STELLINGEN

1. De bepaling van zes watermoleculen in de eerste coördinatiesfeer van het La(III)-ion in aceton-water mengsels, is nog geen reden om aan te nemen dat het coördinatiegetal van dit metaal-ion zes bedraagt.


2. De term 'paramagnetische katalyse' van lanthanide(III)-ionen in de decarboxylering van oxaloacetaat moet met enige terughoudendheid worden behandeld.


3. Veronachtzaming van de vorming van iminodibutandioaat vanuit aspartaat en fumaraat kan tot gevolg hebben dat de evenwichtskonstante van het evenwicht aspartaat naar fumaraat en ammonia en daardoor de geschatte concentratie van ammonia in de 'primitieve' oceaan met een korreltje zeezout genomen moet worden.

Stadnikow, G. Chem. Ber. 1911, 44, 44.
Bada, J.L.; Miller, S.L. Biochemistry 1968, 7, 3403.

4. Hammershøi, Sargeson en Steffen beweren ten onrechte dat het dianion van maleaat niet reageert met primaire amines.

5. De door Rodriguez en Devine berekende tweede associatiekonstante van carboxymethoxysuccinaat volgt niet uit de door hen gegeven formule.


6. De structuur van het NaDy(PPP)$_2^{6-}$ (PPP= trifosfaat) in oplossing, voorgesteld door Springer en medewerkers, is onwaarschijnlijk op grond van stereochemische overwegingen.


7. Het onderzoek van Cheng en medewerkers naar het werkingsmechanisme van de pH-glaselectrode door verpulvering van het pH-gevoelige glas doet vermoeden dat van de nood een deugd gemaakt is.


8. Het bierassortiment is een in belangrijkheid toenemend onderwerp van zinloze discussie.

9. Audiovisuele ondersteuning van de arbitrage van professionele sportontmoetingen kan veel ergenis voorkomen.

10. Het verzweegen van de toenemende informatiestroom kan de vroegtijdige verdrinking betekenen van menig grensverleggend werk.

Jeroen van Westrenen 25-6-90
LANTHANIDE(III) CATALYZED O-ALKYLATION OF HYDROXYL COMPOUNDS WITH MALEATE
LANTHANIDE(III) CATALYZED O-ALKYLATION OF HYDROXYL COMPOUNDS WITH MALEATE

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Jeroen van Westrenen

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Voor Henny en Jim
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CHAPTER I.

INTRODUCTION

General

Among the wide spectrum of industrial, clinical, and environmental applications of selective metal ion complexation,\(^1\) considerable effort has been devoted to the development of 'detergent-builders',\(^2\) i.e. ligands that can complex Ca(II) and Mg(II) ions, disperse precipitates and thus reinforce detergent action. Originally, pentasodium triphosphate (STP) was used in detergents because of its high performance and cost-effectivity. The use of STP in detergents has been restricted by law enforcement due to its contribution to the eutrophication of natural waters. Hence, nitrilotriacetate (NTA) has been used as substitute for STP. Suspected carcinogenicity and enhanced sequestration of heavy metal ions at low concentrations of NTA,\(^3\),\(^4\) have made the use of this ligand less attractive from an environmental point of view. Subsequent research has been focussed on ligands having both carboxylate groups and neutral ether donors, but which do not contain nitrogen donor groups. An example is the recently developed oxidation of polysaccharides like starch,\(^5\)\,-\(^7\) leading to polymers containing oxydiacetate residues with excellent Ca(II) sequestration properties. Their selectivity for Mg(II) is unknown and their biodegradability is not established, as yet.

Another promising approach to synthesize metal ion specific chelates is the template directed one.\(^8\) Herein, the metal ion acts as a template during the synthesis by directing the most favorable organization of the donor groups. In view of the urge for new 'detergent-builders', the use of Ca(II) and Mg(II) as metal ion templates in their preparation is quite tempting. Some examples have, already, been described in the literature for ether group containing polycarboxylates. These ligands have been synthesized by O-alkylation of hydroxyl group containing compounds, like glycolate,\(^9\) malate,\(^10\) and glycerol\(^11\) with maleate\(^12\) in aqueous alkaline slurry (pH>11) in the presence of large amounts of Ca(II). In this reaction open-structured ligands are formed as a result of the use of maleate, an inexpensive mono-functional reagent that is manufactured on a large scale. The ether groups-containing polycarboxylate compounds obtained by this way have
reasonable Ca(II) sequestration properties and are biodegradable.\textsuperscript{13}

The O-alkylation of hydroxyl groups by a Michael-type addition with maleate in the absence of multivalent metal ions is not feasible due to the relatively low nucleophilicity of the hydroxyl group, in contrast to that of the amino group.\textsuperscript{14-19} Apparently, Ca(II) also contributes to the activation of the hydroxyl group. So far, in the literature no attention has been paid to the mechanism of the O-alkylation of hydroxyl groups with maleate catalyzed by multivalent metal ions. The two different modes of action of the metal ion in the O-alkylation, \textit{i.e.} the template effect of the metal ion and the activation of substrates upon coordination of the metal ion, are both interesting from a mechanistic and synthetic point of view.

The application of lanthanide(III) ions (Ln(III)) instead of Ca(II) in the O-alkylations with maleate is very attractive for several reasons. The Ln(III) ions have coordination properties similar to those of Ca(II), as will be outlined in the next section, and therefore in template reactions ligands may be obtained that probably exhibit good sequestration properties for Ca(II). The higher formal charge of the Ln(III) ions with respect to Ca(II) causes a higher degree of activation of the substrate(s) upon coordination, which is even more important. In addition, the lanthanides,\textsuperscript{20} named after the first element of the 4f series, lanthanum (Greek: \textit{lanthano} meaning I am hidden) are less rare than the other term in use, rare earth, suggests and,\textsuperscript{21-23} as a consequence are reasonably priced (Lanthanum oxide: 60-70 Hfl/kg 99.9% Rhône-Poulenc Group).

The aim of this thesis is to study the reaction mechanism of the O-alkylation of hydroxyl containing compounds with maleate catalyzed by lanthanide(III) ions and to explore its synthetic significance in the development of new 'detergent-builders'. Both the activation of the metal
ion of coordinated substrates and the template effect will be discussed in more detail. In order to be able to discuss the template effect of the Ln(III) ions, it is important to know some of their coordination characteristics, and as a consequence, the constraints imposed on the ligand by the metal ion.

Factors governing the stability of the complexes formed with hard metal ions.

For the complexation of Ca(II) and of Ln(III) ions, oxygen donors are preferred over nitrogen, forming bonds that are largely ionic in nature and show little directional character. Hence, Ca(II) and Ln(III) are classified as hard metal ions according to the HSAB principle. Consequently, the affinity of Ln(III) ions for ligands is, usually, in the order of electronegativity, e.g., $F^- > OH^- > H_2O > NO_3^- > Cl^-$. Hancock and Martell have formulated additional factors involved in the stability of the complexes formed. First, the strength of coordination of anionic oxygen
donors is related to the acidity of the metal ion and the proton basicity of the oxygen donor; the selectivity of a ligand for a more acidic metal ion (e.g. Fe(III) and Al(III)) over a less acidic metal ion (e.g. Ca(II)) increases, when the number and the basicity of the charged oxygen groups are increased.\textsuperscript{25} For this reason the catecholate and ionized hydroxamic acids are such excellent sequestering agents for Fe(III).\textsuperscript{26-28} Fe(III) effective donors in decreasing order are:\textsuperscript{28}

- unidentate RO\textsuperscript{−} > RC=CHO\textsuperscript{−} > PhO\textsuperscript{−} > ROP(=O)O\textsubscript{2}\textsuperscript{2−} > RCOO\textsuperscript{−} > R\textsubscript{2}C=N-O\textsuperscript{−}.

- bidentate catecholate > RCH(O\textsuperscript{−})COO\textsuperscript{−} > RC(=O)N(O\textsuperscript{−})R'

A second factor is the number of neutral oxygen donor groups. The introduction of neutral oxygen donors into a ligand increases its selectivity for coordination of large metal ions over small ones.\textsuperscript{25} Thus, ligands with a combination of a relatively large number of ether oxygens and carboxylate groups are selective for the large Ca(II) and Ln(III) ions. The selectivity for Mg(II) drops when the amount of ether oxygens is increased (see Table I for ionic radii).

<table>
<thead>
<tr>
<th>Metal Ion</th>
<th>Ionic\textsuperscript{a} radius (Å)</th>
<th>Coordination number (CN)</th>
<th>Log(k\textsubscript{exch}) (s\textsuperscript{-1}) \textsubscript{c} at 298 K.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg(II)</td>
<td>0.86</td>
<td>6</td>
<td>11.8 5.7</td>
</tr>
<tr>
<td>Ca(II)</td>
<td>1.26</td>
<td>8</td>
<td>12.9 8.4</td>
</tr>
<tr>
<td>La(III)</td>
<td>1.35 (9)</td>
<td>9-8</td>
<td>8.50</td>
</tr>
<tr>
<td>Gd(III)</td>
<td>1.24 (9)</td>
<td>9-8</td>
<td>8.0 9.0</td>
</tr>
<tr>
<td>Lu(III)</td>
<td>1.17 (9)</td>
<td>9-8</td>
<td>7.6 7.6\textsuperscript{d}</td>
</tr>
<tr>
<td>Fe(III)</td>
<td>0.78</td>
<td>6</td>
<td>2.2 2</td>
</tr>
<tr>
<td>Co(III)</td>
<td>0.75</td>
<td>6</td>
<td>1.3 -1.0\textsuperscript{e}</td>
</tr>
<tr>
<td>Al(III)</td>
<td>0.54</td>
<td>6</td>
<td>5.0 -0.1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Ref. 24b corresponding CN in parenthesis. \textsuperscript{b} M\textsuperscript{2+}H\textsubscript{2}O = M\textsuperscript{2+}OH\textsuperscript{−} + H\textsuperscript{+} (ref. 65: I=0, 298 K). \textsuperscript{c}The rate constant of water exchange is determined by NMR for all metal ions except for Ca(II) and Mg(II) (ref. 88). \textsuperscript{d} log k\textsubscript{exch} of Yb(III). \textsuperscript{e}Ref. 24b Low-Spin.
A chelate effect is visible by comparison of the stability of a bidentate complex containing two negatively charged oxygen donors versus the overall stability constant of a complex with two hydroxide ligands. This effect is entropic of origin and is also referred to as the cratic effect. In first approximation it is equal to log 55.5 because in the unidentate case three particles (metal ion and two hydroxide ligands) are joined to one, whereas in the bidentate case two particles combine to one. In both cases two coordinated water ligands are liberated. This chelate effect is independent of the ring size of the chelate as long as the donor groups are coordinated in the first coordination sphere of the metal ion. It is, however, a well-known fact that increasing the chelate ring size beyond five destabilizes the complex. Hancock and Martell have suggested that this effect of chelate ring expansion from a five-membered ring to a seven-membered one is mainly due to less favorable enthalpy contributions. Moreover, it can be stated that the increase of the chelate ring size leads to a greater degree of complex destabilization for larger metal ions (e.g. Ca(II) and Ln(III)) than for smaller ones (e.g. Fe(III) and Mg(II)). Thus, when six-membered or higher membered rings are formed the selectivity for Ca(II) of an ether groups-containing polycarboxylate will level with respect to that for Mg(II). The oxycacacetate ligand forms five-membered rings upon chelation, as a result this ligand shows a large difference between the stabilities of the Mg(II) (logK 1.8) and Ca(II) (logK 3.38) complexes. For the citrate ligand the formation of larger chelate rings is feasible, which can explain the smaller difference for Ca(II) and Mg(II) coordination (logK Mg(II): 3.37 Ca(II): 3.50). In addition, the higher number of carboxylate groups in citrate favors the complexation of the more acidic Mg(II) over Ca(II) (see above), which may also contribute to the small difference in the stability of the Mg(II)- and Ca(II)-citrate complex.

The rate-characteristics of complex formation, and hence, kinetic lability of the complex, will also be an important factor contributing to the catalytic role of metal ions. For unidentate ligands like water, the rate of ligand substitution decreases with increasing acidity of the metal ion (i.e. pK_a of M\_\text{H}_2O) as shown in Table I. For multidentate ligands, usually, high levels of preorganization lead to high stability constants, but, as a rule, the level of kinetic lability of the complex drops off roughly as the level of preorganization increases. The poor rate characteristics of the ligation of chelates forming very stable complexes can become cumbersome in some sequestration problems. For instance, \textit{in vivo}
the rate of metabolization of the free ligand can compete with that of sequestration. In some cases it is advantageous to have a combination of chelates forming kinetically labile complexes and those forming thermodynamically stable complexes, as illustrated in the treatment of iron deposits in tissues of patients suffering from Cooley’s Anemia. The performance of the iron-specific ligand, desferrioxamine B (LogK 30.6), is markedly improved in the presence of ligands that are able to function as a carrier, like NTA or citrate.

Template effect of metal ions.

The template function of a metal ion is closely related to molecular recognition in biological systems; a particular reaction is directed by the structural specificity of substrate-template binding. The template effect can cause, for example, inhibition of side reactions as a result of the specific binding of the metal ion with the substrate, which is illustrated by the elegant synthesis of bicapped TRENCAM by Raymond and coworkers (Scheme II). The formation of the tris-catecholate complex obtained from three equivalents of disuccinimidio-2,3-dihydroxyterephthalate and FeCl₃ in the presence of triethylamine prevents the hydroxyl groups to react with the
active N-hydroxysuccinimide esters. In addition, the perfect spatial orientation of the active esters at the opposing trigonal faces of the ferric complex allows a selective reaction with tris(2-aminoethyl)-amine.

The template effect of a metal ion has both kinetic and thermodynamic origins. The kinetic template effect results mainly from bringing together both reactive ligands in a favorable geometric arrangement around the metal ion in an equilibrium prior to the rate-limiting reaction within the coordination sphere of the metal ion. This mode of action of the metal ion without any further activation of the substrates (see below) has been referred to as the promnastic effect (Greek: to be matchmaker). Obviously, the entropy of activation of a reaction becomes less negative going from a bimolecular reaction in the ‘free state’ to a unimolecular one in the complex. In addition, the promnastic effect of the metal ion has an enthalpic contribution as it reduces the charge repulsion of two anionic reactants, for example, in the metal ion catalyzed phosphorylation of and 1,10-phenanthroline-2-carbinolate by adenosinetriphosphate (ATP) in aqueous solution: the oxy-nucleophile and ATP are both negatively charged (Scheme III).  

The thermodynamic template effect of metal ions is observed for
competing reversible reactions, wherein the metal ion allows the stability of the complex to determine the product formation. This template effect can be illustrated by the aqueous tautomeric equilibrium of N-α-ketoglutaridine and N-pyruridine-α-glutamate which shifts from equal stability to a 10 times larger stability of the latter in the presence of an equimolar amount of Zn(II) (Scheme IV). 39

\[
\begin{array}{c}
\text{N-α-ketoglutaridine} \\
\text{Zn(II)} \\
1 \\
10 \\
\end{array}
\quad \quad 
\begin{array}{c}
\text{N-pyruridine-α-glutamate} \\
1 \\
\end{array}
\]

Scheme IV

Owing to their chelating properties, Schiff bases in general are stabilized by metal ions. 36 The hydrolytic lability of the imine carbon-nitrogen double bond is reduced by coordination to the metal ion, thus allowing the thermodynamically more stable product to accumulate. This effect has led to many elegant syntheses of macrocyclic Schiff base compounds. 40-46 For lanthanide ions this has been done by Fenton 43 and Vallarino 44 and their coworkers using for example two equivalents of the bifunctional reagents, 2,6-diacetylpypyridine and ethylenediamine, in the presence of Ln(III) in methanol or acetonitrile (Scheme V). Although the Ln(III) ions are among the most kinetically labile trivalent cations, in this case very stable complexes are formed that are unable to exchange the cation. Removal of the Ln(III) ion leads to the destruction of the ligand.

The coordination number of the Ln(III) ions can vary between 9 and 8 for most ligands. 47-49 The steady decrease in ionic radii of the Ln(III) ions from La(III) to Lu(III) is a valuable variable in both thermodynamically and
kinetically determined template effects. As a consequence of the little directional character in metal-ligand bonds of Ln(III) ions, the mobility of the ligands within the ternary complex is large. Therefore, the size of these metal ions is an important factor determining the ability of the reactive groups of the ligands to approach each other within the ternary complex. The ionic radius of the Ln(III) ion may govern the thermodynamically determined template effect as well, as shown by Raymond
and coworkers (Scheme VI). In acetonitrile the encapsulation of the Ln(III) ion by Schiff base formation from tris(2-aminoethyl)amine and bis(dimethylamino)methane leads to the tri-bridged ligands for Yb(III), while the larger La(III) only leads to the di-bridged ligand.

One of the major drawbacks of thermodynamically determined template effects of metal ions is that the encapsulation or coordination by the product requires stoichiometric amounts of catalyst. The amount of catalyst that is needed for complete conversion to the product is dependent on the coordination number of the metal ion relative to the number of donor groups in the ligand. If the metal ion also exhibits a kinetic template effect and it activates the substrates upon coordination (see below), then it would be better to use the term promotion rather than catalysis, although the latter will be used throughout this thesis.

Activation of organic ligands by metal ion coordination.

In most cases the mode of action of the metal ion is not limited to the template function. The metal ion is also able to activate organic ligands by polarization of coordinated donor groups. In the metal ion mediated hydrolysis of esters, amides, and nitriles, the α-carbon has become more electrophilic by the metal ion coordination to the carbonyl-oxygen or nitrile-nitrogen and, therefore, has become more susceptible to attack by nucleophiles. These reactions are also catalyzed by protons in a similar fashion. It is generally recognized that the polarizing power of protons even when hydrated is greater than that of the metal ion. The metal ion, however, can operate in neutral solutions whereas the proton cannot, which enables one to use nucleophiles of moderate basicity (pKₐ 7-9).

The basicity of the nucleophiles or leaving groups can also be influenced by metal ion coordination. Coordination of the amino group by its lone-pair decreases its nucleophilicity almost to a zero level similarly to protonation, but vice versa increases its leaving group ability. Metal ion coordination lowers the pKₐ of coordinated ammonia groups, but very strong acidic metal ions such as Co(III) are able to restore part of nucleophilicity by the formation of Co(NH₂⁻) residues. The lowering of the pKₐ upon metal ion coordination also occurs in the case of the water ligand. The pKₐ of metal ion-bound water lays in between -1.7 (pKₐ H₃O⁺), and 15.7 (pKₐ H₂O), the pKₐ’s at maximum and minimum polarization, respectively. The pKₐ of metal ion-bound water decreases at higher charge density of the metal.
The La(III) coordinated water molecule has a $pK_a$ of 8.5 (Table I). According to the Brönsted catalysis law a coherent lowering of the nucleophilicity of the coordinated hydroxyl group takes place by lowering the $pK_a$. The nucleophilicity of the coordinated hydroxide is less than that of the free hydroxide, but larger than that of water. Vice versa the coordinated water is more acidic than free water, but less acidic than H$_3$O$^+$. Thus, a metal ion-bound hydroxide could serve as a general base catalyst in the forward direction, and a metal ion-bound water molecule could serve as a general acid catalyst in the reverse reaction. The same arguments holds for coordinated hydroxyl or amine donor groups that are part of an organic ligand.

The metal ion is also able to exert its influence over a larger distance in the coordinated ligand by stabilizing the developing charge along the reaction path, which merely is an 'electron sink' like function. This particular function, for example, has been supposed to act in the metal ion stabilized C-H deprotonation of substitution inert Co(III) complexes of amino acids. The formation of the carbanion leads to proton exchange or to elimination reactions. The facile carbanion formation of the methylene group of glycine in Cu(glycinate)$_2$ is shown to be the first step in the reaction with acetaldehyde (Scheme VII).

Metal ion stabilized carbanion formation is also demonstrated for the deprotonated form of the Schiff base prepared from pyridoxal and an amino acid. The chelated carbanion is an intermediate in pyridoxal mediated transamination reactions. Moreover, the carbanion can react with acetaldehyde as shown for Zn(II). As a consequence of their influence on the redistribution of the electrons, metal ions can also inhibit a reaction.
by stabilization. This is observed in the case of 2-nitroacetate, which readily decarboxylates in the absence of metal ions, whereas in the presence of Cu(II) and Mg(II) the decarboxylation is inhibited.\textsuperscript{73}

In conclusion, coordination of a metal ion can activate a chemical bond through polarization or by invoking electron displacement. The activation increases at higher charge density of the metal ion.\textsuperscript{64} This leads to a decreased electron density on the atom directly connected to the donor atom, which is translated into a lowering of the pK\textsubscript{a} of coordinated hydroxyl or amine compounds and an increased susceptibility of, for instance, carbonyl or nitrile groups to attack by nucleophiles.

Examples of reactions occurring within the coordination sphere of the metal ion (Scheme VIII).

---

**Scheme VIII**

![Diagram showing template effects of metal ions with pathways A, B, and C, and reactions involving metal ions A and B](Image)

- **PATH A**: Reactant A and B coordinate with metal ion M, resulting in a promnastic effect.
- **PATH B**: Activation and promnastic effect, similar to PATH A.
- **PATH C**: Thermodynamic template effect.

---

*Template effects of metal ions*
An example is the Schiff base formation of the salicylaldehyde anion with glycinate. This reaction occurs irrespective of the presence of a metal ion (path C, Scheme VIII). Some metal ions, however, induce reaction rate enhancements of Schiff base formation that are due to the formation of a reactive ternary complex wherein the reaction occurs. The metal-amine bond of glycinate has to be broken for carbinolamine formation to occur whereafter the Schiff base is formed upon dehydration. Thus, in order to have a reactive ternary complex, it seems advantageous to apply metal ions for accelerating Schiff base formation that hardly activate the ligand upon coordination, which permit metal-amine bond breaking and ligand mobility (Path A, Scheme VIII). No rate enhancements of Schiff base formation were found for metal ions, like Cu(II), Ni(II), and Co(II), forming the strong metal-amine formation and, thereby restricting the ligand mobility. In these cases, only a thermodynamic template effect was observed (Scheme VIII, path C).

In other reactions the function of the metal ion is to bring both reactants together in a ternary complex and to activate the substrate(s) at the same time (Scheme VIII, path B; activated A= α and activated B= β)). This metal ion action is observed in the intramolecular hydrolysis of esters,52, 54, 63, 74 amides,55, 63, 75 phosphate-mono-esters,37, 63, 76, 77 and nitriles.63, 78 A peculiar observation is made for the Cu(II) mediated hydrolysis of 2-cyano-pyridine.78 The intramolecular general base assistance of a coordinated ionized β-hydroxyethyl group of 2[((2-hydroxyethyl)amino)-methyl]-pyrrolidine mainly leads to α-picolinic acid as the product, whereas the assistance of a coordinated hydroxide ligand leads to α-picolinamide (Scheme IX). The selectivity may arise from the template function of the Cu(II) ion as the coordinated intermediate iminoester formed by the alkoxy attack onto the nitrile is not able to tautomerize due to strong tetradentate coordination, whereas the weaker bidentate intermediate formed by hydroxide attack readily tautomerizes to the N-coordinated isomer leading to α-picolinamide.

Another intriguing example of metal ion catalysis occurring intramolecularly within a ternary complex is the reversible phosphoryl transfer between pyridines and carboxylate ions (Scheme X).79 The Mg(II) ion catalyzes these reactions by providing a template for the transition state. Mg(II) is shown to bind the transition state more strongly than either ground state in this equilibrium. The free energy of the transition state is lowered with respect to the ground states.
Scheme IX
Scheme X

A very interesting example with respect to the reactions described in this thesis is the metal ion catalyzed N-alkylation of ethylenediamine with maleate using a substitution inert ternary complex of Co(III) with two ethylenediamine ligands and one maleate ligand (Scheme XI). At neutral pH no reaction occurs between the ligands within the first coordination sphere of the metal ion for reasons outlined above. In the alkaline region, however, the Co(III) coordinated aminate anion is formed and attacks the olefinic bond of maleate within the complex, in a fashion that is probably similar to the O-alkylation of hydroxyl containing compounds with maleate catalyzed by Ca(II).°-11

Scheme XI
The choice of Lanthanide(III) ions.

The similarities of chemical properties along the series make the lanthanide ions a very attractive probe to investigate complex formation in aqueous solution using multinuclear NMR techniques, potentiometry, and luminescence.

Ln(III) ions are used in the present study on the 0-alkylation of hydroxy group containing compounds with maleate for a number of reasons. Firstly, referring to the promnastic effect, the large ionic radius of the Ln(III) ion (Table I) provides ample space in the first coordination sphere to form ternary complexes. Secondly, Ln(III) may form a template for the transition state, which is kinetically of origin. This template function of Ln(III) is very likely, because the little directional character in the coordinative bonds allows large mobility of ligands within complexes and ensures that a favorable conformation for the formation of the transition state can be adopted. On the other hand restricted mobility of the ligands as in complexes of d-block transition metal ions may induce more selectivity, as has been observed for the β-hydroxylate-bound Cu(II) mediated hydrolysis of 2-cyanopyridine. Thirdly, the high formal charge of Ln(III) enables activation of the ligands by polarization to such an extent that neutral pH ranges come within reach for the Ln(III) catalyzed O-alkylation of hydroxy containing compounds with maleate. A template effect that is thermodynamic of origin may be present. This effect is of utmost importance when the equilibrium position is on the product side, because in that case the products form more stable complexes with Ln(III), and consequently also with Ca(II), than both the starting compounds.

Finally, the ionic radius is generally recognized to be an important parameter in reactions taking place within the coordination sphere of the ternary complex, especially when both reactants are bi or higher dentate chelators. Thus, the similar coordination behavior of the Ln(III) ions and the steady decrease of the ionic radii of the lanthanides through the series provides a tool for studying this radius dependence, both for the template effect and the activation of the substrate.

Scope of the thesis.

The reaction mechanism of the Ln(III) catalyzed O-alkylation of glycolate with maleate to yield carboxymethoxysuccinate (cmos) is studied by various techniques. The paramagnetic properties of the Ln(III) ions have been used to confirm the existence of ternary complexes and to observe any
structural changes using the Gd(III)-induced $^{13}$C relaxation rate enhancements and Dy(III)-induced $^{17}$O shift measurements (Chapter II). Due to the fast ligand substitution in most Ln(III) ion complexes it is necessary to calculate the concentration of complexes present with help of their stability constants, which can be done with the newly developed spreadsheet for the Lotus 1-2-3 program as described in Chapter VIII. Potentiometric titrations are used to determine the stability constants of the binary Ln(III) complexes of maleate, glycolate, and cmos and the stability constant of the 'reactive' ternary complex Ln(maleate)(glycolate). These potentiometric measurements are combined with a study of the kinetics of the reaction, resulting in a detailed description of the reaction mechanism (Chapter III). The luminescence properties of the Eu(III) ion are used to develop a method for on-line study of Ln(III) catalyzed reactions, whereby the Eu(III) catalyzed 0-alkylation of glycolate by maleate was taken as the model system (Chapter IV). An extension of the scope of the Ln(III) catalyzed 0-alkylation with maleate is described using polyhydroxyl compounds. Preferably, these reactions are carried out using the polyol as the solvent. Here, less than stoichiometric amounts of metal ion could be used as catalyst. In addition, some other metal ions are tested in these reactions for comparative reasons (Chapter V). The paramagnetic Ln(III) are used to investigated the complexes that are formed during the 0-alkylation of ethylene glycol with maleate catalyzed by Ln(III) ions using a combination of multinuclear NMR techniques and potentiometry (Chapter VI). The uncatalyzed N-alkylation of aminopolysols and amino acids is described in Chapter VII, an example of a combined N-alkylation with the La(III) catalyzed 0-alkylation is given using ethanolamine and maleate as the reactants.

References
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   Lamberti, V.; Konort, M.D.; Weil, I. U.S. 1976 3 954 858; Chem. Abstr. 85, 34979
12. The alkali metal counterions are omitted and the name of the anionic compound is used for the sake of clarity.
20. For history: 1787-1987 Two Hundred Years of Rare Earths; Gschneidner, K.A. Jr.; Capellen, J. Eds.; Rare Earth Information Center Iowa State University, Ames, USA and North-Holland, Amsterdam, The Netherlands 1987.
23. The most abundant of the lanthanides, cerium, is as abundant in the earth’s crust as copper while the least abundant, thulium, is still more plentiful than silver. The family of lanthanides are found
together in minerals as Monazite and Bastanite wherein the lighter lanthanides are more abundant. Due to the troublesome accessibility (Greek dysprosodos), however, the pure elements became not available in kilogram quantities until 1947.


82. Sherry, A.D.; Geraldes, C.F.G.C. In Lanthanide Probes in Life, Medical, and Environmental Sciences; Theory and Practice; Bünzli, J.-C.G.; Choppin, G.R., Eds.; Elsevier, Amsterdam, 1989, Ch. 3.
85. See Chapter II of this thesis.
CHAPTER II.

LANTHANIDE(III) CATALYZED 0-ALKYLATION OF GLYCOLATE WITH MALEATE.
INVESTIGATION OF INTERMEDIATES USING MULTINUCLEAR NMR SPECTROSCOPY.*

Abstract: The lanthanum(III) catalyzed 0-alkylation of glycolate (ga) with maleate (male) to yield carboxymethoxysuccinate (cmos) is described. It is shown that the reaction only proceeds above pH 6, indicating the formation of di-ionized glycolate as a pre-equilibrium for the rate limiting step, i.e. the addition of the CH₂-O⁻ to the olefinic bond. Due to strong complexation of La(III) by the product cmos, the reaction requires one La(III) ion upon two cmos formed. The inhibitory effects of non-reacting strong chelators such as edta, nta, and dpa indicate the formation of ternary complexes leading to the addition reaction. This has been confirmed by Gd(III)-induced 13C relaxation rate enhancements, and Dy(III)-induced 17O shift measurements.

Introduction

The patented synthesis of carboxymethoxysuccinate (cmos) by 0-alkylation of glycolate (ga) with maleate (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 'NMR silent' Ca(II) in multinuclear NMR studies.⁹,¹³ This in fact has been applied by us for structural

investigations of various lanthanide complexes in solution.\textsuperscript{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\textsuperscript{16} and Ln(III)-coordinated alcohol groups have a relatively high acidity.\textsuperscript{17a,b} Therefore, we have investigated the applicability of Ln(III) cations in the O-alkylation of ga with male. The paramagnetic properties of these cations were utilized for the detection and structure elucidation of ternary complexes formed prior to reaction.

Sofar, 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.\textsuperscript{18,19}

**Experimental Part**

**Materials.**

The LnCl\textsubscript{3}⋅xH\textsubscript{2}O salts used were purchased from Alfa Products. The Ln(III) content was determined by an edta 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\textsuperscript{+}-form) was washed several times with demineralized water before use. The 10μ Polygosil C18 was purchased from Macherey-Nagel (Düren G.F.R.). The AG1-X8 (50-100 mesh) anion exchange material (Cl\textsuperscript{-}-form) was purchased from Biorad.

**Kinetic Measurements.**

A stock solution of ga (0.5 M) and male (0.5 M) in water was prepared by neutralization of the corresponding acids with NaOH. The reactions were
carried out with 8 ml of this stock solution, upon addition of the required amount of LaCl$_3$.7H$_2$O, adjustment of the pH to the desired value with a dilute NaOH solution (0.5 M) and bringing the total volume to 10 ml with water. The reaction mixture obtained (0.40 M in both ga and male) was heated at 363 K in a thermostatted reaction vessel with stirring. At suitable time intervals samples (100 μl) were taken, diluted with water (0.5 ml), acidified with Dowex H$^+$ (pH <2), and analyzed by HPLC. The HPLC analyses were carried out using a Waters Assoc. M45 pump, a Rheodyne 7125 injection valve, a 4.6 mm-300 mm 10μ Polygosil C18 column, a Waters Assoc. R401 detector, and a Spectra-Physics SP4100 Computing integrator. Water acidified with 0.01 M trifluoroacetic acid was used as the mobile phase at a flow rate of 1.0 ml/min. 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 male conversion versus time.

NMR Measurements.

All NMR experiments were performed on a Nicolet NT-200 WB spectrometer at 298 K. The longitudinal $^{13}$C relaxation rates were measured in D$_2$O containing 1.0 M of ligand and in case of two ligands 1.0 M each. The pH was adjusted to 8 with a NaOD solution. A 12 mm sample tube containing 5.00 ml of this solution was used for the measurements. The Gd(NO$_3$)$_3$ solution (18 mM) was added via a microsyringe. Six measurements at $\rho$ 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 [($90^0_x$ 180$^0_y$ 90$^0_x$-r-90$^0_x$) pulse sequence]. The magnetization curves were fitted with a three parameter equation suggested by Levy and Peat$^{20}$ to correct for inhomogeneous H1 fields which produce incomplete recovery by the 180$^0$ pulse. The relaxation rate enhancements as a function of $\rho$ were fitted with a linear function to obtain the induced relaxation rates (1/T$_1$) at $\rho$=1. The intermolecular relaxation rate enhancement by Gd(III) was neglected because of its low contribution in D$_2$O solutions.

