Supporting Information

A Gd(III) Complex of a Monophosphinate-bis(phosphonate) DOTA Analogue with a High ^{1}H NMR Relaxivity; Lanthanide(III) Complexes for Imaging and Radiotherapy of Calcified Tissues.

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Figure S22. ^{1}H NMRD profiles of the Gd-DO3AP^{BP}, Gd-BPAMD and Gd-BPAPD complexes adsorbed on HA under analogous conditions (pH = 7.5, 25 °C). Diamagnetic contribution to r_1 was subtracted.

Table S1. Experimental parameters found in the crystal structure of DO3AP^{BP}·2.25H_2O.

Table S2. Hydrogen bond geometries found in the crystal structure of DO3AP^{BP}·2.25H_2O.

Table S3. The relaxivity r_1 and parameters governing it for the Gd-DO3AP^{BP} complex at pH 6 and 7.5 as obtained from simultaneous fitting of ^{17}O NMR and ^{1}H NMRD data.

Table S4. Luminescence lifetimes of the Eu-DO3AP^{BP} complex in the presence of phosphate with and without Zn(II) ions as a function of time.

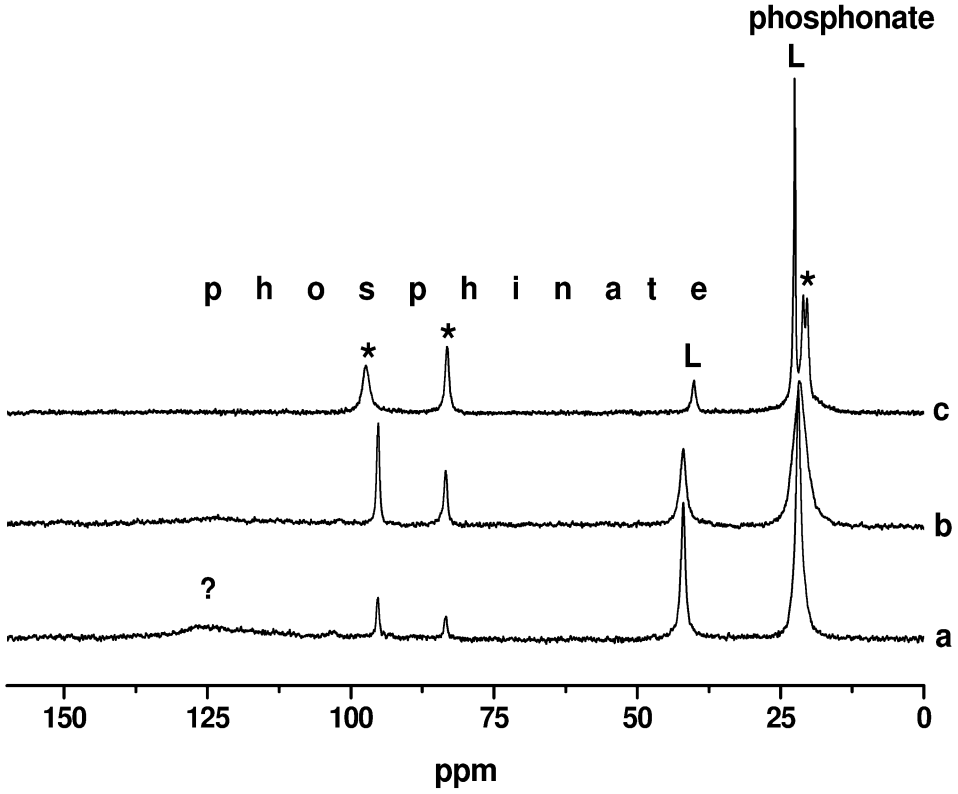

Figure S1. $^{31}P\{^{1}H\}$ spectra monitoring the complexation of the DO3AP^{BP} with Eu(III) ions (*a* – 15 min after mixing the ligand and $EuCl_3$ (0.9 eq.), the initial pH = 9 decreased to 5; *b* – 50 min after mixing, pH = 5; *c* – 2 h after re-adjusting pH to 8). The $^{31}P\{^{1}H\}$ resonances of the free ligand are labelled with 'L'. The $^{31}P\{^{1}H\}$ resonances of the final Eu-DO3AP^{BP} complex are labelled with an asterisk. The question mark labels a very broad peak supposedly of an 'out-of-cage' complex, where the Eu(III) ion is coordinated by phosphinate and carboxylate moieties.

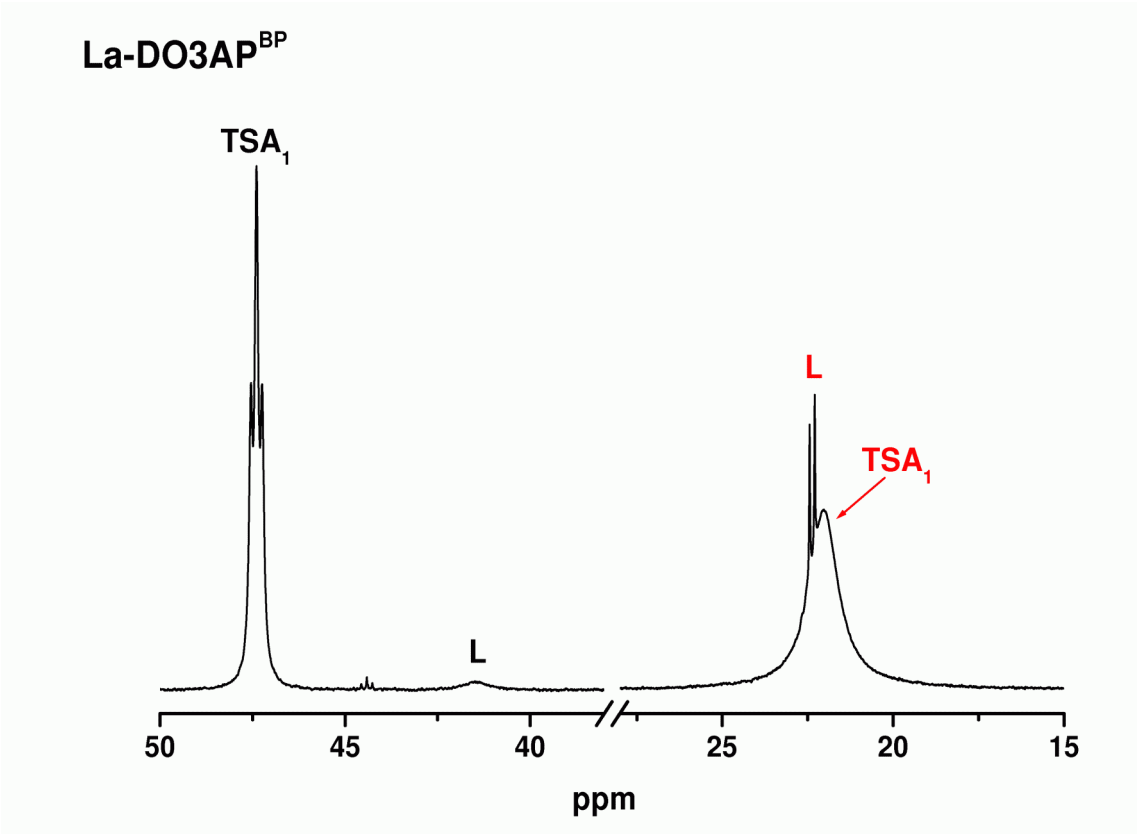

Figure S2. $^{31}P\{^{1}H\}$ spectrum of the La-DO3AP^{BP} complex (pH = 7.3, 25 °C, 400 MHz). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L' (the phosphonate peak at δ ~22 ppm is a doublet due to coupling with the phosphinate P atom). Phosphinate resonances are labelled in black, phosphonate resonances are labelled in red. A small triplet close to δ = 45 ppm is due to a non-coordinating impurity.

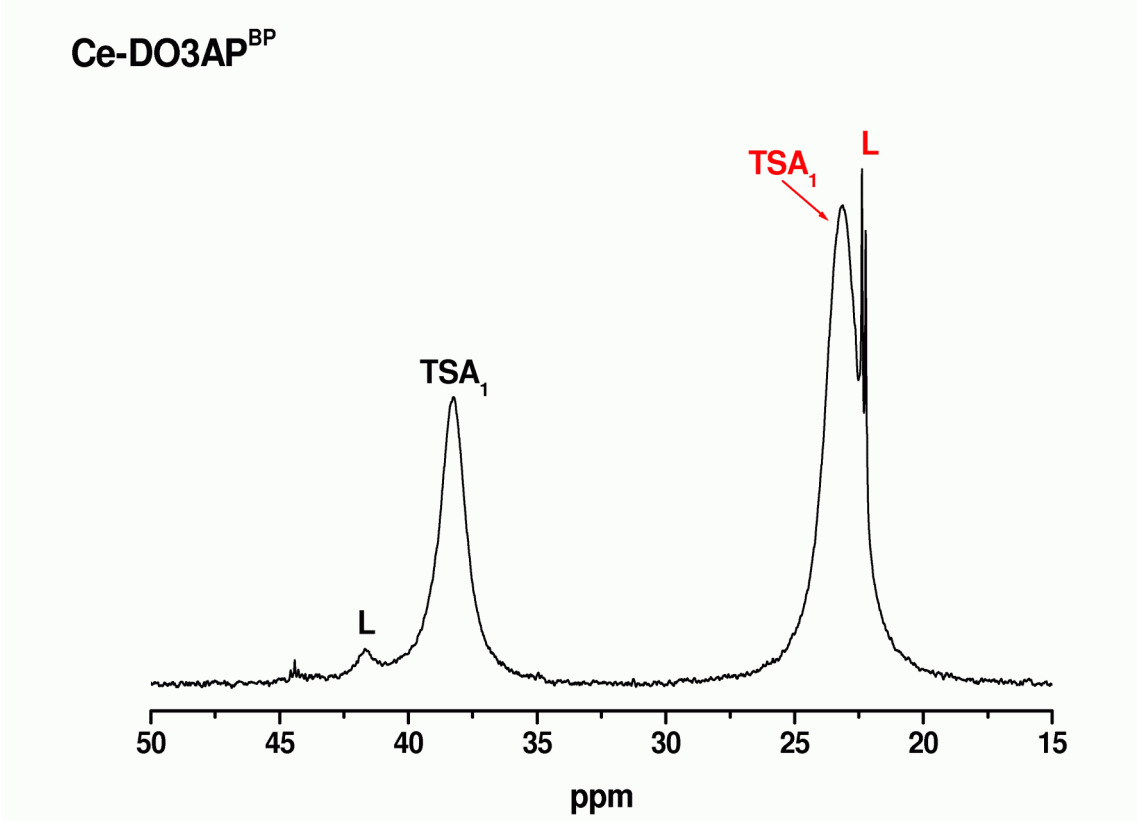

Figure S3. $^{31}P\{^{1}H\}$ spectrum of the Ce-DO3AP^{BP} complex (pH = 7.3, 25 °C, 400 MHz). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L' (the phosphonate peak at δ ~22 ppm is a doublet due to coupling with the phosphinate P atom). Phosphinate resonances are labelled in black, phosphonate resonances are labelled in red. A small triplet close to δ = 45 ppm is due to a non-coordinating impurity.

