

-endo-2,3-dicarboxylic acid upon binding of the Ln(NOTA) paramagnetic complexes. Fast exchange was observed and the measured paramagnetic shifts were purified of existing contact contributions and compared with theoretical values calculated from assumed structures. The results obtained indicate that Ln(NOTA) chelates should be very useful NMR paramagnetic probes to be used in conformational analysis of small ligands or in binding to protein surfaces.

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C.F.G.C. GERALDES *

A.D. SHERRY

Chemistry Department
University of Texas at Dallas
P.O. Box 688, Richardson, TX 75080
U.S.A.

R.D. BROWN, III

S.H. KOENIG

IBM T.J. Watson Research Center
P.O. Box 218, Yorktown Heights, N.Y. 10598
U.S.A.

NMRD INVESTIGATION OF Mn^{2+} AND Gd^{3+} NOTA COMPLEXES, AND A COMPARISON WITH THE ANALOGOUS EDTA COMPLEXES

It is well established that the longitudinal (spin-lattice) and transverse (spin-spin) relaxation rates of solvent protons in solutions of complexes of paramagnetic ions, *e.g.*, metalloproteins or small chelates, depend on the strength of the applied static magnetic field and on the chemical environment of the ions [1,2]. The magnetic field dependence of the proton relaxation rates of water, called nuclear magnetic relaxation dispersion (NMRD) profiles, have been previously studied in detail for complexes of Gd^{3+} and Mn^{2+} with the chelates ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA) [2]. In this work, we report a study of the $1/T_1$ NMRD profiles of Gd^{3+} and Mn^{2+} ions complexed with the cyclic triazamacrocyclic ligand 1,4,7-triazacyclononane-*N,N',N''*-triacetic acid (NOTA), and compare them with results for the analogous EDTA complexes. We also discuss their potential utility as paramagnetic contrast agents in NMR imaging.

Fig. 1 shows the NMRD profiles of solvent protons of $Mn(EDTA)$ and $Mn(NOTA)$ complexes, which are independent of pH in the range of

* Permanent Address: Chemistry Department, University of Coimbra, 3000 Coimbra, Portugal

5.8 to 10.5. Addition of excess EDTA to the Mn(NOTA) solution does not affect the rates, showing that Mn^{2+} forms at least a 50-fold stronger complex with NOTA than it does with EDTA. The Mn(NOTA) NMRD profile shows that its relaxivity is very low, probably arising only from outer sphere effects. The absence of inner sphere water molecules in Mn(NOTA) would agree quite well with X-ray crystal structures of the Cr^{3+} , Fe^{3+} , and Cu^{2+} NOTA complexes [3]. On the other hand, the results strongly suggest that Mn(EDTA) is indeed seven coordinated, with one inner sphere water molecule, as discussed previously [4-6].

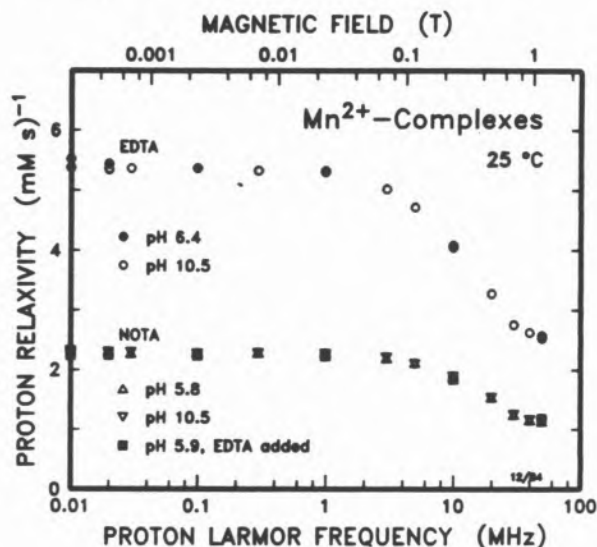


Fig. 1

$1/T_1$ NMRD profiles of solvent protons of solutions of Mn^{2+} complexes with EDTA and NOTA

Fig. 2 shows the Gd(NOTA) NMRD profiles under various conditions and compares them with the Gd(EDTA) results. At pH near neutrality, the Gd(NOTA) NMRD curve has a lower relaxivity than Gd(EDTA), particularly at low fields, due to a combination of a decreased correlation time for the dipolar interaction and a decrease of water coordination number. A water coordination number of 3.3 has been proposed for Eu(NOTA) on the basis of optical [7] and NMR results [8,9] and the present data are certainly compatible with this view. Addition of equimolar quantities of EDTA restores the NMRD profile of Gd(EDTA), indicating that EDTA competes successfully with NOTA for Gd^{3+} at neutral pH, and that the Gd(NOTA)

