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Lanthanide(III) complexes of a pyridine *N*-oxide analogue of DOTA: exclusive *M* isomer formation induced by a six-membered chelate ring†

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The presence of a six-membered chelate ring involving a pyridine *N*-oxide moiety induces exclusive *M* isomer formation throughout the whole lanthanide series endowed with a fast water exchange in the case of the Gd(III) complex.

Gadolinium(III) complexes of polyamino polycarboxylates are widely used as contrast agents (CA) in magnetic resonance imaging (MRI).[1] The efficacy of a CA expressed by *relaxivity* (r_1) depends on a variety of physico-chemical parameters. Those which could be chemically tuned were recognized early. The most easily accessible is the reorientational motion of a Gd(III) chelate (τ_r) which can be modified by the effective molecular size of the paramagnetic complex. Therefore, it is necessary to slow down the thermal tumbling, *i.e.* to increase the molecular size of the complex. However, the r_1 enhancement expected is often quenched by the occurrence of an exceedingly long residence time (τ_M) of the coordinated water molecules. The τ_M was proved to be a subtle function of structural parameters of the complex in solution. In DOTA-like complexes (DOTA = 1, 4, 7, 10-tetraazacyclododecane-*N*, *N*′, *N*″, *N*‴-tetraacetic acid), the steric hindrances of pendant arms near the water-binding site are usually decisive. Considering a wrapping of the pendant arms around the Ln(III) ion, two diastereoisomers are possible, namely *M* (SA, square antiprismatic) and *m* (TSA, twisted square antiprismatic).[2] Moreover, it was found that the complexes with an *m* structure display an exchange of the coordinated water that is as much as 10–100 times faster, which was ascribed to a higher steric crowding facilitating water expulsion.[3] Therefore, the design of systems with a fast water exchange have been commonly pursued through a fine modulation of steric constrains around the water-binding site. Usually, the bound water molecule is located at a longer distance from the paramagnetic center in *m* structures[4] and the magnetic information is, consequently, transferred less effectively. Therefore, a gadolinium(III) complex exhibiting a low τ_M and occurring mostly in the *M* form may have a convenient relaxivity.

In this work, we show that the replacement of a common five-membered chelate ring by a six-membered one significantly favors the *M* isomer *versus* the *m* structure throughout the whole lanthanide series. In addition, due to steric crowding near the water-binding site, the water exchange rate of the Gd(III) complex falls close to the optimal region for MRI applications even for the *M* isomer.

To synthesize the target ligand, 1,4,7,10-tetraazacyclododecane-1-[(*N*-oxido-pyridine-2-yl)methyl]-4,7,10-triacetic acid (H_3DO3A-pyNox), t-Bu_3DO3A[5] was alkylated with 1.1 equiv. of 2-(chloromethyl)pyridine *N*-oxide[6] (acetonitrile–K_2CO_3, 80 °C, 24 h). The solids were filtered off and the solution was evaporated to dryness. Then, the residue was partitioned between water and CH_2Cl_2. Subsequently, the organic phase was dried (anhydrous Na_2SO_4) and evaporated. The pure ester was hydrolyzed in trifluoroacetic acid (24 h, RT). Volatiles were removed to yield a crude ligand H_3DO3A-pyNox. Finally, the solid was dissolved in concentrated hydrochloric acid, evaporated and co-distilled with water to produce the hydrochloride of H_3DO3A-pyNox. It was recrystallized from water to obtain the pure ligand as $L\cdot 2HCl\cdot 3H_2O$.‡

Solutions of lanthanide(III) complexes were prepared by reaction of Ln(III) chlorides with an aqueous solution of the ligand (10% molar excess). The pH of the mixtures were then adjusted to ~8–9 with dilute aqueous KOH and the solutions were stirred for 12 h at RT. Finally, the samples were neutralized to pH = 7. The metal complexes in the solid state were prepared by mixing the 10% molar excess of the Ln(III) chloride with the ligand at pH ~8–9 followed by stirring overnight. The reaction mixture was then neutralized to pH 7 and the target complex was purified by chromatography on Amberlite XAD-1180 (water and water–ethanol 4 : 1) followed by evaporation of the solvent.

