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Substitution of gadolinium ethylenediaminetetraacetate with phosphites: towards gadolinium deposit in nephrogenic systemic fibrosis†

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In neutral media, reactions of gadolinium ethylenediaminetetraacetates with phosphorous acid result in the formation of the mixed-ligand polymeric complex $K_{3n}[Gd(EDTA)(HPO_3)]_n \cdot 7nH_2O$ (**1**) and dimeric complex $Na_6[Gd_2(EDTA)_2(HPO_3)_2] \cdot 2.5NaCl \cdot 21H_2O$ (**2**) (H_4EDTA = ethylenediaminetetraacetic acid) in warm solution. Further substitution with citric acid gives the monomeric gadolinium citrate with EDTA $(NH_4)_2Na[Gd(EDTA)(H_2cit)] \cdot 4H_2O$ (**3**). The compounds were characterized by elemental analysis, single crystal X-ray diffraction, FT-IR, ESI-MS and thermogravimetric analysis. Structural analysis indicates that three coordinated water molecules in the gadolinium ethylenediaminetetraacetate trihydrates are replaced by phosphite ions (HPO_3^{2-}) in the compounds **1** and **2**. Gadolinium atoms are octa-coordinated by EDTA and the phosphite ion, the latter links adjacent Gd–EDTA units to generate an infinite one-dimensional chain in compound **1** and a dimeric octatomic ring in **2**. In complex **3**, coordinated water molecules were substituted by the α-hydroxy, α-carboxy and β-carboxy groups of citrate. Citrate is favourable for inhibiting the formation of Gd–EDTA phosphite. All the complexes are very easily soluble in water. The solution behavior of the isostructural lanthanum complexes was probed with ^{13}C and ^{31}P NMR spectra in D_2O for comparison. ESI-MS analysis and recrystallization proved that complexes **1** and **2** dissociate to the monomeric unit of Gd–EDTA and free HPO_3^{2-} in aqueous solution. Substitutions of gadolinium ethylenediaminetetraacetates to **1** and **2** are attributed to be the cause of nephrogenic systemic fibrosis in some way.

Introduction

Nephrogenic systemic fibrosis (NSF) is a rare but incurable disease that involves the fibrosis of skin, joints and internal organs. It was identified in 1997 and first reported in 2000.[1] The disease is found exclusively in patients with renal failure and is related to the exposure of gadolinium-based contrast agents (GBCAs) used in magnetic resonance imaging (MRI).[2] Tissue samples from patients with NSF have been proved to contain micron-sized Gd containing insoluble deposits, like the $GdPO_4$ structure together with Ca, K, Na.[3] GBCAs are the only significant Gd source in the human body. Generally, in GBCAs, Gd atoms are coordinated by chelating ligands in order to obtain high water solubility, *in vivo* stability and reduction of toxicity of Gd^{3+}.[4] Like the most commonly used Magnevist, namely Gd–DTPA (H_5DTPA = diethylenetriaminepentaacetic acid), the gadolinium chelates exhibit high thermodynamic stability and kinetic inertness.[4,5] However, in NSF, the stable GBCAs transform into insoluble gadolinium phosphates. Till now, there is no consistently effective therapy and the pathogenesis remains unknown.[6]

In this study we have chosen Gd–EDTA as a model compound of GBCAs. Since the mixed-ligand complex of $GdPO_4$–EDTA is difficult to isolate in neutral solution, phosphorous acid is used as a replacement for phosphate due to its similarities. Herein, we make an attempt to investigate the coordination chemistry of Gd–EDTA and phosphorous acid. Two hybrid gadolinium complexes $K_{3n}[Gd(EDTA)(HPO_3)]_n \cdot 7nH_2O$ (**1**) and $Na_6[Gd_2(EDTA)_2(HPO_3)_2] \cdot 2.5NaCl \cdot 21H_2O$ (**2**) were obtained from the substitution of $[Gd(EDTA)(H_2O)_3]^-$. Further substitution of **2** with citric acid leads to the mixed-ligand complex $(NH_4)_2Na[Gd(EDTA)(H_2cit)] \cdot 4H_2O$ (**3**). Structural studies show complexes **1–3** are polymeric, dimeric and monomeric, respectively. The solution behavior of the isostructural lanthanum complexes was investigated by ^{13}C and ^{31}P NMR spectroscopies for comparison. Compounds **1** and **2** are considered as intermediates between gadolinium ethylenediaminetetraacetate and gadolinium phosphite.

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†Electronic supplementary information (ESI) available: Including other NMR spectra (Fig. S1–S4); IR spectra (Fig. S5–S8) and TG-DTG curves (Fig. S9 and S10). CCDC 951555, 951556 and 951762. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3dt52015c

Experimental

Materials and instrumentation

All chemicals were of analytical or reagent-grade purity and used without further purification. The pH value in the synthesis was measured by the potentiometric method with a PHB-8 digital pH meter. Elemental analysis (C, H, N) was performed using an EA1110 elemental analyzer. Infrared spectra were recorded as Nujol mulls between KBr plates using a Nicolet 330 FT-IR spectrophotometer. Thermogravimetric analysis was recorded on a TG 209F1 thermal analyzer, under an air flow of 20 mL min^{-1} at a heating rate of 10 °C min^{-1}. A Bruker esquire 3000^{plus} instrument was used to record the Electrospray ionization (ESI) mass spectra. Solution ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker AV 400 NMR spectrometer with D_2O using DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as the internal reference.

