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THE STRUCTURE OF ADDUCTS OF THE THREE DIASTEREOISOMERIC 1,4:3,6-DIANHYDROHEXITOLS AND LANTHANIDE CHELATES IN ACETONE

J.A. PETERS*, W.M.M.J. BOVÉE, and A.P.G. KIEBOOM
Laboratory of Organic Chemistry, Delft University of Technology,
Julianalaan 136, 2628 BL Delft, The Netherlands

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ABSTRACT - $Gd(dpm)_3$ induced ^1H and ^{13}C relaxation rate enhancements showed that 1,4:3,6-dianhydro-D-glucitol (containing both a *threo* and an *erythro* -O-C-C-OH moiety) acts as a bidentate ligand for $Gd(dpm)_3$. Coordination occurs selectively with the *erythro* -O-C-C-OH moiety, involving the endo-hydroxyl group at C^5 and the neighbouring ether oxygen. From a comparison of the Eu(fod)$_3$ induced ^1H shifts of 1,4:3,6-dianhydro-D-glucitol with those of 1,4:3,6-dianhydro-D-mannitol and 1,4:3,6-dianhydro-L-iditol it is concluded that the mannitol derivative (containing two *erythro* -O-C-C-OH moieties) forms analogous adducts, whereas the iditol derivative (containing two *threo* -O-C-C-OH moieties) has a low association constant.

Lanthanide shift reagents are very valuable tools in NMR spectroscopic structural analysis.[2-4] The effects of Ln(III) cations on the NMR parameters of the various nuclei of the substrate ligand can be translated into structural information of the free ligand and the complex. In addition Ln(III) has been found to be a suitable model cation for Ca(II), for which complexation phenomena cannot be easily studied by NMR spectroscopic methods. Further insight into the interaction of Ca(II) with polyoxygen compounds is of importance, since that plays a crucial role in the regulation of biological processes.

Up to now an overwhelming amount of literature on the use of lanthanides in the stuctural analysis of monofunctional compounds has been published, whereas the complexation of multifunctional compounds is relatively less studied. For a better understanding of the phenomena observed upon complexation of multifunctional compounds with Ln(III) cations, or chelates thereof, it is necessary to have insight into the preferences of Ln(III) for various functional groups. It has been shown that Ln(III) compounds show a high preferency for adduct formation with one or more moieties consisting of two oxygen atoms, separated by two carbon atoms,[4] such as α-hydroxycarboxylates,[5] alditols,[6,7] and anisole derivatives[8] (Figure 1). In such compounds both oxygens of such moieties, usually, act as coordination sites.

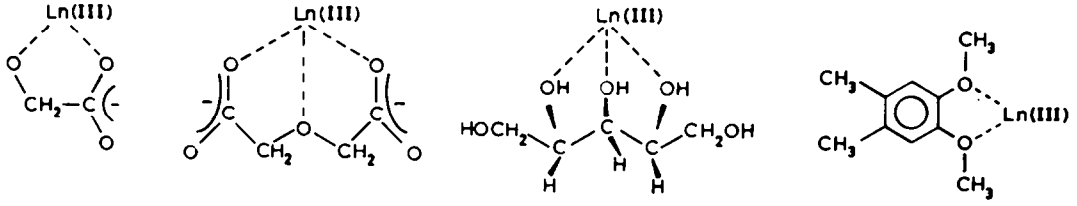
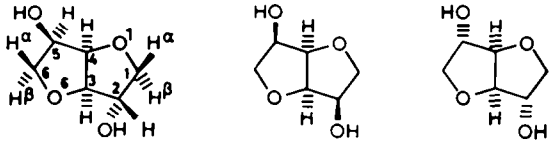


Fig. 1. Examples of Ln(III)-coordination of ligands with a -O-C-C-O- moiety.

