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## Supporting information

# Interaction of Gd-DTPA with Phosphate and Phosphite: toward the Reaction Intermediate in Nephrogenic Systemic Fibrosis

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**S1** Experimental Section.

S2 References.

Table S1 Crystal data and structural refinements for 1, 2 and  $4 \sim 6$ .

**Table S2** The Gd–O and Gd–N bonds distances (Å)  $forK_2[Gd(DTPA)(H_2O)] \cdot 5H_2O$  (1) and  $K_6[Gd_2(DTPA)_2(HPO_4)] \cdot 10H_2O(2)$ .

Table S3 The La–O and La–N bonds distances (Å) for K<sub>4</sub>[La<sub>2</sub>(DTPA)<sub>2</sub>(H<sub>2</sub>O)]·8H<sub>2</sub>O (4).

**Table S4** The La–O and La–N bonds distances (Å) for  $K_6[La_2(DTPA)_2(HPO_3)]$ ·7H<sub>2</sub>O (**5**) and  $K_6[La_2(DTPA)_2(HPO_4)]$ ·10H<sub>2</sub>O (**6**).

**Fig.S1** Olex2 plot of the anionic structure in  $K_6[La_2(DTPA)_2(HPO_3)]$ ·7H<sub>2</sub>O (**5**) (Green, La; Red, O; Blue, N; Grey, C; White, H).

Fig. S2 Solution<sup>13</sup>C NMR spectrum of K<sub>5</sub>DTPA.

**Fig. S3** Solution<sup>31</sup>P NMR spectrum of  $K_6[La_2(DTPA)_2(HPO_3)] \cdot 7H_2O$  (5).

Fig. S4 IR spectrum of  $K_4[La_2(DTPA)_2(H_2O)] \cdot 8H_2O$  (4).

**Fig. S5** IR spectrum of  $K_6[La(DTPA)(HPO_3)] \cdot 8H_2O(5)$ .

Fig. S6 IR spectrum of  $K_6[La_2(DTPA)_2(HPO_4)] \cdot 10H_2O$  (6) and

## $K_6[Gd_2(DTPA)_2(HPO_4)] \cdot 10H_2O(3).$

#### Fig. S7 IR spectrum of H<sub>5</sub>DTPA.

**S1** Experimental Section.

**General procedures**. All chemicals were of analytical or reagent-grade purity and used without further purification. The pH value in the synthesis was measured by the potentiomtric method with a PHB-8 digital pH meter. Elemental analyses (C, H, N) were performed using EA1110 elemental analyzer. Infrared spectra were recorded as Nujol mulls between KBr plates using a Nicolet 330 FT-IR spectrophotometer. Solution <sup>13</sup>C and <sup>31</sup>P NMR spectra were recorded in D<sub>2</sub>O on a Bruker AV 400 NMR spectrometer using DSS (sodium 2, 2-dimethyl-2-silapentane-5-sulfornate) as internal reference. Solid state <sup>13</sup>C and <sup>31</sup>P NMR spectra were recorded on a Bruker AV 400 NMR spectrometer using cross polarization, magic angle spinning (13 kHz) and adamantane as the reference.

