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Synthesis of benzoaza-15(18)-crown-5(6) ethers and study of their complexes with lead(II)

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Content

Materials and Methods

All commercially available reagents were used without further purification. The progress of reactions was followed with TLC using silica gel (Macherey-Nagel, Alurgam Xtra Sil G/UV$_{254}$, 0.20 mm silica gel 60) and aluminum oxide (Merck, 60 F$_{254}$, neutral). 1,2-Bis(2-iodoethoxy)benzene [S1] and diethyl 2,2'-(1,2-phenylenebis(oxy))diacetate [S2] were prepared according to a previously described procedures. Melting points were determined on a «Mel-temp II». Elemental analyses were carried out on a Carlo Erba 1108 elemental analyzer. Electrospray ionization mass spectrometry (ESI-MS) analyses were performed using a Finnigan LCQ Advantage mass spectrometer equipped with an octopole ion-trap mass-analyzer. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on Bruker Avance 400 and Bruker Avance 600 MHz spectrometers. Chemical shifts for ^{1}H and ^{13}C are reported in parts per million (δ) relative to deuterated solvent as an internal reference. Coupling constants (J) are given in hertz. Spectral assignments were based in part on the two-dimensional NMR experiments (COSY, NOESY, HSQC, and HMBC). Numbering of hydrogen and carbon nuclei used to describe the ^{1}H and ^{13}C NMR spectra is given in Figures 1, S1-S3.

Method A is based on the previously described procedure with some modifications [S3]. A solution of 1,2-bis(2-iodoethoxy)benzene (418 mg, 1 mmol) in acetonitrile (10 ml) and a solution of the corresponding polyamine (103 mg, 1 mmol of diethylenetriamine or 146 mg, 1 mmol of triethylenetetramine) in acetonitrile (10 ml) were simultaneously added dropwise to a suspension of K_2CO_3 (552 mg, 4 mmol) in acetonitrile (20 ml) with vigorous stirring. The mixture was stirred at room temperature for 3-4 days. The solvent was evaporated under vacuum. The product was extracted with water from the residue, then with chloroform from water. The organic layer was separated and evaporated under vacuum to give desired azacrown compound **1a** or **1b**.

Method B. Bisamide crown compounds **2a,b** were prepared according to a previously described procedure with some modifications [S4,S5]. Bisamide crown compound **2a,b** (293 mg, 1 mmol of **2a** or 336 mg, 1 mmol of **2b**) was dissolved in 1 M $BH_3 \cdot THF$ solution (10 ml) at 0 °C and stirred under an inert atmosphere overnight. Excess BH_3 was quenched by adding water (10 ml). Next, 1 M HCl (10 ml) was added to the reaction mixture, followed by reflux for 4 h. The solution was then washed with $CHCl_3$ and the pH was adjusted to 10 by adding NaOH. The product was extracted with $CHCl_3$, and the solvent was evaporated under vacuum to give azacrown compound **1a,b** [S6,S7].

3,4,5,6,7,8,9,10,11,12-Decahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine (1a)

M.p. 117–119 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) 2.73 (t, 4H, H(6), *J* = 4.8, 5.3 Hz), 2.87 (t, 4H, H(7), *J* = 4.8, 5.3 Hz), 3.03 (t, 4H, H(5), *J* = 4.8 Hz), 4.13 (t, 4H, H(4), *J* = 4.8 Hz), 6.90 (m 4H, H(1,2)). ^{13}C NMR ($CDCl_3$, 600 MHz) 47.79 (C-7), 48.76 (C-5), 49.48 (C-6), 67.95 (C-4), 112.74 (C-2), 121.08 (C-1), 148.49 (C-3). Elemental analysis, found (%): C, 63.42; H, 8.77; N, 15.83; $C_{14}H_{23}N_3O_2$, calculated (%): C, 63.37; H, 8.74; N, 15.84. ESI-MS, calculated: *m/z* 265.0; found: *m/z* 266.2 $[M+H]^+$. The characteristics correspond to the literature [S6].

