Organic Process Research & Development **2001**, *5*, 361–367

Articles

Hydrates of Gadolinium Diethylenetriaminepentaacetic Acid Bis(methylamide) as Studied by X-ray Diffraction

Audun Aukrust,*[†,‡] Thoralf Engebretsen,[‡] Leiv K. Sydnes,[‡] Leif J. Sæthre,[‡] and Karl W. Törnroos[‡]

Nycomed Imaging AS, P.O. Box 4220 Nydalen, NO-0401 Oslo, Norway, and Department of Chemistry, University of Bergen, Allégt. 41, NO-5007 Bergen, Norway

Abstract:

The crystal structures of two hydrates of the title compound (gadodiamide I and III) have been determined by single-crystal X-ray diffraction. Gadodiamide I crystallises in the noncentrosymmetric orthorhombic space group $P2_12_12_1$, with two complexes in the asymmetric unit and 10 molecules of water. Gadodiamide III crystals are centrosymmetric and monoclinic, belonging to the space group $P2_1/n$, with one independent complex in the unit cell and seven molecules of water. The molecular structures are found to be very similar with respect to metal coordination as well as ligand geometry. Hydrogen-bond interactions appear to be of decisive importance in the evolution of the different hydrates.

Introduction

Gadodiamide (Figure 1) is the active ingredient in OMNISCAN (Nycomed Imaging AS, Oslo, Norway), a paramagnetic contrast agent for magnetic resonance imaging (MRI).[1] During the development of OMNISCAN five different forms of gadodiamide, denoted types **I**−**V**, were obtained, most of which proved to be hydrates with variable water content (Table 1).[2] As reported[2] precipitation or crystallisation of gadodiamide from aqueous solutions affords only type **I** and type **III** hydrates. Type **II** gadodiamide, on the other hand, is produced by drying the type-**III** complex, but during the process only a fine powder is obtained. Finally, the type-**IV** and type-**V** forms are unstable and cannot be handled at ambient conditions.

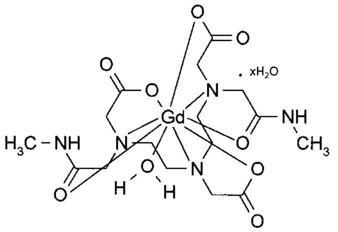

Figure 1. **Structure of gadodiamide (GdDTPA−BMA).**

Table 1. **Water content of the five different crystalline forms of gadodiamide, GdDTPA−BMA·nH$_2$O (compiled from ref 2)**

form	water content, %	nH$_2$O
I	3−14	1−5
II	0−6	0−2
III	18	7
IV	0	0
V	3	1

From Table 1 it is apparent that some of the gadodiamide samples have identical composition and can therefore be regarded as polymorphs or polymorphic forms.[2] To uncover any structural features, which could lead to polymorphism, we wanted to determine the structure of as many types of gadodiamide as possible by X-ray crystallography. Exploratory investigations revealed that only two gadodiamide forms, the type-**I** and type-**III** hydrates, gave crystals of suitable quality for such investigations. Their structures were determined, and as reported here, the results give indications as to why so many forms of gadodiamide are being obtained.

A single-crystal X-ray structure of a gadodiamide sample has been reported.[1] The sample appeared to be a type-**I** hydrate (vide infra), but at the time the structure was published the existence of several forms of gadodiamide was unknown.

Results and Discussion

Crystallisation and Sample Classification. It was not a trivial task to produce crystals of the gadodiamide forms of suitable quality for X-ray investigation. Rapid precipitation of crystalline material of inferior quality or supersaturated solutions without sign of crystallisation were, in general, observed at other conditions than those reported here.

Crystallisation of gadodiamide from a water/acetone system produced colourless needles, whereas crystallisation of gadodiamide from water produced both colourless needles and colourless blocklike crystals. The needles from the two experiments gave identical IR spectra, which were identical to that reported for gadodiamide **I**.[2] In addition the observed water contents, 12.1 and 12.7%, respectively (see Experi-

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* To whom correspondence should be addressed. Correspondence to Audun Aukrust, Nycomed Imaging, P.O. Box 4220 Nydalen, N-0401 Oslo, Norway. Telephone: +47 2318 5050. Telefax: +47 2318 6000. E-mail: Audun.Aukrust@no.nycomed-amersham.com.

[†] Nycomed Imaging AS.

[‡] University of Bergen.

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10.1021/op000106e CCC: $20.00

