

AN NMR STUDY OF GADOLINIUM(III) HYDROXYCARBOXYLATE COMPLEXES IN AQUEOUS
MEDIUM USING Gd(III) INDUCED ^{13}C RELAXATION RATE ENHANCEMENTS

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ABSTRACT — The complexation of gadolinium(III), as a model cation for calcium(II), with a series of (hydroxy)carboxylates in aqueous medium has been studied by NMR using the Gd(III) induced relaxation rate enhancements of the ^{13}C nuclei of the ligands. In this way the coordination behaviour of a number of essential structural units has been investigated, i.e. the carboxylate group, the 2- and the 3-hydroxycarboxylate moiety, the 2,3-dihydroxycarboxylate moiety, and combinations thereof. The results show that (i) an isolated carboxylate group coordinates in a bidentate fashion, (ii) a 2-hydroxycarboxylate moiety coordinates bidentately through a carboxylate oxygen and a hydroxyl oxygen, (iii) a 3-hydroxycarboxylate moiety largely acts as a bidentate ligand through the two carboxylate oxygens, (iv) a 2,3-dihydroxycarboxylate moiety acts largely as a bidentate ligand through one of the carboxylate oxygens and the α -hydroxyl group; the contribution of the β -hydroxyl group to the complexation is of minor importance.

The lanthanide(III) cations are chemically closely related to Ca(II) cations and, therefore, the paramagnetic Ln(III) cations are useful NMR-probes for the 'silent' Ca(II) in the structural analysis of Ca(II) complexes in solution.¹⁻³ Coordination phenomena of polyoxygen compounds with Ca(II) in aqueous medium are of interest because of the essential role of Ca(II) in the regulation of biological processes and also because of the relation with the search for suitable phosphate substitutes in detergent formulations.

In principle Ln(III) induced shifts contain information on the stoichiometry of the complexes, the chelation of the ligands, and the geometry of the complex in solution.^{4,5} In order to fully utilize the information present in the Ln(III) induced shifts it is important to dissect shifts into contributions of the various shift mechanisms.^{6,7} Previously, we have shown that, in this analysis, it may be helpful to identify the coordination sites of the ligands.⁸ Therefore, we have investigated the applicability of Gd(III) induced relaxation rate enhancements to a series of hydroxycarboxylates in aqueous solution.⁹ Since the effect measured usually is inversely proportional to the sixth power of the distance between Gd(III) and the nucleus under consideration, Gd(III) induced relaxation enhancements are particularly suitable for the elucidation of the geometry of the ligand in the proximity of the Gd(III) cation.

THEORY

Of the Ln(III) cations Gd(III) has the longest electronic relaxation times, and therefore that ion is best suited as paramagnetic relaxation reagent. An extensive description of relaxation phenomena can be found in literature.¹⁰

The relaxation rates of ligand nuclei in Gd(III) complexes usually are very large ($> 10^3 \text{ s}^{-1}$). Therefore ^{13}C relaxation time measurements, which are commonly performed at relatively high concentrations of the ligand L (0.1-1 M), are carried out at low molar Gd(III)/L ratios ($\rho < 10^{-3}$). Under these conditions Gd(III) will be mainly present in its highest liganded state GdL_m ($m = 2$ or 3 for hydroxycarboxylates), whereas self-association phenomena³ can be neglected. Assuming that the mean residence time of the ligand in the Gd(III) complex is short with respect to the

longitudinal relaxation time, $T_1(GdL_m)$, the observed relaxation rate, $1/T_1(\text{obs})$, can be expressed as:¹¹⁻¹³

$$1/T_1(\text{obs}) = \omega_0/T_1(GdL_m) + 1/T_1(L) + 1/T_{\text{linter}} \quad (1)$$

Here $1/T_{\text{linter}}$ is the contribution of intermolecular interactions to the relaxation,¹⁴ which is proportional to the amount of Gd(III) added. So, a plot of the relaxation of a nucleus ($1/T_1(\text{obs}) - 1/T_{\text{linter}}$) versus ρ should be linear with a slope, that is determined by the relaxation rate of that nucleus in the Gd(III) complex.

