



Synthesis of New Cryptands Containing 3,5-Disubstituted-1-Methyl or 1-Hexadecyl-Pyrazole by [3+2] Condensation and Reduction

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Abstract

The synthesis of new cryptands containing 1-methyl or 1-hexadecyl-pyrazole is described in high yield using metal templated [3+2] tripodal condensation.

Introduction

There is considerable interest in the design and synthesis of cryptands as these molecules have enormous applications in the field of chemistry, biochemistry and material research [1]. As ligands, these molecules possess several desirable features such as their donor atom topology, binding site rigidity, layer effect etc. that determine the stability, selectivity and properties of their complexes with metal ions. These metal complexes present a multitude of new properties such as interaction between cations [2], electrochemical [3] or photochemical [4] processes and fixation of bridging substrates [5] which are of interest for bioinorganic modelling and for multicenter-multielectron reactions [1] and catalysis [6]. Since the work of Jazwinski *et al.* [7], many new Schiff base and polyaza cryptands which show special coordinative abilities toward transition metal elements, have been synthesized [8, 3, 9] by [3+2] tripodal condensation of dialdehydes and tris(2-aminoethyl)amine followed by reduction, in simple and high yield processes. Although Schiff-base and polyaza cryptands have interesting properties as mentioned above, some Schiff bases readily polymerize in some solvents and the dialdehydes require rigid structures [8]. To circumvent these problems, high dilution techniques and the use of templates such as alkali or transition metal ions or rare earth elements [10] have been used to increase the yields.

Recently, lanthanide (III) complexes with encapsulating ligands have been the subject of numerous studies due to their potential applications in selective extraction of metals, NMR imaging contrast agents, fluoroimmunoassay, diagnostic agents and in other clinical applications such as luminophores and as luminescent concentrators [11]. Luminescent lanthanide complexes of chelating ligands have been used as markers in cytology and immunology and may serve as luminescent biomarkers [11]. One of the most tantalizing applications of lanthanide (III) macrocycles is the

efficient catalytic cleavage of RNA (transesterification of RNA) [11]. Macrocyclic compartmental ligands have been systematically investigated for the preparation of mono- and polynuclear lanthanide complexes [12] but improved protection of the Ln (III) from the solvent is expected to be obtained with macrobicyclic ligands; in fact it has been stated that these types of ligands could enhance some interesting properties that make their lanthanide complexes valuable for the development of technological applications [13]. Many metal complexes with cryptands derived from condensation of tris(2-aminoethyl)amine and 2,6-diformylphenols have been reported in the literature which have been shown to form stable metal complexes: mononuclear [10a,b, 14–16] and binuclear [17] with a wide range of metal ions [18]. To the best of our knowledge none of the above mentioned metal cryptates sought to incorporate pyrazole as a donor. Thus in the present manuscript we have designed and synthesized new cryptands containing pyrazole as one of the donor moieties.

Experimental

M.p.s were determined in capillaries and are uncorrected. ¹H NMR and ¹³C NMR spectra were obtained using a Bruker Ac 200 MHz spectrometer using TMS as an internal standard and CDCl₃/D₂O as solvent. FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using xenon (6 Kv, 10 mA) as the FAB gas. 1-Methylpyrazole-3,5-dicarbaldehyde was prepared by the method already reported by us [19].

Preparation of pyrazole precursors

Dimethyl-1-hexadecyl-3,5-pyrazoledicarboxylate **1b**

Hexadecyl bromide (3.05 g, 10 mmol) was added dropwise over a period of 30 minutes to a solution of dimethyl-3,5-pyrazole dicarboxylate (2.12 g, 10 mmol) in acetone. After

