MHz spectrometer. The methyl group of t-BuOH was used as internal reference at 1.2 ppm (^1H NMR) or 31.2 ppm (^{13}C NMR). For the numbering of the atoms see Schemes II, III, and VI. The HPLC-MS spectra were recorded on a VG 70-250 SE hooked to the HPLC system described above. Ionisation was accomplished by thermoplasm. For the Ca(II) sequestration measurements a Philips IS 561 Ca-ion-selective electrode, an HNU ISE-40-01-100 single junction reference electrode and a Metrohm 654 pH meter and 655 dosimat (automatic burette) were used. The data were processed with a Lotus 1-2-3 spreadsheet. The elemental analyses and the determinations of the water contents according to Karl Fisher were performed at the Analytical Department of T.N.O. in Zeist, The Netherlands. Atomic Absorption Spectroscopy was performed on a PE 1100 in an oven at 3070 K. The Ln(III).xH₂O salts (x=6,7) were purchased from Alfa Products. The metal ion content of the metal salts

was determined by an EDTA titration with xylenol orange as the indicator and using urotropine as the buffer, except for Fe(II), Co(II), Ni(II), and Cu(II) where murexide was used as the indicator and ammonium acetate as the buffer. The HPX-87H and the AGI-X8 (Cl⁻ form, 100-200 mesh) anion exchange materials were purchased from Biorad. The membrane filter (0.2 μm) FP-200 was purchased from Gelman Sciences Inc. Maleic acid anhydride and lithium hydroxide were purchased from Merck-Schuchardt. The other chemicals were purchased from Aldrich. Ethylene glycol, diethylene glycol and glycerol were distilled before use. Disodium maleate (Na₂maleate) was prepared by dissolving maleic acid anhydride (9.8 g, 0.1 mol) in water (50 ml) with NaOH (8.0 g, 0.2 mol). The clear solution was cooled to room temperature before ethanol (200 ml) was added. The dispersion obtained is stored at 278 K for 1 day. The crystals were filtered and washed with ethanol and dried over H₂SO₄ (353 K, 1 mmHg) to yield Na₂maleate (15.73 g, 0.098 mol, 98%). Dilithium maleate was prepared in an analogous way and dried over H₂SO₄ in an exsiccator. Yield Li₂maleate.H₂O (10.03 g, 0.078 mol, 78%). The maleate content was determined by a titration with a standard HCl solution. The chiral ligand (L)-alanine-N,N-diacetic acid was prepared according to Koine.³² (Anal. Calc. for C₇H₁₁NO₆: C, 40.98; H, 5.40; N, 6.83. Found: C, 41.11; H, 5.36; N, 6.99).

Disodium 2-hydroxyethoxybutanedioate (5a).

To a solution of LaCl₃.7.1 H₂O (0.883 g, 2.37 mmol) in ethylene glycol (70 ml) at 363 K was added Li₂maleate (12.79 g, 87.7 mmol). A clear solution was obtained. After 100 h at 363 K the HPLC analysis showed 92% conversion of maleate. The reaction was worked up by pouring out the reaction mixture into acetone (400 ml) under vigorous stirring. After decanting the solution, the sticky precipitate was dissolved in water (25 ml) and further purified by chromatography on a AGI-X8 anion exchange column (formate form, diameter 4 cm, height 50 cm). A gradient elution was applied (0 to 2.0 M formic acid). The obtained fractions were analysed by HPLC and the appropriate fractions were concentrated in vacuo and co-evaporated a few times with water to remove the formic acid. The remaining solution was neutralized with 1.0 M NaOH and heated at 373 K for 15 min to remove the lactones formed. The pH was adjusted to 8 and the solution was lyophilised. Drying in vacuo over P₂O₅ yielded the disodium salt of 5a (8.67 g, 35.5 mmol, 40%), which contained 8.89% water. ¹H NMR (D₂O) δ (ppm): 4.08 (dd, 1H, J= 10.6 Hz, 3.1 Hz), 3.7-3.4 (m, 4H), 2.57 (dd, 1H, J= -15.3 Hz, 3.1 Hz), 2.35 (dd, 1H, J= -15.3 Hz, 10.6 Hz). ¹³C NMR (D₂O) δ (ppm): 181.75, 181.03 (C1', C4'), 80.81 (C2'), 72.41 (C1), 62.27 (C2), 43.19 (C3'). The sideproduct, tetrasodium salt of 6a, was obtained in 16% yield (3.44 g, 8.0 mol).