2,3,4,5,6,7,8,9,10,11,12,13,14,15-Tetradecahydro-1,16,4,7,10,13-benzodioxatetraaza-cyclooctadecine (1b)

M.p. 95-97 ºC. ^{1}H NMR ($CDCl_3$, 600 MHz): 2.80 (s, 4H, H(8)), 2.83 (br.s, 8H, H(6,7)), 3.05 (t, 4H, H(5), *J*=4.6), 4.14 (t, 4H, H(4), *J*=4.6), 6.90 (s, 4H, H(1, 2)). ^{13}C NMR ($CDCl_3$, 600 MHz): 48.60 (C-8), 48.64 (C-7), 48.66 (C-6), 49.00 (C-5), 68.16 (C-4), 112.74 (C-2), 121.03 (C-1), 148.44 (C-3). Elemental analysis, found (%): C, 61.27; H, 9.01; N, 17.17. $C_{16}H_{28}N_4O_2$; calculated (%): C, 62.31; H, 9.15; N, 18.17. ESI-MS, calculated, m/z: 308.4; found: 309.6 $[MH]^+$. The characteristics correspond to the literature [S7].

5,6,7,8,9,10-Hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (2a)

M.p. 233 ºC (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.94 (t, 4H, H(7), *J*=5.4), 3.48 (q, 4H, H(6), *J*=5.4, *J*=5.1), 4.49 (s, 4H, H(4)), 6.85-7.01 (m, 4H, H(1, 2)), 7.82 (br.s, 2H, NH). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 36.13 (C-6), 47.40 (C-7), 66.76 (C-4), 112.15 (C-2), 121.94 (C-1), 146.04 (C-3), 167.11 (C-5). Elemental analysis, found (%): C, 57.31; H, 6.55; N, 14.30. $C_{14}H_{19}N_3O_4$. Calculated (%): C, 57.33; H, 6.53; N, 14.33. ESI-MS, calculated, m/z: 293.3; found: 294.2 $[MH]^+$. The characteristics correspond to the literature [S5].

4,5,6,7,8,9,10,11,12,13-Decahydro-1,16,4,7,10,13-benzodioxatetraazacyclooctadecine-3,14(2*H*,15*H*)-dione (2b)

M.p. 142-144 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.74 (s, 4H), 2.80 (t, 4H, *J*=5.3), 3.48 (q, 4H, *J*=5.3, *J*=4.7), 4.58 (s, 4H), 6.92-7.02 (m, 4H), 7.17 (br.s, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz): 38.33, 48.26, 48.35, 68.05, 113.92, 122.62, 146.89, 168.12. Elemental analysis, found (%): C, 57.09; H, 7.23; N, 16.64; $C_{16}H_{24}N_4O_4$; calculated (%): C, 57.13; H, 7.19; N, 16.66. ESI-MS, calculated, m/z: 336.4; found: 337.4 $[MH]^+$. The characteristics correspond to the literature [S5].

NMR study

Samples of the Pb^{2+} complexes for the NMR measurements were prepared by dissolving the corresponding ligand and 2 eq. $Pb(ClO_4)_2$ in D_2O, followed by adjustment of the desired pD with small volumes of concentrated $HClO_4$ or NaOH. The accurate pD measurements in D_2O were obtained by direct reading in a D_2O solution using combined glass/AgCl electrode after appropriate calibration procedures by usage of standard buffers.

Table S1. ^{1}H NMR (400 MHz, 298 K) chemical shifts (Δδ, ppm) of **1a** recorded in D_2O solution at different pD values in the absence and in the presence of Pb^{2+}. See Figure 1 (main text) for proton labeling and pD values.