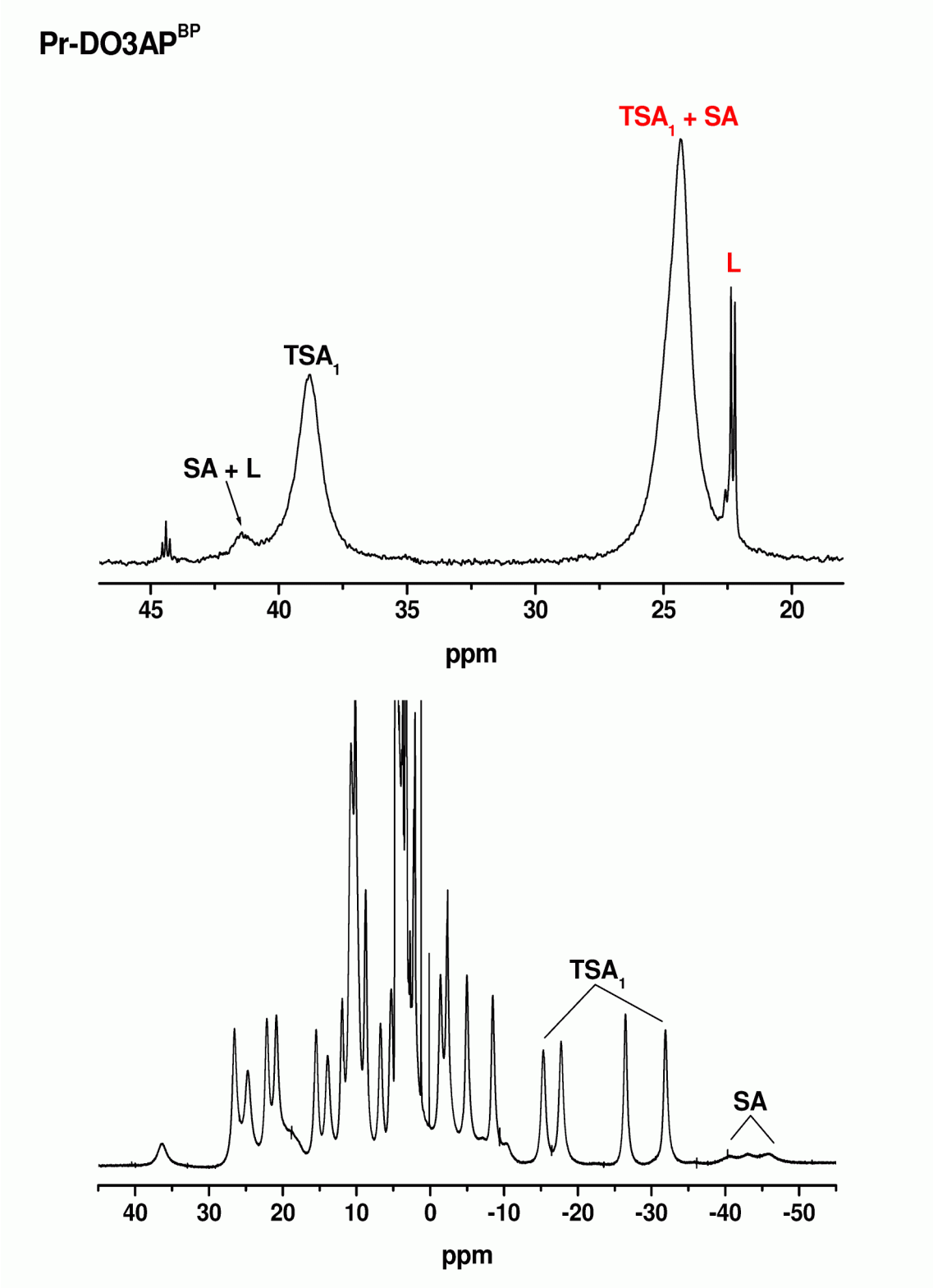

Figure S4. $^{31}P\{^{1}H\}$ (above) and ^{1}H NMR (below) spectra of the Pr-DO3AP^{BP} complex (pH = 7.5, 25 °C, 400 MHz). $^{31}P\{^{1}H\}$ spectrum – phosphinate resonances are labelled in black, phosphonate resonances are labelled in red, resonances of the free ligand in excess are labelled with 'L' (the phosphonate peak at δ ~22 ppm is a doublet due to coupling with the phosphinate phosphorus atom); a small triplet close to δ = 45 ppm is due to a non-coordinating impurity.

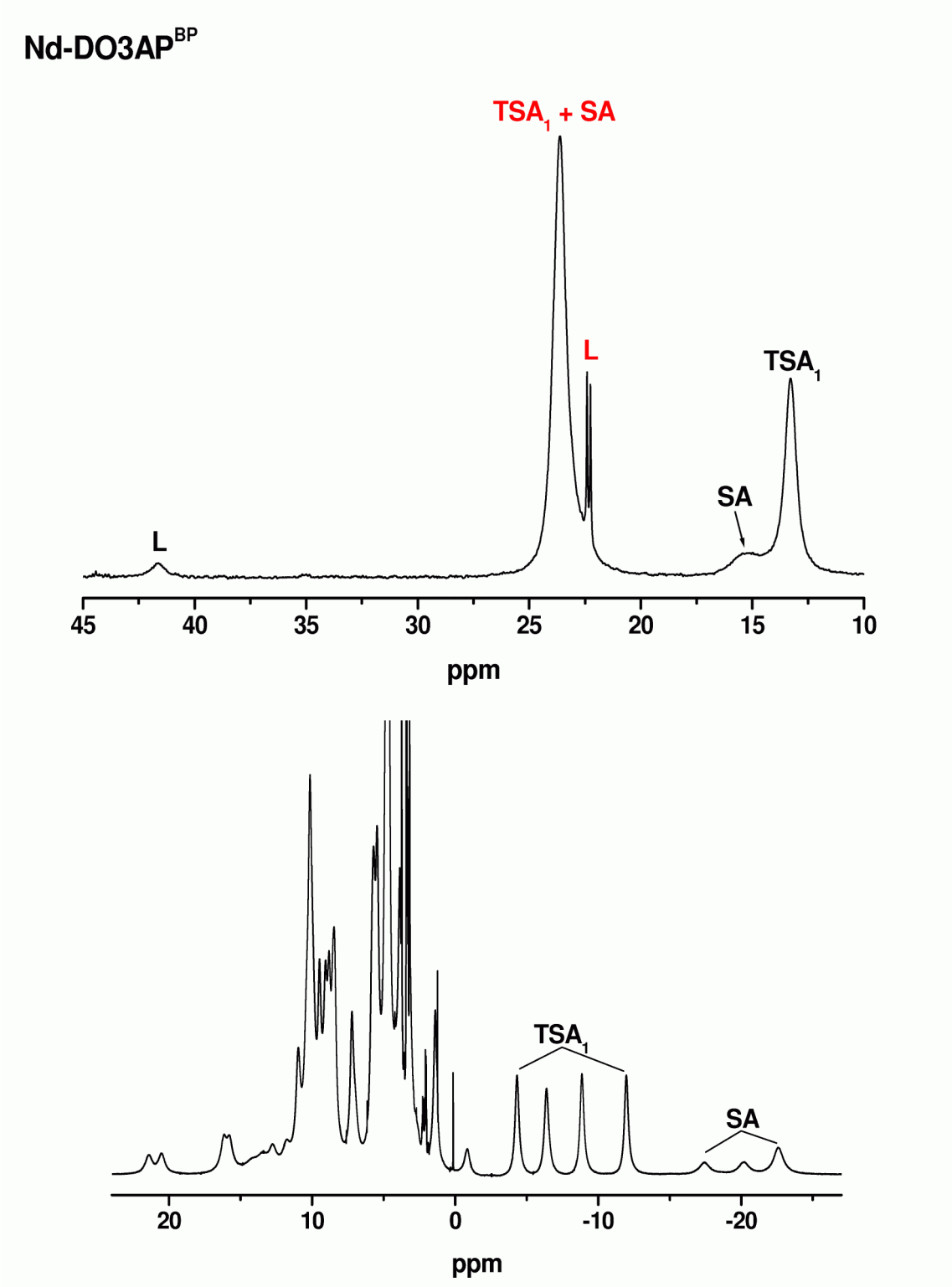

Figure S5. $^{31}P\{^{1}H\}$ (above) and ^{1}H NMR (below) spectra of the Nd-DO3AP^{BP} complex (pH = 7.4, 25 °C, 400 MHz). $^{31}P\{^{1}H\}$ spectrum – phosphinate resonances are labelled in black, phosphonate resonances are labelled in red, resonances of the free ligand in excess are labelled with 'L' (the phosphonate peak at δ ~22 ppm is a doublet due to coupling with the phosphinate phosphorus atom).