Table 2. **Crystal and structural parameters for gadodiamide I and III**

name	gadodiamide **I**	gadodiamide **III**
chemical formula	$C_{32}H_{72}Gd_2N_{10}O_{26}$	$C_{16}H_{40}GdN_5O_{15}$
formula weight	1327.47	699.77
crystal system	orthorhombic	monoclinic
space group	$P2_12_12_1$	$P2_1/n$
Z	4	4
a/Å	12.3789(11)	9.336(2)
b/Å	13.4757(11)	25.173(5)
c/Å	28.897(3)	11.987(2)
α/deg	90	90
β/deg	90	109.61(3)
γ/deg	90	90
V/Å^3	4820.5(7)	2653.7(9)
D_X/Mg m^{-3}	1.829	1.752
diffractometer	Bruker-AXS SMART 2K	Enraf Nonius CAD4
radiation	Mo Kα 0.71073	Mo Kα 0.71073
(Mo Kα)/mm^{-1}	2.83	2.58
crystal dimensions/mm	0.320 × 0.100 × 0.082	0.30 × 0.30 × 0.30
T/K	223(2)	93(2)
scan mode, $2\theta_{max}$/deg	ω-scan, 54.53	ω-scan, 57.96
reflections collected/unique	52227/9910	7022/7020
data/restr/param	9910/27/690	7020/21/378
R_{int}/R_σ	0.0404/0.0242	0.00/0.0361
R-indices	R1 = 0.0330, wR2 = 0.0825	R1 = 0.0202, wR2 = 0.0557
R indices (all data)	R1 = 0.0359, wR2 = 0.0834	R1 = 0.0244, wR2 = 0.0577
goodness-of-fit (S) on F^2	1.065	1.082
$(\Delta\rho/\sigma)_{max}$	0.002	0.001
$\Delta\rho_{min}$, $\Delta\rho_{max}$/eÅ^{-3}	−1.69, 1.23	−1.38, 0.93

mental Section), are typical for what is found for gadodiamide **I** (normally 11−14%, corresponding to 4−5 water molecules per gadodiamide complex). Consequently, these samples are of gadodiamide **I**. Only the gadodiamide **I** sample from the water/acetone system had acceptable quality for X-ray structure determination.

The blocklike crystals of gadodiamide, which crystallised from water, showed an IR spectrum identical to that reported for gadodiamide **III**.[2] Morever, a water content of 17.4% is typical for what is found for gadodiamide **III** (about 18%, corresponding to seven water molecules per gadodiamide complex). This shows that these crystals belong to that of gadodiamide **III**.

The IR spectra of gadodiamide **I** and gadodiamide **III** are shown and interpreted in ref 2.

Crystal Structures. Gadodiamide **I** crystallises in the chiral orthorhombic space group $P2_12_12_1$ (No. 19) with $Z = 4$, whereas gadodiamide **III** crystallises in a monoclinic cell, space group $P2_1/n$ (No. 14), $Z = 4$ (Table 2). As expected from the determined water contents the structure of form **III** contains seven water molecules and the structure of form **I** contains five water molecules per gadodiamide complex.

The Structure of Gadodiamide I. The crystal structure of gadodiamide **I** has an asymmetric unit containing two stereoisomers interrelated through a non-crystallographic centre of inversion. In addition the structure exhibits racemic twinning, the Flack parameter refining to 0.26(1). The geometry of the two molecules is virtually the same with only some minor conformational differences found around the carboxylic acid and the amide groups, cf. Figure 2. Apart from the two water molecules coordinated to the Gd atoms, there are eight crystal water molecules in the asymmetric unit, thus four per gadodiamide complex. The Gd metal engages all available chelating atoms in the ligand, that is, three amine nitrogens, (N2, N3, N4), three carboxylic oxygens (O2, O4, O7), and two amide oxygens (O1, O8) in addition to the one coordinating water molecule (atomic numbering shown in Figure 4). The nine ligand atoms form a coordination polyhedron best described as a distorted tricapped trigonal prism (Figure 3). The central amine sits on the edge, the three caps are occupied by the two other amines and the water molecule. The amide groups are found to be in a *trans* configuration (the amide groups are connected to O1 and O8 in Figure 3). The bond angles

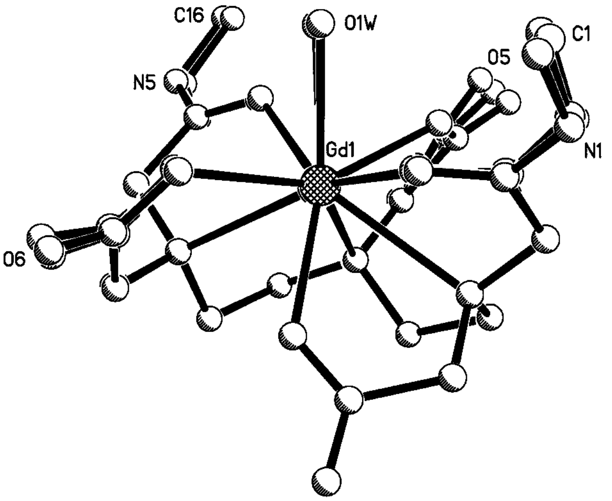

Figure 2. **The two stereoisomers of gadodiamide I (the second isomer of I has been inverted) and the structure of gadodiamide III overlaid by least-squares fit of the Gd atoms and all coordinated ligand atoms.**

