

A Water-Soluble and Water-Coordinated Mn(II) Complex: Synthesis, Characterization and Phantom MRI Image Study

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Materials: All the chemicals and solvents were obtained from commercial sources and were used as supplied, unless noted otherwise. 2-aminobenzylamine was purchased from Sigma-Aldrich. *Tert*-butylbromoacetate and TFA were purchased from Spectrochem. $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$, KHCO_3 and solvents were obtained from Merck (India). HEPES buffer was purchased from SRL. Water used for the experiments was purified by using millipore-water purifier, Milli-Q, Merck.

Physical Methods: X-ray crystallographic data were collected using Super Nova, Single source at offset, Eos diffractometer. Structures were solved by direct methods using SHELXS-97 and refined with full-matrix least squares on F^2 using SHELXL-97. All the non-hydrogen atoms were refined anisotropically. FT-IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). UV-Vis/NIR spectra were recorded on Perkin Elmer, Lambda 750, UV/VIS/NIR spectrometer. Mass spectral data were obtained from either HRMS or QTOF MS Spectrometer. ^1H and ^{13}C NMR analyses were carried out using BRUKER 400 MHz NMR machine. The longitudinal (r_1) relaxivity at 1.41 T was measured using Bruker minispec mq60 NMR Analyzer. The longitudinal and transverse relaxivity at 14.1 T were measured using Bruker Avance II 600 MHz NMR microimager. MRI images were collected using either Bruker Avance II 14.1 T NMR machine or BRIVO MR355 1.5 T MRI Scanner.

Experimental Section:

Synthesis of $[\text{C}_{31}\text{H}_{50}\text{N}_2\text{O}_8]$, (A): To *tert*-butyl bromoacetate (11.70 g, 60 mmol) in DMF (15 mL), KHCO_3 (1.20 g, 120 mmol) was added and the suspension was cooled to 0°C . A solution of 2-aminobenzylamine (1.22 g, 10 mmol) in DMF (2 mL) was added drop wise to the stirred solution. The resulting reaction mixture was stirred at 0°C for 30 min. After that the stirring was continued further at room temperature (25°C) for 22 h. A saturated NaHCO_3 solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic phase was dried over Na_2SO_4 , filtered and then the solvent was removed completely to get the crude product as brown coloured oil. Trituration of the crude product with hexane afforded the pure compound as white solid. Yield = 2.76 g, 48 %. FTIR (KBr, cm^{-1}): 3434, 2978, 2933, 2914, 1742, 1642, 1457, 1370, 1247, 1156, 971, 843, 750, 601. ^1H NMR (CDCl_3 , 399.85 MHz): δ 7.82 (d, $J=7.2$ Hz, 1H), 7.47(d, $J=7.6$ Hz, 1H), 7.43–7.39 (m,1H), 7.24–7.21 (m,1H), 5.16 (s, 2 H), 4.87 (s, 1H), 4.83 (s, 1H), 4.30 (s, 1H), 4.26 (s, 1H), 3.90 (s, 4H), 1.43 (s, 18H), 1.38 (s, 18H) ppm. ^{13}C NMR (CDCl_3 , 100.55 MHz): δ 170.9, 164.6, 149.9, 134.3, 131.6, 126.4, 125.4, 84.5, 82.4, 58.3, 56.6, 54.9, 27.9 ppm. ESI-MS (+) m/z for $[\text{C}_{31}\text{H}_{50}\text{N}_2\text{O}_8 + \text{H}]^+$: Calcd, 579.3645 ; Found, 579.3734.