The $^{17}$O NMR 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$^0$ 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 $^2$H signal of $^2$H$_2$O was used for internal lock. The sample
contained 0.35 M of ligand and in case of two ligands 0.35 M each. The pH was adjusted with a NaOD solution. A 12 mm sample tube containing 5 ml of this solution was used for the measurements. DyCl₃·6H₂O was added in portions varying between 10-20 mg. After addition the pH 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 (Cmos).**

A solution of sodium ga (0.50 M), disodium male (0.50 M), and LaCl₃ (0.25 M) in water (50 ml) 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 proceeds in a clear solution. After standing overnight a slurry was present. After addition of water (150 ml) and Dowex H⁺ (20 ml), 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 M formic acid and the obtained fractions were analyzed by HPLC and concentrated in vacuo. The concentrated solutions were coevaporated with water a few times to remove the formic acid. The remaining solution was neutralized with NaOH (1 M) and lyophilized. After drying in vacuo under P₂O₅, 4.45 g of Na₃cmos.2H₂O was obtained (14.98 mmol, 60%).

**¹H NMR (D₂O, t-BuOH at 1.2 ppm) δ(ppm):** 4.03 (1H, dd, J₃,4' = 9.16 Hz, J₃,4 = 3.91 Hz, CHCH₂), 3.91 (1H, d, J₁,1' = -15.0 Hz, OOC(CH₂)₃), 3.80 (1H, d, J₁,1' = -15.0 Hz, OOC(CH₂)₂), 2.56 (1H, dd, J₃,4' = 3.91 Hz, J₄,4' = -14.9 Hz, CHCH₂), 2.43 (1H, dd, J₃,4' = 9.16 Hz, J₄,4' = -14.9 Hz, CHCH₂).

**Results and Discussion**

**Kinetics.**

The original procedure for preparing cmos consists of refluxing an aqueous slurry of maleic acid and glycolic acid (1.0 M each) with 1.8 M Ca(OH)₂ at pH 11.4. We have now been able to perform this reaction with sodium ga and disodium male at lower pH (about 7-8) and 363 K in a homogeneous solutions with 99% selectivity towards cmos formation by using lanthanum(III)trichloride (0.5 mole equivalent) (Figure 1). Only trace amounts of malate and fumarate were formed by competitive H₂O addition to
Figure 1. O-alkylation of ga (0.5 M) with male (0.5 M) mediated by La(III) (0.25 M) at pH 7.5 and T=363 K. pH determined at 298 K: male (o), cmos (△).

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 of the reaction rate at pH>5 is in agreement with the reported dissociation constant of the CH₂OH-group in Ln(III) coordinated ga.¹⁷a,b In this pH range dissociation of water ligands occurs as well.²¹ This strongly suggests that dissociation of the La(III) coordinated hydroxyl group of ga and/or coordinated water ligands are important in this reaction. The high selectivity towards ether formation (99%), however, shows that the ionization of the CH₂OH-group of La(III) coordinated ga is an essential factor in this reaction. The analogous dependence upon the pH of the reaction catalyzed by Ca(II), where a steep increase occurs at pH 11, corresponds once again with the pKₐ of the Ca(II) coordinated hydroxyl group of ga and with the pKₐ of Ca(II) coordinated water.¹⁷b,²¹ Most probably, within the first coordination sphere an equilibrium of di-ionized glycolate (H₃ga) and mono-ionized glycolate (ga) exists, coupled with a coordinated hydroxide/water equilibrium.
Figure 2. Initial reaction rate as a function of pH. pH measured at 298 K. 1.0 M male, 1.2 M ga, and 0.2 M LaCl₃ in water at 363 K. (/) precipitation.

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 moles of cmos per mole La(III) are formed. This is in accordance with the high complex stability constant of the La(III)-cmos complexes compared to those of the reactants²² and with the fact that below a molar ratio Ln(III)/ligand of 0.5 the complex [Ln(cmos)₂H₂O]³⁻ predominates.¹⁴ The reaction inhibition by the latter complex suggests that ternary complexes of La(III), male, and ga play an important role in the alkylation reaction. In order to establish this, we have performed the synthesis of cmos in the presence of strongly chelating ligands, like ethylenediaminetetra-acetate (edta),¹³,nitritriacetate (nta),²⁴⁻²⁶ and dipicolinate (dpa),²⁷⁻²⁹ which occupy six, four, and three ligand coordination 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 ga and male are coordinated.

Thus, the rate equation at a constant pH may be given by:

\[
d[\text{cmos}]/dt = k_0[\text{La(male)}_m(\text{H}_i\text{ga})_n] + k_1[\text{La}\text{(cmos)}(\text{male})_x(\text{H}_i\text{ga})_y] \quad (1)
\]
in which $\text{La(male)}_m\text{H}_n\text{ga}_n$ is the predominating ternary complex between La(III), male, and glycolate (di-ionized, $\text{H}_n\text{ga}$) and $\text{La(cmos)(male)}_x\text{H}_n\text{ga}_y$ is the analogous one with a cmos ligand added.

Below 50% conversion, it may be assumed that the concentration of the $\text{La(cmos)}_2$ complex is negligible and that each cmos formed is bound to a La(III) cation and, therefore, the mass balance can be given by eq. 2.

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

(2)

If the concentration $\text{cmos}=x$, combination of eqs. 1 and 2 gives eq. 3, where $c=k_1/k_0$.

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

(3)

Upon integration of eq. 3, we obtain eq. 4, where $[\text{cmos}]_t$ is the concentration cmos formed at time $t$.

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

(4)

Figure 3. Effect of chelating agents on the male conversion rate. Male (0.40 M), ga (0.40 M), LaCl$_3$ (0.20 M), edta (■), nta (●), or dpa (▲) (0.20 M) were used. Without chelating agent (○); pH 8 and temperature 363 K.
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 (Table I), which are rather independent of the total La(III) concentration. We obtain an average value of $k_0$ of $7.10^{-4} \text{ s}^{-1}$ and a shielding factor ($1/c$) of ca 6.1 when one cmos ligand is present. This high shielding factor obtained suggests that any cmos that is tetra- or tridentately coordinated to La(III) gives rise to a large inhibition of the reaction. The followed kinetic approach is rather rough, a more detailed kinetic investigation is in progress.

To establish that ternary complexes are involved in the reaction, we have used multinuclear NMR spectroscopy at 298 K, under which condition no reaction occurs. We have selected Gd(III)-induced relaxation rate enhancements and Dy(III)-induced $^{17}O$ shifts to study the Ln(III) coordination in these systems prior to reaction. In all cases averaged spectra of the complexed and free ligands were obtained, due to fast ligand exchange on the NMR time scale. Gd(III)-induced relaxation rate enhancements and Dy(III)-induced $^{17}O$ shifts are both performed at low Ln(III) to ligand ratio, comparable to that in the kinetic experiments.

**Table I. Influence of the La(III) Concentration on the Reaction Rate of the Cmos Formation.**

<table>
<thead>
<tr>
<th>La(III) (M)</th>
<th>$k_1/k_0$</th>
<th>$10^4k_0(\text{s}^{-1})$</th>
<th>cmos (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0726</td>
<td>0.095</td>
<td>6.42</td>
<td>0.095</td>
</tr>
<tr>
<td>0.0872</td>
<td>0.154</td>
<td>6.09</td>
<td>0.117</td>
</tr>
<tr>
<td>0.1120</td>
<td>0.200</td>
<td>5.71</td>
<td>0.160</td>
</tr>
<tr>
<td>0.1311</td>
<td>0.192</td>
<td>6.47</td>
<td>0.209</td>
</tr>
<tr>
<td>0.1471</td>
<td>0.175</td>
<td>7.06</td>
<td>0.229</td>
</tr>
<tr>
<td>0.1678</td>
<td>0.170</td>
<td>8.31</td>
<td>0.256</td>
</tr>
</tbody>
</table>

$a$0.398 M male and 0.401 M ga at $T=363$ K, pH 8 at 298 K. $b$After 2 h reaction.

**Gd(III)-Induced $^{13}C$ Relaxation Rate Enhancements.**

The $^{13}C$ longitudinal relaxation rate enhancements, $^{31} \frac{1}{T_1}$, of solutions in D$_2$O of ga (1.0 M), male (1.0 M), and of a solution containing both of these ligands (each 1.0 M) were measured upon successive additions of small amounts of Gd(III) ($p<3.0 \times 10^{-4}$). In all cases a linear relationship
Left: Figure 4. Gd(III)-induced $^{13}$C relaxation rate enhancement of ga $[\text{COO}^- (\bullet), \text{CH}_2\text{OH} (\Delta)]$ and of ga in a (1:1) mixture with male $[\text{COO}^- (o), \text{CH}_2\text{OH} (\triangle)]$ as a function of the Gd(III) to ga ratio ($\rho$). Concentration of the ligand 1.0 M, $T$=298 K. Right: Figure 5. ibid of male $[\text{COO}^- (\bullet), \text{C}=\text{C} (\blacksquare)]$ and of male in a (1:1) mixture with ga $[\text{COO}^- (o), \text{C}=\text{C} (\lozenge)]$ as a function of the Gd(III) to male ratio ($\rho$). 

between the relaxation rate enhancement and $\rho$ was found (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 eq. 5,

$$
(1/T_1)_i = k n \tau_r / r_i^6 
$$

where $i$ is the nucleus under study, $k$ is a constant, $n$ is the number of coordinated ligands, $\tau_r$ is the rotational correlation time and $r_i$ is the distance between 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)-coordinated ligand structure, eq. 6.
The $R_{i/j}$ value for ga shows that it coordinates in a bidentate fashion via the hydroxyl and carboxylate group, which is in agreement with our previous investigations$^{31}$ (Figure 4, Table II). From the potentiometrically determined Gd(III) association constants$^{16}$, it can be calculated that 96% of the Gd(III) is bound by three ga ligands within the range of the $p$ used (<1.8 $10^{-4}$ M at 1.00 M ga).$^{32}$ Previously, we have determined the structure of the Gd(ga)$_3$ complex in solution.$^{15}$ Using that structure and eq. 5 with n=3 and the Debye-Stokes-Einstein relation, the molecular radius of the complex can be estimated to be about 4.7 Å, which is consistent with the proposed structure.

Table II. -Ratios of the Gd(III)-Induced Longitudinal $^{13}$C Relaxation Rate Enhancements.$^a$

<table>
<thead>
<tr>
<th>ligand</th>
<th>$R_{\text{COO/C=C}}$</th>
<th>$R_{\text{COO/CH}_2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>4.3</td>
<td>-</td>
</tr>
<tr>
<td>ga</td>
<td>-</td>
<td>1.6</td>
</tr>
<tr>
<td>male + ga</td>
<td>4.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

$^a$For conditions see Figures 4 and 5.

A $R_{i/j}$ value of 4.30 is obtained for male (Figure 5, Table II). Using the crystal structure of Ca(male)$^{33}$ 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 coordinated carboxylates (in a monodentate fashion) and a chelate structure in which only one carboxylate is coordinated (in a bidentate fashion), respectively. Both modes of coordination are present in the X-ray structure. The experimental $R_{i/j} = 4.30$ from NMR, therefore, suggests the occurrence of both chelate structures at low Gd(III) to male ratio ($p$) of which the seven-membered chelate is slightly more abundant. In this concentration range the occurrence of binuclear complexes seems not very likely. From the potentiometrically determined association constants,$^{16,34}$ it can be calculated that under the conditions applied, Gd(III) is almost exclusively present as the Gd(male)$_2$ complex.
In a 1:1 mixture of ga and male Gd(III) enhances the longitudinal relaxation rates \((1/T_1)\) of both ga and male (Figures 4, 5, Table III). From a comparison of these relaxation rates, extrapolated to a Gd(III) to ligand (male or ga) 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 male and two-three ga are present. It may be noted that without ternary complex formation the concentration of Gd(III)-bound ga and Gd(III)-bound male would be \(1.0 \times 10^{-4}\) M and \(2.9 \times 10^{-4}\) M, respectively, under these conditions. Comparing these concentrations with those in the experiments with each of the ligands separately (5.2 and 3.6 \(10^{-4}\) M, respectively) a decrease in relaxation rate enhancements of all ligand nuclei should occur for both ga and male, when no ternary complexes are formed. The slightly higher \(1/T_1\) value for ga in the mixed ligand system (Figures 3 and 4) may be the result of a \(\tau_r\) value, which is somewhat higher in the Gd-ga-male than in the Gd-ga complexes. Analogously, the relative decrease of \(1/T_1\) of the male ligand is in accordance with one male ligand bound in the ternary complexes.

The small variation in \(R_{i/j}\) values in all experiments (Table II) shows that the ligands are coordinated in the same way in the binary and ternary systems.

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
 & male & & & ga \\
ligand & COO\(^-\) & C=\(\sim\) & COO\(^-\) & CH\(_2\)OH \\
\hline
male & 14.1 & 3.28 & - & - \\
ga & - & - & 16.9 & 10.4 \\

male + ga & 11.0 & 2.68 & 20.2 & 11.9 \\
\hline
\end{tabular}
\end{table}

\(^a\)For conditions see Figures 4 and 5. Values obtained by extrapolation to Gd(III)/ligand ratio \(\rho = 1\).
Dy(III)-Induced $^{17}$O Shifts of $D_2O$.

To establish the formation of ternary complexes of Ln(III) ions with one male and two or three ga at low Ln(III) to ligand ratios, we have determined the number of coordinated ligand oxygens with the use of Dy(III)-induced $^{17}$O shift measurements. Indirectly, this can be done by determination of the number of coordinated waters in the first coordination sphere of the Dy(III) cation. In the absence of other ligands nine $D_2O$ ligands are coordinated in the first coordination sphere of the Dy(III). The Dy(III)-induced shifts are a linear function of the Dy(III) to $D_2O$ molar ratio ($\rho_{D_2O}$) as shown in Figure 6.

From extrapolation to $\rho_{D_2O} = 1/9$ the shift contribution for each coordinated $D_2O$ ligand was estimated to be 2350 ppm at 298 K. Previously, we have shown that this shift contribution is independent of the presence of other ligands. Thus, the number of $D_2O$ ligands in the first coordination sphere of a Dy(III)-complex can be calculated from extrapolation of the Dy(III)-induced shift to $\rho_{D_2O} = 1$, followed by division by 2350 ppm. The numbers of waters in the first coordination sphere estimated in this way are given in Table IV for the various ligands.

For ga, the number of coordinated waters is constant (2.6) throughout the

![Figure 6. The Dy(III)-induced $^{17}$O chemical shift ($\Delta \delta$) of $D_2O$ as a function of the ratio Dy(III) to $D_2O$ : without organic ligand ($\Delta$), male ($x$) (0.35 M), ga ($o$) (0.35 M, pH 6.5), and male + ga ($o$) (0.35 M); $T$= 298 K.](image)
-35-

Table IV. -Number of Coordinated Waters in Dy(D2O)x(Lig) Complexes as Determined from Dy(III)-Induced 17O NMR Chemical Shifts. a

<table>
<thead>
<tr>
<th>Organic ligand</th>
<th>pD</th>
<th>10^-4 Induced shift (ppm)</th>
<th>Number of coordinated waters</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>4.5</td>
<td>2.12</td>
<td>9</td>
</tr>
<tr>
<td>male</td>
<td>6.5</td>
<td>1.42</td>
<td>6.0</td>
</tr>
<tr>
<td>ga</td>
<td>6.5</td>
<td>0.61</td>
<td>2.6</td>
</tr>
<tr>
<td>ga</td>
<td>5.6</td>
<td>0.59</td>
<td>2.5</td>
</tr>
<tr>
<td>ga</td>
<td>4.5</td>
<td>0.62</td>
<td>2.6</td>
</tr>
<tr>
<td>male+ga</td>
<td>6.5</td>
<td>0.58</td>
<td>2.5</td>
</tr>
</tbody>
</table>

aFor conditions see Figure 6.

pH range of 4.6 to 6.5, although ionization of the α-OH group occurs in this range. 17a,b From the association constants of Dy(ga)ₙ (n=1-3) complexes 16,32 it can be calculated that under the conditions applied (0.0628 M Dy(III) and 0.35 M ga) the average number of coordinated waters is 3.4, assuming that each ga expels two waters upon complexation. This value fits reasonably well with the experimentally found value of 2.6.

Analogously, it can be calculated that in the Dy(III)-male system, a Dy(male)₂ complex with six bound waters predominates. The Gd(III)-induced relaxation rate enhancements have shown that male is bound in two fashions: as a seven-membered chelate with two carboxylate oxygens coordinated and bidentate coordination via a single carboxylate group. The average number of six waters in the first coordination sphere might be explained by expelling of two waters from the first coordination sphere of Dy(III) upon coordination of the seven-membered chelate and only one water upon coordination 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 coordinated waters is 2.5. If the occurrence of ternary complexes were negligible the number of waters coordinated in the system Dy(III)-male-ga can be calculated to be 5.7. This substantial deviation once again confirms ternary complex formation with predominance of complexes with two or three bound ga ligands and one bound male.
Reaction Mechanism.

The NMR data show that the La(III) catalyzed O-alkylation of ga with male occurs via a ternary complex of the lanthanum ion. The chelate structure in which the male is coordinated bidentately forming the seven-membered chelate most likely is the reactive form. In this complex structure the olefinic carbons are in close proximity to the ionized hydroxyl group of ga. So, the La(III) cation is not only responsible for the glycolate hydroxyl ionization, but also functions as a template (Scheme II).

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(male) (27.9 and 91.7°)\textsuperscript{33} and in other crystal structures of male salts.\textsuperscript{36} There probably is 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 ga-male addition reaction. Concomitant proton transfer from water in the first or second coordination sphere towards the developing carbanion, therefore, has to be an important factor in this Michael-type reaction.

The importance of ternary complexes is recently demonstrated by Sargeson and coworkers,\textsuperscript{37} for the N-alkylation of ethylenediamine or glycine with

Scheme II.
male mediated by Co(III). The X-ray structure of the ternary complex between ethylenediamine and male shows a close proximity of the amino 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 ionized water ligand and ionization of the La(III)-coordinated α-OH group of ga (Scheme II). The O-alkylation reaction in 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 coordination to La(III). The relatively high association constant of cmos with respect to that of the ternary La-male-ga complexes is expected to be a driving force in the reaction. Most likely, the T.S. is cmos-like according to the late T.S. in the Hammond-Curtis principle.

The biological counterpart of the addition of ga to male is the enzymic hydration in the citric cycle, as catalyzed by aconitase\(^{38,39}\) and maleate hydratase\(^{40}\). There iron-sulfur clusters are responsible for the catalytic activity. Under physiological conditions the iron-bound water ligands are ionized. In this respect, with La(III) cations we are able to mimic this kind of additions and, even more importantly, we are able to extend the reaction to more complex hydroxyl-containing systems.

Acknowledgements

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22. see Chapter III this thesis.


CHAPTER III.

LANTHANIDE(III) CATALYZED O-ALKYLATION OF GLYCOLATE WITH MALEATE-A KINETIC STUDY.*

Abstract: The reaction mechanism of a Michael-type addition of glycolate (ga, 1) to maleate (male, 2) catalyzed by Lanthanide(III) ions in aqueous solution giving carboxymethoxysuccinate (cmos, 3) is discussed with respect to its reaction kinetics. The reaction takes place in a ternary complex of Ln(male)(ga) with the addition of the ionized Ln(III) coordinated hydroxy group of 1 to the olefinic bond of 2 as the rate determining step. The first order rate constant in the ternary complex is around 1 min⁻¹. Since exchange of the ligands is fast, the amount of the ternary complex Ln(male)(ga) formed in the mixed ligand system has to be calculated by its stability constant. The stability constants of the Ln(ga)ₙ, Ln(male)ₙ, Ln(cmos)ₙ (n=1,2), and Ln(male)(ga), were determined potentiometrically. The pKₐ for the ionization of the Ln(III) coordinated hydroxyl group of 1 could be obtained indirectly from the reaction kinetics. The existence of the Ln(III) coordinated H⁻₁ga ligand was supported by ¹³C NMR. The effective charge density of the cation plays an important role in decreasing the pKₐ of the hydroxyl group of 1 upon coordination. This effect is somewhat counteracted by a concomitant decrease of the nucleophilicity of resulting alcoholate group in the addition reaction. The La(III) catalyzed reverse reaction (3→1+2) was found to be stereoselective, resembling enzyme catalysis.

Introduction

The complexes of Lanthanide(III) ions (Ln(III)) are among the most exchange labile metal complexes, in particular for the 3+ oxidation state. The predominant electrostatic nature of the metal-ligand interaction and the high formal charge in combination with the high coordination number (8-9 in aqueous solution)¹,² may provide unique properties for homogeneous catalysis. In the aqueous reaction systems, the metal ion usually exerts its

influence via polarization of chemical bonds and, in addition, it has the possibility to bring about intramolecular group transfer because of its capability to form ternary complexes. Information on the influence of the ionic radius on intramolecular group transfer reactions can be obtained for the Ln(III) ions, as these ions consist of a family of 15 chemically similar metal ions, wherein the ionic radius decreases going through the series.

A transferable group in the complex can be the hydroxide ligand, which acts as an intramolecular general base. A coordinated hydroxyl ligand is essential in several biologically important reactions such as the metal ion catalyzed hydrolysis of amides and esters in transphosphorylations and in the hydration of unsaturated olefinic bonds. The latter metal ion promoted reaction show similarities with the previously described La(III) catalyzed addition of glycolate (ga, 1) to maleate (male, 2) yielding carboxymethoxysuccinate (cmos, 3) (Scheme 1).

\[
\begin{align*}
\text{HCOO}^- + \text{C} = \text{C} \text{COO}^- & \rightarrow \text{HCOO}^- + \text{C} = \text{C} \text{COO}^- \\
\text{ga, 1} & \quad \text{male, 2} \\
\text{La(III), pH>6} & \rightarrow \text{Aqueous, 363 K} \\
\text{HCOO}^- + \text{CH}_2 \text{COO}^- & \rightarrow \text{HCOO}^- + \text{CH}_2 \text{COO}^- \\
\text{cmos, 3} \\
\end{align*}
\]

Scheme I

On the basis of an NMR study of the complexes that are present in the reaction medium, we have proposed a mechanism in which La(III) acts as a template by forming a ternary complex with 1 and 2. La(III) probably brings about the ionization of the hydroxyl group of 1 upon coordination (4, Scheme II), and then an intramolecular nucleophilic addition of the di-ionized glycolate ligand (H$_2$ga) to 2 in the La(III) complex, results in the formation of 3.

The reaction is marked by a strong product inhibition, upon formation of two molecules of 3 per La(III) cation, the reaction rate drastically reduces. Apparently, the La(cmos)$_n$ (n=1,2) complexes formed are stronger than the La(III) complexes of the starting compounds. The La(cmos) complex is still capable to promote the addition reaction, although, the reaction rate is reduced significantly as a result of the occupation of four
coordination sites.\textsuperscript{22}

Recently, we have shown that addition reactions of diols and polyols to $\alpha,\beta$-unsaturated dicarboxylates are also possible in the presence of multivalent metal ions and that a variety of new chelating agents is accessible with this synthetic route.\textsuperscript{23,24}

This paper describes the results of a more detailed study of the mechanism of the addition reaction of 1 to 2. Special attention was paid to the stereochemistry of the reaction, the ionization of Ln(III)-coordinated 1, the stabilities of the intermediate ternary Ln(III)-complexes and the kinetics of the reaction.

Experimental Part

Equipment.

HPLC analyses were carried out using a 8x100 mm 10 \textmu m Nucleosil C18 cartridge, containing a Waters RCM100 module. An aqueous solution (0.01 M) of trifluoroacetic acid as the mobile phase was used at a flow rate of 1.0 ml/min. A Waters Assoc. R401 detector in conjunction with a Spectra-Physics SP4270 Computing Integration was used for detection. For preparative HPLC a Waters LC-500 with two Waters PrePAK-500/C18 columns were used with 0.01% (v/v) trifluoroacetic acid in water as the eluens.

All potentiometric measurements were performed in double distilled water with a Metrohm 605 pH meter, a combined pH electrode equipped with a Teflon ground joint (sleeve) diagram and an Argenthal reference system (Type HA 405-60-88TE-S7, Ingold) in which the 3 M KCl of the reference compartment was replaced by a saturated NaCl solution. The titrations were performed at 298 K in a thermostatted reaction vessel (50 ml) with two inlets, for electrode and buret. The pH meter was standardized by pH 4.008 (N.B.S. buffer 2.5305 g potassium phthalic acid in 250 ml) and by pH 6.865 (N.B.S. buffer 0.8825 g Na$_2$HPO$_4$ and 0.8475 g KH$_2$PO$_4$ in 250 ml). The hydrogen activity coefficient was determined by measuring the hydrogen ion activity for a set of titration data of a standardized HClO$_4$ solution at an ionic strength of 1.0 M (NaClO$_4$). A value of 1.835 was found.

For the kinetic measurements at 363 K, the pH was measured with a high temperature electrode (Ingold, 405-60-S7, standard combined electrode with Argenthal high-temperature reference system). A Metrohm 654 pH meter was used with automatic temperature correction via an Pt100 ceramics. A thermostatted reaction vessel (270 ml) equipped with a cooler, a pH
electrode, Pt100, and an automatic buret was used in the reactions. The pH of the reaction mixture was kept constant by a pH-stat consisting of a Metrohm impulsomat 614 and a Metrohm dosimat 655.

The pH values are direct readings of a pH meter equipped with an electrode, which was standardized by aqueous buffer solutions at 298 K.

All \(^1\)H NMR data were recorded on a Varian VXR-400 S MHz spectrometer. The \(^{13}\)C NMR spectra were recorded on a Varian VXR-400 S MHz, on a IBM/Bruker WP270SY NMR Spectrometer at 67.93 MHz (FSU facility), or on a Nicolet NT-200 WB spectrometer.

Compounds.

The Lanthanide(III) chlorides were purchased as hydrates from Alfa Products. The Ln(III) oxides were purchased from Janssen. The Ln(ClO\(_4\))\(_3\) solutions were prepared by dissolving the oxides in concentrated HClO\(_4\) (60-62%, Baker a.r.) by heating. The excess of HClO\(_4\) was removed by evaporation (fuming) close to dryness. The residue was diluted with water (double distilled). The Ln(III) contents of the salts of the stock solutions obtained were determined by an edta titration with Xylenol Orange as the indicator and hexamethylenetetramine (urotropine) as buffer. The concentration of stock solutions of maleic acid (H\(_2\)male), glycolic acid (H\(_3\)cma) (both Merck-Schuchardt, a.r.) and H\(_3\)cmos were determined by titration with 0.1 M NaOH solution.

H\(_3\)cmos was synthesized according to a modification of the previously described procedure: \(^{22}\) an aqueous solution (250 ml) of Na\(_2\)male (0.5 M), Naga (1.0 M), and LaCl\(_3\) (0.25 M) was prepared at pH 7.3 and 363 K. After 4 h of heating at 363 K another portion of LaCl\(_3\).7H\(_2\)O (13.4 mmol) was added. The heating was continued for 16 h. HPLC analysis showed 90% conversion of 2 to 3. The reaction mixture was acidified with trifluoroacetic acid and purified by preparative HPLC. The volume of the collected fractions was reduced by evaporation and the residue was lyophilized. The transparent oil was dried in vacuo over NaOH. After 4 days the oil started to crystallize, and after one week no more trifluoroacetic acid could be detected in the product. Yield 30% (38 mmol, 7.39 g) of pure H\(_3\)cmos. Anal. Calcd. for C\(_6\)H\(_8\)O\(_7\)·0.12H\(_2\)O C, 37.07; H, 4.32. Found C, 37.00, H 4.20. \(^1\)H NMR \(\delta\)(ppm) (D\(_2\)O, pD 1.7, t-BuOH at 1.2 ppm): 4.45 (dd, 1H, J\(_3,4\)=4.6 Hz, J\(_3,4\)=6.8 Hz, H\(_3\)), 4.36, 4.26 (AA' system, 2H, J\(_1,1\)'=-16.8 Hz, H\(_1,1\)'), 2.97 (dd, 1H, J\(_4,4\)'=-16.8 Hz, J\(_3,4\)'=4.6 Hz, H\(_4\)), 2.89 (dd, 1H, J\(_4,4\)'=-16.8 Hz, J\(_3,4\)'=6.8 Hz, H\(_4\)').
Potentiometry.

The ionic strengths of all solutions used were adjusted to 1.0 M using NaClO₄. For the determination of the stability constants of the binary and ternary complexes of 1 and 2 two titrations at different concentrations were made. One set of titrations was performed at a lanthanide(III) concentration of 0.002 M. For the 1:1 and 1:2 binary complexes of 1, a solution containing both Naga (0.01 M) and Hga (0.01 M) was titrated to the Ln(ClO₄)₃-solution (50 ml) at 298 K. For the 1:1 binary complex of 2, a solution containing both Na₂male (0.02 M) and Nahmale (0.016 M) was used. Another set of titrations was performed with 50 ml of a Ln(ClO₄)₃ solution (0.005 M) containing Na₂male (0.004 M) and Nahmale (0.001 M). For the 1:2 binary complex of 2, a solution containing both Na₂male (0.04 M) and the Nahmale (0.01 M) was titrated to this solution. The same procedure was used for the 1:1:1 ternary complex, where a solution containing Naga (0.03 M) and Hga (0.01 M) was titrated to the lanthanide(III)-2 solution. For the 1:1 and 1:2 binary complexes of 1, a solution containing Naga (0.03 M) and Hga (0.01 M) was titrated to 50 ml of a Ln(ClO₄)₃ (0.002 M) solution containing Naga (0.0015 M) and Hga (0.0005 M). For the synthesized ligand 3, the pKₐ's at I=1.0 M (NaClO₄) were determined in duplo by titrating a sodium hydroxide solution (0.03 M) to a H₃cmos solution (0.002 M) at 298 K. The stabilities of the 1:1 and 1:2 complexes were determined in duplo by a titration of a solution of Na₃cmos (0.014 M) and HNa₂cmos (0.016 M) to a Ln(ClO₄)₃ solution (0.002 M) at I=1.0 M (NaClO₄).

Computations of the Stability Constants.

The proton stability constants of 3 were calculated with a BASIC computer program written for polyprotic weak acid equilibrium calculations. The stability constants for the binary complexes and the Ln(male)ₙ(ga) ternary complex were calculated with a BASIC computer program written by Cacheris.²⁵ The programs utilize a combined Simplex/Marquardt algorithm for evaluation of the equilibrium constants. A modified Newton-Raphson algorithm²⁶ is used to calculate -log[H⁺] for each data point that is compared to the observed value. In all titrations the average deviation between calculated and observed -log[H⁺] was smaller than 0.01. The association constants for the 1:1 and 1:2 binary complexes were treated as constants in the calculation of the 1:1:1 ternary complex.
Kinetics - pH Variation.

The pH electrode was standardized with the buffers of pH 7 and 9 (Merck) at 298 K. Prior to calibration the electrode was kept at room temperature for 16 h. The electrode was replaced when the asymmetric potential was out of the millivolt range set by Metrohm (+45 mV... -35 mV at pH 7).

A solution (250 ml, pH 8) of Naga (0.510 M) and Na₂male (0.102 M) was heated to 363 K. The pH of this solution was adjusted to the desired value with hydrochloric acid (1 M) or sodium hydroxide (0.5 M). Then LnCl₃ (2.55 M, 5 ml) was added. The pH of the reaction mixture was kept constant, when necessary, by addition of hydrochloric acid (1.0 M). The maximum addition necessary was 2 ml. No volume corrections were made. At certain time intervals samples of 0.5 ml were taken and acidified with 2 M trifluoroacetic acid solution. HPLC analysis was used to determine the amounts of 2 and 3 formed. Compound 3 was the only product formed in all cases. Therefore, the mass balance equation was used to calculate the conversion. The data were processed by a Lotus 1-2-3 spreadsheet. The initial rates were obtained from the curve of the formation of 3 versus time by determining the initial slope.

Kinetics - Variation of the Concentration of 2.

A solution (250 ml) of Naga (0.510 M) and Na₂male (0.204-0.0102 M) was heated to 363 K. Then a LaCl₃ solution (2.55 M, 5 ml) was added and the pH was adjusted to 6.55. A precipitate was formed in the experiments with at concentrations less than 0.02 M.

Reaction in D₂O.

Naga and Na₂male were prepared by neutralization of aqueous solutions of the acids with NaOH, followed by precipitation with ethanol. The precipitates were dried in vacuo over H₂SO₄. LaCl₃·7.1H₂O (0.37 g, 0.99 mmol) was dried in vacuo at 353 K to yield LaCl₃·2.3H₂O. Na₂male (0.49 g, 2.5 mmol) and Naga (1.45 g, 5 mmol) were dissolved in D₂O (25 ml). 20 ml of this solution was added to LaCl₃·2.3H₂O. Then in a period of 2 minutes the reaction mixture was heated up to 363 K. The pD of the reaction mixture was 7.48. Samples were taken at certain time intervals and analyzed by HPLC after acidification. After 3 h at 363 K the reaction mixture was analyzed.

¹H NMR of 3 δ ppm (D₂O, pD 1.7, t-BuOH at 1.2 ppm): 4.43 (broad d, 1H, J₃,₄=4.58 J₁,₁'=5.06 Hz, H₃), 4.35, 4.22 (AA′-system, 2H, J₁,₁'=15.5 Hz, H₁,₁′), 2.98 (d, J₃,₄=4.58 Hz, H₄), 2.92 (d, J₃,₄=5.06 Hz, H₄). After
removing La(III) by Dowex 50W (H\(^+\)) and neutralization with sodium hydroxide:

\(^{1}H\) NMR of 3 δ(ppm) (D\(_{2}\)O, pD 7.5, t-BuOH at 1.2 ppm): 2.56 (d, J\(_{3,4} = 3.4\) Hz, H\(_{4}\)), 2.45 (d, J\(_{3,4} = 8.9\) Hz, H\(_{4}'\)). The integral ratio of H\(_{4}/H_{4}'\) = 1.5.