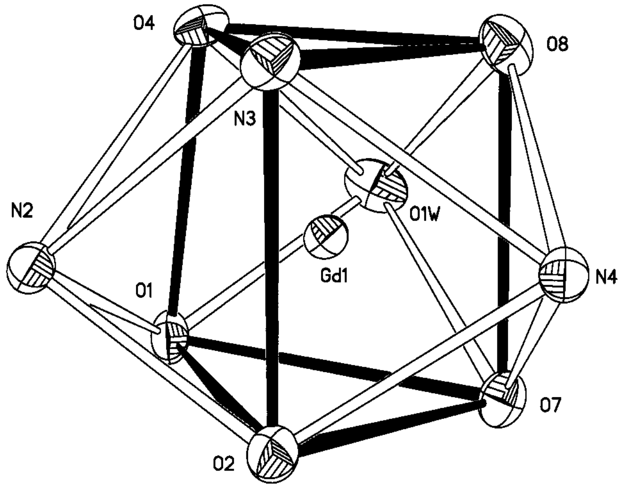

Figure 3. **Illustration of the trigonally prismatic coordination polyhedron around Gd in structures I and III. The trigonal prism is depicted with solid lines, the three-fold axis running vertically. The figure shows stereoisomer 1 in gadodiamide I.**

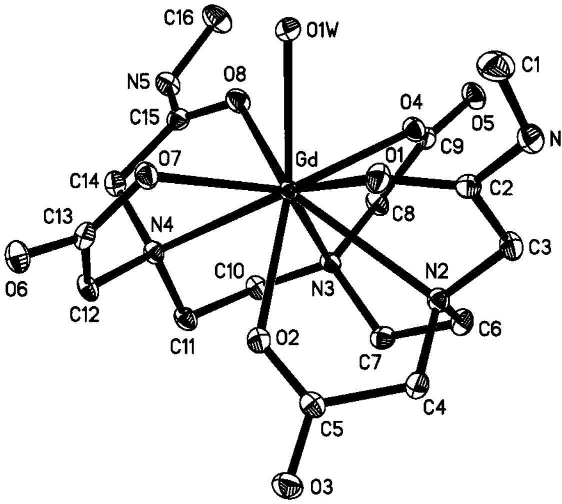

Figure 4. **General view of the gadodiamide III complex with atomic numbering common to all three complexes. The displacement parameters are given at the 50% probability level. Hydrogen atoms and water molecules have been omitted.**

Table 3. **Coordination around gadolinium (Å) in gadodiamide I (two stereoisomers, denoted first and second) and gadodiamide III, with standard uncertainties in parentheses**

coordination	gadodiamide **I** (first)	gadodiamide **I** (second)	gadodiamide **III**
Gd−O$_{water}$			
Gd−O1W	2.502(4)	2.450(4)	2.479(2)
Gd−O$_{carboxylate}$			
Gd−O2	2.342(4)	2.358(4)	2.350(1)
Gd−O4	2.353(3)	2.341(3)	2.378(2)
Gd−O7	2.361(4)	2.430(4)	2.355(1)
Gd−O$_{amide}$			
Gd−O1	2.409(4)	2.416(4)	2.397(2)
Gd−O8	2.415(4)	2.415(4)	2.376(2)
Gd−N			
Gd−N2	2.739(4)	2.745(4)	2.756(2)
Gd−N3	2.615(5)	2.632(4)	2.621(2)
Gd−N4	2.656(4)	2.666(5)	2.629(2)

(available as Supporting Information) in the two stereoisomers are quite consistent. This is particularly true for the coordination around Gd, where only two angles deviate by 10 standard uncertainties, 1.56 and 1.20°, the mean difference for 36 unique angles being 0.01° (0.62).

The Structure of Gadodiamide III. In contrast to gadodiamide **I**, the structure of gadodiamide **III** (Figure 4) comprises a single unique complex in the asymmetric unit with six crystal water molecules in addition to the one water molecule coordinated by the Gd atom. A comparison between gadodiamide **I** and gadodiamide **III** reveals only minor differences in the coordination around the metal, cf. Tables 3 and 5. Although the Gd−O$_{water}$ distance is different in the two complexes, in the unit cell of gadodiamide **I** the *average* Gd−O$_{water}$ distance in the two stereoisomers of gadodiamide **I** is a mere 0.003 Å smaller than in gadodiamide **III**, which is not statistically significant. The Gd−O$_{carboxylate}$ and Gd−N distances are on average quite similar, but some individual differences can be seen. The only distance that is significantly different is the Gd−O$_{amide}$ distance, which is 0.027 Å larger in gadodiamide **I** than in gadodiamide **III**. Regarding bond lengths in the ligand DTPA−BMA it is seen in Tables 4 and 5 that no clearly significant differences are detected. Likewise, the bond angles for types **I** (both stereoisomers considered) and **III**, in particular around Gd where the mean ($n = 36$) difference between structures is 0.01° (0.79) and the largest difference is 1.70°, are again quite alike (cf. Figure 2). Complete angular data are available as Supporting Information.

To authenticate the fact that both of the two crystallographically independent complexes of gadodiamide in structure **I** and in structure **III** are effectively alike, a graphical illustration to this end is given in Figure 2. In the illustration all three unique molecules are overlaid (the second enantiomer of structure **I** has been inverted) by least-squares refinement of the Gd atoms and their nine ligand-atoms in all three structures. Only minor differences can be detected involving the peripheral methyl groups C1 and C16 and carboxylic atoms O5 and O6 (the atomic numbering is common to all three molecules). It follows from Figure 2 that gadodiamide **III**, similarly to gadodiamide **I**, has the amide groups in the *trans* configuration. In conclusion, the geometries of the GdDTPA−BMA complexes in structures **I** and **III** are essentially identical, the differences in experimental temperature taken into account.