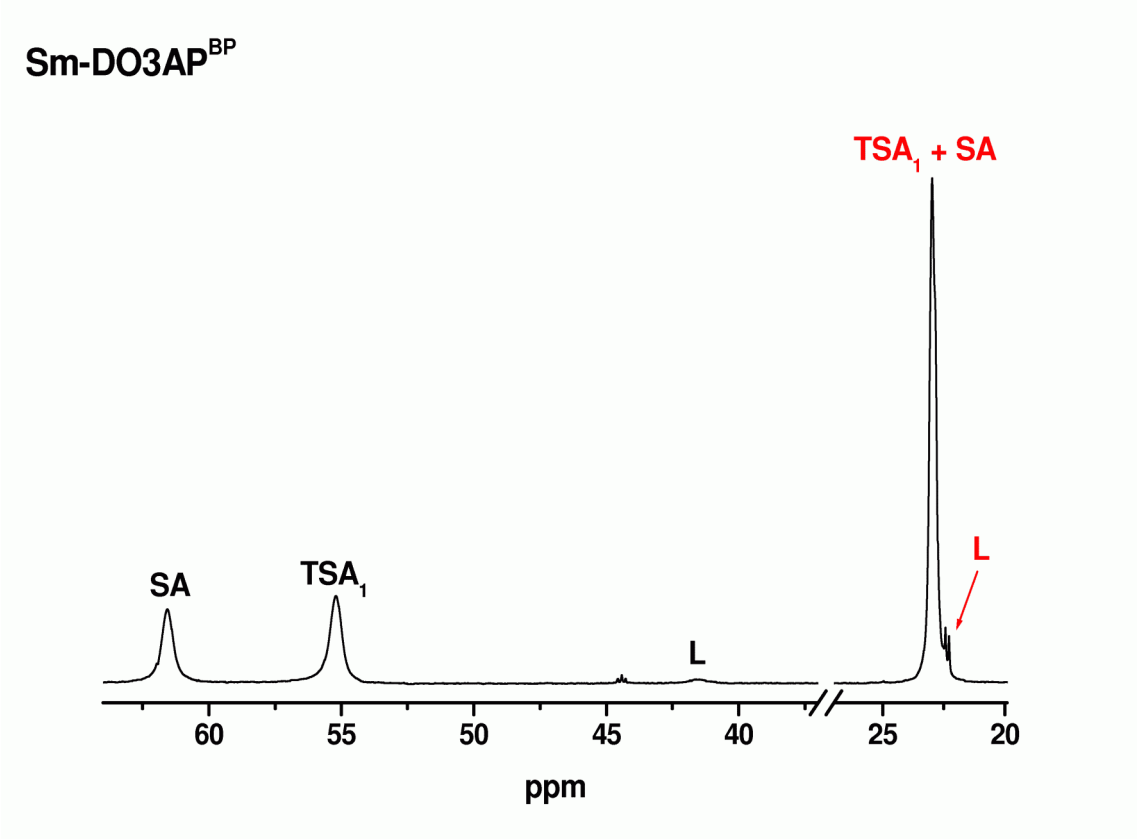

Figure S6. $^{31}P\{^{1}H\}$ spectrum of the Sm-DO3AP^{BP} complex (pH = 7.2, 25 °C, 400 MHz). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L' (the phosphonate peak at δ ~22 ppm is a doublet due to coupling with the phosphinate phosphorus atom). Phosphinate resonances are labelled in black, phosphonate resonances are labelled in red. A small triplet close to δ = 45 ppm is due a non-coordinating impurity.

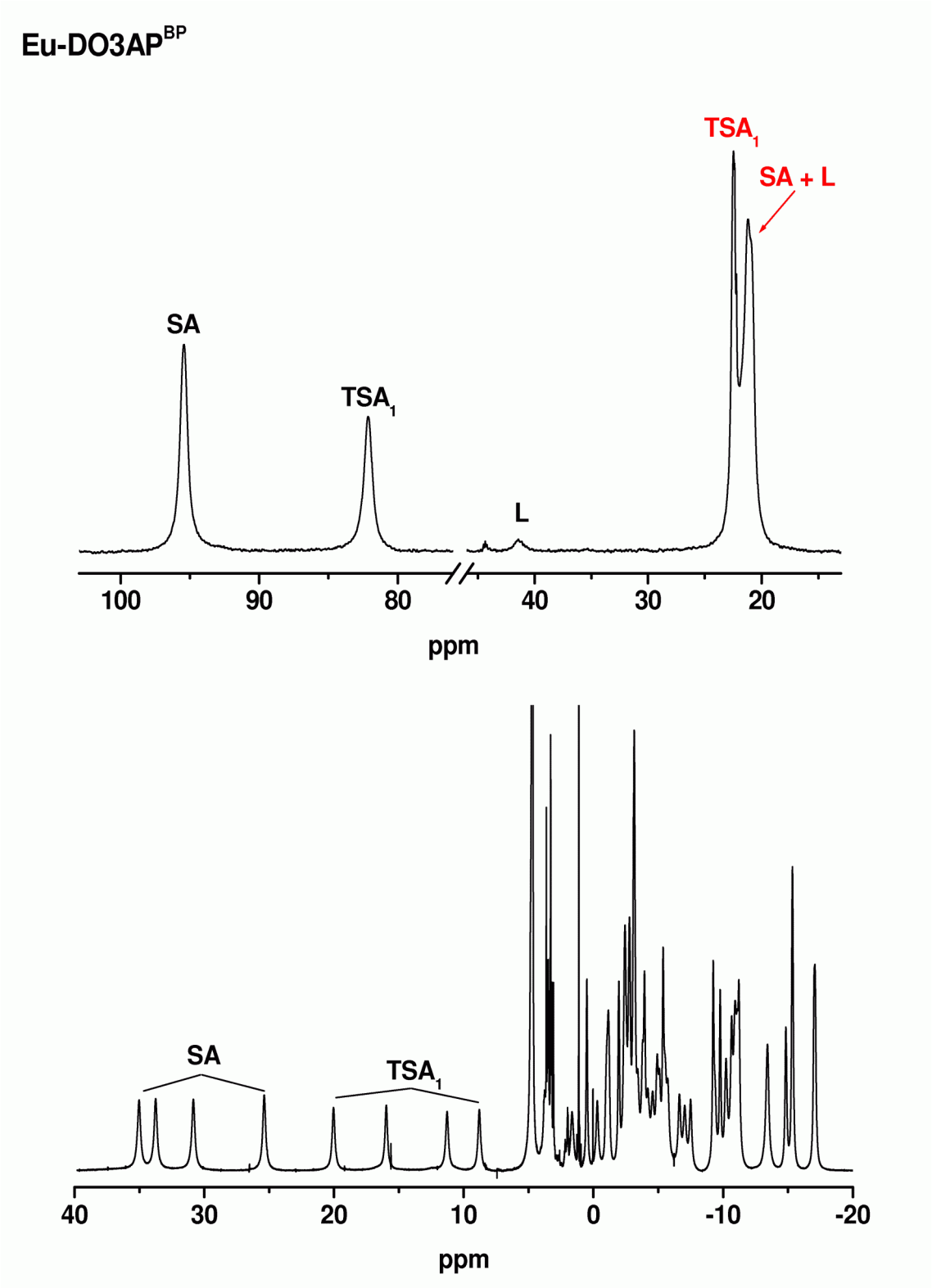

Figure S7. $^{31}P\{^{1}H\}$ (above) and ^{1}H NMR (below) spectra of the Eu-DO3AP^{BP} complex (pH = 7.2, 25 °C, 400 MHz). $^{31}P\{^{1}H\}$ spectrum – phosphinate resonances are labelled in black, phosphonate resonances are labelled in red, resonances of the free ligand in excess are labelled with 'L'; a small triplet close to δ = 45 ppm is due to a non-coordinating impurity.

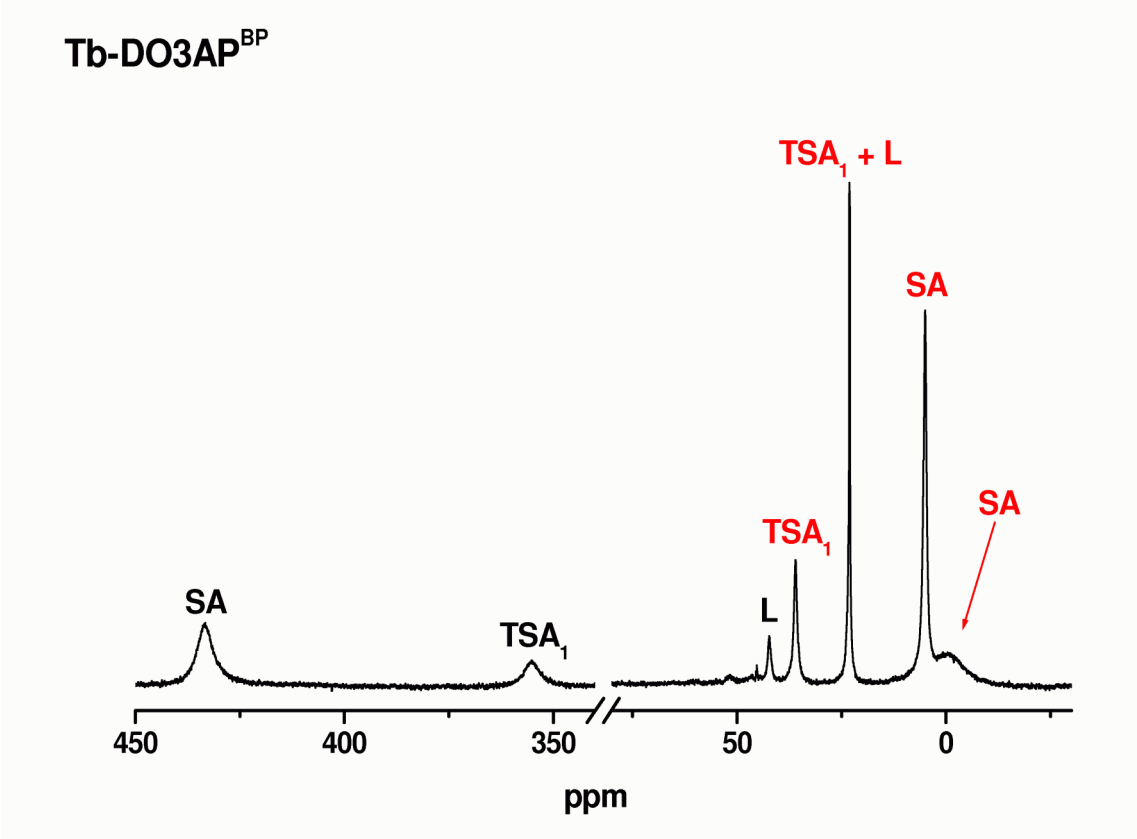

Figure S8. $^{31}P\{^{1}H\}$ spectrum of the Tb-DO3AP^{BP} complex (pH = 7.2, 25 °C, 400 MHz). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L'. Phosphinate resonances are labelled in black, phosphonate resonances are labelled in red.