The relaxation rates in the complex are related to the molecular structure via eqn (2).¹¹⁻¹³

$$1/T_1(GdL_m) = k/r^6 \quad (2)$$

Here r is the distance between Gd(III) and the nucleus under consideration and k is a constant. In case of ligands with two or more modes of coordination different distances between the Gd(III) cation and a certain nucleus have to be considered and therefore an averaging is needed. For two coordination sites A and B the ratio R of two carbon ligand nuclei (1 and 2) is given by the relation:¹⁵

$$R = \frac{f_A \cdot D_{1A} + f_B \cdot D_{1B}}{f_A \cdot D_{2A} + f_B \cdot D_{2B}} \quad (3)$$

in which f_A and f_B are the fractions of the ligand in site A and B, respectively, and D is the inverse sixth power of the Gd(III)-C distance in question.

EXPERIMENTAL

The ^{13}C relaxation times were measured on a Varian CFT-20 apparatus (20 MHz) at four or more different Gd(III) concentrations using either the fast inversion recovery¹⁶ or the inversion recovery pulse sequence. The ^{13}C relaxation times were calculated using a non-linear least squares curve fitting procedure.

The different Gd(III) concentrations were obtained by successive addition of small volumes (5-10 μl) of a stock solution of $\text{Gd}(\text{NO}_3)_3$ in D_2O (0.026 M) to solutions of the sodium salts of the carboxylic acids (1.0-2.0 M) in D_2O containing the internal reference tetramethylammonium chloride. The relative relaxation rate enhancements of the various ligand nuclei were calculated from the slopes of a plot of the observed relaxation rates (corrected for $1/T_{\text{linter}}$) versus ρ .

The experimental data were compared with those calculated from molecular models using eqn (2). The interatomic distances and the valence angles were assumed to be: C-C 1.54 \AA , C-O (COO^-) 1.27 \AA , C-O (OH) 1.43 \AA , Gd-O 2.5 \AA , $\angle \text{O-C-O} (\text{COO}^-)$ 115°, and $\angle \text{C-C-C}$ 109°, unless stated otherwise.

RESULTS AND DISCUSSION

The relaxation rate enhancements of the ^{13}C nuclei of the sodium carboxylates were measured at four different Gd(III) concentrations. In all cases a linear relationship between the relaxation rate and the molar Gd(III)/ligand ratio (ρ) was found as is shown in Fig. 1 for acetate and lactate. This is in accordance with eqn (1).

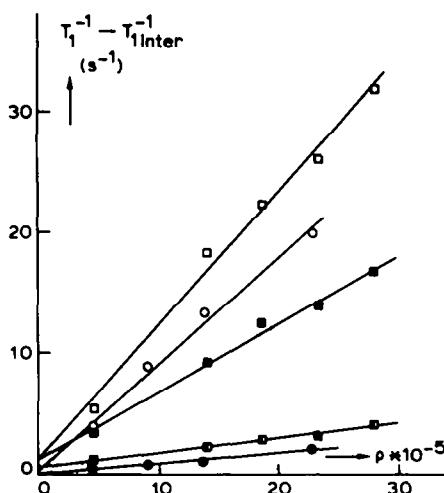


Fig. 1. The longitudinal relaxation rate ($1/T_1 - 1/T_{1\text{inter}}$) of the ^{13}C nuclei in acetate ($\bullet \text{CH}_3$, $\circ \text{COO}$) and lactate ($\blacksquare \text{CH}_3$, $\blacksquare \text{CHOH}$, $\square \text{COO}$) as a function of the Gd(III)/ligand ratio (ρ) at 20 MHz in D_2O and 37 °C; [ligand] = 2 M.

