Notes

Contribution from the Dipartimento di Chimica Inorganica, Chimica Fisica e Chimica dei Materiali, University of Torino, Via Pietro Giuria 7, 10125 Torino, Italy, and Divisione Ricerca e Sviluppo, Bracco Industria Chimica SpA, Via E. Folli 50, 20134 Milano, Italy

Synthesis and NMRD Studies of Gd^{3+} Complexes of Macrocyclic Polyamino Polycarboxylic Ligands Bearing β-Benzyloxy-α-propionic Residues

Silvio Aime,*,† Mauro Botta,† Giuseppe Ermondi,† Franco Fedeli,‡ and Fulvio Uggeri‡

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Introduction

The rapid development of nuclear magnetic resonance imaging techniques has stimulated the interest in studies of magnetic relaxation of solvent protons by complexes of paramagnetic lanthanide ions, because of their potential utility as contrast agents.[1] The anionic complexes $Gd(DTPA)^{2-}$ (diethylenetriaminepentaacetic acid-gadolinium complex)[2] and $Gd(DOTA)^{-}$ (1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-gadolinium complex)[3] are those studied most extensively and have now entered into clinical practice because of their low toxicity and their ability to significantly alter the water proton relaxation times. Currently the search for new contrast agents for MRI is directed toward the synthesis of Gd^{3+} complexes of functionalized derivatives of DTPA[4-6] and DOTA[7] ligands without altering their chelating abilities. We report here the synthesis and the $1/T_1$ NMRD profiles of aqueous solutions of Gd^{3+} chelates of four novel macrocyclic polyamino polycarboxylic ligands bearing β-benzyloxy-α-propionic residues (Figure 1). Such modified complexes may present some advantages such as (i) an increased molecular reorientational time τ_R, which results in increased solvent proton relaxation rates at the imaging magnetic fields, and (ii) an increased residence time in circulating blood and/or an accumulation at the specific target tissue or organ as a result of noncovalent interaction between the aromatic residues and the hydrophobic sites in biological substrates.[8] However, a chemical modification of the chelate basic structure often results in an altered relaxivity of the Gd^{3+} complex, and a better understanding of the relationship between chemical structure and the factors determining relaxivity in aqueous solutions would be a significant aid in the design and characterization of more effective paramagnetic contrast agents.

Experimental Section

All reagents were purchased commercially unless indicated otherwise and were used without further purification. 1,4,7,10-Tetraazacyclododecane (TAZA) was synthesized by the method of Richman and Atkins.[9]

All new products were completely identified by ^1H and ^{13}C NMR and mass spectroscopy, and satisfactory elemental analyses were obtained.

3-Benzyloxy-2-chloropropionic Acid (BzlClPA). The acid was prepared from methyl chloroacrylate using the method reported by Grassmann:[10] mp 28-30 °C. The corresponding potassium salt was obtained by salification with CH_3OK in methanol, and was quantitatively isolated as a white crystalline solid: mp 101-103 °C.

Intermediates 1a-d. A mixture of TAZA (25 g, 0.145 mol) and BzlClPA potassium salt (182 g, 0.718 mol) in DMF (225 mL) was stirred under nitrogen at 50 °C for 30 h. The resulting solution was concentrated in vacuo, and the residue was suspended in water (250 mL), acidified (pH 2.5) with HCl, and extracted with CH_2Cl_2 (3 × 100 mL). The aqueous phase, neutralized by addition of 1 N KOH, was loaded onto an Amberlite IR 120 cation-exchange column (H^+ form). First the column was eluited with water to neutrality and then with 5 N NH_4OH. The alkaline eluate was concentrated, and the residue was treated with 6.5 N HCl in EtOH (60 mL). The solid thus obtained afforded pure **1a**·3HCl after crystallization from absolute ethanol.