Tetrasodium ethylenedioxydibutanedioate (6a).

The same procedure was used as for the synthesis of 5a except for the amount of LaCl₃.7.1H₂O (11.76 g, 31.5 mmol), which was dried before use in vacuo at 343 K for at least 5 h to yield LaCl₃.2.3.H₂O. After 2 h the slurry initially formed was dissolved. After 20 h HPLC analysis showed that maleate was completely converted. The reaction

mixture was poured out into ethanol (500 ml) under vigorous stirring. The precipitate was dissolved in demineralized water (200 ml) and heated at 333 K. A solution of disodium oxalate (0.354 g, 47.5 mmol) in demineralized water (50 ml) was added and the mixture was stirred for 15 min at 333 K. The $\text{La}_2(\text{oxalate})_3$ was filtered off. The product was further purified by anion exchange chromatography as described for 5a to yield the tetrasodium salt of 6a (10.293 g, 23.97 mmol, 55%). ^{13}C NMR (D_2O) mixture of racemic (RR/SS) and meso (RS) $\delta(\text{ppm})$: 181.46 (C1', C1'', C4', C4'' rac), 180.74 (C1', C1'', C4', C4'' meso), 81.15 (C2', C2'' rac), 80.99 (C2', C2'' meso), 70.53 (C1, C2 meso), 70.31 (C1, C2 rac), 43.04 (C3', C3''). Ratio rac/meso 2/3. The ^{13}C signals of the racemic and the meso form were assigned with the use of a chiral shift reagent prepared by grinding (L)-alanine-N,N-diacetic acid and $\text{PrCl}_3 \cdot 7.2\text{H}_2\text{O}$ in a 1/1 molar ratio. This mixture was added in small portions (0.020 g) to a solution of tetrasodium salt of 6a (0.3 M in 5 ml D_2O , 12 mm tube). The pH was maintained at 7.5 with 1 M NaOD and t-BuOH was added as internal standard. The spectra were recorded at 353 K. The molar ratio was increased up to 0.26. The induced shift of $\text{PrCl}_3 \cdot 7.2\text{H}_2\text{O}$ were measured in an analogous way. The Pr(III) induced shift measurements showed that both the meso and rac carboxylate signals were split into signals for C1', C1'' and C4', C4'' upon addition of Pr(III) and that the signal at 43.04 ppm was split into the signal for the meso and racemic form. The low intensity signals at 81.15, 43.04 of the racemic form were split into 2 signals on addition of the chiral shift reagent. The signal at 181.46 (C1', C1'', C4', C4'' rac) was split into 3 signals. The C1, C2 signal showed serious line broadening upon addition of Pr(III). The side product, the disodium salt of 5a, was obtained in a 9% yield (1.989 g, 8.16 mmol).

Disodium [(hydroxyethyleneoxy)ethyleneoxy]butanedioate (5b) and tetrasodium oxybis(ethyleneoxy)dibutanedioate (6b).

A procedure analogous to that described for the synthesis of 5a was used, starting from diethylene glycol (30 ml), Li_2 maleate (5.116 g, 35 mmol), and $\text{LaCl}_3 \cdot 7.1 \text{H}_2\text{O}$ (0.353 g, 0.95 mmol). After 88 h of reaction HPLC analysis showed that 73% conversion of maleate into both 5b and 6b had occurred. The same work-up procedure was used as for 5a yielded the disodium salt of 5b (2.714 g, 9.43 mmol, 27%) and the tetrasodium salt of 6b (1.929, 4.06 mmol, 23%), which contained 7.52% and 10.40% water respectively. 5b: ^{13}C NMR (D_2O) $\delta(\text{ppm})$: 181.51, 180.76 (C1', C4'), 81.17 (C2'), 73.18 (C1), 71.22, 70.36 (C2, C3), 61.91 (C4), 43.26 (C3'). 6b: ^{13}C NMR (D_2O) 1/1 mixture of meso and racemic $\delta(\text{ppm})$: 181.54, 180.84 (C1', C1'', C4', C4''), 81.12, 81.05 (C2', C2''), 71.20 (C1,C4), 70.30, 70.23 (C2, C3), 43.22 (C3', C3'').