The lanthanide(III) complexes of H_3DO3A-pyNox were studied in solution by multinuclear NMR spectroscopy. First, the hydration state (*q*) of the complexes was assessed by the water ^{17}O shift measurement in the presence of a Dy(III) complex[7] to display one water molecule in the first coordination sphere (see ESI, Fig. S1†). To get further insight into the structure of the complexes the water induced ^{17}O shift was measured throughout the whole lanthanide series and the uniformity in the hydration manner of the complexes was proved (see ESI, Fig. S2†). The stability of the Gd(III) complex was qualitatively confirmed by a relaxivity measurement at pH 3–10 (see ESI, Fig. S3†). Furthermore, ^{1}H NMR spectra of Nd(III), Eu(III) and Yb(III) complexes were measured (see ESI, Fig. S4†) to justify coordination of the *N*-oxide pendant arm. Comparing the obtained spectra with those of Ln(III) complexes of DOTA, the similarity of structures and binding of all pendant arms of H_3DO3A-pyNox were confirmed. Inspecting all the ^{1}H NMR spectra, the presence of only *M* diastereoisomer was observed even in the case of the Nd(III) complex where the *m* isomer is strongly preferred for other DOTA-like ligands.[2,8] To study the molecular dynamics, the ^{1}H EXSY spectrum (EXSY = exchange spectroscopy) of the [Eu(DO3A-pyNox)(H_2O)] complex was measured (see ESI, Fig. S5†). The existence of an enantiomeric pair indicates the presence of both the isomerization processes reported for Ln(III) DOTA complexes (arms rotation and ring inversion)[2,8] which take place simultaneously leading to the *M* isomer only.

The *M* isomer was also found in the solid state structure of [Dy(DO3A-pyNox)]$\cdot 3H_2O$ (Fig. 1).§ Despite the hydration of the complex in the solid state, no water is directly coordinated to the central ion. The average twist angle between O4 and N4 planes (35.1°) and the O411–Dy–O22N angle (124.9°) are much lower than the corresponding angles in [Dy(DOTA)(H_2O)]$^-$ (ref. 9) as well as in the Eu(III) complex of DO3A-triamide with one phenolate pendant arm (where a water molecule is bound to a Eu(III) ion).[10] These parameters are closer to those found for complexes

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† Electronic supplementary information (ESI) available: Figs. S1–S7—Dy(III) induced ^{17}O NMR shifts at 25 °C, Ln(III) induced ^{17}O NMR shifts, dependence of relaxivity of Gd-complex on pH, ^{1}H NMR spectra of Nd(III), Eu(III) and Yb(III) complexes, EXSY spectra of Eu(III) complex, variable-temperature ^{17}O $T_{1,r}$, ω_r data and ^{1}H NMRD profiles. Table S1—complete fitting results. See http://www.rsc.org/suppdata/cc/b4/b409996f/

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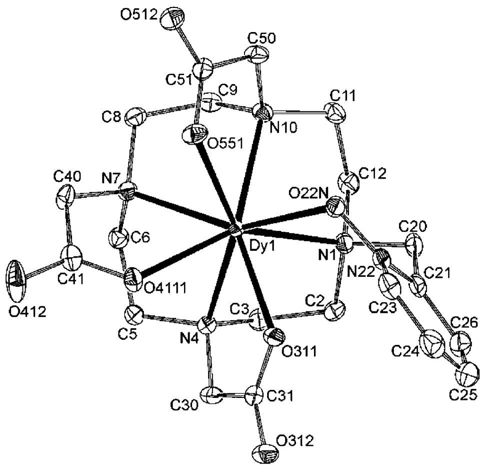

Fig. 1 ORTEP view of [Dy(DO3A-pyNox)] showing thermal ellipsoids at 50% probability level. H-atoms are omitted for clarity.