In this paper we present a study on the coordination of $Gd(dpm)_3$ and Eu(fod)$_3$ (dpm = 2,2,6,6-tetramethylheptane-3,5-dionate; fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)

with the three diastereoisomeric 1,4:3,6-dianhydrohexitols **1-3** (Figure 2). Each of these compounds contains two -O-C-C-OH moieties. In 1,4:3,6-dianhydro-D-glucitol (**1**) one of them has



1 **2** **3**

Fig. 2. The three diastereoisomeric 1,4:3,6-dianhydrohexitols.

an *erythro*- and the other has a *threo* configuration around C^4-C^5 and C^2-C^3, respectively, whereas in 1,4:3,6-dianhydro-D-mannitol (**2**) and 1,4:3,6-dianhydro-L-iditol (**3**) both moieties posses an *erythro* and *threo* configuration, respectively. As complexes of $Ln(dpm)_3$ and $Ln(fod)_3$ usually show coordination numbers up to 8, only mono- and bidentate coordination of **1-3** with these reagents need to be considered.

Important ways to obtain structural information on Ln(III) complexes are comparison of experimental lanthanide induced shifts with those predicted by the McConnell-Robertson equation as well as the analysis of induced relaxation rate enhancements.[2-4] For the latter method Gd(III), usually, is the Ln(III) cation of choice, since that ion has a relatively long electron relaxation time, which results in large enhancements in relaxation rates of the substrate ligand. The magnitude of the enhancements enables measurements at low molar ratios of Gd(III)/substrate ($\rho \leq 10^{-2}$). The relaxation rate in the adduct ($1/T_{1b}$) can be related to the molecular structure via eqn. (1).[9-11]

$$1/T_{1b} = K/r^6 \qquad (1)$$

Here, r denotes the distance of the nucleus under investigation to Gd(III). The strong dependence of the relaxation rate enhancements upon the distance makes this technique particularly suitable for studying molecular geometries near the Gd(III) ion.

The complexation of compound **1** was studied with the use of $Gd(dpm)_3$ induced longitudinal ^1H and ^{13}C relaxation rate enhancements. On this basis conclusions about the complexation of $Eu(fod)_3$ with **1-3** were drawn from, less time-consuming, lanthanide induced ^1H shift measurements.

RESULTS AND DISCUSSION

Conformation of compound 1

The 1,4:3,6-dianhydrohexitols contain two fused five-membered rings. Therefore, these systems have many conformational possibilities: for both five-membered rings a pseudo-rotation manifold has to be considered. In the crystal structure of **1**[12] the five-membered rings adopt an envelope (C_s) conformation, in which atoms C^2 and C^5 are displaced from the planes $C^3C^4O^1C^1$ and $C^4C^3O^6C^6$ into the exo-direction by 0.6 Å. In the crystal structure of the corresponding 2-O-(p-bromobenzenesulphonyl)-5-nitro derivative,[13] however, C^1 and C^6 are on the tips of the flaps of the envelopes. Therefore, it seems likely that the strain in the various conformers shows only small differences. Hydrogen bonds may play a role in the population of the conformers in solution. In the crystal structure of **1** a bifurcated hydrogen bond exists consisting of a weak intramolecular hydrogen bond between O^5H and O^1 and an intermolecular one between O^5H and O^6.[12] The *threo* geometry of the O^6-C^3-C^2-O^2H moiety prohibits intramolecular hydrogen bonding. With the use of IR spectroscopy it has been shown that the *erythro* O^5H-O^1 intramolecular hydrogen bond exists also in dilute CCl_4 solution (<< 0.005 M).[14]

The ^1H coupling constants of **1** in acetone-d_6 were determined at 300 MHz (Table 1) and are in

Table 1. Comparison of experimental and calculated vicinal proton-proton coupling constants in compound I.