Synthesis

Preparation of gadolinium ethylenediaminetetraacetates. $K[Gd(EDTA)(H_2O)_3]\cdot 5H_2O$ was synthesized with a modified method.[7] A mixture of gadolinium chloride hexahydrate (3.8 g, 10 mmol) and excess ethylenediaminetetraacetic acid (3.2 g, 11 mmol) was added to water (20 mL). The pH value of the solution was adjusted to 6.0 by slow addition of 2.0 M potassium hydroxide. The solution was stirred for half an hour and heated at 70 °C for 8 h. Colorless crystalline materials were separated by evaporation of the solution, and were washed with cold water and ethanol, and dried under vacuum. The yield was 73% (4.6 g). In a similar method, $Na[Gd(EDTA)(H_2O)_3]\cdot 5H_2O$ and $M[La(EDTA)(H_2O)_3]\cdot 5H_2O$ (M = K; Na) were obtained. Solution ^{13}C NMR (400 MHz, D_2O) of $M[La(EDTA)(H_2O)_3]$. δ (ppm) 183.0 (CO_2), 64.4 ($-CH_2N$), 57.2 (NCH_2CH_2N).

Preparation of gadolinium phosphate. $GdPO_4\cdot 0.5H_2O$ was synthesised as a model compound of the Gd phosphate deposit in NSF.[3,8] Gadolinium chloride hexahydrate (2.0 mmol, 0.75 g) was dissolved in water (5.0 mL). Then it was rapidly added into a stirred solution of a diluted H_3PO_4 solution (2.0 mmol, 5.0 mL). The pH value was adjusted to 3.0 by addition of sodium hydroxide (1.0 mol L^{-1}). The mixture was stirred for an hour and left for several days. The product was isolated by filtration, washed with water and ethanol and dried in air. Yield: 0.48 g (91.8%). IR (KBr disk, cm^{-1}): 3349 s, 1634 w, 1387 w, 1079 s, 625 w, 578 w.

Preparation of $K_{3n}[Gd(EDTA)(HPO_3)]_n\cdot 7nH_2O$ (1). $K[Gd(EDTA)(H_2O)_3]\cdot 5H_2O$ (1.3 g, 2.0 mmol) and phosphorous acid (0.50 g, 6.0 mmol) were dissolved in water. The pH value of the mixture was adjusted to 7.2 with 2.0 M potassium hydroxide. The mixture was stirred for two hours at room temperature and heated at 70 °C for one week. The solution was left to evaporate for several days at room temperature, and gave a colorless crystalline product of **1**. The product was isolated by filtration, washed with ethanol and dried in air. Yield: 1.0 g (65%). Anal. found (calcd for $C_{10}H_{27}N_2O_{18}PK_3Gd$): C, 15.2 (15.6); H, 3.6 (3.5); N, 3.5 (3.6). IR (KBr, cm^{-1}): 3458 s, 2323 w, 1646 m, 1597 s, 1397 m, 1335 w, 1260 w, 1247 w, 1124 m, 1106 m, 1058 w, 1033 w, 1000 w, 960 w, 926 w, 856 w, 713 w, 640 w. Similarly, $K_{3n}[La(EDTA)(HPO_3)]_n\cdot 7nH_2O$ (**4**) was obtained. Anal. found (calcd for $C_{10}H_{27}N_2O_{18}PK_3La$): C, 15.7 (16.0); H, 3.6 (3.6); N, 3.6 (3.7). Solution ^{13}C NMR (400 MHz, D_2O): δ (ppm) 182.6 (CO_2), 64.6 ($-CH_2N$), 57.4 (NCH_2CH_2N); ^{31}P NMR (400 MHz, D_2O): δ (ppm) 2.3 (HPO_3).

Preparation of $Na_6[Gd_2(EDTA)_2(HPO_3)_2]\cdot 2.5NaCl\cdot 21H_2O$ (2). $Na_3[Gd(EDTA)(H_2O)_3]\cdot 5H_2O$ (1.3 g, 2.0 mmol) and phosphorous acid (0.50 g, 6.0 mmol) were dissolved in water. The pH value of the mixture was adjusted to 7.5 with 2.0 M sodium hydroxide. The solution was stirred for two hours at room temperature and heated at 70 °C for one week. The colorless crystalline material of **2** was separated with a yield of 1.1 g (64%). Anal. found (calcd for $C_{20}H_{68}N_4O_{43}P_2Cl_{2.5}Na_{8.5}Gd_2$): C, 13.8 (14.0); H, 3.8 (4.0); N, 3.1 (3.3). IR (KBr, cm^{-1}): 3406 s, 2918 w, 2359 w, 1601 s, 1435 w, 1402 m, 1328 w, 1261 w, 1116 m, 1084 m, 1000 w, 935 w, 850 w, 714 w, 664 w, 594 w. Similarly, $Na_6[La_2(EDTA)_2(HPO_3)_2]\cdot 2.5NaCl\cdot 21H_2O$ (**5**) was obtained. Anal. found (calcd for $C_{20}H_{68}N_4O_{43}P_2Cl_{2.5}Na_{8.5}La_2$): C, 13.7 (14.3); H, 4.2 (4.1); N, 3.0 (3.3). Solution ^{13}C NMR (400 MHz, D_2O): δ (ppm) 182.6 (CO_2), 64.3 ($-CH_2N$), 57.1 (NCH_2CH_2N); ^{31}P NMR (400 MHz, D_2O): δ (ppm) 2.7 (HPO_3).