The combined organic layers, containing mainly BzlClPA and a mixture of **1b**, **1c**, and **1d**, were extracted with 0.1 N aqueous HCl (5 × 50 mL). The aqueous phase was neutralized to pH 4 by addition of 1 N NaOH. The solution was concentrated to half-volume, yielding **1d**·HCl as a precipitate. After further neutralization to pH 6.8, a mixture of **1b** and **1c** was precipitated. This mixture was suspended in refluxing EtOH, and pure **1c** was isolated by filtration, while **1b** crystallized on cooling.

Yields and melting points: **1a**·3HCl (27 g, 40%), mp 221-224 °C; **1b** (19 g, 25%), mp 173-175 °C; **1c** (13.7 g, 18%), mp 216 °C dec; **1d**·HCl (8.9 g, 8%), mp 105-106 °C.

Ligands 2a-d. General Procedure. The intermediate, **1a**, **1b**, **1c**, or **1d** (0.1 mol), was added to a solution of sodium bromoacetate (0.4 mol) in water (300 mL); the solution was basified to pH 10 with 6 N NaOH and warmed at 50 °C. After 10 h, the reaction mixture was cooled to room temperature, and by acidification (pH 2) the crude product was isolated as a gelatinous solid. The crude solid was dissolved in diluted NaOH, and acidification with HCl resulted in precipitation of the pure ligand: **2a** (yield 75%), mp 173 °C dec; **2b** (yield 46%), mp 155-157 °C; **2c** (yield 43%), mp 193 °C dec; **2d** (yield 95%), mp 175 °C dec.

Gd(III) Complexes 3a-d. General Procedure. A suspension of ligand (0.1 mol), D(-)-*N*-methylglucamine (0.1 mol), and Gd_2O_3 (0.05 mol) in water (1 L) was heated to 70 °C until a clear solution was obtained. The solution was evaporated in vacuo, and the complex as an amorphous solid was quantitatively isolated after drying to constant weight. **3a**: mp 137 °C dec. Anal. Calcd (found) for $C_{31}H_{50}GdN_5O_{14}$: C, 42.56 (42.42); H, 5.76 (5.96); Gd, 17.99 (17.63); N, 8.01 (7.72). **3b**: mp 145 °C dec. Anal. Calcd (found) for $C_{39}H_{58}GdN_5O_{15}$: C, 45.46 (45.39); H, 6.07 (6.09); Gd, 15.26 (15.22); N, 6.80 (6.77). **3c**: mp 155 °C dec. Anal. Calcd (found) for $C_{39}H_{58}GdN_5O_{15}$: C, 47.12 (47.20); H, 5.88 (5.85); Gd, 15.82 (15.72); N, 7.04 (6.77). **3d**: mp 137 °C dec. Anal. Calcd (found) for $C_{47}H_{66}GdN_5O_{16}$: C, 50.66 (50.63); H, 5.97 (6.01); Gd, 14.02 (14.02); N, 6.28 (6.26).

Stability Constant Determinations. Concentration stability constants were measured potentiometrically at 25 °C and μ = 0.1 M [$(CH_3)_4NNO_3$] by competition reactions with GdDTPA.[11,12] Calculations were performed using the software SUPERQUAD.[13]

NMR Measurements. The $1/T_1$ NMRD profiles of water protons were measured over a continuum of magnetic fields from 2.5 × 10^{-4} to 1.4 T (corresponding to 0.01-50-MHz proton Larmor frequencies) using the Koenig-Brown[14] relaxometer installed at the Department of Chemistry of the University of Florence. The spectrometer works under com-

* To whom correspondence should be addressed.
† University of Torino.
‡ Bracco Industria Chimica SpA.