H-atoms	Experimental[a] ± 0.2 (Hz)	Calculated[b] (Hz)
1α-2	3.3	2.9
1β-2	< 1	0.8
2-3	< 1	1.8
3-4	4.2	4.7
4-5	4.5	4.1
5-6α	7.3	10.7
5-6β	6.4	8.4

[a] Obtained from first order analysis of a 300 MHz spectrum of a solution of I in acetone-d_6 at 20 °C; [b] With the use of the generalized Karplus equation[16,17] and the structure of I as obtained from X-ray spectroscopy.[12]

agreement with those obtained by Hopton and Thomas at 100 MHz.[15] In Table 1 a comparison is made between the experimental values and those calculated with the generalized Karplus equation, developed by Altona et al.,[16] using the dihedral angles as obtained by X-ray spectroscopy.[12]

The agreement between the calculated and the experimental values is rather good, except for $J_{5,6\alpha}$ and $J_{5,6\beta}$. The relatively low experimental values for the latter might be ascribed to contributions of other conformers in solution. E.g. a conformer, in which C^5 is displaced from the plane $C^4C^3O^6C^6$ into the endo direction would give rise to relatively small vicinal coupling constants between H^5 and $H^{6\alpha}/H^{6\beta}$ (< 4 Hz). Although on the basis of the vicinal coupling constants no definitive conclusions about the precise conformation of I can be drawn, it seems likely that the predominant conformation in solution is the same as the X-ray crystal structure,[12] viz. a double envelope with C^2 and C^5 on the flaps.

$Gd(dpm)_3$ induced longitudinal relaxation rate enhancements in I

In order to prevent excessive measurement times for the determination of ^{13}C longitudinal relaxation rates, samples with high concentrations of I were preferred. Therefore, acetone-d_6 was chosen as solvent for all measurements. The addition of $Gd(dpm)_3$ had a negligible influence on the longitudinal relaxation rates of acetone-d_6, whereas those of the nuclei in compound I were appreciably enhanced. The observed selective adduct formation of $Gd(dpm)_3$ with I, despite the high association constant for complexation of $Gd(dpm)_3$ with ketones allows us to conclude that I acts as a bidentate ligand.

Under the conditions applied, viz. a low molar ratio $Gd(dpm)_3$/substrate ($\rho < 10^{-2}$) and a high association constant, eqn (2) is valid,[18]

$$1/T_{1exp} = \rho/(T_{1b} + \tau_m) + 1/T_{1o} + 1/T_{1inter} \qquad (2)$$

in which T_{1b} is the longitudinal relaxation time in the adduct, τ_m is the residence time of the substrate ligand in the adduct, T_{1o} is the longitudinal relaxation time in the free ligand and $1/T_{1inter}$ is the contribution to the relaxation of intermolecular interactions. As shown before, it is very important to obtain a good estimate for $1/T_{1inter}$.[19] In this case this parameter was estimated from the relaxation rate enhancements of the nuclei in the internal standard TMS, taking into account the difference in diameter between the standard and compound I.[20] The corrected $1/T_1$ values thus obtained are given in Table 2. From the value of $1/T_1$ of C^4, and eqn (2) it can be calculated that $T_{1b} + \tau_m \approx 3.10^{-5}$ s, thus $\tau_m < 3.10^{-5}$ s. Therefore, at least for the ^1H nuclei of I, τ_m in eqn (2) can be neglected. Since the trends in the $1/T_1$ values of

Table 2. Experimental and calculated relaxation rates (x 10^{-4} s^{-1}) for the system 1, $Gd(dpm)_3$ in acetone-d_6.

Nucleus	$1/T_{1exp} - 1/T_{1o} - 1/T_{1inter}$ [a]	$1/T_{1calc}$ [b]
C^1	2.07	2.09
C^2	0.53	0.32
C^3	0.52	0.38
C^4	2.98	2.98
C^5	2.42	2.46
C^6	0.79	0.76
$H^{1\alpha}$,$H^{1\beta}$ [c]	0.198	0.201
H^2, H^5 [d]	0.094	0.043
H^3	0.068	0.017
H^4	0.195	0.205
$H^{6\alpha}$	0.223	0.220
$H^{6\beta}$	0.073	0.033