Preparation of $(NH_4)_2Na[Gd(EDTA)(H_2cit)]\cdot 4H_2O$ (3). $Na[Gd(EDTA)(H_2O)_3]\cdot 5H_2O$ (1.3 g, 2.0 mmol) and excess citric acid (0.88 g, 4.0 mmol) were added to water. The pH value of the mixture was adjusted to 4.5 with ~3.0 mL 5% ammonium hydroxide and then heated at 70 °C for two days. The colorless crystalline material of **3** was separated after evaporation of the solution. The solids were washed with cold water and ethanol, and dried in air. The yield of **3** was 0.80 g (52%). Anal. found (calcd for $C_{16}H_{38}N_4O_{19}NaGd$): C, 24.8 (24.9); H, 5.1 (5.0); N, 7.2 (7.3). IR (KBr, cm^{-1}): 3439 s, 3196 s, 1593 s, 1410 s, 1352 m, 1309 w 1254 m, 1102 w, 1075 w, 1029 w, 998 w, 924 w, 885 w, 843 w, 733 w, 616 w, 510 w.

Transformation of 2 to 3

Compound **2** (0.86 g, 0.5 mmol) and twice the amount of citric acid (0.88 g, 4.0 mmol) were mixed in 5 mL water with constant stirring. The pH value of the solution was adjusted to 4.5 with the addition of 5% ammonium hydroxide. The mixture was heated for 2 days at 70 °C. A slow evaporation of the filtrate at room temperature gave **3**.

X-Ray crystallography

Suitable single crystals of **1–3** were selected and quickly mounted onto thin glass fibers to prevent the loss of water molecules. X-ray intensity data for compounds **1–3** were measured at 173 K on an Oxford CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å). Empirical adsorption was applied to all data using SADABS and CrysAlis (multi-scan) programs. The initial model was obtained through direct methods and the completion of the rest of the structure achieved by difference Fourier strategies. The structures were refined by least squares on F^2, with anisotropic displacement parameters for non-H atoms. Hydrogen atoms unambiguously defined by the stereochemistry were placed at their calculated positions and

Table 1 Crystal data and structure refinements for **1–3**

Compounds	**1**	**2**	**3**
Chemical formula	$C_{10}H_{27}N_2O_{18}PK_3Gd$	$C_{20}H_{68}N_4O_{43}P_2Cl_{2.5}Na_{8.5}Gd_2$	$C_{16}H_{38}N_4O_{19}NaGd$
Formula mass	768.86	1713.25	766.71
Crystal system	Monoclinic	Triclinic	Monoclinic
a/Å	10.497(1)	10.428(1)	9.330(1)
b/Å	8.818(1)	16.335(1)	21.307(1)
c/Å	14.851(2)	17.392(1)	14.066(1)
α/°		94.06(1)	
β/°	110.16(1)	103.85(1)	106.25(1)
γ/°		93.89(1)	
Unit cell volume/Å^3	1290.3(2)	2858.2(4)	2684.6(3)
Temperature/K	173		
Space group	$P2_1$	$P\bar{1}$	$P2_1/c$
No. of formula units per unit cell, Z	2	2	4
No. of reflections measured	6996	20 606	18 172
No. of independent reflections	4785	10 596	5201
R_{int}	0.0475	0.0494	0.120
Final R_1 values ($I > 2\sigma(I)$)	0.0418	0.0518	0.0594
Final w$R(F^2)$ values ($I > 2\sigma(I)$)	0.0768	0.1011	0.0961
Final R_1 values (all data)	0.0490	0.0790	0.0954
Final w$R(F^2)$ values (all data)	0.0813	0.1142	0.1111
Goodness of fit on F^2	0.949	1.060	1.012

allowed to ride onto their host carbons both in coordinates as well as in thermal parameters (C–H, 0.97 Å). Those attached to oxygen atoms and needed for the H-bonding description were located in a late Fourier map and refined with similarity restraints [O–H, 0.85(1) Å; H···H, 1.39(1) Å]. All calculations to solve and refine the structures and to obtain derived results were carried out with SHELXS 97 and SHELXL 97 programs. Full use of the CCDC package was also made for searching in the CSD Database.[8] CCDC deposition numbers are 951555, 951556, 951762. Crystal data and structure refinements for **1–3** are summarized in Table 1.