Synthesis of [C₁₅H₁₈N₂O₈], H₄bedik: Compound A (0.579 g, 1 mmol) in CH₂Cl₂/TFA (1:1, 4 mL) was stirred at room temperature (25 °C) for 16 h. The solvent was evaporated in *vacuo*. The product was obtained as white solid by adding excess diethyl ether. The solid was then filtered, washed with diethyl ether (10 mL) and then dried under vacuum. Yield = 0.339 g, 96%. FTIR (KBr, cm⁻¹): 3450, 3013, 2964, 2925, 1732, 1630, 1603, 1496, 1407, 1199, 968, 891, 782, 721, 601. ¹H NMR (CDCl₃, 399.85 MHz): δ 7.28 (d, *J* = 8 Hz, 1H), 7.20–7.16 (m, 1H), 7.06 (d, *J* = 6.8 Hz, 1H), 6.96–6.93 (m, 1H), 4.44 (s, 2 H), 3.87 (s, 4H), 3.76 (s, 4H) ppm. ¹³C NMR (CD₃OD, 100.55 MHz): δ 174.8, 169.3, 151.2, 134.3, 132.8, 127.9, 127.4, 125.9, 58.5, 56.6, 55.4, 49.8 ppm. ESI-MS (+) *m/z* for [C₁₅H₁₈N₂O₈ + H]⁺: Calcd, 355.1141; Found, 355.1175.

Synthesis of complex 1: To a solution of H₄bedik (0.177 g, 0.5 mmol) in water (3 mL) was added MnCl₂•4H₂O (0.082 g, 0.48 mmol) and stirred for 10 min. The solution became transparent and then the pH of the solution was adjusted to ~ 6.5 by adding aq. NaOH solution drop wise. Stirring was continued at room temperature (30 °C) for 24 hours. The resulted clear solution was kept at room temperature (25 °C) for slow evaporation to obtain crystal. The appeared colourless crystals were washed thoroughly with MeOH. The obtained crystals were suitable for single crystal X-ray diffraction study. Yield = 0.098g, 64% (or 32% if it is considered that maximum yield would be 50 in percentage scale). FTIR (KBr, cm⁻¹): 3389, 1591, 1496, 1412, 1316, 1102, 1010, 939, 905, 779, 748, 711, 618. ESI-MS (-) *m/z* for [C₁₅H₁₄MnN₂O₈ + H]⁻: Calcd, 406.0209; Found, 406.0095. Anal. Calcd. for C₁₅H₃₂Mn₂N₂O₁₇: C, 28.94; H, 5.18 ; N, 4.50. Found: C, 28.80; H, 4.68; N, 4.38.

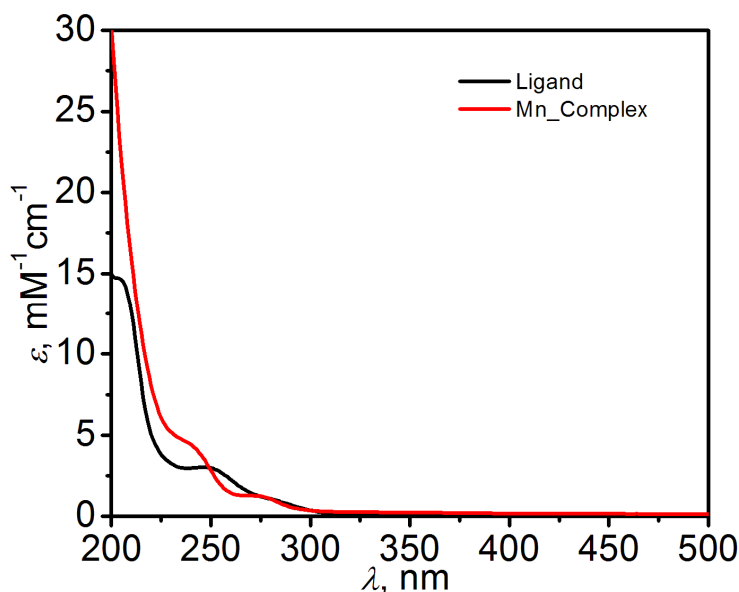


Figure 1: UV-Vis spectra of the aqueous solutions of the ligand H₄bedik and the complex.

