Supplementary Material

Effect of the nature of donor atoms on the thermodynamic, kinetic and relaxation properties of Mn(II) complexes formed with some trisubstituted 12-membered macrocyclic ligands

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1 Supplementary Data

Details of the synthesis:

The ligands $PC3AM^{H}$ and $PC3AM^{Pip}$ were prepared by alkylating the pyclen macrocycle with a suitable bromoacetamide derivative obtained form commercial sources (2-bromoacetamide) or prepared according to published procedures (2-bromo-1-(piperidin-1-yl)ethanone).

$PC3AM^{H}$: A solution of pyclen (0.25 g, 1.21 mmol), commercially available 2-bromoacetamide (0.55 g, 4.00 mmol) and potassium carbonate (1.20 g, 8.68 mmol) in anhydrous acetonitrile was heated to 65 °C with stirring for 3 days. The solution was then filtered and the filtrate evaporated under vacuum. The resulting residue was redissolved water and acetonitrile mixture (50:50 by volume and s purified by preparative HPLC using Luna 10u-Prep C18(2) 100A (250×21.20 mm) column and ACN:H2O/TFA was applied as eluent (the TFA was present only in water at 0.005 M concentration). The product was collected by freeze-drying as white fluffy solid. Yield: 0.33 g (45%).

^{1}H NMR (270 MHz, D_2O): δ 8.06 ppm (t, 1H, aromatic ring), 7.52 ppm (d, 2H, aromatic ring), 4.82 ppm (s, 4H, $ArCH_2Nring$), 4.25 ppm (s, 4H, glycinate methylene), 3.64 ppm (s, 2H, glycinamide methylene), 3.54 ppm (b, 4H, $NringCH_2$), 2.97 ppm (b, 4H, $NringCH_2$).

^{13}C NMR (270 MHz, D_2O): δ 174.78 ppm (1C, amide carbonyl), 168.60 ppm (2C, amide carbonyl), 150.31 ppm (1C, aromatic ring), 141.34 ppm (1C, aromatic ring), 123.37 ppm (1C, aromatic ring), 60.00 ppm (2C, $ArCH_2Nring$), 57.51 ppm (2C, acetamide methylene), 56.29 ppm (1C, acetamide methylene), 55.23 ppm (2C, $NringCH_2$), 52.02 ppm (2C, $NringCH_2$);

ESI-MS m/z (%): 378.3 (100%) $[M+H]^+$, 400.2 (34%) $[M+Na]^+$= 416.2 (14%) $[M+K]^+$.

Anal. Calcd for $PCTMA^H$×1.95 CF_3COOH×0.90 H_2O: C, 39.96; H, 5.05; N, 15.54. Found: C, 40.28; H, 5.11; N, 15.61.

$PC3AM^{Pip}$: A solution of pyclen (0.25 g, 1.21 mmol), synthesized 2-bromo-1-(piperidin-1-yl)ethanone (0.80 g, 3.88 mmol) and potassium carbonate (1.20 g, 8.68 mmol) in anhydrous acetonitrile was heated to 65 °C with stirring for 3 days. The solution was then filtered and the filtrate evaporated under vacuum. The resulting residue was redissolved water and acetonitrile mixture (50:50 by volume and purified by preparative HPLC using Luna 10u-Prep C18(2) 100A (250×21.20 mm) column and ACN:H2O/TFA was applied as eluent (the TFA was present only in water at 0.005 M concentration). The product was collected by freeze-drying as white fluffy solid. Yield: 0.52 g (58%).

^{1}H NMR (270 MHz, D_2O): δ 7.92 ppm (dt, 1H, aromatic ring), 7.39 ppm (dd, 2H, aromatic ring), 4.73 ppm (s, 4H, $ArCH_2Nring$), 4.41 ppm (s, 4H, amide methylene), 3.69 ppm (s, 2H, amide methylene), 3.05-3.42 ppm (b, 20H, $NringCH_2$ and piperidine CH_2), 1.46-1.53 ppm (b, 18H, piperidine CH_2).

^{13}C NMR (270 MHz, D_2O): δ 169.05 ppm (1C, amide carbonyl), 168.71 ppm (2C, amide carbonyl), 158.73 ppm (1C, aromatic ring), 137.52 ppm (1C, aromatic ring), 137.35 ppm (1C, aromatic ring), 121.30 ppm (1C, aromatic ring), 62.44 ppm (2C, $ArCH_2Nring$), 58.10 ppm (2C, acetamide methylene), 55.22 ppm (1C, acetamide methylene), 53.01 ppm (2C, $NringCH_2$), 45.99 ppm (2C, $NringCH_2$) 42.93 42.86 (4C, piperidine ring), 44.44, 43.36 (4C, piperidine ring), 42.93, 42.86 (4C, piperidine ring), 26.24, 25.58, 24.43 (6C, piperidine ring), 25.99, 25.32 24.24 (3C, piperidine ring).

ESI-MS m/z (%): 582.4 (100%) $[M+H]^+$, 604.4 (41%) $[M+Na]^+$= 620.4 (17%) $[M+K]^+$.

Anal. Calcd for $PCTMA^{Pip}$×1.90 CF_3COOH×0.75 H_2O: C, 52.23; H, 6.70; N, 11.84. Found: C, 52.17; H, 6.61; N, 11.73.

2 Supplementary Table S1. Protonation constants of the hexa-, hepta- and octadentate ligands (*I*=0.15 M NaCl, 25 °C) compared to the data available in the literature.

Ligand	*I*	log K_1^H	log K_2^H	log K_3^H	log K_4^H	log K_5^H	log K_6^H	Σ logK_2^H
DO3A	**0.15 M NaCl**	**10.07(5)**	**8.93(6)**	**4.43(9)**	**4.11(7)**	**1.88(7)**	**–**	**19.00**
$DO3A^n$	0.1 M NMe_4Cl	11.59	9.24	4.43	3.48	–	–	20.83

DO3A[o]	0.5 M KNO_3	11.96	9.66	4.23	3.51	–	–	21.62
DO3A[p]	0,1 M NaCl	10.51	9.08	4.36	–	–	–	19.59
DO3A[q]	0,1 M KCl	11.55	9.15	4.48	–	–	–	20.70
DO3AM[H]	**0.15 M NaCl**	**9.40(5)**	**6.28(8)**	**–**	**–**	**–**	**–**	**15.68**
DO3P	**0.15 M NaCl**	**12.55(2)**	**11.37(1)**	**8.57(2)**	**7.02(2)**	**5.36(2)**	**1.84(2)**	**23.92**
DO3P [l]	0.1 M $TBANO_3$	13.24	11.3	8.47	7.1	5.3	n.d.	24.54
DO3P [m]	0.1 M KCl	12.9	11.4	8.69	7.09	5.53	1.42	24.3
ODO3A	**0.15 M NaCl**	**8.74(2)**	**7.58(2)**	**3.99(3)**	**2.39(3)**	**–**	**–**	**16.32**
ODO3A [r]	0.1 M $NMe_4(NO_3)$	11.61	7.70	4.05	2.77	–	–	19.31
PCTA	**0.15 M NaCl**	**9.97(3)**	**6.73(5)**	**3.22(6)**	**1.40(9)**	**–**	**–**	**16.70**
PCTA [g]	0.1 M $NMe_4(NO_3)$	10.90	7.11	3.88	2.27	–	—	18.01
PCTA [h]	1.0 M KCl	11.36	7.35	3.83	2.12	1.29		18.71
PCTA [i]	0.1 M KCl	10.73	7.52	4.2	2.4	–	–	18.25
PC3AM[H]	**0.15 M NaCl**	**8.76(3)**	**4.10(4)**	**–**	**–**	**–**	**–**	**12.86**
PC3AM[Gly]	**0.15 M NaCl**	**8.85(1)**	**4.55(1)**	**3.81(1)**	**3.21(1)**	**2.80(1)**	**1.38(1)**	**13.40**
PC3AM[Gly] [j]	1.0 M KCl	9.35	4.47	3.73	3.20	2.72	–	13.82
PC3AM[Pip]	**0.15 M NaCl**	**8.74(1)**	**5.77(2)**	**1.42(9)**	**–**	**–**	**–**	**14.51**
DOTA	0.15 M NaCl	11.41	9.83	4.38	4.63	1.92	1.58	21.24
DOTA[a]	0.1 M NMe4Cl	11.74	9.67	4.68	4.11	2.37	–	21.41
DOTA[b]	0.1 M NMe4Cl	12.6	9.70	4.50	4.14	2.32	–	22.30
DOTA[c]	0.1 M NMe4Cl	11.9	9.72	4.60	4.13	2.36	–	21.62
DOTMA	0.15 M NaCl	11.72	9.06	4.74	5.59	1.92	–	20.78
DOTMA [k]	1.0 M KCl	12.59	9.28	4.66	5.78	1.84	–	21.87
DOTAM	**0.15 M NaCl**	**7.31(1)**	**6.07(1)**	**–**	**–**	**–**	**–**	**13.38**
DOTP	**0.15 M NaCl**	**13.6(2)**[a]	**12.23(3)**	**8.63(5)**	**7.45(4)**	**5.84(5)**	**5.02(5)**	**25.83**
DOTP [d]	0.1 M $NMe_4(NO_3)$	13.7	12.2	9.28	8.09	6.12	5.22	25.9
DOTP [e]	0.15 M NaCl	10.9	9.2	8.1	6.3	5.4	1.8 and 1.3 pK_7^H	20.1
DOTP [f]	0.1 M NMe_4Cl	12.6	9.3	8.0	6.0	5.2	–	21.9

