Journal of Alloys and Compounds 374 (2004) 325–329

Journal of ALLOYS AND COMPOUNDS

www.elsevier.com/locate/jallcom

Heterobimetallic gadolinium(III)–iron(III) complex of DTPA-bis(3-hydroxytyramide)

Tatjana N. Parac-Vogt*, Kristof Kimpe, Koen Binnemans

Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

Abstract

A derivative of diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid (DTPA), carrying two catechol functional groups has been synthesised by the reaction between DTPA-bis(anhydride) and 3-hydroxytyramine (dopamine). The ligand DTPA-bis(3-hydroxytyramide), [DTPA$(HTA)_2$], is able to form stable heterobimetallic complexes with gadolinium(III) and iron(III) ions. The gadolinium(III) occupies the internal coordination cage of DTPA formed by three nitrogens, two carboxylate and two amide oxygens, while the [Fe(NTA)$(H_2O)_2$] (nitrilotriacetic acid, NTA) binds to catechol units by the substitution of two water ligands. The formation of polymeric species was avoided by using the tripodal NTA ligand. The heterobimetallic complex was characterised by means of visible absorption spectroscopy, electron spray ionisation–mass spectrometry (ESI–MS), and nuclear magnetic resonance (NMR) spectroscopy.

Keywords: Aminopolycarboxylates; Gadolinium; Iron; Lanthanides; MRI contrast agents; Rare earths

1. Introduction

Complexes of lanthanides with diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetate (DTPA) and with its amide derivatives have in recent years attracted considerable attention as potential contrast agents [1]. The $[Gd(DTPA)(H_2O)]^{2-}$ was the first contrast agent approved for use in humans and is nowadays routinely used in clinical magnetic resonance imaging (MRI) for contrast enhancement under the name Magnevist® (Schering, Berlin, Germany). This paramagnetic complex contains one water molecule in the first coordination sphere, and fast exchange of this water molecule with the bulk water in the human body provides an efficient mechanism for the enhancement of the relaxation rates of the water protons [1–5]. However, the rapid development of magnetic resonance imaging technique for medical diagnostics has led to an increasing demand for even more effective contrast reagents. The overall paramagnetic relaxation enhancement referred to by a 1 mM concentration of a given gadolinium(III) chelate, the so called *relaxivity*, depends on factors such as paramagneticity, molecular mobility, the water dynamics and the noncovalent interactions between the complex and endogenous proteins. Besides increasing relaxivity, parallel efforts are being directed towards the finding of tissue specific contrast agents. Some recent results indicated that the presence of aromatic group in the ligand seems to bring some tissue specificity as well as increase of relaxivity [6].

An interesting approach towards achieving higher relaxivity was discovered by Desreux and co-workers and relies on the formation of a supramolecular entity by self-assembly of the gadolinium(III) complex around iron(II) [7]. The increase of molecular weight accompanying the self-assembly results in a slowdown of the tumbling rate, and hence a higher relaxivity. In one example, the DTPA ligand was modified in such a way that besides the gadolinium(III) ion, which co-ordinated to DTPA moiety, the binding of two iron(III) ions by two salicylamide group was also possible [8]. Although, the relaxometric studies showed that binding of iron(III) lead to the increase in overall relaxivity, the complexes were not completely characterised, and the presence of polymeric complexes and different species due to the multiple equilibrium in solution was possible.

Here we report a route to a monomeric gadolinium(III)–iron(III) complex derived from the ligand DTPA-bis(3-hydroxytyramide), DTPA$(HTA)_2$, described for the first time by White [9]. The complexes were characterised in solution by means of visible absorption spectroscopy, electron spray ionisation–mass spectrometry (ESI–MS), and nuclear

* Corresponding author. Fax: +32-16-327992.
E-mail address: tatjana.vogt@chem.kuleuven.ac.be (T.N. Parac-Vogt).

0925-8388/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.jallcom.2003.11.102

magnetic resonance (NMR) spectroscopy and the results indicate that only one type of species with well-defined structure has been formed in solution.