[a] Extrapolated to ρ = 1, relative error 5%. [b] Obtained by eqn (1) using the geometry of 1 in the crystal structure,[12] r = 2.5 Å, θ = 108° and φ = 27°. [c] Coinciding, calculated values are averages of values for $H^{1\alpha}$ and $H^{1\beta}$. [d] H^2, H^5 and O^2H were coinciding, calculated values are averages of H^2 and H^5.

the ^{13}C nuclei are analogous to those in the adjacent ^1H nuclei, we assume that for the ^{13}C nuclei τ_m can be neglected too. Consideration of the $1/T_{1b}$ values obtained suggests that the coordination of Gd(III) to 1 occurs predominantly near O^5H and O^1. This could be confirmed by fitting the $1/T_{1b}$ values to those calculated with the use of eqn (1). The number of experimental values is too low to allow inclusion of the various possible conformers into the fitting procedure. Therefore, the X-ray structure of 1 was used as an approximation of the conformation of 1 in the adduct with $Gd(dpm)_3$. The Gd(III) cation was placed at a distance of 2.5 Å from O^5 and the $Gd\text{-}O^5\text{-}C^5$ angle (ϑ) and the $Gd\text{-}O^5\text{-}C^5\text{-}C^4$ torsion angle (φ) were varied until an optimum

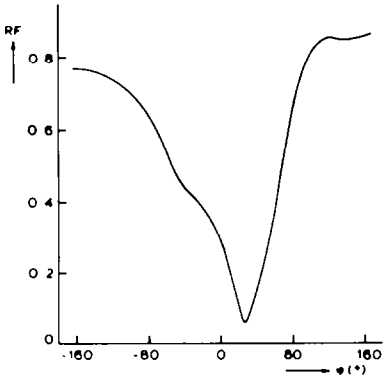


Fig. 3. Fit between observed and calculated relaxation rates of the adduct of 1 and $Gd(dpm)_3$ as function of the torsion angle $Gd\text{-}O^5\text{-}C^5\text{-}C^4$ (φ).

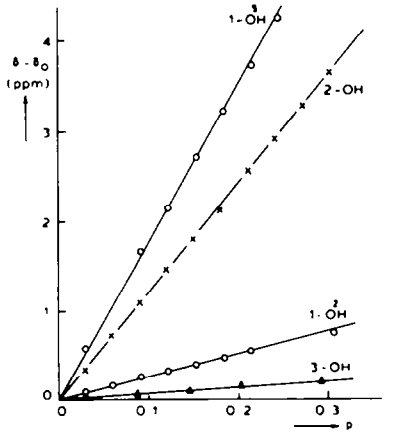


Fig. 4. $Eu(fod)_3$ induced shifts of the OH-signals of compounds **1-3** versus ρ; 200 MHz, 25 °C; 0.3 M solutions.

fit was obtained for the ^{13}C data. The goodness of the fit was expressed in the crystallographic agreement factor RF.[21] A sharp minimum was obtained for θ = 108° and ϕ = 27° (Fig. 3). For that minimum the distance between Gd(III) and O^1 is 2.22 Å, showing that indeed bidentate complexation occurs. The agreement factor appeared to be rather insensitive for changes in the Gd-O^5 distance. A shallow minimum could be found at the unreasonable long-distance of 3.4 Å. Use of a complete different geometry for the substrate ligand, viz. a twist conformer generated with force field calculations gave an optimum fit for an analogous position of Gd(III) with respect to the substrate ligand. Apparently the conformational changes in this case are too small to be detected by relaxation rate measurements. Comparison of the calculated and the experimental longitudinal relaxation rates (Table 2) shows the good agreement: most of the relaxation rates are identical within the experimental error. The deviations found for C^2, C^3, H^3 and $H^{6\beta}$ can easily be attributed to a minor contribution (< 10%) of an adduct of 1 and $Gd(dpm)_3$, in which Gd(III) is coordinated at O^2H and O^6. This may also explain the observed low sensitivity of RF for changes in the Gd-O^5 distance. The consistency of the ^{13}C and ^1H results justifies the assumption made that τ_m is negligible in eqn (2).