***trans*-DO2A**	0.15 M NaCl	11.69	9.75	3.97	2.68	–	–	21.44
***cis*-DO2A**	0.15 M NaCl	11.44	9.51	4.14	1.55	–	–	20.95
***cis*-DO2AM$^{Me2.}$**	0.1 M KCl	10.14	8.38	–	–	–	–	18.52
***cis*-Bz2DO2AM^{Me2}**	0.1 M KCl	11.11	8.22	–	–	–	–	19.33
***cis*-DO2AM$^{Bz2.}$**	0.1 M KCl	9.62	6.90	–	–	–	–	16.52

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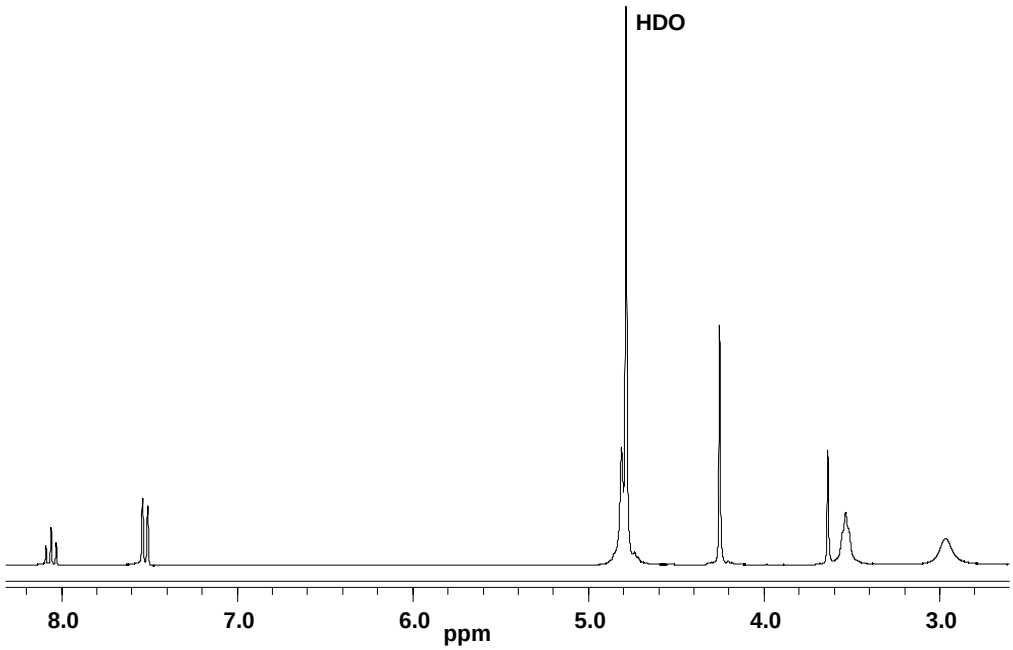
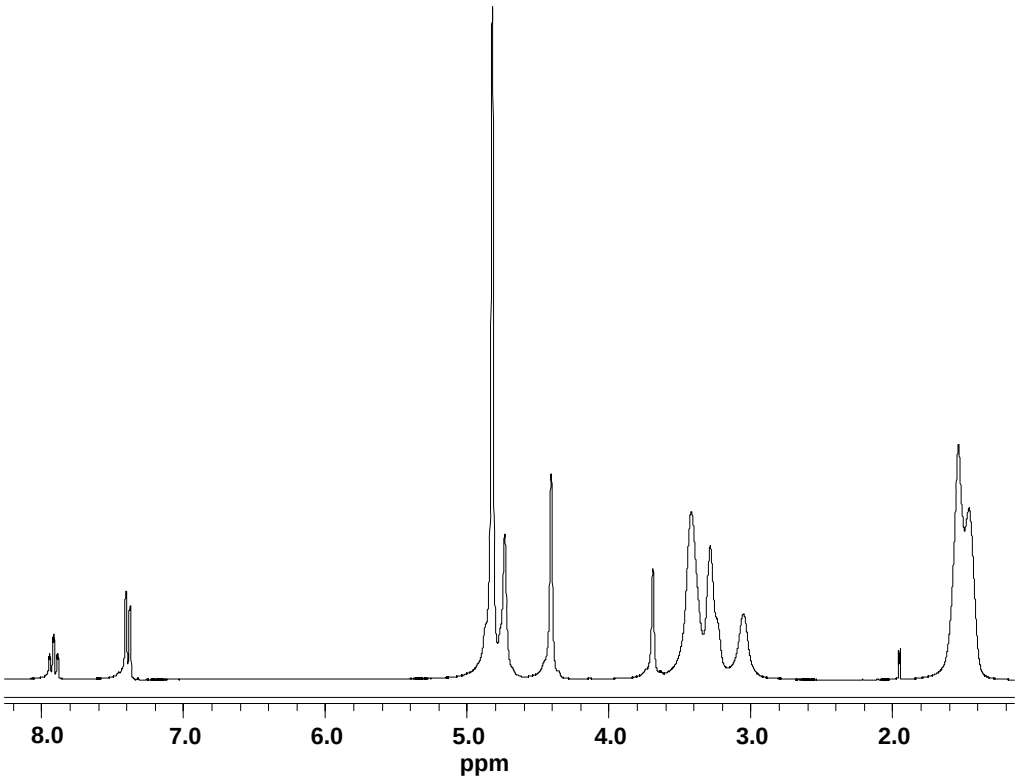
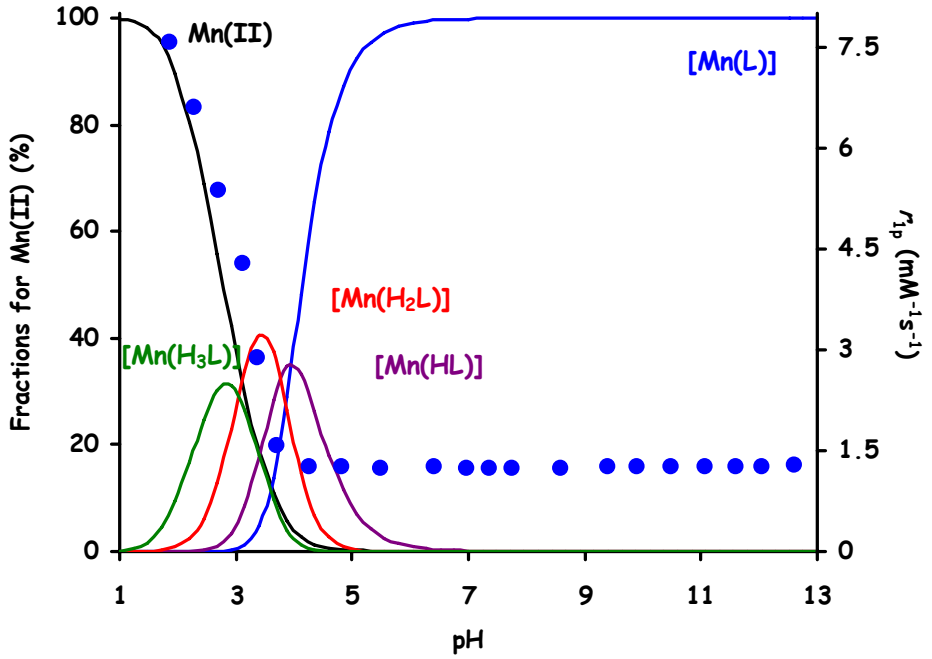
3 Supplementary Figures