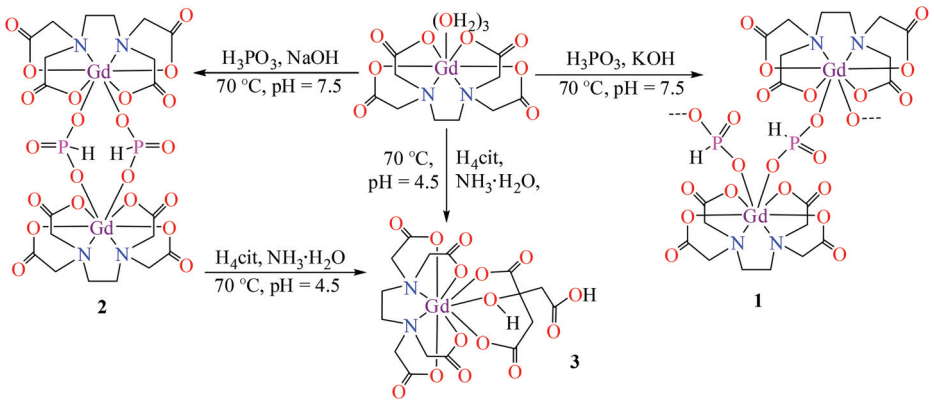
Results and discussion

Among the gadolinium amino-carboxylates, the thermodynamic stability of the Gd(III) complexes follows the order: DOTA > DTPA > EDTA (DOTA = 1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododecane).[5b] Furthermore, research has shown that the injection of Gd–EDTA is more likely to cause NSF than the other GBCAs.[9] Therefore; Gd–EDTA is chosen as a model compound of GBCAs to investigate the interaction with phosphorous acid. Substitutions of gadolinium ethylenediaminetetraacetate trihydrates with phosphorous acid result in the formation of complexes **1** and **2**. The molar ratio of Gd–EDTA to H_3PO_3 in the reaction is 1 : 3 with an excess of H_3PO_3 and the optimized pH value is in the range of 7.0–7.5, close to the pH value of the human body. Previously, it has been reported that the reaction of gadolinium salts with phosphorous acid directly results in insoluble polymers of gadolinium phosphites.[10] However, in the present experiment the formation of gadolinium phosphites is inhibited by strong coordination of ethylenediaminetetraacetate, which finally produces mixed-ligand complexes of EDTA and phosphite. Further substitution of **2** with citric acid leads to the formation of complex **3**, which can also be obtained from the direct reaction of gadolinium ethylenediaminetetraacetates with citric acid at pH 4.5. The conversion of Gd–EDTA to **1–3** and the transformation of **2** to **3** are shown in Scheme 1. It is worth mentioning that all the compounds are easily soluble in water, with the solubilities of **1** about 0.5 g mL^{-1}, **2** about 0.4 g mL^{-1}, and **3** about 1.0 g mL^{-1}.

Crystal structure descriptions

The molecular structure of **1** consists of an anionic unit of $[Gd(EDTA)(HPO_3)]^{3-}$, potassium cations and water molecules. As shown in Fig. 1, each Gd(III) cation exists in an octadentate coordination environment, which is different from that of the usual nonadentate coordination in gadolinium ethylenediaminetetraacetate trihydrate.[7] EDTA acts as a hexadentate ligand with two nitrogen atoms of the ethylenediamine group and four oxygen atoms of acetates. The other two coordinated oxygen atoms are from the phosphite ions. Coordinated water molecules are completely replaced by phosphite ions, which act as bridged ligands connecting adjacent Gd–EDTA units in the mode of Gd–O–P–O–Gd, forming a one-dimensional chain. The detailed chain structure is shown in Fig. 2.

Complex **2** consists of the dimeric anionic unit $[Gd_2(EDTA)_2(HPO_3)_2]^{6-}$. Like complex **1**, three coordinated water molecules are fully substituted by two phosphite ions. Each Gd(III) cation is octa-coordinated by an EDTA and phosphite ions, forming a dinuclear structure. Other dimeric structures of lanthanide ethylenediaminetetraacetates can be found in the mixed-ligand complexes $K_8[Ln_2(Hcit)_2(EDTA)_2]\cdot16H_2O$ (Ln = La; Ce), $K_6[Ln_2(Hmal)_2(EDTA)_2]\cdot14H_2O$ (Ln = La; Ce) and $Na_4[Er_2(EDTA)_2(\mu_2\text{-}C_2O_4)]\cdot8H_2O$.[11] The most noticeable difference between **2** and these dimeric complexes is that the bridge ligand in **2** is inorganic phosphorous acid rather than a polycarboxylic acid. The molecular structure of the anionic complex **2** is shown in Fig. 3.



Scheme 1 Conversion of gadolinium ethylenediaminetetraacetate trihydrates to $K_{3n}[Gd(EDTA)(HPO_3)]_n \cdot 7nH_2O$ (**1**), $Na_6[Gd_2(EDTA)_2(HPO_3)_2] \cdot 2.5NaCl \cdot 21H_2O$ (**2**) and the citrate derivative $(NH_4)_2Na[Gd(EDTA)(H_2cit)] \cdot 4H_2O$ (**3**).

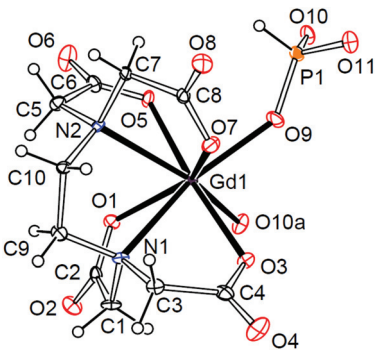


Fig. 1 Ortep plot of the anionic unit of $K_{3n}[Gd(EDTA)(HPO_3)]_n \cdot 7nH_2O$ (**1**) at 30% probability levels.