Syntheses of K<sub>2</sub>[Gd(DTPA)(H<sub>2</sub>O)]·5H<sub>2</sub>O (**1**) and K<sub>4</sub>[La<sub>2</sub>(DTPA)<sub>2</sub>(H<sub>2</sub>O)]·8H<sub>2</sub>O (**4**). A mixture of gadolinium chloride hexahydrates (3.8 g, 10.0 mmol) and equal amount of diethylenetriaminepentaacetic acid (4.0 g, 10.0 mmol) were dissolved in water (40 mL). The pH value of the solution was adjusted to 7.0 by slow addition of 2.0 M potassium hydroxide. The solution was stirred for 2 h and heated at 60 °C for 8 h. The mixture was evaporated at room temperature for several weeks to give a colorless crystalline material of **1**, which was washed with cold water and ethanol, and dried under vacuum. The yield was 83% (6.1g). Anal. Calcd for C<sub>14</sub>H<sub>30</sub>O<sub>16</sub>N<sub>3</sub>K<sub>2</sub>Gd: C 23.0; H 4.1; N 5.7. Found. C 22.9; H 4.1; N 5.5. IR (KBr, cm<sup>-1</sup>): 3425<sub>8</sub>, 1601<sub>8</sub>, 1406<sub>m</sub>, 1330<sub>w</sub>, 1272<sub>w</sub>, 1095<sub>w</sub>, 932<sub>w</sub>, 709<sub>w</sub>, 601<sub>w</sub>, 482<sub>w</sub>. Similarly, K<sub>4</sub>[La<sub>2</sub>(DTPA)<sub>2</sub>(H<sub>2</sub>O)]·8H<sub>2</sub>O (**4**) was obtained in a yield of 70% (4.8 g). Anal. Calcd for C<sub>56</sub>H<sub>108</sub>O<sub>58</sub>N<sub>12</sub>K<sub>8</sub>La<sub>4</sub>: C 24.5; H 4.0; N 6.1. Found. C 23.9; H 4.3; N 5.7. Solution <sup>13</sup>C NMR (400MHz, D<sub>2</sub>O) of **2**:  $\delta$ (ppm) 183.5, 183.4, 182.8 (CO<sub>2</sub>), 65.7 (-CH<sub>2</sub>N), 59.9, 59.4, 58.7 (NCH<sub>2</sub>CH<sub>2</sub>N). Solid <sup>13</sup>C NMR (400MHz):  $\delta$ (ppm) 185.4, 180.1, 178.0 (CO<sub>2</sub>), 60.1, 58.4 (-CH<sub>2</sub>N), 54.9, 53.2 (NCH<sub>2</sub>CH<sub>2</sub>N). IR (KBr, cm<sup>-1</sup>): 3448<sub>s</sub>, 1591<sub>s</sub>, 1411<sub>m</sub>, 1335<sub>w</sub>, 1098<sub>w</sub>, 930<sub>w</sub>, 703<sub>w</sub>, 540<sub>w</sub>.

Syntheses of  $K_6[Gd_2(DTPA)_2(HPO_3)] \cdot 7H_2O$  (2) and  $K_6[La_2(DTPA)_2(HPO_3)] \cdot 7H_2O$  (5).  $K_2[Gd(DTPA)(H_2O)] \cdot 5H_2O$  (1) (1.5 g, 2.0 mmol) and triple amount of  $H_3PO_3$  (0.49 g, 6.0 mmol) were dissolved in a stirred solution (10 mL). The pH value was adjusted to 7.3 by 2.0 M potassium hydroxide to give clear solution and heated in a water bath at 40°C for three days. After evaporation for several weeks, colorless crystal of **2** appears at the bottom of the beaker. The product was washed with cold water and ethanol, and dried under vacuum. The yield was 59% (0.90 g). Anal. calcd. for  $C_{28}H_{51}N_6O_{30}PK_6Gd_2$ : C 22.0; H 3.4; N 5.5. Found. C 21.6; H 3.7; N 5.4. IR (KBr, cm<sup>-1</sup>): 3427<sub>s</sub>, 1606<sub>s</sub>, 1407<sub>m</sub>, 1328<sub>w</sub>, 1263<sub>w</sub>, 1150<sub>m</sub>, 1093<sub>m</sub>, 1060<sub>m</sub>, 986<sub>w</sub>, 929<sub>w</sub>, 719<sub>w</sub>, 594<sub>w</sub>. In a similar method,  $K_6[La_2(DTPA)_2(HPO_3)] \cdot 7H_2O$  (**5**) was obtained in a yield of 55% (0.82 g). Anal. calcd. for  $C_{28}H_{51}N_6O_{30}PK_6La_2$ : C 22.5; H 3.4; N, 5.6. Found. C 22.2; H 3.5; N 5.3. IR (KBr, cm<sup>-1</sup>): 3421<sub>s</sub>, 1600<sub>s</sub>, 1405<sub>m</sub>, 1331<sub>m</sub>, 1264<sub>w</sub>, 1122<sub>m</sub>, 1095<sub>m</sub>, 1058<sub>m</sub>, 982<sub>w</sub>, 928<sub>w</sub>, 856<sub>w</sub>, 803<sub>w</sub>, 709<sub>w</sub>, 586<sub>w</sub>. Solution <sup>13</sup>C NMR (400MHz, D<sub>2</sub>O):8 (ppm) 183.7, 183.6, 183.0(CO<sub>2</sub>), 67.4, 65.8 (-CH<sub>2</sub>N), 60.8, 60.0 58.8 (NCH<sub>2</sub>CH<sub>2</sub>N). Solid <sup>13</sup>C NMR (400MHz):  $\delta$  (ppm) 182.9, 180.7, 179.5 (CO<sub>2</sub>), 64.1 (-CH<sub>2</sub>N), 56.8 (NCH<sub>2</sub>CH<sub>2</sub>N).