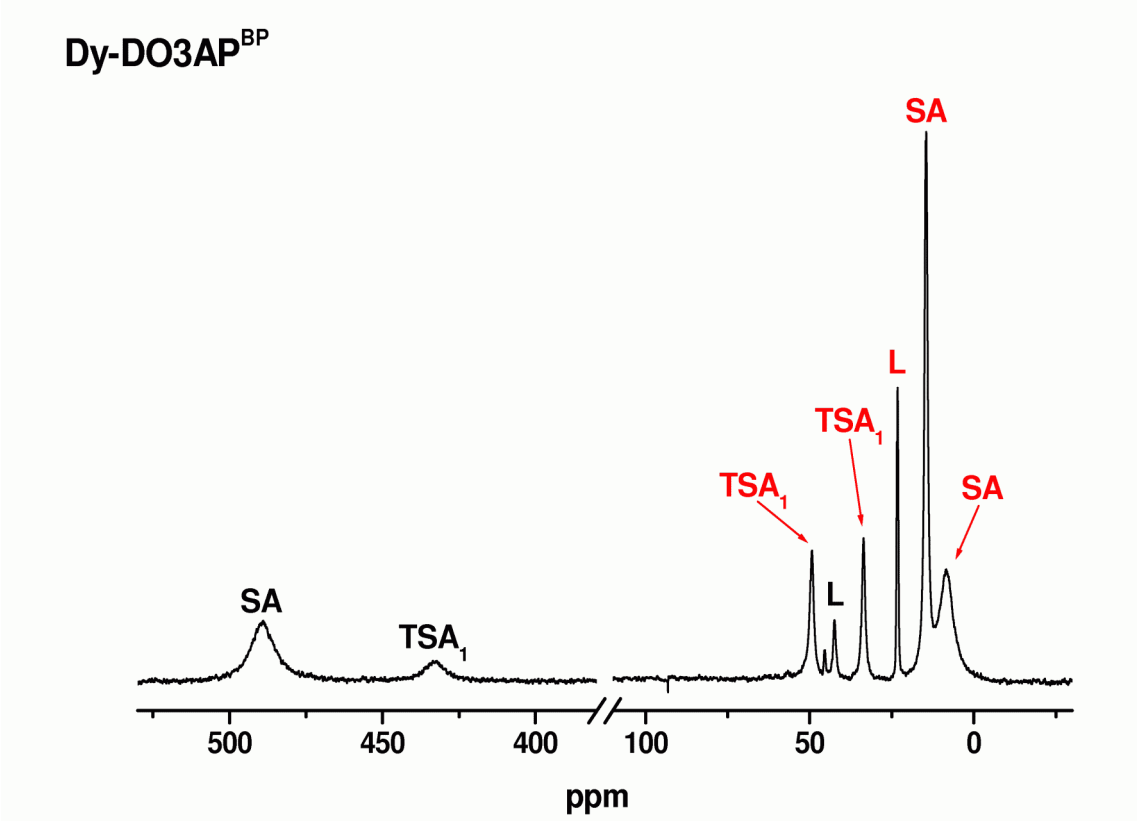

Figure S9. $^{31}P\{^{1}H\}$ spectrum of the Dy-DO3AP^{BP} complex (pH = 7.2, 25 °C, 400 MHz). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L'. Phosphinate resonances are labelled in black, phosphonate resonances are labelled in red. A small peak close to δ = 45 ppm is due to a non-coordinating impurity.

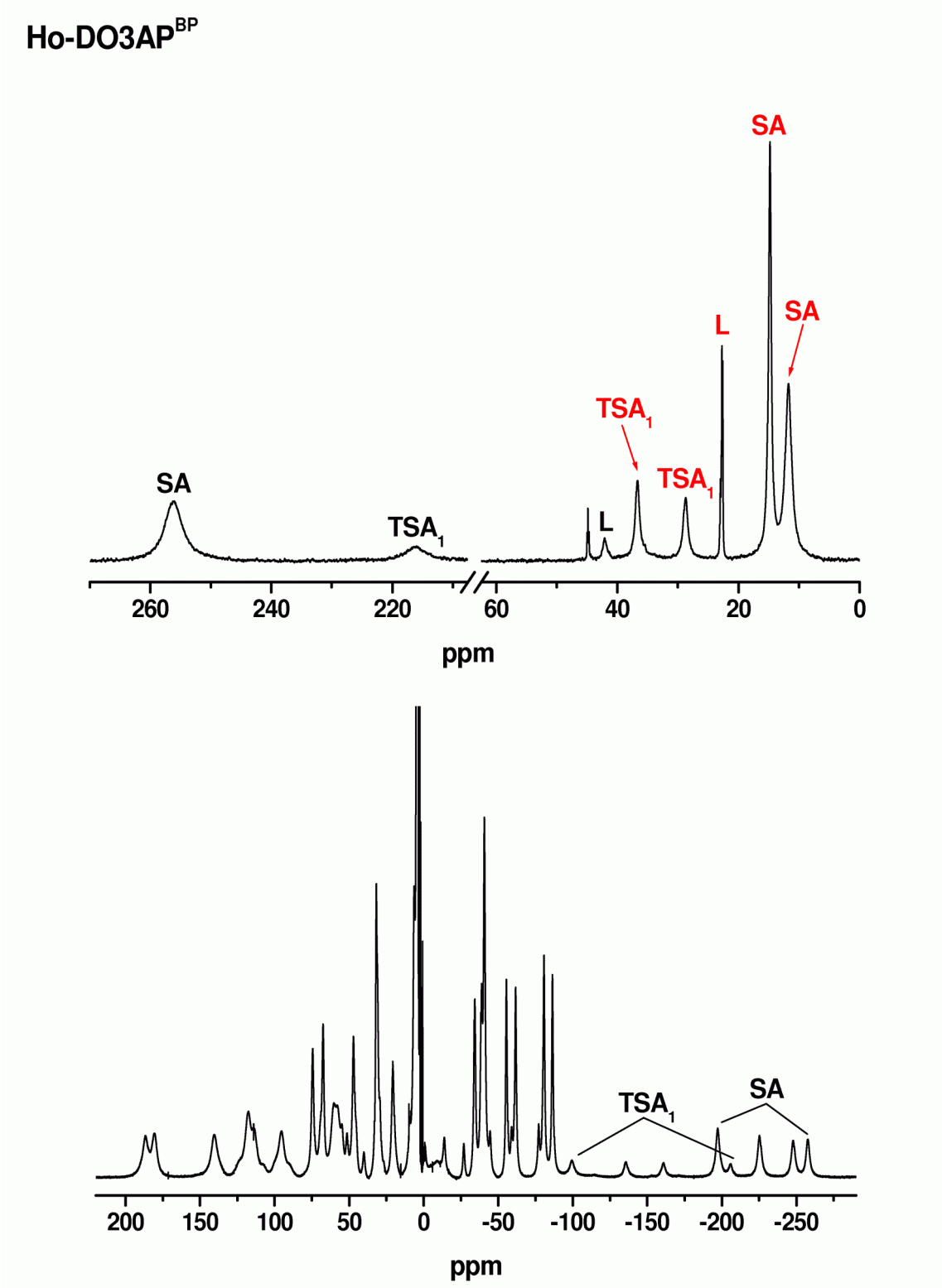

Figure S10. $^{31}P\{^{1}H\}$ (above) and ^{1}H NMR (below) spectra of the Ho-DO3AP^{BP} complex (pH = 7.3, 25 °C, 400 MHz). $^{31}P\{^{1}H\}$ spectrum – phosphinate resonances are labelled in black, phosphonate resonances are labelled in red, resonances of the free ligand in excess are labelled with 'L'; a small triplet close to δ = 45 ppm is due to a non-coordinating impurity.