$Eu(fod)_3$ induced shifts of **1-3**

Addition of increasing amounts of $Eu(fod)_3$ to solutions of **1** or **2** in acetone-d_6 gave appreciable downfield shifts for all ^1H nuclei in the ligands. Compound **3** under analogous conditions gave only rather small induced shifts (Fig. 4, Table 3), indicating that the formation constants of adducts of **3** with $Eu(fod)_3$ are much smaller than those for **1** and **2**. This result is in accordance with the picture that bidentate coordination by an *erythro* -O-C-C-OH moiety is a prerequisite for substantial adduct formation with the lanthanide reagent. Such a moiety is absent in the case of compound **3**.

Table 3. Relative $Eu(fod)_3$ induced shifts (ppm) in compounds **1-3**.[a]

nucleus	1	2	3
$H^{1\alpha}$	0.510	0.967	0.773
$H^{1\beta}$	0.510	0.689	0.588
H^2	0.289	0.692	0.875
H^3	0.428	1.000	1.000
H^4	1.000	1.000	1.000
H^5	0.541	0.692	0.875
$H^{6\alpha}$	0.779	0.967	0.773
$H^{6\beta}$	0.523	0.689	0.588
O^2H	0.308	1.693	1.857
O^5H	2.099	1.693	1.857

[a] Measured at 200 MHz and 25 °C with a 0.3 M solution of **1-3** in acetone-d_6.

In the spectra of **1-3** without $Eu(fod)_3$ the OH-signals were sharp doublets. Upon addition of $Eu(fod)_3$ to compound **1** a large downfield shift of O^5H is observed, accompanied by a large broadening. On the other hand the signal O^2H has a rather small downfield shift and remains relatively sharp; even the coupling remains observable (up to ρ = 0.3). So, the $Eu(fod)_3$ induced shifts again show that the Ln(III) cation selectively coordinates with O^5 and O^1 of compound **1**.

From the slopes of the plots of the induced shifts of the various ^1H nuclei versus those of H^4, with increasing amounts of shift reagent, the relative $Eu(fod)_3$ induced shifts were obtained (see Table 3).[22,23] From the high selectivity of $Eu(fod)_3$ for coordination with O^5H and O^1 in comparison with O^2H and O^6 in compound **1**, it may be anticipated that in compound **2** an

Table 4. Comparison of experimental and estimated relative $Eu(fod)_3$ induced shifts (ppm) in compound **2**.

nucleus	experimental	estimated
$H^{1\alpha}, H^{6\alpha}$	0.97	0.90
$H^{1\beta}, H^{6\beta}$	0.69	0.72
H^3, H^4	1.00	1.00
O^2H, O^5H	1.69	1.69

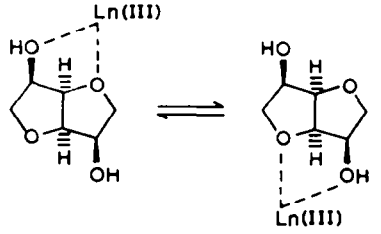


Fig. 5. Adducts of $Eu(fod)_3$ and **2**.

equilibrium of two identical adducts exists (Fig. 5). Therefore, the relative $Eu(fod)_3$ induced shifts in compound **1** can be used to estimate those in compound **2**. The relative induced shifts of H^3 and H^4, $H^{1\alpha}$ and $H^{6\alpha}$, $H^{1\beta}$ and $H^{6\beta}$, and O^2H and O^5H were averaged to yield the estimates for compound **2** (see Table 4). The agreement between these estimates and the experimental values is very good, showing that the equilibrium mentioned above is a good description of the complexation behaviour of **2**.

Upon mixing a sample of **1** and $Eu(fod)_3$ ($o = 0.3$) with an analogous sample of **2**, the chemical shifts of the nuclei in both **1** and **2** hardly changed. Therefore, it may be concluded that the association constants for adduct formation are about the same for **1** and **2**.