Sodium acetate

From Fig. 1 the relative relaxation rates for C_1 and C_2 of acetate in the Gd-complex were determined to be 1.0 and 0.08, respectively. For carboxylates two modes of coordination have to be envisaged: bidentately via both oxygens (1) or monodentately (2). A comparison of the experimental relaxation rates with calculated values for 1 and 2 (Fig. 2) unambiguously shows that under the conditions applied a bidentate coordination occurs, which is in agreement with the molecular structure of Ln-acetates in the solid state.¹⁷⁻¹⁹

Experimental

Calculated

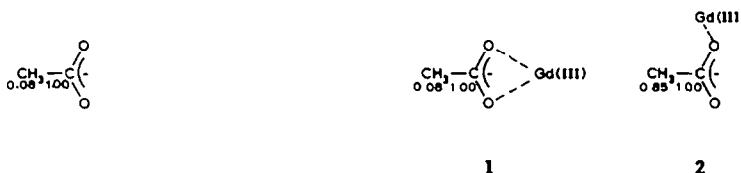


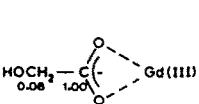
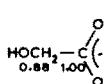
Fig. 2. Comparison of experimental and calculated relative ^{13}C relaxation rates in Gd-acetate complexes.

Sodium glycolate

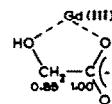
The relative Gd(III) induced relaxation rates for glycolate differ substantially from those of acetate. From a comparison of the experimental and calculated values (Fig. 3) it is obvious that simultaneous coordination of the COO^- and the $\alpha\text{-OH}$ occurs. This mode of complexation is in agreement with the results of a complete analysis of Ln(III) induced multinuclear shifts in the Ln-glycolate- D_2O system.⁵ An analogous mode of coordination is found in the crystal structure of $\text{Gd}(\text{C}_2\text{H}_3\text{O}_3)_3$.^{20,21} It should be noted that the similarity between crystal and liquid molecular structure holds only for the binding mode. The geometry of the Ln(III) coordination polyhedron appears to be different in crystal^{20,21} and in solution structures.⁵

Experimental

Calculated



3



4

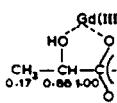
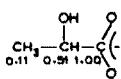
Fig. 3. Comparison of experimental and calculated relative ^{13}C relaxation rates in Gd-glycolate complexes.

Sodium lactate

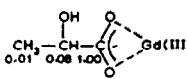
Comparison of the experimental relative relaxation rates of C_1 and C_2 with those obtained for acetate and glycolate points to a simultaneous coordination of the COO^- group (in a monodentate fashion) and the OH group as the predominant mode of coordination. However, a minor contribution of a complex in which Gd(III) is coordinated to the COO^- group in a bidentate way cannot be excluded (Fig. 4). This result is in agreement with the stability constants ($\log K_1$) of the

Experimental

Calculated



5



6

Fig. 4. Comparison of experimental and calculated relative ^{13}C relaxation rates in Gd-lactate complexes.

Gd(III) complexes of lactate, glycolate, and acetate, being 2.53 (25 °C, $\mu = 2.0$), 2.79 (25 °C, $\mu = 1.0$), and 1.34 (25 °C, $\mu = 0.1$), respectively.²² The crystal structure of the Gd(III) lactate complex is not known but simultaneous coordination of the COO^- group (in a monodentate fashion) and the OH group is observed in the crystal structure of $\text{Zn}(\text{C}_3\text{H}_5\text{O}_3)_2 \cdot 3\text{H}_2\text{O}$.²³ Moreover, Brittain *et al.* have proved this mode of coordination in several mixed ligand complexes of Eu(III) or Tb(III) and lactate.²⁴⁻²⁸