2. Experimental

Reagents were obtained from Aldrich Chemical Co. Inc., Acros Organics and used without further purification. DTPA was obtained from Koch Light Laboratories. The DTPA-bis(anhydride) and [Fe(NTA)(H_2O)$_2$], where NTA is nitrilotriacetic acid, were synthesised according to previously reported procedures [10,11]. ^{1}H NMR spectra were run on a Bruker Avance 300, operating at 300 MHz. IR spectra were measured on a FTIR-spectrometer Bruker IFS66, using KBr discs. Elemental analysis was performed on a CE Instruments EA-1110 elemental analyser. UV-Vis spectra were measured on a Shimadzu UV-1601PC spectrometer. The ESI–MS measurements were performed on a Thermo Finnigan LCQ Advantage mass spectrometer.

2.1. Synthesis of the [DTPA(HTA)$_2$] (1)

To a solution of DTPA-bis(anhydride) (0.357 g; 1 mmol) in dry DMF (30 ml), 3-hydroxytyramine hydrochloride (0.379 g; 2 mmol) was added and the reaction mixture was heated at 60 °C for 5 h. After removal of the solvent by evaporation, the product was dissolved in water (10 ml) and the pH was adapted to 8.5 with a 0.1 M solution of NaOH. The solvent was removed under reduced pressure and the compound was washed with ethanol and dried in *vacuo* overnight (yield 95%). Elem. Anal. Calcd.: (found): $C_{30}H_{38}N_5O_{12}Na_3(H_2O)$: C, 48.18 (48.63), H, 5.39 (5.60) N, 9.37 (8.97). ES–MS(+): 664, [M+H]$^+$. ^{1}H NMR (D_2O), δ (ppm): 2.61 (t, 4 H, 2 × N–C**H**$_2$); 2.95 (t, 4 H, 2 × N–C**H**$_2$); 3.10 (m, 4 H, 2 × C**H**$_2$–NH–CO); 3.37 (m, 4 H, 2 × C**H**$_2$–Ph); 3.50 (s, 2 H, C**H**$_2$–COOH); 3.56 (s, 4 H, 2 × C**H**$_2$–COOH); 3.68 (s, 4 H, 2 × C**H**$_2$–CO–NH); 6.56–6.82 (m, 6 H, Ph); IR (KBr, cm^{-1}): 1740 (CO free acid), 1647 (amide I), 1521 (amide II).

2.2. Synthesis of [Gd-DTPA(HTA)$_2$] (2)

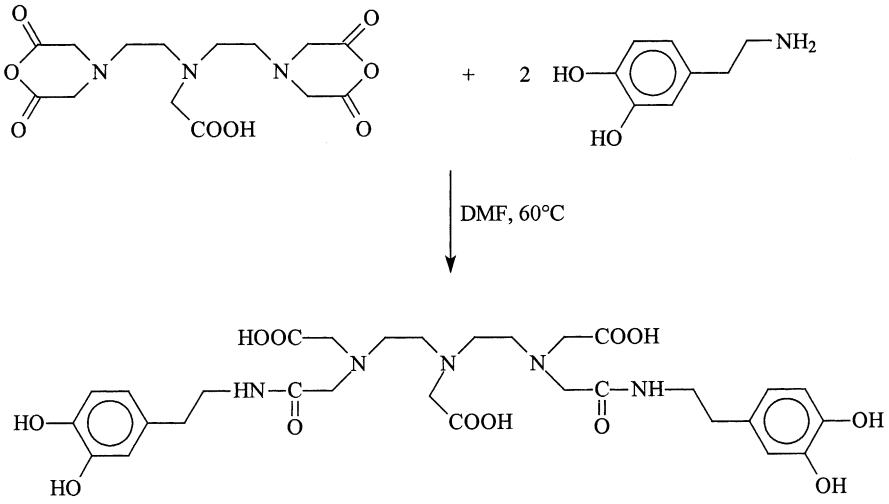
To a solution of hydrated $GdCl_3$ salt (1.1 mmol in 1 ml of H_2O) was added a solution of the ligand DTPA(CAT)$_2$ (1.0 mmol in 30 ml of pyridine), and the mixture was heated at 70 °C for 3 h. The solvents were evaporated under reduced pressure and the crude product was then refluxed in ethanol for 1 h. After cooling to room temperature, the complex was filtered off and dried in vacuo (yield: 95%). ES–MS(+): 841, [M+Na$^+$]$^+$. IR (KBr, cm^{-1}): 2923, 2852 (CH alkyl), 1602 (COO$^-$ asym. stretch), 1408 (COO$^-$ sym. stretch).