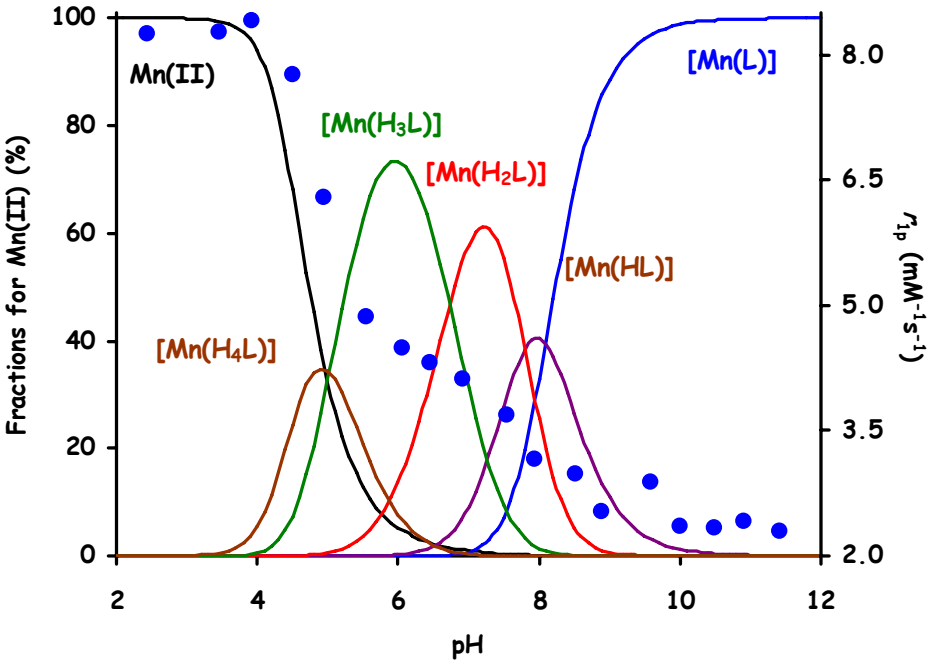
Supplementary Figure 1. ^{1}H-NMR of the PC3AM^{H} recorded in D_2O at 270 MHz at 25 ^{o}C.



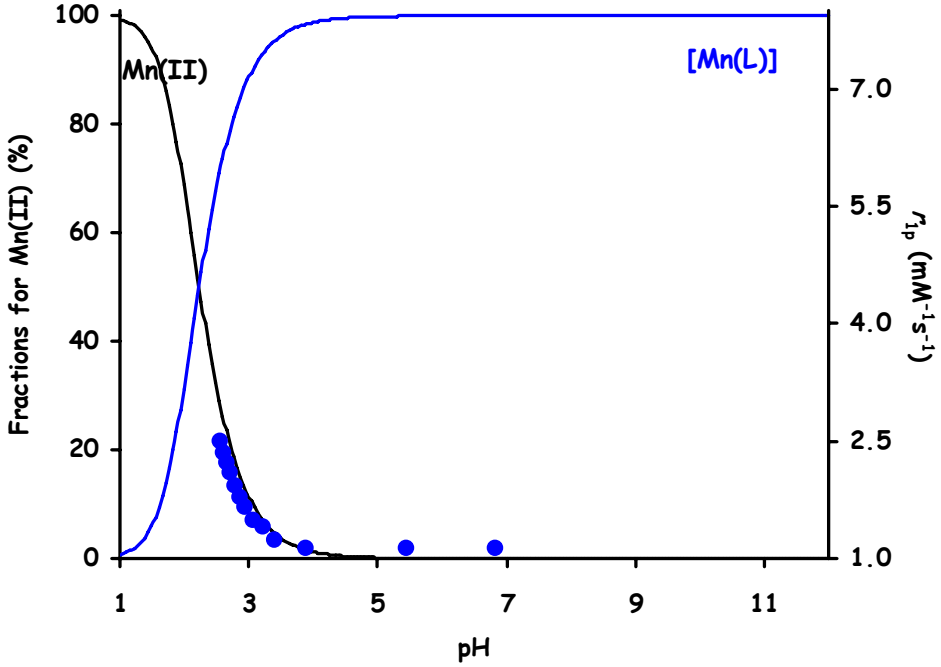
Supplementary Figure 2. ^{1}H-NMR of the PC3AM^{Pip} recorded in D_2O at 270 MHz at 25 ^{o}C.



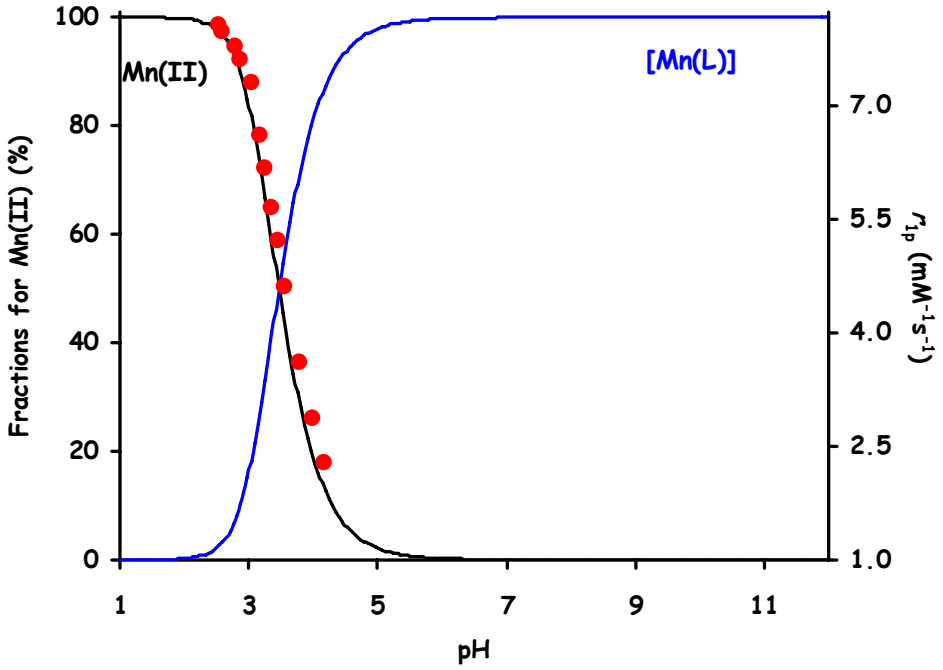
Supplementary Figure 3. Speciation distribution curves of $[Mn(DOTA)]^{2-}$ complex with the pH dependence of its relaxivity (I=0.1 M KCl, T=25 °C, 20 MHz).