Sodium glycerate

The experimental relative relaxation rates of CH_2OH and COO^- (1.27 and 1.00, respectively) suggest a simultaneous coordination of the COO^- and the α -OH as was found for glycolate and lactate. In order to determine whether tridentate coordination of glycerate occurs, i.e. simultaneous coordination of COO^- and both OH groups, Gd-C distances for these two possible models are required. These were estimated from the crystal structures of related Ca-complexes. The crystal structure of calcium glycerate ($\text{Ca}(\text{C}_3\text{H}_5\text{O}_4)_2 \cdot 2\text{H}_2\text{O}$)^{29,30} shows bidentate coordination by a carboxylate O and the α -OH. The Ca(II)-C distance ratios of the CH_2OH and CH_2OH with respect to COO^- are 1.05 and 1.41, respectively. Tridentate coordination of a carboxylate O and the α - and β -OH's is found in the crystal structure of Ca(II) lactobionate ($\text{Ca}(\text{C}_{12}\text{H}_{21}\text{O}_{12})\text{Br} \cdot 4\text{H}_2\text{O}$)³¹ and of Ca(II) arabonate ($\text{Ca}(\text{C}_5\text{H}_9\text{O}_6)_2 \cdot 5\text{H}_2\text{O}$).³² In these crystal structures the Ca(II)-C distance ratios for α - CH_2OH and β - CH_2OH with respect to COO^- are 1.00 and 1.09, respectively. If it is assumed that the Ca(II)-O and Gd(III)-O distances are about the same, the present relaxation data point to the occurrence of both bidentate and tridentate coordination of glycerate to Gd(III) in

aqueous solution (Fig. 5).

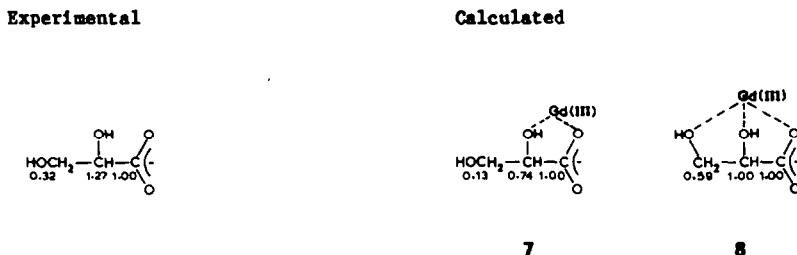


Fig. 5. Comparison of experimental and calculated relative ^{13}C relaxation rates in Gd-glycerate complexes.

This is in accordance with Dy(III) induced shift measurements which suggest a 10% participation of β -OH in the coordination of glycerate.³³

Sodium 3-hydroxybutyrate

For the interpretation of the Gd(III) induced relaxation rate enhancements of 3-hydroxybutyrate the coordination models 9 and 10 are taken into consideration (Fig. 6).

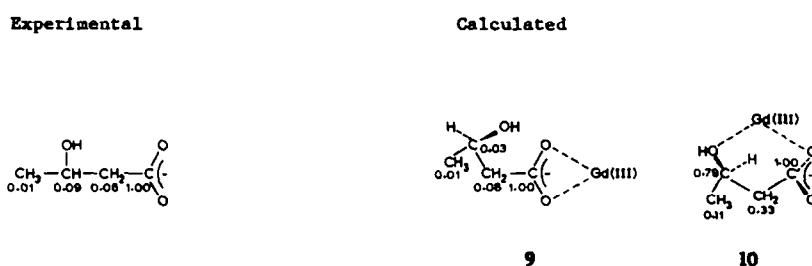


Fig. 6. Comparison of experimental and calculated relative ^{13}C relaxation rates in Gd-3-hydroxybutyrate complexes.