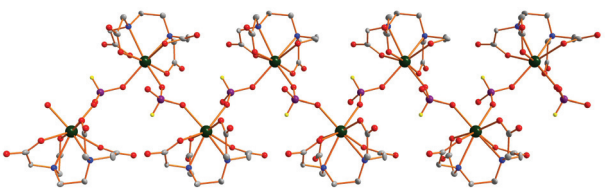


Fig. 2 Structure of one-dimensional chain in $K_{3n}[Gd(EDTA)(HPO_3)] \cdot 7nH_2O$ (**1**).

The molecular structure of $Na(NH_4)_2[Gd(H_2cit)(EDTA)] \cdot 4H_2O$ (**3**) consists of a citrato gadolinium EDTA anion, one sodium and two ammonium cations, and four lattice water molecules. The anion structure is shown in Fig. 4. The Gd(III) ion exists in a nonadentate coordination environment, which is the same as those of the usual gadolinium ethylenediaminetetraacetates.[7] Two phosphite ions are further substituted by the α-hydroxy (O1), α-carboxy (O2) and β-carboxy groups (O5) of the citrate, forming an interesting monomeric mixed-ligand complex. A similar coordination mode is found for the transition metal citrates (Ti, Ga, Mn, Co, Ni, Mo, W).[12] It is interesting to note that the other free β-carboxy group in **3** was protonated and forms a hydrogen bond with O3w [O6···O3w 2.55(1) Å, $-x + 1, +y + 1/2, -z + 3/2$] and the protonated α-hydroxy group forms a hydrogen bond with O8 from

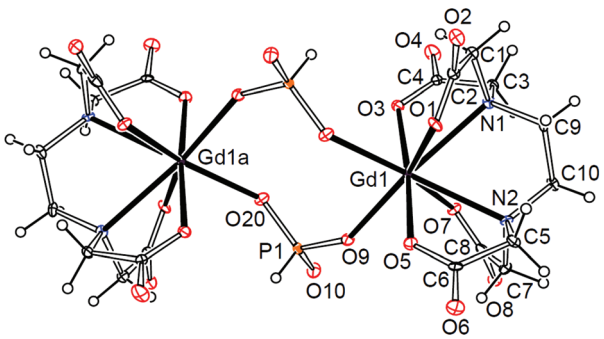


Fig. 3 Ortep plot of the anionic unit of $Na_6[Gd_2(EDTA)_2(HPO_3)_2] \cdot 2.5NaCl \cdot 21H_2O$ (**2**) at 30% probability levels.

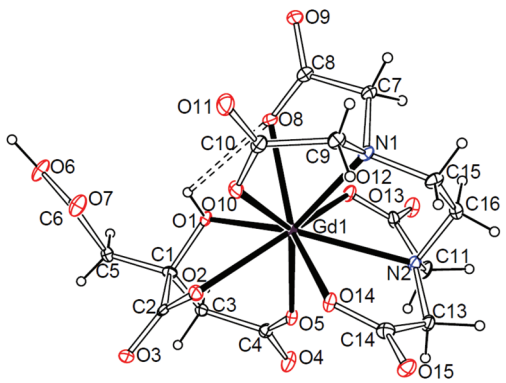


Fig. 4 Ortep plot of the anionic unit of $(NH_4)_2Na[Gd(EDTA)(H_2cit)] \cdot 4H_2O$ (**3**) at 30% probability levels.

EDTA [O1···O8 2.811(9) Å]. Furthermore, the sodium was penta-dentated by two water molecules, α-carboxy (O2) and β-carboxy groups of citrate (O7) and a carboxy group (O8) from the EDTA ligand.

Complex **3** was obtained from the substitution of **2** with citric acid, which indicates that the mixed-ligand $GdHPO_3$–EDTA complex can be substituted by citrate. It implies that citrate could serve as a potential inhibitor in the transformation of GBCAs to gadolinium phosphates. As citric acid is harmless

Table 2 Comparison of Gd–O, Gd–P and Gd–N bond distances (Å) and coordination number (CN) in gadolinium complexes and gadolinium phosphate in NSF

Interaction		Gd/CN	$Gd–O_{EDTA}$ (av, Å)	$Gd–O_{others\ (av)}$ (Å)		$Gd–N_{(av)}$ (Å)/CN	$Gd–P_{(av)}$ (Å)/CN	$Gd–Gd_{(av)}$ (Å)
$K_{3n}[Gd(EDTA)(HPO_3)]_n·7_nH_2O$ (**1**)		8	2.406	$Gd–O_{phosphite}$	2.308	2.616/2	3.618/2	6.772/2
$Na_6[Gd_2(EDTA)_2(HPO_3)_2]·2.5NaCl·21H_2O$ (**2**)	Unit 1	8	2.422		2.299	2.617/2	3.658/2	5.555/1
	Unit 2	8	2.365		2.339	2.602/2	3.600/2	5.652/1
$(NH_4)_2Na[Gd(EDTA)(H_2cit)]·4H_2O$ (**3**)		9	2.396	$Gd–O_{citric\ acid}$	2.422	2.656/2		
$K[Gd(EDTA)(H_2O)_3]·5H_2O$[7b]		9	2.399	$Gd–O_{water}$	2.472	2.655/2		
$Na[Gd(EDTA)(H_2O)_3]·5H_2O$[7c]		9	2.362		2.483	2.674/2		
$K_2[Gd(DTPA)(H_2O)]$[13]		9	2.404		2.490	2.640/3		
Gadolinium phosphate in NSF[3a]		8		$Gd–O_{phosphate}$	2.385		3.111–3.715/2.55	4.053/2.47

and edible, improving the concentration of citrate in the human body might be helpful to prevent the generation of NSF.