**H-D Exchange of 3**.

A solution of H\(_{3}\)cemos (0.1416 g, 0.728 mmol) in 10 ml D\(_{2}\)O was neutralized with 3 equivalents NaOD. Then LaCl\(_{3}\) (0.1869 g, 0.501 mmol) was added and the pD of the solution was adjusted to 8.0. After 24 h the reaction mixture was acidified with a DCI solution. \(^{1}H\) NMR δ(ppm) (D\(_{2}\)O, pD 1.6, t-BuOH at 1.2 ppm): 6.31 (s, 0.24 H, male), 4.40 (m, 1H, H\(_{3}\)cemos), 4.40, 4.15 (AA' system, 2H, J\(_{1,1} = -14.9\) Hz, H\(_{1}, \)cemos), 4.16 (s, 0.4 H, ga), 3.02 (dd, J\(_{4,4}' = -17.4\) Hz, J\(_{3,4} = 4.6\) Hz, H\(_{4}\)H cemos), 2.98 (d, J\(_{3,4} = 4.5\) Hz, H\(_{4}\)D cemos), 2.90 (d, J\(_{3,4} = 3.7\) Hz, H\(_{4}\)D cemos), 2.90 (dd, J\(_{4,4}' = -17.4\) Hz, J\(_{3,4} = 3.7\) Hz, H\(_{4}\)H cemos).

No fumarate was detected. About 20% of 3 was decomposed into 2 and 1. The lower intensity of the peak for 2 in the \(^{1}H\) NMR spectrum in comparison to that for 1 suggests that 2 is partly deuterated (40%). About 85% of H\(_{4}\) or H\(_{4}'\), of 3 has been replaced by deuterium. A low amount of H-D exchange (<5%) had occurred on the H\(_{3}\) position of 3. No H-D exchange was found in Hga, and on positions H\(_{1}\) and H\(_{1}'\), of 3.

**Results and Discussion**

**Description of the Reaction.**

In the absence of a multivalent metal ion, no addition reaction of 1 to 2 occurs. When La(III) is added, however, an addition reaction yielding 3 takes place. At 363 K a solution of 1 (1.0 M) and 2 (0.5 M), in the presence of La(III) (0.25 M), showed 90% conversion of 2, after 24 h. The reaction is reversible: heating a solution of 3 in the presence of La(III) gave partial decomposition of 3 into 1 and 2. After 24 h, the reaction mixture had about the same composition as that obtained starting from 1 and 2. The reaction is highly stereoselective as negligible amounts of the thermodynamically more stable fumarate were formed. Apparently, coordination of 3 by La(III) favors the elimination reaction towards 2 by holding the carboxylate groups of the succinate part in the 'cis'-configuration. Because of this remarkable stereoselectivity the reaction resembles the hydration of Z-aconitate catalyzed by the enzyme aconitase in the Krebs cycle. 28-30 This enzyme, which has a 4Fe-4S cluster in its active site, catalyzes the addition of a coordinated hydroxide ligand to both sites of the Z-aconitate. In this way
an equilibrium is formed between citrate and isocitrate.

The protonation of the carbanion (5) is stereoselective to some extent as was reflected in the results of experiments performed in D$_2$O. Starting from 1 and 2, 3 was obtained with about equal amounts of deuterium and hydrogen at the methylene positions 4 and 4'. The ratio D$_4$ and D$_4'$ was 2:3. The same preference for deuteration of the 4' position was obtained starting from pure 3. In this reaction the total amount of deuterium at 4 and 4' 42%, whereas 2 contained 40% D in total. Almost no H-D exchange had occurred for the proton positions 3 (<10%), 1, 1' (both <5%) in 3 and in compound 1.

The selectivity observed in the H-D exchange at the 4 position, with respect to that at the 4' position indicates that the protonation-deprotonation of carbanion 5 in the reaction mechanism (see Scheme II) occurs from one side with some preference, obviously the sterically less hindered one. Most likely, this step occurs via water in the second coordination sphere.

In this addition reaction the assignment of the rate limiting step is complicated by fast exchange of the Ln(III) complexes formed, which makes an
exact determination of the concentration of the 'reactive complex' troublesome. A similar reaction, the intramolecular addition of a coordinated ethylenediamine to 2 in an isolated inert ternary complex of Co(III),\textsuperscript{21} shows no general base catalysis. In that case the addition is rate limiting. Therefore, we suppose that in the Ln(III) catalyzed addition of 1 to 2, the addition of H\textsubscript{2}ga to coordinated 2 in a ternary complex is rate limiting and is followed by fast protonation of the carbanion (5).

Stabilities of Ternary Complexes of Ln(III) with 1 and 2 (I=1.0 M NaClO\textsubscript{4}, 298 K).

Gd(III)-induced \textsuperscript{13}C relaxation rate enhancements and Dy(III)-induced \textsuperscript{17}O shifts have revealed the presence of considerable amounts of ternary complexes with both 1 and 2 in the reaction medium at 298 K.\textsuperscript{22} The extent to which ternary complexes are formed, however, cannot be obtained quantitatively from NMR. Therefore, the conditional stability constants (\(\beta\)) for these ternary complexes must be determined, which are defined as:

\[
\beta_{pqq}\textsubscript{s} = \frac{[\text{Ln}_p(H)_q(ga)_r][\text{male}]_s}{[\text{Ln}(III)]^p[H]^q[male]^r[ga]^s}
\]  

(1)

Our aim is to determine the stability constants of the Ln(male)(ga) ternary complexes (\(\beta_{101}\)), to be able to calculate the amount of the ternary complexes present in the mixed ligand system of 1 and 2. The stability constants were measured at an ionic strength of 1.0 M in order to be able to use these data in the analysis of the kinetic measurements (see below). No addition reaction of 1 to 2 occurred under the conditions applied for the determination of the stability constants (pH<6, 298 K). The stability constants of Ln(ga), Ln(ga)_2, Ln(male), and Ln(male)_2 were determined independently at two different concentrations. The stability constants obtained are shown in Table I and II.

The stability constants \(\beta_{1001}\) and \(\beta_{1010}\) are in agreement with those reported in literature.\textsuperscript{32} The stability constant of the 1:1 complex of 1 (\(\beta_{1001}\)) increases going from La(III) to Nd(III) and then remains constant up to Dy(III). \(\beta_{1001}\) increases again at the end of the Ln(III) series. \(\beta_{1010}\) shows a different behavior; it increases up to Eu(III), whereafter the stability constant decreases. Similar breaks in the lanthanide series are also observed for the stability of other lanthanide complexes. Enthalpy factors like metal-ligand bond formation, steric hindrance in the coordination sphere and entropy factors like chelation, internal motion of
Table I. -Stability Constants of Ln-1 Complexes.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Ln</th>
<th>$\beta_{1001}$</th>
<th>$\beta_{1002}$</th>
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</thead>
<tbody>
<tr>
<td>La</td>
<td>2.13</td>
<td>4.09</td>
</tr>
<tr>
<td>Pr</td>
<td>2.39</td>
<td>4.46</td>
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<tr>
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<td>4.54</td>
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<tr>
<td>Eu</td>
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<td>4.80</td>
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<td>Er</td>
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<td>4.92</td>
</tr>
<tr>
<td>Yb</td>
<td>2.65</td>
<td>5.12</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Log values are given. 
$I=1.0 \ M \ NaC\textsubscript{2}O\textsubscript{4} \ 298 \ K$, 
$pK_a=3.62$ (ref. 32).

Table II. -Stability Constants of Ln-2 Complexes.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Ln</th>
<th>$\beta_{1010}$</th>
<th>$\beta_{1020}$</th>
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<tr>
<td>La</td>
<td>2.64</td>
<td>4.19</td>
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<td>Pr</td>
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<tr>
<td>Yb</td>
<td>2.82</td>
<td>4.41</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Log values are given. 
$I=1.0 \ M \ NaC\textsubscript{2}O\textsubscript{4} \ 298 \ K$, 
$pK_{a1}=1.63$, $pK_{a2}=5.62$ (ref. 32).

the ligand in the complex, and the rigidity of the second coordination sphere may all contribute to the stability of Ln(III) complexes with each factor depending on the ionic radius.\textsuperscript{4,33,34} For many Ln(III) complexes, the break occurs around Gd(III) and this phenomenon is often referred to as the 'Gd(III)-break'. The stability constant of the 1:2 complex ($\beta_{1002}$) of 1 shows an increase up to Eu(III). After a slight decrease for Dy(III) the stability constant increases sharply to the end of the Ln(III) series. The second stepwise stability constant $K_{1002}$ ($\beta_{1002}/\beta_{1001}$) is only 0.63 times smaller than that of the first. The ligand present in the La(ga) complex apparently has a small influence on the second incoming ligand 1. $\beta_{1020}$ of 2 shows a similar behavior as $\beta_{1010}$ when going through the Ln(III) series. The ligand 2 present in the Ln(III) complex has a big effect on the second incoming ligand, as the stepwise stability constant $K_{1020}$ is about 10 times smaller than $\beta_{1010}$.

The stability constants of the ternary Ln(male)(ga) complexes are given in Table III. The magnitudes of the stability constants of the ternary complexes increase going from La(III) to Eu(III) and then remain constant for the heavier lanthanides, which probably reflects an averaging of the effects of 1 and 2. The ratios of the stability constants of the binary
Table III. Stability Constants of the Ternary Complex Ln(ga)(male).  

<table>
<thead>
<tr>
<th>Element</th>
<th>$\beta_{1011}^a$</th>
<th>$\beta_{1011}^{stat}^b$</th>
<th>$10^3[\text{Ln(male)}(\text{ga})]^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>4.45</td>
<td>4.44</td>
<td>0.81</td>
</tr>
<tr>
<td>Pr</td>
<td>4.74</td>
<td>4.77</td>
<td>0.93</td>
</tr>
<tr>
<td>Nd</td>
<td>4.90</td>
<td>4.91</td>
<td>1.08</td>
</tr>
<tr>
<td>Eu</td>
<td>5.09</td>
<td>5.04</td>
<td>1.25</td>
</tr>
<tr>
<td>Dy</td>
<td>5.01</td>
<td>4.85</td>
<td>1.23</td>
</tr>
<tr>
<td>Er</td>
<td>4.94</td>
<td>4.92</td>
<td>1.06</td>
</tr>
<tr>
<td>Yb</td>
<td>5.10</td>
<td>5.07</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Log values are given. $I=1.0 \ M \ NaClO_4$ 298 K. See Table I and II for association constants of binary complexes used in the calculation of $\beta_{1011}$. $\beta_{1011}^{stat}$ according to eq. 2. Concentration $\text{Ln(male)}(\text{ga})$ complex at pH 6 and $\text{Ln(III)}$ total $= 5 \times 10^{-3} \ M$, $G_{tot} = 0.01 \ M$, Male$^{tot} = 0.01 \ M$. Higher order complexes are assumed to be negligible.

Complexes and ternary complexes determine the concentration of the ternary complex formed. For a particular set of 1, 2, and Ln(III) concentrations the amount of species present at pH 6 can be calculated with the use of the stability constants determined, if higher order complexes can be neglected (Table III). The same trend for the concentration of $\text{Ln(male)}(\text{ga})$ is observed as for $\beta_{1011}$. The statistical value of the stability constant of the ternary complex ($\beta_{1011}^{stat}$), which is the value of the stability constant if there were no interactions between the ligands 1 and 2, is calculated from the stability constants of the individual binary complexes ($\beta_{1002}$ and $\beta_{1020}$) with the use of eq. 2.

$$\beta_{1011}^{stat} = 2 \cdot (\beta_{1002} \cdot \beta_{1020})^{\frac{1}{2}}$$  \hspace{1cm} (2)$$

The observed stability constants are very close to those calculated with eq. 2 (Table III). The ternary complex formation apparently is governed by statistical factors. This implies that the geometry of the coordinated ligands in the ternary complex is similar to that of the binary complexes, which is in agreement with the results of the Ln(III) induced NMR experiments. There is no indication of synergic cooperation of the ligands.
Figure 1. Speciation in the La(III)-1-2 mixed ligand system versus pH.  
\[ \text{La}_{\text{tot}} = 0.5 \times 10^{-3} \text{ M}, \text{Male}_{\text{tot}} = \text{Ga}_{\text{tot}} = 10^{-2} \text{ M}. \]

in the ternary complex, in contrast to what is often observed for the d-block transition metal ions.\(^{36}\)

The predominance of statistical contributions to the stabilities of the complexes of the Ln(III) cations with 1 and 2 is probably due to the large ionic radius of the Ln(III) ion in combination with the purely electrostatic coordinative bonds. The same probably holds for other small ligands and this is in our view very promising for extending the scope of the intramolecular catalysis of Ln(III) ions as no special ligand-ligand interactions will restrict the ternary complex formation.

A plot of the distribution of the species as function of the pH calculated with the use of stability constants determined for the La(III)-male-ga mixed ligand system (see Table I, II, III) is given in Figure 1.

An estimation of the stability constants at 363 K can be made by using the Van 't Hoff equation, assuming that \( \Delta C_P = 0 \) (Table IV).\(^{32}\) The stability constants measured for the binary complexes can be used in combination with the literature values of \( \Delta H_{298} \) (measured with calorimetry).\(^{32}\) No value of \( \Delta H_{298} \) is available for the Ln(male)(ga) complex formation. Therefore, the stability of the ternary complex is determined from \( \beta_{1002} \) and \( \beta_{1020} \) at 363 K using eq. (2). The stability constants calculated this way are compiled in Table IV.
Table IV. -Calculated Stability Constants for 363 K.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Complex</th>
<th>(\Delta H^b)</th>
<th>(K_{298})</th>
<th>(K_{363})</th>
<th>(\Delta H^b)</th>
<th>(K_{298})</th>
<th>(K_{363})</th>
<th>(\Delta H^b)</th>
<th>(K_{298})</th>
<th>(K_{363})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln(male)</td>
<td>10.5\textsuperscript{c}</td>
<td>2.81</td>
<td>3.2</td>
<td>10.5\textsuperscript{c}</td>
<td>2.99</td>
<td>3.4</td>
<td>15.5\textsuperscript{d}</td>
<td>2.82</td>
<td>3.4</td>
</tr>
<tr>
<td>Ln(male)\textsubscript{2}</td>
<td>20.1</td>
<td>4.47</td>
<td>5.2</td>
<td>19.7\textsuperscript{c}</td>
<td>4.68</td>
<td>5.4</td>
<td>23.8\textsuperscript{d}</td>
<td>4.41</td>
<td>5.4</td>
</tr>
<tr>
<td>Ln(ga)</td>
<td>-5.0\textsuperscript{e}</td>
<td>2.39</td>
<td>2.2</td>
<td>-3.3</td>
<td>2.44</td>
<td>2.3</td>
<td>-0.8</td>
<td>2.65</td>
<td>2.6</td>
</tr>
<tr>
<td>Ln(ga)\textsubscript{2}</td>
<td>-9.2\textsuperscript{e}</td>
<td>4.46</td>
<td>4.1</td>
<td>-5.9</td>
<td>4.80</td>
<td>4.5</td>
<td>-2.5</td>
<td>5.12</td>
<td>5.0</td>
</tr>
<tr>
<td>Ln(male)(ga)</td>
<td>4.74</td>
<td>5.0\textsuperscript{f}</td>
<td>5.09</td>
<td>5.3\textsuperscript{f}</td>
<td>5.10</td>
<td>5.5\textsuperscript{f}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(I = 1.0 \text{ M NaClO}_4, 298 \text{ K}. \) Using the following data from ref. 32: \(\Delta H \text{ (kJ/mol)}: 0.84 \text{ (Hmale)}, 0.42 \text{ (H}_2\text{male)}, -2.34 \text{ (Hga, I}=2.0 \text{ M NaClO}_4\text{). At 363 K for 2: } pK_{a1}=1.65, pK_{a2}=5.65; \text{ for 1: } pK_a=3.53. \text{b}\ \Delta H \text{ (kJ/mol) at 298 K at I=1.0 M NaClO}_4 \text{ for 2 and I}=2.0 \text{ M NaClO}_4 \text{ for 1. For the calculation of } K_{363}, \text{ it is assumed that } \Delta C=0. \text{c}\text{Values for Sm(III). } \text{d}\text{Values for Ho(III). } \text{e}\text{Values for Nd(III). } \text{f}\text{Statistical value calculated according to eq. 2.}

The Stability Constants of Ln(III)-3 Complexes (I=1.0 M NaClO\textsubscript{4}, 298 K).

The product 3 displaces 1 and 2 from the La(III) complexes upon its formation due to the difference in stability constants. The ligand 3 can form 1:1 and 1:2 complexes.\textsuperscript{27} Polynuclear complexes are formed at concentrations higher than 0.01 M as shown by \textsuperscript{1}H NMR.\textsuperscript{27} Both \(\beta_{101}\) and \(\beta_{102}\) were determined (Table V).

Table V. -Stability Constants of Ln-3 Complexes.\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>(\beta_{101})</th>
<th>(\beta_{102})</th>
<th>(\beta_{101})</th>
<th>(\beta_{102})</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>5.72</td>
<td>9.05</td>
<td>Tb</td>
<td>6.20</td>
</tr>
<tr>
<td>Pr</td>
<td>5.80</td>
<td>9.49</td>
<td>Dy</td>
<td>5.83</td>
</tr>
<tr>
<td>Nd</td>
<td>5.93</td>
<td>9.75</td>
<td>Ho</td>
<td>6.05</td>
</tr>
<tr>
<td>Sm</td>
<td>6.11</td>
<td>10.23</td>
<td>Er</td>
<td>6.25</td>
</tr>
<tr>
<td>Eu</td>
<td>5.85</td>
<td>9.98</td>
<td>Yb</td>
<td>6.11</td>
</tr>
<tr>
<td>Gd</td>
<td>6.08</td>
<td>10.28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(I = 1.0 \text{ NaClO}_4, 298 \text{ K}. pK_{a1}= 2.46, pK_{a2}= 3.60, pK_{a3}= 4.64.\)
Figure 2. Association constants \( (I = 1.0 \text{ M NaClO}_4, 298 \text{ K}) \) as a function of the Ln(III) ion. (▲) \( \log \beta_{1011} \) of ternary complex Ln(ga)(male) determined experimentally, (▲) \( \log \beta_{1011} \) (stat) of ternary complex Ln(ga)(male) calculated according to eq. 2, (●) \( \log \beta_{101} \) of binary complex Ln(cmos).

The stability constants of the Ln(cmos) complexes are about \( 10^3 \) times higher than the Ln(male) or Ln(ga) complexes. In Figure 2, \( \beta_{1011} \) of the ternary complex Ln(male)(ga) is compared with \( \beta_{101} \) of 3. For all Ln(III) measured the latter stability constant is approximately 10 times higher. For the formation of Ln(male)(ga) versus Ln(cmos) there is a difference in entropy as the first has three particles forming one, while the second has only two forming one. According to Rossotti this cratic effect corresponds with a \( \Delta S^0 \) difference of 7.9 e.u., \( ^{37} \log \beta_{101} - \log \beta_{1011} \) would be 1.7 \( (\Delta(\Delta S^0)/(2.3RT)) \), which reasonably agrees with the observed difference. This entropy effect mainly contributes in shifting the equilibrium of the reaction to the side of 3. The strive for stronger complexes in metal ion catalyzed reactions is, for example, also observed for the metal ion catalyzed enolization and hydration of oxalacetate \(^{38} \) and for the addition of the enolic form of pyruvate to its keto form in the dimerization of pyruvate. \(^{39} \) In these reactions, the metal ion stabilizes the final products with respect to the starting compounds, which is supposed to be a quantitative measure for the activation by the metal ion in the reactions. \(^{38,39} \)
The Ionization of a Ln(III) Coordinated 1 (H₇ga).

Some indications for the formation of a Ln(III) coordinated H₇ga can be found in literature. The crystal structure of Er(ga)(H₇ga) shows unambiguously the presence of the H₇ga ligand in the solid state. The structure is a three-dimensional network in which the alcoloholate group of H₇ga acts as a bridge between two erbium ions. Comparison of IR data of this crystal structure with IR data of an alkaline solution containing a ratio of Er(III)/1 of 1/3 also shows the C=O⁻ vibration of the H₇ga ligand in solution. From anion exchange experiments, the existence of the Eu(ga)₂(H₇ga) complex has been proposed. The use of potentiometric methods to determine the pKₐ of a coordinated ga ligand cannot be decisive due to concomitant ionization of a coordinated water.¹⁻¹¹H NMR has been valuable studying the ionization of the hydroxyl group of La(2-hydroxyethyl-ethylenediaminetriacetate). Therefore, we have chosen NMR to determine the pH range in which the ionization of the hydroxyl of Ln(III) coordinated 1 occurs.¹³C NMR was used because 1 contains two different carbon atoms that are connected to the donor groups in the La(III) complex. The La(nitrilotriacetate) (La(nta)) complex was used as a model for the reactive ternary complex La(male)(ga)ₙ (n=1,2) to prevent La(OH)₃ precipitation. The diamagnetic La(III) coordinates firmly with the nta ligand (β₁₀₁⁻¹₀.⁴⁷, I=0.1 M 298 K), and is able to coordinate simultaneously with 1 as five coordination sites are still available.

In the mixed ligand system La/nta/1 (molar ratio 1/1/2) no change in the¹³C NMR chemical shifts was observed until pH 7.7. At pH 8.2 precipitation occurred during the measurement. Upon raising the pH to 8.9 the precipitate dissolved again. At the same time an upfield shift of 0.5 ppm and 0.3 ppm was observed for the methylene and carboxylate carbons of 1, respectively (Figure 3). The chemical shifts of these ligands were close to those of the free ligand.

Some changes also occurred in the spectrum of the nta ligand. At pH 7.7 a second signal of the methylene carbons of nta was observed, which became the only signal present at pH 8.9 (Figure 3). The formation of a second nta complex is supported by¹³⁹La NMR. A second La(III) signal appeared at pH>7.7 that is shifted 120 ppm downfield from the signal for the La(nta)(ga) complex. At pH 9 the latter signal disappeared. The chemical shift of the new signal indicates that a La(nta)₂ complex is formed upon formation of La(III) complexes of H₇ga or OH⁻ ligands. The same change of the¹³⁹La spectrum as a function of the pH was observed in the absence of 1, when
Figure 3. $^{13}$C chemical shift (ppm) in the La(III)-nta-I ternary complex system 0.1 M La(III), 0.1 M nta, 0.2 M I in aqueous solution containing 10% $D_2O$ at 298 K versus pH. 1: $CH_2$ (△), $COO^-$ (▲); nta: $CH_2$ (●), $COO^-$ (●) of La(nta) and $CH_2$ (▼) of La(nta)$_2$. For comparison the chemical shift of the free ligands at pH 10.4 are included (open symbols).

La(III) hydroxo complexes were formed. Apparently, ionization of the ga and water ligand is accompanied by a disproportion of the La(III) complexes towards La(nta)$_2$ and probably relatively stable dimeric or polynuclear La(III) complexes involving OH$^-$ or H$_2$ga ligands, which escape observation due to excessive line-widths.

Support for the involvement of the H$_2$ga ligand in these complexes was obtained from a $^{13}$C NMR experiment analogous to that described above but now with the diamagnetic Y(III). The signals for 1 at pH higher than 7 appeared to be broaden beyond detection, whereas those for nta remained sharp. Even
at pH 9 no free I could be detected. This can be ascribed to a decrease of the exchange rate of I between the bound and free form, upon deprotonation of the coordinated OH group.\textsuperscript{50}

Obviously, H$_{-1}$ga will coordinate the La(III) stronger than I. Its stability constant $\beta$(H$_{-1}$ga) can be deduced from Table VI with the use of $\beta$(H$_{-1}$ga) = $K_{\text{ion}} \cdot \beta_{1001}/\beta_{0-101}$, where $K_{\text{ion}}$ is the ionization constant of the Ln(III) coordinated hydroxyl group of I. For the calculation of $\beta$(H$_{-1}$ga), $\beta_{0-101}$ is needed. Beck has determined by optical rotation the pK$_{a}$ of the first hydroxyl group of tartaric acid to be 13.8.\textsuperscript{51} The same value was obtained for the pK$_{a}$ of gluconic acid.\textsuperscript{52} For pK$_{\text{ion}}$ we took the value determined kinetically (see below), which is in agreement with the results of the $^{13}$C NMR study on the La/nta/ga mixed ligand system. Using these data the stability constant $\beta$(H$_{-1}$ga) is calculated to be 8.0.

With the estimated stability constants that are compiled in Table VI, the distribution of the various species as function of the pH was calculated (see Figure 4). The trend of the concentration of the La(H$_{-1}$ga) complex is consistent with the $^{13}$C chemical shifts (see Figure 3). The concentration of LaOH is small with respect to that of La(H$_{-1}$ga), which is in agreement with the insignificance of the addition of the water to 2, as a side reaction of the addition of 1 to 2.

Table VI. -Stability Constants of I.

<table>
<thead>
<tr>
<th>equilibrium</th>
<th>$\log \beta_{pqrs}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{0101}$ HOCH$_2$COO$^- + H^+$ = HOCH$_2$COOH</td>
<td>3.63</td>
</tr>
<tr>
<td>$\beta_{0-101}$ $^-\text{OCH}_2\text{COO}^- + H^+$ = HOCH$_2$COO$^-$</td>
<td>-13.8\textsuperscript{b}</td>
</tr>
<tr>
<td>$\beta_{0-100}$ $^-\text{OH} + H^+$ = $H_2$O</td>
<td>-13.78</td>
</tr>
<tr>
<td>$\beta_{1-100}$ La$^{3+} + ^-\text{OH}$ = LaOH$^{2+}$</td>
<td>-9.1\textsuperscript{c}</td>
</tr>
<tr>
<td>$\beta_{1001}$ La$^{3+} + $HOCH$_2$COO$^- = $La(HOCH$_2$COO)$^{2+}$</td>
<td>2.55</td>
</tr>
<tr>
<td>$\beta_{1-101}$ La$^{3+} + ^-\text{OCH}_2\text{COO}^- = $La(OCH$_2$COO)$^+$</td>
<td>-5.8\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}I=0.1, 298 K. \textsuperscript{b}See text. \textsuperscript{c}I=0.3, 298 K (ref. 49). \textsuperscript{d}See text.
Figure 4. Speciation in the La(III)-1 ligand system as a function of the pH, calculated with the association constants given in Table VI. 0.005 M La(III), 0.010 M 1 at 298 K.

Reaction Kinetics.

The reaction mechanism outlined in Scheme II needs further kinetic support. Initial reaction rates were used in order to limit the number of species that have to be taken into account. A ten times excess of 1 with respect to Ln(III) was taken as a means to keep the amount of hydroxide coordinated to the Ln(III) low (see above) and to diminish the change of the overall concentration of Ln(III) bound 1 (Ga tot-ga), upon formation of H−1ga. Furthermore, the reaction can then be considered as pseudo first order in 1 and the range of pH's used can be extended without the risk of precipitation.

First, the concentration of 2 in a La(III) catalyzed reaction was varied at constant pH in order to determine the molar ratio 2/Ln(III), where the reaction rate is optimal. These experiments were performed at pH 6.5 (363 K). Small variations of the pH around 6.5 have almost no influence on the reaction rate. Figure 5 shows the initial reaction rate as a function of the concentration of 2. The maximum initial rate (5.5 \times 10^{-4} \text{ M min}^{-1}) was obtained at ratios of 2/Ln(III) higher than 1.5. This suggests that in the 'reactive' ternary complex one ligand of 2 is present.
Figure 5. Dependence of the initial rate of the addition of 1 to 2 on the concentration of 2 in a reaction mixture containing 0.05 M La(III) and 0.5 M 1. pH is maintained at 6.55 (363 K), reaction temperature 363 K.

For the sake of simplicity La(male)(ga) is considered the only 'reactive' ternary complex present. If it is assumed, as already discussed, that the reaction from compound 4 to 5 (see Scheme II) is the rate limiting step and that $k_2 << k_3$ then the initial rate can be given by equation:

$$r = k_2 \cdot [\text{Ln(male)}(H_{-1}ga)]$$  \hspace{1cm} (3)

Since an excess of 1 was employed, one can neglect the Ln(male)$_n$ (n=1,2) complexes under the conditions applied (molar ratio Ln(III)/2 of 1/2). Then with substitution of the ionization constant of 4 (eq. 4):

$$K_{ion} = [\text{Ln(male)}(H_{-1}ga)][H^+]/[\text{Ln(male)}(ga)]$$  \hspace{1cm} (4)

and the mass balance (eq. 5):

$$\text{Male}_{tot} = [\text{Ln(male)}(ga)] + [\text{Ln(male)}(H_{-1}ga)] + [\text{male}] + [\text{Ln(male)}] + 2 \cdot [\text{Ln(male)}_2]$$  \hspace{1cm} (5)

into eq. 3 gives:

$$r = k_2 \cdot C/(1 + H^+/K_{ion})$$  \hspace{1cm} (6)
which can be rearranged to:

\[
1/r = H^+/(K_{ion} \cdot C \cdot k_2) + 1/k_2 \cdot C
\]  

(7)

wherein \( C = \text{Male}_{\text{tot}} - \text{male} = [\ln(\text{male})(\text{ga})] \), which holds as the concentration of bound 1 (\( \text{Ga}_{\text{tot}} - \text{ga} \)) is constant.

The initial reaction rate as a function of the pH of the La(III) catalyzed reaction is shown in Figure 6. A precipitate was present above pH 7.3. The rate of the addition increased upon the raising the pH. Upon formation of 3, which is stronger coordinated than the starting compounds, 1, 2, and the intermediate complexes (see Scheme II) will be released from the La(III) coordination sphere and consequently the free proton concentration in the solution will decrease (Table VII). This phenomenon can be mimicked by titrating 3 to a solution containing 1 and La(III) at pH 8 at room temperature. A raise of the pH upon addition of 3 was observed until a ratio of 3 to La(III) of two was reached (Figure 7).

![Graph](image)

**Figure 6.** Dependence of the initial rate of the addition of 1 to 2 on the pH in the La(III) catalyzed reaction at 363 K. 0.50 M 1, 0.10 M 2, and 0.05 M LaCl\(_3\).
Table VII. Influence of the pH on the Initial Rate of the Addition of 1 to 2 Catalyzed by La(III) at 363 K.\textsuperscript{a}

<table>
<thead>
<tr>
<th>pH (363 K)</th>
<th>HCl\textsuperscript{b} (ml)</th>
<th>10\textsuperscript{3} initial rate (M·min\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.40</td>
<td>-</td>
<td>0.537</td>
</tr>
<tr>
<td>6.60</td>
<td>-</td>
<td>0.785</td>
</tr>
<tr>
<td>6.77</td>
<td>0.051</td>
<td>1.11</td>
</tr>
<tr>
<td>6.86</td>
<td>0.120</td>
<td>1.58</td>
</tr>
<tr>
<td>6.99</td>
<td>0.372</td>
<td>1.90</td>
</tr>
<tr>
<td>7.05</td>
<td>0.679</td>
<td>2.75</td>
</tr>
<tr>
<td>7.30</td>
<td>1.618</td>
<td>3.74</td>
</tr>
<tr>
<td>7.47\textsuperscript{c}</td>
<td>-</td>
<td>1.38</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Conditions see Figure 6. \textsuperscript{b}Amount of HCl solution (1.0 M) added for keeping the pH constant. \textsuperscript{c}D\textsubscript{2}O used as solvent.

Figure 7. pH of a La(III)-1 ligand system as a function of the amount of added 3. Initial conditions: 0.64 M 1 and 0.05 M La(III) (50 ml, pH 7.9).
In Figure 8 the reciprocal of the initial rate for various Ln(III) ions is given as a function of the $H^+$ concentration. At a free proton concentration of $0.41 \times 10^{-6}$ (pH 6.4), Dy(III) and Er(III) are the best catalysts among the Ln(III) ions (Figure 8). A good correlation with equation 5 is consistent with the assignment of the rate-limiting step (scheme II). From the slopes and intercepts of these lines, the $pK_{\text{ion}}$ were calculated, using eq. 7. The $pK_{\text{ion}}$ values for the different Ln(III) ions are given in Table VIII.

In $D_2O$ the initial rate at pH 7.47 appears to be three times as low as in water at pH 7.3, which suggests that an isotope effect is present (Table VII). The difference in $pK_{\text{ion}}$ in $H_2O$ and $D_2O$ may account for this effect.

The $pK_{\text{ion}}$ shows a decreasing trend when going through the Ln(III) series (Figure 9). The $pK_{\text{ion}}$ is related to the effective charge density of the Ln(III) ion in question, which increases going from La(III) to Lu(III). At higher effective charge density the polarization of the hydroxyl group of

![Figure 8](image.png)

**Figure 8.** The reciprocal initial rate of the addition of 1 to 2 as a function of $[H^+]$ at 363 K. 0.50 M 1, 0.10 M 2, and 0.05 M LnCl$_3$. La(III) (○), Pr(III) (Δ), Nd(III) (○), Eu(III) (■), Dy(III) (Δ), Er(III) (●), Yb(III) (●).
Table VIII. -Addition of 1 to 2 Catalyzed by Various Ln(III) Ions.