Disodium (2,3-dihydroxypropoxy)butanedioate (8) and [2-hydroxy-1-(hydroxymethyl)ethoxy]-butanedioate (9).

A procedure analogous to that described for the synthesis of 5a was used, starting from glycerol (30 ml), Li_2 maleate (5.116 g, 35 mmol), and $\text{LaCl}_3 \cdot 7.1 \text{H}_2\text{O}$ (0.353 g, 0.95 mmol).

The products 8 and 9 could be separated with the use of an anion exchange column yielding the disodium salts of 8 (2.875 g, 10.4 mmol, 30%) and of 9 (0.960 g, 3.5 mmol, 10%), which contained 8.88% and 8.28% water, respectively. 8: ^{13}C NMR (D_2O) mixture of racemic and meso $\delta(\text{ppm})$: 181.59, 181.66, 180.97 (C1', C4'), 81.49, 80.99 (C2'), 72.58, 72.28 (C1), 72.21, 71.85 (C2), 64.16, 64.11 (C3), 43.21, 43.13 (C3'). 9: ^{13}C NMR (D_2O) $\delta(\text{ppm})$: 182.03, 180.69 (C1', C4'), 82.69, 80.02 (C2, C2'), 62.84, 62.81 (C1, C3), 42.87 (C3'). The di-0,0'-alkyl products 10 and 11 were obtained in 19% yield (1.749 g, 3.84 mmol). The 1,3-0,0'-di-alkyl product 11 was present in a 3/1 ratio over the 1,2-0,0'-di-alkyl product 10 according to ^{13}C NMR.

Tetrasodium [(hydroxymethyl)ethylenedioxy]dibutanedioate (10) and (2-hydroxytrimethylenedioxy)dibutanedioate (11).

The synthesis was performed analogous to that of 6a starting from glycerol (30 ml) and $\text{Li}_2\text{maleate}$ (4.320 g, 30 mmol) and $\text{LaCl}_3 \cdot 7.1 \text{ H}_2\text{O}$ (4.71 g, 12.6 mmol). After stirring for 16 h at 363 K the reaction mixture was worked up as described for 6a, yielding the tetrasodium salts of 10 and 11 in a 1/1 mixture (1.079 g, 2.372 mmol, 16%), which contained 9.44% water. 10: ^{13}C NMR (D_2O) $\delta(\text{ppm})$: 182.22, 182.18, 181.54, 180.91, 180.88, 180.69 (C1', C1'', C4', C4''), 81.60, 81.37, 81.20, 81.12, 80.45, 80.26, 80.01, 79.86, 79.32, 79.17 (C2, C2', C2''), 71.31, 70.81, 70.06, 69.59 (C1), 63.24, 63.14, 62.56, 62.17 (C3), 43.55, 43.31, 43.22, 42.81 (C3', C3''). 11: ^{13}C NMR (D_2O) $\delta(\text{ppm})$: 181.57, 181.51, 180.77 (C1', C1'', C4', C4''), 81.46, 80.89 (C2', C2''), 72.85, 72.74, 72.54, 72.45 (C1, C3), 70.68, 70.33 (C2), 43.11, 43.05 (C3', C3'').

Disodium (meso)-erythritol 1-butanedioate ether (15) and (meso)-erythritol 2-butanedioate ether (16).

