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Synthesis Soluble Non-Ion Transition Metal Manganese(II), Cobalt(II), Nickel(II) Complexes of Diethylenetriamine-N,N',N"-tri(acetyl-phydroxybenzoyl hydrazine)- N,N"- Bisacetic Acid as Potential Contrast Enhancement Agent

Xue-Li Zhang^a, Ding-Wa Zhang^b, Hui-Jiao Zhang^a, Shi-Ni He^a & Yao-Ting Chen^a ^a College of Chemistry and Chemical Engineering, Shenzhen University, Guangdong, P. R. China

^b School of Chemistry and Chemical Engineering, Provincial Key Laboratory of Coordination Chemistry, Jingganshan University, Jiangxi, P. R. China Accepted author version posted online: 01 Jul 2014.Published online: 09 Oct 2014.

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Synthesis Soluble Non-Ion Transition Metal Manganese(II), Cobalt(II), Nickel(II) Complexes of Diethylenetriamine-N,N', N"-tri(acetyl-*p*-hydroxybenzoyl hydrazine)- N,N"- Bisacetic Acid as Potential Contrast Enhancement Agent

XUE-LI ZHANG¹, DING-WA ZHANG², HUI-JIAO ZHANG¹, SHI-NI HE¹, and YAO-TING CHEN¹

¹College of Chemistry and Chemical Engineering, Shenzhen University, Guangdong, P. R. China ²School of Chemistry and Chemical Engineering, Provincial Key Laboratory of Coordination Chemistry, Jingganshan University, Jiangxi, P. R. China

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A novel ligand, diethylenetriamine-N,N',N"-tri(acetyl-*p*-hydroxybenzoyl hydrazine)-N,N"-bisacetic acid, and its three soluble nonion transition metal complexes, $ML \cdot nH_2O$ (M = Mn, n = 4; M = Co, Ni, n = 2) have been synthesized and characterized on the basis of elemental analysis, molar conductivities, ¹H NMR, FAB-MS, TG-DTA analysis, and IR methods. In addition, relaxivity of complexes are determined, The relaxivity (R₁) of MnL, CoL, NiL, and Gd(DTPA)²⁻ used as control are 6.33, 2.71, 2.60, and 4.34L·mmol⁻¹·s⁻¹, respectively. The spin-lattice relaxivity of MnL are larger than that of Gd(DTPA)²⁻. The results showed that complex of MnL may be a potential MRI contrast agent with high spin-lattice relaxivity, good solubility, low osmotic pressure due to non-ion complex.

Keywords: diethylenetriamine-N, N', N"-tri(acetyl-p-hydroxybenzoyl hydrazine)-N, N"-bisacetic acid, transition metal complexes, relaxation properties, MRI contrast agent

Introduction

Magnetic resonance imaging (MRI) is at present well established as a safe and efficient imaging technique for the human body in clinical diagnosis.^[1] Therefore, studying MRI contrast agents is more important. Several types of paramagnetic metal ion-chelate complexes with various ligands have been proposed for use as contrast-enhancing agents in MRI.^[1-3] Gd (DTPA)²⁻ was well-established contrast agent in clinical use for MRI due to its high relaxivity, high chemical stability, and low toxicity.^[3] However, its passive and nonspecific distribution in vivo limits its utility in focal lesion detection, and moreover its ionic characteristic leads to some side effects associated with its hyperosmolality at clinical dose.^[1,4,5] In attempts to decrease the side effects and improve the tissue- and/or organspecificity, considering that *p*-hydroxybenzoyl hydrazine molecule holds a hydroxyl which can enhance affinity to water and hydrazide is a very useful medicament that we designed and synthesized a novel ligand from DTPA and *p*-hydroxybenzoyl hydrazine. Its three soluble non-ion transition metal complexes holding promise of magnetic resonance imaging were synthesized, and relaxivity of complexes and $Gd(DTPA)^{2-}$ were determined in water solution. The relaxivity of MnL was'larger than that of $Gd(DTPA)^{2-}$. The results showed that complex of MnL may be a potential MRI with low osmotic pressure due to non-ion complex and high relaxivity.

