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An NMR Study of the Structures of Lanthanide Diethylenetriaminepentaacetates

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Abstract—The paramagnetic chemical shifts in the ^{1}H and ^{13}C NMR spectra of lanthanide complexes (Ln = Eu, Yb, and Pr) with diethylenetriaminepentaacetic acid were analyzed. It was demonstrated that Eu^{+3} in aqueous solution can coordinate to one of the carboxylate groups in a chelating bidendate fashion through two O atoms.

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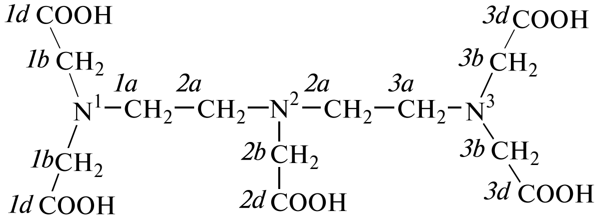
INTRODUCTION

Diethylenetriaminepentaacetate (DTPA) is known to be a very efficient chelant forming stable complexes with a great number of metal ions [1]. Some of its complexes have found medical use. Specifically, a gadolinium complex with DTPA is employed as a contrast agent in magnetic resonance imaging for diagnostic purposes [2–5] and as a drug in distant binary (neutron capture and photon capture) radiotherapy of malignant tumors [3–6]. These complexes are excellent relaxation reagents. The magnetic spin–lattice relaxation rate $1/T_1$ of water protons for solutions of gadolinium-containing complexes are widely used for characterization of diagnostic agents. It is known [7] that Gd^{+3} complexes with DTPA-like ligands exist in the solid state as distorted trigonal prisms made up of five carboxyl O atoms of DTPA and three N atoms. The coordination sphere of Gd^{+3} is completed with a water molecule. The lanthanide cation deviates from the plane of the oxygen atoms by only 0.07 nm. Similar structures have been also found in Bi^{+3} and Nd^{3+} complexes with DTPA [8, 9].

The structures of complexes in solution have been studied by NMR spectroscopy [10–12]. Note that ^{1}H NMR spectroscopy is unsuitable for solutions of Gd^{3+} complexes because the Gd^{3+} ion is a broadening paramagnetic reagent. Other lanthanide ions are shift reagents. Since lanthanide complexes with DTPA are usually isostructural, the data obtained for complexes of other lanthanides can be applied to structural studies of Gd^{+3} complexes in solution. Room-temperature ^{1}H NMR spectra of solutions of lanthanide complexes with DTPA are complicated by the presence of two structures in equilibrium [10–12]. At 343 K, the ^{1}H NMR spectra of lanthanide complexes show lines due to CH_2 groups (five acetate and four ethylene ones). The ^{13}C NMR spectra of complexes in solution also provide evidence for the octadentate coordination of the metal atom. The close spin–lattice relaxation times of the methylene protons of all acetate fragments are not inconsistent with this conclusion [11]. Although the NMR spectra of lanthanide complexes with DTPA have been extensively studied, the influence of the lanthanide cation on the ligand atoms and the position of one of five ^{13}C NMR signals for the carbonyl groups (substantially different from the positions of the other four signals) have been passed over [11, 12]. The ^{13}C chemical shift of the signal for the carbon atom of the methylene group bound to that carboxyl fragment in the Eu(III) complex also differs from the chemical shifts for the methylene groups in the other carboxyl fragments (δ 100 and ~70).

The numbering of the atoms in the ligand molecule is given below:



The ^{13}C chemical shifts depend on the electron density at the carbon atom involved, which in turn

Table 1. Paramagnetic shifts for the lanthanide and Bi^{3+} complexes with DTPA at 353 K*

Group	Bi^{3+}_{obs} [15]	Eu^{3+}_{obs}	Eu^{3+} (5.0, –7.0)	Pr^{3+} (–9.5, –1)	Yb^{3+} (20, –0.25)
N^2CH_2COOH	4.23	2.4	–1.83	2.6	13.0
N^1CH_2COOH	4.00	–7.2	–11	11.7	–30.7
	3.75	–2.1	–6		
N^3CH_2COOH	3.70	–7.2	–10.9	15.0	–31.7
	3.90		–11.1		
N^2CH_2	3.27	4.0	+0.73	–3.2	0.14
	3.30	4.0	+0.7		
N^1CH_2	3.0	2.4	–0.6	–9.4	46.7
N^3CH_2	3.85	6.4	+2.55	–16.9	46.7

* The K_d and K_c/K_d values are given in parentheses.

depends on the distance between the carbon atom and a paramagnetic ion as well as the nature of the carboxylate–metal ion bond [13, 14].