$\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ (0.247 g, 1.02 mmol) was added to an aqueous solution of 2 M $\text{Li}_2\text{maleate}$ (20 ml). The pH was adjusted to 11.4 with a 1 M LiOH solution. (meso)-Erythritol (30 g, 0.246 mol) was added (molar ratio H_2O /erythritol approximately 4.5/1). The clear solution obtained was heated for 6 days at 363 K. The reaction mixture was worked up by diluting it with water (50 ml) to dissolve the solid formed upon cooling the reaction mixture to room temperature. The solution obtained was applied to an AG1-X8 anion exchange column (formate form). After elution and work-up according to the usual procedure the disodium salts of 15 (1.962 g, 6.46 mmol, 16%) and 16 (0.520 g, 1.71 mmol, 4%) were obtained. 15: ^{13}C NMR (D_2O) mixture of RRS/SSR and RSR/SRS $\delta(\text{ppm})$: 181.84, 181.78, 181.20, 181.13 (C1', C4'), 81.50, 80.77 (C2'), 73.51 (C3), 72.60, 72.22 (C1), 72.19, 71.78 (C2), 64.20, 64.12 (C4), 43.12, 43.10 (C3'). 16: ^{13}C NMR (D_2O) mixture of RRS/SSR and RSR/SRS $\delta(\text{ppm})$: 182.19, 181.85, 180.95, 180.77 (C1', C4'), 83.44, 80.96, 80.74, 78.61 (C2, C2'), 72.65, 71.85 (C3), 64.52, 63.89, 61.54, 61.00 (C1, C4), 43.32, 42.77 (C3').

Disodium mannitol 1-butanedioate ether (18), mannitol 2-butanedioate ether (19) mannitol 3-butanedioate ether (20).

Following the same procedure as for 15 and 16, but now with mannitol (30 g, 0.165 mol) gave the disodium salts of 18 (1.80 g, 4.95 mmol, 12%), a mixture of 19 and 20 (1.135 g, 3.12 mmol, 8%) and a mixture of 18, 19, and 20 (1.397 g, 3.84 mmol, 10%). 18: ^{13}C NMR (D_2O) mixture of RRRR and SRRR $\delta(\text{ppm})$: 181.94, 181.88, 181.29, 181.22 (C1', C4'), 81.56, 80.82 (C2'), 73.16, 72.76 (C1), 72.54, 72.41, 71.28, 70.93, 70.97, 70.88, 70.78, 70.68 (C2, C3, C4, C5), 64.82 (C6), 43.16, 43.09 (C3'). MS, m/e 281 (M-18), 263 (M-36), 183 (M-116), 165 (M-134). 19: ^{13}C NMR (D_2O) mixture of RRRR and SRRR $\delta(\text{ppm})$: 182.6, 182.3, 181.4 (C1', C4'), 82.41, 80.89, 80.66, 80.05 (C2, C2'), 73.26, 73.05, 72.91, 72.69, 72.50, 70.66 (C3, C4, C5), 65.06, 64.93, 63.93, 60.84 (C1, C6), 43.63, 43.21 (C3'). 20: ^{13}C NMR (D_2O) mixture of RRRR and SRRR $\delta(\text{ppm})$: 182.04, 182.02, 181.20, 181.17 (C1', C4'), 79.67, 79.24 (C2'), 79.71, 77.21 (C3), 73.35, 72.18, 73.11, 72.15, 71.18, 69.30 (C2, C4, C5), 65.12, 64.27, 63.62, 59.97 (C1, C6), 43.35, 42.73 (C3').

Standard procedure for testing catalytic activity of metal ions.

The metal ions as their chlorides (0.5 mmol) were dissolved in ethylene glycol (15 ml). Then $\text{Li}_2\text{maleate}\cdot\text{H}_2\text{O}$ (2.558 g, 17.5 mmol) was added. At certain time intervals samples (100 μl) were taken from the reaction mixture. The reaction was quenched by adding 1.0 M trifluoroacetic acid (500 μl). The reaction mixture was analysed with HPLC.

Disodium salt of 5a catalysed by $\text{Ti}(\text{OiPr})_4$.

$\text{Na}_2\text{maleate}$ (16.0 g, 100 mmol) was dissolved in ethylene glycol (50 ml). The solution was heated under stirring at 363 K. $\text{Ti}(\text{OiPr})_4$ (0.700 g, 2.5 mmol) was added. After 48 h the reaction mixture was poured out in ethanol (600 ml). The obtained sticky crystals were boiled in ethanol (150 ml) to remove the ethylene glycol. After filtration the disodium salt of 5a was obtained (14.2 g), with a purity of 96%. Ti(IV) was removed by adding water (25 ml). The TiO_2 was filtered off on a membrane filter. A solution obtained in this way could be used directly in the synthesis of the di-0,0'-alkyl product 6a. After evaporation in vacuo, ethanol was added to recrystallize 5a (13.9 g, 0.057 mmol, 57%), which contained 0.17 mol% Ti(IV) as measured by Atomic Absorption Spectroscopy.