Packing Structure of Gadodiamide I and Gadodiamide III. A selection of hydrogen bonds in the two structures are listed in Tables 6 and 7 (H-atoms on OW9 in gadodiamide **I** have not been located). The two unique complexes in gadodiamide **I** has three and four hydrogen-bond (donor) contacts with neighbouring complexes, respectively, whereas gadodiamide **III** only has two. No intramolecular hydrogen bonds are found in either structures. The structure of gadodiamide **I** has a lower per-complex water content and a higher crystal density than gadodiamide **III** (cf. Table 2), a fact that reflects the main difference between gadodiamides **I** and **III**. In gadodiamide **I** (Figure 5) there are direct hydrogen bonds between the enantiomers via the water ligand

Table 4. **Bond lengths in the ligand DTPA−BMA (Å) in gadodiamide I (two stereoisomers, denoted first and second) and gadodiamide III, with standard uncertainties in parentheses**

bond	gadodiamide **I** (first)	gadodiamide **I** (second)	gadodiamide **III**
$C{=}O_{amide}$			
O1−C2	1.245(6)	1.260(7)	1.254(2)
O8−C15	1.250(7)	1.229(7)	1.254(3)
$C{=}O_{carboxylate}$			
O2−C5	1.259(7)	1.260(7)	1.263(2)
O3−C5	1.237(7)	1.242(7)	1.247(2)
O4−C9	1.248(7)	1.262(7)	1.267(2)
O5−C9	1.236(7)	1.220(7)	1.243(2)
O6−C13	1.231(6)	1.223(6)	1.253(3)
O7−C13	1.284(7)	1.259(7)	1.258(2)
$N_{amine}-C_{sp^3}$			
N2−C3	1.481(7)	1.465(7)	1.468(2)
N2−C4	1.462(7)	1.472(7)	1.477(2)
N2−C6	1.486(7)	1.482(7)	1.472(2)
N3−C7	1.477(7)	1.495(7)	1.486(2)
N3−C8	1.482(7)	1.487(7)	1.480(2)
N3−C10	1.502(7)	1.489(7)	1.491(2)
N4−C11	1.500(6)	1.490(6)	1.480(2)
N4−C12	1.488(7)	1.476(7)	1.471(2)
N4−C14	1.484(6)	1.458(7)	1.482(2)
$N_{amide}-C_{amide}$			
N1−C2	1.311(7)	1.306(7)	1.316(3)
N5−C15	1.308(8)	1.327(7)	1.312(3)
$N_{amide}-C_{sp^3}$			
N1−C1	1.450(7)	1.426(7)	1.457(3)
N5−C16	1.463(8)	1.461(8)	1.457(3)
$C_{sp^3}-C_{sp^2}$			
C2−C3	1.523(7)	1.529(8)	1.517(3)
C4−C5	1.530(7)	1.509(8)	1.524(3)
C8−C9	1.541(8)	1.536(8)	1.522(3)
C12−C13	1.514(8)	1.534(8)	1.517(3)
C14−C15	1.513(8)	1.512(8)	1.507(3)
$C_{sp^3}-C_{sp^3}$			
C6−C7	1.517(8)	1.502(8)	1.520(3)
C10−C11	1.529(7)	1.524(8)	1.515(3)

Table 5. **Average bond lengths (Å) of the metal coordination and ligand for gadodiamide (gadodiamide I (Gd I), two stereoisomers, denoted first and second, and gadodiamide III (Gd III))**[a]

bond	N[b]	Gd **I**, first	Gd **I**, second	Gd **III**
$Gd-O_{water}^{s.u.}$	1	2.502(4)	2.450(4)	2.479(2)
$Gd-O_{carboxylate}$	3	2.352(10)	2.38(5)	2.361(15)
$Gd-O_{amide}^{s.u.}$	2	2.412(4)	2.416(4)	2.387(2)
Gd−N	3	2.67(6)	2.68(6)	2.67(8)
$C{=}O_{amide}^{s.u.}$	2	1.248(7)	1.245(7)	1.254(3)
$C{=}O_{carboxylate}$	6	1.249(20)	1.244(19)	1.255(9)
$N_{amine}-C_{sp^3}$	9	1.485(12)	1.479(12)	1.479(7)
$N_{amide}-C_{amide}^{s.u.}$	2	1.310(8)	1.317(7)	1.314(3)
$N_{amide}-C_{sp^3}^{s.u.}$	2	1.457(8)	1.444(8)	1.457(3)
$C_{sp^3}-C_{sp^2}$	5	1.524(12)	1.524(13)	1.517(7)
$C_{sp^3}-C_{sp^3}^{s.u.}$	2	1.523(8)	1.513(8)	1.518(3)

[a] Numbers in parentheses refer to the highest value of either statistical standard variation of sample (s) or highest standard uncertainty (s.u.) [b] Number of bonds.