<table>
<thead>
<tr>
<th></th>
<th>$10^{-9}/K_{ion} \cdot k_2 \cdot C^a$</th>
<th>$1/k_2 \cdot C^a$</th>
<th>$pK_{ion}$</th>
<th>$k_2 \cdot C$</th>
</tr>
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<tr>
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<td>8.1</td>
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<td>7.9</td>
<td>0.037</td>
</tr>
<tr>
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<tr>
<td>Yb</td>
<td>0.8</td>
<td>716</td>
<td>6.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

$^a$See equation 5.

Ln(III) bound 1 becomes larger and consequently the $pK_{ion}$ decreases when going through the Ln(III) series. A 'Gd-break' seems to be present for the $pK_{ion}$ and, thus for the stability of the ternary complex La(male)(H$_2$ga). This transition could have the same origin as the break observed for the stability constants for the Ln(ga) and Ln(ga)$_2$ complexes.

Figure 9. $pK_{ion}$ (▲) and $k_2 \cdot C$ (●) (see equation 5) versus the ionic radius of the Ln(III) ion.
An estimation of the rate constant \( k_2 \) can be obtained with \( C = [\text{Ln(male)}(\text{ga})] \), which is allowed if the concentrations of the \( \text{Ln(ga)}_3 \) and \( \text{Ln(male)}(\text{ga})_2 \) complexes can be neglected. At pH 6 (363 K) the concentration of the \( \text{Ln(male)}(\text{ga}) \) complexes can be calculated (0.0212 M (Pr(III)), 0.0198 M (Eu(III)), and 0.0146 M (Er(III))) using the data from Table IV. From these concentrations and \( k_2 \cdot C \) (Table VIII) \( k_2 \) can be calculated: 1.8 \( \text{min}^{-1} \) Pr(III), 1.5 \( \text{min}^{-1} \) Eu(III) and 0.07 \( \text{min}^{-1} \) Er(III). If the reaction would also take place with \( \text{Ln(male)}(\text{ga})_2 \), the trend would be the same.

Apparently, the decrease of \( pK_{\text{ion}} \) of the hydroxyl group of 1 upon coordination to the Ln(III) ion is accompanied by a similar decrease of the nucleophilicity of \( \text{H}^{-1}_2\text{ga} \), which is in agreement with the Brønsted catalysis law.\(^3\)

Conclusions

The formation of 3 from 1 and 2 catalyzed by Ln(III) ions is an equilibrium reaction, in which the driving force is the stronger complexation of the product 3. The reaction takes place in a ternary complex of \( \text{Ln(male)}(\text{ga}) \) with the addition of the ionized Ln(III) coordinated hydroxyl group of 1 to the olefinic bond of 2 as the rate determining step. The first order rate constant of the reaction is around 1 \( \text{min}^{-1} \) for the Ln(III) ions at 363 K. The effective charge density of the cation plays an important role in decreasing the \( pK_a \) of a hydroxyl group of 1 upon coordination. This effect is somewhat counteracted by a concomitant decrease of the nucleophilicity of the resulting alcoholate group.

Acknowledgements.

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References
23. This thesis Chapter V.
35. This thesis Chapter VIII.
48. Using the stability constants of the La(nita)$_n$ (n=1,2) complexes in ref. 32 and the La(OH) complex in ref. 49 to calculate the speciation for the mixture containing a ratio of La/nta of 1/1 as a function of the pH shows that the formation of the La(OH) complex is accompanied by the formation of the La(nita)$_2$ complex.

50. An alternative explanation would be that at pH>7 an exchange mechanism
Ln(nta)(ga) +OH− = Ln(nta)(OH) + ga becomes predominant (Cf. Choppin, G.R.; Baisden, P.A.; Rizkalla, E.N. In The Rare Earth In Modern Science and Technology; Plenum, 1982, Vol. 3, p. 187.) with a smaller exchange rate (on the NMR time scale) than the corresponding substitution reaction with water at lower pH. It should be expected however, that if that would be the case a further increase of the pH would lead to a shift of the above mentioned equilibrium to the right and then it would be possible to observe free ga (Cf. Chen, Z.; van Westrenen, J.; Peters, J.A.; van Bekkum, H. submitted to Inorg. Chem.)


CHAPTER IV.

EU(III) CATALYZED O-ALKYLATION OF GLYCOLATE WITH MALEATE AS STUDIED ON-LINE BY LUMINESCENCE.*

Abstract: The O-alkylation of glycolate with maleate yielding carboxymethoxysuccinate (cmos) is a lanthanide(III) catalyzed reaction. It is demonstrated that the reaction can be studied on-line with help of an optical fiber setup, monitoring the luminescence of the Eu(III) optical probe. During the reaction the $^5D_0 \rightarrow ^7F_0$ transition shifts to lower wavenumbers and the average lifetime of the excited $^5D_0$ level of the Eu(III) ion increases, when substantial amounts of Eu(cmso)$_2$ are formed. The average number of OH oscillators in the first coordination sphere of the Eu(III) ion is decreased by two if one cmso per Eu(III) is formed. The concentration of cmso can be obtained by on-line measurements of the lifetime of the $^5D_0$-excited state.

Introduction

Sequestering agents for lanthanide (Ln(III)) and alkaline earth metal ions are of special interest in the field of NMR imaging$^{1-3}$ and phosphate substitution in detergents.$^{4-7}$ Concerning the matter of phosphate substitution, oxygen containing polycarboxylates have been synthesized avoiding nitrogen in the chelate because of its potential threat to resolve heavy metal ion deposits in the environment. A possibility to synthesize these oxygen containing polycarboxylates is given by the Ln(III) catalyzed O-alkylation of hydroxycarboxylates and polyols with maleate.$^{6,8,9}$ The applicability of Ln(III) ions as a catalyst prompted us to study the Eu(III) catalyzed O-alkylation of glycolate with maleate (Scheme I) by luminescence as a means of following the reaction on-line.

Luminescence studies on europium(III) complexes in aqueous solutions and solids have shown their versatility as analytical tool.$^{10}$ The $^5D_0 \rightarrow ^7F_0$ transition is non-degenerated by the crystal field Hamiltonian and,

therefore, gives information on the number of crystallographic sites in a solid and on the minimum number of complexes present in solution.\textsuperscript{11-13} The so-called 'nephelauxetic effect' is responsible for small shifts of the $^{5}D_{0} \rightarrow ^{7}F_{j}$ line position when Eu(III) is located in different environments.\textsuperscript{11} Furthermore, the splitting of the $^{5}D_{0} \rightarrow ^{7}F_{j}$ ($j>0$) manifold by the ligand field provides structural information on the Eu(III) complexes.\textsuperscript{14} In addition, the lifetime of the $^{5}D_{0}$-excited state is used to determine the average number of waters (OH oscillators) in the first coordination sphere of the Eu(III) ion.

The on-line monitoring of the reaction was eased by using an optical fiber setup wherein one fiber conducted the excitation laser beam to the solution and six other fibers collected and guided the emitted light to the spectrometer. The use of optical fibers is one of the fastest growing areas in analytical and biomedical chemistry.\textsuperscript{15,16} The fluorescence of the medium can be monitored as such, or by specially attached physical or chemical sensors at the end of the optical fiber that emits light.\textsuperscript{17} The method is, especially, suited for analysis in inaccessible or hazardous environments. For instance, the analysis of the ground water\textsuperscript{18} or the determination of the uranium(VI) content in a nuclear fuel reprocessing facility\textsuperscript{19} have been described. The sensitivity of the analyses does not change upon extending the fiber length to one kilometer. The fact that one laser can handle several fiber devices makes the method of analysis extremely valuable for a remote on-line analysis in industrial processes.
Experimental

Materials.

The EuCl₃·6.5 H₂O (99.9%) was purchased from Aldrich. The Eu(III) content was determined by ethylenediaminetetra-acetate titration with xylolino orange as the indicator. Glycolic acid (Hga) was obtained from Merck-Schuchardt. The other chemicals were obtained from Aldrich. The trisodium salt of cmos was prepared as described previously. The sodium salts of glycolate (Naga) and maleate (Na₂male) were made by neutralization of an aqueous solution of the acids by NaOH, followed by precipitation with an excess of ethanol.

O-Alkylation of Glycolate with Male Catalyzed by Eu(III).

The aqueous solutions of Na₂male, Naga, and Eu(III) were heated in a reaction vessel at 363 K in a glycerol bath. The pH of the solution was recorded during the reaction at 363 K as described previously. The samples from the reaction mixture were analyzed by HPLC.

The reaction in D₂O was performed with EuCl₃·4H₂O, which was obtained after drying EuCl₃·6.5H₂O in vacuo at 353 K for 300 min. The reaction mixture was prepared by dissolving EuCl₃·4H₂O (1.648 g, 5 mmol), Na₂male (2.407 g, 12.52 mmol), and Naga (1.481 g, 12.76 mmol) in 25 ml D₂O.

Fluorescence Measurements during the Reaction.

The experimental setup for in situ monitoring of the Eu(III) luminescence consists of three components: the reaction vessel, the spectroscopic part and the optical fiber device.

A specially designed reaction vessel was used in order to monitor the pH and luminescence simultaneously, by dipping both the pH electrode and optical fiber bundle into the solution. The tips of the fibers were just below the surface (<2 mm) and 4 cm above the bottom of the vessel if 15 ml of reaction mixture was used. Under these conditions the overlapping cone between the exciting light and the light collection cones was sufficient to ensure a high signal to noise ratio.

A pulsed nitrogen laser-pumped dye laser system (Jobin Yvon LA04/ELT) was used for the selective excitation into the ⁵D₂ level of Eu(III). The maximum emission was observed for exciting at 4646 Å (21522 cm⁻¹) at 363 K and the dye laser was tuned to this wavelength for all the experiments. The ⁵D₀→⁷F₇ emission was analyzed by a Coderg PHO double monochromator spectrometer equipped with a Hamamatsu 1477 photomultiplier. The ⁵D₀→⁷F₂ emission was
recorded at 6156 Å (16244 cm⁻¹) for measuring the lifetime (τ) of the ⁵D₀ level. For each excitation pulse the shape of the ⁵D₀ decay (I=f(t)) was extracted from a Tektronix 2430 digital oscilloscope by a hooked on BFM 187 16 bit computer. A program has been written in order to calculate the ⁵D₀ lifetime at equal intervals during the reaction. The numerical I=f(t) values were averaged by the oscilloscope and transmitted at a frequency of about 0.5 Hz. Between two transmissions the computer calculated the lifetime τ by linear regression of the slope of logI(t). The first 50 μs after the pulse were not taken into account so that the parasitic effects on the feeding of ⁵D₀ level from the upper ⁵D₁, ⁵D₂ levels as well as those of scattered incident light at very short delays do not affect the numerical values. The lifetime of the ⁵D₀ level was calculated for three time intervals after the pulse: Δt to 6Δt, 6Δt to 12Δt, and 12Δt to 16Δt using Δt= 50 μs in water at 363 K for lifetimes ranging from 200 to 500 μs. After a selected number of iterations (300) the three averaged values of τ were saved in an array and the process was repeated during the reaction time (up to 3h). The τ values calculated for the three time intervals were in very good agreement (± 3%) proving that the ⁵D₀ decays were single exponential. The time required for 300 iterations including the calculation of τ was 175 s. The average values of τ were assigned to the average time of each interval (175 s).

Emission lines originating from various ⁵D_j levels or from ⁵D₀ of Eu(III) ions in different environments often exhibit differences in time evolutions. These differences are shown by different relative intensities of the emission recorded at short and long delays after the pulse. The same setup of the spectrometer was used as described above to record the time-resolved spectra. The computer numerically integrates the I=f(t) function with selected gates and delays after the pulse. During one scan of the spectrometer, several time resolved spectra were recorded.

The third part of the experimental setup was an optical fiber device employed to guide the exciting laser light into the solution, collect the emitted light, and guide it back to the entrance slits of the spectrometer. Another experimental setup with an optical coupler between the incident and collection fibers had already been described by some of us, ²⁰ which was particularly useful for collecting spectroscopic information at low temperatures with small (all silica, 200μm core) fibers. For the experiments described here, however, bigger fibers (Quartz et Silice plastic clad silica, 600 μm core) were perfectly suited using one fiber carrying the laser light to the sample and 6 collecting the light of the luminescence
signal. The tips of the seven fibers were fixed in a compact hexagonal arrangement. The central fiber was used for the input light, while its other end was positioned in front of the dye laser, the laser beam was focused by a microscope objective (focal length 2 cm). The six fibers for collecting the signal were arranged in a line parallel to the slit of the spectrometer and the output was imaged by a collecting optical system on the entrance slit, this setup is analogous to that described by Schwab. A very good signal to noise ratio was achieved with this fiber device for the lifetime measurements (spectral resolution is 12 cm\(^{-1}\)) and an acceptable signal remained for most of the spectra recorded at 4 cm\(^{-1}\) spectral resolution.

Optical fibers proved to be more easier to install than conventional heated cells and allowed measurements on a relatively small volume of solution at 363 K. This could even be reduced to 1 ml if the pH was not monitored. The major experimental problem appeared to be the evolution of gas bubbles in the heated solution, even after degassing, that set on the fiber tips and decreased the signal collected. These phenomena hampered the determination of the kinetics via monitoring the peak intensities at a particular wavelength. This artefact, however, did not affect the lifetimes values.

Results and Discussion

**Reaction Characteristics.**

The O-alkylation of ga with male yielding carboxymethoxysuccinate (cmos) catalyzed by Ln(III) ions occurs in a relatively concentrated reaction medium (0.2 M Eu(III)) at 363 K and at a pH that is high enough to ensure the ionization of the hydroxyl group of a coordinated ga ligand in the ternary complex Eu(male)(ga)_n (n=1,2). A pK_a of 7.8 of the hydroxyl group of a Eu(III) coordinated ga ligand has been determined for the ternary complex Eu(male)(ga)_n (n=1,2) at 363 K. The formation of Ln(cmos)\(_2\) complexes captures the Ln(III) ion from being involved in the reaction and, therefore, inhibits the reaction. The Ln(cmos) complex is still able to serve as a catalyst for the formation of a second molecule of cmos, but with a lower reaction rate constant than that of the Ln(III) ion (about 6 times for La(III)).

Binary and ternary complexes of male and ga with lanthanide(III) ions are formed in the mixed ligand system. The complexes are in fast exchange with each other. Their stability constants have been measured by potentiometry at
Table I. -Association Constants$^a$

<table>
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<tr>
<th>Species</th>
<th>Log$\beta^b$</th>
<th>Species</th>
<th>Log$\beta^b$</th>
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<tr>
<td>Eu(ga)</td>
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<td>Eu(cmos)</td>
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<td>9.98</td>
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<td>Eu(cmos)(ga)</td>
<td>7.7$^c$</td>
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<td>7.6$^c$</td>
</tr>
<tr>
<td>Eu(ga)(male)</td>
<td>5.09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$I=1.0 (NaClO$_4$), 298 K; ga: $pK_a$ = 3.62; male: $pK_a^1$ = 1.63, $pK_a^2$=5.62; cmos: $pK_a^1$=2.46, $pK_a^2$=3.60, $pK_a^3$=4.64 from ref. 9.

$^b$Beta= [Eu(L)(Z)]/([Eu(III)]*[L]*[Z]). $^c$Estimated statistically from both Eu(cmos)$_2$ and Eu(ga)$_2$ or Eu(male)$_2$ according to ref. 9 and 20.

298 K (I=1.0 M, NaClO$_4$) (Table I).$^9$ NMR$^{22}$ and potentiometric studies$^9$ have shown that the product, cmos, can form 1:1 and 1:2 complexes with Ln(III) ions. As Eu(cmos)(L) (L=ga, male) complexes can be formed during the reaction, their stability constants were estimated statistically at 298 K according to Martin et al. (see Table I).$^{23}$ These estimated stability constants were shown to be a good approximation of the experimentally determined ones for the Ln(male)(ga) ternary complex.$^9$

The reaction at 363 K is sufficiently slow to allow recording of changes of the speciation in the reaction mixture during the Eu(III) catalyzed 0-alkylation with the use of the $^5$D$_0$-7F$_0$ transitions and the lifetime of the $^5$D$_0$ level as a function of the reaction time. All reactions were followed for 3 h at 363 K.

$^5$D$_0$-7F$_0$ Emission Spectra.

In Figure 1A and B the $^5$D$_0$-7F$_0$ transition is shown for two ratios of Eu(III)/cmos ($\rho_{\text{CMOS}}$) at 363 K. At Eu(III)/cmos ratios in between, it was shown that the $^5$D$_0$-7F$_0$ transition for both complexes are well separated. From these spectra it can be concluded that the wavenumbers of the Eu(cmos)$^0$ and Eu(cmos)$_2$ complexes are 17270 cm$^{-1}$ and 17256 cm$^{-1}$, respectively. This is in agreement with the generally observed shifting to lower wavenumbers for higher charged complexes.$^{11}$ The shoulder in the spectrum measured at $\rho_{\text{CMOS}}$ = 0.5 might be assigned to the Eu(cmos) complex that is still present under these conditions. No change in the spectrum was observed upon cooling.
Figure 1A, B. $^5D_0 \rightarrow ^7F_0$ emission at 363 K for the molar ratio Eu(III)/cmos = 0.5 (Spectrum a, Eu(III)= 0.2 M, pH 6.15), and Eu(III)/cmos is 1.4 (Spectrum β, Eu(III)= 0.1 M, pH 5.26). Spectrum c is the $^5D_0 \rightarrow ^7F_0$ emission at 363 K for the reaction mixture formed after 3 h at 363 K using a ratio Eu/male/ga= 1/1.3/1.3. Spectrum a, ibid using a ratio Eu/male/ga= 1/2.7/2.7. The labeling of the curves (a, c) corresponds to the experiments described in Table III. Excitation 21522 cm$^{-1}$.

to 298 K. Only a slight displacement (3 cm$^{-1}$) towards lower energies was observed for both peaks. Changing the pH at this temperature from 6.55 to 4.5 does not affect the position of the peaks.

At 298 K the $^5D_0 \rightarrow ^7F_0$ emission for the Eu(III)-male-ga mixed ligand system can be studied because no reaction takes place at this temperature. A single peak was observed at 17264 cm$^{-1}$ at a molar ratio of Eu(III)/male/ga of 1/2/2 (Eu(III)= 0.2 M), which is at the same wavelength as that of the Eu(cmos) complex at 298 K, although a larger line width is observed in the case of the mixed ligand system.

In Figure 1A the $^5D_0 \rightarrow ^7F_0$ emission of the final reaction product of a reaction started with a Eu(III)/male/ga ratio of 1/1.4/1.4 (Eu(III)= 0.2 M) resulting in $\rho_{CMOS} = 0.92$ (81% conversion) after 3 h is shown. This spectrum exhibits the $^5D_0 \rightarrow ^7F_0$ signals of the Eu(cmos) complex and starting complexes, but the signal is much broader and displaced slightly to lower wavenumbers. This suggests that other complexes are formed, like ternary complexes of
Eu(cmos)(L) (L=male, ga), or polynuclear complexes, which have $^5D_0 \rightarrow ^7F_0$ transitions that are slightly shifted with respect to the transitions of the initial reaction mixture and Eu(cmos). In Figure 1B the emission of the final reaction product is shown of a reaction with a ratio of Eu(III)/male/ga 1/2.7/2.7 (Eu(III)= 0.2 M). A $\rho_{\text{cmos}} = 0.72$ (51% conversion) is reached after 3 h. The broad peak (a) shows by its position that a considerable amount of Eu(cmos)$_2$ complex is present in this reaction mixture.

An estimation of the speciation at 298 K can be obtained using the association constants of Table I. For the reaction mixture of Figure 1A a distribution of Eu(cmos) (0.069 M), Eu(cmos)$_2$ (0.047 M), Eu(cmos)(male) (0.02 M), Eu(cmos)(ga) (0.03 M) can be calculated assuming that the concentration of other complexes are negligible. Analogously, the speciation in the reaction mixture of Figure 1B can be estimated: Eu(cmos) (0.003 M), Eu(cmos)$_2$ (0.094 M), Eu(cmos)(male) (0.04 M), and Eu(cmos)(ga) (0.045 M). The signal intensity at 17256 cm$^{-1}$ of the $^5D_0 \rightarrow ^7F_0$ spectrum of the reaction mixture in Figure 1A seems to be too low for the calculated concentration of the Eu(cmos)$_2$ complex. This may be attributed to the relative intensity of the $^5D_0 \rightarrow ^7F_0$ emission versus $^5D_0 \rightarrow ^7F_1$ and $^5D_0 \rightarrow ^7F_2$, which is low for Eu(cmos)$_2$ compared to Eu(cmos), or to the assumptions in the model used (e.g. the neglect of polynuclear complexes).

These experiments demonstrate that large effects on the wavenumber of the $^5D_0 \rightarrow ^7F_0$ transition are only observed when the ligand concentration is high enough to ensure the formation of high concentration of Eu(cmos)$_2$. The information of the $^5D_0 \rightarrow ^7F_0$ transition is somewhat limited due to the considerable overlapping of the emission lines because of their relative broadness and of the small difference in wavenumbers between the complexes formed (at most 15 cm$^{-1}$ between the Eu(cmos) and Eu(cmos)$_2$ emissions).

On-Line Study of the Reaction by the Lifetime of the $^5D_0$-Excited State.

Lifetime of the $^5D_0$-Excited State.

Single exponential decay curves of the $^5D_0$-excited state were observed at 298 K and 363 K, showing that the various species present in solution are in fast exchange with respect to the lifetime of the $^5D_0$-excited state. The average decay can be expressed as $n_t = n_0 e^{-Pav \cdot t}$, where $n^*$ is the number of Eu(III) ions in the excited state and Pav is the average decay probability which is the inverse of the average lifetime ($\tau$). In the fast exchange
region \( n^* \) is defined by \( K_i = n^*/n^* = n_i/n \) (\( n \) is the number of Eu(III) ions at the ground state level). \( P_a = \sum K_i \cdot P_i \) with \( K_i \) being the relative concentration of species \( i \) per total concentration of Eu(III) present in the equilibrium.\(^{26}\) The main pathway for non-radiative depopulation of the \( ^5D_0 \) level of Eu(III) in aqueous solutions is by coupling with the high-energy OH vibrations, which will be discussed below.

**On-Line Study of the Reaction by the \( ^5D_0 \) Lifetime: Effect of the Molar Ratio of Eu(III)/Ligand(s).**

The lifetimes \( \tau (1/P) \) of the \( ^5D_0 \)-excited state for mixtures with various molar ratios Eu(III)/ligand (\( \rho_{\text{ligand}} \)) are given in Table II. The lifetime measured for \( \rho_{\text{CMOS}} = 0.5 \) is the weighted average of a mixture of Eu(cmos) and Eu(cmos)\(^2\). Comparison of the values obtained at 298 K and 363 K shows that the lifetime is hardly dependent on the temperature. At \( \rho_{\text{CMOS}} = 0.2 \) the lifetime is 500 \( \mu s \) at 298 K. This value was used as an estimate of the lifetime of the Eu(cmos)\(^2\) complex at 298 K and 363 K. The lifetime of the Eu(cmos) complex is calculated from the lifetime at \( \rho_{\text{CMOS}} = 1.4 \) using the stability constants in Table I, to be around 180 \( \mu s \). At \( \rho_{\text{male}} = 0.5 \) a large increase of the \( ^5D_0 \) lifetime (56 \( \mu s \)) is observed when raising the temperature to 363 K, which is in contrast to the generally observed decrease in lifetime at elevated temperatures.\(^{27}\) A possible explanation is given by thermodynamic data, which show that the concentration of Eu(male)\(_n\) (\( n=1,2 \)) increases at higher temperatures.\(^{28}\) Unfortunately, the lifetime of the complexes at a ratio of Eu(III)/ga of 1/2 could not be measured due to their low solubility.

The data of Table II show that there is a general trend towards longer lifetimes upon increasing ligation of Eu(III) with organic ligands. This is accompanied by a shift to lower wavelength of the \( ^5D_0 \rightarrow ^7F_0 \) transition (see Figure 1). These phenomena can be explained by the decrease of the number of Eu(III) coordinated water ligands upon an increase of the number of Eu(III) coordinated organic ligands, which lowers the efficiency of the quenching of the \( ^5D_0 \)-excited state, whereas the increased negative charge in the first coordination sphere of the Eu(III) ion lowers the wavelength of the \( ^5D_0 \rightarrow ^7F_0 \) transition.\(^{11}\)

As a consequence, the 0-alkylation reaction with maleate can be monitored optimal by luminescence at a low molar ratio Eu/ligand, because in that case the increase of the lifetime of the \( ^5D_0 \)-excited state during the course of the reaction is relatively large. This is nicely demonstrated in Figure 2.
Table II. - The Lifetime of the $^{5}D_{0}$-Excited State for Various Eu(III)-Ligand Solutions. Excitation: 21522 cm$^{-1}$. Observation: 16244 cm$^{-1}$.

<table>
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<th>Ligand(L)</th>
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<th>pH</th>
<th>τ(μs)</th>
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<td>-</td>
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<tr>
<td>male,ga</td>
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<td>363</td>
<td>5.67</td>
<td>239$^b$</td>
</tr>
<tr>
<td>male,ga,cmos</td>
<td>1,1,1</td>
<td>363</td>
<td>6.03</td>
<td>296</td>
</tr>
</tbody>
</table>

0.2 M Eu(III). $^a$pH measured at the temperature indicated. $^b$Obtained by extrapolation of reaction (g) in Figure 5.

Figure 2. On-line measurements of the $^{5}D_{0}$ lifetime during the reaction at various molar ratios Eu(III)/ligand at 363 K. The labeling of the curves corresponds to the experiments described in Table III. Excitation 21522 cm$^{-1}$. Observation 16244 cm$^{-1}$.
At a high Eu(III)/(ga and male) ratio a small increase in lifetime is observed although the conversion to cmos is 81% after 3h (Figure 2, c). When a lower Eu(III)/(ga and male) ratio was used, a larger increase in lifetime is observed (Figure 2, a). This is probably due to the formation of higher concentrations of Eu(cmos)(L) (L=ga, male, or cmos), which is in agreement with the higher lifetime of the $^5D_0$-excited state compared to the lifetimes of the starting compounds and Eu(cmos) (Table II).

Previously, we have studied the kinetics of the O-alkylation reaction by means of HPLC, using an excess of ga with respect to Eu(III) and male. Under these conditions there is also a big effect on the lifetime of the $^5D_0$-excited state (Figure 3), demonstrating that this technique is very suitable for monitoring this reaction on-line. The lifetimes of the initial reaction mixtures were much higher than in experiments performed with a lower amount of ga.

Addition of extra ga to diluted samples of the starting solution (0.1 M Eu(III), reaction a) and final reaction mixtures showed increased lifetimes of 320 $\mu$s and 515 $\mu$s, respectively, at pH 6.7 and 363 K. This suggests that a shift of complex equilibria occurs to species with a higher number of coordinated ligands under these conditions.

The effect of the formation of cmos on the lifetime in both experiments is similar to that observed at a ratio of Eu/male/ga 1/2/2, which shows that the reaction can be monitored via the lifetime of the $^5D_0$-excited state at a large range of molar ratios male/ga.

Effect of the pH on the Lifetime of the $^5D_0$-Excited State.
Eu(III) coordinated di-ionized ga is a key intermediate in the O-alkylation reaction; and as a result the reaction rate is strongly dependent upon the pH of the reaction medium. Therefore, we also have investigated the influence of the pH on the lifetime for the initial and final reaction mixtures in the pH range where O-alkylation takes place. Since no reaction occurs at 298 K, at this temperature the influence of the pH was studied with the initial reaction mixture (Eu(III)/male/ga= 1/2/2) and with a reaction mixture, wherein 68% of cmos was present (reaction b, Table III). Figure 4 shows that for both reaction mixtures the $^5D_0$ lifetime increases gradually (10 $\mu$s per pH unit) up to pH 6.8 and 7.5, respectively, and then steeply increases (100 $\mu$s per pH unit).

The point at which the steep increase of the lifetime starts off corresponds with the pK$_{a1}$'s of coordinated H$_2$O and the coordinated hydroxyl
Figure 3. On-line measurements of the $^5D_0$ lifetime during the reaction using an excess of ga: 0.10 M Eu(III), 0.20 M male, and 1.0 M ga. Two reactions are monitored at 363 K having a difference in pH. The labeling of the curves corresponds to the experiments described in Table III. Excitation 21522 cm$^{-1}$. Observation 16244 cm$^{-1}$.

Figure 4. Dependence of the lifetime of the $^5D_0$-excited state on the pH of an initial and a final reaction mixture at 298 K. Initial reaction mixture (△): 0.20 M Eu(III), 0.41 M ga, and 0.40 M male. Final reaction mixture (●): 0.20 M Eu(III), 0.138 M ga, 0.128 M male, and 0.272 M cmos, obtained by heating the initial reaction mixture for 3 h at 363 K.
group of Ga\textsuperscript{29} and is probably caused by a decrease of the amount of OH oscillators in the first coordination sphere.\textsuperscript{30} This may be explained by the displacement of bound waters by the di-ionized glycolate (H\textsubscript{2}Ga) or by hydroxide ligands and by the formation of binuclear complexes. The sensitivity of the \textsuperscript{5}D\textsubscript{0}-excited state to the formation of OH\textsuperscript{-} and H\textsubscript{-}Ga ligands can be used to determine the optimal pH for a particular reaction mixture employed in the O-alkylation reaction.

The \textsuperscript{5}D\textsubscript{0}-\textsuperscript{7}F\textsubscript{0} transition shows a small increase in linewidth (17-22 cm\textsuperscript{-1}) going from low to high pH. For the reaction mixture, containing cmos, two broad peaks were observed at pH 8.8 having different lifetimes. This points to two different complexes that might be formed by disproportion of the Eu(III) complexes to Eu(cmos)\textsubscript{2}, and oligonuclear Eu(H\textsubscript{-}Ga)\textsubscript{n} or Eu(OH)\textsubscript{n} complexes. An analogous phenomenon was observed for the La(nitrilotriacetate) complex at high pH with the use of \textsuperscript{139}La NMR.\textsuperscript{9}

On-Line Study of the Reaction by the \textsuperscript{5}D\textsubscript{0} Lifetime: Effect of the pH.

In the previous paragraph it is shown that the effect of the pH on the lifetime during the reaction is small when the O-alkylations are performed below the pH of the transition-point of the initial reaction mixture (pH 6.7, 298 K) (Figure 4). This transition point can vary with temperature. When the O-alkylations were performed below pH 6.10 (363 K), only small variations of the lifetime as a function of the pH of the initial reaction mixture (30 \mu s per pH unit) were observed. Therefore, the increase in lifetime of the \textsuperscript{5}D\textsubscript{0}-excited state of the Eu(III) ion upon progress of the reaction is mainly due to the increased amount of cmos in the speciation (Figure 5). This, probably, also holds for the previously described experiments performed at various molar ratios Eu/ligands.

The Amount of Eu(III) Coordinated Waters as Measure for the Amount of Cmos Formed.

As already straightened out, the on-line monitoring of the reaction by the \textsuperscript{5}D\textsubscript{0}-excited state is most useful to follow the progress of the reaction. To be able to quantify the cmos formed using these lifetime measurements, the difference in lifetimes of the \textsuperscript{5}D\textsubscript{0}-excited state of final and initial reaction mixtures were compared to the amount of cmos formed as determined by HPLC.

The observed decay probability P per species in aqueous solution is commonly described by the sum of a purely radiative part P\textsubscript{rad} and a non-
Figure 5. On-line measurements of the $^5D_0$ lifetime during the reaction at slightly different pH values in the pH range from 6.1 to 5.7. A reaction mixture with a ratio Eu/male/ga of 1/2/2 was heated at 363 K ((b), (e), (f), (g)) or at 343 K ((h), (i)). Evolution of the lifetime as a function of time of a Eu/cmos mixture at 363 K (d). The labeling of the curves corresponds to the experiments described in Table III. Excitation 21522 cm$^{-1}$. Observation 16244 cm$^{-1}$.