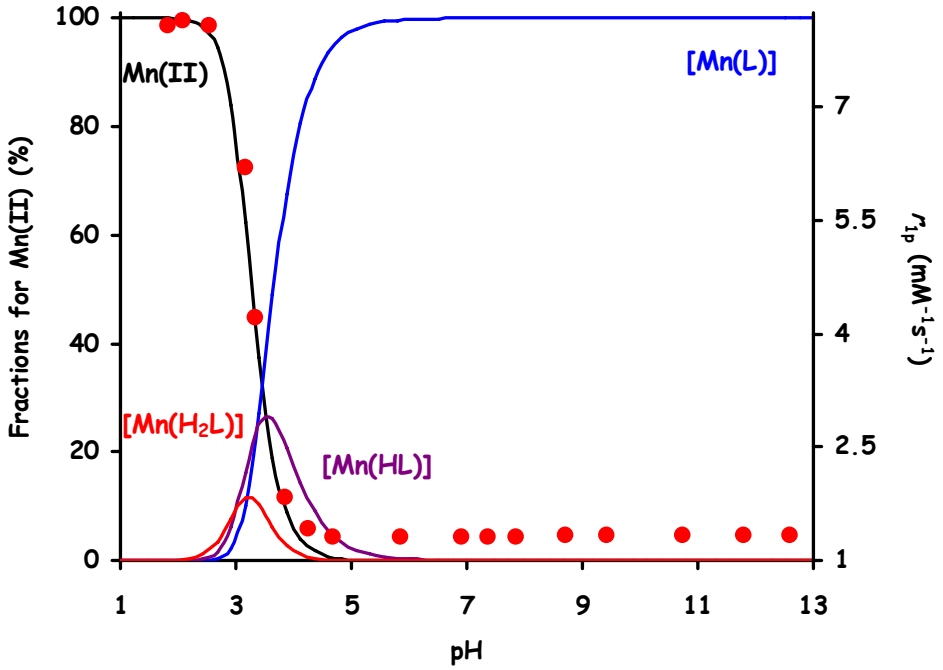
Supplementary Figure 4. The speciation distribution of $[Mn(DOTP)]^{6-}$ complex with the pH dependence of its relaxivity (I=0.15 M NaCl, T=25 °C, 20 MHz).



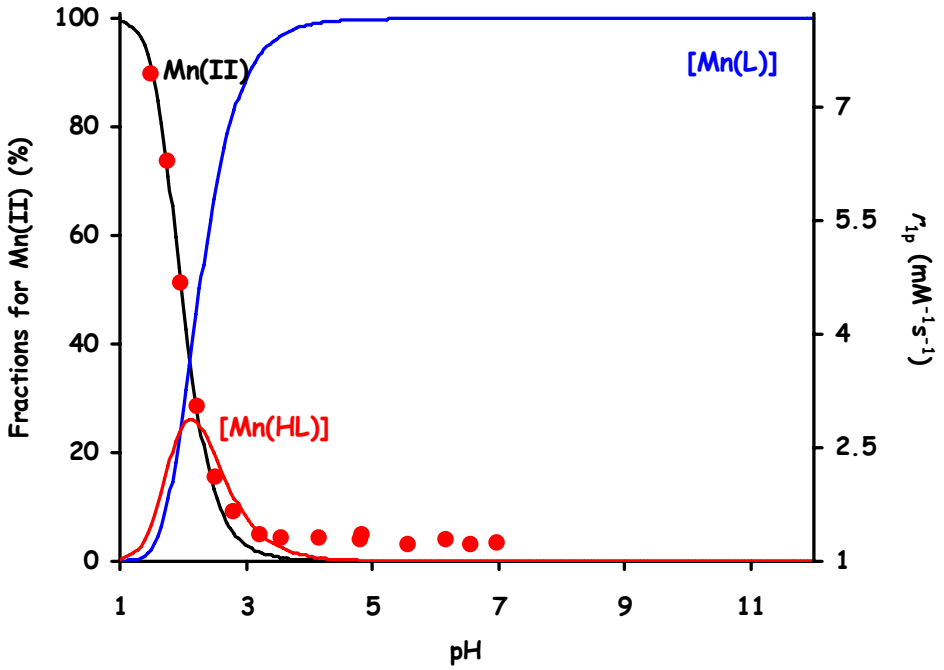
Supplementary Figure 5. Relaxivity (r_{1p}) measured for "batch" samples of $[Mn(DOTAM)]^{2+}$ complex as a function of pH and species distribution curves obtained from the analysis of the relaxivity data (T=25 ºC, I=0.15 M NaCl, 20 MHz).



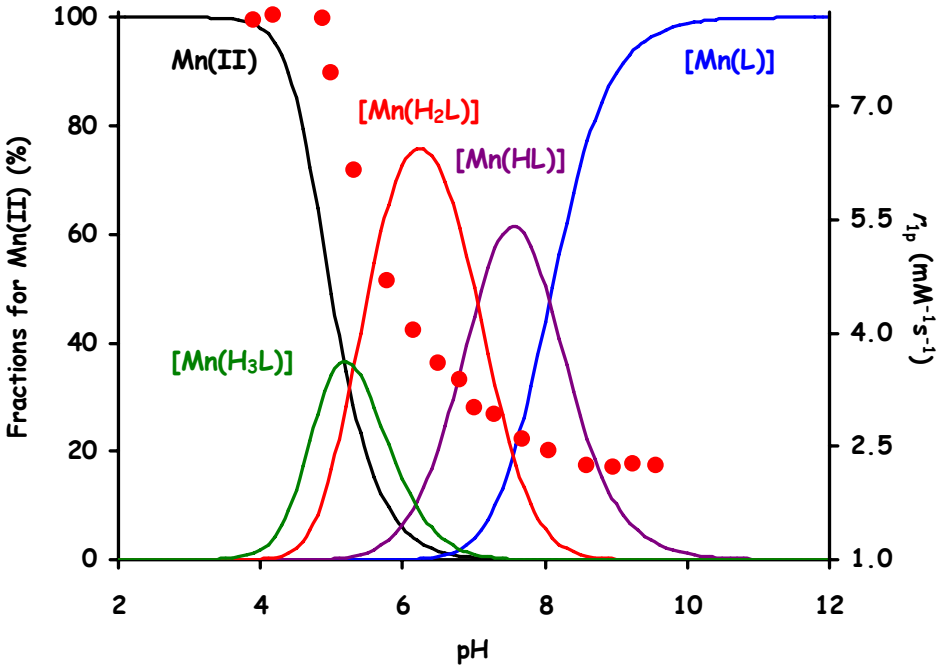
Supplementary Figure 6. Relaxivity (r_{1p}) measured for "batch" samples of $[Mn(DO3AM^{H})]^{2+}$ complex as a function of pH and species distribution curves obtained from the analysis of the relaxivity data (T=25 ºC, I=0.15 M NaCl, 20 MHz).