Experimental

Materials

All MCO₃ (M = Mn, Co, Ni) compounds were purchased from Shanghai Yuelong Chemical Works. DTPA, EDTA and *p*-hydroxybenzoyl hydrazine were purchased from Shanghai Reagent Factory. All other chemicals used were of analytical grade.

Measurements

Carbon, hydrogen, and nitrogen were analyzed on an Elemental Vario EL analyzer. The metal content of the complexes were determined by titration with EDTA. Melting points of the compounds were determined on an XT4-100× microscopic melting point apparatus (Beijing Electrooptical Instrument Factory, China). The IR spectra were obtained in KBr discs on a Nicolet 5-DX spectrometer in the 4000–400 cm⁻¹ region.

Address corresponding to Ding-Wa Zhang, School of Chemistry and Chemical Engineering, Jingganshan University, Jiangxi, 343009, P. R. China. E-mail: zhangdingwa@hotmail.com.



Fig. 1. The synthetic route of the ligand.

¹H NMR spectra were recorded on a Varian VR 300-MHz spectrometer. Conductivity measurement was performed in DMF with a DDS-11A conductometer at 25°C (Shanghai Jingke Instrument Factory, China). The thermal behavior was monitored on a PCT-2 differential thermal analyzer (Beijing Guangxue Instrument Factory, China). Mass spectrum was performed on a VG ZAB-HS (FAB) instrument.

Relaxation time of complexes were measured referring to literature^[6] on a Bruker AC-80 NMR spectrophotometer, using the INVREC Au program at a 90° pulse width $t_p (90^\circ) = 2.8 \mu s$ by an inversion-recovery pulse sequence.

Preparation of Ligand

The ligand was synthesized as following: diethylenetriamine pentaacetic bi-anhydride (DTPAA) prepared according to references.^[7,8]

p-hydroxybenzoyl hydrazine (3 mmol) was dissolved in 25 cm³ of distilled water, put with DTPAA (1 mmol) and 5 cm³ of pyridine (Py) into the aqueous solution, and stirred for 24 h at room temperature. H₂O and Py were removed under reduced pressure, and the residue was diluted with H₂O and filtrated. Then drop the solution of EtOH and Et₂O (v/v = 1/2)

into filtrate, and a large amount of white precipitate separated out. Filter and was washed three times with a little EtOH. Finally, product was dried in a vacuum with P_4O_{10} . Recrystallization from H₂O-Et₂O-EtOH gained the final product. Yield: 88.9%. Melting point: 239–240°C. ¹H NMR (300 MHz, D₂O): $\delta 2.56$, 2.73 (s, each 4H, -NCH₂CH₂N-), $\delta 2.91$ (s, 10H, -CO-CH₂-N-), $\delta 3.34$ (s, 6H, -NH-NH-), $\delta 6.90$ (t, 6H, J = 7.8, J = 7.2, Ar-H). $\delta 7.41$ (t, 6H, J = 7.8, J = 7.2, Ar-H), $\delta 7.85$ (d, 3H, J = 7.8, Ar-H), 10.44 (s, 2H, -COOH). FAB-MS: m/z = 796. The synthetic route is shown in Figure 1.

Ligand was easily soluble in water, DMF, and DMSO; slightly soluble in ethanol; insoluble in acetone, chloroform, and Et_2O ; and quite stable at room temperature and normal pressure. Elemental analysis and empirical formulas are showed in Table 1. Elemental analysis was in good agreement with the structure. Mass spectrum reveals that the molecular ion peak was in accordance with the given structure. ¹H NMR and IR were conformed to the given structure.

Preparation of Complexes

First, 1 mmol of ligand was dissolved in 25 cm^3 of water to form a homogeneous solution which pH is approximately 3.