	1a	$\mathbf{H^+}$	$\mathbf{Pb^{2+}}$
H^1	6.94	6.99 (Δδ = 0.05)	6.99 (Δδ = 0.05)
$H^{1'}$			7.18 (Δδ = 0.24)
H^2			7.22 (Δδ = 0.28)
$H^{2'}$			7.05 (Δδ = 0.11)
H^{4a}	4.07	4.24 (Δδ = 0.14)	4.30 (Δδ = 0.23)
H^{4e}			4.10 (Δδ = 0.03)
$H^{4'a}$			4.21 (Δδ = 0.14)
$H^{4'e}$			3.73 (Δδ = -0.34)
H^{5a}	2.90	3.44 (Δδ = 0.54)	3.83 (Δδ = 0.93)
H^{5e}			3.03 (Δδ = 0.13)
$H^{5'a}$			3.52 (Δδ = 0.62)
$H^{5'e}$			3.13 (Δδ = 0.23)
H^{6a}	2.69	3.14 (Δδ = 0.45)	3.99 (Δδ = 1.30)
H^{6e}			3.09 (Δδ = 0.40)
$H^{6'a}$			3.87 (Δδ = 1.18)
$H^{6'e}$			2.83 (Δδ = 0.14)
H^{7a}	2.64	2.89 (Δδ = 0.25)	3.49 (Δδ = 0.85)
H^{7e}			2.80 (Δδ = 0.16)
$H^{7'a}$			3.76 (Δδ = 1.12)
$H^{7'e}$			2.63 (Δδ = -0.01)

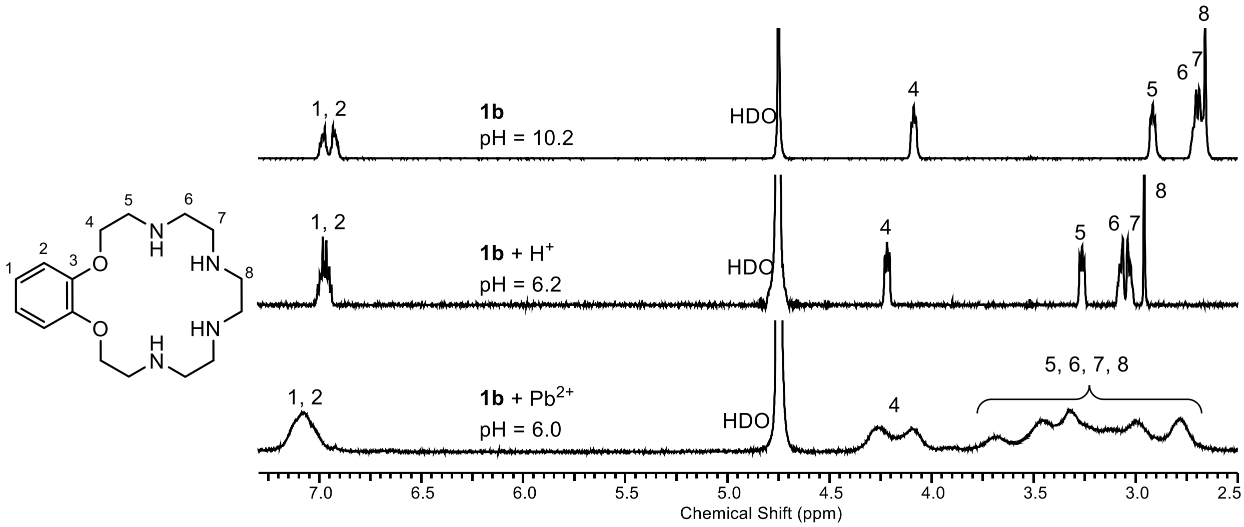

Figure S1. ^1H NMR spectra of free ligand **1b** (C_L = 10 mM, pD = 10.2) and in the presence of H^+ (C_L = 10 mM, pD = 6.2) and Pb^{2+} (C_L = 10 mM, pD = 6.0) in D_2O.

Table S2. ^1H NMR (400 MHz, 298 K) chemical shifts (Δδ, ppm) of **1b** recorded in D_2O solution at different pD values.