The goal of this study was to analyze the NMR spectra of lanthanide complexes with DTPA for gaining more insight into the electronic structure and character of the coordination bonding between the lanthanide ions and DTPA.

EXPERIMENTAL

Lanthanide oxides and DTPA (99.9% purity) were used. Lanthanide complexes with DTPA were obtained by reactions of Eu, Yb, and Pr oxides with concentrated aqueous solutions of DTPA [15] and isolated as the disodium salts $Na_2MC_{14}H_{20}O_{10}N_3$ (M = Eu, Yb, and Pr). The complexes obtained were identified by X-ray fluorescence on an X-art-M analyzer (Komita, St. Petersburg). The lanthanide concentration was determined from preliminary calibration curves plotted for each lanthanide. The purity of the lanthanide complexes with DTPA was checked from the lanthanide content of the complex.

For $Na_2EuC_{14}H_{20}O_{10}N_3$

anal. calcd., %:	Eu, 25.91.
Found, %:	Eu, 26.07.

For $Na_2YbC_{14}H_{20}O_{10}N_3$

anal. calcd., %:	Yb, 28.49.
Found, %:	Yb, 28.77.

For $Na_2PrC_{14}H_{20}O_{10}N_3$

anal. calcd., %:	Pr, 24.50.
Found, %:	Pr, 23.95.

The ^1H NMR spectra of the Eu^{3+}, Yb^{3+}, and Pr^{3+} PMR spectra of the complexes with DTPA were recorded on Avance-300 and Avance-600 instruments (Bruker) in D_2O at room temperature and at 343 K (pH 8–8.5, C = 50 mg/mL, sweep width 150 ppm, pulse delay 5 s, number of transients ~400).

The ^{13}C NMR spectra of the Eu^{3+} complex with DTPA were recorded on Avance-400 and Avance-600 instruments (Bruker) in D_2O at 343 K (pH 8–8.5, C = 120 mg/mL, sweep width 300 ppm, pulse delay 5 s, number of transients >1000).

RESULTS AND DISCUSSION

The electronic effect of Ln^{3+} on the shielding of the DTPA protons in lanthanide complexes was estimated as described in [16]; according to that procedure, the paramagnetic ^1H chemical shifts ($\delta_{p\text{-}m}$) for a number of lanthanide complexes are represented as a sum of contact (δ_c) and dipolar shifts (δ_d) with the respective coefficients K_c and K_d (their values are given in [16–18]):

$$\delta_{p\text{-}m} = K_c\delta_c + K_d\delta_d. \quad (1)$$

The contact shift resulting from a direct coupling of a proton with the unpaired spin density of a paramagnetic ion is isotropic and depends on the proton–ion distance r. The dipolar shift resulting from a dipolar coupling of a proton with an ion is determined by the magnetic susceptibility tensor of the ion (i.e., the symmetry of the complex) and is proportional to r^{-3}.

The paramagnetic ^1H chemical shifts for the complexes with the Eu^{3+}, Yb^{3+}, and Pr^{3+} ions were calculated as a difference between the observed chemical shift and that occurring in a diamagnetic octadentate Bi^{3+} complex with DTPA [19] (Table 1).

The paramagnetic shifts were separated into the dipolar and contact contributions [16] using the equation:

$$\delta_{p\text{-}m}/K_d = \delta_d + (K_c/K_d)\delta_c. \quad (2)$$

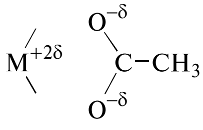
Linearization of the paramagnetic shifts gave a straight line (2) for the ^1H shifts of the signals of the methylene protons at the carboxylate groups of the ligand:

$$\delta_{\text{p-m}}\,(C^{2b}H_2) = 0.04K_c - 0.1K_d,$$
$$\delta_{\text{p-m}}(C^{1b}H_2) = 0.085K_c - 1.44K_d, \qquad (3)$$
$$\delta_{\text{p-m}}(C^{3b}H_2\,) = -1.44K_d.$$

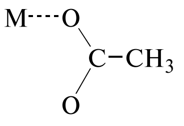
The factor in front of K_c for the CH_2 protons at the carboxyl fragment is appreciably lower than the factors in front of K_d, in agreement with the conclusion that the chemical shifts for the methylene protons at carboxyl groups are mainly of dipolar origin [11]. Note that the contact and dipolar contributions for the methylene protons at the middle N^2 atom do not differ as largely as those for the same protons at the N^1 and N^3 atoms; i.e., the contact contribution to the chemical shift of these protons is more considerable.