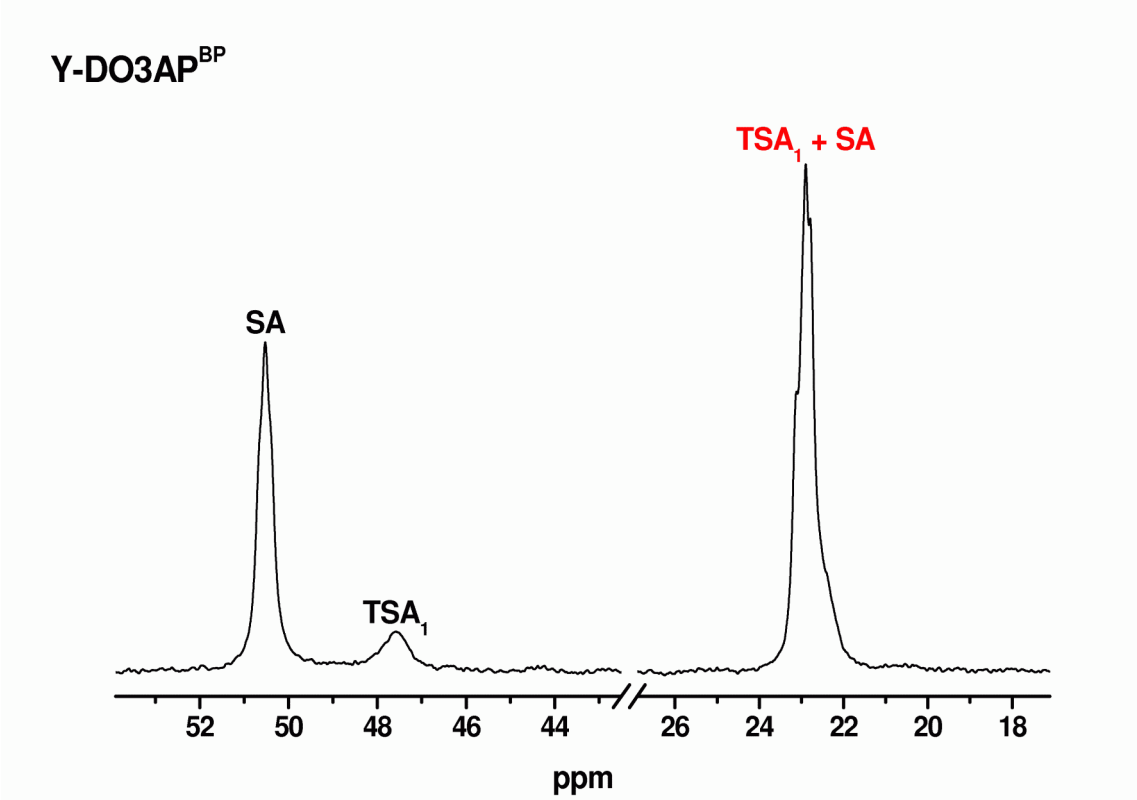

Figure S11. $^{31}P\{^{1}H\}$ spectrum of the Y-DO3AP^{BP} complex (pH = 7.0, 25 °C, 400 MHz). In this case no excess of free ligand was used. Phosphinate resonances are labelled in black, phosphonate resonances are labelled in red.

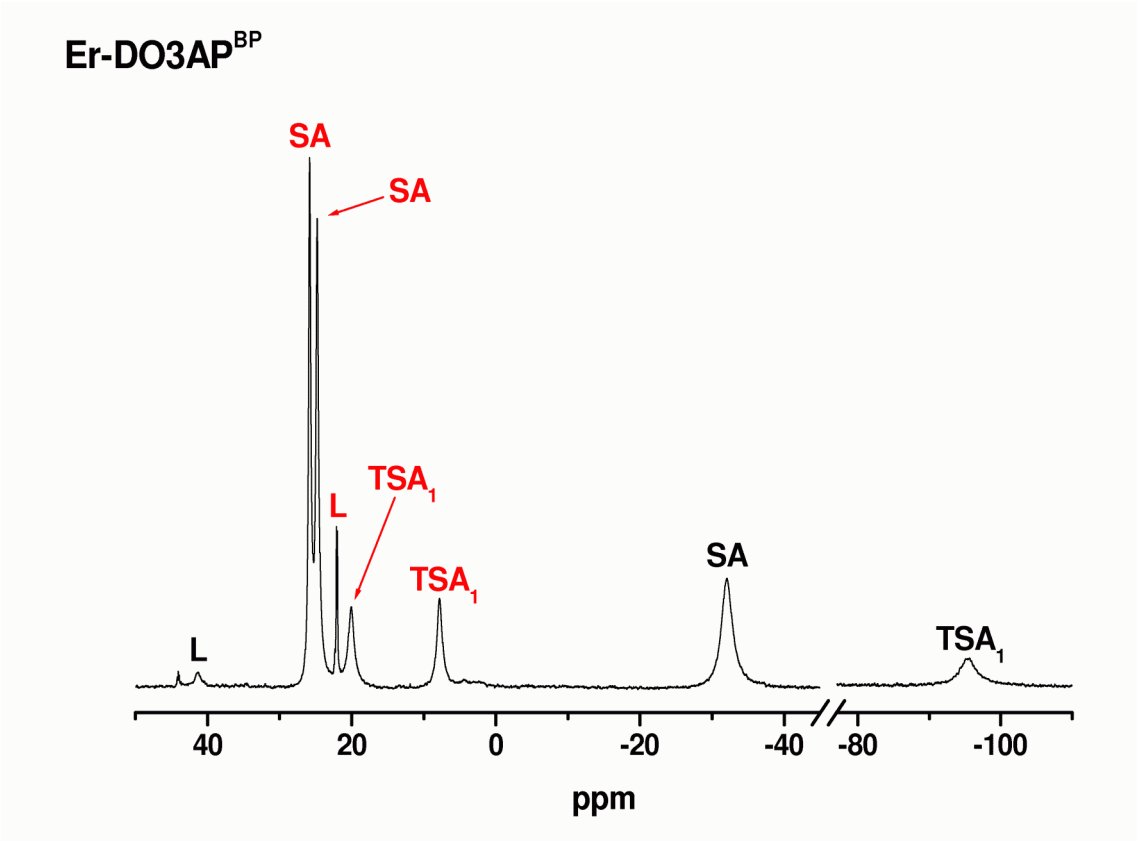

Figure S12. $^{31}P\{^{1}H\}$ spectrum of the Er-DO3AP^{BP} complex (pH = 7.4, 25 °C, 400 MHz). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L'. Phosphinate resonances are in black, phosphonate resonances are in red. A small triplet close to δ = 45 ppm is due to a non-coordinating impurity.

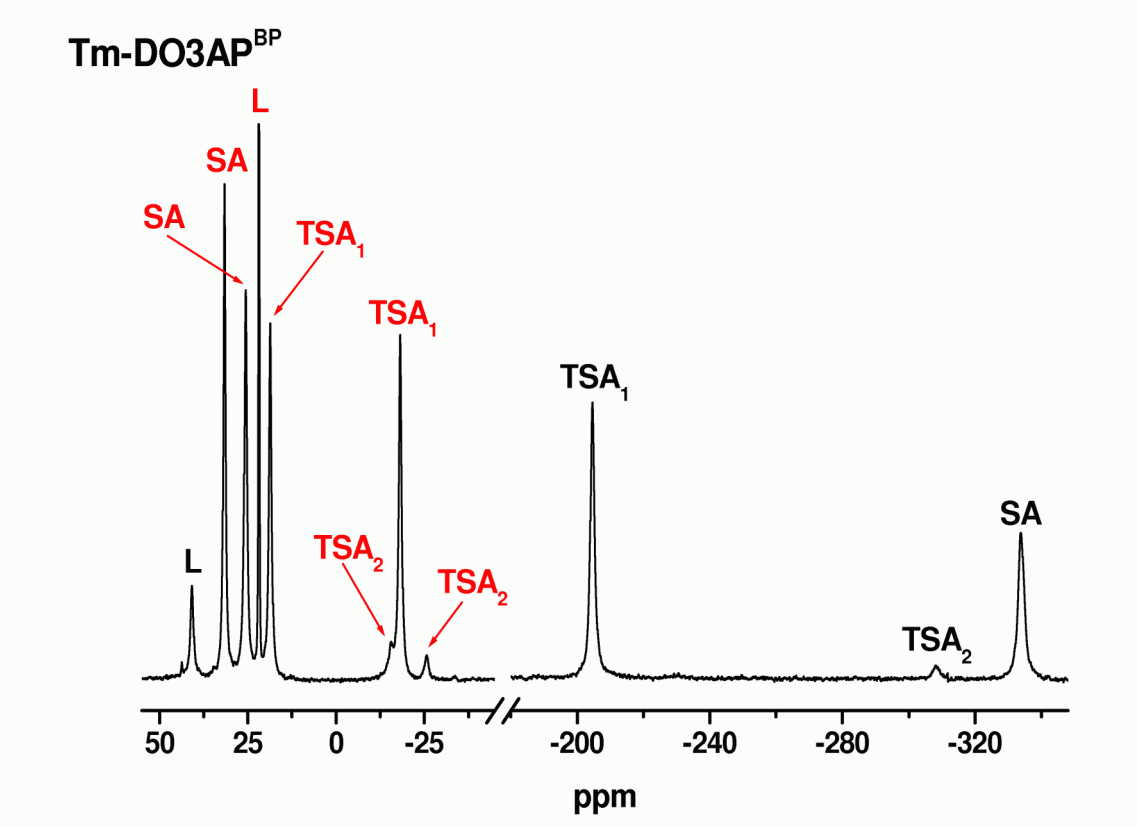

Figure S13. $^{31}P\{^{1}H\}$ spectrum of the Tm-DO3AP^{BP} complex (pH = 7.3, 25 °C, 400 MHz). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L'. Phosphinate resonances are labelled in black, phosphonate resonances are labelled in red.