Syntheses of  $K_6[Gd_2(DTPA)_2(HPO_4)] \cdot 10H_2O$  (3) and  $K_6[La_2(DTPA)_2(HPO_4)] \cdot 10H_2O$  (6).  $K_2[Gd(DTPA)(H_2O)] \cdot 5H_2O$  (1) (1.5 g, 2.0 mmol) and  $K_2HPO_4$  (0.91 g, 4.0 mmol) were dissolved in water. The pH value of the mixture was adjusted to 7.4 by diluted hydrochloric acid solution and heated in a water bath at 50 °C for three days. After the evaporation of the solution at room temperature for a month, white precipitated material of 3 was isolated. The solids were washed with cold water and ethanol, and dried in air. The yield was 0.99 g (62%). Similarly, decrease of the temperature at 40 °C will result in the reaction for one month. Anal. calcd. for C<sub>28</sub>H<sub>57</sub>O<sub>34</sub>N<sub>6</sub>PK<sub>6</sub>Gd<sub>2</sub>: C 21.0; H 3.6; N 5.2. Found. C 20.7; H 3.8; N 5.1. IR (KBr, cm<sup>-1</sup>): 3424<sub>s</sub>, 1607<sub>s</sub>, 1408<sub>m</sub>, 1331<sub>w</sub>, 1268<sub>w</sub>, 1094<sub>m</sub>, 1066<sub>m</sub>, 995<sub>w</sub>, 931<sub>w</sub>, 709<sub>w</sub>, 554<sub>w</sub>. Similarly,  $K_6[La_2(DTPA)_2(HPO_4)] \cdot 10H_2O$  (6) obtained from the is mixed solution of K4[La2(DTPA)2(H2O)]·16H2O (4) (1.4 g, 1.0 mmol) and K2HPO4 (0.91 g, 4.0 mmol). The mixture was heated in a water bath at 50 °C for three days then evaporated at room temperature. Colorless crystal of 6 deposited at the bottom of the beaker after several weeks. The product was washed with cold water and ethanol, and dried in air. The yield was 0.94 g (60%). Anal. calcd. for C<sub>28</sub>H<sub>57</sub>O<sub>34</sub>N<sub>6</sub>PK<sub>6</sub>La<sub>2</sub>: C 21.5; H 3.7; N 5.4. Found. C 21.2; H 3.7; N 5.2. IR (KBr, cm<sup>-1</sup>): 3425<sub>s</sub>, 1600<sub>s</sub>, 1407<sub>m</sub>, 1334<sub>w</sub>, 1259<sub>w</sub>, 1097<sub>m</sub>, 1069<sub>m</sub>, 992<sub>w</sub>, 930<sub>w</sub>, 709<sub>w</sub>, 542<sub>w</sub>. Solution <sup>13</sup>C NMR (400MHz, D<sub>2</sub>O): δ (ppm) 183.9, 183.8, 183.2 (CO<sub>2</sub>), 66.0 (-CH<sub>2</sub>N), 60.3, 59.0 57.0 (NCH<sub>2</sub>CH<sub>2</sub>N). Solid <sup>13</sup>C NMR (400MHz): δ(ppm) 182.3, 179.6 (CO<sub>2</sub>), 66.3, 63.8 (-CH<sub>2</sub>N), 57.0 (NCH<sub>2</sub>CH<sub>2</sub>N).

**X-ray crystallography.** Suitable single crystals of 1, 2 and  $4 \sim 6$  were selected and quickly mounted onto thin glass fibers to prevent the loss of water molecules. X-ray intensity data for the lanthanides were measured at 173 K on an Oxford CCD diffractometer with Mo Ka radiation ( $\lambda = 0.71073$  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 structure was 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 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 restrains [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.<sup>S1</sup>Full use of the CCDC package was also made for searching in the CSD Database.<sup>S2</sup> CCDC deposition numbers is 1413289 ~ 1413293. Crystal data and structure refinements for the lanthanides are summarized in Table S1. Selected bond distances of Gd-O, Gd–N, La–O and La–N in complexes 1, 2 and  $4 \sim 6$  are listed in Table S2 to S4.