Table 6. **Selected hydrogen bonds in gadodiamide I (stereoisomers I and IA)**

	H⋯A/Å	D⋯A/Å	D−H⋯A/°
O1W−H1A⋯O7A[a]	1.96	2.783(6)	172(4)
O2W−H2A⋯O5[b]	2.05	2.793(7)	148(4)
O2W−H2B⋯O4[b]	2.42	2.908(5)	119(4)
N1−H1⋯O5A[c]	1.95	2.819(6)	176(4)
N1A−H3⋯O5[d]	1.93	2.782(7)	166(4)
N1A−H3⋯O10W	2.21	2.535(10)	102(10)
N5−H5⋯O6A[e]	1.98	2.833(6)	167(4)
N5A−H5A⋯O6	1.95	2.806(6)	169(4)
O3W−H27⋯O3A[f]	2.07	2.811(8)	148(8)
O4W−H29⋯O3[g]	2.01	2.832(8)	172(6)
O5W−H31⋯O3A[f]	1.97	2.755(8)	156(8)
O6W−H32⋯O3[g]	2.18	2.771(8)	128(8)
O7W−HH34⋯O6	2.24	2.750(10)	120(10)
O8W−H37⋯O6A	2.04	2.792(10)	151(15)

[a] −1/2 + *x*, 1/2 − *y*, 2− *z*. [b] 1/2 + *x*, 1/2 − *y*, 2 − *z*. [c] *x*, 1 + *y*, *z*. [d] 1 + *x*, −1 + *y*, *z*. [e] −1 + *x*, *y*, *z*. [f] 2 − *x*, −1/2 + *y*, 3/2 − *z*. [g] 1 − *x*, 1/2 + *y*, 3/2 − *z*.

Table 7. **Selected hydrogen bonds in gadodiamide III**

	H⋯A/Å	D⋯A/Å	D−H⋯A/°
N1−H1A⋯O5[a]	1.94	2.823(2)	175(2)
N5−H5A⋯O6[b]	1.93	2.798(2)	168(2)
O1W−H1A⋯O2W	1.92	2.743(2)	170(2)
O1W−H1B⋯O7W[c]	2.07	2.87(2)	162(3)
O2W−H2A⋯O5W	1.96	2.776(2)	169(2)
O2W−H2B⋯O3[d]	1.94	2.758(2)	167(2)
O3W−H3A⋯O4W[e]	1.96	2.777(2)	171(2)
O3W−H3B⋯O6W[c]	2.11	2.938(2)	175(3)
O4W−H4A⋯O6W	2.01	2.830(3)	172(2)
O4W−H4B⋯O5[e]	2.03	2.857(2)	177(3)
O5W−H5B⋯O1W[b]	2.33	3.105(2)	155(2)
O5W−H5B⋯O3[f]	2.03	2.850(2)	168(3)
O6W−H6A⋯O6[b]	1.90	2.725(2)	176(2)
O6W−H6B⋯O2W[g]	2.05	2.871(2)	170(2)
O7W−H7A⋯O3W[e]	2.03	2.856(3)	172(3)
O7W−H7B⋯O4[g]	1.97	2.750(2)	157(2)

[a] −*x*, −*y*, −*z*. [b] 1/2 + *x*, 1/2 − *y*, 1/2 + *z*. [c] −1 + *x*, *y*, *z*. [d] −1/2 + *x*, 1/2 − *y*, 1/2 + *z*. [e] 1 − *x*, −*y*, 1 − *z*. [f] *x*, *y*, 1 + *z*. [g] 1 + *x*, *y*, *z*.

molecule O1WA and carboxylic oxygen O7AA in the opposite enantiomer. The latter molecule reconnects to the first via its water ligand molecule O2WA, engaging both its available hydrogens to the carboxylic oxygen atoms O4A and O5A. The crystal water molecules (O3W−O10W) of gadodiamide **I** are mainly engaged by the carboxylate O atoms (O3, O3A, O6, and O6A) into what effectively becomes a hydrogen-bonded layer of water molecules, capping the complex and separating layers of dimers of complexes. All complexes in the two structures donate their amino hydrogens in the same manner (N1−H⋯O5′ and N5−H⋯O6′), thereby creating links with two additional neighbours establishing an infinite intermolecular network.

Gadodiamide **III** (Figure 6) on the other hand has no direct intermolecular contacts via its water ligand. Instead an extensive hydrogen-bond network involving all water molecules creates a less densely packed structure than for gadodiamide **I**. Whereas gadodiamide **I** has a close, directly hydrogen-bonded dimeric arrangement of the complexes, the water ligand in gadodiamide **III** only reaches the water ligand