Tetrasodium salt of 6a via a $\text{La}(\text{III})$ catalysed reaction.

A solution of 5a (57.4 mmol in 25 ml) was mixed with a solution of disodium maleate (64 mmol in 25 ml). The pH was adjusted to 10.5 by a 1 M NaOH solution. After heating the solution to 363 K $\text{LaCl}_3\cdot 7.1\text{H}_2\text{O}$ (11.93 g, 32 mmol) was added in small portions within 1 h. After 18 h at 363 K, a precipitate was present and 54% of 3c was formed (pH 7, 298 K). Again $\text{LaCl}_3\cdot 7.1\text{H}_2\text{O}$ (11.93 g, 32 mmol) was added in portions and the pH was adjusted to 8 (298 K) with 1M NaOH solution. After 47 h at 363 K, HPLC analysis showed 93% conversion into 6a. The reaction mixture was diluted with water (25 ml) and cooled to 278 K. The precipitate was filtered off and dried above H_2SO_4 in vacuo yielding pure

$\text{Na}_3\text{La}_2\text{OH}(\text{6a})_2(\text{H}_2\text{O})_2$ (26.5 g, 27.0 mmol, 84%). Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{O}_{23}\text{La}_2\text{Na}_3$: C, 24.51; H, 2.57; Na, 7.04. Found: C, 24.43; H, 2.75; Na, 7.20. This salt was converted into its tetrasodium salt by dissolving it in water (250 ml) followed by the addition of Dowex 50W (H-form) (150 g). The solution (pH 1.45) was neutralized with NaOH, concentrated and crystallized with ethanol (200 ml) yielding the tetrasodium salt of 6a (22.24 g, 46.8 mmol, 82%).

Ca(II) complexation measurements.

Calibration of the Ca(II) ion-selective electrode was performed using 10^{-2} , 10^{-3} , 10^{-4} , 10^{-5} and 10^{-6} M solutions of CaCl_2 buffered at pH 10 (NH_4OH) at ionic strength $\mu = 0.02$ (NaCl). Linear calibration plots were obtained up to 10^{-8} M Ca(II), provided that doubly distilled water and polyethylene storage bottles were used for the 10^{-5} and 10^{-6} M solutions. A solution of CaCl_2 (0.1 M) was titrated in portions of 0.2 ml to a 100 ml of an aqueous solution of the ligand ($0.5 \cdot 10^{-3}$ M, $I = 0.02$, at 298 K) with 2 minutes interval. The $\log K_{\text{Ca}}$ were calculated according to $n_{\text{Ca}}/(1-n_{\text{Ca}}) = K_{\text{Ca}} * [\text{Ca}]^{33}$ in which $K_{\text{Ca}} = [\text{CaL}]/([\text{Ca}][\text{L}])$ and n_{Ca} is the mean number of bound Ca(II) ions per ligand. The mean coordination number of the ligand, was calculated to be around 0.5 and 1 for the mono-O- and di-O,O'-alkyl products, respectively, which seems to be in agreement with the presence of 1/1 complexes.

Acknowledgement

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 Scientific Research (N.W.O.).

References

1. Hancock, R.D.; Martell, A.E. *Chem. Rev.* 1989, 89, 1875.
2. Nieuwenhuizen, M.S.; Kieboom, A.P.G.; van Bekkum, H. *J. Am. Oil Chem. Soc.* 1983, 60, 120.
3. Floor, M.; Kieboom, A.P.G.; van Bekkum, H. *Starch* 1989, 41, 348.
4. Heesen, J.G. *Neth. Pat.* 1973, 7 215 180, *Chem. Abstr.*, 81, 176040.
5. van Duin, M.; Peters, J.A.; Kieboom, A.P.G.; van Bekkum, H. *J. Chem. Soc., Perkin Trans. 2* 1987, 473.
6. van Duin, M.; Peters, J.A.; Kieboom, A.P.G.; van Bekkum, H. *Carbohydr. Res.* 1987, 162, 65.
7. Kemper, H.C.; Martens, R.J.; Nooi, J.R.; Stubbs, C.E. *Tenside Deterg.* 1975, 12, 47.
8. Konort, M.D.; Lamberti, V. *G.P.* 1971, 2 057 258, *Chem. Abstr.*, 75, 89458.
9. Lamberti, V.; Konort, M.D.; Weil, I. *U.S.* 1976, 3 954 858, *Chem. Abstr.* 85, 34979.
10. Bush, R.D.; Heinzman, S.W.; Connor, D.S.; Kretschmar, H.C.; Mackey, L.N. *Eur. Pat. Appl. E.P.* 1987, 236 007, *Chem. Abstr.* 107, 201022.

