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MRI Contrast Agents: Macrocyclic Lanthanide(III) Complexes with Improved Relaxation Efficiency

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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 EuIII, YbIII and GdIII ions which satisfy both requirements. Ligand 3 was synthesised as shown in Scheme 1.

3,6,10,16-Tetraazabicyclo[16.3.1]hexadeca-1(16),12,14-triene 1 was prepared according to the procedure of Costa and Delgado. The three carboxymethyl moieties on N3, N6 and N10 were introduced by the reaction of compound 1 with 3 equiv. of methyl bromoacetate in the presence of silver(1) carbonate in THF at room temperature. The reaction mixture was filtered through Celite, the filtrate evaporated to dryness and the residue acidified with hydrochloric acid. After addition of sodium sulfide, the silver(1) sulfide precipitated was filtered off. The solution was made basic to pH 11 and extracted with dichloromethane. The resulting triester 2 was obtained in 80% yield.

By treating compound 2 with 3 equiv. of KOH in methanol, the potassium salt of the triacid 3 was isolated in quantitative yield and used for the preparation of the LnIII complexes. EuIII, YbIII and GdIII complexes of ligand 3 were prepared by mixing stoichiometric amounts of the ligand and the lanthanoid(III) chloride at neutral pH.

The high-temperature-limit 400 MHz 1H NMR spectrum of the EuIII-3 complex (363 K) shows 23 resonances [Fig. 1 (A)] spread over a range of ca. 30 ppm. The resonances could be assigned to the 23 different protons by use of homo- and hetero-correlated 2D experiments carried out at 2.1 T in order to minimize the magnetic-field-induced line-broadening. On cooling to room temperature and below, all resonances markedly broaden, indicating that a dynamic process is slowing down although it was not possible to obtain the spectrum corresponding to the 'frozen' structures.

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 LnIII-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 (δ (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 isomers may have quite different populations. This has been proved in the low-temperature-limit 1H NMR spectrum of the isomers. As expected the broadening is much more severe as some resonances

relaxation pathway was gained from the analysis of the NMRD of the Yb-3 complex does not allow the

condition of fast exchange to be obtained as some resonances

for

at 266 K. As the temperature is increased an exchange takes place between the exchanging sites in the Yb-3 complex 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.

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Footnotes

1. MS(El); m/z (rel. int.) 436 (M+, 28); 1H NMR (200.13 MHz; CDCl3); δ 1.81 (m, 2 H), 2.11 (m, 2 H), 3.48 (s, 2 H), 3.52 (s, 2 H), 3.65 (s, 3 H), 3.73 (s, 3 H) 3.74 (s, 3 H) 7.16 (d, 1 H, J 7.5 Hz), 7.18 (d, 1 H, J 7.4 Hz), 7.62 (s, 1 H, J 7.4 Hz); 13C NMR (50.32 MHz; CDCl3); 23.3 (CH3), 47.9 (2CH3), 50.5 (CH5), 50.9 (CH5), 51.3 (CH3), 51.5 (2CH5), 56.1 (CH5), 56.9 (2CH5), 59.0 (2CH5), 124.2 (2CH5), 136.6 (C), 157.0 (C), 157.2 (C), 171.6 (C), 181.1 (C), 181.2 (C)

References


6 European Patent 0352218 A2 (1990)