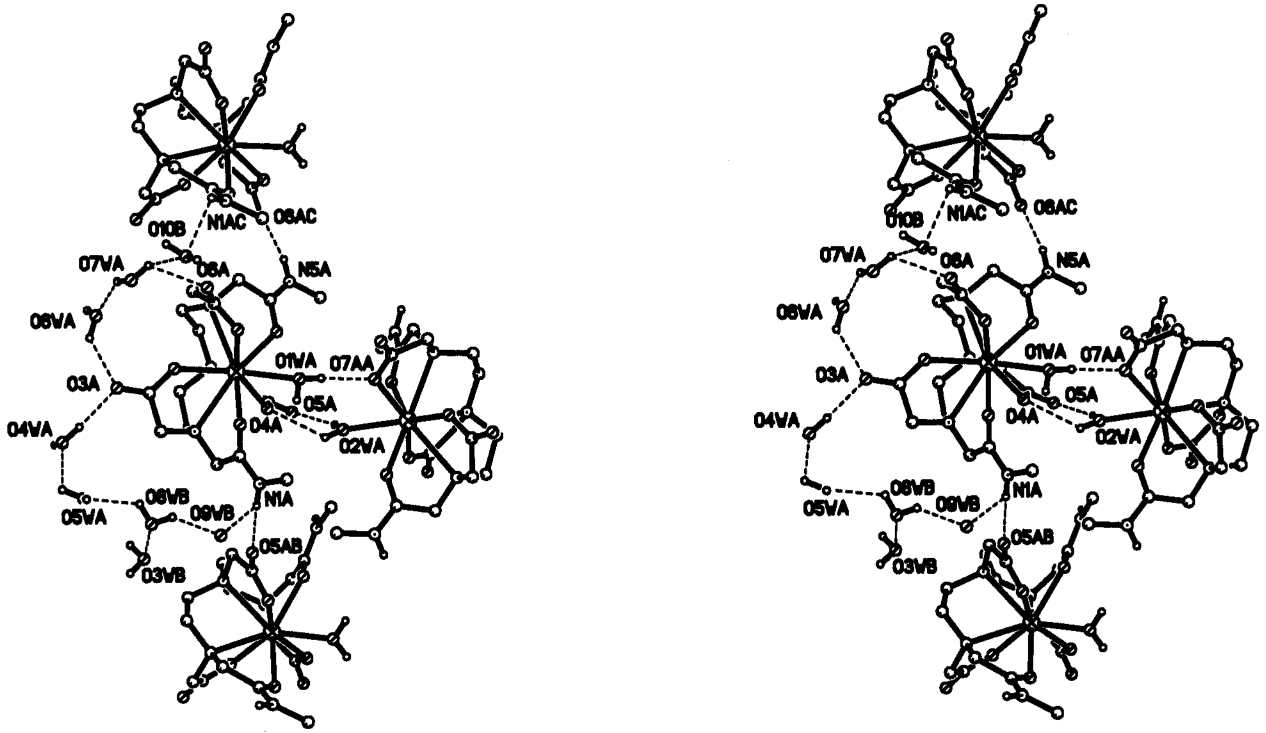

Figure 5. **Stereoscopic view of the packing pattern and hydrogen bonding network of gadodiamide I.**

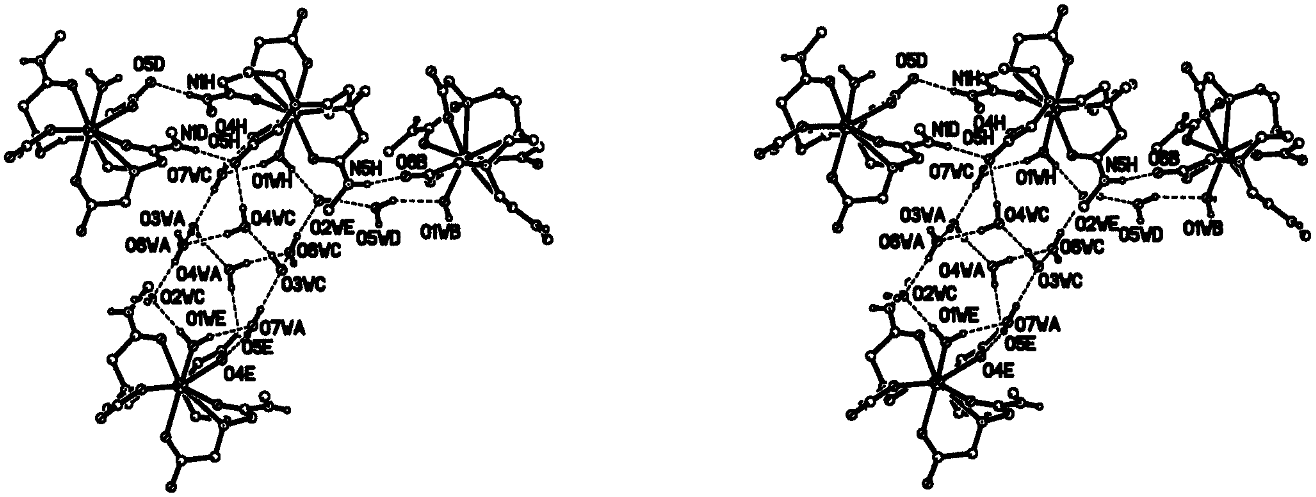

Figure 6. **Stereoscopic view of the packing pattern and hydrogen bonding network of gadodiamide III.**

of an opposite neighbour through hydrogen bonding via two paths involving eight inversion-symmetry-related crystal water molecules. Both hydrogens on each water ligand are involved in shaping a chair-conformed 10 O-atom-membered ring system (by the bridging of two six-membered rings) in the sequence, O1W, O2W, O6W, O3W, O7W, O1W′ O2W′, O6W′, O3W′, O7W′, O1W′ (cf. Figure 6). In addition, O1W in gadodiamide **III** also acts as an acceptor of H−O5W, which in turn bonds to O2W itself, connecting to H−O1W′, thus completing an intermolecular link to a nearest-neighbour via only two crystal water molecules.