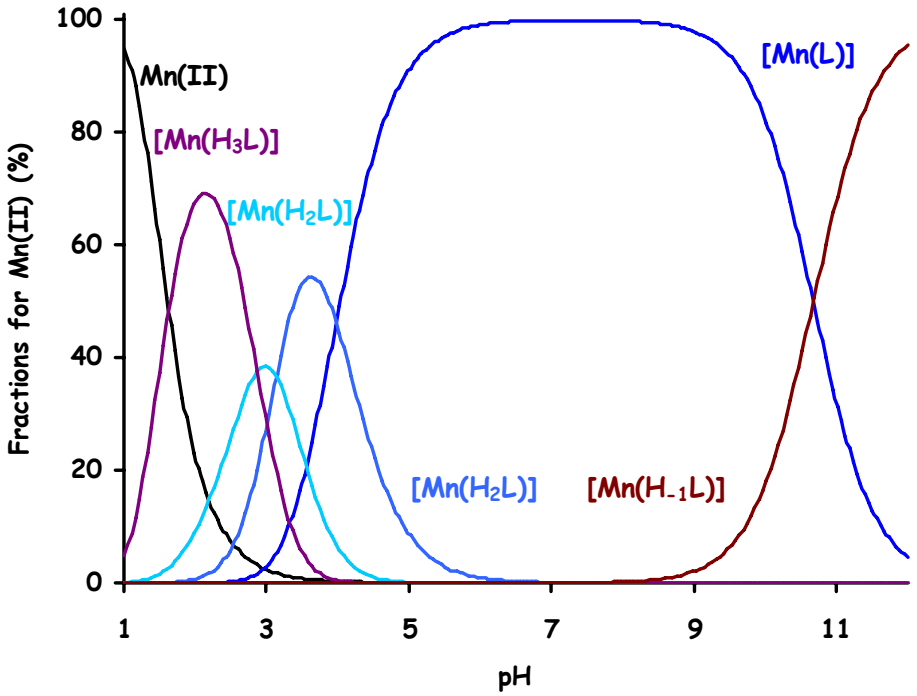
Supplementary Figure 7. Speciation distribution curves of $[Mn(DO3A)]^{-}$ complex with the pH dependence of its relaxivity (I=0.1 M KCl, T=25 °C, 20 MHz).



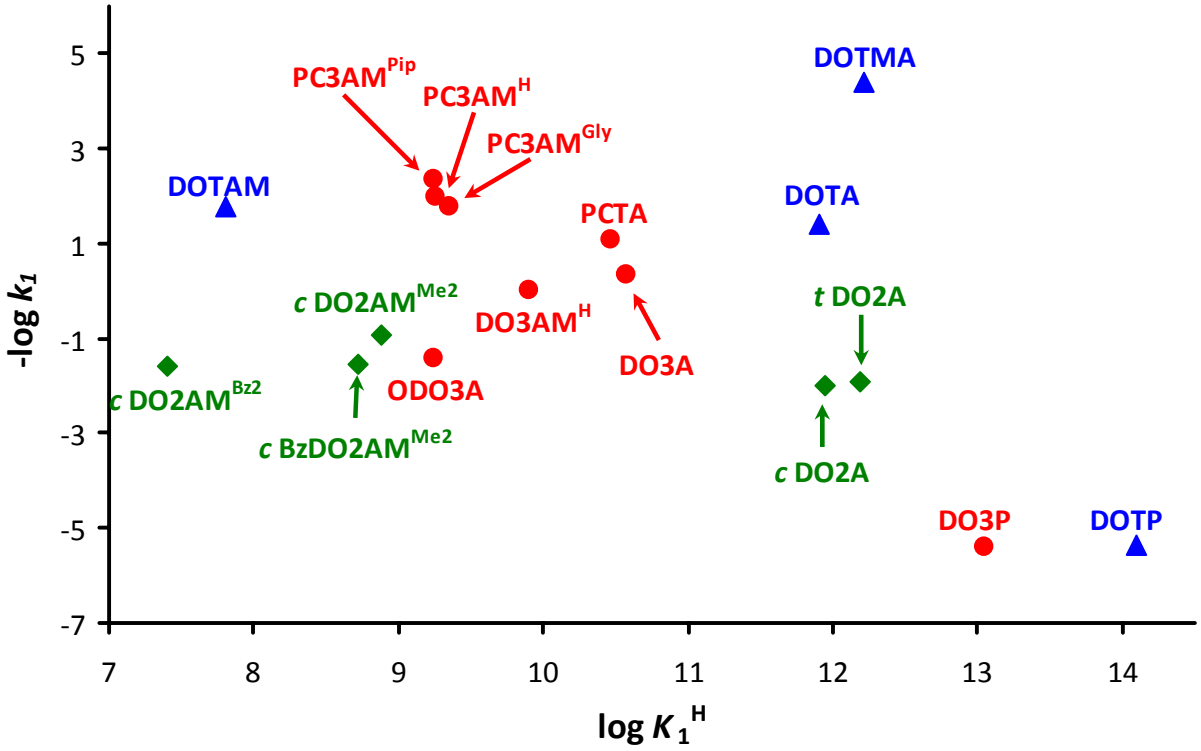
Supplementary Figure 8. Speciation distribution curves of $[Mn(PCTA)]^{-}$ complex co-plotted with the pH dependence of its relaxivity (*I*=0.15 M NaCl, *T*=25 °C, 20 MHz).



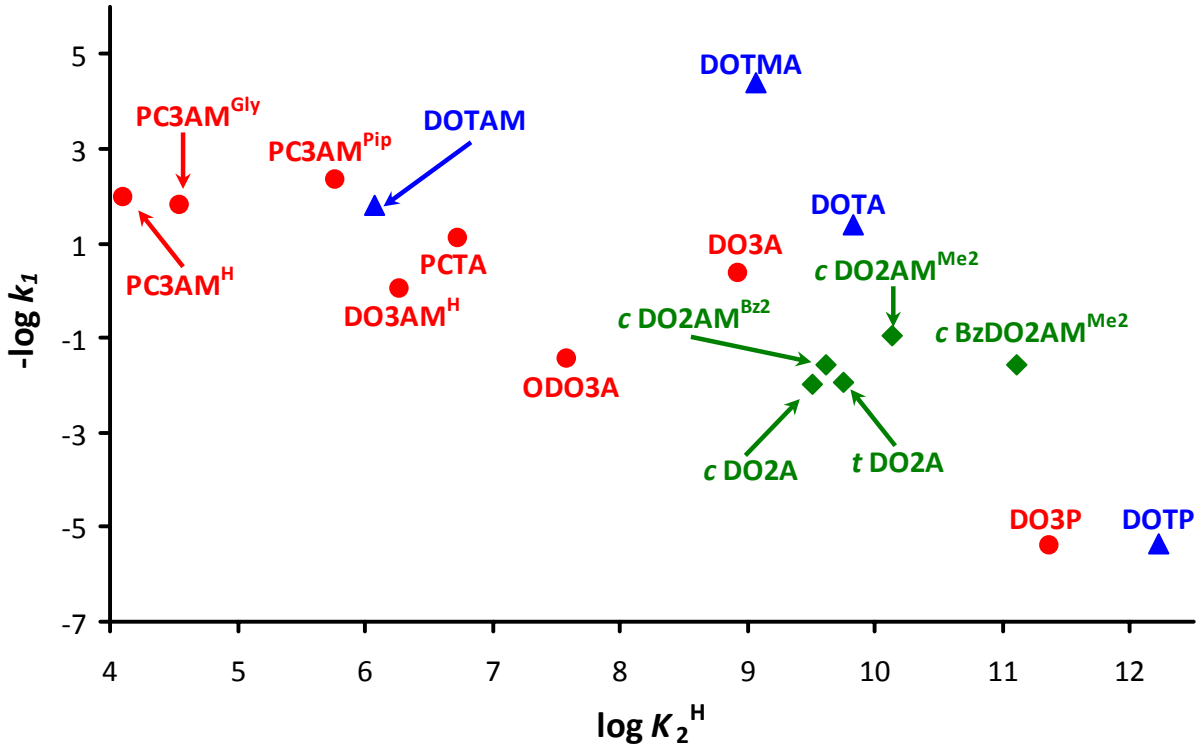
Supplementary Figure 9. Speciation distribution curves of $[Mn(DO3P)]^{4-}$ complex with the pH dependence of its relaxivity (I=0.15 M NaCl, T=25 °C, 20 MHz).