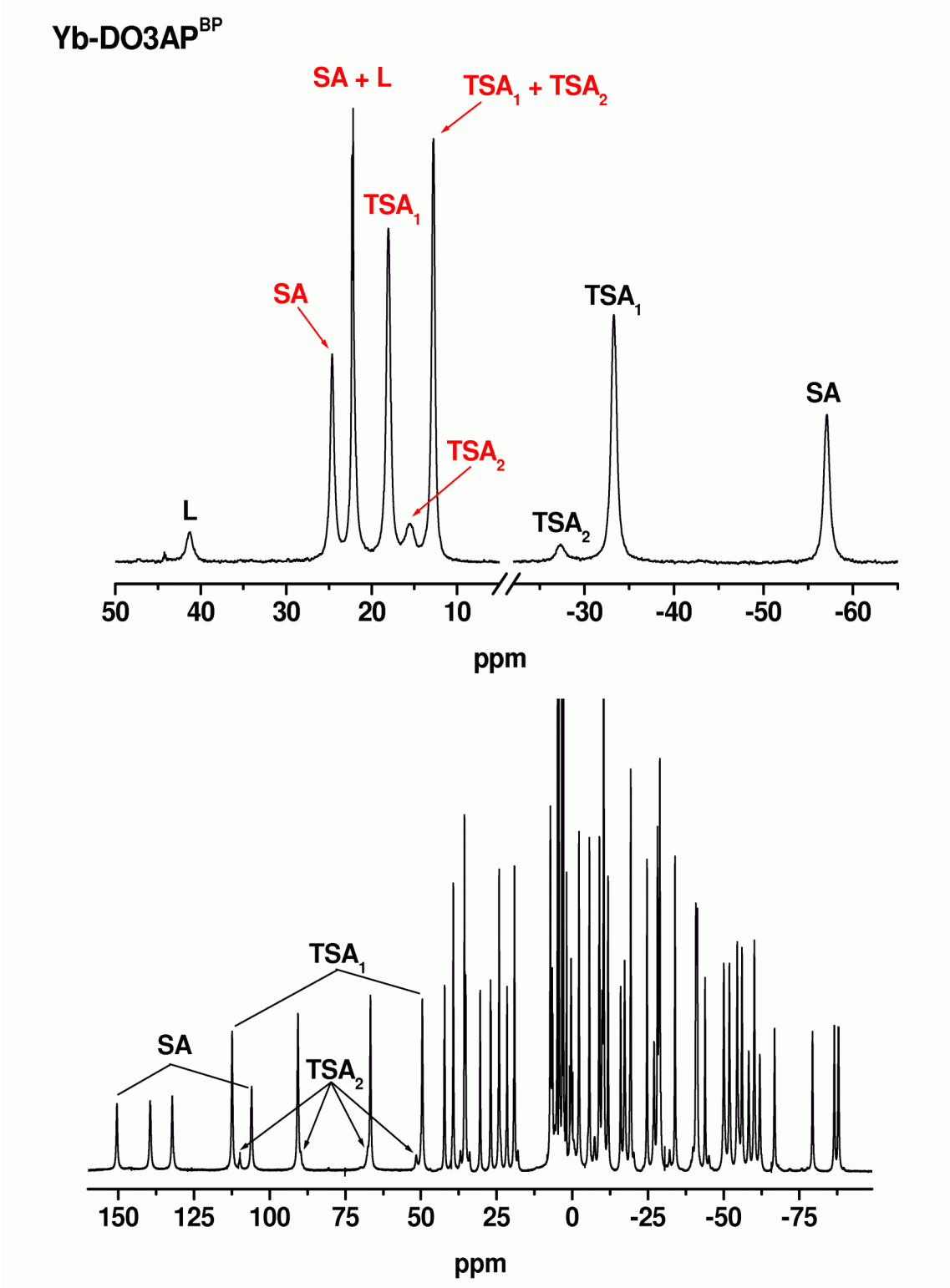

Figure S14. $^{31}P\{^{1}H\}$ (above) and ^{1}H NMR (below) spectra of the Yb-DO3AP^{BP} complex (pH = 7.3, 25 °C, 400 MHz). $^{31}P\{^{1}H\}$ spectrum – phosphinate resonances are labelled in black, phosphonate resonances are labelled in red, resonances of the free ligand in excess are labelled with 'L'; a small peak close to δ = 45 ppm is due to a non-coordinating impurity.

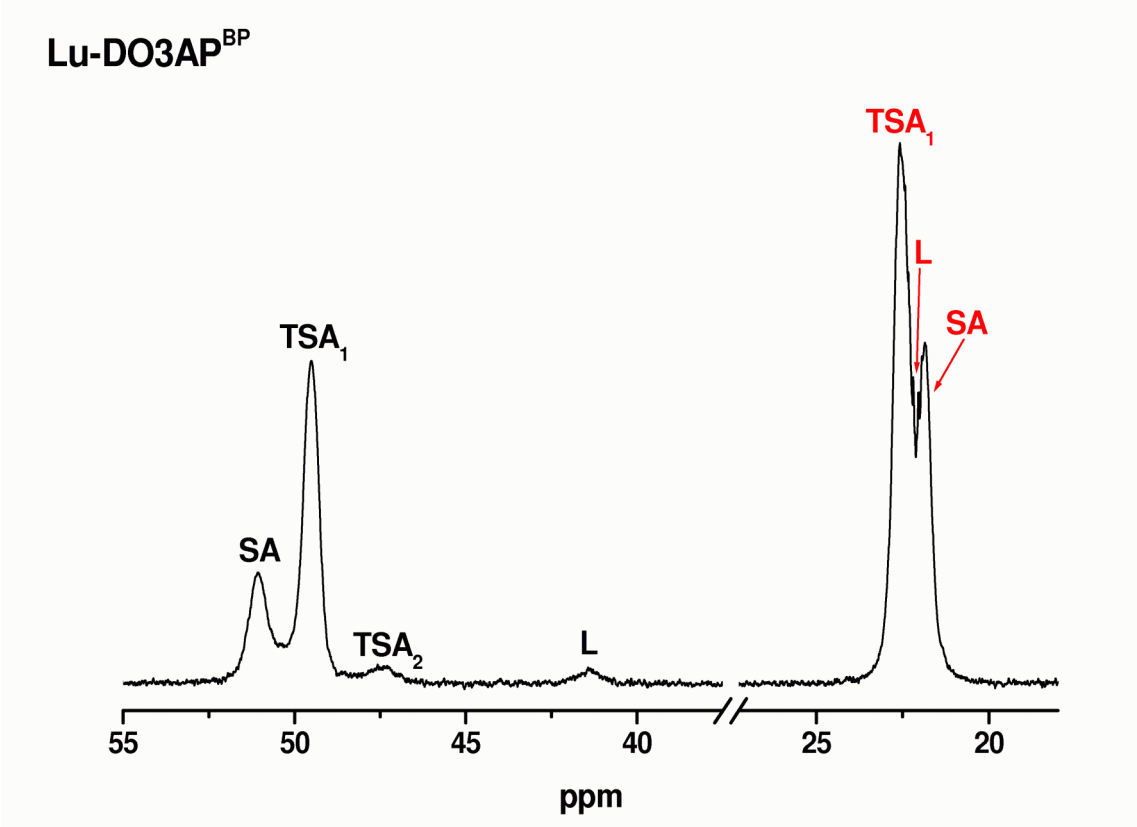

Figure S15. $^{31}P\{^{1}H\}$ spectrum of the Lu-DO3AP^{BP} complex (pH = 7.0, 25 °C, 400 MHz). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L'. Phosphinate resonances are labelled in black, phosphonate resonances are labelled in red.

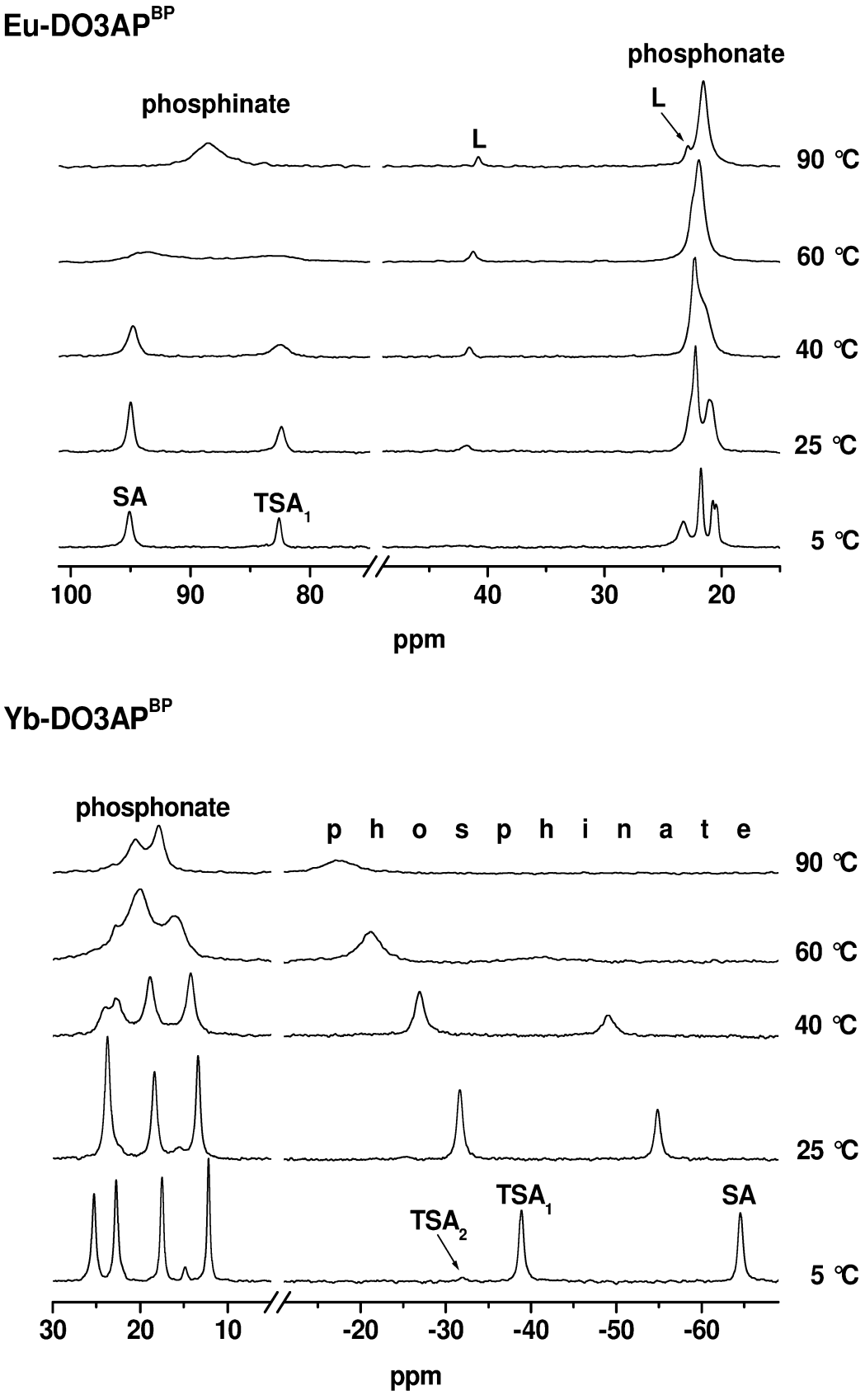

Figure S16. $^{31}P\{^{1}H\}$ spectra of the Eu-DO3AP^{BP} (above) and Yb-DO3AP^{BP} (below) complexes at different temperatures (pH = 7). The $^{31}P\{^{1}H\}$ resonances of the free ligand in excess are labelled with 'L'.