	1b	**H^+**
H^1	6.93	6.97 (Δδ = 0.04)
H^2		
H^4	4.09	4.22 (Δδ = 0.13)
H^5	2.92	3.26 Δδ = 0.34)
H^6	2.70	3.06 (Δδ = 0.36)
H^7	2.69	3.04 (Δδ = 0.35)
H^8	2.66	2.96 (Δδ = 0.30)

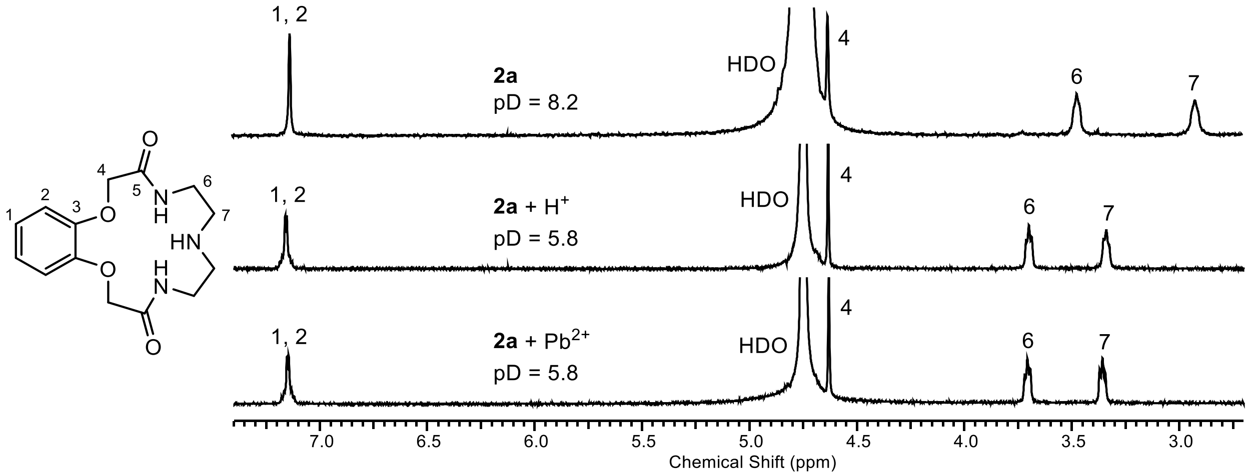

Figure S2. ^1H NMR spectra of free **2a** (C_L = 10 mM, pD = 8.2) and in the presence of H^+ (C_L = 10 mM, pD = 5.8) and Pb^{2+} (C_L = 10 mM, pD = 5.8) in D_2O.

Table S3. ^{1}H NMR (400 MHz, 298 K) chemical shifts (Δδ, ppm) of **2a** recorded in D_2O solution at different pD values in the absence and presence of Pb^{2+}.

	2a	**H^+**	**Pb^{2+}**
H^1	7.13	7.15 (Δδ = 0.02)	7.14 (Δδ = 0.01)
H^2			
H^4	4.63	4.63 (Δδ = 0)	4.63 (Δδ = 0)
H^6	3.47	3.70 (Δδ = 0.23)	3.71 (Δδ = 0.24)
H^7	2.92	3.34 (Δδ = 0.42)	3.36 (Δδ = 0.44)