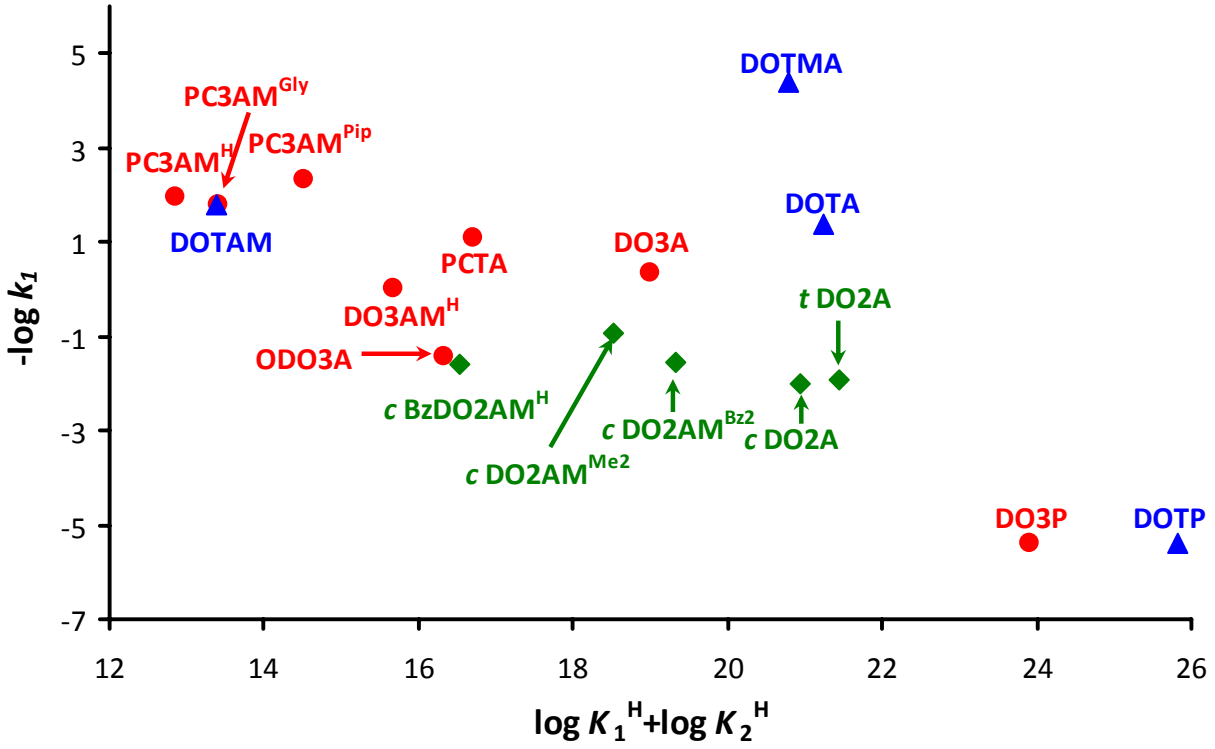
Supplementary Figure 10. Speciation distribution curves of $[Mn(PC3AMGly)]^{-}$ complex (c_L=c_{Mn2+}=0.002 M, I=0.15 M NaCl and T=25 °C).



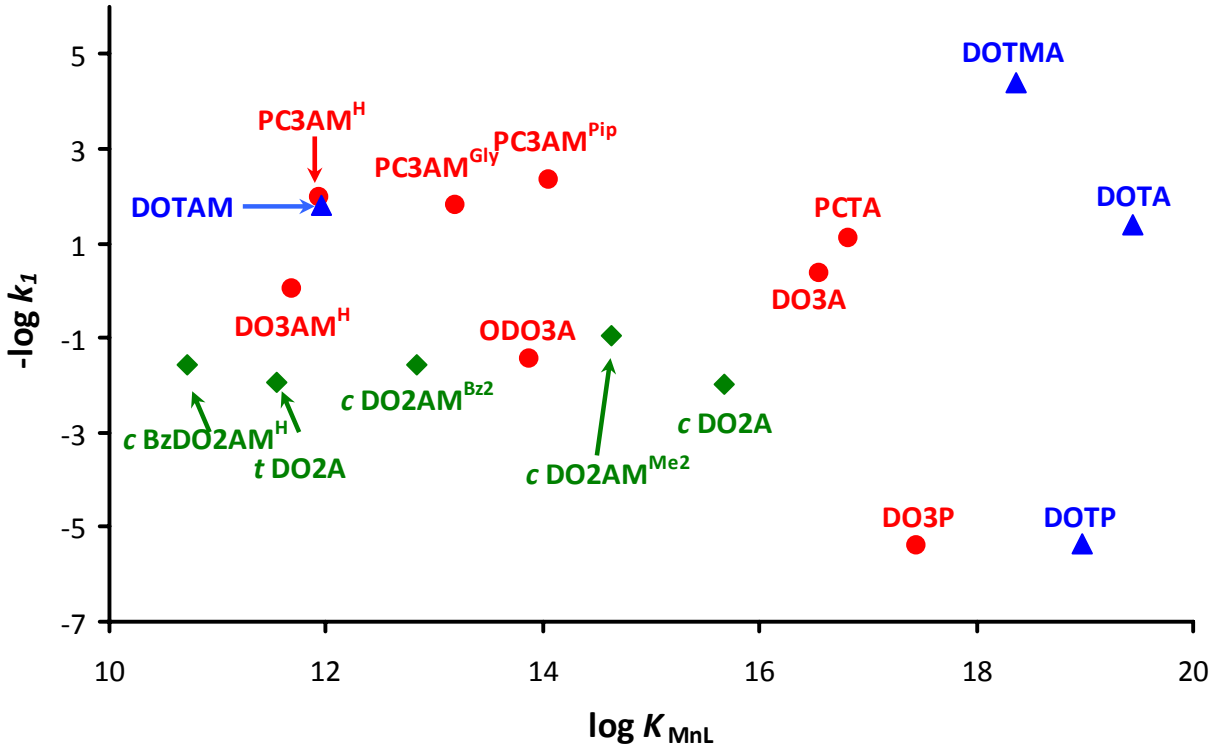
Supplementary Figure 11. Plot of – log k_1 values (k_1 is the rate constant of the acid catalyzed dissociation) as a function of log log K_1^H for derivatives of 12-membered macrocycles (I=0.15 M NaCl and 25 ^oC). Disubstituted ligands are shown in green, trisubstituted derivatives are in red (for these the -log k_1 = -1.61×log K_1^H + 15.64 with R^2 = 0.69) and tetrasubstituted derivatives are in blue.



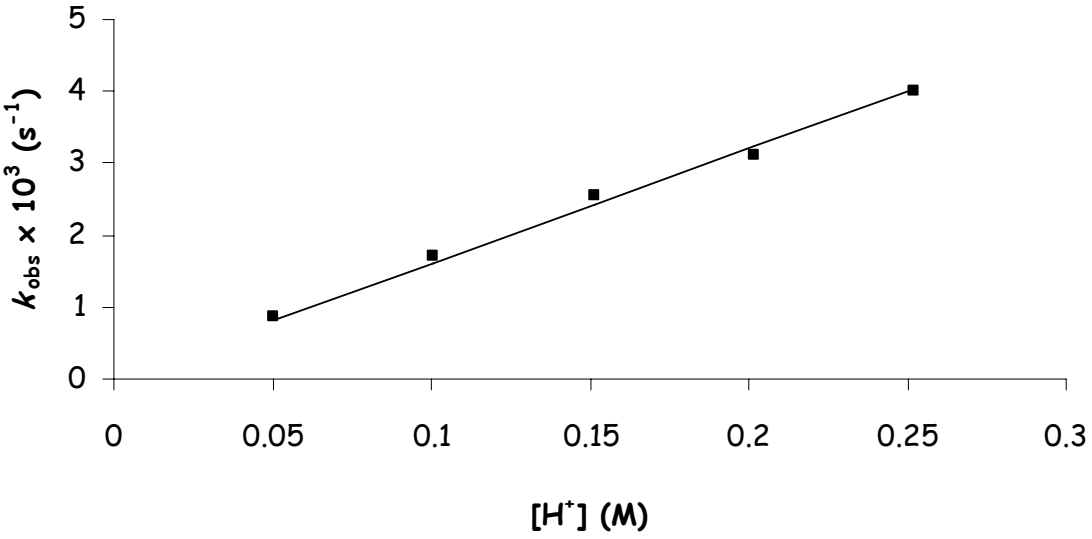
Supplementary Figure 12. Plot of – log k_1 values (k_1 is the rate constant of the acid catalyzed dissociation) as a function of log log K_2^H for derivatives of 12-membered macrocycles (I=0.15 M NaCl and 25 °C). Disubstituted ligands are shown in green, trisubstituted derivatives are in red (-log k_1 = -0.93×log K_2^H + 6.53 with R^2 = 0.77) and tetrasubstituted derivatives are in blue.