The radiative part. The latter can be separated into coupling with OH vibrators, $P_{OH}$, and coupling with all other non-radiative pathways $P_{nr}$. Upon coordination of the aquo ion of Eu(III) by the ligands used in this study, a number of Eu..H$_2$O bonds in the first coordination sphere are replaced by Eu..COO$^-$ bonds. So, Pav of the $^5D_0$-excited state may be expressed by:

$$Pav = \sum_i \left( \left( P_{rad} + P_{nr} + n_{OH} + n_{COO} \right) i \right)$$  \hspace{1cm} (1)

When Pav is altered e.g. by the formation of cmos, the change of the decay probability can be expressed by equation 2.

$$\Delta Pav = \sum_i \left( \Delta P_{rad} + \Delta P_{nr} \right) i + \Delta OH \cdot (P_{OH} + P_{COO})$$  \hspace{1cm} (2)

In this equation $\Delta OH = \Delta (\sum_i n_{OH})(i) = -\Delta (\sum_i n_{COO})(i)$ is the variation of the average number of OH oscillators per Eu(III). If it is assumed that the variations in lifetime observed during the reaction are only dependent on
the change of OH oscillators one neglects \((\Delta P_{\text{rad}} + \Delta P_{\text{nr}})\) e.g. other factors contributing to the decay of the \(^5D_0\)-excited state. Using this simplification one can write equation 3 for the difference of the decay probability between the starting and final composition:

\[
P_{\text{av initial}} - P_{\text{av final}} = \Delta \text{OH} \cdot (P_{\text{OH}} - P_{\text{COO}})
\]  

(3)

An estimation of \((P_{\text{OH}} - P_{\text{COO}})\) may be obtained from the decay probability for the \(\text{Eu(H}_2\text{O})_9\) species, and the \(\text{Eu doped (Gd}_2\text{(H}_2\text{O})_6(\text{oxalate})_3\cdot4\text{H}_2\text{O}}\) complex in which each \(\text{Eu(III)}\) is coordinated to 3 \(\text{H}_2\text{O}\) and 6 carboxylate groups.\(^{32}\) A \((P_{\text{OH}} - P_{\text{COO}})\) value of 0.45 ms\(^{-1}\) per OH vibrator is obtained. About the same value is found using the lifetimes of the \(\text{Eu(H}_2\text{O})_9\), \(\text{Eu(cmso)}\cdot5\text{H}_2\text{O}\), and \(\text{Eu(cmso)}\cdot2\cdot1\text{H}_2\text{O}\) complexes in solution at 298 K (see above). From the \(r\) values of 105, 180, and 500 \(\mu\)s, respectively, a \((P_{\text{OH}} - P_{\text{COO}})\) = 0.44±0.3 ms\(^{-1}\) can be calculated. A decay probability of the \(^5D_0\) by coupling with an OH vibrator is estimated to be 0.5 ms\(^{-1}\) by measuring the lifetimes of the \(^5D_0\)-excited state as function of the amount of water in acetonitrile.\(^{33}\) These values are in reasonable agreement with each other and show that coupling with the carboxylate group is a very inefficient non-radiative pathway. For the numerical estimation of the variation in coordinated water during the reaction \(\Delta \text{OH}\), the average value of 0.45 ms\(^{-1}\) was used at 363 K, thereby neglecting the temperature effect. In Table (III) the calculated values of \(\Delta \text{OH}\) for the reactions (a)-(c), (e)-(k) are given. The variation of the coordinated OH oscillators is within a small range of 2-3 OH oscillators. Performing the reaction in \(\text{D}_2\text{O}\) enables one to calculate the number of coordinated water ligands for the initial and final reaction mixture by the empirical relation used by Horrocks.\(^{10}\)

\[
q=1.05(P_{\text{av H}_2\text{O}} - P_{\text{av D}_2\text{O}})
\]  

(4)

This gives a number of 6.4 for the initial reaction mixture and 4 for the final one, resulting in a \(\Delta \text{OH}\) of 2.4. This value is within the range found by the other method of calculation using eq. 3 for reaction a.

The \(\Delta \text{OH}\) values calculated for the final and initial reaction mixture are plotted against the amount of cmso formed per amount of \(\text{Eu(III)}\) ion \((1/\rho_{\text{cmso}})\), wherein the amount of cmso formed is determined by HPLC (Figure 6).
**Table III.** Reaction Conditions, Amount of Cmos Formed and Calculated Amount of OH Oscillators for the Reaction Mixtures Formed.

<table>
<thead>
<tr>
<th>initial reaction mixtures [Eu],[male],[ga] (M)</th>
<th>pH-range</th>
<th>cmos conc. (M)</th>
<th>$P_i$ (ms$^{-1}$)</th>
<th>$P_f$ (ms$^{-1}$)</th>
<th>$\Delta$OH$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 0.200, 0.534, 0.547</td>
<td>6.24-6.09</td>
<td>0.276</td>
<td>3.69</td>
<td>2.39</td>
<td>2.9</td>
</tr>
<tr>
<td>(b) 0.200, 0.400, 0.410</td>
<td>6.01-5.97</td>
<td>0.272</td>
<td>3.97</td>
<td>2.73</td>
<td>2.7</td>
</tr>
<tr>
<td>(c) 0.200, 0.267, 0.267</td>
<td>5.31-5.01</td>
<td>0.216</td>
<td>4.72</td>
<td>3.80</td>
<td>2.1</td>
</tr>
<tr>
<td>(d)$^a$</td>
<td>6.15</td>
<td>0.397</td>
<td>2.30</td>
<td>2.42</td>
<td>0.3</td>
</tr>
<tr>
<td>(e) 0.200, 0.400, 0.410</td>
<td>6.07-6.17</td>
<td>0.282</td>
<td>3.97</td>
<td>2.70</td>
<td>2.8</td>
</tr>
<tr>
<td>(f) 0.200, 0.400, 0.410</td>
<td>5.85-5.72</td>
<td>0.258</td>
<td>4.10</td>
<td>2.94</td>
<td>2.6</td>
</tr>
<tr>
<td>(g) 0.200, 0.400, 0.410</td>
<td>5.67-5.43</td>
<td>0.238</td>
<td>4.18</td>
<td>3.05</td>
<td>2.5</td>
</tr>
<tr>
<td>(h) 0.200, 0.400, 0.410</td>
<td>6.15-6.04$^f$</td>
<td>0.198</td>
<td>4.12</td>
<td>3.20</td>
<td>2.1</td>
</tr>
<tr>
<td>(i) 0.200, 0.400, 0.410</td>
<td>5.69-5.62$^f$</td>
<td>0.134</td>
<td>4.27</td>
<td>3.72</td>
<td>1.2</td>
</tr>
<tr>
<td>(j) 0.100, 0.200, 1.00</td>
<td>6.07-7.64</td>
<td>0.160</td>
<td>3.32</td>
<td>2.02</td>
<td>2.9</td>
</tr>
<tr>
<td>(k) 0.100, 0.200, 1.00</td>
<td>6.29-6.00</td>
<td>0.076</td>
<td>3.61</td>
<td>2.84</td>
<td>1.7</td>
</tr>
<tr>
<td>(l)$^g$ 0.200, 0.500, 0.510</td>
<td>6.58-7.14</td>
<td>0.281</td>
<td>0.67</td>
<td>0.50</td>
<td></td>
</tr>
</tbody>
</table>

$^a$[Eu],[cmos]= 0.2, 0.398 M. $^b$pH of the initial and final reaction mixture as measured at the reaction temperature (363 K). $^c$Concentration of cmos formed in final reaction mixture as determined by HPLC. $^d$Decay probability for initial ($P_i$) and final ($P_f$) reaction mixture. $^e$Variation of the concentration of OH oscillators in the first coordination sphere per Eu(III) in initial and in final reaction mixture as calculated by equation (3) with $\left( P_{OH} - P_{COO} \right) = 0.45$ ms$^{-1}$. $^f$Reaction at 343 K. $^g$Reaction in D$_2$O at 363 K.

A linear relation is obtained with a coefficient of 0.5. Apparently, an average of two OH oscillators are removed from the first coordination sphere when in a Eu(III)-ga-male mixed ligand system one male and ga are converted into one cmos per Eu ion. Both water and coordinated hydroxyl groups of alcohols are efficient quenchers of the $^5$D$_0$-excited state. The decrease of two OH oscillators might originate from a water ligand that is released from the Eu(III) ion. However, an additional contribution of the coordinated hydroxyl group of ga, which is converted into a coordinated ether oxygen of cmos or which is released from the Eu(III) ion, is expected.
Figure 6. Plot of the calculated change of the amount of water ligands in the first coordination sphere of Eu(III) as a function of the amount of cmos formed for reactions (a)-(c) and (e)-(k) (●), as given in Table III.

The plot in Figure 6 can be used to determine the concentration of cmos in a reaction mixture from the $^5D_0$ lifetime, which is, evidently, a rather good method to monitor this reaction at its reaction temperature. In general, one may add that the luminescence-optical fiber setup cannot only be applied to this particular reaction, but also to the study of, for instance, the kinetics of the coordination of ligands to Eu(III), if the reaction is slow enough. The increase in lifetime of the $^5D_0$-excited state and the $^5D_0-^7F_0$ transition provide the tools for studying these reactions by luminescence.

Conclusions

It has been demonstrated that the luminescence-optical fiber setup can be used to study reactions on-line in which fluorescent rare earth ions are involved. This has been done for the Eu(III) catalyzed 0-alkylation of ga with male at 363 K and 343 K by continuously monitoring the lifetime of the $^5D_0$ emitting level. It can be concluded that the conversion of male and ga to cmos decreases the average number of OH oscillators by two in the Eu(III) coordination sphere if one cmos per Eu(III) is formed, which is translated into a higher lifetime of the $^5D_0$-excited state. Moreover, a linear relation was established between the observed variation in lifetime and the amount of cmos formed, which enables one to calculate the amount of cmos formed at
the reaction temperature based on the lifetime of the $^5D_0$ emission of the reaction mixture.

References
8. This thesis Chapter V.
9. This thesis Chapter III.
24. This thesis Chapter VIII.
29. The pKₐ for the ionization of a coordinated ga ligand in the Eu(male)(ga)ₙ ternary complexes is calculated to be 7.8 (363 K) and the pKₐ of a coordinated water is 8.3 (I=0.3, 298 K).
CHAPTER V.

O-ALKYULATION OF POLYOLS WITH MALEATE HOMogeneously CATALYZed BY MULTIVALENT METAL IONS.*

Abstract: A Michael-type addition reaction of polyhydroxyl compounds to maleate, homogeneously catalyzed 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. With small ions with a high charge density, such as Ti(IV) and Al(III), mono O-alkyl dicarboxylates are obtained exclusively, whereas metal ions with a large ionic radius give rise to higher O-alkylated polyhydroxyl compounds. The formation of the latter products can be enhanced by the use of stoichiometric amounts of catalyst. The reactions are performed in the polyol as solvent, whenever possible. With solid polyols some water is used as co-solvent. Large amounts of water interfere in the first O-alkylation step, but not in subsequent steps.

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. 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, the borate-glucarate system, in which two sugar acid entities are linked via borate generating an improved cation coordination site, and several low molecular weight carboxylate containing chelators. The latter category includes trisodium carboxymethoxysuccinate (3), which is formed by the O-alkylation of glycolate (1) with maleate (2) promoted by a

twofold excess of calcium hydroxide. This reaction is an interesting pathway towards some other oxygen containing ligands.

Recently, the homogeneous La(III) catalyzed O-alkylation reaction of 1 with 2 has shown to be a convenient way to synthesize 3 (Scheme I). A mechanistic study of this La(III)-catalyzed 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 ionization of the α-hydroxyl group of 1. Product inhibition occurs because of the relatively high stabilities of the La(III) complexes of the product 3, and, in practice, limits the formation of 3 to two molecules per La(III) ion present, which corresponds to the maximum number of coordinated 3 ligands for the La(III) ion. The Ca(II) sequestering ability of 3 is moderate compared to sodium triphosphate, but might be sufficient for combined use with zeolite NaA.

\[
\begin{align*}
\text{OOCCH}_2\text{OH} & \quad + \quad \text{OCOCCH}_2\text{OH} \\
\text{La}^{3+}, \text{pH}>6 & \quad \rightarrow & \quad \text{OOCCH}_2\text{OCH}_2\text{COO}^- \\
\text{Aqueous, } 363 \text{ K} & 
\end{align*}
\]

Scheme I

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

In this paper the La(III) catalyzed 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,0'-alkyl products are obtained. Obviously, a consecutive reaction can occur in which the second hydroxyl group of the polyol is O-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 O-alkylation reaction are studied in some detail. The 
synthesized compounds have been tested for their Ca(II) sequestering 
properties.

**Experimental Part**

**Equipment and Compounds.**

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 µl) were taken from the reaction mixture. The reactions were 
quenched by adding 1.0 M trifluoroacetic acid (500 µl). The products were 
characterized by ¹H and ¹³C 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 (¹³C 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. Ionization 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 xylene 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 AG1-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 Koiné.20 (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 AG1-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 analyzed 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 lyophilized. 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 LaCl₃·2.3H₂O. 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 La₂(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 (D₂O) mixture of *racemic* (RR/SS) and *meso* (RS) δ(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-diaceitic acid and PrCl₃·7.2H₂O 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 D₂O, 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 PrCl₃·7.2H₂O 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 [(hydroxyethylenedioxy)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), Li₂maleate (5.116 g, 35 mmol), and 
LaCl₃·7.1 H₂O (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: ¹³C NMR (D₂O) 
δ(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: ¹³C NMR (D₂O) 1/1 mixture of meso and 
racemic δ(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), Li₂maleate (5.116 g, 35 mmol), and LaCl₃·7.1 
H₂O (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: ¹³C NMR (D₂O) mixture of racemic and meso 
δ(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: ¹³C NMR 
(D₂O) δ(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 ¹³C 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 Li₂maleate (4.320 g, 30 mmol) and LaCl₃·7.1 H₂O (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.
Disodium (meso)-erythritol 1-butanedioate ether (15) and (meso)-erythritol 2-butanedioate ether (16).

AlCl₃·6H₂O (0.247 g, 1.02 mmol) was added to an aqueous solution of 2 M Li₂malate (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 H₂O/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 (D₂O) δ(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 (D₂O) mixture of RRS/SSR and RSR/SRS δ(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 (D₂O) mixture of RRRR and SRRR δ(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 (D₂O) mixture of RRRR and SRRR δ(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$_2$O) mixture of RRRR and SRRR δ(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 Li$_2$maleate.H$_2$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 analyzed with HPLC.

**Disodium Salt of 5a Catalyzed by Ti(OiPr)$_4$.**

Na$_2$maleate (16.0 g, 100 mmol) was dissolved in ethylene glycol (50 ml). The solution was heated under stirring at 363 K. Ti(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 La(III) Catalyzed 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 LaCl$_3$·7H$_2$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 LaCl$_3$·7H$_2$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$_2$SO$_4$ in vacuo yielding pure Na$_3$La$_2$OH(6a)$_2$(H$_2$O)$_2$ (26.5 g, 27.0 mmol, 84%). Anal. Calcd. for C$_{20}$H$_{15}$O$_{23}$La$_2$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^{-6} 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 10^{-3} M, I=0.02, at 298 K) with 2 minutes interval. The \( \log K_{Ca} \) were calculated according to \( \tilde{n}_{Ca}/(1-\tilde{n}_{Ca}) = K_{Ca}[Ca]^{21} \) in which \( K_{Ca} = [CaL]/([Ca][L]) \) and \( \tilde{n}_{Ca} \) 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-0- and di-0,0'-alkyl products, respectively, which seems to be in agreement with the presence of 1/1 complexes.

**Results and Discussion**

**La(III) Promoted O-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 ionization of ethylene glycol by addition of sodium, the reaction remained sluggish (Table I). In the presence of 3 mol\% of LaCl_3.7H_2O (relative to 2), however, a dramatic improvement of the reaction rate was obtained. Now both the mono-O- (5a) and the di-0,0'-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.

We assume that the mechanism of this reaction is analogous to that of the previously studied O-alkylation of glycolate (1) with 2 (Scheme I). Thus the rate determining step is most likely a nucleophilic attack of a coordinated alcohoholate 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. 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.

The La(III) catalyzed 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-O- and di-O,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.
Figure 1A and 1B. The formation of mono-O- and di-O,0'-alkyl products (5a and 6a) by O-alkylation of ethylene glycol (4a) with Li\textsubscript{2}maleate (2, 17.5 mmol) catalyzed by LaCl\textsubscript{3} in 15 ml ethylene glycol at 363 K. Fig. 1A: conversion of 2 using 0.5 mmol LaCl\textsubscript{3}(A) and 12.6 mmol LaCl\textsubscript{3}(A), 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).

The reaction can be directed towards the di-O,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) catalyzed O-alkylation of diethylene glycol (4b) with 2 is in many respects analogous (Figure 2), yielding mono-O- and di-O,0'-alkyl products (5b, 6b respectively). 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 ionized hydroxyl groups coordinated per La(III) ion. Once again increase of the amount of La(III) favored the formation of the di-O,0'-alkyl product (6b).\textsuperscript{23} No diastereomeric preference was observed in this case.
Figure 2. The formation of mono-O- and di-O,0'-alkyl products 5b (○) and 6b (△) by O-alkylation of diethylene glycol (4b, 30 ml) with Li$_2$maleate (2, 30 mmol, △) catalyzed by LaCl$_3$ (1 mmol) in 4b at 363 K.

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

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{CHOH} & \quad \text{CH}_2\text{OH} \\
& \quad 2, \text{La}^{3+} \quad \rightarrow \quad \text{C}^1\text{H}_2\text{OR} & \quad \text{C}^1\text{H}_2\text{OH} & \quad \text{C}^1\text{H}_2\text{OR} & \quad \text{C}^1\text{H}_2\text{OH} \\
& \quad \text{363 K} \quad & \quad \text{C}^2\text{HOH} & \quad \text{C}^2\text{HOR} & \quad \text{C}^2\text{HOR}' & \quad \text{C}^2\text{HOH} \\
& \quad 7 \quad & \quad \text{C}^3\text{H}_2\text{OH} & \quad \text{C}^3\text{H}_2\text{OH} & \quad \text{C}^3\text{H}_2\text{OH} & \quad \text{C}^3\text{H}_2\text{OR}' \\
& \quad & \quad 8 & \quad 9 & \quad 10 & \quad 11
\end{align*}
\]

\[
\begin{align*}
R = -\text{C}^2'\text{HCl}^1'\text{OO}^- & \quad R' = -\text{C}^2''\text{HCl}^1''\text{OO}^- \\
\text{C}^3''\text{H}_2\text{C}^4'\text{OO}^- & \quad \text{C}^3''\text{H}_2\text{C}^4''\text{OO}^-
\end{align*}
\]

Scheme III
With 3 mol% La(III) as the catalyst, the ratio of 1-O-(8) and 2-O-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), 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. 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.

Figure 3. The formation of mono-0- and di-0,0'-alkyl products by O-alkylation of glycerol (7, 30 ml) with Li₂maleate (2, 30 mmol, Δ) catalyzed by LaCl₃ (1 mmol) in 7 at 363 K. 8 (○), 9 (□), and a mixture of 10 and 11 (◇).

The Effect of the Choice of the Metal Ion on the Rate and the Selectivity of the O-Alkylation of Ethylene Glycol (4a) with Maleate (2).

The effect of various metal ions on the course of the O-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.

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,0'-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 0-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 $pK_a$ 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)\(^{25}\) 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.\(^{22}\) The former increase with decreasing ionic radius, whereas those of the more bulky 6a decrease in that order.

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 ionization of Ti(IV) coordinated ethylene glycol by virtue of the higher basicity of isoproxide 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.)\(^{26}\) of the metal ion used as catalyst. This supports the idea that the extent of ionization 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)\(^{28}\) 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
Table I. The Influence of Various Metal Ions on the O-Alkylation of 4a by 2 at 363 K.\textsuperscript{a}

<table>
<thead>
<tr>
<th>M\textsuperscript{ii}⁺</th>
<th>Conversion of maleate (2) after 33 h (%)</th>
<th>Molar ratio 5a/6a</th>
<th>Conversion of maleate (2) after 33 h (%)</th>
<th>Molar ratio 5a/6a</th>
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<td>-</td>
<td>4</td>
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<td>Cu(II)\textsuperscript{c}</td>
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<td>20.8</td>
<td>Ti(OiPr)\textsubscript{4}</td>
<td>94</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Li\textsubscript{2}maleate (17.5 mmol) was added to a solution of metal chloride (0.5 mmol) dissolved in 4a (15 ml) (Ref. 27). \textsuperscript{b}RO⁻ = sodium 2-hydroxyethanolate (ref. 25), formed by dissolving sodium (Na(O)). The disodium salt of 2 was used. \textsuperscript{c}Color 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). \textsuperscript{d}A white precipitate was present during the reaction.

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)\textsubscript{2}(2) ternary complex\textsuperscript{29} show that in an octahedral rearrangement of the ligands around the transition metal ion, the ionized hydroxyl group of 4a or 5a is located in an ideal position for attack on the olefinic bond of 2 (Scheme IV).
Figure 4. Left: The molar ratio 5a/6a after 33 hrs of reaction as a function of the Ln(III) ion used (●). Right: Initial rate of the conversion of 2 as a function of the Ln(III) ion used as catalyst (■). Conditions: see Table I.

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), except for Cu(II). An analogous behavior is observed for the third stability constants of transition metal ion-ethylenediamine complexes. 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.
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.

The Effect of the Water on La(III) Promoted O-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) catalyzed 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, which slowly dissolved over 48 h. HPLC and $^{13}$C 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.
Synthesis of Di-O,0'-alkyl Tetracarboxylates by a Two-Step Synthesis Using Two Different Metal Ions.

In the synthesis of the di-O,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-O,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), TiO₂ was filtered off. Optimal results were obtained with a molar ratio of La/5a/2 of 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 polyhydroxyl compound with two different α,β-unsaturated dicarboxylates.
Extension of the Scope of the 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-0-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 aluminat esters of polyols is very likely. Some water addition to 2 had also occurred (< 7%).

Performing the reaction at this pH with meso-erythritol (14) resulted in the formation of the 1-0-alkyl product (15, 16%) and the 2-0-alkyl product (16, 4%) (Scheme VI). Mannitol (17) resulted in the formation of all possible mono-0-alkyl compounds, in which the 1-0-alkyl compound (18) was more abundant than both the 2-0- and 3-0-alkyl compounds (19 and 20, respectively) (Scheme VI). Of the latter two components, the 3-0-alkylated compound was predominant. Probably, as a result of steric effects, a rather high selectivity for 0-alkylation of the terminal positions exists.

![Figure 6](image-url)

**Figure 6.** The formation of the mono-0-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.
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.

The values of logK\textsubscript{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 catalyzed 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,0′-alkyl products can be prepared in a
Table II. Stability Constants of Ca(II) Complexes.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>LogK\textsubscript{Ca}^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>2.4</td>
</tr>
<tr>
<td>6a</td>
<td>5.1</td>
</tr>
<tr>
<td>5b</td>
<td>2.7</td>
</tr>
<tr>
<td>6b</td>
<td>5.2</td>
</tr>
<tr>
<td>8</td>
<td>2.4</td>
</tr>
<tr>
<td>9</td>
<td>2.3</td>
</tr>
<tr>
<td>10/11\textsuperscript{c}</td>
<td>4.4</td>
</tr>
<tr>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>13</td>
<td>5.8\textsuperscript{b}</td>
</tr>
<tr>
<td>12</td>
<td>2.66\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\( I=0.02, 298 \text{ K, pH 10 (Ref. 34).} \) \( b \text{ Ref. 7.} \) \( c \text{ Predominately 11.} \) \( d \text{ I=0, 298 K (Ref. 35).} \)

High yield by a second 0-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-0,0'-alkyl products.

Acknowledgement

This investigation was carried out under the auspices of the Netherlands Foundation for Chemical Research (S.O.N.) with support from the Netherlands Organization for Scientific Research (N.W.O.).

References

16. This thesis Chapter 11.
22. This thesis Chapter VI.
23. 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 catalyze the O-alkylation of 4b (30 ml) at 363 K.
24. 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.
25. Hydroxyethanolate is the conjugated base of ethylene glycol.
27. 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.
28. Co\(^{2+}\)(Coordination number (CN) 6: 88.5 pm), Ni\(^{2+}\)(CN 6: 83), Zn\(^{2+}\)(CN 6: 88 pm).
32. pH of the initial reaction mixture measured at room temperature.
33. 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.
CHAPTER VI.

METAL ION CATALYZED 0-ALKYLATION OF ETHYLENE GLYCOL WITH MALEATE. A MULTINUCLEAR NMR STUDY OF THE LANTHANIDE(III) COMPLEXES PRESENT IN THE REACTION MIXTURE OF THE LANTHANIDE(III) CATALYZED REACTION.*

Abstract: The structures and stabilities of Ln(III) complexes occurring in the reaction mixture of a Ln(III) catalyzed 0-alkylation of ethylene glycol with maleate have been investigated with the use of $^{139}$La, $^{17}$O, and $^{13}$C NMR shift and relaxation measurements and with potentiometry. In ethylene glycol the Ln(III) ion appears to be coordinated by 9 oxygen atoms of that compound. The chloride anion is not present in the first coordination sphere of the Ln(III) ion. The Ln(III) ions have some preference for coordination of ethylene glycol over that of water. Maleate is able to coordinate with the Ln(III) ions in ethylene glycol medium. The mono-0-alkylation product of ethylene glycol forms 1:1 and 1:2 complexes with the Ln(III) ions, in which the ligand is bound in a tetradeinate fashion via the two carboxylate groups and the two oxygens of the ethylene glycol residue. The Ln(III) coordination of the di-0,0'-alkylation product is analogous, all carboxylate groups and ether oxygens are coordinated.

Introduction

Polyfunctional carboxylates containing an $\alpha$-(hydr)oxy function are known to be good sequestering agents for metal ions.¹ Using a retro-synthetic approach, precursors for these compounds can be proposed, that are still reasonably good metal ion chelators. Metal ions may then be able to catalyze the concerning reactions, for example by functioning as a template.

Recently, we have reported on a metal ion catalyzed 0-alkylation reaction of di- and polyhydroxy compounds with maleate.² For instance, 0-alkylation of ethylene glycol (1) with maleate (2), in the presence of multivalent metal cations as catalyst, yields 2-hydroxyethoxybutanedioate (3). In a consecutive reaction step another 0-alkylation with maleate can occur to

give ethylenedioxydibutane dioate (4, Scheme I). Preferably, ethylene glycol is used as the solvent. The function of the metal ion is probably that of a template, and, in addition, it may activate a hydroxyl group of 1 and of 3 via ionization upon coordination.

\[
\begin{align*}
\text{HO} - \text{CH}_2 - \text{CH}_2 - \text{OH} + & \quad \text{HO} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{CH} - \overset{\text{M}^{n+}}{\longrightarrow} \quad \text{HO} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{CH} \\
\text{1} & \quad \text{2} & \quad \text{3} \\
\text{COO} - \quad & \quad \text{COO} - \quad & \quad \text{COO} - \\
\overset{\text{1'}}{\text{H}} & \quad \overset{\text{6'}}{\text{H}} & \quad \overset{\text{2'}}{\text{H}} \\
\text{4} & \quad \text{C} & \quad \text{C} \\
\text{COO} - \quad & \quad \text{COO} - \quad & \quad \text{COO} - \\
\overset{\text{1''}}{\text{H}} & \quad \overset{\text{6''}}{\text{H}} & \quad \overset{\text{2''}}{\text{H}} \\
\text{2} & \quad \text{3} & \quad \text{4} \\
\end{align*}
\]

Scheme I

It appears that the extent to which the consecutive reaction (3 → 4) takes place, is strongly dependent upon the nature of the metal ion. Metal ions with large ionic radii and high coordination number (e.g. La(III)) or metal ions that form complexes with the reactants in a favorable geometry for O-alkylation (e.g. Ni(II)) give rise to relatively much di-O,0'-alkylation whereas application of small cations with relatively low coordination number (such as Ti(IV) and Al(III)) results in almost exclusively mono-O-alkylation.

This paper reports on the characterization of the metal ion complexes, that are present in the reaction mixture of the lanthanide(III) catalyzed O-alkylation reaction of ethylene glycol (1) with maleate (2), using multinuclear NMR spectroscopy and potentiometry.

The valence electrons of the Ln(III) ions are in the 4f orbital, which is effectively shielded by the outer 5s and 5p orbitals. Consequently, ligand field stabilization is small and the bond between these ions and ligands are predominantly of an electrostatic nature. The geometry of complexes is therefore determined by the steric requirements of the ligands rather than by electronic interactions. Usually, complexes of the various Ln(III) ions
with a particular ligand are isostructural, and often are similar to the corresponding complexes with alkaline earth ions. The ions La(III) and Lu(III) have noble gas configuration and are diamagnetic, whereas the other Ln(III) ions have 1-7 unpaired 4f electrons and are paramagnetic. As a consequence the differences among these ions with regard to NMR spectroscopic properties are quite large, which is useful in the structural analysis of Ln(III) complexes and which makes the Ln(III) ions attractive NMR probes for 'NMR silent' metal ions, such as Ca(II).

Experimental Part

Materials.

Perchlorate solutions of the lanthanides were prepared by dissolution of the reagent grade oxides into perchloric acid. The lanthanide content was determined by titration with EDTA using xylene orange as the indicator. The lanthanide chlorides were obtained from Alfa products. 170 enriched water was purchased from Rohstoff-Einfuhr, Dusseldorf. 2-Hydroxyethoxybutanedioate (3) and ethylenedioxybutanedioate (4) were prepared as described previously. 170-enrichment of the carboxylate groups of 2 and 3 was achieved by heating a solution of the concerning acid in 170-enriched water at 363 K following the procedure described previously for other carboxylates.

NMR Measurements.

The 139La and 35Cl NMR spectra were recorded with a Nicolet NT-200 WB spectrometer at 28.3 and 19.6 MHz, respectively, using 12 mm sample tubes. The chemical shifts were determined with respect to a 0.1 M solution of LaCl3 in D2O as external standard. The chemical shifts and the line-widths were determined by fitting the experimental peaks with Lorentzian curves. The 170 NMR spectra were recorded with a Nicolet NT-200 WB or with a Varian VX-400 S spectrometer at 27.3 and 54.2 MHz, respectively. The deuterium signal of D2O was used for internal lock, when possible. The Dy(III)-induced shifts of samples in ethylene glycol as the single solvent were measured with a coaxial inner tube with acetone-d6 for internal lock. The 170 signal of acetone was then used as standard for the chemical shifts. Chemical shifts obtained in these measurements were corrected for bulk magnetic susceptibility effects.

All 1H and 13C NMR measurements were measured with the Varian VX-400 S
spectrometer at 100.1 MHz. The methyl group of t-BuOH was used as internal standard (1.2 and 31.2 ppm for $^1$H and $^{13}$C NMR, respectively). Longitudinal relaxation times were measured with the use of an $[(90^\circ_x, 180^\circ_y, 90^\circ_x, \gamma - 90^\circ_x \text{-acq}]]$ inversion recovery pulse sequence. The relaxation times were calculated using a three parameter fit of the experimental data.$^9$ Some of the $^{13}$C NMR signals of 4 almost coincided. In these cases a deconvolution program was used for the determination of the peak intensities.

The pH of the samples was determined with a calibrated MI 412 micro-combination from Microelectrodes Inc. The pH values quoted are direct pH meter readings, no correction was made for the presence of deuterium.

**Viscosity Measurements.**

The viscosities of the solutions of LaCl$_3$ in ethylene glycol-water mixtures were determined with the use of an Ubbelohde viscometer.

**Potentiometry.**

All potentiometric measurements were performed as described previously.$^{10}$ The pK$_a$'s of compound 3 (I = 1.0 M NaClO$_4$) were determined in duplo by titrating a NaOH solution (0.04 M) to the solution of diprotonated 3 (0.002 M), which was obtained by passing the disodium salt through a Dowex 50 W (H$^+$) cation exchange column. For the determination of the pK$_a$'s of compound 4, a solution of the tetraprotonated 4 (0.0036 M) and NaOH (0.145 M) were used. The stabilities of the 1:1 and 1:2 complexes of 3 were determined by a titration of a solution containing ligand 3 (0.03 M) and 0.015 M H$^+$ to a Ln(ClO$_4$)$_3$ solution at I = 1.0 M NaClO$_4$. For the determination of $\beta_{101}$ of 4 a ligand solution containing 0.02 M 4 and 0.01 M H$^+$ was used. The computation of the stability constants from the titration data obtained were performed using the BASIC computer program described in Chapter III.

**Results and Discussion**

**Solvation of LnCl$_3$ in Ethylene Glycol (1).**

The O-alkylation reactions of ethylene glycol (1) with maleate (2) mentioned above were performed in the former compound as solvent and with the hydrated lanthanide chlorides as catalyst.$^2$ It is well known that in dilute aqueous solutions of LnCl$_3$ ($< 1$ M) the Ln(III) ion is completely solvated with water and that Cl$^-$ counterions are not in the inner coordination sphere.$^{11-15}$ It has been reported that in organic solvents,
such as methanol, acetonitrile, and N,N-dimethylformamide, Cl⁻ forms inner sphere complexes with Ln(III) ions. Therefore, first the solvation of the Ln(III) ions in ethylene glycol (1) was investigated by $^{139}$La, $^{35}$Cl, and $^{17}$O NMR.