Selected average bond distances of **1–3** are shown in Table 2. Gd–EDTA, Gd–DTPA and gadolinium phosphate deposited in NSF are summarized in the same table for comparison.[3a,7,13] The average bond distances of $Gd–O_{EDTA}$ are similar in all the listed gadolinium complexes because of the same coordination mode of EDTA. In complex **1** the average $Gd–O_{phosphite}$ bond distance (2.308 Å) is obviously shorter than the bond distances of $Gd–O_{water}$ (2.422 Å) in $K[Gd(EDTA)(H_2O)_3]·5H_2O$.[7b] The short and strong bonds provided by the phosphite ions are favorable for the substitution of coordinated water molecules in Gd–EDTA. Similar results can be found for complex **2**. The data further suggest that the bonds of $Gd–O_{phosphite}$ are more stable than those of $Gd–O_{water}$. The $Gd–O_{citrate}$ bond distances of compound **3** in citrate range from 2.376(5) to 2.446(6) Å. The shortest Gd–O bond is provided by β-carboxy of citrate while the bond distances of α-hydroxy and α-carboxy are similar. The coordination of α-hydroxy is weak due to the protonation.

Compared with the gadolinium phosphate in NSF, the average $Gd–O_{phosphite}$ distances in **1** (2.308 Å) and **2** (2.319 Å) are shorter than those of the $Gd–O_{phosphate}$ distances in NSF (2.385 Å). The average Gd–P distances in **1** (3.618 Å) and **2** (3.629 Å) are in the range of those in the NSF deposits (3.111–3.715 Å). The coordination number of Gd–P in NSF is 2.55, indicating that there are more phosphates coordinated with the gadolinium ion.

NMR analysis and solution behavior

As mentioned both **1** and **2** are soluble in water, while the gadolinium phosphites are insoluble. So it is essential to understand the solution behavior of the complexes. Due to the paramagnetic property of the gadolinium complexes, we synthesised isostructural lanthanum complexes $K_{3n}[La(EDTA)(HPO_3)]_n·7nH_2O$ (**4**) and $Na_6[La_2(EDTA)_2(HPO_3)_2]·2.5NaCl·21H_2O$ (**5**) for comparison, which were characterized by solution ^{13}C and ^{31}P NMR spectra. The observed positions for **4** and **5** are listed in Table 3. The NMR data for $K[La(EDTA)(H_2O)_3]·5H_2O$, free $EDTA^{4-}$ and hydrogen phosphite are included in the same table for comparison.

Solution ^{13}C NMR spectra of **4** and **5** are shown in Fig. 5. Only one set of ^{13}C NMR peaks was observed for both of the complexes. For **4** the peaks at 182.7, 65.1 and 57.9 ppm correspond to carboxy groups ($–CO_2$), CH_2 groups of acetates ($–NCH_2CO_2$) and CH_2 groups of acetates ($–NCH_2CH_2N–$), respectively. An obvious downfield shift can be found when comparing with the free $[EDTA]^{4-}$. Similar results can be found for complex **5**. Both of the spectra are quite similar to that of $[La(EDTA)(H_2O)_3]^-$, which indicates that there is no decomposition of La–EDTA in aqueous solution. The solution ^{13}C NMR spectra of $K[La(EDTA)(H_2O)_3]·5H_2O$ and K_4EDTA are shown in Fig. S1 and S2.†

As anticipated, the solution ^{31}P NMR spectra of both complexes show single sharp peaks as shown in Fig. S3 and S4.† Their chemical shifts are quite close to that of the corresponding HPO_3^{2-}, which implies the dissociation of the HPO_3^{2-} unit.

Table 3 ^{13}C and ^{31}P data (in ppm) of complexes **4** and **5**, $K[La(EDTA)(H_2O)_3]·5H_2O$, K_4EDTA and K_2HPO_3

Compound	$–CH_2N$	$–NCH_2CO_2$	$–CO_2$	$–HPO_3$
4	57.9 (4.2)	65.1 (5.0)	182.7 (4.2)	2.3
5	57.1 (3.4)	64.3 (4.2)	182.6 (4.1)	2.7
$[La(EDTA)-(H_2O)_3]^-$	57.2 (3.5)	64.4 (4.3)	183.0 (4.5)	
$[EDTA]^{4-}$	53.7	60.1	178.5	
HPO_3^{2-}				2.8

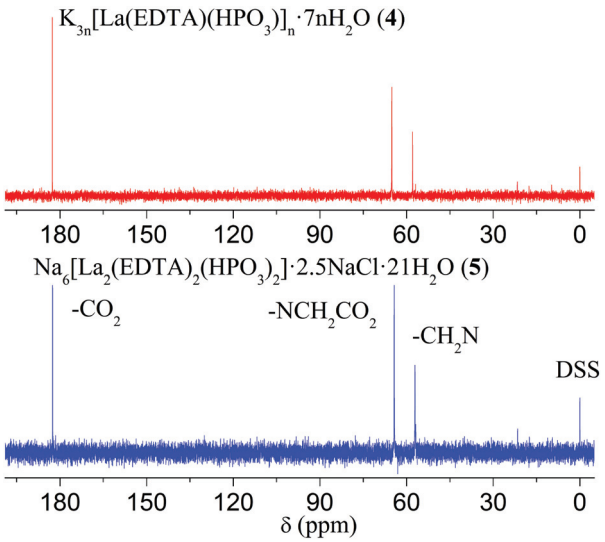


Fig. 5 Solution ^{13}C NMR spectrum of $K_{3n}[La(EDTA)(HPO_3)]_n·7nH_2O$ (**4**) and $Na_6[La_2(EDTA)_2(HPO_3)_2]·2.5NaCl·21H_2O$ (**5**).

