MRI Contrast agents: macrocyclic lanthanide(III) complexes with improved relaxation efficiency

This is the author's manuscript

Original Citation:
MRI Contrast agents: macrocyclic lanthanide(III) complexes with improved relaxation efficiency / Silvio Aime ; Mauro Botta ; Simonetta Geninatti Crich ; Giovanni B. Giovenzana ; Giancarlo Jommi ; Roberto Pagliarin; Massimo Sisti. - In: JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS. - ISSN 0022-4936. - -(1995), pp. 1885-1886.

Availability:
This version is available http://hdl.handle.net/2318/121201 since

Published version:
DOI:10.1039/C39950001885

Terms of use:
Open Access
Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.
MRI Contrast Agents: Macrocyclic Lanthanide(III) Complexes with Improved Relaxation Efficiency

Silvio Aime,*a Mauro Botta,a Simonetta Geninatti Crich,a Giovanni B. Giovenzana,a Giancarlo Jommi,*b Roberto Paglieriib and Massimo Sistib

*a Dipartimento di Chimica Inorganica, Chimica Fisica e Chimica dei Materiali, via P. Giuria 7, I-10125 Torino, Italy
b Dipartimento di Chimica Organica ed Industriale, viale Venezian 21, I-20133 Milano, Italy

Lanthanide(III) complexes of a novel heptadentate chelating ligand display structural and dynamic properties that are particularly interesting in view of potential applications in magnetic resonance imaging (MRI).

The search for new contrast agents (CA) for MRI is currently orientated towards the synthesis of paramagnetic complexes, possibly neutral, of increasing ability to enhance the water proton relaxation rates, while maintaining the favourable complexing properties of dota and dtpa-like ligands. We report here the synthesis and solution state NMR characterisation of a novel macrocyclic ligand 3 and its complexes with Eu(III), Yb(III) and Gd(III) ions which satisfy both requirements. Ligand 3 was synthesised as shown in Scheme 1.

Analogous behaviour was observed in the variable-temperature 13C NMR spectra. The observed exchange process may be accounted for in terms of an interconversion mechanism analogous to that reported for Ln(III)-dota complexes (Scheme 2).

Fig. 1 (A) 1H NMR spectrum of Eu-3 recorded at 9.4 T (400 MHz) and 363 K in D2O at pH 7. (B) 1H NMR spectrum of Yb-3 recorded at 2.1 T (90 MHz) and 266 K in D2O, at pH 7 with presaturation of the solvent peak. In both spectra, the resonance labelled * refers to BuOH (ca. 1%) added as an internal reference [6 (ppm) = 0]. In the Eu-3 spectrum the additional peak labelled W refers to HDO.

Scheme 1

Scheme 2
There are, however, two main differences between the complexes with dota and those with the heptadentate ligand 3: (i) the flexibility of the macrocycle is partially lost following the introduction of the pyridine moiety in the macrocyclic ring; (ii) the layout of the acetate arms is affected by the asymmetry in the macrocycle. This means that the two interconverting isomers may have quite different populations. This has been proved in the low-temperature-limit 1H NMR spectrum of the Yb-3 complex whose higher spread of chemical shifts allows the observation of the separate resonances of the two isomers [Fig. 1(B)]. The isomeric ratio is about 15:1 at 266 K. As the temperature is increased an exchange takes place between the two isomers. As expected the broadening is much more severe for the minor isomer whose resonances quickly disappear in the spectral noise. The large frequency separation between the exchanging sites in the Yb-3 complex does not allow the condition of fast exchange to be obtained as some resonances are still rather broad at the highest attainable temperature (363 K).

The thermodynamic formation constant for the EuIII complex was estimated through competition experiments between ligand 3 and EuIII-dota (logK = 19.5). From the intensities in the 1H NMR spectrum of the species Eu-3, cdta and Eu-3-cdta in several experiments carried out with different concentrations of 3 and Eu-cdta we obtained a Ky value of 3 ± 2 × 1018. The good thermodynamic stability calculated for this complex prompted us to investigate the relaxometric properties of the GdIII-3 complex in view of its potential application as a contrast agent for MRI. The relaxivity of GdIII-3 complex was found to be 6.3 mmol dm−3 s−1 (20 MHz; 298 K), about 35% higher than for Gd-dota and similar to that reported for Gd-dota. This is in good agreement with the value of 7.64 obtained in plasma at 40 °C reported in a patent dealing with a closely related GdIII complex containing a 12-N-4 ring moiety.

The observed relaxivity value is consistent with the presence of two exchangeable water molecules in the inner coordination sphere of the complex. More insight into the paramagnetic relaxation pathway was gained from the analysis of the NMRD (nuclear magnetic resonance dispersion) profile obtained from the measurement of the solvent proton relaxation rate over a wide range of proton Larmor frequencies (0.01−50 MHz). The fitting of the experimental data to the values calculated on the basis of the Solomon−Bloembergen−Morgan analysis (for the inner sphere contribution) and Freed analysis (for the outer sphere contribution) equations for the paramagnetic relaxation yields the following parameters: τSO (electronic relaxation time at zero field) = 1.41 × 10−10 s; τc (correlation time responsible for the modulation of τSO) = 3.20 × 10−11 s; τex (exchange lifetime of the coordinated water) = 5.00 × 10−9 s; r (H2O−Gd distance); = 3.20 × 10−8 cm; a (distance of closest approach of the water molecules diffusing in the proximity of the complex) = 3.80 × 10−8 cm; D (relative diffusion coefficient for water and complex) = 2.24 × 10−5 cm2 s−1.

The presence of two coordinated water molecules is responsible for both the enhanced relaxivity and the rather short value of τex thus ruling out a possible quenching effect on the relaxation efficiency caused by long exchange lifetimes as recently shown to occur in related neutral GdIII complexes containing a single coordinated water molecule.

An insight into the kinetic stability of this complex has been gained by the observation that R10 does not vary in the pH range 3–9. At lower pHs, the acid-promoted dissociation occurs to a significantly lower extent than in Gd-dtpa. Furthermore, the relaxivity in serum was constant after several hours at ambient temperature.

In conclusion we think that the structural, dynamic, thermodynamic and relaxometric properties of this novel class of lanthanoid(III) complexes make them potential candidates for the development of new, neutral contrast agents for MRI. Furthermore the inclusion of the pyridine moiety in the macrocyclic will provide an anchoring site for the introduction of a number of functionalities on the surface of the complex aimed at an improved specificity in the targeting of tissue and organs.

Support from Bracco SpA and from Italian CNR (Progetto Strategico Tecnologie Chimiche Innovate) is gratefully acknowledged.

Received, 7th April 1995; Com. 5/02269J

Footnotes

1 data = 1,4,7,10-tetraazacyclododecane-N,N′,N′′,N′′′-tetrasacetic acid, dpa = diethylimerinpentacetic acid, cdta = 1,2-diaminocyclohexane-N,N′,N′′,N′′′-tetracetic acid, do3a = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

Refereces


6 European Patent 0352218 A2 (1990)