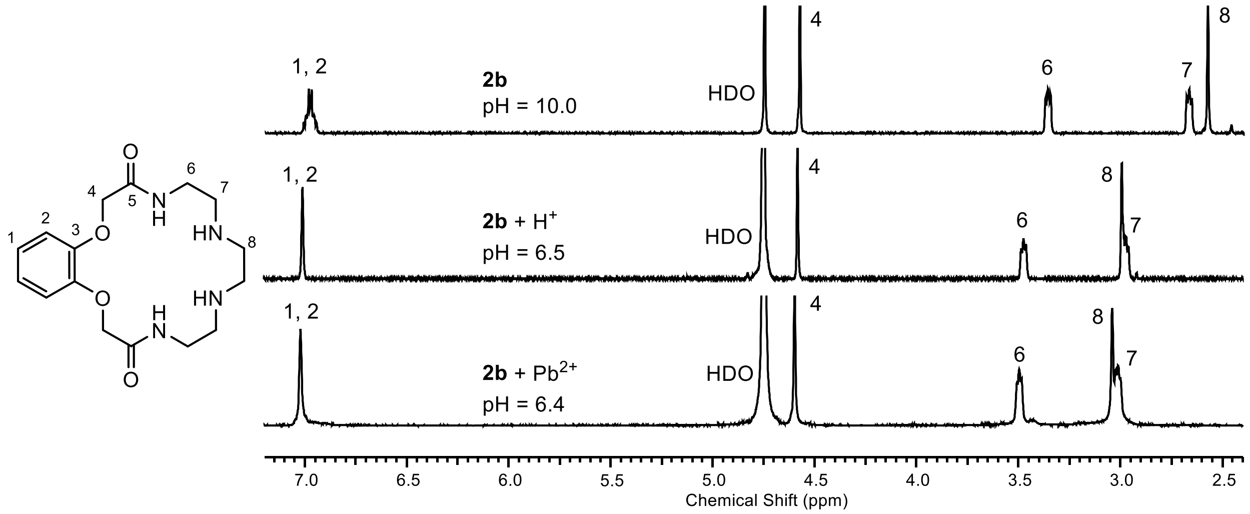

Figure S3. ^{1}H NMR spectra of free ligand **2b** (C_L = 10 mM, pD = 10.0) and in the presence of H^+ (C_L = 10 mM, pD = 6.5) and Pb^{2+} (C_L = 10 mM, pD = 6.4) in D_2O.

Table S4. ^{1}H NMR (400 MHz, 298 K) chemical shifts (Δδ, ppm) of **2b** recorded in D_2O solution at different pD values in the absence and presence of Pb^{2+}.

	2b	**H^+**	**Pb^{2+}**
H^1	6.97	7.01 (Δδ = 0.04)	7.02 (Δδ = 0.05)
H^2			
H^4	4.58	4.58 (Δδ = 0)	4.60 (Δδ = 0.02)
H^6	3.36	3.47 (Δδ = 0.11)	3.50 (Δδ = 0.14)
H^7	2.67	2.97 (Δδ = 0.30)	3.01 (Δδ = 0.34)
H^8	2.58	2.99 (Δδ = 0.41)	3.04 (Δδ = 0.46)

Potentiometric titration

Potentiometric titration was performed using an 848 Titrino Plus autotitrator equipped with a 5-ml autoburette and Metrohm combined pH glass electrode (model 60262100). A constant temperature of 25.0±0.1 °C was maintained in the cell using a water-jacketed titration vessel with a circulating bath. The combined pH glass electrode was calibrated by titration of a preliminarily standardized (by 0.1 N $Na_2B_4O_7$) solution of $HClO_4$ with NaOH solution of known concentration, and the equivalent point was calculated using the Gran method [S8]. The latter allowed E^0, the standard electrode potential, and the slope of electrode function to be defined. The ionic product of water in 0.1 M KNO_3 ($pK_w = 13.78$) was taken from the literature [S9]. To determine the protonation constants of the ligand, potentiometric titration of a solution (16 ml) containing ligand (1 mM), $HClO_4$ (5–6 mM), and KNO_3 (0.1 M) was conducted in a glass cell using 9–11×10^{-2} M NaOH as titrant. Titration was performed in the range of pH 2.5–11, with electrode electromotive force values measured after adding each 0.03-ml increment of standard NaOH solution. After each addition of titrant, an equilibrium was considered to be established if the potential variation was <0.2 mV min^{-1}. The stability constants of complexes were determined in a similar manner with the addition of an equimolar amount of $Pb(ClO_4)_2$. Protonation constants of the ligand and complexation constants were calculated using Hyperquad software. A minimum of two replicates were performed for titration procedures of L and Pb+L.