2.3. Synthesis of [Fe(NTA)]$_2$–[Gd-DTPA(HTA)$_2$] (3)

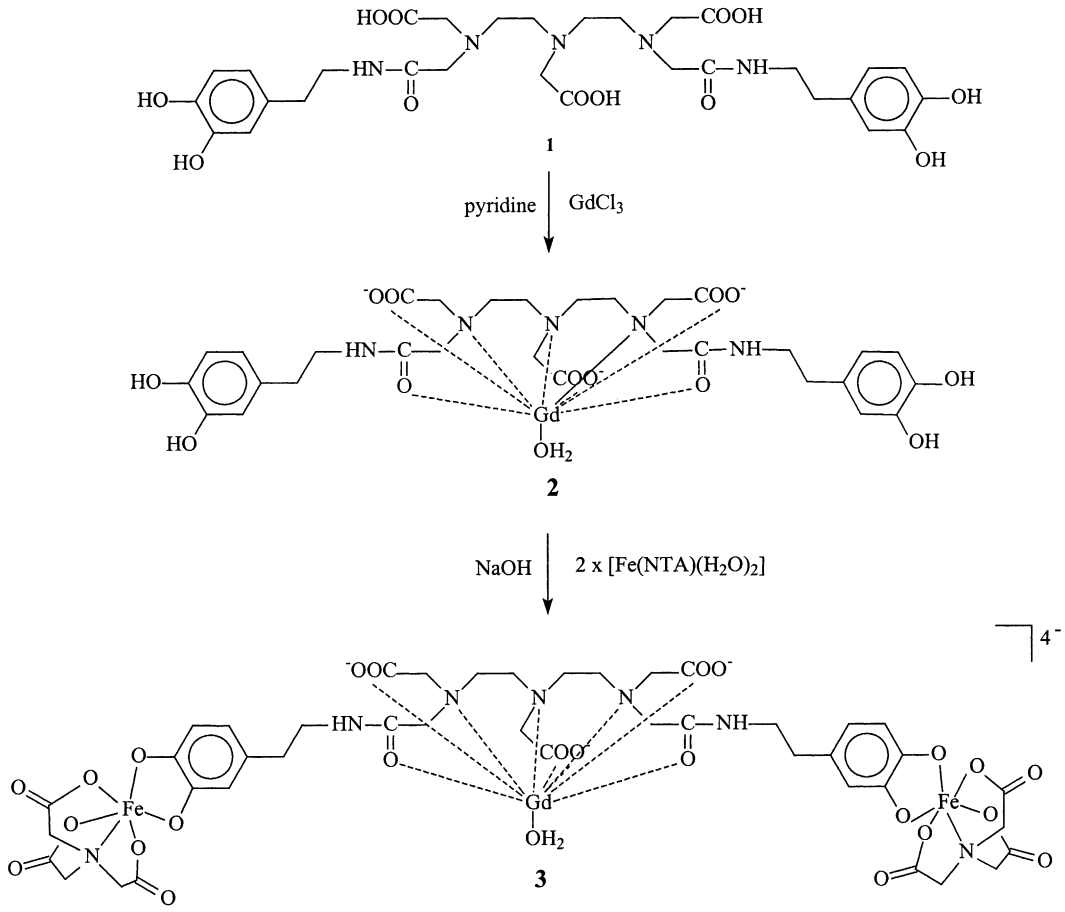
The pH of a 1 mmol solution of [Gd-DTPA(HTA)$_2$] in 5 ml of water was adjusted to 8.0 with 0.1 M NaOH, and 5 ml of 2 mmol [Fe(NTA)(H_2O)$_2$] solution was slowly added. After the volume of the solution was reduced by solvent evaporation in vacuo, acetone was added upon which the bimetallic complex precipitated as microcrystalline solid. It was filtered off and dried in vacuum over night. ES–MS(−): 682, [M+2Na$^+$]$^{2-}$ IR (KBr, cm^{-1}): 2923, 2852 (CH alkyl), 1610 (COO$^-$ asym. stretch), 1417 (COO$^-$ sym. stretch). UV-Vis, λ_{max} = 595 nm.