Table I. Elemental analyses and molar conductiv
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Empirical formula	Yield (%)	Color	C% (Calcd.)%	N% (Calcd.)%	H% (Calcd.)%	M (Calcd.)%	Λ S·cm ² ·mol ⁻¹
H ₂ L	88.9	white	52.58	15.75	5.27	16.2	
C35H41N9O13			(52.83)	(15.84)	(5.19)	(16.7)	
MnL·4H ₂ O	97.6	light yellow	45.26	13.73	5.21	5.72	12.6
C35H47N9O17Mn			(45.66)	(13.69)	(5.15)	(5.97)	
CoL·2H ₂ O	98.0	white	47.89	14.07	4.78	6.59	12.1
C ₃₅ H ₄₃ N ₉ O ₁₅ Co			(47.30)	(14.18)	(4.88)	(6.63)	
NiL·2H ₂ O	98.1	light green	37.44	11.512	4.80	6.53	13.0
C35H43N9O15Ni		2 0	(47.31)	(11.19)	(4.88)	(6.61)	

MnL·4H₂O CoL·2H₂O H_2L NiL·2H₂O Compound 3500b 3218-3487b 3220-3444b 3225-3422b VOH 3185 3186w 3184m 3189m $v_{\rm NH}$ $\nu_{C=O}$ (COOH) 1707s 1574s 1582s 1571s d_{HOH} 1226w 1215m 1217w 1218 ν_{C-N} $v_{as} (CO_2^-)$ 1550m 1552m 1547m 1395m $\nu_{\rm s} ({\rm CO}_2^-)$ 1398m 1410m 518w ν (M-O) 515w 521w

Table 2. Some main IR data of the ligand and its complexes.

s = strong m	= meduum: w =	week $b =$	bread

Then excess MnCO₃ was added to the system which was stirred on a water bath until the pH of the system is approximately 7. The excess MnCO₃ was filtered off. Then the filtrate was concentrated on a water bath until it is nearly dry. The light yellow powder was obtained after the mother liquor was removed. Finally, dry it in vacuum with P_4O_{10} . Yield: 97.6%. Other complexes were synthesized by the same way. Yield: CoL = 98.0%, NiL = 98.1%.

Results and Discussion

The Composition and General Character of Complexes

All of complexes are easily soluble in water, DMF, and DMSO; slightly soluble in ethanol, insoluble in acetone, chloroform, and Et₂O; quite stable at room temperature and normal pressure; and not sensitive to light. Elemental analyses and empirical formula are showed in Table 1. The elemental analyses show that the formulas of the complexes are ML • nH_2O (M = Mn, n = 4; M = Co, Ni, n = 2). Elemental analysis was in good agreement with the structures, respectively. The molar conductivities of the complexes are around 12.1–13.0 S·cm²·mol⁻¹ in DMF (Table 1), showing that all complexes are non-electrolytes in DMF.^[9]

Infrared Spectra

The main stretching frequencies of the IR spectra of the ligands and their complexes are tabulated in Table 2. It can be found that the characteristic absorption peaks of all complexes are similar. In the spectra of H_2L , the carboxylic ν (COOH) appears at 3500 cm⁻¹, the peak is absent in the complexes, but there is a broad peak at around

Table 4. Relaxivity of the complexes.

Table 3. Thermal analyses data of the compounds.

	D^{a}	M.p.	H ₂ O Loss	Decor	mpositio	n (°C)
Compound	°C		(Calcd.)%	t_1	t_2	t ₃
H ₂ L		240		378		
$MnL \cdot 4H_2O$	98-110		7.75 (7.82)	355	409	522
CoL·2H ₂ O	102-115		4.01 (4.06)	362	411	527
$NiL \cdot 2H_2O$	104–114		4.11 (4.05)	365	407	524