Conclusions

The $Eu(fod)_3$ and $Gd(dpm)_3$ reagents show high selectivity for bidentate coordination with an -O-C-C-OH group in an *erythro* configuration. This is reflected in high association constants for **1** and **2** and a relatively low association constant for **3**. In addition in compound **1**, which has both a *threo* and an *erythro* -O-C-C-OH moiety, coordination occurs predominantly with the *erythro* moiety. The structure of the adduct of **1** is depicted in Fig. 6.

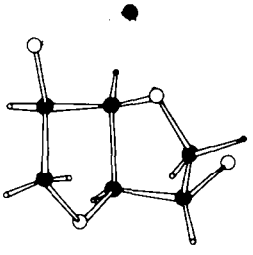


Fig. 6. The coordination of Ln-chelates with **1**.

EXPERIMENTAL

The ^1H NMR spectra were measured at 100 MHz on a Varian XL-100-15 spectrometer system in the pulse-FT mode, at 200 MHz on a Nicolet NT-200WB spectrometer and at 300 MHz on a spectrometer built at the Department of Applied Physics.[24] The ^1H relaxation times (T_1) were measured at the 300 MHz spectrometer. As the T_1^{-1} value was taken the slope of the magnetization recovery curve at the time zero after the inverting 180°-pulse in a 180°-τ-12° pulse sequence.

The ^{13}C spectra were measured at 20 MHz on a Varian CFT-20 and at 25 MHz on the XL-100-15 spectrometer. The ^{13}C NMR relaxation times (T_1) were measured with the use of the 180°-τ-90° pulse sequence under ^1H decoupling conditions.

All solvents were dried on zeolite KA. $Gd(dpm)_3$ was purchased from Fluorochem Ltd. (Glossop, Great Britain) and $Eu(fod)_3$ was synthesized according to the procedure described by Sievers et al.[25] The lanthanide reagents were recrystallized from CH_2Cl_2 or sublimed and subsequently dried over zeolite KA *in vacuo*. The samples were prepared in a glove box flushed with dry nitrogen. The samples used for ^1H relaxation time measurements were degassed and sealed under vacuum.

The longitudinal relaxation times were determined as a function of ρ ($\rho < 10^{-2}$). Straight lines of the induced relaxation rate enhancements versus ρ were obtained.

The ^{13}C signals in the spectrum of compound 1 were assigned by means of selective ^1H decoupling.

1,4:3,6-Dianhydro-D-glucitol (**1**) *and 1,4:3,6-dianhydro-D-mannitol* (**2**) were prepared from the corresponding hexitols according to the procedure given by Shen.[26] Purification was achieved by recrystallization from dry acetone at −30 °C. Compound 1; ^{13}C NMR (25 MHz, acetone-d_6): δ 76.2 (t, C^1), 77.0 (d, C^2), 88.7 (d, C^3), 82.2 (d, C^4), 73.3 (d, C^5), 72.7 (t, C^6).

1,4:3,6-Dianhydro-L-iditol (**3**). L-Sorbose (25 g, 0,14 mol) in 250 ml MeOH was hydrogenated at 30 atm and 70° with 1 g Raney nickel as the catalyst.[27] After 3 h the hydrogen-uptake ceased. Then the catalyst was filtered off and the solvent was evaporated under vacuo to give 11.6 g of an oil consisting of D-glucitol and L-iditol (0.064 mol, 46%). To the crude reaction mixture 0.2 g H_2SO_4 was added and then the mixture was heated at 150°/30 mm for 1 h. Distillation yielded a fraction (6.9 g, 0.047 mol, 73%), which boiled at 162–166°/0.6 mm, containing 62% 1 and 38% 3. Separation was achieved by preparative HPLC over a 10 μ Nucleosil C_{18} column (8 x 100 mm, Waters Associates Radial Pak Cartridge) using H_2O as the mobile phase. Most of the H_2O was evaporated under vacuo. From the residue H_2O was removed via azeotropic distillation with benzene. After that the product was recrystallized twice from EtOAc to yield 2.48 g pure **3**; m.p. 44–47°.

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