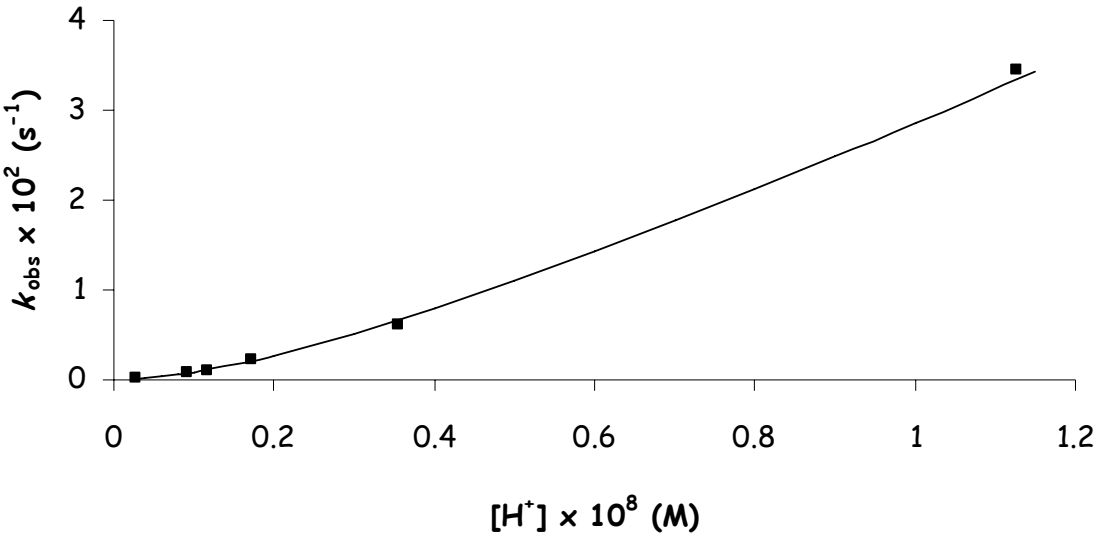
Supplementary Figure 13. Plot of – log k_1 values (k_1 is the rate constant of the acid catalyzed dissociation) as a function of log K_1^H+ log K_2^H for derivatives of 12-membered macrocycles (I=0.15 M NaCl and T=25 °C). Disubstituted ligands are shown in green, trisubstituted derivatives are in red (-log k_1 = -0.63×(log K_1^H + log K_2^H) + 10.52 with R^2 = 0.79) and tetrasubstituted derivatives are in blue.



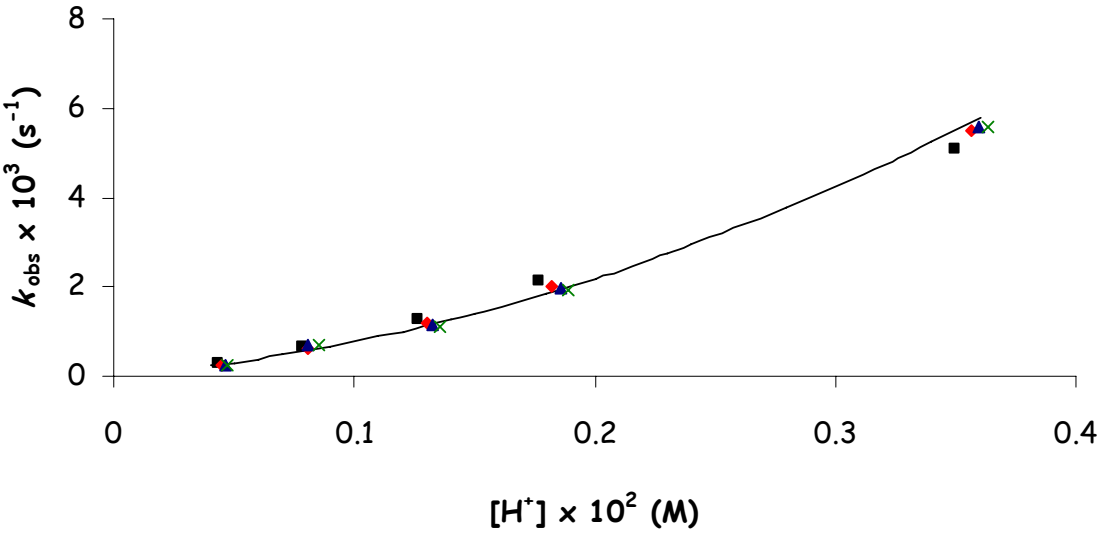
Supplementary Figure 14. Plot of – log k_1 values (k_1 is the rate constant of the acid catalyzed dissociation) as a function of log $K_{[Mn(L)]}$ for derivatives of 12-membered macrocycles (I=0.15 M NaCl and T=25 °C). Disubstituted ligands are shown in green, trisubstituted derivatives are in red (-log k_1 = -0.58 × log K_{MnL} + 8.42 with R^2 = 0.26) and tetrasubstituted derivatives are in blue.



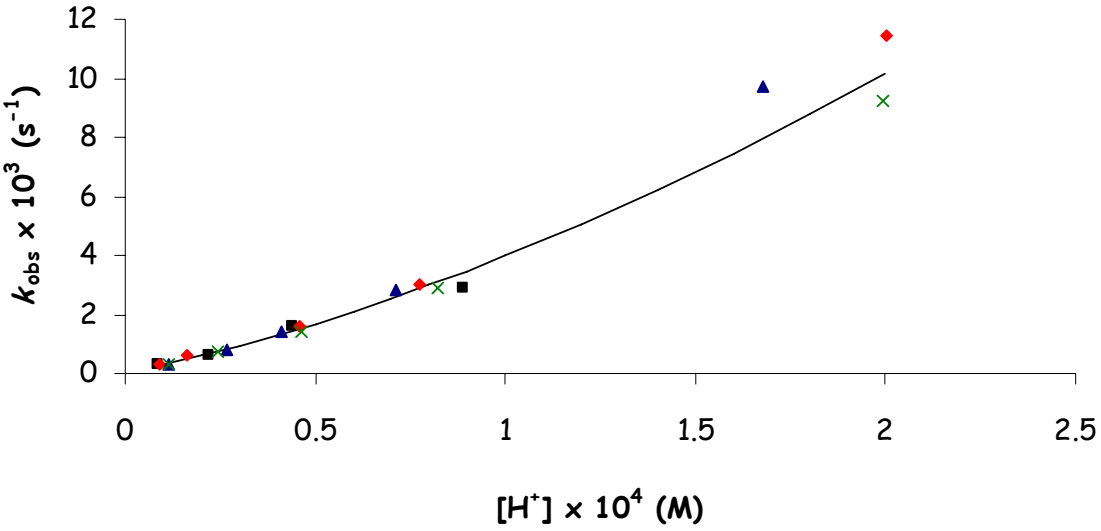
Supplementary Figure 15. Dependence of the pseudo-first-order rate constants (k_{obs}) on the concentration of H^+ ion for the $[Mn(DOTAM)]^{2+}$ complex (T=25 °C).