In Figure 1, the $^{139}$La and $^{35}$Cl chemical shifts and line widths are plotted of 0.1 M solutions of LaCl₃ in D₂O-1 mixtures. The $^{35}$Cl chemical shift increases slightly going from D₂O to 1. The increase is, however, much smaller than that observed upon replacement of water by methanol (180 ppm). Therefore, it can be concluded that in 1, the inner sphere

![Graph showing linewidth/viscosity ratios and chemical shifts of $^{139}$La and $^{35}$Cl versus % ethylene glycol (v/v) in ethylene glycol-D₂O solutions containing 0.1 M LaCl₃ at 350 K. The viscosities were 0.386, 0.552, 0.827, 1.240, 1.989, and 3.226 cSt for 0, 20, 40, 60, 80, and 100% ethylene glycol, resp.](image-url)
coordination of La(III) by Cl\(^-\) is of minor importance. This is confirmed by the \(^{139}\)La chemical shifts. For coordination of each Cl\(^-\) ion to La(III) an induced shift of 100 ppm has to be expected.\(^{14,17}\) Upon increasing the ratio 1/D\(_2\)O in the system, the \(^{139}\)La chemical shifts, initially show a slight increase (Figure 1), but when the amount of 1 becomes larger than 70\% (v/v), the \(^{139}\)La chemical shift declines until it reaches a value of -19 ppm in pure 1. This has to be ascribed to coordination of La(III) by 1. The rather small effect on the \(^{139}\)La chemical shift of substitution of a D\(_2\)O oxygen in the first coordination sphere of La(III) by an oxygen of 1 indicates that, under the conditions applied, the ionization of the hydroxy group of coordinated 1 is probably negligible; for negatively charged oxygens a high-frequency shift of about 30 ppm per oxygen should be expected.\(^{5,18,19}\)

The \(^{139}\)La and \(^{35}\)Cl line widths (Figure 1) are also indicative for the absence of inner sphere complexes between La(III) and Cl\(^-\). The line widths of signals for those nuclei are governed by the quadrupolar relaxation. The spin-spin quadrupolar relaxation rate is related to an asymmetry parameter \(\eta\) and to the molecular reorientational correlation time \(\tau_c\) under extreme narrowing conditions \((\omega_0^2\tau_c^2 \ll 1)\).\(^{20}\) The latter can be estimated by the Debye-Stokes-Einstein equation (1), if it is assumed that the molecules concerned are spherical.

\[
\tau_c = \frac{4\pi r^3 \eta_S}{3kT} \quad (1)
\]

Here \(\eta_S\) is the solution viscosity. A change of the coordination of a quadrupole nucleus results in a change of the asymmetry parameter, \(\eta\), and of the correlation time \(\tau_c\). In the present case, formation of an inner sphere La(III)-Cl\(^-\) complex would result in a large increase of the line-width \((\Delta \nu^{1/2})\) of both the \(^{139}\)La and the \(^{35}\)Cl signal. For this complex in methanol it has been reported that the \(\Delta \nu^{1/2}/\eta_S\) values are 1370 and 1670 for \(^{139}\)La and \(^{35}\)Cl, respectively. Figure 1 shows, however, that the increase of \(\Delta \nu^{1/2}/\eta_S\) of the \(^{35}\)Cl signal is relatively small (380) going from D\(_2\)O to 1. The \(^{139}\)La line-width initially increases upon replacement of D\(_2\)O by 1, but when the amount of 1 is more than 70\%, it decreases again. This behavior can be attributed to substitution of D\(_2\)O by 1 in the first coordination sphere of La(III), yielding initially relatively asymmetric La(III)-1-D\(_2\)O complexes and finally a D\(_2\)O free complex La(III)-1, that has a lower asymmetry parameter \(\eta\). It should be noted that the maximum in the curve of the \(^{139}\)La line widths and that in the curve of the \(^{139}\)La chemical shifts occur at the
same concentration of 1.

The increase of the concentration of the La(III)-1 complexes at high concentrations of 1 (>70%), as witnessed by the $^{139}$La chemical shifts and line-widths is accompanied by some increase of the viscosity corrected $^{35}$Cl line-width (Figure 1). Probably this is caused by the presence of a solvent (1) separated ion pair of La(III) and Cl$^-$. Such a complex has a relatively large radius and consequently $\tau_c$ and $\Delta \nu_4$ for $^{35}$Cl of that complex are large in comparison to ‘unbound’ Cl$^-$. 

Previously, we have observed that, for paramagnetic lanthanides, the contact contribution to the Ln(III)-induced shift of a Ln(III)-bound $^{170}$O nucleus is almost independent of the nature of the ligand in question and also of the other ligands coordinated to the Ln(III) ion. Therefore, the Ln(III)-induced $^{170}$O shifts can be utilized to establish the oxygen coordination sites of the ligand and to determine the stoichiometry of the complex. For Dy(III) as the lanthanide, the induced shift is dominated by the contact shift and a laborious dissection of the observed induced shift into the contact and pseudocontact contributions is not needed.

The exchange of the $^{170}$O nuclei of bound and free ligands was fast on the NMR time scale. Straight lines were obtained in plots of the $^{170}$O chemical shifts versus the molar ratio Dy(III)/ligand ($\rho$, $\rho < 0.1$, correlation coefficients $> 0.999$). The $^{170}$O shifts extrapolated to $\rho = 1$ are given in Table I. These extrapolated induced shifts correspond to nA, where n is the number of bound oxygens of the concerning ligand per Dy(III) and A is the bound shift of that oxygen nucleus.

The hydration of the Ln(III) ions is a subject of some controversy; hydration numbers of 8 and 9 have been proposed. Recently, Merbach et al. have concluded from neutron scattering difference studies that the coordination number of Dy(III) is 8 for 0.3 and 1 M solutions of DyCl$_3$ and Dy(ClO$_4$)$_3$ in D$_2$O. On the other hand, Brücher et al. have established, using $^1$H NMR studies at low temperature, that the hydration number of Lu(III) is increasing upon dilution. A hydration number of $\geq 9$ is deduced for dilute solutions. Therefore, we assume that, for the low Dy(III) concentrations that we have used, Dy(III) is hydrated by 9 D$_2$O molecules. Then from the Dy(III)-induced shift of D$_2$O extrapolated to $\rho = 1$ (-17458 ppm, Table I), it can be calculated that the bound shift of an $^{170}$O donor site is -17458/9 = -1940 ppm.

Upon addition of Dy(III) to 1 only a single ethylene glycol $^{170}$O signal was observed. The exchange between the complex and the bulk is fast on the
Table I. - The Solvation of Dy(III) as Deduced from Dy(III)-Induced $^{17}$O NMR Shifts.

<table>
<thead>
<tr>
<th>System(^a)</th>
<th>Temp. (K)</th>
<th>Dy(III)-induced shift (ppm)(^b)</th>
<th>Bound O-atoms(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\text{D}_2\text{O}$</td>
<td>alcohol-O</td>
</tr>
<tr>
<td>$\text{D}_2\text{O}$</td>
<td>353</td>
<td>-17458</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>353</td>
<td>-</td>
<td>8408</td>
</tr>
<tr>
<td>$\text{D}_2\text{O}$-$\text{D}_2\text{O}$ -1 (37:63)</td>
<td>353</td>
<td>-5814</td>
<td>-6581</td>
</tr>
<tr>
<td>$\text{D}_2\text{O}$-$\text{D}_2\text{O}$ -1 (44:56)</td>
<td>353</td>
<td>-6322</td>
<td>-4589</td>
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<tr>
<td>$\text{D}_2\text{O}$-$\text{D}_2\text{O}$ -1 (67:33)</td>
<td>353</td>
<td>-9902</td>
<td>-3537</td>
</tr>
<tr>
<td>$\text{D}_2\text{O}$</td>
<td>298</td>
<td>-20401</td>
<td>-</td>
</tr>
<tr>
<td>$\text{CD}_3\text{OD}$</td>
<td>298</td>
<td>-12182</td>
<td>-</td>
</tr>
<tr>
<td>$\text{D}_2\text{O}$-$\text{CD}_3\text{OD}$  (1:1)</td>
<td>298</td>
<td>-19248</td>
<td>-2636</td>
</tr>
<tr>
<td>$\text{CD}_3\text{OD}$-$\text{CD}_3\text{OD}$ -1 (1:1)</td>
<td>298</td>
<td>-</td>
<td>8307 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)Molar ratios between parentheses. \(^b\)Extrapolated to $\rho = 1$, where $\rho$ is the molar ratio of Dy(III) added as DyCl$_3$·6H$_2$O and the concerning ligand. \(^c\)Average number per Dy(III) ion. For calculation: see text.

NMR time scale. The Dy(III)-induced shift extrapolated to $\rho = 1$ is -8408 ppm (Table I). The average number of bound ethylene glycol oxygens per Dy(III) can then be calculated to be -8408·2/-1940 = 9. The multiplication by 2 is needed because each ethylene glycol ligand contains two indistinguishable oxygens. No conclusions concerning the denticity of 1 can be made on the basis of these data; mono- and bidentately bound 1 give the same Dy(III)-induced shift extrapolated to $\rho = 1$, if it is assumed that the coordination number of Dy(III) for monodentately bound 1 is twice that of bidentately bound 1, and that the Dy(III)-induced shift of a non-coordinated oxygen is negligible. Anyway, these data confirm that Dy(III) is completely solvated by 1 and that Cl$^-$ is not able to substitute 1 in the first coordination sphere of Dy(III).

For comparison, we have also performed measurements on the system DyCl$_3$-methanol. From the Dy(III)-induced shift extrapolated to $\rho = 1$ (Table I), it can be concluded that Dy(III) is coordinated by 5.4 methanol ligands. The first coordination sphere is then completed by 3 Cl$^-$ ligands,
which is in good agreement with conclusions in the literature, based on other techniques.\textsuperscript{16,17} Apparently the affinity of Ln(III) ions for methanol is less than for water and 1, which are both able to expel Cl\textsuperscript{-} from the first coordination sphere of the Ln(III) ions. This is confirmed by the results of competition experiments with 1:1 mixtures of methanol with D\textsubscript{2}O and 1, respectively (Table I). The Dy(III)-induced shifts obtained, show that in the former experiment D\textsubscript{2}O is bound preferentially, whereas in the latter coordination of 1 to Dy(III) is predominant.

The strong preference of Dy(III) for coordination of 1 in the competition experiment with 1 and methanol suggests that at least some bidentate coordination of the former occurs. Steric effects may account for the difference in stability of the Dy(III)-methanol and Dy(III)-D\textsubscript{2}O complexes.

Likewise the average number of coordinated D\textsubscript{2}O and ethylene glycol oxygens per Dy(III) was determined from the Dy(III)-induced $^{17}$O shifts in mixtures of D\textsubscript{2}O and 1 (Table I). It appears that the ratio coordinated ethylene glycol oxygens/coordinate waters is always somewhat larger than the molar ratio of 1 and D\textsubscript{2}O.

From these data it may be concluded that the order of affinity of Ln(III) is: 1 > D\textsubscript{2}O > Cl\textsuperscript{-} > methanol.

\textit{Ln(III)-Maleate (2) in Ethylene Glycol (1).}

The Dy(III)-induced shifts of the $^{17}$O nuclei of both maleate (2) and ethylene glycol (1) were determined (Table II). The $^{17}$O signals of

\begin{table}[h]
\centering
\begin{tabular}{lllll}
\hline
Carboxylate & solvent & Dy(III)-induced shift$^a$ & Dy(III)-bound O-atoms$^b$ & \\
& carboxylate solvent & carboxylate solvent & \\
\hline
1 & -496 & -7848 & 1.0 & 8.1 \\
3 & 1 & - & -7848 & - & 8.1 \\
3 & D\textsubscript{2}O & -1531$^d$ & -2154 & 3.2$^d$ & 1.1 \\
4 & D\textsubscript{2}O & - & -3773 & - & 2.0 \\
\hline
\end{tabular}
\caption{Dy(III)-Induced $^{17}$O Shifts of 0.35 M Solutions of Carboxylates 2-4 in Ethylene Glycol (1) or D\textsubscript{2}O at 353 K.}
\end{table}

$^a$Extrapolated to $p = 1$. $^b$Average number of Dy(III)-bound O-atoms per Dy(III) ion. $^c$Not observable due to excessive line broadening. $^d$See text.
carboxylic acids usually show appreciable line broadening in the presence of Dy(III), and, therefore, their observation is often difficult in natural abundance. In order to facilitate the measurements of the Dy(III)-induced shifts, 2 with 5% $^{17}O$-enrichment was used. In all spectra only a single carboxylate $^{17}O$ signal was observed, indicating that the exchange between the two carboxylate oxygens and that between the free and the Dy(III)-bound ligand is fast on the NMR time scale. From the slopes of the lines obtained upon plotting the Dy(III)-induced shifts versus $\rho$, where $\rho$ is the molar ratio of Dy(III) and the ligand in question (viz. 1 or 2), the induced shifts of 1 and 2 extrapolated to $\rho = 1$ were evaluated to be -7848 and -496 ppm, respectively. As outlined in the previous section, the average number of oxygens of these ligands attached to Dy(III) can then be calculated to be 8.1 (-7848/-1940) and 1.0 (4.496/-1940), respectively. This shows that maleate (2) is rather weakly bound to Dy(III), probably in a monodentate fashion. Previously, we have shown that 2 in $D_2O$ under similar conditions forms Dy(maleate) and Dy(maleate)$_2$ complexes, in which 2 is proposed to be bound in two fashions: (i) as a seven-membered chelate with two carboxylate groups coordinated and (ii) bidentately via a single carboxylate group. This once again demonstrates that the affinity of Ln(III) ions for ethylene glycol (1) is larger than for $D_2O$.

Ln(III)-2-Hydroxyethoxybutanedioate (3) in Ethylene Glycol (1) and in $D_2O$.

From the Dy(III)-induced shifts, extrapolated to $\rho = 1$, of the $^{17}O$ nuclei of the solvent in a 0.35 M solution of 3 in 1 and in $D_2O$, the average number of coordinated solvent oxygens appeared to be one in both cases (Table II). If it is assumed that the coordination numbers of the Dy(III)-3-1 and Dy(III)-3-$D_2O$ complexes are the same, it may be concluded that 2-hydroxyethoxybutanedioate (3) is coordinated to Dy(III) in the same fashion in these solvents. Apparently the stability of the Dy(3) complex is large enough to preclude any competition of the solvent in the coordination. Since 3 has four functional groups, and the coordination number of Dy(III) is usually 8-9, it is inferred that the stoichiometry of the concerning complexes is Dy(3)$_2$(solvent)$_1$.

Upon addition of Dy(III) to a sample of 3, of which the carboxylate oxygens were 5% $^{17}O$-enriched, in $D_2O$ severe line broadening was observed in the $^{17}O$ signals for the carboxylate groups. The initially well-separated signals collapsed after a small addition to one broad signal. Further additions of Dy(III) did not result in any separation of these signals, both
signals have about the same Dy(III)-induced shift showing that both
carboxylate groups of 3 are attached to the Dy(III) ion. A calculation,
using the procedure described above, of the average number of coordinated
carboxylate oxygens per Dy(III) yields 3.2. This number is somewhat low,
considering the stoichiometry of the complex and the fact that no separation
of the carboxylate signals could be observed at higher $\rho$ values. Probably
the exchange of the carboxylate oxygens between the free and the
Dy(III)-coordinated state is not in the fast exchange region on the NMR time
scale. This is supported by the extreme broadening observed and by the
smaller Dy(III)-induced shift at higher magnetic field.

$^{17}$O NMR is a very convenient technique to study coordination phenomena in
ethylene glycol solutions. This solvent causes, however, serious problems in
$^{13}$C and $^1$H NMR techniques, due to interfering big solvent signals. Because
of the similarity of the Dy(III)-3 complexes in 1 and D$_2$O suggested by the
results of the experiments described above, we decided to perform further
investigations on the structure of these complexes in D$_2$O or water as the
solvent.

First the stability constants of the complexes of 3 and the various
Ln(III) ions in aqueous solution ($I = 1.0$ M (NaClO$_4$); 298 K) were
determined with the use of potentiometry. The over-all stability constants
are defined as:

$$\beta_{101} = [\text{Ln(3)}]/[\text{Ln}]^{[3]}$$

(2)

$$\beta_{102} = [\text{Ln(3)}_2]/[\text{Ln}]^{[3]^2}$$

(3)

The values obtained are compiled in Table III. The stability constants for
the Ln(III)-3 complexes show the usual trend: a regular increase from La
through Sm, then a decrease up to Ho, followed by another increase at the
end of the series. Several explanations for this phenomenon, in terms of
effects related to the decreasing ionic radii going from La(III) to Lu(III),
have been proposed in the literature. 25-27

The stability constants complexes of a metal ion with a series of related
ligands is expected to be linearly correlated with the summed acidity
constants of the donor groups involved, when the interaction is strongly
ionic and no variations in steric effects occur. 28 Choppin has shown that
the magnitudes of $\beta_{101}$ of the Sm(III)-complexes of a variety of mono- and
di-carboxylates and aminopolycarboxylates confirm with such a linear
Table III. Stability constants of the Ln(III) complexes of 3 and 4 in water, $I = 1.0 \text{ M (NaClO}_4\text{)}$; 298 K.

<table>
<thead>
<tr>
<th>Ln(III)</th>
<th>$3^a$</th>
<th>$4^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\log \beta_{101}$</td>
<td>$\log \beta_{102}$</td>
</tr>
<tr>
<td>La</td>
<td>3.94</td>
<td>6.79</td>
</tr>
<tr>
<td>Pr</td>
<td>4.44</td>
<td>7.42</td>
</tr>
<tr>
<td>Nd</td>
<td>4.48</td>
<td>7.39</td>
</tr>
<tr>
<td>Sm</td>
<td>4.63</td>
<td>7.74</td>
</tr>
<tr>
<td>Eu</td>
<td>4.47</td>
<td>7.49</td>
</tr>
<tr>
<td>Gd</td>
<td>4.40</td>
<td>7.55</td>
</tr>
<tr>
<td>Tb</td>
<td>4.29</td>
<td>7.45</td>
</tr>
<tr>
<td>Dy</td>
<td>4.20</td>
<td>7.34</td>
</tr>
<tr>
<td>Ho</td>
<td>4.22</td>
<td>7.23</td>
</tr>
<tr>
<td>Er</td>
<td>4.24</td>
<td>7.18</td>
</tr>
<tr>
<td>Tm</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yb</td>
<td>4.41</td>
<td>7.31</td>
</tr>
</tbody>
</table>

$^a pK_{a1} = 3.07$; $pK_{a2} = 4.40$. $^b pK_{a1} = 2.48$; $pK_{a2} = 3.29$; $pK_{a3} = 4.08$; $pK_{a4} = 4.77$.

In Figure 2 the $\beta_{101}$ values of a series of $\alpha$-(hydr)oxycarboxylates are plotted as a function of the $\Sigma pK_a$ of these compounds. The data used were taken from the literature. For comparison the line observed by Choppin for the mono- and di-carboxylates is included. The latter line appears to be somewhat below that of the (hydr)oxycarboxylates. This probably reflects an increase of stability as a result of the formation of a five-membered chelate of the $\alpha$-(hydr)oxycarboxylate function and Sm(III). The data for compound 3 fall on the line for the $\alpha$-(hydr)oxycarboxylates, suggesting that all carboxylate functions of 3 are coordinated to the lanthanide ion. If this would not be the case, a much lower stability should be expected. Obviously, conclusions about the involvement of 6-OH function in the coordination are not possible, on the basis of stability constants.

An unambiguous assignment of the Ln(III) coordination sites of 3 could be achieved with the use of Gd(III)-induced $^{13}$C longitudinal relaxation rate enhancement measurements. Among the Ln(III) cations Gd(III) has the longest electronic relaxation time, and therefore this ion is very suitable for
Figure 2. Log\(\beta_{101}\) for a series of Sm(III) complexes of (hydr)oxycarboxylates versus the summed acidity constants (\(\Sigma pK_{an}\)) of these ligands, 298 K (solid line); a = pyruvate, b = glyoxylate, c = glycolate, d = D-tartrate, e = malate, f = citrate, g = oxydiacetate, h = 2-hydroxyethoxybutanedioate (3), i = ethylenedioxydibutane dioate (4). The broken line gives the relationship for non-hydroxyl groups containing mono- and dicarboxylates (refs. 29, 30).

the study of the geometry of bound ligands. Since Gd(III) can be applied in very low concentrations with respect to the ligand (\(\rho<10^{-4}\)), information will be obtained on complexes in which Gd(III) is coordinated by the maximum number of ligands possible, the Gd(3)\(_2\) complex in this case. Assuming that the mean residence time of a ligand in its Gd(III) complex is short with respect to the longitudinal relaxation time (\(T_1c\)) and that the contribution of intermolecular interactions to the relaxation is negligible, the observed relaxation rate of a nucleus (\(1/T_{1obs}\)) can be expressed as:

\[1/T_{1obs} = n\rho/T_{1c} + 1/T_{1f}\] (4)

where \(n\) is the number of ligands bound in the Gd(III) complex and \(1/T_{1f}\) is the relaxation rate of that nucleus in the undoped sample. The relaxation rate in the complex is related to the molecular structure via equation (5).35-37
1/T\textsubscript{1C} = k/r^6 \quad (5)

Here r is the distance between Gd(III) and the nucleus under consideration and k is a constant.

The relaxation rates of the \textsuperscript{13}C nuclei of 3 were measured at five different Gd(III) concentrations (r = 0 - 1.3 \times 10^{-4}). A linear relationship between the relaxation rates and r was found (correlation coefficients > 0.999). This is in accordance with equation (4). From the slopes of the lines the relative relaxation rate enhancements were calculated. These are shown in Figure 3.

The relaxation rate enhancements of the two carboxylate \textsuperscript{13}C nuclei of 3 are of the same magnitude, proving that both carboxylates are coordinated to Gd(III), as was already expected on the basis of the stability constants. The relaxation rate enhancement of C(2) is of the same magnitude as well, which shows that O(2) is also coordinated to Gd(III). Similar relative relaxation rate enhancements were previously determined for malate (5)\textsuperscript{38} and carboxymethoxysuccinate (6),\textsuperscript{39} which both contain, like 3, a malate structural unit. It was shown, with the use of several techniques, that this unit in Gd(III) complexes of 5 and 6 is also predominantly bound in a tridentate fashion via the two carboxylates and O(2). The relaxation rate

Figure 3. Comparison of the relative Gd(III)-induced \textsuperscript{13}C relaxation rate enhancements of 2-hydroxyethoxybutanediolate (3), malate (5), and carboxymethoxysuccinate (6). Schematic representations of the mode of coordination in the predominant Gd(III) complexes are given.
enhancements of C(5) and C(6) of 3 are of the same magnitude as C(1), C(2), and C(4), and, therefore, it is concluded that O(6) is also coordinated to Gd(III). It can be calculated with equation (5) and distances estimated from Dreiding models that, if O(6) were not coordinated, the relative relaxation rate enhancement of C(6) would be 0.1. It can be concluded that in the predominant complex 3 coordinates via the two carboxylate groups and O(2) and O(6).

Thus in the 1:2 Ln(III)-3 complex 8 positions on the Ln(III) cation are occupied by the two 3 ligands and, as was shown by the Dy(III)-induced water $^{17}$O shifts, the first coordination sphere of the cation is completed with one water ligand. This leads to a coordination number of 9 for Ln(III).

For the coordination of 3 a drastic change of conformation is required. This could be shown with the use of the changes of the vicinal proton-proton coupling constants that occur upon coordination of 3 with the diamagnetic La(III) (Figure 4). From the magnitudes of vicinal coupling constants $^3J(2,3)$ and $^3J(2,3')$ at pH 7 it may be concluded that the free ligand is almost exclusively in an anti-periplanar conformation (Figure 5). The preference for this conformation is higher than that of the succinate, where, as has been shown by Gil et al., its population is about 60%. Upon addition of La(III) to an aqueous solution of 3, the magnitude of $^3J(2,3')$ decreases substantially and that of $^3J(2,3)$ increases slightly (Figure 4). From the experimental coupling constants at various $p$-values and molar fractions of the ligand 3 present as free ligand, 1:1, and 1:2 La(III) complex as calculated from the stability constants in Table III, the $^1$H chemical shifts and the coupling constants in the 1:1 and in the 1:2 complex could be evaluated with the use of a multiple regression method. The results obtained are given in Table IV.

Previously, we have shown that coordination of a rigid ligand to a Ln(III) ion has no observable influence on the vicinal proton-proton coupling constants. Therefore, it can be concluded that the dramatic changes in $^3J(2,3)$ and $^3J(2,3')$ are caused by a conformational change of 3 upon coordination to La(III), the magnitudes of these coupling constants show that in the complex the carboxylate groups are in the syn-clinal configuration, which is actually the conformation that is dictated by a tetradentate coordination of 3. It should be noted that the geminal coupling constant $^2J(3,3')$ also changes going from the free ligand to the complexes. It is known that geminal coupling constants, in contrast to the vicinal ones, are sensitive to coordination of neighboring groups by a Ln(III)
Figure 4. Vicinal coupling constants of 2-hydroxyethoxybutanedioate (3) in the presence of La(III) as a function of $\rho$ at pH 7, 298 K.

Figure 5. Conformational change of 2-hydroxyethoxybutanedioate (3) upon coordination to a Ln(III) cation.
Table IV. $^1$H Chemical Shifts (ppm) and Coupling Constants (Hz) of (3) and its \textit{La(III)} Complexes in D$_2$O at pH 7, 298 K.

<table>
<thead>
<tr>
<th></th>
<th>3 free ligand</th>
<th>La(3)$^+$</th>
<th>La(3)$_2^-$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta$(2)</td>
<td>4.08</td>
<td>4.24</td>
<td>4.12</td>
</tr>
<tr>
<td>$\delta$(3)</td>
<td>2.56</td>
<td>3.05</td>
<td>2.85</td>
</tr>
<tr>
<td>$\delta$(3$'$)</td>
<td>2.34</td>
<td>2.92</td>
<td>2.69</td>
</tr>
<tr>
<td>$^3$J(2,3)</td>
<td>2.9</td>
<td>5.4</td>
<td>4.8</td>
</tr>
<tr>
<td>$^3$J(2,3$'$)</td>
<td>10.9</td>
<td>1.2</td>
<td>4.3</td>
</tr>
<tr>
<td>$^2$J(3,3$'$)</td>
<td>-15.3</td>
<td>-18.7</td>
<td>-17.5</td>
</tr>
</tbody>
</table>

ion.\textsuperscript{42} So this is in agreement with coordination of COO (4). Unfortunately, we were not able to evaluate the vicinal coupling constants for the ethoxy group of the ligand. The \textsuperscript{1}H signals for these protons were overlapping too much to allow an analysis. The behavior of the vicinal coupling constants $^3$J(2,3) and $^3$J(2,3$'$) is very similar to that observed previously for carboxymethoxysuccinate (5),\textsuperscript{39} and this supports the great similarity in coordination of these ligands.

In Figure 6 the \textsuperscript{1}H shifts of 3 in the presence of the paramagnetic Pr(III) cation are shown as a function of $\rho$. The bend in the curves at $\rho = 1/2$ confirms the existence of 1:1 and 1:2 complexes. These complexes have somewhat different bound shifts. It should be noted that the induced shifts for nuclei in the succinate part and those in the ethylene glycol part have opposite signs. If it is assumed that these induced shifts are of a pseudocontact origin, and that internal reorientations in the complex result in effective axial symmetry, their magnitudes are given by:\textsuperscript{43-45}

$$\Delta = C \cdot (3\cos^2\theta - 1)/r^3$$ \hspace{1cm} (6)

Here $\Delta$ is the bound shift of a nucleus, $r$ is its distance to the Pr(III) ion, $\theta$ is the angle between the vector $r$ and the pseudo-axial axis, and $C$ is a constant. The sign of $\Delta$ reverses at $\theta = 54.7^\circ$. From previous studies we know that the sign of $C$ is negative for Pr(III).\textsuperscript{46} Therefore, positive bound shifts of the nuclei in the succinate part of 3 indicate that these nuclei are in the equatorial region ($55^\circ < \theta < 125^\circ$), whereas the nuclei of the ethylene glycol part are in the axial region ($0^\circ < \theta < 55^\circ$, $125^\circ < \theta < 180^\circ$).
Figure 6. $^1$H chemical shifts of 2-hydroxyethoxybutanedioate (3) in the presence of Pr(III) as a function of pH at pH 7, 298 K.

The pK$_a$ of the Ln(III) coordinated OH group of 3 is of importance in relation with the mechanism of the O-alkylation of ethylene glycol with maleate, in which attack of the ionized OH group to the olefinic bond is supposed to be a crucial step. Therefore, we have investigated the effect of the pH on the $^1$H chemical shifts of 3 in the presence of Pr(III) (Figure 7). The curves obtained have a bell-shape, with a plateau at pH 5-6. At lower pH's, decomplexation occurs due to protonation of the successive carboxylate groups. The steep decline of the induced shifts at pH > 7 can be ascribed to a decomplexation caused by the formation of polynuclear Pr(III)-hydroxide complexes. At pH > 8 the samples became somewhat turbid.
and at higher pH values precipitation of the hydroxide occurred. Apparently the pK$_a$ of the Pr(III)-coordinated hydroxyl group of 3 is higher than that of coordinated water. Previously, we have observed that the pK$_a$ of the hydroxyl group of a Ln(III)-coordinated α-hydroxycarboxylate is somewhat below of that of coordinated water.$^{10,47}$ Since the order of pK$_a$'s of
hydroxyl groups of the uncoordinated compounds is \( \alpha \)-hydroxycarboxylate < \( \text{H}_2\text{O} \) < ethylene glycol (1),\(^{48-50}\) it is reasonable that the order of the coordinated ligands is the same.

\textit{Ln(III)-Ethylenedioxydibutanedioate (4) in Water.}

The \( \text{Ln(III)} \) catalyzed O-alkylation of ethylene glycol (1) with maleate (2) affords the diastereomers of ethylenedioxydibutanedioate (4), the \textit{meso} compound being slightly more abundant than the \textit{racemic} mixture. No attempt was made to separate these diastereomers.

With potentiometry the stability constants of the 1:1 complexes with the \( \text{Ln(III)} \) cations were determined (Table III). The \( \log \beta_{101} \) values of the \( \text{Ln(4)} \) complexes are of the same magnitude as the \( \log \beta_{102} \) values of the \( \text{Ln(III)} \) complexes of 3. They show a ‘tetrad-like’ pattern, similar to that observed for \( \text{Ln(III)} \) complexes of other ligands.\(^{27}\) Inclusion of the data for 4 in the plot of the \( \log \beta \) values \textit{versus} \( \Sigma \text{pK}_a \) (Figure 2) shows that the stability constant is lower than should be expected for coordination of 4 in a hexadentate mode. This may point to a decreased stability due to steric strain or to coordination in a pentadentate fashion.

The \( \text{Dy(III)} \)-induced \(^{17} \text{O} \) shifts (Table II) show that the \( \text{Dy(4)} \) complex contains two water ligands in the first coordination sphere. So if it is assumed that the coordination number is 8 or 9 than this suggests a hexadentate coordination of 4.

The \( \text{Gd(III)} \)-induced longitudinal \(^{13} \text{C} \) relaxation rates of 4 as a function of \( \rho \) (\( \rho < 5 \cdot 10^{-4} \)) appeared to behave linear again. From the slopes of these lines the longitudinal relaxation rate enhancements of the \( \text{Gd(4)} \) complex were deduced (Table V). The assignments of the peaks in the \(^{13} \text{C} \) NMR spectrum were made previously with the use of a chiral shift reagent, except for the peaks of the carboxylate groups, which almost coincided. The relative relaxation rates enhancements of the carboxylate carbons were 1.0 and 0.8, which is very similar to the values observed for the related nuclei in compound 3. On the basis of the comparison of the magnitudes of the relative relaxation rates the signal with the relative relaxation rate enhancement of 1.0 is assigned to C(1), C(1)'. The other relative relaxation rates are also very similar to those observed for 3. Therefore, it can be concluded that 4 is bound to \( \text{Gd(III)} \) in an analogous way as 3, thus in a hexadentate fashion with the carboxylates and the ether oxygens as donor sites. The small differences in the relaxation rate enhancements between the two diastereomers can be ascribed to small differences in the conformation of
Table V. Relative Gd(III)-Induced Longitudinal $^{13}$C Relaxation Rate Enhancements (s$^{-1}$) in Compound 4 at pH 7 and 298 K.

<table>
<thead>
<tr>
<th>Nuclei</th>
<th>meso-4</th>
<th>racemic-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1), C(1')</td>
<td>1.00$^a$</td>
<td>1.00$^a$</td>
</tr>
<tr>
<td>C(2), C(2')</td>
<td>0.46</td>
<td>0.59</td>
</tr>
<tr>
<td>C(3), C(3')</td>
<td>0.25</td>
<td>0.54</td>
</tr>
<tr>
<td>C(4), C(4')</td>
<td>0.82</td>
<td>0.76</td>
</tr>
<tr>
<td>C(5), C(5')</td>
<td>0.40</td>
<td>0.55</td>
</tr>
</tbody>
</table>

$^a$The absolute relaxation rate enhancements are $10.7 \cdot 10^3$ and $9.9 \cdot 10^3$ s$^{-1}$ for meso-4 and racemic-4, respectively.

The bound ligands. The largest differences occur in C(3), C(3'). With the use of equation (5) it can be calculated that the differences observed for these nuclei correspond with only 13% difference in Gd(III)-C distance. These nuclei are part of six-membered chelate rings and an inspection of molecular models shows that these rings are rather flexible.

Conclusions

Multinuclear NMR techniques have been proven to be very valuable for the establishment of the structures of species occurring in the reaction mixture of the lanthanide catalyzed 0-alkylation of ethylene glycol with maleate. Ln(III) cations have a preference for the coordination of ethylene glycol over that of water. This is in agreement with the observation made previously,$^2$ that water does not interfere in the 0-alkylation reaction as long as it is not present in a large amount. The Cl$^-$ ion is not present in the first coordination sphere of the Ln(III) cation. Maleate is able to compete with ethylene glycol for coordination. The products of the first and the second 0-alkylation step (3 and 4, respectively) are strong chelators for the Ln(III) ions. Therefore, the water addition is not an important side reaction in the second 0-alkylation step (3-4). Another consequence of the rather high stabilities of 3 and 4 is that product inhibition occurs in the 0-alkylation reactions.