#### S2 References

SHELXS-97, SHELXL-97, and SHELXTL/PC: G. M. Sheldrick, *Programs for solution and refinement of crystal structures*, University of Göttingen: Göttingen, Germany, 1997.
S2A. J. C. Wilson, *International Tables for Crystallography*, Kluwer Academic Publishers, 1995, Vol. C, pp. 685.

Compounds	$K_2[Gd(DTPA)(H_2O)]$	K <sub>6</sub> [Gd(DTPA)(HPO <sub>3</sub> )]·	$K_4[La_2(DTPA)_2$	$K_6[La_2(DTPA)_2$	K <sub>6</sub> [La(DTPA) (HPO <sub>4</sub> )]·10H <sub>2</sub> O ( <b>6</b> )		
	5H <sub>2</sub> O ( <b>1</b> )	7H <sub>2</sub> O ( <b>2</b> )	$(H_2O)]\cdot 8H_2O(4)$	(HPO <sub>3</sub> )]·7H <sub>2</sub> O ( <b>5</b> )			
Chemical formula	$C_{28}H_{60}O_{32}N_6K_4Gd_2$	C <sub>28</sub> H <sub>51</sub> O <sub>30</sub> N <sub>6</sub> PK <sub>6</sub> Gd <sub>2</sub>	$C_{56}H_{108}O_{58}N_{12}K_8L$	C <sub>28</sub> H <sub>51</sub> O <sub>30</sub> N <sub>6</sub> PK <sub>6</sub> L	C <sub>28</sub> H <sub>57</sub> O <sub>34</sub> N <sub>6</sub> PK <sub>6</sub> La		
	$a_4$ $a_2$ $2$						
Formula mass	731.86	1531.82	2745.98	1495.14	1565.19		
Crystal system	triclinic						
$a/\text{\AA}$	9.034(1)	9.449(1)	13.570(1)	9.722(1)	9.818(1)		
b/Å	12.122(1)	9.609(1)	16.810(1)	9.781(1)	9.829(1)		
c/Å	12.147(1)	15.259(1)	20.721(1)	30.400(1)	30.466(1)		
$\alpha/^{\circ}$	98.211(4)	84.825(5)	88.961(4)	81.296(3)	80.858(4)		
$\beta/^{\circ}$	109.214(5)	86.241(6)	87.494(3)	83.677 (3)	82.993(4)		
$\gamma/^{\circ}$	92.023(4)	67.371(7)	89.396(4)	65.438(4)	64.922(5)		
Unit cell volume/Å <sup>3</sup>	1238.4(2)	1272.8(2)	4721.1(4)	2595.2(2)	2624.0(2)		
Temperature/K	173						
Space group	Pī						
No. of formula units per unit cell, Z	2	1	2	1	1		
No. of reflections measured	16649	16776	43849	21130	21664		
No. of independent reflections	5567	5668	19482	10740	10862		
R <sub>int</sub>	0.0388	0.0478	0.0553	0.0379	0.0441		
Final $R_l$ values ( $l > 2\sigma(l)$ )	0.0221	0.0335	0.0548	0.0532	0.0392		
Final $wR(F^2)$ values $(I > 2\sigma(I))$	0.0512	0.0820	0.1012	0.1248	0.0690		
Final $R_1$ values (all data)	0.0236	0.0367	0.0736	0.0666	0.0535		
Final $wR(F^2)$ values (all data)	0.0520	0.0843	0.1098	0.1321	0.0737		
Goodness of fit on $F^2$	0.991	1.027	1.057	1.033	1.031		

Table S1 Crystal data and structure refinements for 1, 2 and  $4 \sim 6$ .

	$K_2Gd(DTPA)(H_2O) \cdot 6H_2O(1)$		$K_6[Gd(DTPA)(HPO_3)] \cdot 4H_2O(2)$		
Gd–O <sub>carboxy</sub> (Å)	Gd1-01	2.430(2)	Gd1-01	2.438(6)	
	Gd1-03	2.379(2)	Gd1-03	2.411(6)	
	Gd1-05	2.373(2)	Gd1-05	2.391(6)	
	Gd1-07	2.387(2)	Gd1-07	2.419(7)	
	Gd1-09	2.388(2)	Gd1-09	2.426(8)	
Gd-N (Å)	Gd1-N1	2.638(2)	Gd1-N1	2.678(7)	
	Gd1-N2	2.635(2)	Gd1-N3	2.649(7)	
	Gd1-N3	2.704(2)	Gd1-N3	2.723(7)	
Gd-O <sub>water</sub> (Å)	Gd1–O1w	2.448(2)			
Gd-O <sub>phosphite</sub> (Å)			Gd-011	2.320(8)	

**Table S2** The Gd–O and Gd–N bonds distances (Å)forK2[Gd(DTPA)(H2O)]·5H2O (1) and<br/> $K_6[Gd_2(DTPA)_2(HPO_4)]$ ·10H2O (2).

