



Supporting Information

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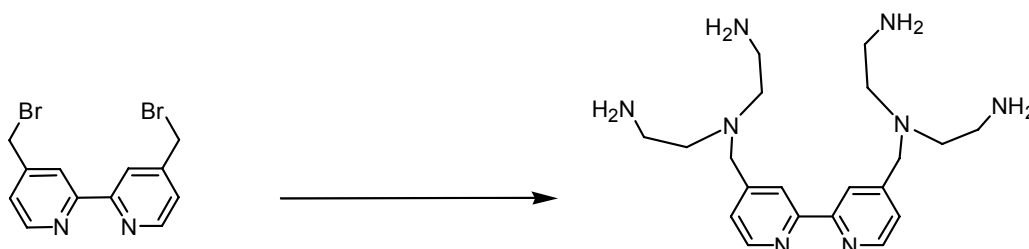
69451 Weinheim, Germany

High Relaxivity Confined to a Small Molecular Space: A Metallostar-based, Potential MRI Contrast Agent

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Synthesis of the ligand.

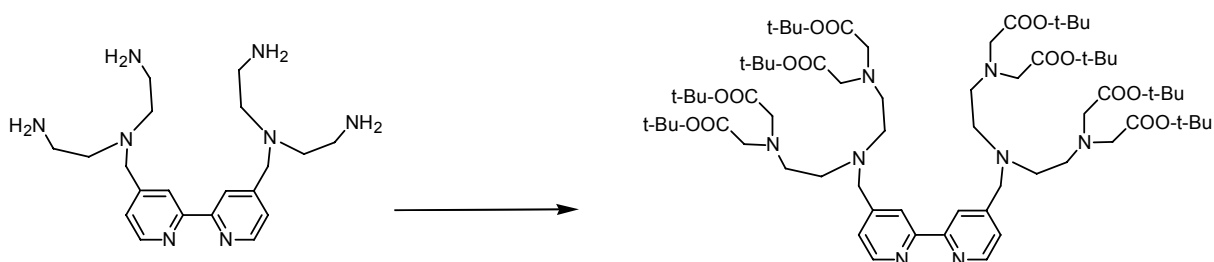
Bpy(CH₂-dien)₂



To a stirred solution of 4.86 g (14.3 mmol) of 4,4'-bis(bromomethyl)-2,2'-bipyridine (synthesized according to A. P. Smith, J. J. S. Lamba, C. L. Fraser, *Org. Synth.* **2002**, 78, 82; R. S. Ward, D. Branciard, R. A. Dignan, M. C. Pritchard, *Heterocycles* **2002**, 56, 157) in 80 ml of dry acetonitrile, 15.5 g (42.9 mmol) of protected triamine (N,N'-bis(phthalimido)diethylenetriamine, synthesized according to the C. -Y. Ng, R. J. Motekaitis, A.E. Martell, *Inorg. Chem.* **1979**, 18, 2982) and 7.8 g (56 mmol) K₂CO₃ were added, and the resulting mixture was refluxed for 16 h and then cooled to room temperature (complete reaction of starting material was monitored by ¹H NMR). The suspension was filtered and the filtrate concentrated under reduced pressure. The resulting yellow oil was then refluxed in 250 ml HCl 6 M for 14 h. The suspension was cooled to room temperature and evaporated to dryness. The residue was dissolved in 160 ml NaOH 5 M and extracted 3 times with CHCl₃. The combined organic phases were washed with brine, dried over Na₂SO₄ and the solvents removed in the rotary evaporator. The crude product was purified by flash chromatography on silica gel (NH₃/EtOH, 0:100 to 60:40). 1.0 g (obtained yields between 18 and 35%) of the

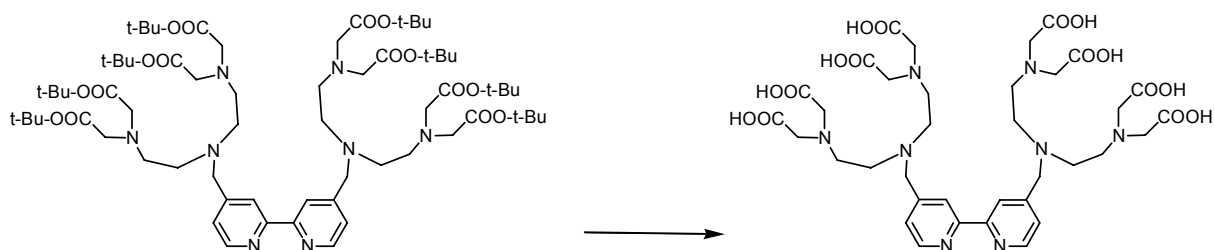
product was obtained as a yellow oil; ^1H NMR (CDCl_3 = 7.25 ppm, 200 MHz) δ : 2.51 (t, J = 5.9 Hz, 8H), 2.73 (t, J = 6.1 Hz, 8H), 3.63 (s, 4H), 7.27 (dd, J = 4.9, 1.4 Hz, 2H), 8.27 (s, 2H), 8.54 (d, J = 4.9 Hz, 2H).