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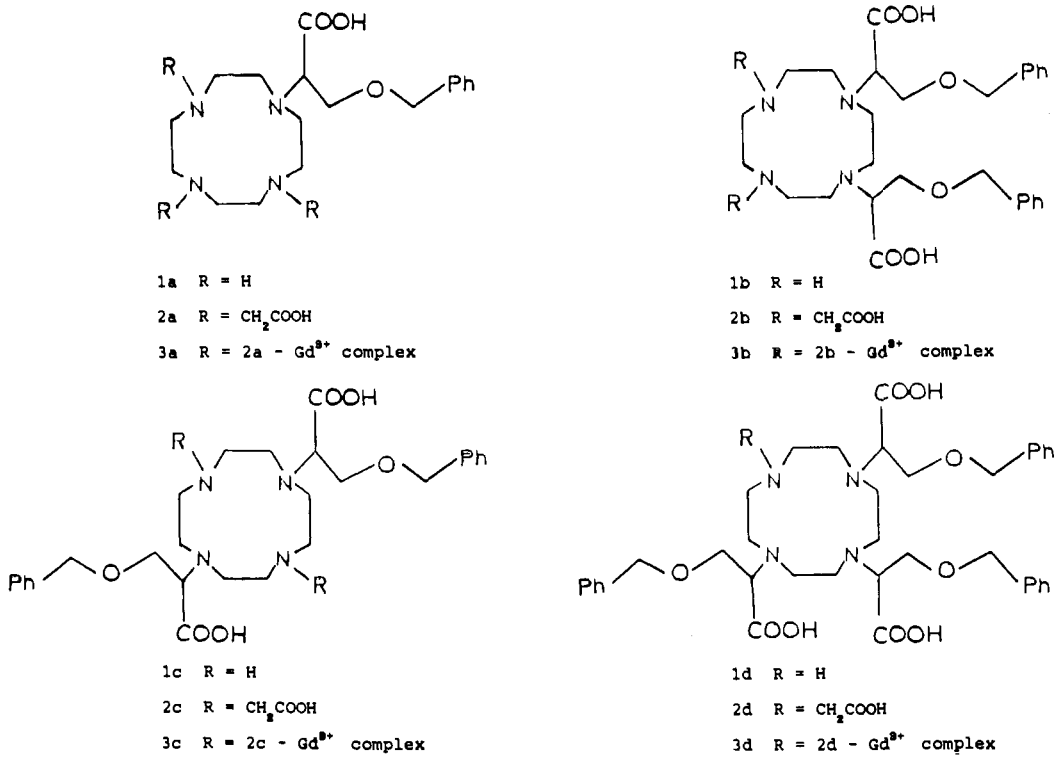

Figure 1. Chemical structures of the ligands and the complexes investigated in this study.

Table I. Longitudinal and Transverse Relaxivities[a] of Gd^{3+} Complexes at 20 MHz, 39 °C, and pH 7.3

	DOTA	3a	3b	3c	3d
R_{1p}, mM^{-1} s^{-1}	3.56	4.16	5.10	4.87	5.66
R_{2p}, mM^{-1} s^{-1}	4.70	5.70	6.95	6.94	8.00

[a] The accuracy of the measurement, repeated at least five times, is estimated as better than 2%.

plete computer control with an accuracy in $1/T_1$ of ±1%.

Solutions of the Gd^{3+} complexes (1.5 mM) were used after adjusting the pH to 7.3 with 0.2 N aqueous NaOH. Longitudinal and transverse relaxivities were measured at 39 °C on a Stelar Spinmaster spectrometer operating at 20 MHz.

Results and Discussion

The **2a–d** chelating ligands were synthesized by stepwise alkylation of 1,4,7,10-tetraazacyclododecane first with 2-chloro-3-benzyloxypropionic acid and then with bromoacetic acid. The stability constants measured for **3a** and **3b**[15] (log K = 25.93 and log K = 25.95, respectively) are only 1 order of magnitude lower than that found for the $Gd(DOTA)^-$ complex (log K = 27.01) and significantly higher than those reported for other Gd^{3+} complexes of DTPA- and DOTA-amide and -ester conjugates.[7,16] This indicates that the introduction of benzyloxymethyl residues does not alter the very favorable thermodynamic stability of the DOTA basic structure. On this ground, the type of substitution introduced in **3a–d** reduces the in vivo toxicity associated with the release of Gd^{3+} ions. Furthermore, the phenyl groups could either interact with the hydrophobic sites in biological molecules or be anchored through a covalent bond to such molecules after suitable functionalization.