Deprotonation of the Ln(III) coordinated hydroxyl groups of compounds 1 and 3 could not be observed, in contrast to that of the previously studied glycolate, for which the pK$_a$ was determined to be about 8.$^{10}$
complexes with deprotonated hydroxyl groups are supposed to be the key intermediates in the 0-alkylation of hydroxy compounds with maleate. The observations on compounds 1 and 3, suggesting a relative high $pK_a$ of the Ln(III) coordinated hydroxyl group of these compounds, is therefore in agreement with the relative low reaction rates in the 0-alkylation reaction of 1 with 2 in comparison to the corresponding reaction with glycolate.\textsuperscript{24,10}

Acknowledgments

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CHAPTER VII.

N-ALKYLATION OF AMINO COMPOUNDS BY A MICHAEL-TYPE ADDITION WITH MALEATE.*

Abstract: The N-alkylation of aminopolyols and amino acids by a Michael-type addition with maleate or fumarate in aqueous medium occurs readily at 363 K. Maleate reacts faster than fumarate by virtue of the higher free energy of the ground state. For a series of amino compounds the second order rate constants are related to the nucleophilicity of the nitrogen and the steric hindrance involved. Subsequent N-alkylation of aminohydroxyl compounds and La(III) ion catalyzed O-alkylation of hydroxyl groups with maleate is shown to be a promising way to synthesize new chelating agents.

Introduction

The developments in the realm of specific metal ion chelation have urged many chemists to synthesize new chelators.¹ Much interest exists in inert gadolinium(III) complexes for MRI applications as diagnostic tools, in medicine.² Environmental concern has stimulated the research on ligands for selective metal ion complexation.³ For instance, it is important to have available chelators that are unable to resolubilize heavy metal ion deposits in surface water when disposed after use, for example, as sequestering agents for Ca(II) and Mg(II) ions in the laundry process.⁴⁻⁶ These compounds should be preferably free of nitrogen donor sites, since these may increase the selectivity of the ligand for heavy metal ions. On the other hand there is a need for chelators that are able to remove selectively toxic heavy metal ions from deposits.¹,³ In such a case the ligand should preferably contain nitrogen donor sites because of their potential to increase the affinity for heavy metal ions. The ethylenediaminetetra-acetate (edta) ligand has been applied for this purpose but it suffers from the disadvantage that it is a general chelating agent that strongly complexes almost all metal ions.⁷

Polyhydroxycarboxylates are versatile non-phosphorus and -nitrogen

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chelators. A possible route to these compounds is the O-alkylation of polyols and α-hydroxycarboxylates with maleate (male), catalyzed by metal ions. A nitrogen containing polycarboxylate can be prepared by an analogous alkylation with maleate using an amine as the nucleophile; here catalysis by metal ions is not required. As early as in 1850, it was shown that (RS)-aspartic acid can be synthesized by Michael-type addition of ammonia to fumarate (fum) in alkaline aqueous solution at elevated temperatures (Scheme I, R,R' = H). Bada and Miller have measured the equilibrium constants for this reaction at various temperatures, and used these data to estimate the minimum concentration of ammonia in the oceans of the primitive earth. Later, it was demonstrated that the reaction could be employed for the synthesis of a variety of other aspartic acid derivatives. For example, N-alkylation of ethylenediamine with male afforded both N-mono- and N,N'-di-alkylation products, in a ratio depending on the molar ratio of the starting compounds. Hammershøi et al. have shown that the mono-N-alkylation of ethylenediamine (en) selectively occurs within a [Co(male)(en)]^{1+} ternary complex. N-alkylated aspartates are good metal ion sequestering agents, as already demonstrated for ethylenediaminedisuccinate. Furthermore, it may be expected that these amino acids are readily biodegradable, and therefore are attractive from an environmental point of view.

In the literature, there are only a few patents that describe the N-alkylation of polyamines. Here, we report on the N-alkylation of aminopolyols with male. N-alkylated aspartates containing one or more hydroxyl groups are intermediates for the synthesis of new chelators, because of the ability of the hydroxyl group(s) to react in a subsequent reaction with another male in a La(III) catalyzed reaction. One such an example is described in the present paper. Alternatively, the N-alkylated aminopolyols may be used in combination with borate, which often alters the sequestration properties of chelates that contain hydroxyl groups.

**Experimental**

The NMR experiments were performed on a Varian T-60, a Nicolet NT-200 WB, or a Varian VXR-400S Spectrometer. The methyl group of t-BuOH was used as internal reference at 1.2 ppm (1H NMR) or 31.2 ppm (13C NMR). The APT (attached proton test) pulse sequence was used to establish the multiplicity of the 13C NMR signals. A MI-412 electrode (Microelectrodes, Inc.) hooked to a Corning pH meter 125 was used for pH measurements. The pH values given are
direct readings. Aqueous buffers of pH 7 and 9 were used for calibration. \( \text{LaCl}_3 \cdot 7\text{H}_2\text{O} \) was purchased from Alfa Products. Its metal content was determined by an edta titration. \( D\)-Glucamine was purchased from Hüls, while the other chemicals were obtained from Janssen. Dowex 50 W (\( \text{H}^+ \), 100 mesh) was used as column material for chromatographic purification of some of the products. About 1 g resin per mmol amino compound was used. \( \text{Na}_2\text{maleate.2H}_2\text{O} \) and \( \text{Li}_2\text{maleate.H}_2\text{O} \) were prepared as described previously. The reaction kinetic experiments were performed using a solution of the disodium salt of the \( \alpha,\beta \)-unsaturated dicarboxylate (2.0 M) and the amino compound (2.0 M) in \( \text{D}_2\text{O} \). The solution was heated in a thermostatted reaction vessel at 363 K. The course of the reaction was followed with \( ^1\text{H} \) NMR (60 MHz, or 400 MHz) of samples that were taken from the solution at certain time intervals and cooled down to room temperature. The concentrations of the compounds were determined by integration of the signals of the spectra obtained, the error in the concentrations obtained is estimated to be 5-10%. The potentiometric measurements were performed with the equipment as described previously. An aqueous solution (50 ml, pH 6) of the amino compound (0.001 M) was prepared by dissolving the amino compound in double distilled water (carbonate-free). When necessary, dilute hydrochloric acid (0.01 M) was added for acidification. A solution of \( \text{NaOH} \) (0.01 M) was used as the titrant. Both solutions were adjusted to an ionic strength of 0.1 M by addition of \( \text{NaClO}_4 \). The titrations were performed under nitrogen. The N.B.S. buffers 6.86S and 9.180 were used for standardization of the pH electrode. For the calculations of the \( \text{pK}_a \) at \( \text{I}=0.1 \) an activity coefficient 0.83 was used.

General Procedure for the Synthesis of the N-Alkylated Products of Aminopolyols with Maleate.

An aqueous solution (pH 11) of \( \text{Li}_2\text{maleate} \) (1.73 M) and aminopolyol (1.0 M) was heated at 363 K for 65 h. The reaction mixture was cooled down to room temperature and acidified by addition of hydrochloric acid to pH 2. After 1 day the precipitated fumaric acid was removed by filtration. The filtrate was adjusted to pH 5 by addition of LiOH and then purified via a Dowex 50 W (\( \text{H}^+ \)) cation exchange column. A gradient was applied from 0 to 0.7 M \( \text{NH}_4\text{OH} \) and the fractions obtained were concentrated in vacuo and then analyzed by \( ^1\text{H} \) NMR. The excess of ammonia in the solution was removed by coevaporation with water. Then the di-ammonium salts of the products were obtained by evaporation of the residual solvent in vacuo.
N-(2,3-dihydroxypropyl) aspartate (4b).

1-Amino-2,3-propanediol was used as the amino compound. The di-ammonium salt of pure 4b was obtained as a yellow syrup in 78% yield (42.2 g, 175 mmol).

\(^{13}C\) NMR (D\(_2\)O, pD 5.4) mixture of diastereomers (RR/SS and meso) \(\delta\)(ppm): 178.97, 178.80, 174.48 (C1', C4'), 69.01, 68.62 (C2), 64.91, 64.85 (C3), 61.32, 61.17 (C2'), 50.42, 50.23 (C1), 37.04, 36.47 (C3').

N-(1-deoxy-D-gluco) aspartate (4c).

D-glucamine was used as the amino compound. The di-ammonium salt of pure 4c was obtained as a yellow syrup in 59% yield (7.50 g, 22.7 mmol).

\(^{13}C\) NMR (D\(_2\)O, pD 5.4) mixture of diastereomers (RR/SS and meso) \(\delta\)(ppm): 179.07, 178.89, 174.57 (C1', C4'), 72.50, 72.31, 70.10, 69.70 (C2, C3, C4, C5), 64.26 (C6), 61.36, 61.16 (C2'), 50.43, 50.25 (C1), 37.10, 36.54 (C3').

N-methyl-N-(1-deoxy-D-gluco) aspartate (4d).

N-methyl-D-glucamine was used as the amino compound. The di-ammonium salt of 4d was obtained as a yellow syrup in 18% yield (4.90 g, 14.2 mmol).

\(^{13}C\) NMR (D\(_2\)O, pD 4.6) mixture of diastereomers (RR/SS and meso) \(\delta\)(ppm): 178.59, 178.40, 173.16 (C1', C4'), 72.44, 72.19, 71.99 (C2, C3, C4, C5), 68.37 (C2'), 64.18 (C6), 57.97 (C1), 40.11, 39.88 (C7), 35.70, 34.90 (C3').

N-(2-hydroxyethyl) aspartate (4a).

An aqueous solution (50 ml, pH 11.2) of Na\(_2\)maleate (19.6 g, 100 mmol) and aminoethanol (6.1 g, 100 mmol) was heated at 363 K for 48 h. The reaction mixture was cooled down to room temperature and poured into ethanol (200 ml), whereupon a sticky precipitate was formed. After decanting, the remaining precipitate was boiled with methanol (150 ml) and acetone (50 ml). The white precipitate was filtered off and was boiled again with methanol (100 ml) giving 15.1 g of compound 4a (51 mmol, 51%) after filtration, which contained 8% of each male and fum as impurities.

\(^{13}C\) NMR (D\(_2\)O, pD 11.2) \(\delta\)(ppm): 182.82, 181.27 (C1', C4'), 62.39 (C2'), 61.70 (C2), 50.04 (C1), 42.52 (C3').

\(^{13}C\) NMR (D\(_2\)O, pD 7.0) acidified with hydrochloric acid \(\delta\)(ppm): 178.79, 174.54 (C1', C4'), 60.39 (C2'), 58.21 (C2), 49.30 (C1), 36.62 (C3').

\(^1H\) NMR 200 MHz (D\(_2\)O, pD 5.4) of the di-ammonium salt purified as described for 4b \(\delta\)(ppm): 3.85-3.80 (m, 3H, C2'H and C2H\(_2\)), 3.28-3.12 (m, 2H, C1H\(_2\)).
2.80 (dd, 1H, J= 4.03 Hz, J= -17.58 Hz, C3'H), 2.66 (dd, 1H, J= 8.97 Hz, J= -17.58, C3'H).

General Procedure for the Reactions of Amino Acids with Maleate.
An aqueous solution (pH 7) containing the amino acid (2 M) and Na₂maleate (2 M) was heated at 363 K during 24 h. The reaction mixtures obtained were cooled down to room temperature and then analyzed by ¹H and ¹³C NMR.

N-carboxylato-methyl aspartate (4f).
Glycine was used as the amino acid. Maleate was converted into 71% 4f and 29% fum as determined by ¹H NMR.
¹H NMR 60 MHz (D₂O, pD 7.4) δ(ppm): 3.80 (dd, 1H, J= 5.8 Hz, C2'H), 3.63 (s, 2H, CH₂), 2.75 (d, 2H, J= 5.8 Hz, C3'H₂).
¹³C NMR (D₂O, pD 7.4) δ(ppm): 178.85, 174.79 (C1', C4'), 173.14 (C2), 60.59 (C2'), 49.62 (C1), 36.70 (C3').

N-(1-carboxylato-2-hydroxyethyl) aspartate (4g).
L-Serine was used as the amino acid. Maleate was converted into 61% 4g and 39% fum as determined by ¹H NMR.
¹³C NMR (D₂O, pD 5.5) mixture of diastereomers (RR/SS and meso) δ(ppm): 179.02, 178.79, 174.80, 174.69 (C1', C4'), 173.18 (C3), 64.14, 63.81 (C1), 61.05, 60.59 (C2), 60.19, 59.92 (C2'), 37.09, 36.14 (C3').

Iminodibutanedioate (4h).
A solution (10 ml, pD 9.5) in D₂O containing disodium aspartate (1.77 g, 10.0 mmol) and Na₂maleate (1.98 g, 10.0 mmol) was heated at 363 K during 48 h. The reaction mixtures obtained were cooled down to room temperature and analyzed by ¹H and ¹³C NMR. Maleate was converted into 22% 4h and 70% fum as determined by ¹H NMR.
¹³C NMR (D₂O, pD 9.5) mixture of diastereomers (RR/SS and meso) δ(ppm): 179.44, 179.31, 176.43, 176.29 (C1, C1', C4, C4'), 60.05, 59.41 (C2, C2'), 37.72, 37.31 (C3, C3').

N-{(1,2-dicarboxyethyl)oxyethyl} aspartic acid (5).
An aqueous solution (75 ml, pH 11.9) of Na₂maleate (39.2 g, 200 mmol) and aminoethanol (6.1 g, 100 mmol) was heated at 363 K for 24 h. Then LaCl₃·7H₂O (18.65 g, 50 mmol) was added in small portions in the course of 30 min (pH 9.50 at 298 K). After 24 h the reaction mixture was cooled down
to room temperature. The clear solution was acidified with hydrochloric acid. A precipitate was formed at about pH 3, which dissolved again at pH 2. The La(III) was removed by adding a hot solution of oxalic acid (75 ml 1.0 M at 333 K) to the acidified solution, which also was heated at 333 K. After stirring for 15 min at 333 K, the precipitated La$_2$(oxalate)$_3$ was filtered off. The filtrate was acidified to pH 1.5 with concentrated hydrochloric acid. The volume was reduced in vacuo to 50 ml and cooled to 278 K. After 1 day the side product, fumaric acid, was precipitated (6.95 g, 60 mmol). After filtration, the filtrate was allowed to stand for a few days at 278 K, whereupon the crystallized compound 5·1H$_2$O was collected (8.45 g, 27.1 mmol, 27% yield). Anal. Calcd. for C$_{10}$H$_{17}$NO$_{10}$·C, 38.59; H, 5.50; N, 4.50. Found: C, 38.33; H, 5.54; N, 4.21. M.p. 431-433 K.

$^{13}$C NMR (D$_2$O, pD 10) mixture of diastereomers (RR/SS and meso) δ(ppm): 182.83, 181.52, 181.25, 180.67 (C1', C4', C1", C4"), 80.79 (C2"), 70.44 (C2), 62.93 (C2'), 48.02 (Cl), 43.04, 42.87 (C3', C3"

Results and Discussion

Reaction Mechanism.

The N-alkylation of aminoethanol (1a) by a Michael-type addition with fum (see Scheme I) at pH 11 and 363 K to give racemic N-(2-hydroxyethyl) aspartate (4a) has a second order rate constant of 5.2 $10^{-6}$ M$^{-1}$·s$^{-1}$ as determined by $^1$H NMR, which is ten times higher than the rate constant of the corresponding NH$_3$ addition (3.53 $10^{-7}$ M$^{-1}$·s$^{-1}$) (see Table I). When male was used instead of fum, 74% of male was converted into 4a at pH 11 after heating the reaction mixture for 24 h at 363 K. Here, however, fum emerged as a side product (7%). The same reaction at pH 7.5 yielded 64% of 4a and 26% of fum. Fum was not formed by isomerization of male as was shown by performing the reaction in the absence of aminoethanol. Deamination of 4a to fum is of minor importance; starting from pure 4a, even at pH 8 only 1% of fum was formed after 48 h at 363 K. For this reason, the fum formed during the reaction starting from 1a is assumed to originate from an elimination reaction of the intermediate carbanion (3a) rather than from an elimination reaction of 4a.

Most likely, the N-alkylation of amino compounds with male occurs via the same reaction mechanism as the addition of ammonia to fum (Scheme I). For the latter system, it was observed that the proton exchange of the methylene protons of the resulting aspartate occurs with a half-life time of 51 h,
a \( R = -C_1^1H_2C_2^2H_2OH, R' = H \)
b \( R = -C_1^1H_2C_2^2(OH)C_3^3H_2OH, R' = H \)
c \( R = -C_1^1H_2C_2^2H(OH)C_4^4H_2OH, R' = H \)
d \( R = -C_1^1H_2C_2^2H(OH)C_5^5H_2OH, R' = C_7^7H_3 \)
e \( R, R' = -CH_2CH_2OH \)
f \( R = -C_1^1H_2C_6^6O_2^2, R' = H \)
g \( R = -C_1^1H(C_2^2H_2OH)C_3^3O_2^2, R' = H \)
h \( R = -C_1^1H(C_2^2O_2^2)C_3^3H_2C_4^4O_2^2, R' = H \)

**Scheme I**

whereas the halflife time of deamination is 383 h at 389 K (at pH 8.36 measured at 298 K). The low deamination rate of aspartate is in agreement with the low amount of fum formed after 48 h for the deamination of 4a. No male was detected either in the deamination of 4a or in that of aspartate.

The rate equation for the formation of the intermediate carbanion 3 is given by:

\[
\frac{-d[\text{male}]}{dt} = k \cdot [\text{male}] \cdot [\text{am}]
\]

in which am is the amino compound. After substituting the mass balances into
eq. 1 followed by integration, one obtains:

\[ \ln ([\text{male}] - (am_0 + [\text{fum}])) - \ln (\text{male}_0 - (am_0 - [4]))/ (\text{male}_0 - (am_0 + [\text{fum}])) = k \cdot t \]  

(2)

where \( \text{male}_0 \) and \( am_0 \) are the initial concentrations of male and the amino compound, respectively. For all N-alkylation reactions studied (Table I) a good correlation (.99) of the concentrations in the reaction mixture as a function of time according to eq. 2 was obtained.

**Table I. -Second Order Rate Constants of N-Alkylation of Amino Compounds with Male and Fum Measured at 363 K in D_2O.**

<table>
<thead>
<tr>
<th>olefin</th>
<th>R-NH_2</th>
<th>dicarboxylate</th>
<th>pH</th>
<th>(10^5 k , (M^{-1}s^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>male</td>
<td>11.7</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>1a</td>
<td>fum</td>
<td>11.5</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>male</td>
<td>7.5</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>male</td>
<td>11.0</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>male</td>
<td>11.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>1d</td>
<td>male</td>
<td>11.3</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>1e</td>
<td>male</td>
<td>11.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1f</td>
<td>male</td>
<td>7.4</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>1g</td>
<td>male</td>
<td>7.6</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>1h</td>
<td>male</td>
<td>9.5</td>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>

^a\text{see Scheme I.} ^b\text{pD of the reaction mixture at 298 K.}

The N-alkylation of aminoethanol with male is found to proceed 4.4 times faster than that with fum, which gives a difference in free energy of activation of -4.5 kJ/mol. If the nucleophilic addition of the amine compound to the olefinic dicarboxylate is the rate determining step, the difference in the free energy of the respective transition states (\(\Delta\Delta G^\#(\text{male-fum})\)) can be estimated as follows. In the case of fum, the developing transition state has probably the carboxylate groups in an anti-conformation (t), whereas for male the transition state with both the carboxylates (C1', C4') in a gauche-conformation (g) is more likely to be formed (4, R,R'-H). In the rotameric equilibrium of aspartate at 298 K the
anti- and the gauche-conformer are present in 61\% and 28\%, respectively, giving a $\Delta G(g-t)$ of 1.9 kJ/mol. This free energy difference is small compared to the difference in free energy of the ground states of the disodium salts of male and fum, which can be estimated to be 7.5 kJ/mol at 363 K from isomerization experiments of maleic and fumaric acid ($\Delta G(H_2\text{male-H}_2\text{fum})$).\textsuperscript{25} The calculated $\Delta G^\#(\text{male-fum})$ of -5.6 kJ/mol is in good harmony with the experimental value. It may be concluded that the higher rate of the N-alkylation of aminoethanol with male compared to fum is mainly caused by the free energy difference in the ground states of these di-anions.

The stereochemistry of the protonation of the carbanion (3a) was determined by performing the reaction in D\textsubscript{2}O. The erythro and threo isomers of the N-(2-hydroxyethyl)-3-deutério aspartate\textsuperscript{26} (see Scheme I) were formed in equal amounts at pH 11, and in a ratio 3:2 at pH 8. Bada and Miller found the same ratio of 3:2 of erythro and threo isomers for the addition of ammonia to fum to give (RS)-aspartate at pH 8 (Scheme I, R,R'=H).\textsuperscript{13} The non-stereoselectivity is consistent with a planar structure of the carbanion intermediate 3a, as has been proposed for the addition of ammonia to fum.\textsuperscript{13}

\textit{pH Dependence.}

The measured rate constants $k$ of the addition of aminoethanol to male to form 3a were almost independent of the pH (Table I), despite the decrease of the concentration of aminoethanol due to protonation, upon lowering the pH ($pK_a = 7.57$ at 363 K).\textsuperscript{27} The 2-hydroxyethylammonium cation is considered to be unreactive as a nucleophile. Bada and Miller pointed out that the ratio of the second order rate constants of NH\textsubscript{3} addition to the di-anion versus the mono-anion of fumaric acid is 1:7700.\textsuperscript{13} Probably, a similar microscopic rate constant difference exists for the amine addition to the mono- and di-anion of maleic acid,\textsuperscript{28} which explains that the macroscopic rate constant is about the same at pH 7 and 11 (Table I).

The formation of the side product, fum, increases with decreasing pH of the reaction medium of the N-alkylation of aminoethanol with male (see above) because the protonated secondary amine group in 3 is a better leaving group. In order to suppress the formation of fum the N-alkylations of aminopolyol compounds with male should be carried out preferably at high pH.

\textit{N-Alkylation of Aminopolyols with Male.}

The reactions were carried out by heating an aqueous solution of male and the amino compound (1b or 1c) at pH 11 and 363 K. An excess of male was used
with the aim to shift the equilibrium to the side of the N-alkylated product with respect to the amino compound. High isolated yields of both products 4b (78%) and 4c (59%) were obtained.

The secondary amine, N-D-methylglucamine (4d), could also be alkylated by male (18% after isolation). Another secondary amine, diethanolamine (4e), did not show any product formation after 48 h at 363 K, as neither the N-alkylated product nor fum were detected.

The N-alkylations of the aminopolyols used with male are assumed to occur via the reaction mechanism outlined for 1a (Scheme I). Factors affecting the reaction rate constant will be dependent on the nucleophilicity of the amino compound and the steric hindrance in its approach to the maleate di-anion. According to the Brönsted catalysis law the pKₐ's of the aminopolyols can be used to estimate the nucleophilicity of the aminopolyols with respect to each other (Table II). The somewhat larger rate constant of 1a compared to 1b and 1c can be explained by its higher nucleophilicity, supposing the steric hindrance is similar for these primary aminopolyols. Methylation of the primary amino group of D-glucamine increases its nucleophilicity, but at the same time the steric hindrance on attacking the maleate di-anion increases, which results in a rate constant for 1d that is slightly larger than that of 1c. For the non-reactive secondary amine 1e a low pKₐ is combined with increased steric crowding of the nitrogen.

**Table II. -pKₐ Values of Amino Compounds as Obtained by Potentiometry (0.1 M NaClO₄, 298 K).**

<table>
<thead>
<tr>
<th>R-NH₂</th>
<th>pKₐ a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>9.42 (9.52)</td>
</tr>
<tr>
<td>1b</td>
<td>9.17</td>
</tr>
<tr>
<td>1c</td>
<td>9.14</td>
</tr>
<tr>
<td>1d</td>
<td>9.43</td>
</tr>
<tr>
<td>1e</td>
<td>8.86 (8.90)</td>
</tr>
<tr>
<td>1f</td>
<td>9.46 (9.56)</td>
</tr>
<tr>
<td>1g</td>
<td>8.99 (9.05)</td>
</tr>
<tr>
<td>1h</td>
<td>(9.69)</td>
</tr>
</tbody>
</table>

a pKₐ values (± 0.02), I=0.1 NaClO₄ at 298 K. Values from literature (ref. 7) are in parentheses.
N-Alkylation of Amino Acids with Male.

The amino acids, glycine (1f) and L-serine (1g), could also be N-alkylated upon reaction with male at 363 K. In 1911 Stadnikow already described the alkylation of aspartate (1h) as a subsequent reaction product in the addition of ammonia to fum.29 Glycine and other amino acids were also reported to be N-alkylated with male in a Ca(OH)$_2$ catalyzed reaction, wherein Ca(OH)$_2$ was added in excess with respect to male and the amino acid.30 The addition of the cation is not necessary, although the reaction times reported seem shorter than those we have observed in the uncatalyzed reaction.30

Glycine and serine were allowed to react as such, giving a reaction mixture of pH 7.5. Both amino acid compounds reacted faster than 1a at pH 7.5. The second macroscopic $pK_a$ dissociation constant of 1f is equal to the microscopic protonation-deprotonation equilibrium of the amino group at 298 K.31 The second order rate constant of the N-alkylation of 1f with male is 2.8 times larger than that of 1a at pH 7.5, although the $pK_a$'s of the respective amino groups are the same. Apparently, the α-carboxylate group of the amino acid has an enhancing effect on the reaction rate by acting as intramolecular base. The reaction rate constants for glycine and serine are related according to their $pK_a$'s, but the rate constant for aspartate is rather low with respect to its $pK_a$. Moreover, the predominant pathway for intermediate 3h is deamination rather than C-protonation as 70% of fum and only 20% of 4h were formed after 48 h at 363 K, compared to 71% of 4f (29% fum) and 61% of 4g (31% fum) in similar experiments. Steric effects and accumulation of negative charges in the reaction of 1h may account for this. Bada and Miller did not consider the formation of 4h in the addition reaction of NH$_3$ to fum giving 1h, which can have some impact on the determined equilibrium constants.13 2-Amino-2-deoxy-D-gluconic acid was allowed to react with male too. The $^{13}$C NMR of the reaction mixture showed the characteristic aspartate signals, but a substantial amount of degradation products was formed.

O-Alkylation with Male of 4a Catalyzed by La(III).

The product 4a can be used as an intermediate in the synthesis of di-alkylated products. For O-alkylation with male it is necessary to use a multivalent metal ion as the catalyst. For the all oxygen analog of 4a, La(III) has proved to be the best catalyst for obtaining the di-0,0'-alkylated product of ethylene glycol by male.6 With the use of
stoichiometric amounts of La(III) the N,O-di-alkylated product 5 was obtained. The synthesis of 5 can be performed in a one-pot procedure. First, aminoethanol is N-alkylated with male in the absence of La(III) in an aqueous solution (pH 9.5) with a ratio of 1a/2 of 1/2, at 363 K. After 24 h the La(III) salt is added and the clear solution is heated for another 24 h (Scheme II). Addition of La(III) in the first stage of the reaction caused heavy precipitation which lowers the reaction rate initially.

Scheme II

Conclusions
The N-alkylation of amino compounds with the mono- and di-anion of male or fum occurs readily, no metal ion catalyst is required. Male reacts faster by virtue of its higher free energy of the ground state compared to fum. Both the nucleophilicity and steric hindrance determine the reactivity of the amino compound towards the olefinic bond of maleate. The formation of fum, as a side product in the reactions with male, is suppressed at higher pH. The combination of La(III) ion catalyzed O-alkylation of hydroxyl groups by male with the non-catalyzed N-alkylation of aminoethanol compounds is shown to be a way to synthesize new chelating agents.

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6. Chapter V of this thesis.
9. Chapter III of this thesis.
26. The assignment of the signals of the erythro- and threo isomers was done by $^1$H NMR based on the chemical shifts and coupling constants of aspartate: see ref. 13 and Ishizuka, H.; Yamamoto, T; Arata, Y.; Fujiwara, S. *Bull. Chem. Soc. Japan* 1973, 46, 468. The proton exchange of the methylene protons of the aspartate residue does not affect the ratio measured by $^1$H NMR as the -CO$_2$COO$^-$ formed cannot be detected.
27. Calculated with $\Delta H=-50.45$ kJ/mol (I=0, 298 K) and the Van 't Hoff equation assuming $\Delta C_p=0$.
CHAPTER VIII.

SPECIATION OF COMPLEXES BY LOTUS 1-2-3.*

Abstract: The Lotus 1-2-3 program is used for the calculation, with a set of known complex stability constants, of the distribution of complexes in aqueous solution as a function of the pH. After the minimization routine, a graph can be obtained with the graph option in the Lotus menu. Some examples of metal-ligand and metal-mixed-ligand systems from the literature are shown to be in excellent agreement with the calculations from this program. The ease of programming and the ready access to the graph options in Lotus 1-2-3 make this an attractive approach to calculation of speciation of complexes.

Introduction

Metal ions play important roles in biological systems.¹ For example, the catalytic transition in enzymes is often mediated by a metal ion bound in the active center. Metal ions are also important in maintaining or in altering the structure of enzymes or peptides. To elucidate the function of metal ions in biological systems, many model studies on binary and ternary complexes are performed. The metal ion catalyzed hydrolysis of ester or amide bonds, which serves as a model for carboxypeptidase A, is dependent on pH. It seems that the catalysis of the metal ion is significant in both the OH⁻ and the H₂O catalyzed reactions.²,³ Both reaction mechanisms take place in the pH range, in which a significant concentration of the ‘reactive’ complex exists. The concentration of ‘reactive’ ternary complexes also is of interest, e.g. with respect to the synthesis of (poly)hydroxycarboxylates catalyzed by lanthanide ions in aqueous solution.⁴

Applications of the calculation of the concentration of complexes is also quite important in such fields as analytical, environmental and geochemistry.

*van Westrenen, J.; Khizhnyak, P.L.; Choppin, G.R. submitted for publication to Comp. & Chem.
Large databases of metal ion complexes have been compiled for binary and for ternary complexes. These stability constants can be used to calculate the distribution of the concentration of the species as a function of the pH, ligand concentration, etc. Programs for this purpose can be divided in two different approaches:

i. Free-energy minimization methods as used in the program SOLWATER

ii. Utilization of non-linear equations based on the mass balance as used in CHEMEQUIL-2, COMPLEX and in the COGS procedure which is a subroutine of COMICS. These programs have been reviewed recently. Tripathi has compared the execution times of these programs using a DEC-20 computer at single precision showed CHEMEQUIL-2 was fastest. For a system containing 28 components and 282 complexes over a range of pH from 2 to 10 with increments of 0.2, the execution time was about 30 seconds.

In this article, we describe a simple computational method based on the mass balance for the calculation of the species distribution using the Lotus 1-2-3 (release 2) software and a modification of the Newton-Raphson method. Lotus 1-2-3 is a spreadsheet program for personal computers. The worksheet calculates the distribution of the species at each pH increment of a whole pH range. The well-organized style of the programming of the spreadsheets and the ready access to build-in plotting and viewing facilities, make the usage of the Lotus 1-2-3 software very attractive for calculating the distribution of species. Lotus 1-2-3's ability to plot six curves simultaneously is probably sufficient for most speciation problems.

With help of the macros commands menu and menubranch, the entire procedure can be made menu-driven. The minimization procedure, necessary for these calculations, is an iterative non-gradient method which can be adjusted easily in Lotus for many entries.

The scope of this program is demonstrated for a number of examples based on experimental data taken from the literature.

**Principle**

The concentration of protonated ligands and their (ternary) complexes can be expressed generally as

\[ [M\text{ }^m \text{ }H\text{ }^n \text{ }A\text{ }^a \text{ }B\text{ }^b] = \beta_{mnab} [M]^m [H]^n [A]^a [B]^b \]  

(1)

in which \( \beta_{mnab} \) is the stability constant for the complex present and \( M, H, A, \) and \( B \) are, respectively, concentrations of the free metal, hydrogen, and
ligands A and B. The integers m, n, a, and b refer to the number of M, H, A, and B in a particular complex (m, a, b ≥ 0).

If m=0, a or b =0 and n (n≥0) is dependent on the number of associated protons on A or B. In case m=1, n=0 the binary complexes MA, and MB, and ternary complexes MAaBb can be present. The situation with m=1 and n<0 refers to a metal-hydroxide complex, M(OH)\(_i\), (a=b=0) and to complexes with A and/or B and additional hydroxide ligands (e.g., MA\(_a\)(OH)\(_i\)) or complexes in which ligand A or B are more highly deprotonated (a=b≠0). The MA\(_a\)(OH) and M\(H\)\(_{-1}\)A\(_a\) complexes cannot be distinguished simply from the stability constants.

