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Luminescence of gadolinium complexes with 1,4,7,10-tetraaza-2,6-pyridinophane[12]-1,4,7-triacetic acid

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Gadolinium complexes of tetraaza-2,6-pyridinophane[12] derivatives have been synthesized and some luminescence characteristics obtained.

In addition to the traditional applications of lanthanide complexes the study of these complexes (namely, gadolinium complexes) as contrast substances in NMR imaging is of increasing interest.[1,2] The important feature of this method is the possibility of determining both free and complexed ion. Usually, radioisotopic[3] and atomic-emission[4] techniques are used for this purpose. However, luminescence properties, which are very specific for lanthanides, have found no applications in the analysis of contrast agents. A reverse-phase chromatographic method with luminescence detection of the gadolinium complex has only recently been developed.[5]

The 1,4,7,10-tetraaza-2,6-pyridinophane[12]-1,4,7-triacetic acid trisodium salt L† and its gadolinium complex‡ (Scheme 1) were synthesized and its spectral-luminescence properties were studied.

Preliminary biochemical data indicate the potential of this complex as an NMR contrast agent.

In complexes with the ligands under investigation the gadolinium ion exhibits luminescence properties. Under optimal conditions of complexation the luminescence intensity (I_{lum}) was kept constant over a long period. I_{lum} does not change under illumination for 40 min. The luminescence and excitation spectra of the gadolinium ion for chloride and complex solutions are shown in Figure 1.

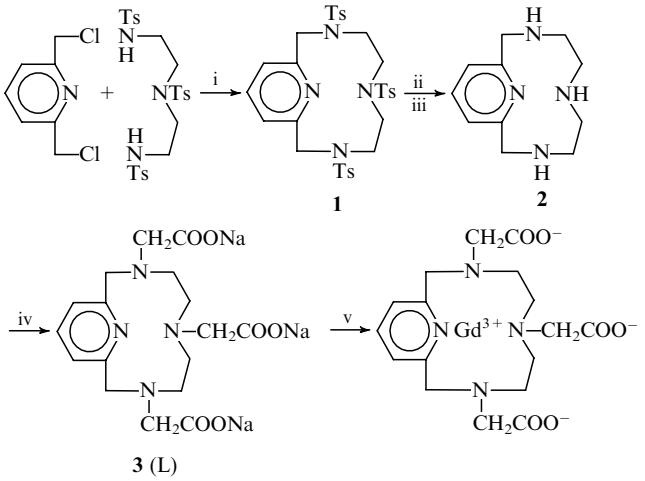
† *Experimental*. Silufol UV-254 plates were used for TLC. ^{1}H NMR spectra were recorded on a Bruker AM-250. Mass spectra were obtained on a Varian MAT CH-112. Luminescence and excitation spectra were recorded on a SDL-2 spectrometer (Leningrad Optic-Mechanical Association, Russia). Luminescence was excited by a DKs EL-1000-5 xenon lamp. The initial compound diethylenetriamine tritosylate was prepared according to the procedure reported previously.[6]

Synthesis. 1,4,7-Tris-(*p*-toluenesulfonyl)-1,4,7,10-tetraaza-2,6-pyridinophane[12] **1**. 4 g of K_2CO_3 was added to a solution of diethylenetriamine tritosylate (5.7 g, 0.01 mol) in 100 ml of DMF and heated up to 100 °C with stirring. The reaction mixture was allowed to stand for 2 h, then a solution of 2,6-bis(chloromethyl)pyridine (1.8 g, 0.01 mol) in 500 ml of DMF was added. The mixture was stirred for a further 6 h, cooled and poured into 350 ml of water. The resulting precipitate was treated with methanol and the raw product was recrystallised from chloroform–ethanol. Yield 4.2 g (63%). Mp 220–222 °C. ^{1}H NMR ($CDCl_3$) δ_H 2.47 (s, 9H, Me), 3.48 (m, 8H, CH_2NTs), 3.81 (s, 4H, $CH_2C_5H_3N$), 7.51 (m, 15H, C_6H_4, C_5H_3N); *m*/*z* 513 (M^+−Ts, 100%), 358 (M^+−2Ts, 28%).

1,4,7,10-Tetraaza-2,6-pyridinophane[12] **2**. A mixture of 20 ml of 96% H_2SO_4 and compound **1** (8.7 g, 0.013 mol) was heated up to 100 °C and stirred for 32 h. The mixture was then cooled, 300 ml of ether was added, and the resulting precipitate was filtered and dissolved in the minimal amount of H_2O saturated with granulated alkali. The product **2** was isolated by extraction with hot benzene and recrystallized from hexane. Yield 1.7 g (65%), mp 94–95 °C. ^{1}H NMR ($CDCl_3$) δ_H 2.06 (s, 3H, NH), 2.69 (m, 8H, CH_2N), 3.69 (s, 4H, $CH_2C_5H_3N$), 7.36 (d, 2H, C_5H_3N), 7.85 (t, 1H, C_5H_3N); *m*/*z* 206 (M^+, 5%).