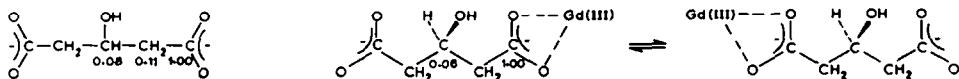
In model 9 the backbone of 3-hydroxybutyrate has a zig-zag conformation with the C-atoms, the O-atoms, the COO^- group, and the Gd(III) cation positioned in one plane. In model 10 only the C-atoms of 3-hydroxybutyrate are positioned in a plane, whereas the COO^- group makes an angle of about 70° with that plane. From the data given in Fig. 6 it can be concluded that 3-hydroxybutyrate coordinates predominantly with its COO^- group in a bidentate fashion (model 9). In addition, the relaxation rate of CHOH indicates a minor contribution of 10. This is in agreement with the small difference in stability constants of the Ca(II) complexes of acetate and 3-hydroxybutyrate (0.53 at 20°C and $\mu = 0.2$ and 0.60 at 25°C and $\mu = 0.2$, respectively).²² From Dy(III) induced ^{17}O shift measurements it was concluded that the contribution of the 10-mode coordination is about 15%.³³

Disodium 3-hydroxyglutarate

The experimental relative ^{13}C relaxation rates of Gd(III) 3-hydroxyglutarate show that the enantiomeric species 11 occur predominantly (Fig. 7). The calculated values are based on a zig-zag conformation, with the C-atoms all positioned in one plane, together with an averaging of the enantiomeric complexes.

Experimental

Calculated



11

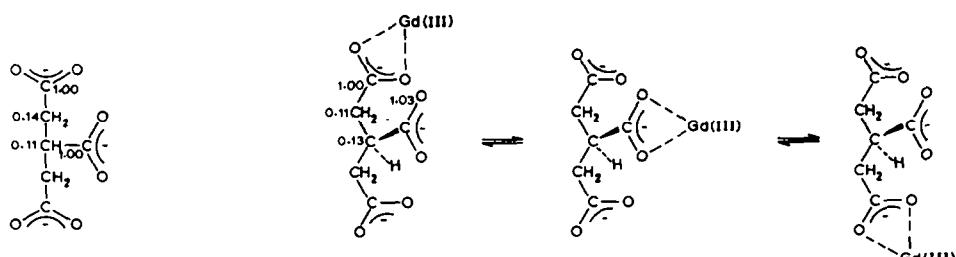
Fig. 7. Comparison of experimental and calculated relative ¹³C relaxation rates in Gd-3-hydroxyglutarate complexes.

Trisodium 1,2,3-propanetricarboxylate

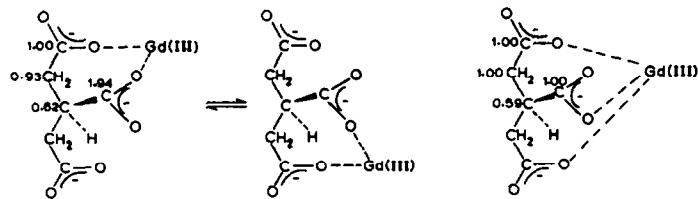
For the coordination behaviour of propanetricarboxylate the models 12, 13, and 14 are considered (Fig. 8). In models 12 and 13 the C-backbone has a zig-zag conformation. In model 14 it is

Experimental

Calculated



12



13

14

Fig. 8. Comparison of experimental and calculated relative ¹³C relaxation rates in Gd-1,2,3-propanetricarboxylate complexes.

assumed that the residence times of Gd(III) at the three COO⁻ groups are equal. The experimental data show that model 12 is preferred over simultaneous coordination by two or three COO⁻ groups (each in a monodentate fashion) as shown in the models 13 and 14. This is supported by the stability constants of the Ca(II) complexes of acetate and succinate (0.53 at 20 °C and $\mu = 0.2$ and 1.20 at 25 °C and $\mu = 0.2$, respectively);²² the enhancement of the complex strength can be explained on statistical grounds.