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the completion of the reaction (t.l.c., 4 h), the solvent was removed under reduced pressure and the residue in water was extracted with 3 × 50 mL portions of chloroform. The organic layer was dried over anhydrous Na₂SO₄, filtered and distilled to yield compound **1b**. Yield 60%. M.p. 80 °C (Hexane). I.R. (KBr) 1730 cm⁻¹ (COO); ¹H NMR (CDCl₃): δ 7.34 (1 H, s, PzH), 4.61 (2H, t, J = 7.6Hz, NCH₂CH₂), 4.33 (2H, q, J = 7.2Hz, OCH₂CH₃), 4.36 (2H, q, J = 7.2Hz, OCH₂CH₃), 1.81–1.84 (2H, m, CH₂), 1.40 (3H, t, J = 7.2Hz, CH₂CH₃), 1.24 (24H, s, CH₂), 0.87 (5H, distorted t, J = 6.6Hz, CH₂CH₃); ¹³C NMR (CDCl₃): δ 161.60, 158.98 (CO), 141.88 (C₃Pz), 133.19 (C₅Pz), 113.90 (C₄Pz), 61.25 (OCH₂), 61.05 (OCH₂), 52.83 (NCH₂), 31.82 (CH₂), 30.59 (CH₂), 29.59 (CH₂), 29.42 (CH₂), 29.35 (CH₂), 29.26 (CH₂), 29.05 (CH₂), 26.39 (CH₂), 22.58 (CH₂), 14.27 (CH₃); *m/z* 408 (M⁺). Anal. Calcd. for C₂₃H₄₀N₂O₄ C, 67.64; H, 9.30; N, 6.86. Found: C, 67.43; H, 9.18; N, 6.74.

1-Hexadecyl-3,5-bis(hydroxymethyl)pyrazole 2b

A solution of dimethyl-1-hexadecyl-3,5-pyrazoledicarboxylate (2.62 g, 6.02 mmol) in 100 mL of dry ether was added dropwise under nitrogen to a suspension of 0.8 g (21.62 mmol) of LiAlH₄ in 100 mL of the same solvent. After the addition was completed (2 h) the reaction mixture was allowed to reflux for 24 h. The excess of LiAlH₄ was hydrolysed by slow and consecutive addition of 25 mL of MeOH and 100 mL of saturated NH₄Cl solution. After the separation of the ppt in the suspension by filtration and by evaporation of the solvents an oily residue was obtained. The water was removed from this residue azeotropically with ethanol to yield the title compound in 60% yield. ¹H NMR (CDCl₃): δ 6.17 (1H, s, PzH), 4.65 (2H, s, PzCH₂), 4.62 (2H, s, PzCH₂), 1.82–1.86 (2H, m, CH₂), 1.26 (24H, s, CH₂), 0.89 (5H, distorted t, J = 6Hz); ¹³C NMR (CDCl₃): δ 150.71 (C₃Pz), 142.09 (C₅Pz), 103.94 (C₄), 58.71 (OCH₂), 55.31 (OCH₂), 49.48 (NH₂), 31.85 (CH₂), 30.51 (CH₂), 29.61 (CH₂), 29.52 (CH₂), 29.45 (CH₂), 29.30 (CH₂), 29.20 (CH₂), 26.71 (CH₂), 22.63 (CH₂), 14.05 (CH₃); *m/z* 352 (M⁺).

Preparation of 1-hexadecyl-3,5-(1H-pyrazole)-dicarbaldehyde 3b

To a refluxing solution of 1-methyl-3,5-bis(hydroxymethyl)pyrazole (40 mmol) in dioxane was added solid MnO₂ (40 g, 460 mmol) portionwise. The refluxing was then continued and the reaction was complete after four hours. Insoluble material was then removed by filtration through a celite bed and washed with hot dioxane. The solution was decolorized with charcoal and after filtration, evaporated to dryness to yield the title compound in 70% yield. M.p. 56 °C. I.R. (KBr) 1675 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 9.90 (s, 1H, CHO), 9.89 (s, 1H, CHO), 7.39 (1H, s, PzH), 4.60 (2H, t, J = 7.2Hz NCH₂), 1.82–1.88 (2H, m, CH₂), 1.25 (24H, s, CH₂), 0.84–0.90 (m, 5H CH₂CH₃); ¹³C NMR (CDCl₃): δ 185.51 (CO), 179.55 (CO), 114.38 (C₄), 53.14 (CH₂), 31.90 (CH₂), 30.17 (CH₂), 29.66 (CH₂), 29.44 (CH₂), 29.3 (CH₂), 29.03 (CH₂), 26.35 (CH₂), 22.64 (CH₂), 14.07 (CH₃); *m/z* 348 (M⁺). Anal. Calcd. for C₂₁H₃₆N₂O₂ C, 72.41; H, 11.49; N, 3.04. Found: C, 72.15; H, 11.13; N, 2.73.