11. Bush, R.D.; Connor, D.S.; Heinzman, S.W.; Mackey, L.N. *Eur. Pat. Appl. E.P.* 1987, 233 010, *Chem. Abstr.* 108, 7919.
12. Valenty, V.B. *Eur. Pat. Appl. E.P.* 1985, 150 930, *Chem. Abstr.* 104, 90988.
13. van Westrenen, J.; Peters, J.A.; Kieboom, A.P.G.; van Bekkum, H. *J. Chem. Soc., Dalton Trans.* 1988, 2723.
14. van Duin, M.; Peters, J.A.; Kieboom, A.P.G.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* 1989, 108, 57.
15. Vijverberg, C.A.M.; Peters, J.A.; Bovée, W.M.M.J.; Vroon, H., Kieboom, A.P.G.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* 1983, 102, 255.
16. van Westrenen, J.; Peters, J.A.; Kieboom, A.P.G.; van Bekkum H.; Rizkalla, E.N.; Choppin, G.R. to be published.
17. Cheng, B-D. *G.P.* 1977, 2 656 251, *Chem. Abstr.*, 87, 54908.
18. Hachmann, K. *G.P.* 1980, 2 852 285, *Chem. Abstr.*, 93, 97311.
19. Kieboom, A.P.G.; Spoomaker, T.; Sinnema, A.; van der Toorn, J.M.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* 1975, 94, 53.
20. Chen, Z.; van Westrenen, J.; Peters, J.A.; van Bekkum, H. to be published.
21. Li₂maleate (2, 30 mmol) was converted into 5b and 6b in a molar ratio of 1/1, when 12.6 mmol LaCl₃ was added to catalyse the O-alkylation of 4b (30 ml) at 363 K.
22. 12.6 mmol LaCl₃ was used instead of 1 mmol in the reaction mixture described under Fig. 3. After 16 h 2 was converted into the O-alkyl products of 7, completely. The product ratio did not change from 16 h up to 48 h.
23. Hydroxyethanolate is the conjugated base of ethylene glycol.
24. Brown, P.L.; Sylva, R.N.; Ellis, J. *J. Chem. Soc., Dalton Trans.* 1985, 723.
25. Co²⁺(Coordination number (CN) 6: 88.5 pm), Ni²⁺(CN 6: 83), Zn²⁺(CN 6: 88 pm).
26. Hammershøi, A.; Sargeson, A.M.; Steffen, W.L. *J. Am. Chem. Soc.* 1984, 106, 2819.
27. Irving, H.; Williams, R.J.P. *J. Chem. Soc.* 1953, 3192.
28. Philips, C.S.G.; Williams, R.J.P. '*Inorganic Chemistry*', Oxford University Press, Oxford, 1965.
29. pH of the initial reaction mixture measured at room temperature.
30. The yields are given after purification because the peaks were only partly resolved with the HPLC column used. With help of the anion exchange column separation could be realized except for 19 and 20.
31. Smith, M.; Martell, A.E. '*Critical Stability Constants*.' Plenum Press, New York, 1977, 3.
32. Koine, N.; Sakota, N.; Hidaka, J.; Shimura, Y. *Bull. Chem. Soc. Jpn.* 1970, 43, 1737.
33. Rossotti, F.J.C.; Rossotti, H. '*The Determination of Stability Constants and Other Equilibrium Constants in Solution*.' Mc Graw-Hill, New York, 1961.
34. Both Li(I) and Na(I) can be used. At higher concentrations of metal chloride, though, Li(I) is preferred to avoid precipitation of NaCl.
35. Schubert, J. in '*Methods of Biochemical Analysis*.' Ed. D. Glick, Interscience Publishers Inc., New York, 1956, 3.