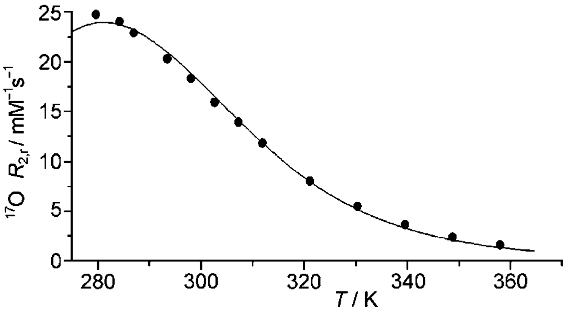

Fig. 2 Variable-temperature water ^{17}O reduced transversal relaxation rates in the presence of the [Gd(DO3A-pyNox)(H_2O)] complex (pH 7, 400 MHz).

with an *m* structure where no water is coordinated.[4] The *N*-oxide O22N is located 0.234 Å above the O3 carboxylate plane. Altogether, it causes a significantly higher steric tension totally "expelling" the water molecule. In solution, such steric hindrances are relaxed but facilitate the water exchange.

With this information, relaxometric measurements were performed on the [Gd(DO3A-pyNox)(H_2O)] complex to learn more about the influence of the exclusive presence of the *M* isomer on the water residence time τ_M and other determinants of relaxivity r_1. Variable-temperature ^{17}O NMR T_1, T_2 and $\Delta\omega$ data and NMRD profiles at 5, 25 and 37 °C were acquired and simultaneously fitted on the basis of established theory (see ESI, Figs. S6 and S7†).[1] The water residence time τ_M determined mostly by the ^{17}O T_2 data (Fig. 2) is surprisingly low (39 ns at 298 K) and close to the optimal range which is in contrast with common expectations. The proton relaxivity r_1 of the complex (4.05 mM^{-1} s^{-1}; 310 K, 20 MHz) is comparable with that of [Gd(H_2O)(DOTA)]$^-$ (3.98 mM^{-1} s^{-1})[11] which could be accounted for in terms of almost the same rotation correlation time (τ_r) for both complexes. For the complete fitting results see ESI, Table S1.†

In conclusion, we have synthesized a new "pilot" ligand (with an *N*-oxide pendant arm) and a series of its Ln(III) complexes. The exclusive *M* isomer formation throughout the whole lanthanide series was observed for the first time and is ascribed to a rigid arrangement of the six-membered chelate ring stabilized by a planar pyridine *N*-oxide moiety. Because of the increased steric crowding near the water-binding site, the τ_M falls close to the optimal region. Our study shows that even complexes with the structure of an *M* isomer should be considered when designing new MRI CA if the ligand structure is to be properly tuned. The rigid elongated chelate chain could lead to the desired properties of such MRI CA.

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Notes and references

‡ All new compounds prepared gave spectroscopic (multinuclear NMR and ESI-MS) and analytical data in accordance with structures and compositions given.

§ Crystal data: $C_{20}H_{34}N_5O_{10}Dy$, M = 667.02, triclinic, a = 7.29510(10), b = 10.7100(2), c = 15.7375(3) Å, α = 82.0772(12), β = 86.8978(12), γ = 90.0588(10)°, U = 1216.03(4) Å^3, T = 150 K, space group $P\bar{1}$ (No. 2), Z = 2, μ (Mo–Kα) = 3.137 mm^{-1}, D_c = 1.822 g cm^{-3}, 21215 reflections measured, 5585 unique (R_{int} = 0.0404), the final R_1 0.0181 ($I > 2\sigma(I)$), $wR(F^2)$ 0.0463 (all data). CCDC 244292. See http://www.rsc.org/suppdata/cc/b4/b409996f/ for crystallographic data in .cif or other electronic format.

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