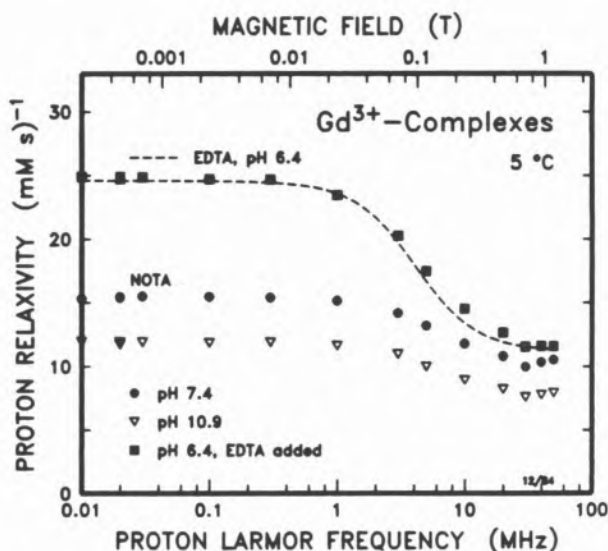


Fig. 2

$1/T_1$ NMRD profiles of solvent protons of solutions of Gd^{3+} complexes with EDTA and NOTA. The dashed line is computed from a least squares comparison of theory and experimental data [2]

complex is substantially weaker than Gd(EDTA). We also see a gradual decrease of relaxivity of Gd(NOTA) as the pH is increased from 7.4 to 10.9, equivalent to an effective decrease of approximately one proton. This is not due to $\text{Gd}(\text{OH})_3$ precipitation, and we propose that inner sphere water molecules of Gd(NOTA) are involved at high pH, giving mixed $\text{Gd}(\text{NOTA})(\text{H}_2\text{O})_m(\text{OH})_n$ species. This is in agreement with high resolution NMR observations on the La^{3+} and Lu^{3+} NOTA complexes [10].

In conclusion, the very stable Mn(NOTA) complex, although allowing an estimate of outer sphere effects for other Mn^{2+} complexes, probably would not be an efficient relaxation enhancement agent. The Gd(NOTA) complex is quite an efficient relaxation agent, particularly at high frequencies, but could be quite a toxic contrast agent in NMR imaging due to its ready release of the Gd^{3+} caused by a relatively modest stability constant.

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KELLEY WOODRING
 RICHARD W. TAYLOR
 Department of Chemistry
 University of Oklahoma
 Norman, OK. 73019
 U.S.A.

SUBSTITUENT EFFECTS ON THE DISSOCIATION KINETICS OF HEAVY METAL ION CRYPTATES

The dissociation kinetics of the cryptates of 2.2.2, 2.2.2_D, 2_B.2_B.2 and 2_C.2_C.2 with Tl⁺ and Pb²⁺ have been studied in water and methanol-water (90:10) at 25.0°C. The dissociation reactions generally displayed parallel solvolytic (*k_s*) and acid-catalyzed (*k_H*) pathways consistent with the rate law:

$$-d[\text{MCryp}^{n+}]/dt = (k_d + k_H[H^+]) [\text{MCryp}^{n+}]$$

The introduction of a decyl side chain (2.2.2_D) produced only minor variations in the values of *k_d* and *k_H* when compared with the parent cryptand, 2.2.2. Larger effects are observed with the dibenzo-derivative (2_B.2_B.2) with Tl⁺ and for the dicyclohexano-derivative (2_C.2_C.2) with both Pb²⁺ and Tl⁺. The rate constants for the uncatalyzed and acid-catalyzed pathways in methanol-water decrease by 20- to 200-fold compared with the corresponding values obtained in water.

INTRODUCTION

The macrobicyclic polyoxa-diamines (cryptands) introduced by LEHN and co-workers form stable complexes with alkali-, alkaline-earth- and heavy metal cations [1,2]. The relative rigidity of these ligands results in peak type selectivity related to the ratio of ligand cavity to metal cation diameter. In addition to cavity size, parameters such as donor atom type and ligand backbone substituents also affect the complexation properties of the cryptands [1-3]. The introduction of hydrophobic decyl-, benzo-, and cyclohexano-moieties into the cryptand (see Fig. 1) structure increases their ability to solubilize salts in non-polar media [4] and

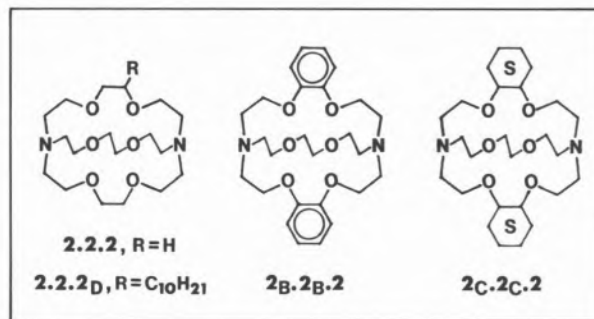


Fig. 1
 Structures of 2.2.2 Cryptands

membranes [5,6]. In view of the demonstrated ability of the parent compound, cryptand 2.2.2, to enhance elimination of toxic heavy metal ions [7,8] an evaluation of substituent effects on the complexation properties with Pb²⁺ and Tl⁺ was carried out and the results are reported in this communication.

EXPERIMENTAL

Cryptands 2.2.2, 2.2.2_D, 2_B.2_B.2 and 2_C.2_C.2 were obtained from E. Merck and used without further purification. Stock cryptand solutions were analyzed spectrophotometrically [9]. Kinetic studies were carried out by mixing equal volumes of the appropriate cryptate (3.0-7.0 × 10⁻⁵ M) with a solution of known HClO₄ concentration (1.12-74.5 mM). The reactions were monitored in the wavelength region of 245-255 nm on either a Durrum stopped-flow or a Hitachi 80-100 spectrophotometer. The cell temperature was maintained at 25.0 (±0.1)°C using a thermostated water bath.