Template synthesis of 4

Tris(2-aminoethyl)amine (1.0 mmol) in 40 mL of methanol was added dropwise to a solution of dialdehyde **3** (1.5 mmol) and lanthanum nitrate (1.0 mmol) in methanol. The reaction mixture was refluxed for 12 hours. A yellow powder separated which was filtered, washed and dried under vacuum to give the pure cryptate in 70% yield. m.p. > 220 °C. I.R. 1620 cm⁻¹ (>C=N). Anal. Calcd. for C₃₀H₄₂N₁₄La₂(NO₃)₆·4H₂O. Found: C, 27.03; H, 3.63; N, 20.95, requires C, 27.27; H, 3.78; N, 21.21.

General procedure for the synthesis of 5a–b

A solution of 1-methyl-3,5-pyrazoledicarbaldehyde **1a–b** (276 mg, 2.00 mmol) in 20 mL of methanol was added dropwise to a stirred solution of TREN (1.33 mmol) in 60 mL of methanol. The reaction was monitored by tlc (CHCl₃: MeOH), and when it was complete, (ca. 4 h) NaBH₄ (500 mg, 6.00 mmol) was added portionwise. After 2 h the solvent was evaporated under reduced pressure to give a residue. This residue was then dissolved in water and extracted with chloroform. The chloroform solution was then dried with anhydrous sodium sulphate and distilled under reduced pressure to give **5a–b**.

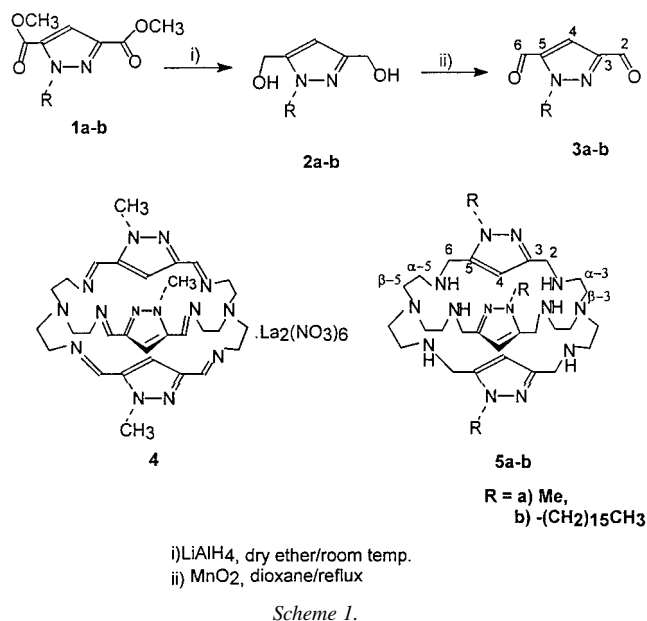
5a: yield 55% thick liquid. ¹H NMR (CDCl₃) δ 5.95 (1H, PzH), 5.87 (s, 2H, PzH), 3.68, 3.65 (s, 9H, NCH₃), 3.60 (12H, br, m, PzCH₂NH), 2.73 (br, s, 12H, NHCH₂CH₂), 2.60 (br, s, 12H, NHCH₂CH₂), 1.96 (br, s, NH, disappears in D₂O). ¹³C NMR (CDCl₃): 149.64 (PzC₃), 141.81 (PzC₅), 102.94 (PzC₄), 54.30 (C_{β-3}), 53.82 (C_{β-5}), 47.99 (C_{α-3,α-5}), 47.25 (C₂—NH), 44.61 (C₆—NH), 35.94 (NCH₃); *m/z* 612 (M⁺).

5b: yield 50% thick liquid. ¹H NMR (CDCl₃) δ 5.80 (s, 1H, PzH), 5.73 (s, 2H, PzH), 3.87 (distorted triplet, 6H, —CH₂—), 3.51 (s, 6H, PzCH₂NH), 3.47 (s, 2H, PzCH₂NH), 3.43 (s, 4H, PzCH₂NH), 2.58–2.62 (m, 24H, NHCH₂), 1.66 (m, 6H, —CH₂—), 1.18 (s, 78H, —CH₂—), 0.81 (distorted triplet, 9H, CH₃). ¹³C NMR (CDCl₃): δ 149.74 (PzC₃), 141.90 (PzC₅), 102.36 (PzC₄), 54.29 (C_{β-3}), 53.81 (C_{β-5}), 49.10 (C_{α-3}), 48.40 (C_{α-5}), 47.52 (C₂—NH), 44.62 (C₆—NH), 31.86 (CH₂), 30.43 (CH₂), 29.66 (CH₂), 29.29 (CH₂), 26.79 (CH₂), 22.64 (CH₂), 14.03 (CH₃); *m/z* 1240 (M⁺).