Analysis of the chemical shifts in the ^{13}C NMR spectra of Ln^{3+} complexes with DTPA (Ln = Ce, Pr, Nd, Sm, Eu, and Tb) with allowance for shift separation into contact and dipolar contributions [12] (under the assumption of a mirror plane passing through the N^2 and C^2 atoms) suggests that the positions of the signals for the carbon atoms are greatly influenced by the dipolar contribution. However, the Gd^{3+} complex with DTPA has no mirror symmetry (X-ray diffraction data) [7], so these results cannot be used to estimate the effect of the paramagnetic contribution to the ^{13}C chemical shifts of the signals for the carboxyl C atoms. The aforementioned estimates of the effect of the paramagnetic contributions on the shielding of the protons of the CH_2 groups *1b*, *2b*, and *3b* leave it unclear why the ^{13}C NMR signal for one carboxyl carbon is shifted. The low-field signal (δ 206) for the carbonyl C atom of one carboxyl group in the ^{13}C NMR spectrum of the Eu^{3+} complex with DTPA suggests that this group is coordinated in a different fashion compared to the coordination of the other carboxyl groups.

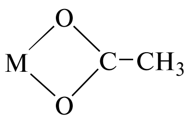
In DTPA complexes, metal atoms can be coordinated to the carboxylate anions in three ways:



(I)



(II)



(III)

Structure **I** is common in most organic salts. Structures **II** and **III** can be found in Li, Ca, and Zn carboxylates as well as in transition metal salts [13, 14]. The metal atom has the maximum coordination number, and the difference in the chemical shifts of the signals for the carbonyl C atoms of the acetate groups can be due to different patterns of bonding between the O atoms of these groups and the lanthanide atom. Apparently, the terminal acetate 1*d*- and 3*d* groups are coordinated to the metal atom according to pattern **II**, while the acetate 2*d* group bound to the middle N atom forms structure **III** because of possible unrestricted rotation of this carboxylate group in solution. For Zn^{2+} complexes, the ^{13}C chemical shifts in the chelate structure **III** (δ 184) are higher by ~8 ppm than those for the monodentate coordination in **II** (δ 176) [14]. For Ln complexes, this difference may be even larger.

Table 2. Chemical shifts of the signals in the ^{13}C NMR spectra of the Eu^{3+} and Bi^{3+} complexes with DTPA at 353 K

Group	Eu^{3+} with DTPA	Bi^{3+} with DTPA [15]
N^2CH_2COOH	98.6	60.4
N^1CH_2COOH	68.46	61.7
N^3CH_2COOH	70.36	59.8
$N^1CH_2CH_2N^2$	94.6	54.95
$N^2CH_2CH_2N^1$	114	60.07
$N^3CH_2CH_2N^2$	100.1	60.07
$N^2CH_2CH_2N^3$	114	
C=O	206.0, 182.38 w.s.	179.89, 178.6, 180.1

The ^{13}C chemical shifts for solutions of the Eu^{3+} and Bi^{3+} complexes with DTPA are given in Table 2. The signal assignment in the tabulated ^{13}C NMR spectrum somewhat differs from that cited in [11, 12]. The signals for the methylene and acetate groups appear in a wide range (δ 115–70), and their chemical shifts differ substantially from those of the corresponding ^{13}C nuclei in the spectra of the octadentate Bi^{3+} complex with DTPA (according to NMR data, the latter has structure **II**). If the bond length differences for the bonds between the metal ion and the cation-withdrawing atoms of the ligands are taken into consideration when assigning NMR signals, then one can believe that the chemical shifts for the acetyl ^{13}C nuclei at the N^1 atom most distant from the metal ion should not differ strongly from those for analogous ^{13}C nuclei in the bismuth complex (Table 2). The signals for the ethylene C atoms adjacent to the middle N^2 atom are also shifted downfield; the lower-field signal refers to the chain between the N^2 and N^3 atoms.

To sum up, our experimental data suggest that the Eu^{3+} complex with DTPA in solution can have a structure in which the acetate group attached to the middle N^2 atom of the DTPA molecule is coordinated to the lanthanide atom in a different way compared to the coordination of the other acetate groups of the ligand. According to our estimation of the dipolar and contact shifts, the former are main contributors to the chemical shifts of the signals for the protons in the spectra of the complexes studied. We demonstrated that the changes in the chemical shifts of both the protons and ^{13}C nuclei can be attributed to all the factors. Since K_c and K_d differ substantially in magnitude and sign for different ions, the positions of the signals for both the carbonyl and methylene ^{13}C nuclei [12] should be expected to depend on the properties of a complexing metal as well as on the way in which it is coordinated to the carboxyl O atoms.

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