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^{1}H NMR Titration Studies of Two Novel DTPA Derivatives*

Zhang Shanrong Ren Jimin Pei Fengkui
(Applied Spectroscopy Laboratory, Changchun Institute of Applied Chemistry, Academia Sinica, Changchun 130022)

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Polyaminopolycarboxylate gadolinium (Ⅲ) complexes have been studied intensively in recent years because of their potential uses as contrast agents for magnetic resonance imaging (MRI)[1]. The research interests are mainly focussed on Gd^{3+} complexes of DTPA, DOTA and their various derivatives. Four kinds of Gd^{3+} complexes can be used presently in clinical MRI, which are Gd(DTPA)[2], Gd(DOTA)[3], Gd(DTPA-BMA)[4] and Gd(HP-DO3A)[5]. Here report two new DTPA bis (amide) derivatives-diethylenetriaminepentaacetic acid-*N*, *N*″-bis (dimethylamide) (DTPA-BDMA) and -bis (diethylamide) (DTPA-BDEA).

1 Experimental

DTPA-BDMA and DTPA-BDEA were synthesized similarly to the published procedu -re[6]. The purities were checked by elemental analysis and ^{1}H NMR measurements, which were all consistent with purities≥95%. They were dissolved in D_2O at 0.2mol·L^{-1}. The pH were adjusted by HCl/NaOH and tested on PHS-2 type pH meter. Their Gd^{3+} complexes were obtained by mixing stoichiometric amount of $GdCl_3$ with DTPA-BDMA and DTPA-BDEA solutions and adjusting to pH 7.3±0.1. ^{1}H NMR spectra were recorded on Varian Unity-400 superconducting spectrometer with observing frequency 400MHz. 0.5%(*V*/*V*) *t*-butyl alcohol was served as internal reference (δ_H=1.23ppm).

2 Results and Discussion

DTPA-BDMA (DTPA-BDEA) has six functions, three carboxyls and three amines, which could be deprotonated by adding the base. The electric densities would increase if the proton ions were removed from the compounds, which would lead the resonances of ethylenic protons nearby to shift to higher field.

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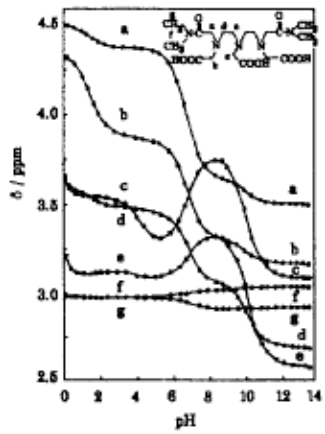

Fig.1 ^{1}H NMR titration curve for DTPA-BDMA

Shown in Fig.1 is ^{1}H NMR titration curve for DTPA-BDMA (similarly for DTPA-BDEA). There are five inflection points which correspond to six proton dissociation processes. The mechanism of proton dissociation processes can be deduecd from the chemical shift values and their directions, which are in the order of the central amine (pH<0.5), the terminal carboxyls (0.5<pH<3.1), the central carboxyl (3.1<pH<5.4), the terminal amines (5.4<pH<8.5) and the central amine (8.5<pH<12.5). A very complicated pattern was observed in pH 5.4 to 8.5. The resonances of H_a, H_b and H_d have very large higher field shifts (0.68, 0.52 and 0.44ppm, respectively), but the resonances of H_c and H_e have reversible changes (0.43 and 0.22ppm, respectively). The fact means that both the deprotonation and the protonation are occured at the same time. It is likely that one proton ion on the terminal amine dissociates and the another one transfers from the terminal amine onto the central amine. The existance of proton transfer proceses is also confirmed by the fact that all resonances are broadened (especially for backbone protons) because of the chemical exchange in this pH range. The fact that the resonances separate from each other for about 0.12ppm for the two methyl protons binding on the same amide reveals that the structure of DTPA-BDMA changes dramatically when the proton ions on the terminal amines are removed by deprotonation and/or proton transfer. The similar phenomena have also been observed for DTPA[7] and DTPA-BMA[8].

The pK_a values are equal to the pH values at the inflection points[7], which are listed in Table 1. It is stated that the complex stability is closely related to the value of $\sum pK_a$[9]. From this point, it could be concluded that Gd (DTPA-BDMA) and Gd(DTPA-BDEA) would be more stable than that of Gd (DTPA-BMA).

Table 1 Proton dissociation constants for DTPA bis (amide) derivatives

	pK_{a_1}	pK_{a_2}	pK_{a_3}	pK_{a_4}	pK_{a_5}
DTPA-BDMA	~ 0.2	1.5	4.0	7.0	10.0
DTPA-BDEA	~ 0.2	2.0	4.0	7.0	10.1
DTPA-BMA*		1.43	3.31	4.38	9.37

* from reference [10]

The relaxation rates of water protons increase linearly with the adding of Gd^{3+} complexes ($0 \sim 5$ mmol·L^{-1}). From the slope, the normalized relaxivities are obtained to be 4.01 and 4.97 L·mmol^{-1}·s^{-1} for Gd (DTPA-BDMA) and Gd (DTPA-BDEA), respectively, which are very close to that of MRI contrast agents used presently[1].

In summary, two novel DTPA bis (amide) derivatives, DTPA-BDMA and DTPA-BDEA, were synthesized and their proton dissociation processes were studied. The relaxation analysis indicates that their Gd^{3+} complexes are very usefully potential MRI contrast agents.

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两种新DTPA衍生物的^{1}H NMR滴定研究

张善荣　任吉民　裴奉奎

(中国科学院长春应用化学研究所应用谱学开放实验室，长春　130022)

摘要　合成了两种新的DTPA双酰胺衍生物，DTPA-BDMA和DTPA-BDEA. 通过^{1}H NMR滴定研究发现这两种化合物的质子解离过程为：中部胺基(pH<0.5)，端部羧基(0.5<pH<3.1)，中部羧基(3.1<pH<5.4)，端部胺基(5.4<pH<8.5)和中部胺基(8.5<pH<12.5). 在质子解离过程中端部胺基上的一个质子能转位到中部胺基上，同时分子结构将发生较大变化. Gd(DTPA-BDMA)和Gd(DTPA-BDEA)的弛豫效率分别为4.01和4.97L·mmol^{-1}·s^{-1} (400MHz, pH=7.3, 25°C)，说明这两种化合物是非常有应用前景的MRI造影剂.

关键词：核磁共振，　DTPA-BDMA，　DTPA-BDEA，　质子解离过程