The spin–lattice and transverse relaxivities of the Gd^{3+} complexes **3a–d** and $Gd(DOTA)^-$, measured at 20 MHz and 39 °C, are reported in Table I.

Since the theory of relaxation of solvent protons by small complexes of paramagnetic metal ions is well-known[17] and it has been reviewed in detail in several papers,[1,18] we only summarize here the essential equations pertinent to the Gd^{3+} case.

The observed water proton longitudinal relaxation rate is given by the sum of three contributions:

$$R_1^{obs} = R_{1p}^{is} + R_{1p}^{os} + R_{1W} \quad (1)$$

where R_{1W} is the gadolinium-free water relaxation rate, R_{1p}^{is} represents the contribution due to the exchange of water molecules from the inner coordination sphere of the metal ion to the bulk water and R_{1p}^{os} is the contribution of the water molecules diffusing in the outer coordination sphere of the paramagnetic center. The inner-sphere relaxation rate is described in terms of the following set of equations:

$$R_{1p}^{is} = \frac{Mq}{55.6}\frac{1}{T_{1M} + \tau_m} \quad (2)$$

$$\frac{1}{T_{1M}} = \frac{2}{15}\frac{\gamma_H^2 g^2 \beta^2 S(S+1)}{r^6}\left[\frac{7\tau_{c2}}{1+(\omega_S\tau_{c2})^2} + \frac{3\tau_{c1}}{1+(\omega_H\tau_{c1})^2}\right] \quad (3)$$

$$\frac{1}{\tau_{ci}} = \frac{1}{\tau_R} + \frac{1}{\tau_M} + \frac{1}{\tau_{Si}} \quad (4)$$

where i = 1 or 2 and

$$\frac{1}{\tau_{S1}} = \frac{1}{5\tau_{S0}}\left[\frac{1}{1+(\omega_S\tau_V)^2} + \frac{4}{1+(2\omega_S\tau_V)^2}\right] \quad (5)$$

$$\frac{1}{\tau_{S2}} = \frac{1}{10\tau_{S0}}\left[3 + \frac{5}{1+(\omega_S\tau_V)^2} + \frac{2}{1+(2\omega_S\tau_V)^2}\right] \quad (6)$$

In eqs 2–4, M is the molar concentration of the paramagnetic complex; q is the number of water molecules coordinated to the metal ion; τ_M is their mean residence lifetime; T_{1M} is their longitudinal relaxation time; S is the electron spin quantum

(15) The stability constants for **3c** and **3d** were not determined due to the poor solubility in water (0.001 M) of **2c** and **2d**.

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number; γ_H is the proton nuclear magnetogyric ratio; g and β are the electronic g factor and Bohr magneton, respectively; r is the distance between the metal ion and the protons of the coordinated water molecules; ω_H and ω_S are the proton and electron Larmor frequencies, respectively; τ_R is the rotational correlation time; and τ_{S1} and τ_{S2} are the longitudinal and transverse electron spin relaxation times. These last two are frequency dependent, according to eqs 5 and 6 and characterized by the correlation time of the modulation of the zero-field splitting[19] (τ_V) and the electronic relaxation time at zero magnetic field (τ_{S0}).