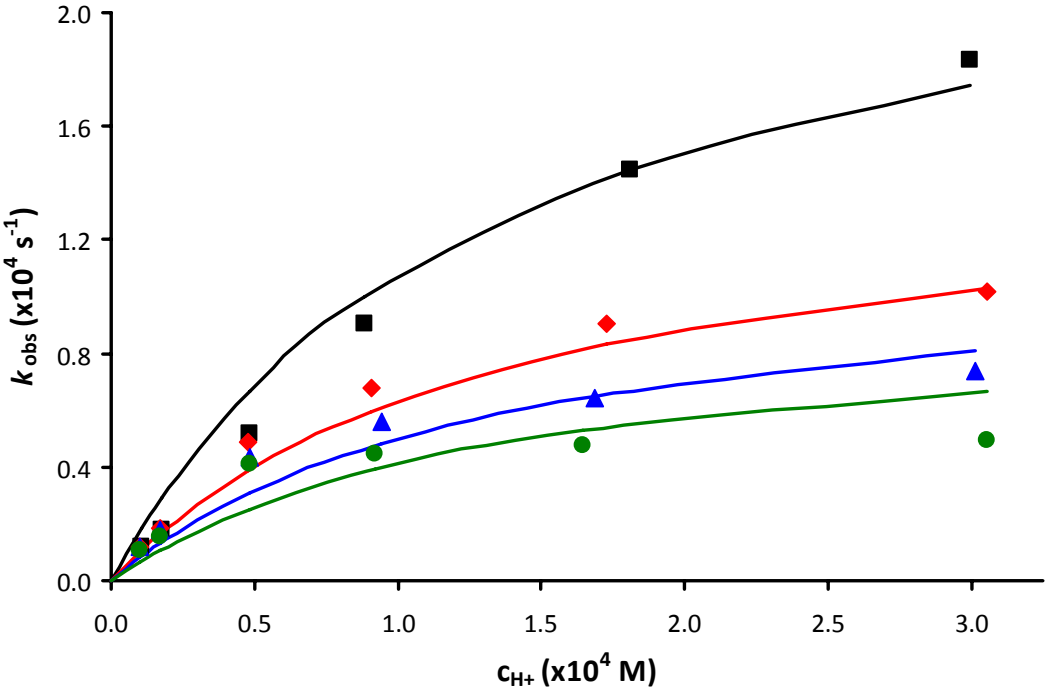
Supplementary Figure 16. Dependence of the pseudo-first-order rate constants (k_{obs}) on the concentration of H^+ ion for the $[Mn(DOTP)]^{6-}$ complex (T=25 °C).



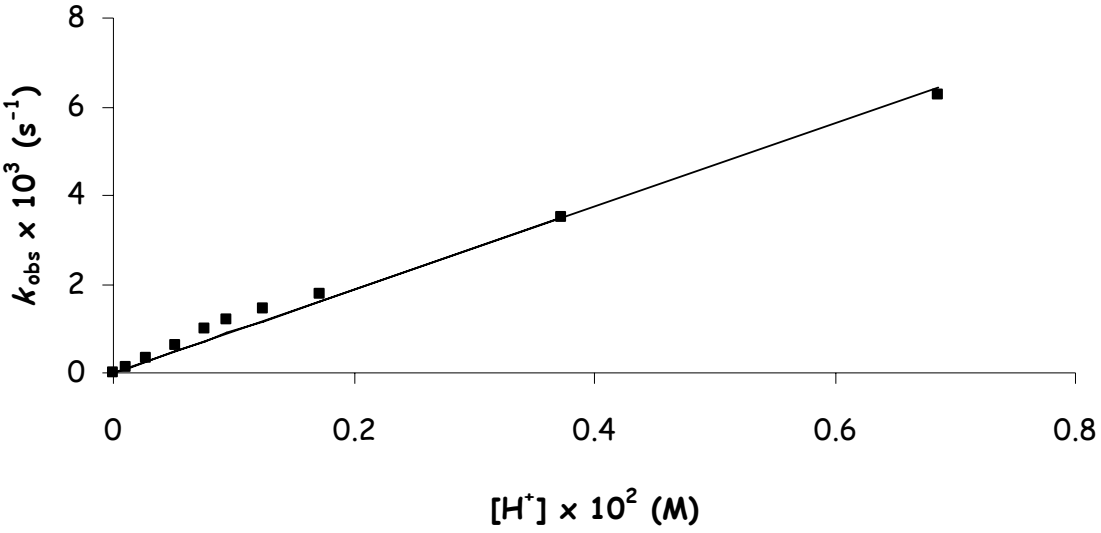
Supplementary Figure 17. Dependence of the pseudo-first-order rate constants (k_{obs}) on the concentration of the Cu^{2+} and H^+ ions for the $[Mn(DO3A)]^-$ complex. The excess of the exchanging metal ion was ×12(■), ×24(♦), ×32(▲) and ×41(×) folds (T=25 °C).



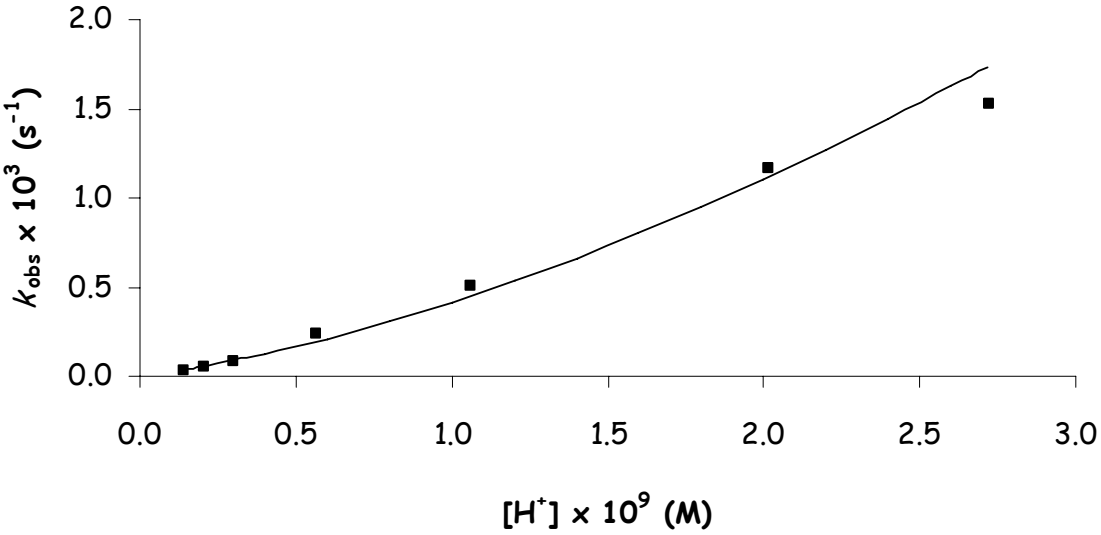
Supplementary Figure 18. Dependence of the pseudo-first-order rate constants (k_{obs}) on the concentration of the Cu^{2+} and H^+ ions for the $[Mn(ODO3A)]^-$ complex. The excess of the exchanging metal ion was ×10(■), ×20(♦), ×30(▲) and ×40(×) folds (T=25 °C).



Supplementary Figure 19. Dependence of the pseudo-first-order rate constants (k_{obs}) on the concentration of H^+ and Cu^{2+} ions for the $[Mn(DO3AM^H)]^{2+}$ complex (T=25 °C). The excess of the exchanging metal ion was ×10(■), ×20(♦), ×30(▲) and ×40(●) folds.



Supplementary Figure 20. Dependence of the pseudo-first-order rate constants (k_{obs}) on the concentration of H^+ ion for the $[Mn(DO3AM^H)]^{2+}$ complex (T=25 °C).



Supplementary Figure 21. Dependence of the pseudo-first-order rate constants (k_{obs}) on the concentration of H^+ ion for the $[Mn(DO3P)]^{4-}$ complex (T=25 °C).