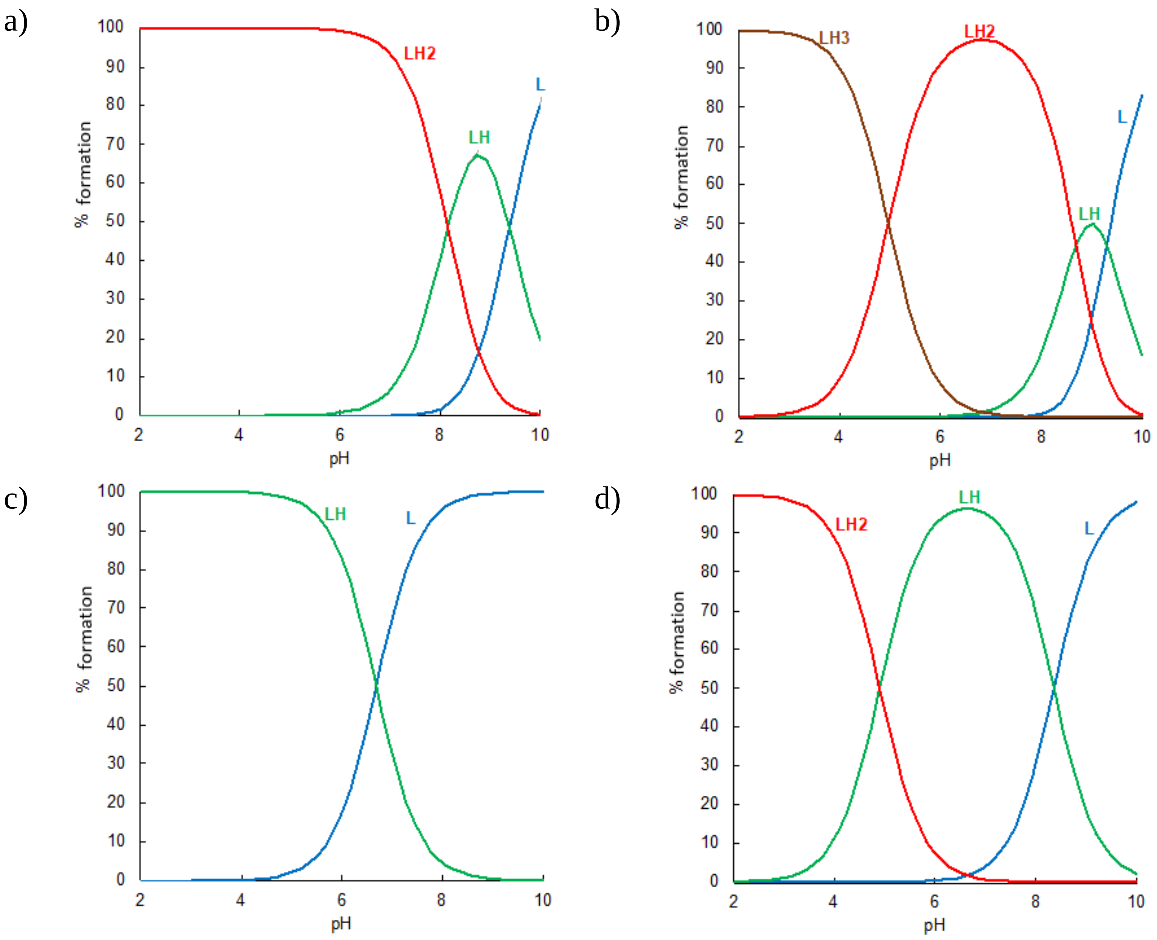

Figure S4. Speciation of ligands as a function of pH, $c(L)_{tot}$=1 mM, I=0.1 M KNO_3: a) **1a**; b) **1b**; c) **2a**; d) **2b**.