The outer-sphere term represents a relevant contribution to the observed relaxation rate for the case of these low molecular weight complexes and therefore must be evaluated accurately before analyzing the data in terms of eqs 2–6. This can be done experimentally by (1) measuring the solvent proton relaxation times of aqueous solutions of chemically and structurally similar complexes without water molecules in their inner coordination sphere ($Gd(TETA)^-$ represents a good outer-sphere reference for polyamino carboxylate complexes)[5] and (2) measuring the relaxation times of deuterium nuclei of a D_2O solution of the paramagnetic complex under conditions of high viscosity and high magnetic field.[20]

The outer-sphere contribution may be calculated from Freed's equation:[21]

$$R_1^{os} = \frac{32\pi}{405}\gamma_H^2 g^2\beta^2 S(S+1)\frac{N_A}{1000}\frac{M}{aD}[3j(\omega_H\tau) + 7j(\omega_S\tau)] \quad (7)$$

where N_A is Avogadro's number, a is the distance of closest approach between the paramagnetic center and the water molecules, and D is the relative diffusion coefficient for the water and the paramagnetic complex. The spectral density function $j(\omega)$ is given by

$$j(\omega) = \mathrm{Re}\left[\frac{1 + \frac{1}{4}(i\omega\tau)^{1/2}}{1 + (i\omega\tau)^{1/2} + \frac{4}{9}(i\omega\tau) + \frac{1}{9}(i\omega\tau)^{3/2}}\right] \quad (8)$$

where $\tau = a^2/D$.

The data reported in Table I show that the substitution for acetate of β-benzyloxy-α-propionate groups in the DOTA basic structure results in a linear increase in the longitudinal and transverse relaxivities of **3a–d** at 20 MHz and 39 °C. Since we may assume that, to a first approximation, outer-sphere contributions are similar for all complexes having similar chelate structures and bearing similar functional groups, the differences in the relaxivities among **3a–d** can be attributed to the inner-sphere term. For small, low molecular weight Gd^{3+} complexes only τ_R, which is proportional to the size and the molecular weight of the complexes, makes a sizable contribution to τ_C at high magnetic fields,[22] and therefore the data of Table I can be interpreted as a simple correlation between relaxivity and molecular weight indicating that the chemical modification of the DOTA acetic groups did not result in an increase in the number of water molecule coordinated to the metal ion, as also suggested by the high values of the stability constants.

However, a detailed analysis of the magnetic field dependence of water proton relaxation times may provide additional structural and dynamic information, related to the parameters of eqs 2–8. Experimentally this is done by measuring solvent longitudinal relaxation rates over a wide range of magnetic fields with the NMRD technique.[14]

The $1/T_1$ NMRD profiles of $Gd(DOTA)^-$ and **3a–d** were measured at 25 °C and pH 7.3 and are compared in Figures 2 and 3. The experimental data were fitted by eqs 2–8 using r, τ_R, τ_{S0}, and τ_V as adjustable parameters and assuming a single

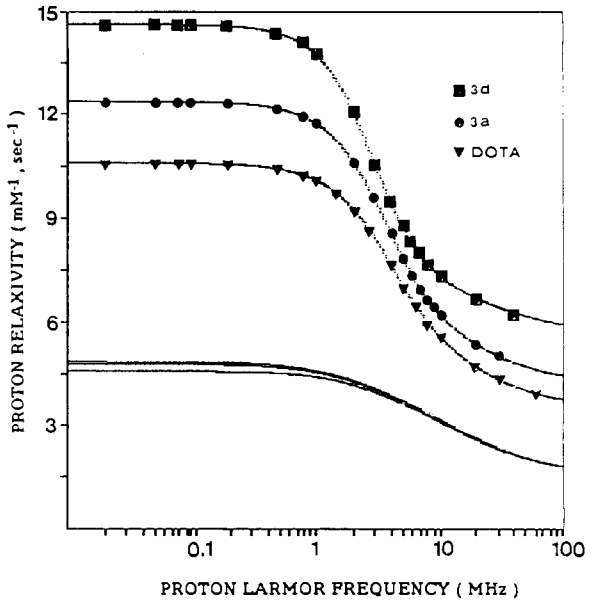

Figure 2. $1/T_1$ NMRD profiles of aqueous solutions of $Gd(DOTA)^-$, **3a**, and **3d** at pH 7.3 and at 25 °C. The solid lines through the experimental data are calculated with the parameters of Table II. The lower curves represent the outer-sphere contribution assigned, from the higher to lower R_1 values, to $Gd(DOTA)^-$, **3a**, and **3d**, respectively, as expected on the basis of their τ_{S0} values.