We speculate that the isostructural gadolinium complexes **1** and **2** display the same solution behavior. This can be further proved by recrystallization experiments. For the purpose of obtaining purer products, complexes **1** and **2** were purified by recrystallization in water. However, both the complexes transformed into gadolinium ethylenediaminetetraacetates. It is confirmed that the mixed-ligand complexes dissociate into free HPO_3^{2-} and $Gd(EDTA)^-$ units in aqueous solution, which also suggests that the substitution of $K[Gd(EDTA)(H_2O)_3]\cdot 5H_2O$ with phosphorous acid is reversible.

From previous research of solution behavior in $(NH_4)_8[La_2(Hcit)_2(EDTA)_2]\cdot 9H_2O$,[11a] the β-carboxy group of citrate may dissociate from Gd^{3+}. In turn, complex **3** is a good example of the fast exchange between two β-carboxy groups in $(NH_4)_8[La_2(Hcit)_2(EDTA)_2]\cdot 9H_2O$ in aqueous solution.[11a] Compared with complexes **1** and **2**, the dissociation of citrate in complex **3** is considered to be proof that the coordination of citrates with $Gd(EDTA)^-$ is stronger than that of the phosphite ions for the chelating properties of citrate.

Electrospray ionization mass spectrometry (ESI-MS)

The ion signals of the solution mass spectra for compounds **1–3** were measured in the negative ionization mode by ESI. As shown in Fig. 6, each compound exhibited a peak at 446.7 *m*/*z* with an isotope pattern, which corresponds to the calculated $[Gd(EDTA)]^-$ unit. The isolated ionic Gd–EDTA species supports the dissociation of the compounds, as revealed by the solution NMR spectra of La–EDTA-phosphites. It is notable that in Fig. 6, the free citrate is observed at a peak of 191.2 *m*/*z*, which indicates compound **3** was also decomposed during the ionization process.

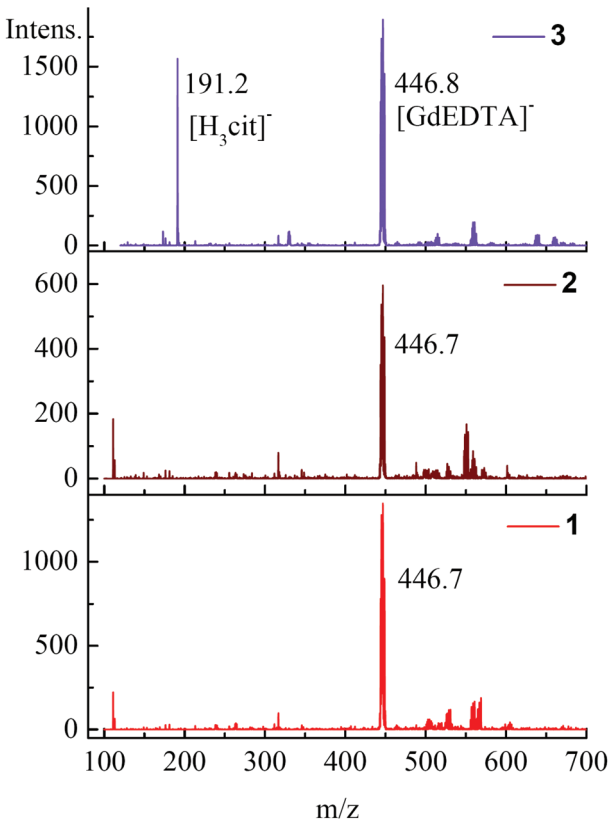


Fig. 6 ESI-MS spectra of $K_{3n}[Gd(EDTA)(HPO_3)]_n\cdot 7nH_2O$ (**1**), $Na_6[Gd_2(EDTA)_2(HPO_3)_2]\cdot 2.5NaCl\cdot 21H_2O$ (**2**) and $(NH_4)_2Na[Gd(EDTA)(H_2cit)]\cdot 4H_2O$ (**3**) in aqueous solution detected in negative ion mode.