For the species distribution of a mixed two-ligand system, if only monomeric complexes are assumed to be formed, it is possible to deduce three mass balance equations (charges are omitted for simplicity):

\[
\hat{C}_M = \Sigma \beta_{10ab}[M][A]^a[B]^b \tag{2}
\]

\[
\hat{C}_A = \Sigma a\beta_{10ab}[M][A]^a[B]^b + \Sigma \beta_{0na0}[H]^n[A] \tag{3}
\]

\[
\hat{C}_B = \Sigma b\beta_{10ab}[M][A]^a[B]^b + \Sigma \beta_{0no0}[H]^n[B] \tag{4}
\]

To take into account the hydrolysis of M ions term (5) is added to the right side of equation (2):

\[
\Sigma \beta_{1n00}[M][H]^n \quad \text{whereby } n<0. \tag{5}
\]

Since \(\beta_{10ab}, \beta_{0na0}, \beta_{0no0}, [M], [A], [B], [H] > 0\), the partial derivatives:

\[
\frac{\partial \hat{C}_M}{\partial [M]}, \frac{\partial \hat{C}_M}{\partial [A]}, \frac{\partial \hat{C}_M}{\partial [B]} > 0 \tag{6}
\]

\[
\frac{\partial \hat{C}_A}{\partial [M]}, \frac{\partial \hat{C}_A}{\partial [A]}, \frac{\partial \hat{C}_A}{\partial [B]} > 0 \tag{7}
\]

\[
\frac{\partial \hat{C}_B}{\partial [M]}, \frac{\partial \hat{C}_B}{\partial [A]}, \frac{\partial \hat{C}_B}{\partial [B]} > 0 \tag{8}
\]

At a constant pH the calculated overall concentrations \(\hat{C}_M, \hat{C}_A, \text{ and } \hat{C}_B\) do not depend on [H], i.e.:

\[
\frac{\partial \hat{C}_M}{\partial [H]} = \frac{\partial \hat{C}_A}{\partial [H]} = \frac{\partial \hat{C}_B}{\partial [H]} = 0 \tag{9}
\]
At given $C_M$, $C_A$, $C_B$ the functions $\Delta C_M = C_M - \hat{C}_M$, $\Delta C_A = C_A - \hat{C}_A$, and $\Delta C_B = C_B - \hat{C}_B$ change simultaneously with $[M]$, $[A]$, and $[B]$, respectively. Here, the demand to determine $[M]$, $[A]$, and $[B]$ is equivalent to the demand to determine $[M]$, $[A]$, and $[B]$ when, simultaneously, $\Delta C_M = 0$, $\Delta C_A = 0$, and $\Delta C_B = 0$. For computation, this problem is reduced to the minimization in general ($X = M, A, B$):

$$|\Delta C_X| \rightarrow \text{Min}$$ (10)

which can be solved by an iterative non-gradient method close to the relaxation method:

$$[M]_{t+1} = [M]_t * f(\Delta C_M)$$

$$[A]_{t+1} = [A]_t * f(\Delta C_A)$$

$$[B]_{t+1} = [B]_t * f(\Delta C_B)$$

where $f(0) = 1$ (11).

The most difficult problem is the choice of the function $f(\Delta C_X)$. This function is responsible for the success of the iteration procedure. We suggest the following function $f(\Delta C_X)$ in the general case ($X = M, A, B$):

$$f(\Delta C_X) = (1 - \text{Rand} \times \Delta C_X / (C_X + \hat{C}_X))$$ (12).

The Rand function is a random value uniformly distributed in the range $(0, 1)$. This function protects the iteration procedure from getting stuck. A direct verification shows that the function (12) meets all the conditions indicated above.

**Worksheet Organization**

The Lotus 1-2-3 program can be used for these kind of formulae and many $H^+$ concentrations at the same time. For instance, pH range from 1 increasing with 0.05 to 14 (fill option Lotus). The random number is generated by Lotus using the function @RAND. For using the iteration method in this calculation, one has to reset the automatic recalculation of the worksheet to the manual and the columnwise recalculation. In this way, the $[M]$, $[A]$, and $[B]$ in the first column can be substituted after using these values in the $[M]_n, [A]_n, [B]_n$ column calculation by the new $[M],[A]$, and $[B]$ calculated in the last three columns according to equation (11 and 12). This can be done because the addresses in the first three columns refer to the last columns. In this way Lotus provides a circular change of $[M],[A]$, and
[B] (CIRC flag activated).

The iteration procedure is started by copying the estimated [M], [A], and [B] from equation (13) into the first three columns. After having recalculated the entire worksheet the absolute column addresses of the last three columns are copied into the first three columns.

\[
[M] = \hat{C}_M / \Sigma \beta_{mnab}; \quad [A] = \hat{C}_A / \Sigma \beta_{mnab}; \quad [B] = \hat{C}_B / \Sigma \beta_{mnab} \tag{13}
\]

The iteration criterium in case of more \(H^+\) concentration entries is defined as in equation (10) with the extension that, from the columns for the calculated \(\hat{C}_M\), \(\hat{C}_A\), and \(\hat{C}_B\), the maximum absolute deviation with the used total concentrations \(C_M\), \(C_A\), and \(C_B\) is taken. This is provided by the functions \(\text{MAX}(\text{column-addresses})\) and, for the negative values, \(\text{MIN}(\text{column-addresses})\) in the Lotus menu. The iteration is repeated until the maximum deviation of \(|\Delta C_X|\) (X=M, A, B) is smaller than 0.001% of \(C_X\).

A fully preprogrammed approach to calculate the species distributions can be prepared by making a menu-driven guidance, which is readily available by the menu and menubranch commands in 1-2-3, in combination with the automatically execution option upon retrieval (\(\backslash O\) macro command). This approach is, especially, convenient for those, who are unfamiliar with programming in 1-2-3.

When familiar with programming in 1-2-3, it is also possible to program the worksheets without supplementary menus. In this case, a more simple macro is sufficient, which only directs the circular calculation procedure (see APPENDIX), all other necessary actions can be performed with the ordinary 1-2-3 menu commands. The simplicity of these macro-directed worksheets is advantageous to the large macros of the menu-driven worksheet, when small adjustments to the worksheets are needed. For additional editing of the worksheets, one should preferably use the move command in 1-2-3, which assures automatic readjustments of the remaining cell-formulae. Upon entering (deleting) \([M_H A B]\) columns, one also have to adjust the \(\hat{C}_M\), \(\hat{C}_A\), \(\hat{C}_B\) columns and the estimated [M], [A], and [B] from equation (13) (see APPENDIX for their cell positions). A change of the number of ligands requires a more radical reorganization; almost the entire worksheet has to be reset according to the procedure described above for the ligands A and B. Special attention must be paid to the macro. The macro is not automatically readjusted by the move command, and therefore, has to be changed on changing the number of ligands.
Results

The worksheets in Lotus have been tested for a variety of metal ligand systems with an M240 Olivetti equipped with a CPU 8086 and with 640 KB available memory for program execution.

For the mixed ligand system M-ligand A-ligand B, the concentration of binary complexes MA\textsubscript{A}, MB\textsubscript{B}, and ternary complexes MA\textsubscript{A}B\textsubscript{B} are calculated as a function of the pH by fitting the free metal ion, and ligand A and B concentrations into the equilibrium equations defined by eq. (1). An example of the speciation of the mixed ligand systems is that of Cu(II)-histamine-serine in the pH range from 2 to 8, in which hydrolysis of the metal ion can be omitted.\textsuperscript{12}

![Graph showing pH vs. Concentration of various species.]

Figure 1. Calculated species distribution for the Cu(II)-histamine-serine mixed ligand system as a function of pH, using the data of Perrin (ref. 12). Ha = histamine, ser = serine; I = 0.15 M (KNO\textsubscript{3}), 298 K, [Cu]\textsubscript{tot} = [Ha]\textsubscript{tot} = [Ser]\textsubscript{tot} = 10^{-3} M.

<table>
<thead>
<tr>
<th>Species</th>
<th>log $\beta_{\text{mnnab}}$</th>
<th>Species</th>
<th>log $\beta_{\text{mnnab}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hha</td>
<td>9.569</td>
<td>Cu(ha)</td>
<td>9.278</td>
</tr>
<tr>
<td>$H_2$ha</td>
<td>15.581</td>
<td>Cu(ha)$_2$</td>
<td>15.577</td>
</tr>
<tr>
<td>Hser</td>
<td>8.841</td>
<td>Cu(ser)</td>
<td>7.565</td>
</tr>
<tr>
<td>Hser$_2$</td>
<td>11.021</td>
<td>Cu(ser)$_2$</td>
<td>14.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cu(ha)(ser)</td>
<td>16.27</td>
</tr>
</tbody>
</table>
The resulting graph with pH increments of 0.05 (95 entries in Lotus) given in Figure 1 is in excellent agreement with the plots shown and calculated by Sigel.\textsuperscript{13} The calculation took an hour for a precision of 0.001 % (750 iteration are performed).

The dimensions of this worksheet are rather limited; the speciation of the mixed ligand system can only be calculated using dibasic ligands A and B and for complexes $MA_{a}B_{b}$ with $a,b=0-3$ and $a+b\leq 3$. Many metals, however, can form additional hydroxy complexes. Tri- or polybasic ligands are quite common in ligand distributions as, for example, is shown in the complexation of Al(III) by citrate.\textsuperscript{14} It is quite conceivable to extend the menu-driven worksheet to a more general one, which can be applied for almost all speciation problems, but this worksheet will become very lengthy and, might even become too big to fit into memory for most personal computers. Lengthy worksheets also result in undesirable long execution times for comparably small speciation problems. Therefore, it is more convenient to work with worksheets that are adjusted to each specific speciation problem. This is a less useful approach for newcomers in 1-2-3's worksheet operation, but for the skilled 1-2-3 user, a few minutes are required to make the changes. The editing of worksheets is described in the WORKSHEET ORGANIZATION.

For Al(III)-citrate the adjustments of the worksheet have been performed. The resulting worksheet is described in the APPENDIX. In the speciation of Al(III)-citrate,\textsuperscript{14} four mononuclear hydroxy-complexes are present. The citrate ligand forms three different Al(III):citrate 1:1 complexes varying in ionization state of the citrate. Ionization of the hydroxyl group of citrate upon coordinating the Al(III) is claimed.

The free metal and citrate concentration were fitted into equations (1). Because of the large number of species dependent on these two variables, it took 3 hours for a deviation ($\Delta C_{x}/C_{x}$) of 0.1 % with a pH increment of 0.1. The plot made with this precision shows an excellent agreement with the results of Motekaitis and Martell (Figure 2).\textsuperscript{14} As the curves drawn in a plot by Lotus is limited to 6 species, two plots were overlaid.

Metal hydrolysis alone can also be calculated. In this case only the free metal ion concentration has to be fitted, which leads to a reduction of the length of the worksheet. The hydrolysis of Fe(II) was taken as an example. At the concentration Fe(II) used, the presence of binuclear complexes can be neglected.\textsuperscript{15} The plot in Figure 3 with a pH increment of 0.1 shows a good agreement with the results of Baes and Mesmer.\textsuperscript{15} These calculations with
Figure 2. Calculated species distribution for the Al(III)-citrate system as a function of the pH, using the data of Motekaitis and Martell (Ref. 14). cit = citrate; [Al(III)]_{tot} = [Cit]_{tot} = 2 \cdot 10^{-3} \text{ M}, I=0.1 \text{ M (KNO}_3), 298 \text{ K. aBaes and Mesmer, } I=0.1 \text{ M (NaClO}_4) (Ref. 16). bBaes and Mesmer, } I=0 (Ref. 15).

<table>
<thead>
<tr>
<th>Species</th>
<th>log$\beta_{mnab}$</th>
<th>Species</th>
<th>log$\beta_{mnab}$</th>
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</thead>
<tbody>
<tr>
<td>Hcit</td>
<td>5.71</td>
<td>AlOH$_3$$^a$</td>
<td>-15.6</td>
</tr>
<tr>
<td>$H_2$cit</td>
<td>10.1</td>
<td>AlOH$_4$$^a$</td>
<td>-23.0</td>
</tr>
<tr>
<td>$H_3$cit</td>
<td>13.13</td>
<td>Al(Hcit)</td>
<td>10.92</td>
</tr>
<tr>
<td>AlOH$^a$</td>
<td>-5.30</td>
<td>Al(cit)</td>
<td>7.98</td>
</tr>
<tr>
<td>AlOH$_2$$^a$</td>
<td>-9.90</td>
<td>Al(H$_{-1}$cit)</td>
<td>4.67</td>
</tr>
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</table>

Lotus took about 3 minutes.

Although, the calculations are much slower than with CHEMEQUIL-2, the ease of programming, of adjustments of the worksheets and of direct entrance to the graph options make these worksheet calculations useful, especially for problems containing up to 20 complexes. The fully automatic spreadsheet, which is presented, can be used by newcomers in the field without the knowledge of programming 1-2-3. The memory limitations of the computer withholds the preparation of one general automatic spreadsheet for a large number of speciation problems. This makes adjustments of the worksheets to
Figure 3. Calculated species distribution for the Fe(OH)ₙ complexes as a function of the pH, using the data of Baes and Mesmer (Ref. 15). [Fe(II)]ₜₐₜ=10⁻³ M, I= 1.0 M, 298 K.

<table>
<thead>
<tr>
<th>Species</th>
<th>log βₜₐₜ₅</th>
<th>Species</th>
<th>log βₜₐₜ₅</th>
</tr>
</thead>
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<tr>
<td>FeOH</td>
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<td>FeOH₃</td>
<td>-31.21</td>
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<tr>
<td>FeOH₂</td>
<td>-21.061</td>
<td>FeOH₄</td>
<td>-45.318</td>
</tr>
</tbody>
</table>

each specific speciation problem necessary, which somewhat limits the practicability for less experienced users of 1-2-3.

The minimization procedure adjusted to 1-2-3 shows a good convergence in all cases. Similar procedures can be used for other minimization procedures within 1-2-3.

Acknowledgements

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References

### Appendix

Al-Citrate. M=Al(III), B=Citrate, A=hydroxide.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
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<td>[B]</td>
<td>[MA_n]</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>BH</td>
<td>5.13E+05</td>
<td>2.00</td>
<td>10(^{(-C3)})</td>
<td>+$L3</td>
<td>+$M3</td>
<td>+$B$(6/9)*$E3/($D3)^n</td>
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<tr>
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<td>\textit{Total M concentration}</td>
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<tr>
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<td>C_B</td>
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<td></td>
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<td>\textit{Total B concentration}</td>
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<table>
<thead>
<tr>
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<tr>
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<td>[M]</td>
<td>[B]</td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

28 \(+L28\) \(+M28\) \textit{Provides circ. calc.}

29 \(+B14/\text{SUM(B3..B12)}\) \(+B15/\text{SUM(B3..B12)}\) \textit{Initial estimations of free M, free B determined by eq (13). These cell formulae are copied into the species columns by copy commands in the macro.}

32 \% M = \ldots \left| \hat{C}_M - C_M \right| \quad @MAX(@ABS(@MAX($J3..$J100) - $B$14)),

33 \% B = \ldots \left| \hat{C}_B - C_B \right| \quad @MAX(@ABS(@MAX($K3..$K100) - $B$15)),

34 MAX = \ldots \left| \Delta C_X \right| \quad @MAX($B$32..$B$33)

36 Criterion \quad 1.00E-05
$H$

$\begin{array}{l}
01 \quad [MB_n] \\
02 \\
03 +$BS$(10/12)*$D3^n*$E3*$F3 \\
\end{array}$

$J$

$\begin{array}{l}
01 \quad \hat{c}_M \\
02 \\
03 +$E3+$G3+$H3 \\
\end{array}$

$K$

$\begin{array}{l}
01 \quad \hat{c}_B \\
02 \\
03 +$F3+$H3*$n+$I3 \\
\end{array}$

$L$

$\begin{array}{l}
01 \quad [M]_{\text{new}} \\
02 \\
03 +$E3*(1-@RAND*($J3-$BS$14)/($J3+$BS$14)$)$
\end{array}$

$M$

$\begin{array}{l}
01 \quad [B]_{\text{new}} \\
02 \\
03 +$F3*(1-@RAND*($K3-$BS$15)/($K3+$BS$15)$)$
\end{array}$

Macro:

```
/Z '/c$A$29.$B$29-$E$3- ............... Copy procedure to enter
  (goto)$E$3-/c(right)-.(end)(down)- estimated M, B into columns
  (calc) E and F.
/c$A$28.$B$28-$E$3- ............... Copy procedure to enter
  (goto)$E$3-/c(right)-.(end)(down)- cell-addresses of the new M
  (home) and new B of the last two
  (calc) columns that provides the
 LOOP (if $BS$34<$BS$36)(branch QUIT)
  (branch LOOP) circular calculation.
 QUIT /qn- Minimization procedure
     with selection test.
```
SUMMARY.

This thesis describes the synthesis of ether carboxylates by O-alkylation of hydroxyl-containing compounds with maleate homogeneously, catalyzed by Lanthanide(III) ions (Ln(III)). The synthesized compounds can be applied in detergent formulations as sequestering agents for Ca(II) and Mg(II) ions. The use of maleate, a widely available α,β-unsaturated dicarboxylate, in a Michael-type addition reaction leads to the introduction of butanedioate (also: succinate) residues in hydroxyl containing compounds. The O-alkylation requires a metal ion as catalyst, which is able to serve as a focal point for both reactants and activates the hydroxyl donor group by deprotonation. The recycling of the Ln(III) ion is feasible.

The O-alkylation of glycolate (ga) with maleate (male) is catalyzed by Ln(III) in aqueous solution and yields carboxymethoxysuccinate (cmos). This reaction was studied by reaction kinetics, potentiometry, NMR, and luminescence giving a vast amount of information on the reaction mechanism (Chapter II, III, IV). Based on this knowledge the scope of the O-alkylation could be extended and other ether carboxylates were prepared using Ln(III) ions as well as other metal ions as the catalyst (Chapter V, VI, VII).

In Chapter I the different modes of action of a metal ion in promoting reactions upon coordination are discussed with emphasis on its Lewis acidity and coordination characteristics. The factors that determine the coordination behavior of hard metal ions are reviewed, followed by a discussion on the template effect of metal ions and on the activation of chemical bonds upon coordination of the metal ion. Some examples of intramolecular metal ion catalyzed reactions are given. Finally, specific considerations for the usage of Ln(III) ions and an outline of the thesis are presented.

In Chapter II it is shown that the La(III) catalyzed O-alkylation of ga with male yielding cmos only proceeds above pH 6, which indicates that the La(III) coordinated hydroxyl group of ga is ionized (H$_{-}$1ga) in a pre-equilibrium for the rate limiting addition of the CH$_{2}$O$^{-}$ to the olefinic bond. Due to strong complexation of La(III) by cmos, the reaction requires about one La(III) per two cmos formed. The inhibitory effects of
non-reacting strong chelators such as ethylenediaminetetra-acetate, nitrilotriacetate, and dipicolinate indicate that ternary complexes are formed, wherein the addition reaction occurs. This has been confirmed by Gd(III)-induced $^{13}$C relaxation rate enhancements, and Dy(III)-induced $^{17}$O shift measurements.

In Chapter III the same reaction including other Ln(III) ions as catalyst is discussed. The additional information obtained from reaction kinetics has resulted in a more refined understanding of the reaction mechanism. The reaction takes place in a ternary complex of Ln(male)(ga) with the addition of the ionized Ln(III) coordinated hydroxyl group of ga to the olefinic bond of male as the rate determining step with a first order rate constant in the ternary complex of about 1 min$^{-1}$. The fast equilibrium between binary and ternary complexes made it necessary to calculate, the amount of the ternary complex Ln(male)(ga) formed in the mixed ligand system from its stability constants. The stability constants of the binary complexes Ln(ga)$_n$, Ln(male)$_n$, Ln(cmose)$_n$ (n=1,2), and the ternary complex Ln(male)(ga), were determined potentiometrically. It appears that the ternary complex formation is determined statistically. The stability constant of the ternary complex can be estimated from the averaged contribution of the ligands in the binary complexes Ln(ga)$_2$ and Ln(male)$_2$ multiplied with a the statistical factor of two.

The pK$_a$ for the ionization of the Ln(III) coordinated hydroxyl group of ga could be obtained indirectly from the reaction kinetics. The existence of the Ln(III) coordinated H$_2$ga ligand was supported by $^{13}$C NMR. The effective charge density of the cation plays an important role in decreasing the pK$_a$ of a hydroxyl group of ga upon coordination. This effect is somewhat counteracted by a concomitant decrease of the nucleophilicity of resulting alcoholate group in the addition reaction.

A remarkable stereoselectivity is observed for the Ln(III) catalyzed reverse reaction, wherein the building units male and ga were formed from cmose. During the reaction, the Ln(III) ion apparently holds the carboxylate groups of the butanedioate part in the 'cis'-configuration. This reaction resembles enzymatic reactions as that of aconitase.

In Chapter IV it is demonstrated that the Ln(III) catalyzed O-alkylation of ga with male can be studied on-line with help of an optical fiber setup, monitoring the luminescence of the Eu(III) optical probe. During the reaction the $^5$D$_{0}$→$^7$F$_0$ transition shifts to lower wavenumbers and the average lifetime of the excited $^5$D$_{0}$ level of the Eu(III) ion increases, when
substantial amounts of Eu(cmos)₂ are formed. The average number of OH oscillators in the first coordination sphere of the Eu(III) ion is decreased by two if one cmos per Eu(III) is formed. The concentration of cmos can be obtained by on-line measurements of the lifetime of the ⁵D₀-excited state.

A Michael-type addition reaction of polyhydroxyl compounds, e.g. ethylene glycol and glycerol, to maleate, homogeneously catalyzed by multivalent metal ions, is described in Chapter V. 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. With small ions with a high charge density, such as Ti(IV) and Al(III), mono-O-alkyl dicarboxylates are obtained exclusively, whereas metal ions with a large ionic radius give rise to higher O-alkylated polyhydroxyl compounds. The formation of the latter products can be enhanced by the use of stoichiometric amounts of catalyst. The reactions are performed in the polyol as solvent, whenever possible. With solid polyols, as erythritol and mannitol, some water is used as co-solvent. Large amounts of water interfere in the first O-alkylation step, but not in subsequent steps.

In Chapter VI the structures and stabilities of Ln(III) complexes occurring in the reaction mixture of a Ln(III) catalyzed O-alkylation of ethylene glycol with maleate have been investigated with the use of ¹³⁹La, ¹⁷⁰, and ¹³C NMR shift and relaxation measurements and with potentiometry. In ethylene glycol the Ln(III) ion appears to be coordinated by 9 oxygen atoms of that compound. The chloride anion is not present in the first coordination sphere of the Ln(III) ion. The Ln(III) ions have some preference for coordination of ethylene glycol over that of water. Maleate is able to coordinate with the Ln(III) ions in ethylene glycol medium. The mono-O-alkylation product of ethylene glycol forms 1:1 and 1:2 complexes with the Ln(III) ions, in which the ligand is bound in a tetradeinate fashion via the two carboxylate groups and the two oxygens of the ethylene glycol residue. The Ln(III) coordination of the di-O,O'-alkylation product is analogous; all carboxylate groups and ether oxygens are coordinated.

The N-alkylation of aminopolyols and amino acids by a Michael-type addition with maleate or fumarate in aqueous medium is presented in Chapter VII. This reaction occurs readily at 363 K in the absence of metal ions. Maleate reacts faster than fumarate by virtue of the higher free energy of the ground state. For a series of amino compounds the second order rate constants are related to the nucleophilicity of the nitrogen atom and the steric hindrance involved. N-Alkylation of aminohydroxyl compounds and,
subsequent Ln(III) ion catalyzed O-alkylation of hydroxyl groups with maleate in aqueous solution is shown to be a promising way to synthesize new chelating agents.

In Chapter VIII, the Lotus 1-2-3 program is used for the calculation, with a set of known complex stability constants, of the distribution of complexes in aqueous solution as a function of the pH. After the minimization routine, a graphical presentation can be obtained with the graph option in the Lotus menu. Some examples of metal-ligand and metal-mixed-ligand systems from the literature are shown to be in excellent agreement with the results obtained from this program. The ease of programming and the ready access to the graph options in Lotus 1-2-3 make this an attractive approach to calculation of speciation of complexes.
SAMENVATTING

Dit proefschrift beschrijft de synthese van etherpolycarboxylaten door O-alkylieing van hydroxylgroep bevattende verbindingen met maleaat, waarbij lanthanide(III)-ionen (Ln(III)) worden gebruikt als homogene katalysator. De gesynthetiseerde verbindingen kunnen vanwege hun Ca(II)- en Mg(II)-sekwesterende vermogen worden toegepast in wasmiddelformuleringen. Het gebruik van maleaat, een op grote schaal verkrijgbaar α,β-onoverzadigd-dicarboxylaat, in een Michael-achtige reactie leidt tot de introductie van butaadioaat (ook: succinaat) eenheden in hydroxylgroep bevattende verbindingen. De O-alkylieing wordt gekatalyseerd door een metaal-ion, dat in staat is door middel van coördinatie de beide reactanten bij elkaar te brengen en de gecoördineerde hydroxylgroep door deprotonering te activeren. Het terugwinnen van het Ln(III) ion voor hergebruik is mogelijk.

De bestudering van de Ln(III)-gekatalyseerde O-alkylieing van glycolaat met maleaat, gebruikmakend van reactiviekinetiek, potentiometrie, multikern magnetische resonantie en luminescentie heeft een grote hoeveelheid informatie opgeleverd over het reactiemechanisme (Hoofdstukken II, III, IV). Gebaseerd op dit reactiemechanisme zijn syntheses van andere etherpolycarboxylaten met Ln(III)-ionen en andere metaal-ionen als katalysator ontwikkeld (Hoofdstukken V, VI, VIII).

In Hoofdstuk I worden de verschillende mogelijkheden van beïnvloeding door metaal-ion coördinatie op diverse reacties besproken, waarbij de nadruk ligt op het Lewis-zure karakter van het metaal-ion en zijn coördinatiegedrag. De factoren, die het coördinatiegedrag van ‘harde’ metaal-ionen bepalen, worden belicht als basis voor de daaropvolgende discussie over het template-effect van metaal-ionen. Vervolgens wordt de activering van functionele groepen door metaal-ioncoördinatie in gekatalyseerde reacties besproken. Er worden enkele voorbeelden van intramoleculaire metaal-ionegekatalyseerde reacties gegeven. Tot besluit worden enkele specifieke overwegingen voor het gebruik van Ln(III)-ionen in intramoleculair verlopende reacties gegeven, gevolgd door een overzicht van de opzet van het proefschrift.

In Hoofdstuk II wordt getoond dat de La(III)-gekatalyseerde O-alkylieing van glycolaat met maleaat resulterend in carboxymethoxysuccinaat (cmos)
alleen boven pH 6 verloopt. Dit duidt erop dat de La(III)-gecoördineerde hydroxylgroep van glycolaat wordt geioniseerd in een evenwicht voorafgaande aan de snelheidsbepalende stap: de additie van het gecoördineerde alkoholaat aan de olefinische band van maleaat. Als gevolg van de sterke coördinatie van cmos aan La(III), is voor de vorming van twee moleculen cmos ongeveer één La(III)-ion nodig. De remmende werking van sterk coördinerende niet-reagerende chelaten, zoals ethyleendiaminetetraacetaat, nitrilotriacetaat en dipicolinaat, duiden op de vorming van ternaire complexen, waarin de additie plaatsvindt. NMR technieken als Gd(III)-geïnduceerde $^{13}$C-relaxatieversnellingen en Dy(III)-geïnduceerde $^{17}$O-shifts bevestigen de vorming van ternaire complexen.

Dezelfde reactie met inbegrip van andere Ln(III)-ionen als katalysator wordt beschreven in Hoofdstuk III. De extra informatie, die is verkregen met behulp van reactiekinetiek heeft geleid tot een beter begrip van het mechanisme dat ten grondslag ligt aan de Ln(III)-gekatalyseerde 0-alkylering van glycolaat met maleaat. De reactie vindt plaats in een ternair-complex Ln(male)(ga) met een eerste orde reactiesnelheidsconstante van ongeveer 1 min$^{-1}$. De additie van de geioniseerde gecoördineerde hydroxylgroep van glycolaat aan maleaat is snelheidsbepalend. Omdat de evenwichtsinstelling tussen binaire- en ternaire-complexen snel is, moest de concentratie van het ternaire-complex Ln(male)(ga) in een gemengd ligand systeem berekend worden uit de bijbehorende stabiliteitsconstanten. De stabiliteitsconstanten van de binaire-complexen Ln(ga)$_n$, Ln(male)$_n$ en Ln(cmos)$_n$ (n=1,2) en het ternaire-complex Ln(male)(ga) werden potentiometrisch bepaald. Het blijkt dat de ternaire-complexvorming statistisch is bepaald. De stabiliteitsconstante van het ternaire-complex kan geschat worden uit de gemiddelde bijdrage van de liganden in de 1:2 binaire-complexen vermengd volgend met de statistische factor van twee.

De pK$_a$ van de ionisatie van de Ln(III)-ion gecoördineerde hydroxylgroep van glycolaat kon indirect worden verkregen uit de reactiekinetiek. Het voorkomen van de ionisatie van de Ln(III)-ion gecoördineerde hydroxylgroep van het glycolaat ligand kon worden bevestigd met $^{13}$C-NMR. De effectieve ladingsdichtheid van het metaal-ion speelt een belangrijke rol in de verlaging van de pK$_a$ van de gecoördineerde hydroxylgroep van glycolaat. Dit effect wordt gedeeltelijk gecompenseerd door de gelijktijdig optredende verlaging van de nucleophiliciteit van de gecoördineerde hydroxylaaggroep in de additierreactie.
Een opmerkelijke stereoselectiviteit is waargenomen voor de Ln(III)-gekatalyseerde teruggaande reactie. Vanuit cmos worden de oorspronkelijke bouwstenen, maleaat en glycoaat, teruggevormd gelijk enzymkatalyse (bv. aconitase). Het Ln(III)-ion houdt door coördinatie het butaandioaat-gedeelte in de overgangstoestand vast in de cis-configuratie.

In Hoofdstuk IV wordt aangetoond dat de Ln(III)-gekatalyseerde 0-alkylering van glycoaat aan maleaat "on-line" bestudeerd kan worden met lasergekoppelde optische fibers, waarmee het luminescentie-sinaal van het Eu(III)-ion wordt gemeten. Tijdens de reactie verschuift de $^5D_0\rightarrow^7F_0$-overgang naar lagere golfgetallen en wordt de levensduur van het aangeslagen $^5D_0$-nivo van het Eu(III)-ion groter bij de vorming van voldoende hoge concentraties Eu(cmos)$_2$. Het gemiddelde aantal OH-vibratoren in de eerste coördinatiesfeer van het Eu(III)-ion neemt af met twee zodra één molekuil cmos per Eu(III) is gevormd. Met behulp van de "on-line" metingen van de levensduur van het $^5D_0$-nivo kan de concentratie van het gevormde cmos worden bepaald.


In Hoofdstuk VI zijn de structuren en stabiliteiten van Ln(III) complexen, die voorkomen in het reactiemengsel van de Ln(III)-gekatalyseerde O-alkylering van ethyleenglycol met maleaat onderzocht gebruikmakend van $^{139}$La, $^{170}$, $^{13}$C NMR shift- en relaxatiemetingen en van potentiometrie. In ethyleenglycol blijkt dat het Ln(III)-ion gecoördineerd is door negen zuurstofatomen van deze verbinding. Het chloride-anion bevindt zich niet in de eerste coördinatiesfeer van het Ln(III)-ion. De Ln(III)-ionen hebben enige voorkeur voor de coördinatie van ethyleenglycol boven water. Maleaat
is in staat met Ln(III)-ionen te coördineren in een medium van ethyleenglycol. Het mono-O-gealkyleerde product van ethyleenglycol vormt 1:1 en 1:2 complexen met Ln(III)-ionen, waarin het ligand op tetradentate wijze, via beide carboxylatgroepen en de twee zuurstofgroepen van het ethyleenglycolgedeelte, is gebonden. De Ln(III)-coördinatie van het di-O,O'-gealkyleerde product is analoog; alle carboxylaat- en ethergroepen zijn gecoördineerd.

De N-alkylering van aminopolyolen en aminozuren door Michaelachtige-reactie met maleaat of fumaraat in waterig milieu wordt in Hoofdstuk VII gepresenteerd. Deze reactie verloopt eenvoudigweg in afwezigheid van metaal-ionen bij 363 K. Maleaat reageert sneller dan fumaraat doordat de vrije energie van de grondtoestand hoger is. Voor een aantal aminoverbindingen zijn de tweede orde reactiesnelheidsconstanten gerelateerd aan de nucleofiliciteit van het stikstof atoom en de mate van sterische hindering. Een tweestapssynthese van de niet-gekatalyseerde N-alkylering van aminoethanol met maleaat gevolgd door een Ln(III)-gekatalyseerde O-alkylering van de hydroxylgroep met maleaat is een veelbelovende syntheseroute naar nieuwe chelatoren.

In Hoofdstuk VIII is het Lotus 1-2-3 programma gebruikt voor de berekening van concentraties van deeltjes in oplossing als functie van de pH uitgaande van een bekend stel stabiliteitsconstanten. De resultaten kunnen grafisch worden weergegeven met behulp van de 'graph'-optie in het Lotusmenu. Enkele voorbeelden van metaal-ligand en metaal-gemengd-ligand systemen uit de literatuur zijn uitgekend in overeenstemming met de resultaten verkregen met dit programma. Het gemakkelijke programeren en de eenvoudige toegang tot 'graph'-opties in Lotus 1-2-3 maken dit programma aantrekkelijk om de verdeling van complexen als functie van de pH te berekenen.
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CURRICULUM VITAE.