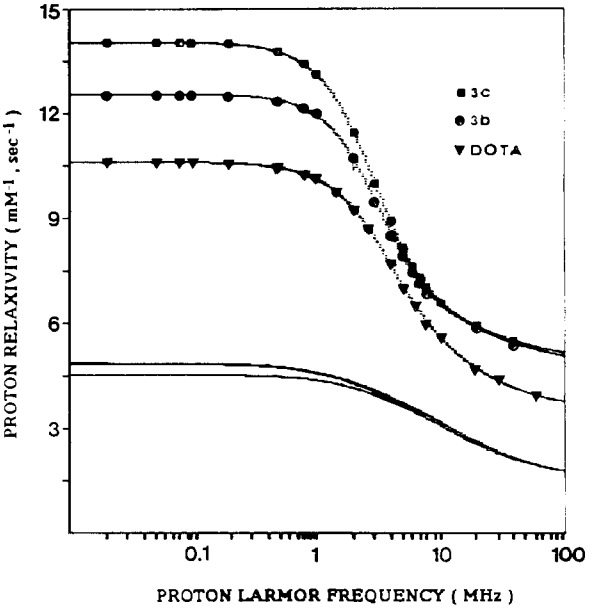

Figure 3. Comparison of $1/T_1$ NMRD profiles of $Gd(DOTA)^-$ and two isomeric complexes **3b** and **3c**. The lower curves represent the outer-sphere contribution; the outer-sphere profiles of $Gd(DOTA)^-$ and **3c** are overlapped owing to their similar τ_{S0} values.

coordinated water molecule ($q = 1$) with a residence lifetime (τ_M) of 5 ns. It must pointed out that the fitting results are insensitive to the exact value of τ_M, since the conditions $T_{1M} \gg \tau_M$ and $\tau_R \ll \tau_M$ hold. However, τ_M values of the order of nanoseconds have been reported for Gd^{3+} complexes, obtained by ^{17}O NMR spectroscopy[23] and NMRD measurements,[23b] and for Dy^{3+} complexes, evaluated by the analysis of the field dependence of the water proton transverse relaxivity.[24]

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Table II. NMRD Parameters Obtained from the Fitting[a] of NMRD Profiles with the Inner- and Outer-Sphere Relaxation Theory

	DOTA	3a	3b	3c	3d
τ_{S0}, ps	460 ± 20	417 ± 18	275 ± 14	443 ± 20	300 ± 13
τ_V, ps	26 ± 8	20 ± 6	21 ± 6	14 ± 4	22 ± 6
τ_R, ps	72 ± 1	86 ± 1	115 ± 2	115 ± 2	133 ± 2
r, Å	3.16 ± 0.01	3.06 ± 0.01	3.09 ± 0.01	3.07 ± 0.01	3.03 ± 0.01

[a] The standard deviation for the calculated relaxivity is less than 0.01 in all data.

An outer-sphere contribution to the relaxation rate[25,26] was also taken into account in the fitting procedure, using a value of 3.6 Å for the distance of closest approach of Gd^{3+} complex and water molecule (a) and a value of 2.6×10^{-5} cm^2 s^{-1} for their relative diffusion constant (D). The fitting parameters are reported in Table II.