1,4,7,10-Tetraaza-2,6-pyridinophane[12]-1,4,7-trisodiumacetate **3**(L). Compound **2** (2.5 g, 0.012 mol) was dissolved in 5 ml H_2O and a mixture of monochloroacetic acid (3.8 g, 0.04 mol) and NaOH (1.6 g, 0.04 mol) was added, heated at 80 °C and stirred for 20 h. The mixture was cooled, evaporated under reduced pressure, and to the residue 50 ml isopropyl alcohol was added with heating. After the mixture was cooled, the resulting sodium salt was filtered and dried in air. Yield 3.1 g (59%). Mp > 230 °C (decomp.). ^{1}H NMR (D_2O) δ_H 3.54 (m, 8H, CH_2N), 3.77 (s, 4H, $NCH_2C_5H_3N$), 3.99 (s, 6H, CH_2COONa), 7.44 (d, 2H, C_5H_3N), 7.96 (t, 1H, C_5H_3N). Found: C, 45.79; H, 4.67; N, 12.50. Calc. for $C_{17}H_{21}N_4O_6Na_3$: C, 45.74; H, 4.71; N, 12.56%.

‡ Gadolinium complex of 1:1 composition was obtained by interaction of an equimolar amount of aqueous solutions of gadolinium chloride and L at pH 6.0–6.5. When isolated as a solid, the resulting solution of complex was evaporated to small volume (5 ml), cooled and precipitated from ethanol–acetone. The complex was characterized by elemental analysis and IR spectroscopy. Found: C, 38.27; H, 3.89; N, 10.45. Calc. for $C_{17}H_{21}N_4O_6Gd$: C, 38.20; H, 3.93; N, 10.49%. IR (KBr) ν/cm^{-1} 1650 (COO^-) for ligand, 1678 for complex. This complex contains two water molecules in the inner coordination sphere. This was determined from the luminescence decay of the corresponding terbium complex as described previously.[7]



Scheme 1 *Reagents and conditions:* i, K_2CO_3, DMF; ii, H_2SO_4; iii, NaOH; iv, $ClCH_2COONa$, H_2O; v, Gd^{3+}.

It can be seen from Figure 1 that the excitation spectrum consists of two bands at 276 and 303 nm. The most intense band in the spectrum is the former, therefore, luminescence spectra of Gd^{III} were recorded at its maximum. Luminescence spectra of the Gd^{III} ion, both in complex and chloride solutions, contain two narrow bands at 311 and 306 nm. The most intense band is the former ($^6P_{7/2} \rightarrow {}^8S_{7/2}$ transition).

The I_{lum} ratio (113) of the bands at 311 nm for Gd-L and chloride is the highest for gadolinium complexes. For comparison similar relations are given in Table 1 for other complexones, two of which (DTPA and DOTA) are the basis for commercial contrast agents in NMR imaging.

Three main factors are known to determine the luminescence intensity of lanthanide ions in their complexes: the efficiency of energy transfer from the triplet level of the ligand to the emission level of the lanthanide ion; the non-radiative energy deactivation of excitation arising from the presence of water molecules in the inner coordination sphere of the lanthanide ion; and the symmetry of the environment (as a rule, complexes of lower symmetry exhibit higher luminescence intensity).

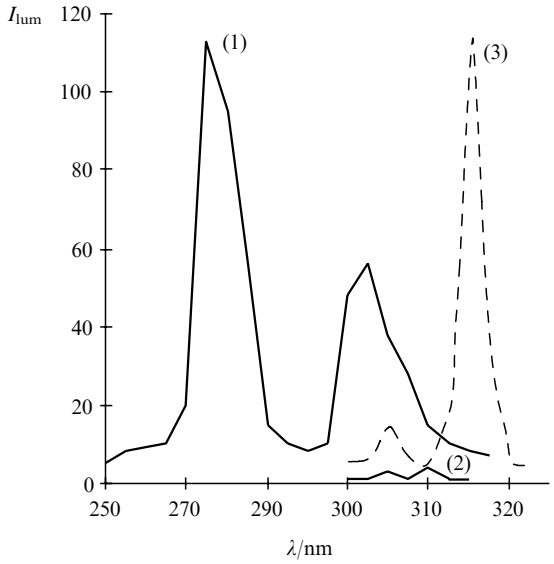


Figure 1 The excitation spectrum of Gd-L complex (1) and luminescence spectra of $GdCl_3$ (2) and Gd-L (3).

Table 1 Luminescence intensity of Gd^{III} ion in complex solutions.

Complexone	$I_{lum.comp.}/I_{lum.chloride}$
Ethylenediaminetetraacetate	41
Diethylenetriaminepentaacetate (DTPA)	57
1,4,7,10-Tetraazacyclododecane-*N*, *N*′, *N*″, *N*‴-tetraacetate (DOTA)	85
1,4,7,10-Tetraaza-2,6-pyridinophane[12]-1,4,7-triacetate (L)	113

It is clear that the gadolinium ion is incapable of receiving the excitation energy from the ligand because its emission level lies much higher than the triplet levels of any known ligands. An increase in its luminescence in complexes is accounted for by replacement of the water molecules in the aqua-ion by ligand donor atoms upon complexation.

It can be seen from Table 1 that the luminescence intensity in the complexes considered increases in the order: Gd-DTPA < Gd-DOTA < Gd-L. Of these compounds, Gd-DOTA contains one water molecule but is the most symmetric complex. Gd-L contains two water molecules, as does Gd-DTPA, but it is the least symmetric complex. It may be supposed that the two latter factors determine the luminescence intensity of the complexes considered.

In conclusion, the results presented appear to be useful in determining the nature of the gadolinium complexes and their use as paramagnetic contrast agents.

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