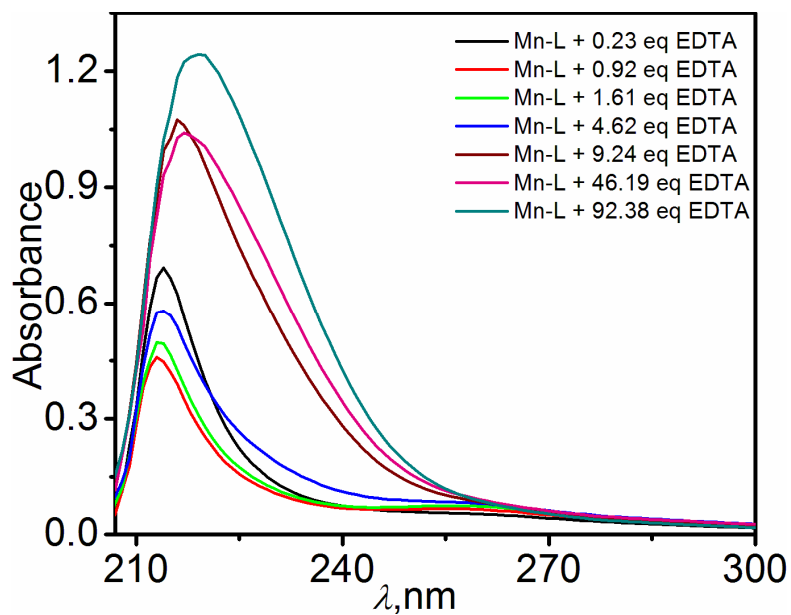


Figure 2. Spectral changes during the competitive study.

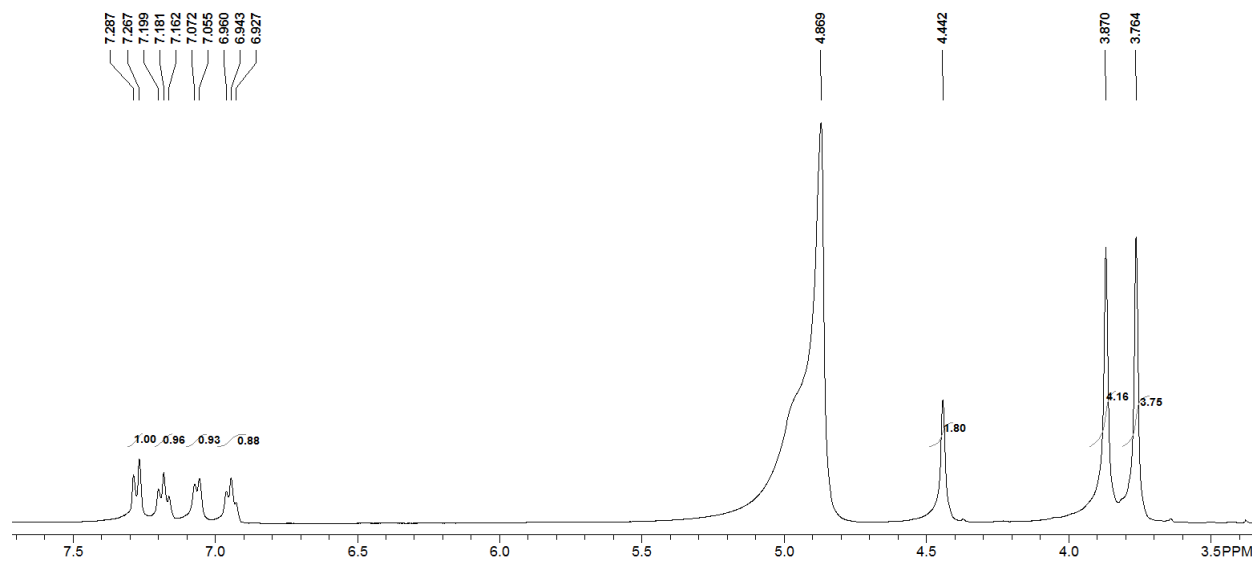


Figure 3. ^1H NMR spectrum of ligand H_4bedik measured in CD_3OD solvent.