	$K_8[La_2(DTPA)_2(H_2O)]_2 \cdot 16H_2O$ (4)					
La–O <sub>carboxy</sub>	La1–O1	2.663(4)	La2-011	2.602(4)		
(A)	La1–O3	2.554(4)	La2-013	2.500(4)		
	La1-O5	2.453(4)	La2-015	2.579(4)		
	La1–O7	2.520(5)	La2-017	2.489(5)		
	La1–O9	2.520(5)	La2-019	2.513(4)		
	La1-011	2.534(4)	La2–O1	2.601(4)		
La-N (Å)	La1-N1	2.792(5)	La2–N4	2.881(5)		
	La1–N2	2.805(5)	La2-N5	2.866(5)		
	La1-N3	2.868(5)	La2-N6	2.852(5)		
La-O <sub>water</sub> (Å)			La2–O1w	2.677 (5)		

Table S3 The La–O and La–N bonds distances (Å) for  $K_4[La_2(DTPA)_2(H_2O)] \cdot 8H_2O$  (4).

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	$K_6[La_2(DTPA)_2(HPO_3)] \cdot 8H_2O$ (5)			K <sub>6</sub> [La(DTPA)(HPO <sub>4</sub> )]·10H <sub>2</sub> O ( <b>6</b> )				
La–O <sub>carboxy</sub> (Å)	La1-O1	2.544(4)	La2-011	2.535(5)	La1–O1	2.507(3)	La2-011	2.548(3)
	La1-O3	2.506(5)	La2-013	2.516(5)	La1–O3	2.507(3)	La2-013	2.513(3)
	La1-O5	2.536(5)	La2-015	2.526(5)	La1–O5	2.505(3)	La2-015	2.543(3)
	La1–O7	2.509(5)	La2-017	2.513(4)	La1–O7	2.533(3)	La2-017	2.515(3)
	La1-09	2.514(5)	La2019	2.497(4)	La1–O9	2.513(3)	La2-019	2.637(3)
La-N (Å)	La1–N1	2.761(5)	La2–N4	2.866(5)	La1–N1	2.842(4)	La2–N4	2.920(3)
	La1-N2	2.825(5)	La2–N5	2.780(5)	La1–N2	2.832(3)	La2–N5	2.813(3)
	La1-N3	2.792(5)	La2–N6	2.762(5)	La1-N3	2.772(3)	La2–N6	2.827(3)
La–O <sub>phosphite</sub> (Å)	La1–O21	2.440(5)	La2–O22	2.416(5)				
La-O <sub>phosphate</sub> (Å)					La1–O21	2.478(3)	La2–O22	2.420(2)

**Table S4** The La–O and La–N bonds distances (Å) for  $K_6[La_2(DTPA)_2(HPO_3)]$ ·7H<sub>2</sub>O (5) and $K_6[La_2(DTPA)_2(HPO_4)]$ ·10H<sub>2</sub>O (6).



**Fig.S1** Olex2 plot of the anionic structure in  $K_6[La_2(DTPA)_2(HPO_3)]$ ·7H<sub>2</sub>O (**5**) (Green, La; Red, O; Blue, N; Grey, C; White, H).



**Fig. S2** Solution<sup>13</sup>C NMR spectrum of K<sub>5</sub>DTPA.



**Fig.S3** Solution<sup>31</sup>P NMR spectrum of  $K_6[La_2(DTPA)_2(HPO_3)] \cdot 7H_2O(5)$ .



Fig. S4 IR spectrum of  $K_4[La_2(DTPA)_2(H_2O)] \cdot 8H_2O$  (4).



Fig. S5 IR spectrum of  $K_6[La(DTPA)(HPO_3)] \cdot 8H_2O(5)$ .



Fig. S6 IR spectrum of  $K_6[La_2(DTPA)_2(HPO_4)] \cdot 10H_2O$  (6) and  $K_6[Gd_2(DTPA)_2(HPO_4)] \cdot 10H_2O$  (3).



Fig. S7 IR spectrum of H<sub>5</sub>DTPA.