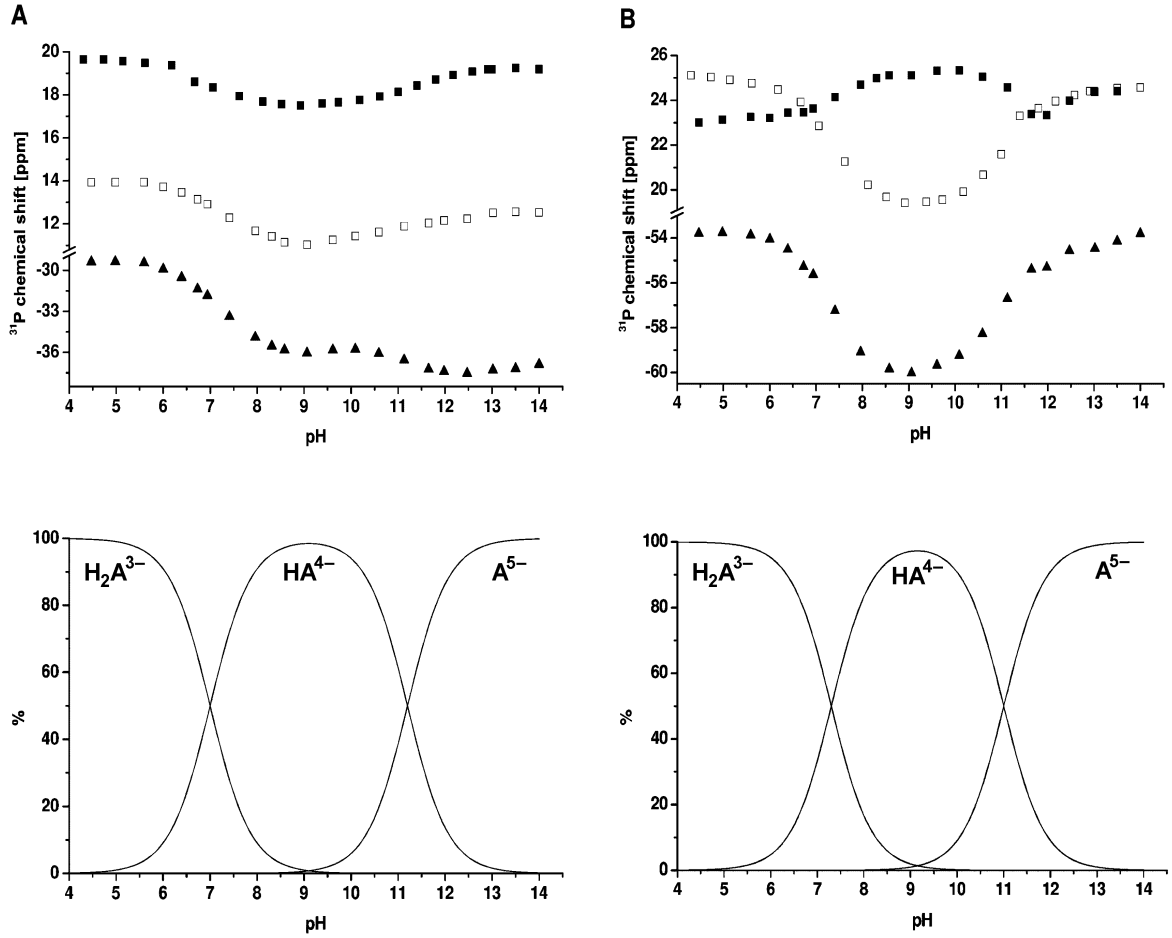

Figure S17. $^{31}P\{^{1}H\}$ titration curves of phosphinate (▲) and two non-equivalent ^{31}P atoms of bis(phosphonate) moiety (■, □) of the SA (A) and TSA (B) diastereoisomers in the Yb-DO3AP^{BP} complex, and corresponding distribution diagrams (below), A^{5-} denotes the fully deprotonated Yb-DO3AP^{BP} complex.

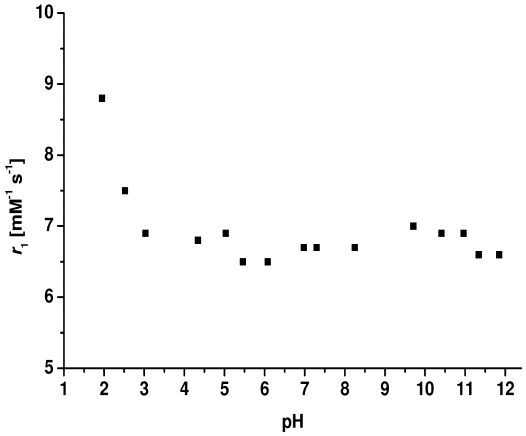

Figure S18. pH dependence of the relaxivity for the Gd-DO3AP^{BP} complex (2 mM, 20 MHz, 25 °C).

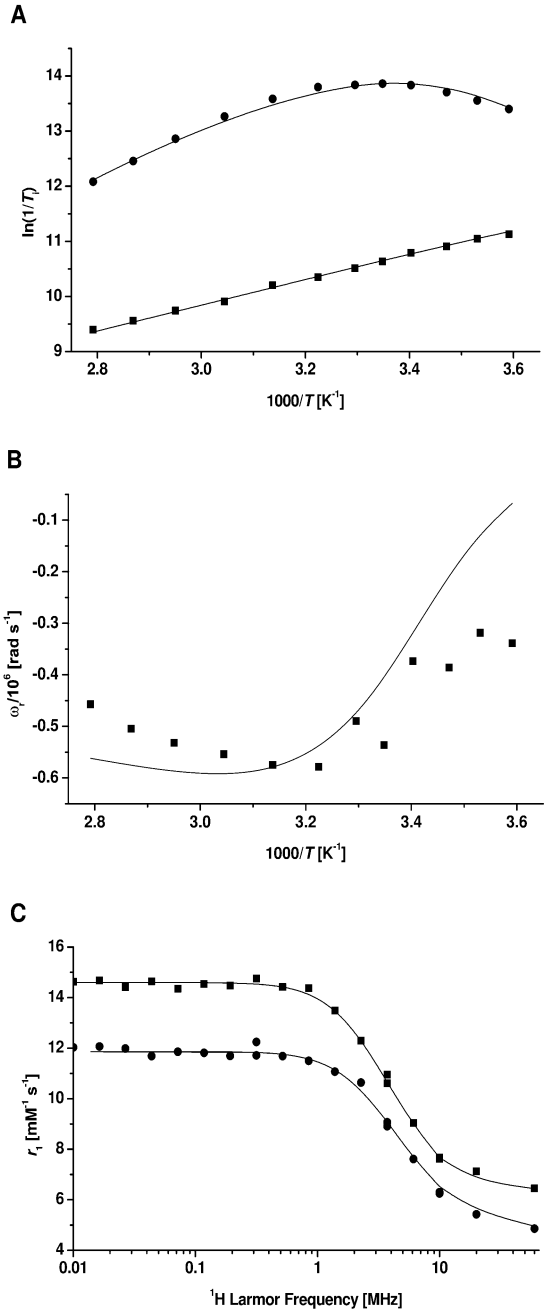

Figure S19. The temperature dependence of longitudinal (A, ■) and transverse relaxation times (A, ●) and reduced ^{17}O NMR chemical shifts (B) of water for the Gd-DO3AP^{BP} complex (87 mM, pH = 6, 400 MHz). ^{1}H NMRD profiles of the Gd-DO3AP^{BP} complex in aqueous solution at 25 °C (C, ■) and 37 °C (C, ●) (2.5 mM, pH = 6). The curves represent simultaneous least-squares fits of the ^{17}O data and the ^{1}H NMRD profiles.

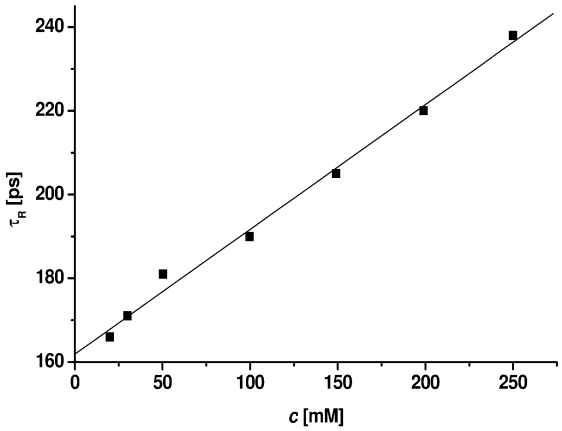

Figure S20. The τ_R values of the deuterated La-DO3AP^{BP} complex as a function of concentration (20–250 mM, pH = 7.5, 25 °C). The equation of a linear fit: $y = 0.299x + 161.7$; correlation coefficient $R^2 = 0.993$.