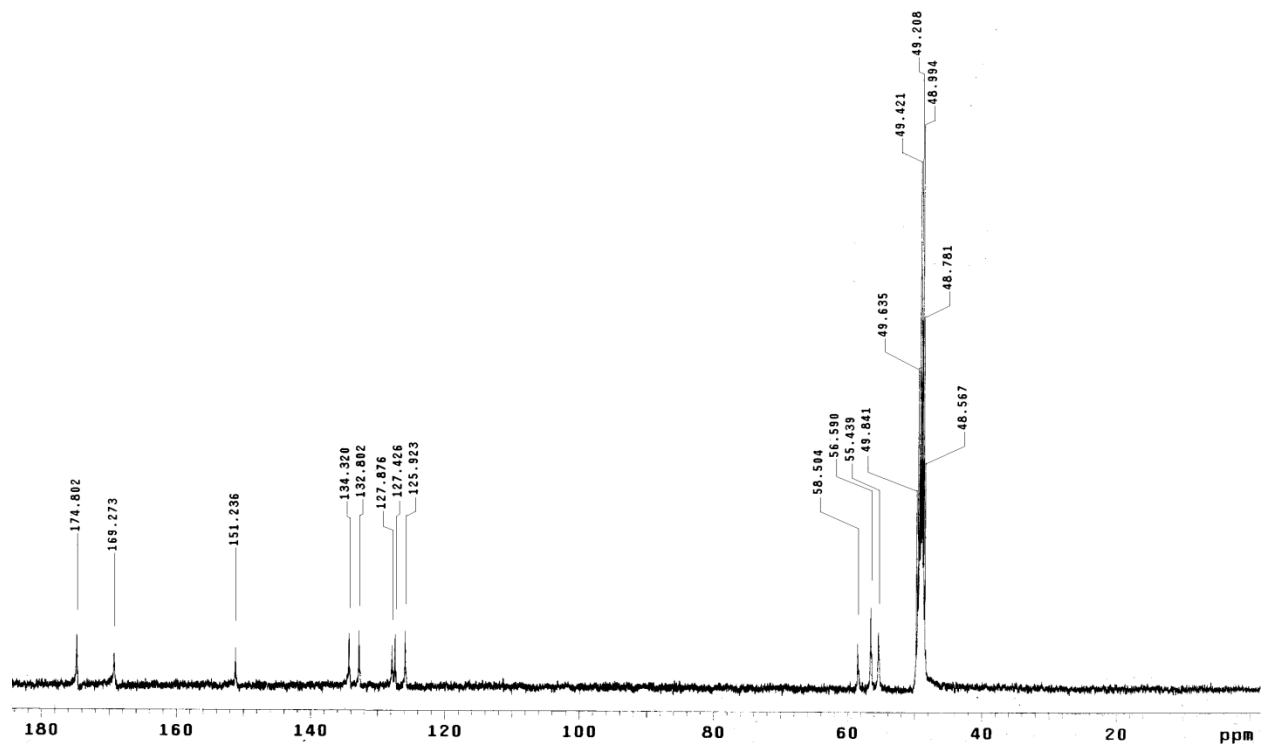


Figure 4. ^{13}C NMR spectrum of ligand H_4bedik measured in CD_3OD solvent.

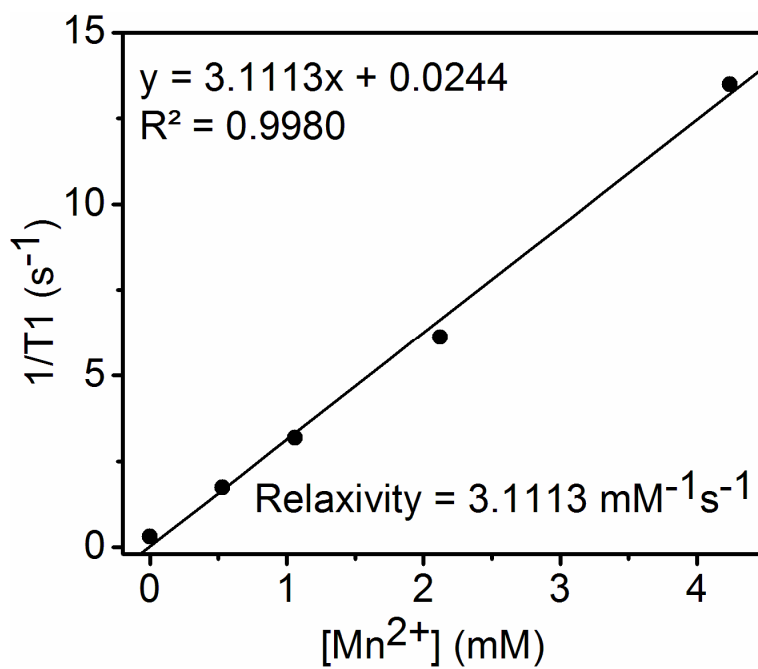


Figure 5. $1/T_1$ vs $[\text{Mn}(\text{II})]$ plot. Measurements were performed using complex **1** at 1.41 T, 25 °C, and pH = 7.4.