Discussion of the Gadodiamide Complexes. All gadolinium (III)-based chelates approved for use in MRI are nine-coordinate complexes in which a ligand occupies eight binding sites at the metal center and the ninth coordination site is occupied by a solvent water molecule.[3] The most common coordination numbers for the lanthanides are 8 and 9.[4] For nine-coordinate complexes the idealized coordination geometries are tricapped trigonal prism (TPP) and capped square antiprism (CSAP). In the absence of chelate ring steric effects the tricapped trigonal prism has been identified as the most favourable polytopal form for an ML_9 coordination complex.[5] Generally for lanthanide DTPA−bis(amide) systems it is seen that (1) the ligand is octadentate, including both amide oxygens, (2) the weaker ligands, with longer bond

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lengths, prefer to sit on the face caps, and (3) bond strength order, from weakest to strongest, is amine **N** < H_2**O** < NC═**O** < **O**C═O. Since all three amines cannot simultanously cap the prism, the central amine (N3) sits on the edge, and water occupies the third cap. Once bound to the metal, the terminal amines of the backbone are chiral.[6] In the configuration of the terminal amines with lowest energy (*R*, *S*), both the coordinating amide groups are in neighbouring positions to the central carboxylate group, thus maximizing charge separation between the negatively charged carboxylate groups in the complexes.[7] In gadodiamide **I** and **III** the configuration of the amide groups are in a *trans* configuration, again similar to that reported for DyDTPA−BMA[8] and GdDTPA−BEA.[9] In this type of complex there are generally seen short metal−oxygen bonds and long metal-nitrogen bonds compared to the sum of the ionic radii.[8] This is readily explained from (2) above; the weaker ligands have longer bond lengths. In both gadodiamide **I** and **III** the nine ligand-atoms form a coordination polyhedron best described as a distorted tricapped trigonal prism, totally in accordance with the general description above. The gadodiamide structures are also consistent with earlier studies of closely related compounds: The structure of GdDTPA−BEA (the bis(ethylamide) derivative) is described with the same coordination geometry, with seven water molecules in the structure (similar to gadodiamide **III**).[9] The same coordination geometry is also found for the dysprosium analogue, DyDTPA−BMA (sprodiamide).[8] Also DyDTPA−BMA crystallises with seven water molecules, similar to gadodiamide **III**. Additionally, DyDTPA−BMA and gadodiamide **III** crystallise in the same space group and have very similar cell dimensions. Work related to sprodiamide forms studied by single-crystal X-ray and comparison with the gadodiamide forms is in progress.[10] Also the GdDTPA−bis(Bz-amide) is found in a tricapped trigonal prismatic metal coordination polyhedron.[11] In contrast, a capped square antiprism (CSAP) coordination polyhedron is found in some other structures, for instance in GdDTPA[12] and $[C(NH_2)_3]_2[Gd(Httha)]5H_2O$.[13]

When comparing the structures of the gadodiamide forms with that of the free ligand DTPA−BMA,[14] some differences can be noted. In DTPA−BMA the structure is stabilised by two intramolecular hydrogen bonds, the hydrogen-bond donors being the protonated amine nitrogen atom (N3) and one of the amide nitrogen atoms (N1), and the amide oxygen (O8) at the opposite end of the molecule being the acceptor. On the other hand, in the gadodiamide forms no intramolecular hydrogen bonds are found. The hydrogen bonding in DTPA−BMA results in a folded conformation, resembling the conformation the molecule adopts as ligand in chelates with lanthanide ions.[3] It is therefore reasonable to believe that complexation of Gd^{3+} to DTPA−BMA requires little energy.

Discussion of the Gadodiamide Forms. How should gadodiamide forms **I** and **III** be classified? They are certainly hydrates, as shown by the water present in the structures, but since gadodiamide **I** and gadodiamide **III** are hydrates of different composition (five and seven water molecules per gadodiamide complex, respectively), polymorphism is not involved (polymorphism requires that a given chemical entity exists in at least two different crystal forms[15]). Another relevant term is pseudopolymorphism, which is defined as the existence of one or more solvated crystalline forms of the same compound.[16] Such a relationship exists between gadodiamide **I** and gadodiamide **III**, which therefore might be classified as pseudopolymorphs. The definition of a hydrate is more clear-cut than that of a pseudopolymorph, and thus we prefer to classify gadodiamide **I** and **III** as hydrates.[17]

When two polymorphs are formed in the same crystallisation experiment, one speaks of concomitant polymorphism.[18] Gadodiamide **III** and gadodiamide **I** were formed in the same crystallisation experiment and can by analogy be viewed as an example of concomitant hydration. In the crystallization process the occurrence domain[19] for gadodiamide **I** and gadodiamide **III** must be overlapping.