3. Results and discussion

The ligand DTPA-bis(3-hydroxytyramide), DTPA(HTA)$_2$, was obtained by reaction between DTPA bis(anhydride) and 3-hydroxytyramine (dopamine) (Scheme 1). The modification of the parent DTPA ligand to the bis-amide derivative 1, does not affect the ability of DTPA to bind lanthanide ions



Scheme 1. Synthesis of DTPA-bis(3-hydroxytyramide), DTPA(HTA)$_2$ **1**.



Scheme 2. Synthesis of the gadolinium(III)–iron(III) heterobimetallic complex of DTPA-bis(3-hydroxytyramide).

(Scheme 2) [12–14]. Under slightly alkaline solution the ligand readily formed complex **2** with the gadolinium(III) ion. IR spectra of the ligand showed strong absorptions in the regions 3000–3700 and 1650–1750 cm^{-1}, corresponding to the NH and CO stretching modes, respectively. Shifts of ca. 40 cm^{-1} to lower energy were observed for the carbonyl stretching frequencies upon complexation, indicating amide oxygen coordination to the lanthanide ion. These findings are consistent with previous studies which have shown that DTPA bis(amide) derivatives co-ordinate to lanthanide(III) ions via three acetate oxygens, three nitrogen atoms and two carbonyl oxygens of the amide group, while the ninth co-ordination site is occupied by a water molecule [12,13]. Since the IR stretching frequencies for the catechol group overlap to some extent with the carbonyl stretching frequencies it was difficult to say based on the IR spectra whether the catechol group was involved in coordination to gadolinium(III). However, proton NMR spectrum of analogous diamagnetic [La-DTPA(HTA)$_2$] complex indicated that catechol resonances remained unaffected upon coordination of **1** to lanthanum(III), while the DTPA resonances broadened significantly, which is indicative of the lanthanum(III) coordination [15]. Further, evidence for the existence of **2** in the solution was obtained from the electrospray mass spectrum, in which a peak detected in positive mode at *m/z* 841 corresponds to $[\mathbf{2}+Na^+]^+$ species.

Complexation of **2** with [Fe(NTA)(H$_2$O)$_2$] proceeded rapidly in a slightly basic water solution (Scheme 2). An immediate colour change from yellow to dark violet was a strong indication of formation of an iron catecholate complex [11]. This is illustrated in Fig. 1 which shows the visible absorption spectra of [Fe(NTA)(H$_2$O)$_2$] and of complex **3**. The [Fe(NTA)(H$_2$O)$_2$] has no chromophores absorbing in the visible region, but its addition to **2** resulted in the appearance of a strong absorption band with a maximum at 595 nm. This band has been assigned as catechol-to-Fe(III) charge-transfer transitions, and has been earlier detected in several [Fe(NTA)]–catechol complexes [16]. The spectrum of **3** below 400 nm was not very informative, since a strong and very broad absorption band has been observed.

The role of the NTA ligand is to prevent formation of polymeric species in the solution which would be likely to form if $[Fe(H_2O)_6]^{3+}$ was used as a source of iron. The evidence that definite species were formed in solution was provided from the negative mode electrospray ionisation mass spectrometry. Only the single cluster in the region from 678 to 686 *m/z* was detected, which corresponds to $[\mathbf{3} + 2Na^+]^{2-}$.