Results and discussion

Previously, one of us reported the synthesis of different series of macrocycles and macrobicycles containing two or three 3,5-disubstituted pyrazole units linked to the polyamine chains by imines or amine bonds [9, 20]. In basic medium, these ligands formed di- or tripyrazolate sodium salts from which di- and/or tetranuclear Zn(II) and Cu(II) complexes were formed [9, 21]. The acid-base behaviour of these polyamines have also been reported recently [22]. Apart from this we have also reported a series of new bis-calix[4]arenes with imine units at the lower rim [23]. Now, we have synthesized (Scheme 1) new cryptands containing 1-methyl and 1-hexadecylpyrazole moieties by

[3+2] tripodal condensation. Thus, the metal templated reaction between 1-methyl-3,5-(1H-pyrazole)dicarbaldehyde **3a** and tris(2-aminoethylamine)amine (TREN) in the presence of lanthanum nitrate in a 3:2:2 mole ratio in ethanol for ca. 12 h yields a yellow powder of formula $C_{30}H_{42}N_{14}La_2(NO_3)_6 \cdot 4H_2O$. Unfortunately, suitable crystals of this complex could not be obtained for x-ray crystallography. The FAB mass spectrum of this complex displayed an intense peak at m/z 1186 corresponding to the fragment $[La_2L(NO_3)_5]^+$ confirming the presence of a macrobicyclic in the complex. The IR spectrum of this complex shows a band at 1620 cm^{-1} and there is no band corresponding to free carbonyl and free amino groups which indicates the cyclization reaction has taken place. Similarly, the polyamine tripyrazolate-bisTREN was synthesized in 55% yield by condensation of **3a** (4.00 mmol) and TREN (2.66 mmol) in methanol (150 mL) followed by reduction *in situ* of the resulting Schiff base with $NaBH_4$ (10 mmol). The structure of the resulting macrobicyclic polyamine has been established on the basis of the spectroscopic data. In the 1H NMR spectra of **5a–b** the presence of the 1-alkyl substituent breaks the magnetic equivalence of the pyrazole environment. In the ^{13}C NMR spectrum of **5**, different signals can be observed for the quaternary carbon atoms labeled as C_3 and C_5 [the pyrazole $N=C_3$ appears at lower field than $C_4 = C_5$]. The carbon atoms $C_{\alpha-5}$ and $C_{\beta-5}$ which are closer to the pyrazole 1-alkylsubstituent appear at higher field than $C_{\alpha-3}$ and $C_{\beta-3}$ which are close to the sp^2 nitrogen. The 1H NMR spectrum of polyamine **5a** shows singlets at δ 5.94 (1H) and 5.85 (2H) corresponding to the protons of the pyrazole ring, two singlets at δ 3.68 and 3.65 corresponding to NCH_3 protons and a multiplet at 3.55–3.60 corresponding to $PzCH_2NH$ protons. Another broad singlet appears at δ 2.73 and 2.60 corresponding to NCH_2 ($\alpha-3$, $\alpha-5$) and NCH_2 ($\beta-3$, $\beta-5$) protons. In the mass spectrum of this compound a peak appears at 612 ($M^+ + 2$). These spectroscopic data corroborate the structure **5a** for this compound. This ligand is a good host for rare earth and transition metal elements. Similarly, when 1-hexadecyl-3,5-(1H-pyrazole)dicarbaldehyde **3b** was condensed with TREN in methanol no solid separated from the reaction mixture. The Schiff base formed *in situ* was reduced with $NaBH_4$ to give polyamine tripyrazole bis TREN **5b** in 50% yield. The structure of this polyamine tripyrazole (**5b**) has been established on the basis of spectroscopic data. In its FAB mass spectrum a peak appears at m/z 1240 (M^+). The 1H NMR spectrum of this compound shows a distorted triplet at δ 0.81 corresponding to CH_3 of the hydrocarbon chain, a singlet corresponding to 78 protons appears at δ 1.18, a multiplet corresponding to 6 protons appears at δ 1.66, another multiplet corresponding to 24 protons (NCH_2) appears at δ 2.58–2.62. The methylene protons adjacent to the pyrazole ring appear as singlets at δ 3.43 (4H), 3.47 (2H) and δ 3.51 (6H), and two singlets corresponding to the protons of the pyrazole ring at δ 5.80 (1H) and 5.80 (2H) respectively. These spectroscopic data corroborates the structure **5b** for this compound.



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