Vibrational spectra

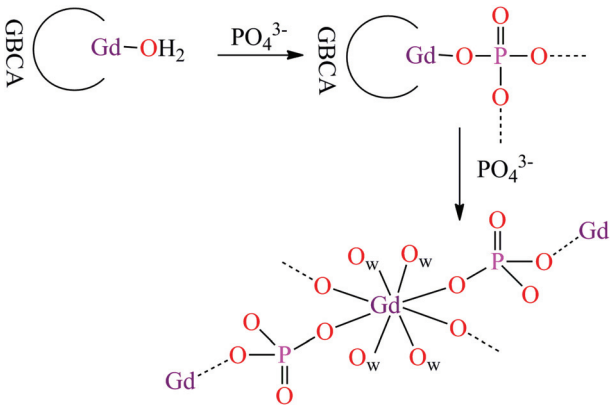
The IR spectra of **1–3** are listed in Fig. S5–S7.† The strong peaks at 1646, 1597, 1397, and 1335 cm^{-1} for **1** correspond to the coordinated carboxy groups of $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$, respectively. The $\nu_{as}(COO^-)$ is at 1597 cm^{-1} and red-shifts 94 cm^{-1} compared to that of H_4EDTA (1691 cm^{-1}). The $\nu_s(COO^-)$ is at 1397 cm^{-1} and blue-shifts 6 cm^{-1} compared to that of H_4EDTA (1391 cm^{-1}). These changes confirm that the oxygen atoms from the carboxy groups of $[EDTA]^{4-}$ have coordinated with the Gd^{3+} ion. This is also observed for **2** and **3**. In complex **1**, anti-symmetric stretching vibrations $\nu_{as}(P{=}O)$ appeared at 1124 and 1106 cm^{-1}. The corresponding symmetric stretching vibration $\nu_s(P{=}O)$ appeared at 1058 cm^{-1}. In complex **2**, the anti-symmetric $\nu_{as}(P{=}O)$ and symmetric stretching vibrations $\nu_s(P{=}O)$ appear as a broad peak around 1100 cm^{-1}. The IR spectrum of the gadolinium phosphate deposit $GdPO_4\cdot 0.5H_2O$ is shown in Fig. S8,† in which the strong broad peak appearing around 1100 cm^{-1} can be attributed to the anti-symmetric stretching vibration $\nu_{as}(P{=}O)$ and symmetric stretching vibration $\nu_s(P{=}O)$.

Thermogravimetric analysis

The TG and DTG curves of **1** and **2** are shown in Fig. S9 and S10† and were carried out in an air atmosphere from room temperature to 1000 °C. The thermal stability and decomposition patterns of the complexes were investigated by thermogravimetric analysis. The first part of the big weight losses of **1** and **2** from 30 to 180 °C corresponds to the loss of five and nineteen water molecules for **1** and **2**, respectively. The next mass reductions occurred in the ranges 320 to 380, 380 to 580 and 600 to 750 °C and can be assigned to the loss of the other water molecules and organic ligands. Over 850 °C a big weight loss can be observed, which may be due to the oxidative decomposition of the phosphites. According to the mass changes, the residue of complex **1** may contain mixed-compounds of $K_3Gd(PO_4)_2$ and K_3GdO_3 and the residue of complex **2** contains $Na_3Gd(PO_4)_2$ and Na_3GdO_3.

Speculative formation of gadolinium deposit in NSF

Compared with the other lanthanide ions, one key feature of the gadolinium chelates is that, when proper ligands are chosen, they actually do remain chelated in the body and are excreted intact with normal patients.[5a] In the present paper, water molecules in Gd–EDTA can be reversibly replaced by a high concentration and ratio of phosphite ions, resulting in an intermediate compound of mixed-ligand Gd–EDTA with phosphite ions. This provides a new way to consider the formation of insoluble gadolinium phosphate in NSF. Moreover, it is



Scheme 2 Possible reaction process from GBCAs to gadolinium phosphate deposits in NSF.

noted that the citrate chelate can substitute the phosphate in **2**, indicating the potential use of citrate in the inhibition of the deposit in NSF.

According to the intermediate structures of **1** and **2**, we predict the reaction process from GBCAs to gadolinium phosphate deposits in NSF as shown in Scheme 2. The whole process can be divided into two stages. In the first stage the water molecule in GBCAs is substituted by phosphate ions. In the second stage more phosphate ions bond with the central Gd(III) cation, forming Gd–$O_{phosphate}$ bonds while Gd–$O_{carboxy}$ bonds break. Gradually the insoluble gadolinium phosphate precipitates. The final product is considered to be a model of phosphate-bound gadolinium in NSF.

Conclusions

In summary, two substituted gadolinium ethylenediaminetetraacetates $K_{3n}[Gd(EDTA)(HPO_3)]_n{\cdot}7nH_2O$ (**1**) and $Na_6[Gd_2(EDTA)_2(HPO_3)_2]{\cdot}2.5NaCl{\cdot}21H_2O$ (**2**) have been isolated from the reactions of gadolinium ethylenediaminetetraacetate trihydrates and phosphorous acid in neutral solution. Coordinated water molecules in gadolinium ethylenediaminetetraacetate were replaced by HPO_3^{2-}. Further substitution with citric acid gave $(NH_4)_2Na[Gd(EDTA)(H_2cit)]{\cdot}4H_2O$ (**3**). Complexes **1–3** are polymeric, dimeric and monomeric, respectively. All the complexes are easily soluble in water. In aqueous solution complexes **1** and **2** dissociate into free HPO_3^{2-} and Gd–EDTA units. They are supposed to be the intermediates between gadolinium ethylenediaminetetraacetate and gadolinium phosphite. We speculate that in GBCAs, coordinated water molecules can be replaced by phosphate groups in the first step. This may in some way explain the formation of gadolinium phosphate in NSF.

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