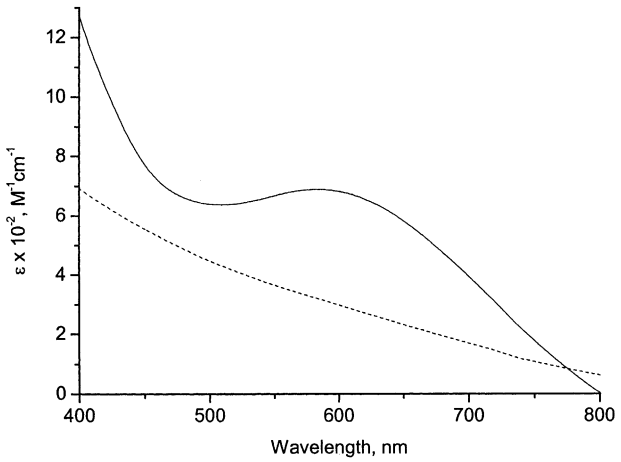


Fig. 1. Visible absorption spectra of 5×10^4 M solution of $[Fe(NTA)(H_2O)_2]$ at pH 9.8 (dashed line) and of complex **3** at pH 5.6 (full line) in water.

The isotopic distribution of this cluster is very similar to the theoretically calculated patter, as shown in Fig. 2. The simplicity of the ES–MS spectrum can be attributed to the thermodynamic stability and kinetic inertness of the complex. The possibility of iron(III) replacing gadolinium(III) ion in the DTPA-like coordination cage of the ligand is very unlikely, since no change in UV-Vis spectra and no discoloration of **3** have been observed, even not in solutions which were standing for several weeks. The exchange between the lanthanide(III) and iron(III) centres was also not detected in relaxation studies on analogous heterobimetallic gadolinium(III)–iron(III) complexes in which DTPA ligand was di-substituted with the *p*-amino-salicilic moiety [8].

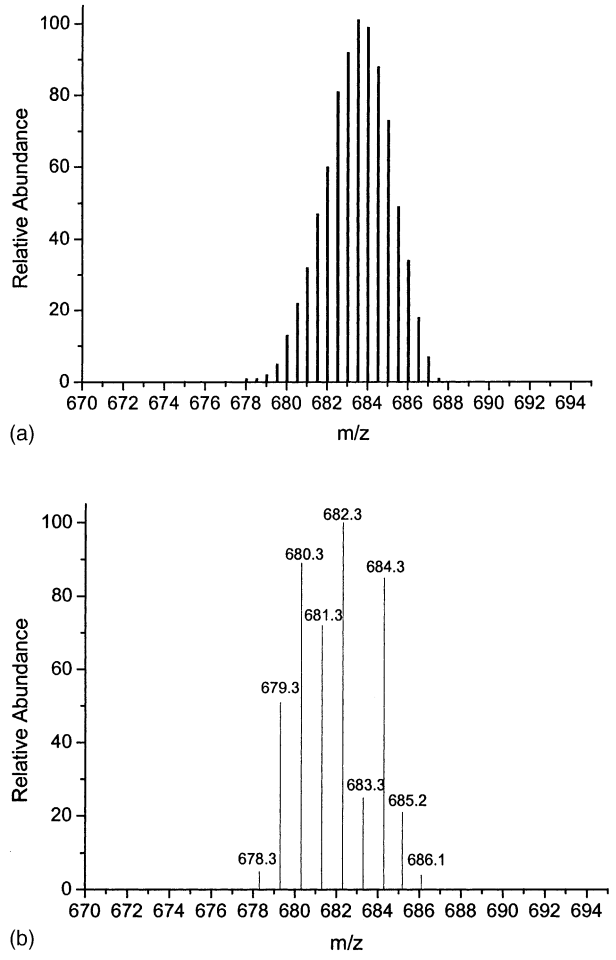


Fig. 2. The isotopic distribution of the peak cluster at *m/z* 682.3 for the gadolinium(III)–iron(III) complex **3**: (a) calculated; (b) experimental.