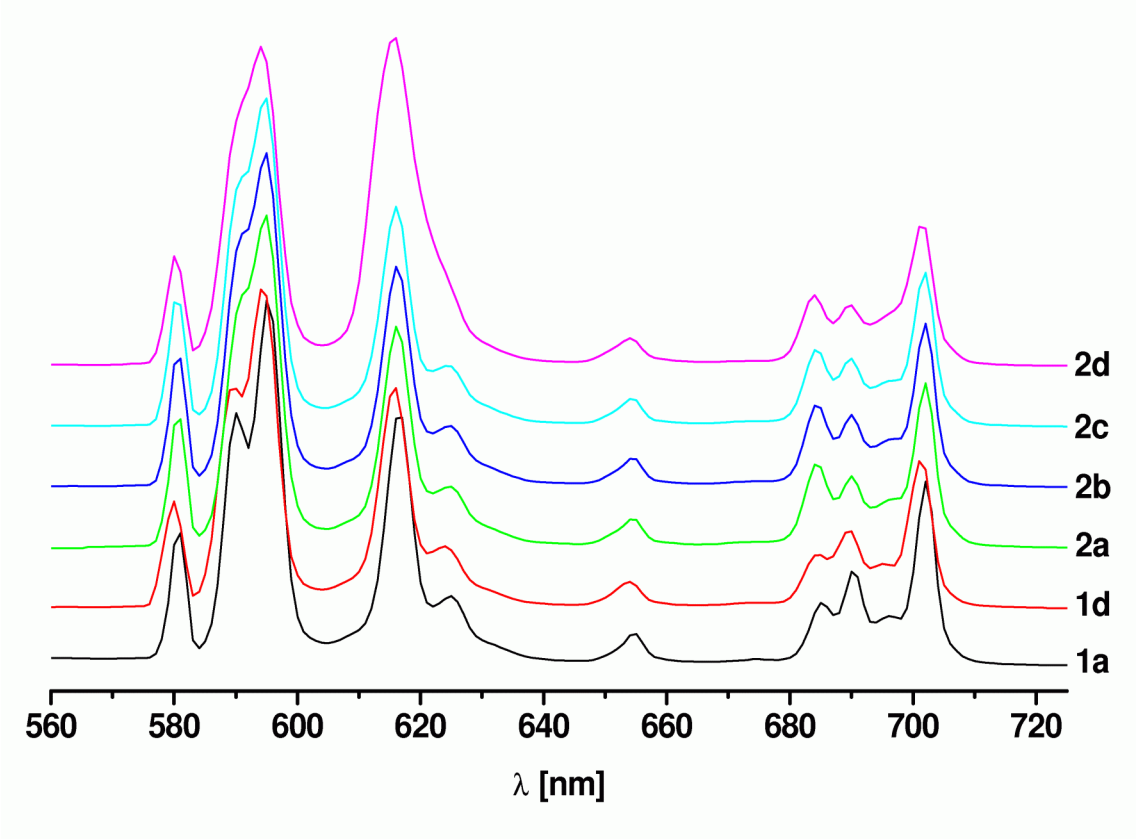

Figure S21. Luminescence emission spectra of the Eu-DO3AP^{BP} complex (62 mM, pH = 7) in the presence of phosphate (67 mM) (labelled with1); and in the presence of phosphate (67 mM) and 3 eq. of Zn(II) ions (labelled with 2) as a function of time (*a* – 0 min, *b* – 5 min, *c* – 90 min, *d* – 3 days).

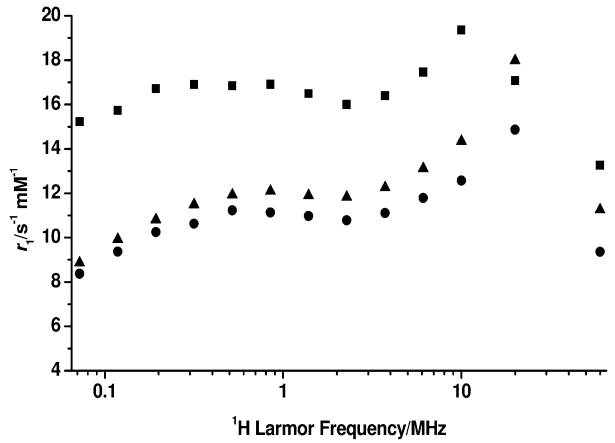

Figure S22. ^{1}H NMRD profiles of the Gd-DO3AP^{BP} (■), Gd-BPAMD (●) and Gd-BPAPD (▲) complexes adsorbed on HA under analogous conditions (pH = 7.5, 25 °C). Diamagnetic contribution to r_1 was subtracted.

Table S1. Experimental parameters found in the crystal structure of $DO3AP^{BP}\cdot 2.25H_2O$.

Formula	$C_{17}H_{39.50}N_4O_{16.25}P_3$
M_r	652.94
Size (mm)	0.25×0.25×0.50
Crystal shape	Prism
Colour	Colourless
Crystal system	Monoclinic
Space group	$P2_1/n$ (No. 14)
a (Å)	8.78940(10)
b (Å)	24.6443(3)
c (Å)	12.78370(10)
β (°)	95.0428(6)
U (Å^3)	2758.34(5)
Z	4
D_c (g cm^{-3})	1.572
μ (mm^{-1})	0.298
F(000)	1378
Range of θ (°)	1.80–27.44
Range of indexes (*hkl*)	$-11 < h < 11$ $-31 < k < 31$ $-16 < l < 16$
Collected refl.	47012
Unique refl.	6277
Observed refl. [$I > 2\sigma(I)$]	5560
R_{int}	0.0290
Restrictions, parameters	0, 370
G-o-f	1.047
R; wR (all data)	0.0310; 0.0813
R'; wR' [$I > 2\sigma(I)$]	0.0365; 0.0853
Residual min/max of electronic density (e Å^{-3})	–0.424; 0.495

Table S2. Hydrogen bond geometries found in the crystal structure of $DO3AP^{BP}\cdot 2.25H_2O$.

D–H	d(D–H) / Å	d(H···A) / Å	<D-H-A / °	d(D···A) / Å	A
N1–H11	0.910	2.276	131.5	2.958	O512
N1–H11	0.910	2.511	107.7	2.920	N4
N1–H11	0.910	2.600	108.6	3.016	N10
N7–H71	0.910	2.277	132.5	2.969	O312
N7–H71	0.910	2.618	108.1	3.028	N4
N7–H71	0.910	2.426	108.6	2.850	N10
O21-H21P	0.857	1.678	175.7	2.533	O12
O31-H31P	0.933	1.558	171.0	2.484	O22 [-x+2, -y+1, -z+1]
O32-H32P	0.937	1.566	169.2	2.492	O23 [-x+2, -y+1, -z+1]
O311-H311	0.919	1.671	170.2	2.582	O11 [x+1/2, -y+1/2, z+1/2]
O411-H411	0.883	1.687	162.5	2.543	O33 [x+1/2, -y+1/2, z+1/2]
O511-H511	0.830	1.796	163.3	2.601	O1W
O1W-H11W	0.761	2.184	143.1	2.830	O11 [x+1, y, z]
O1W-H12W	0.835	2.057	158.1	2.849	O22
O1W-H12W	0.835	2.502	120.6	3.014	O32
O2W-H21W	0.838	2.098	166.7	2.920	O11 [x+1/2, -y+1/2, z+1/2]
O2W-H22W	0.887	2.076	176.5	2.961	O33 [x-1/2, -y+1/2, z+1/2]

Table S3. The ^{1}H relaxivity r_1 (20 MHz) and parameters governing it in the Gd-DO3AP^{BP} complex at pH 6, 7.5 and 10 as obtained from the simultaneous fitting of ^{17}O NMR and ^{1}H NMRD data. Experimental points of the ^{1}H relaxivity are given in brackets.

parameter	pH = 6	pH = 7.5
$^{298}r_1$/s^{-1} mM^{-1}	6.8 (7.1)	6.9 (7.4)
$^{310}r_1$/s^{-1} mM^{-1}	5.5 (5.4)	5.7 (5.6)
k_{ex}^{298}/10^6 s^{-1}	4.45 ± 0.47	5.06 ± 0.75
τ_M^{298}/ns	224 ± 24	198 ± 29
$\Delta H^{\neq}$/kJ mol^{-1}	51.1 ± 3.2	51.1 ± 4.0
E_R/kJ mol^{-1}	19.4 ± 0.9	21.6 ± 1.2
τ_R^H/ps	122.7 ± 5.0	134.0 ± 7.7
(τ_R^O/τ_R^H)	1.41 ±0.08	1.19 ± 0.09
τ_V^{298}/ps	8.8 ± 1.4	7.1 ± 1.3
Δ^2/10^{19} s^{-2}	4.08 ± 0.93	5.99 ± 1.54
($A/\hbar$)/MHz	–3.04 ± 0.26	–3.24 ± 0.36
δg_L^2	0.038 ±0.012	0.024 ± 0.015
q_{ss}	1.42 ± 0.08	1.81 ± 0.10

Fixed parameters:

$D^{298}_{GdH} = 2.39\times10^{-9}$ m^2 s^{-1}
$E_{DGH} = 18.2$ kJ mol^{-1}
$r_{GdH} = 3.1$ Å
$r_{GdO} = 2.5$ Å
$r_{GdHss} = 3.5$ Å
$r_{Oss} = 4.1$ Å
$k_{ss}^{298} = 2\times10^{10}$ s^{-1}
$\tau_{Mss}^{298} = 56$ ps
$\Delta H^{\neq ss} = 30$ kJ mol^{-1}
$E_V = 1$ kJ mol^{-1}
$\chi(1+\eta^2/3)^{1/2} = 7.58$ MHz

Table S4. The luminescence lifetimes measured for the Eu-DO3AP^{BP} complex in the presence of phosphate (67 mM, pH = 7) and 3 eq. of $ZnCl_2$, and for the reference sample without Zn(II) ions.

time [days]	lifetime τ_{H2O} [µs]	
	Eu-DO3AP^{BP} + 3 eq. $ZnCl_2$	Eu-DO3AP^{BP} (reference sample)
0	704	720
3	745	752