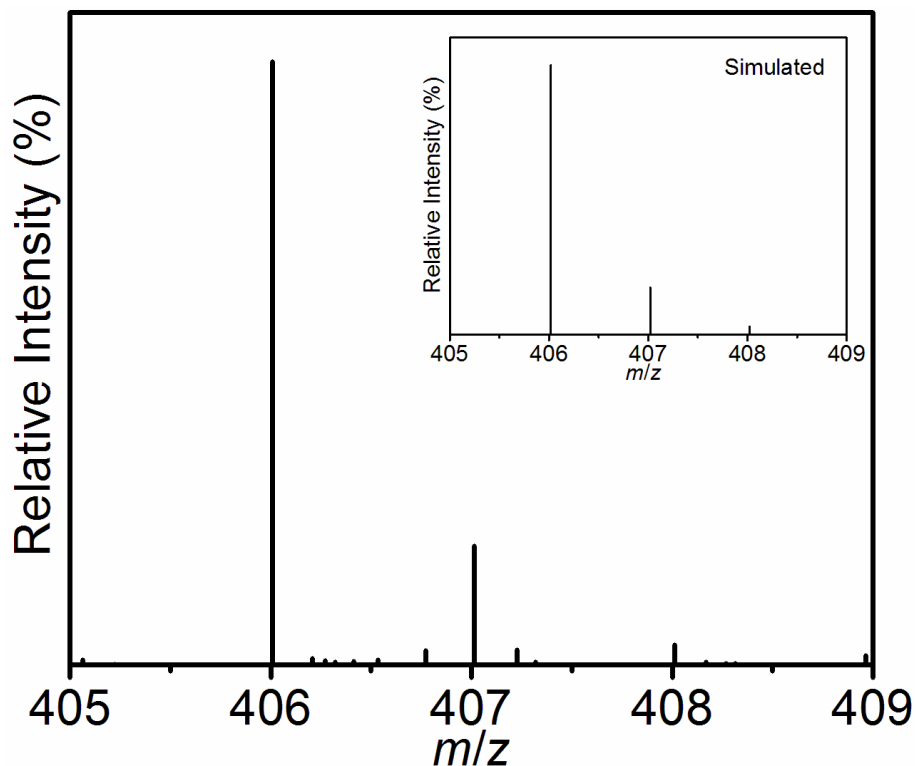


Figure 6. ESI-MS (-ve) mass spectrum of complex **1**. Simulated spectrum has been given as inset.

Table 1. Crystallographic and Structural refinement parameters for complex **1**.

Empirical formula	$C_{30}H_{64}Mn_4N_4O_{34}$
Formula weight	1244.61
Crystal habit, colour	Plates/ colourless
Crystal size, mm^3	$0.30 \times 0.28 \times 0.24$
Temperature, T	293(2)
Wavelength, λ (Å)	0.71073
Crystal system	triclinic
Space group	' $P-1$ '
Unit cell dimensions	$a = 10.4029(8)$ Å, $b = 11.7222(8)$ Å, $c = 11.8865(7)$ Å $\alpha = 71.602(6)^\circ$, $\beta = 64.303(7)^\circ$, $\gamma = 77.400(6)^\circ$
Volume, V (Å ³)	1233.77(15)
Z	1
Calculated density, $mg \cdot mm^{-3}$	1.675
Absorption coefficient, μ (mm^{-1})	1.106
$F(000)$	644.0
θ range for data collection	2.99 to 25
Limiting indices	$-12 \leq h \leq 12$, $-13 \leq k \leq 13$, $-14 \leq l \leq 11$
Reflection collected / unique	6911/3840

Completeness to θ	88.3% ($\theta = 25.00^\circ$)
Max. and min. transmission	0.767/0.725
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	3840/0/324
Goodness-of-fit on F^2	1.074
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0423$, $wR_2 = 0.0890$
R indices (all data)	$R_1 = 0.0583$, $wR_2 = 0.1012$
Largest diff. peak and hole	0.451/-0.385 e \AA^{-3}