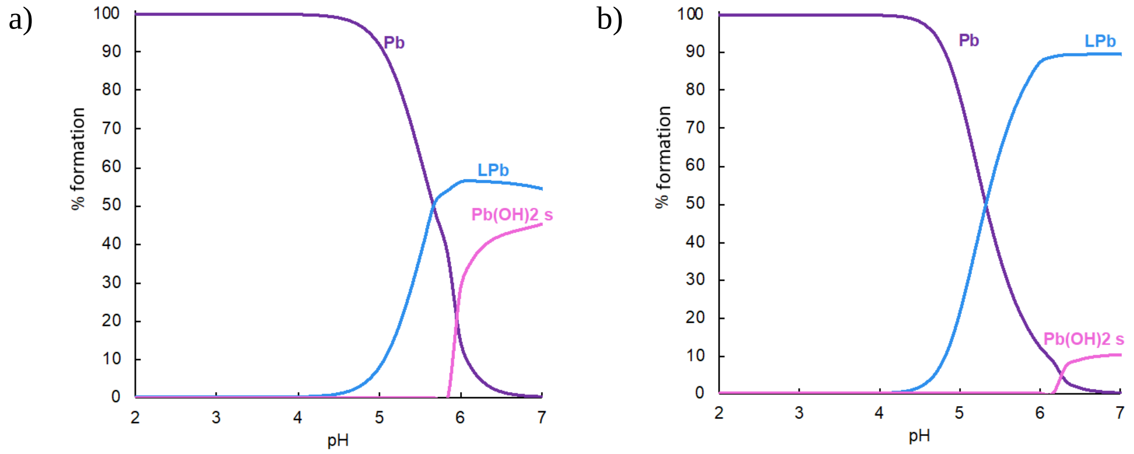

Figure S5. Speciation of Pb^{2+} in presence of **1a** (a) and **1b** (b) as a function of pH, $c(Pb^{2+})_{tot}=c(L)_{tot}=1$ mM, I=0.1 M KNO_3.

References

[S1] O. A. Fedorova, A. I. Vedernikov, O. V. Yescheulova, Y. V. Pershina, P. V. Tsapenko, S. P. Gromov, *Synth. Commun.*, 2002, **32**, 1909.

[S2] C. A. Strassert, L. E. Dicelio, J. Awruch, *Synthesis*, 2006, **5**, 799.

[S3] M. S. Oshchepkov, V. P. Perevalov, L. G. Kuzmina, A. V. Anisimov, O. A. Fedorova, *Russ. Chem. Bull., Int.Ed.*, 2011, **60**, 478.

[S4] H. Sharghi, R. Khalifeh, A. R. S. J. Beni, *J. Iran. Chem. Soc.*, 2010, **7**, 275.

[S5] A. D. Zubenko, B. V. Egorova, S. N. Kalmykov, N. E. Shepel, V. A. Karnoukhova, I. V. Fedyanin, Y. V. Fedorov, O. A. Fedorova, *Tetrahedron*, 2019, **75**, 2848.

[S6] G. Y. Aleshin, B. V. Egorova, A. B. Priselkova, L. S. Zamurueva, S. Y. Khabirova, A. D. Zubenko, V. A. Karnoukhova, O. A. Fedorova, S. N. Kalmykov, *Dalton Trans.*, 2020, **49**, 6249.

[S7] E. V. Matazova, B. V. Egorova, E. A. Konopkina, G. Y. Aleshin, A. D. Zubenko, A. A. Mitrofanov, K. V. Karpov, O. A. Fedorova, Y. V. Fedorov, S. N. Kalmykov, *MedChemComm*, 2019, **10**, 1641.

[S8] P. Gans, *Talanta*, 2000, **51**, 33.

[S9] F. H. Sweeton, R. E. Mesmer and C. F. J. Baes, *J. Solution Chem.*, 1974, **3**, 191.