The $1/T_1$ NMRD profiles (Figures 2 and 3) of **3a–d** are consistent with the presence of one water molecule in the inner coordination sphere. The results indicate that the Gd^{3+} complexes of macrocyclic ligands **2a–d** have significantly higher relaxivities than $Gd(DOTA)^-$ over the entire magnetic field range investigated (0.01–50 MHz). The differences in relaxivity among the five Gd^{3+} chelates are due to their different values of τ_R and τ_{S0} (Table II). At high fields (>5 MHz), the relaxivities depend entirely on τ_R, which is proportional to the size and the molecular weight of the complexes, while at lower fields the contribution of τ_{S0} also becomes important. The effect of the latter parameter is particularly evident when the relaxivity profiles of the isomeric complexes **3b** and **3c** are compared with each other (Figure 3). In this case, the low-field differences in their inner- and outer-sphere relaxivities are completely accounted for by the different electronic relaxation times of the two complexes. The value of τ_{S0} seems to reflect the changes in symmetry introduced in the coordination sphere of the Gd^{3+} ion by the insertion of one, two, or three β-benzyloxy-α-propionate residues. In fact, τ_{S0} of the monosubstituted (Gd–**2a**) complex (417 ps) is lower than that of the highly symmetric $Gd(DOTA)^-$ complex (460 ps). Moreover, the difference in τ_{S0} between Gd^{3+} complexes of disubstituted ligands **2b** (275 ps) and **2c** (443 ps) is particularly impressive and may result from the lower symmetry of the 1,4-disubstituted isomer. The value of τ_{S0} depends not only on the change introduced in the molecular geometry but also on the nature of the substituent group. In fact, as reported by Sherry et al.,[7] the amidation of a DOTA carboxyl group produces a dramatic decrease in τ_{S0}, which results in a lower water proton relaxivity at low fields. Nevertheless, it must be pointed out that to ascribe the changes in τ_{S0} entirely to geometric changes represents an approximation. The electronic relaxation time at zero field, τ_{S0}, is related to τ_V through the equation[27]

$$\tau_{S0} = (12\Delta^2\tau_V)^{-1} \qquad (9)$$

where Δ^2, the quadratic zero-field splitting, is the parameter which is sensitive to the symmetry and the electronic structure of the metal ion. From eq 9 it is evident that the variation in τ_{S0} among the complexes could well arise in part from variation in τ_V. However, even though the changes in τ_{S0} have not a simple and obvious relationship to geometric changes and the product $\tau_{S0}\tau_V$ only shows a slight increase from **3b** to **3d**, we do not believe that the changes in the τ_V values reported in Table II for the five Gd^{3+} complexes have a real physical meaning, since the fitting results are quite insensitive to the actual value of this parameter. In fact, very similar τ_V values have been reported for a variety of Gd^{3+} complexes with ligands of different sizes and structures (HEDTA, EDTA, DTPA, aquo ion, etc.[14,28]). If this is true, the results of this work support the view that both τ_R and τ_{S0} may be conveniently modulated by introducing suitable substituents in the DOTA basic structure. The concomitant occurrence of long τ_R and τ_{S0} makes **3a,d** candidate contrast agents which would be particularly useful for applications at low magnetic field strength.

Registry No. **1a**·3HCl, 124628-31-5; **1b**, 124627-96-9; **1c**, 124627-98-1; **1d**·HCl, 138666-91-8; **2a**, 124628-08-6; **2b**, 124628-02-0; **2c**, 124628-04-2; **2d**, 124628-06-4; BzlClPA, potassium salt, 138666-92-9; TAZA, 294-90-6; sodium bromoacetate, 1068-52-6.

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Contribution from the Department of Chemistry, Clemson University, Clemson, South Carolina 29634-1905

Synthesis and Structure of Infinite-Chain Copper(II) Polymer Systems

Larry W. Morgan, Kevin V. Goodwin, William T. Pennington,* and John D. Petersen*

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Introduction

Polymeric copper complexes are of interest for their magnetic and electronic properties[1–5] and have served as model systems for biological studies.[3,6,7] Structural studies have revealed that many of these polymers involve molecular units bound together by longer-range interactions,[2–4,8,9] while relatively few others are bound by stronger, molecular interactions.[5,10–12]

Of the latter category, two compounds involve bridging pyrazine ligands to form one-dimensional chains[11] or two-dimensional sheets.[5] Hatfield and co-workers[1,15–17] have shown that the ori-

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