In gadodiamide **I** a hydrogen-bonded layer of water molecules is found around the gadolinium complex. Gadodiamide **I** can therefore be classified as a channel hydrate,[17] with water molecules in channels. In gadodiamide **III**, on the other hand, the gadolinium complex is surrounded by an extensive network involving all water molecules which constitute a chair-conformed 10 O-atom-membered ring system (by bridging of two six-membered rings). This structure has a resemblance to the structure of ice-**I**, which has a rather open structure consisting of puckered, six-membered rings.[20] The open water structure found in gadodiamide **III** probably explains why this hydrate is easily dried to gadodiamide **II**.

On the basis of these observations it seems as if the structure of the water-rich hydrate gadodiamide **III** is dominated by the structure of water itself, while in gadodiamide **I** the gadodiamide dimeric complex directs the hydration process and the position of the water molecules in channels. It is relevant to recall that gadodiamide **III** is crystallised from water, while gadodiamide **I** is crystallised from water/acetone. Water as solvent therefore can give a

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gadodiamide structure dominated by the structure of water itself (gadodiamide **III**).

In water there must be a fine balance between the gadodiamide **I** and gadodiamide **III** structures, since they are produced concomitantly. Addition of acetone to water changes the solvent properties by lowering the polarity, making direct hydrogen bonds between the gadodiamide enantiomers more favourable, thereby resulting in the gadodiamide **I** structure. Hydrogen bonding is recognised as being of great importance in determining intermolecular interactions.[21,22] It can be mentioned that commercially gadodiamide **I** is produced in large-scale batches by acetone-induced precipitation from aqueous solution.

The earlier published structure of gadodiamide (ref 1 and unpublished results) is shown to be that of gadodiamide **I**.

Experimental Section

General. Water purified by reversed osmosis was used.

Water Content. The water content of the samples was determined by Karl Fischer titration.

Infrared Spectroscopy. Diffuse reflectance infrared spectra were recorded in the 4000−400 cm^{-1} region on a BRUKER IFS 66 FT-IR spectrometer or a Perkin-Elmer Spectrum 2000 Explorer FT-IR spectrometer equipped with a Harrick Scientific “Praying Mantis” diffuse reflectance accessory. Samples were ground with potassium bromide (KBr, 1−2% w/w), in an agate mortar, and the resulting powder was packed and leveled in the sample cup of the diffuse reflectance accessory. For each sample 256 scans were recorded at a resolution of 4 cm^{-1}. The spectra were measured relative to a reference background obtained with pure KBr and transformed into the Kubelka−Munk format. The sample compartment of the infrared spectrometer was continuously flushed with dry air to avoid bands from atmospheric water.

Preparation of Gadodiamide I. Crystals were grown from an aqueous solution as follows: Water (30 mL) was added to a sample of gadodiamide (type **I**, 20.00 g). The resulting mixture was kept at 45 °C until the solid had dissolved (1 h). Acetone (30 mL) was added slowly to facilitate crystallization, and the solution was transferred to a glass with a screw cap and left at room temperature. After 16 h colourless needlelike crystals started to grow, and after one week the crystals were filtered on a Büchner funnel and dried in air to constant weight. Yield: 8.36 g (42%). An IR spectrum of the colourless needles was recorded and the water content was determined to be 12.1%.

Preparation of Gadodiamide III. Crystals were grown from an aqueous solution as follows: Water (25 mL) was added to a sample of gadodiamide (type **I**, 25.00 g). The resulting mixture was heated at 70 °C until the solid had dissolved. The solution was filtered and left in a covered crystallisation dish at room temperature. After 2 days crystals started to form. The mixture was left standing for 14 days. Two types of crystals, both firmly attached to the glass, had been formed; one consisted of large, colourless blocklike crystals and the other of small, colourless needles. The large crystals were first liberated and filtered from the mother liquor; subsequently, the colourless needles were liberated from the glass and collected. The two crops of crystals were then dried in air to constant weight. Yield: 0.28 g (1%) of the large, blocklike crystals, 6.43 g (26%) of the colourless needles. The IR spectra of both samples were recorded. The large, blocklike crystals had a water content of 17.4% determined after the X-ray analysis. The needles had a water content of 12.7%.

Crystal Structure Analysis. The crystal data and experimental details for gadodiamide **I** and **III** are summarised in Table 2. Structure **I** was collected and reduced, and the absorption was corrected by numerical integration using SMART and SAINT[23] and SHELXTL.[24] Structure **III** was collected and reduced using EXPRESS[25] and XCAD4,[26] respectively. No absorption correction was made. Both structures were solved, refined, and illustrated using SHELXTL.[24] All non-hydrogen atoms were refined anisotropically and the geometrically idealised hydrogen atoms given isotropic displacement parameters equal to 1.5 times the equivalent isotropic displacement factor of the parent atom. The geometry of water molecules was constrained to an O−H distance of 0.83 Å and a H−O−H angle of 104.5°. In structure **I**, the two hydrogens could not be localised for water−oxygen O9W. No structure showed any significant decay during data collection.

Acknowledgment

Nycomed Imaging AS is acknowledged for the permission to publish the present study. Financial support from the Research Council of Norway and constructive criticism from one of the reviewers are highly appreciated.

Supporting Information Available

Bond angle data. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review October 19, 2000.

OP000106E

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