 $3218-3487 \text{ cm}^{-1}$ in the complexes. The peak at around 1571–1582 cm⁻¹ is assigned to δ_{HOH} , which shows that there is the coordinating H_2O in the complexes. The carboxylic $\nu_{(C=O)}$ of free ligands is at 1707 cm⁻¹, which does not appear in the complexes. However, two new vibrations of CO_2^- for v_{as} and v_s show themselves at 1550 and 1398 cm⁻¹, the $\Delta v(v_{as}-v_s)$ of which is approximately equal to 152 cm⁻¹. The IR spectra obtained when the sodium salt of the ligands is used as a control show that its v_{as} and v_s are at 1550 and 1410 cm⁻¹, respectively, and $\triangle v(v_{as}-v_s)$ is 140 cm⁻¹, suggesting that carboxyl oxygen atom coordinated to metal ion with single-dentate.^[10] The vibration at 1226 cm⁻¹ in the ligand was shifted to 1215 cm^{-1} , indicating the M-N band is really formed but weak.^[10] A new peak for the complex at 515 is assigned to v_{M-O} . This further confirms that the coordinate bond has formed between ligand and metal ion. The ligand provided three nitrogen atoms, five carboxyl oxygen atoms bonding to metal ion. At least one water molecule takes part in coordination to metal ion confirming DAT-TG.

Thermal Analyses

Some data of thermal analyses are listed in Table 3. The DTA curves of ligand have an endothermic peak at 240°C, but there is no weight lost on the corresponding TG curves, showing that this is a phase transition process, which is the same as the melting point of the ligand. In addition, there is one exothermic peak for the ligand at 278°C. The complexes have an endothermic peak between 98°C and 115°C. The corresponding TG curves show that the weight loss is equal to two water molecule or four water molecules. The results are in accordance with the composition of the complexes as determined by elemental analyses. Three exothermic peaks appear around $355-557^{\circ}$ C. The initial temperature of decomposition is greater than 278° C, which indicates that the thermal stability of the complexes is higher than that of the free

Compound	$[M]/ mmol \cdot L^{-1}$	t_0/s	T_1/s	$(1/T_1)_p/s^{-1}$	$R_1/mmol \cdot L \cdot s^{-1}$	Temp./ °C
H ₂ O		5.40	0.128			35
MnL·4H ₂ O	0.095	0.95	0.729	0.601	6.33	35
CoL·2H ₂ O	0.095	1.80	0.385	0.257	2.71	35
NiL·2H ₂ O	0.094	1.85	0.375	0.247	2.60	35
Gd-DTPA	0.148	0.90	0.770	0.642	4.34	35



Fig. 2. Measurement of relaxation time of MnL.

ligand which decomposed at 3478°C, showing that there may be large conjugation in the chelate ring in the complexes.

Relaxivity of the Complexes in Water Solution

The enhancement value of the relaxation rate of the complex for water protons is calculated by the equation.^[6]

$$(1/T_1)_p = (1/T_1)_o - (1/T_1)_d$$

 $R_1 = (1/T_1)_p / [M]$

Where $(1/T_1)_o$ is the observed solvent relaxation rate in the presence of a paramagnetic species, $(1/T_1)_d$ is the solvent relaxation rate in the absence of a paramagnetic species, and $(1/T_1)_p$ represents the additional paramagnetic contribution. [M] is the concentration of paramagnetic metal ion.

The relaxivity mainly consists of two components: the inner-sphere and outer-sphere relaxivity. The high relaxivity is favorable of tissue imaging. The relaxivity (R_1) of complexes and Gd(DTPA)²⁻ used as a control were given in Table 4. The results showed that the spin-lattice relaxivity of MnL was larger than that of Gd(DTPA)²⁻. Measurement of relaxation time of MnL was showed in Figure 2.

Conclusion

Taken together, non-ion complexes of MnL derivative from diethylene triamine pentaacetic acid and benzoyl hydrazine are prospective MRI contrast agent with high spin-lattice relaxivity and stability, low cost, good solubility and binding affinity for the serum protein.

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