Disodium malate

Three modes of complexation are considered to describe the coordination of Gd(III) to malate (Fig. 9). In model 15 the C-backbone of malate has a zig-zag conformation and so all C-atoms

Experimental

Calculated

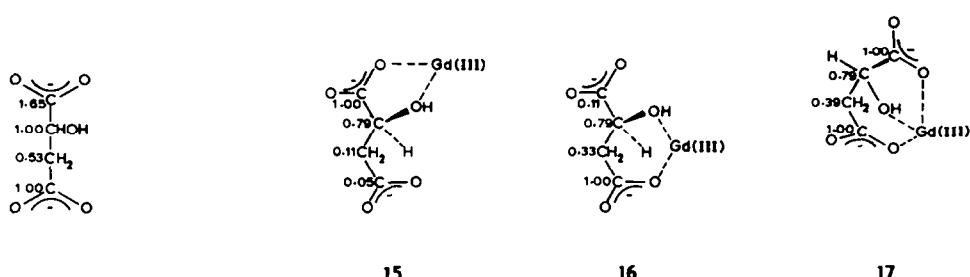


Fig. 9. Comparison of experimental and calculated relative ^{13}C relaxation rates in Cim-malate complexes.

are positioned in a plane, whereas model 16 resembles model 10 for 3-hydroxybutyrate. In 17 tridentate coordination is assumed with Gd(III)-O-C angles of 120°. Comparison of the experimental and calculated relative relaxation rates shows that the latter mode of coordination is dominant, although a contribution of 15 has to be taken into account. Tridentate coordination is also found in the crystal structure of Ca(II) malate ($\text{Ca}(\text{C}_4\text{H}_4\text{O}_5) \cdot 2\text{H}_2\text{O}$).³⁵ In addition, it may be noted that tridentate coordination was also indicated by the results of Dy(III) induced ¹⁷O shift measurements.³³ Circularly polarized luminescence measurements of Eu(III) and Tb(III) complexes with malate as ligand showed that the bonding mode is dependent on the pH and on the presence of other ligands.^{25-28,36-38}

Trisodium citrate

In the case of citrate tridentate coordination as found for malate is also possible. In Fig. 10 a comparison is made between the experimental relaxation rates and those calculated for model

Experimental

Calculated

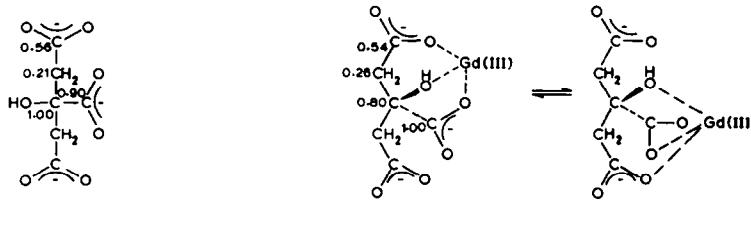


Fig. 10. Comparison of experimental and calculated relative ^{13}C relaxation times for the CH_2 group in CH_2Cl_2 .

18, in which the C-backbone is in a zig-zag conformation. The data show that 18 is in a fairly good agreement with the experimental relaxation ratios. In the solid state tridentate coordination analogous to that in 18 is found for Ca hydrogen citrate ($\text{Ca}(\text{C}_6\text{H}_6\text{O}_7)\cdot 3\text{H}_2\text{O}$).³⁹ The solid state picture probably is just a snapshot of the situation in aqueous solution, since there the citrate complex occurs as a rapid interconversion of two forms, which might proceed without complete decomplexation of the cation. In addition, this dynamic behaviour explains the higher association constant for citrate with respect to malate ($\Delta\text{pK}_{\text{a}} = 2.2$).²²

CONCLUSIONS

For the elucidation of the structure of Gd(III) complexes of hydroxycarboxylates in aqueous medium ^{13}C relaxation time measurements are very helpful. By comparison of the experimental data with relative relaxation rates calculated for the various possible binding modes, usually an unambiguous choice can be made. In most cases the mode of coordination of a ligand is the same in aqueous solution and in the solid state.

The solution structure show that a high preference exists for a 5-membered chelate ring. An α -hydroxycarboxylate moiety strongly favours metal ion complexation. Furthermore, this moiety induces the cooperation of a second COO^- group in the coordination.

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