4. Conclusions

In summary, we have shown that monomeric heterobimetallic paramagnetic complexes can be obtained by using DTPA-bis(3-hydroxytyramide) as the ligand, and with gadolinium(III) and iron(III) as the paramagnetic centres. Special attention has been paid to avoid the formation of polymeric species. These paramagnetic polymetallic species have a potential as MRI contrast agents [7].

Acknowledgements

This study was supported by the K.U. Leuven (VIS/01/006.01/20002-06/2004 and GOA 03/03) and by the FWO-Flanders (G.0117.03). KB acknowledges the FWO-Flanders for a Postdoctoral Position. We thank Ms. Leen Van Nerum for measuring the mass spectra.

References

[1] (a) W. Krause (Ed.), Contrast Agents I, Magnetic Resonance Imaging, Springer-Verlag, Berlin, 2002;
(b) R.B. Lauffer, Chem. Rev. 87 (1987) 901;
(c) P. Caravan, J.J. Ellison, T.J. McMurry, R.B. Lauffer, Chem. Rev. 99 (1999) 2293.
[2] J.A. Peters, Inorg. Chem. 27 (1988) 4686.
[3] C.F.G.C. Geraldes, A.D. Sherry, W.P. Cacheris, K.T. Kuan, R.D. Brown Jr., S.H. Koenig, M. Spiller, Magn. Reson. Med. 8 (1988) 191.
[4] C.A. Chang, H.G. Brittain, J. Telser, M.F. Tweedle, Inorg. Chem. 29 (1990) 4468.
[5] K. Micskei, L. Helm, E. Brucher, A.E. Merbach, Inorg. Chem. 32 (1993) 3844.
[6] S. Laurent, L. Vander Elst, S. Houzé, N. Guérit, R.N. Muller, Helv. Chim. Acta 83 (2000) 394.
[7] (a) V. Comblin, D. Gilsoul, M. Hermann, V. Humblet, V. Jacques, M. Mesbahi, C. Sauvage, J.F. Desreux, Coord. Chem. Rev. 186 (1999) 451;
(b) J.F. Desreux, V. Jacques, V. Humblet, M. Hermann, V. Comblin, M.F. Tweedle, *Self assembling heteropolymetallic chelates as imaging agents and radiopharmaceuticals*, US Patent 6,056,939 (2000);
(c) V. Jacques, J.F. Desreux, Top. Curr. Chem. 221 (2002) 123.
[8] S. Aime, M. Botta, M. Fasano, E. Terreno, Spectrochim. Acta A 49 (1993) 1315.
[9] (a) D.L. White, R.G. Eason, US Patent 5,562,894 (1993);
(b) D.L. White, US Patent 5,914,097 (1999).
[10] V. Montembault, J.C. Soutif, J.C. Brosse, React. Funct. Polym. 29 (1996) 29.

[11] L. Que Jr., R.C. Kolanczyk, L.S. White, J. Am. Chem. Soc. 109 (1987) 5373.
[12] L. Ehnebom, B.F. Pedersen, Acta. Chem. Scand. 46 (1992) 126.
[13] S.W.A. Bligh, A.H.M.S. Chowdhury, M. McPartlin, T.J. Scowen, R.A. Bulman, Polyhedron 14 (1995) 567.
[14] K. Kimpe, T.N. Parac-Vogt, S. Laurent, C. Piérart, L. Vander Elst, R.N. Muller, K. Binnemans, Eur. J. Inorg. Chem. (2003) 3021.
[15] S. Aime, M. Botta, Inorg. Chim. Acta 177 (1990) 101.
[16] D.D. Cox, S.J. Benkovic, L.M. Bloom, F.C. Bradley, M.J. Nelson, L. Que Jr., D.E. Wallick, J. Am. Chem. Soc. 110 (1988) 2026.