Octa-*tert*-butyl ester of $\text{H}_8\text{bpy}(\text{CH}_2\text{-DTTA})_2$



0.90 g (2.33 mmol) of $\text{bpy}(\text{CH}_2\text{-dien})_2$ were dissolved in 80 ml of dry DMF. 5.33 g (27.6 mmol) *tert*-butyl bromoacetate, 4.82 g (37.3 mmol) DIEA and 0.61 g (3.7 mmol) KI were added. The mixture was stirred at room temperature for 90 h and then evaporated to dryness. The residue was dissolved in NaOH 5M and extracted 3 times with diethyl ether. The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (MeOH/ CH_2Cl_2 , 1:99 to 3:97). 1.05 g (35%) of a bordeaux oil of octa-*tert*-butyl ester of $\text{H}_8\text{bpy}(\text{CH}_2\text{-DTTA})_2$ were obtained. ^1H NMR (CDCl_3 , 400 MHz) δ : 1.39 (s, 72H), 2.63 (t, J =7.2 Hz, 8H), 2.84 (t, J =7.2 Hz, 8H), 3.39 (s, 16H), 3.72 (s, 4H), 7.37 (d, J = 4.8 Hz, 2H), 8.23 (s, 2H), 8.55 (d, J = 4.8 Hz, 2H); MS (ESI): m/z (%): 650.8 (100) [MH_2^{2+}].

H₈bpy(CH₂-DTTA)₂



H₈L

1.05 g (0.81 mmol) of the octa-*tert*-butyl ester of H₈bpy(CH₂-DTTA)₂ were refluxed in 300 ml HCl 6 M for 10 h. The solvents were removed, the remaining solid was dissolved in 100 ml H₂O and the solution thus formed was evaporated to dryness. Dissolution in H₂O and evaporation were repeated two times. The resulting solid was then dissolved in a minimum amount of H₂O, loaded onto a conditioned cation-exchange column (Bio-Rad AG 50W-X4, H⁺ form, 3.0 x 6.5 cm) and washed with H₂O till neutral pH. The sample was then eluted with a 1 M solution NH₃. The presence of the product in the eluate was determined by a Fe^{II} test. The absence of Cl⁻ was evaluated with a AgNO₃/HNO₃ test. Concentration of the appropriated fractions, dissolution in H₂O and evaporation to dryness (repeated 2 times) yielded 0.559 g (70 %) of the product as a colorless solid. ¹H NMR (D₂O ≈ 4.80 ppm, pD = 4.5, 400 MHz) δ: 3.00 (t, J = 6.7 Hz, 8H), 3.49 (t, J = 6.7 Hz, 8H), 3.71 (s, 16H), 3.96 (s, 4H), 7.77 (d, J = 5.1 Hz, 2H), 8.31 (s, 2H), 8.70 (d, J = 5.1 Hz, 2H); MS (ESI): *m/z* (%): 851.4 (29) [MH⁺], 426.3 (100) [MH₂²⁺]; Elemental Analysis calc (%) for C₃₆H₅₀N₈O₁₆ × 4.5H₂O × 3.5NH₃ (H_{4.5}(NH₄)_{3.5}L × 4.5H₂O): C 43.61, N 16.25, H 7.07, O 33.08, found C 43.79, N 16.05, H 7.08, O 33.12.

Molecular Modeling

In order to assess the volume of the FeL_3 complex and the distance between the Gd^{3+} ions, a molecular model was built using the CACHE program. The structure of a Sr^{2+} complex was partially optimized using molecular mechanics (MM2 force field) and semi-empirical quantum calculations (PM5 method). A second water molecule was manually added so as to reproduce the experimental hydration number $q=2$. The sphere radius was set to the van der Waals radius for all atoms.