

Inhibition of metal ion complexation by an N₂O₂-donor macrocycle by incorporation of an intramolecularly hydrogen-bonding pendant phenolic group

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Abstract The synthesis and X-ray structure of a new pendant-arm derivative of a parent 14-membered N₂O₂-donor macrocycle bearing an *N*-substituted 6-methylene-2,4-dimethylphenol group is presented. A single crystal X-ray study shows a strong intramolecular hydrogen-bond between the pendant phenol proton and the tertiary nitrogen of the macrocyclic ring, which may inhibit its ability to bind with selected transition and post-transition metal ions.

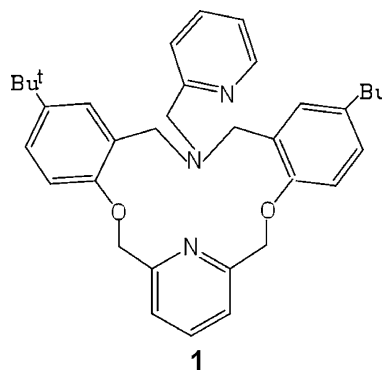
Keywords Crystal structure · Hydrogen bond · Macrocycle · *N*-substitution · Pendant arm · Phenol substituent

Introduction

The metal-ion chemistry of macrocycles that incorporate additional donor functional groups incorporated in side chains appended to their macrocyclic ring has been investigated for many years [1–3]. For example, we have undertaken studies in which various pendant arms have been attached to both nitrogen [4–7] and carbon [8] atoms of a macrocycle ring. Such pendant-arm derivatives

characteristically resemble both simple macrocyclic and open-chain ligand categories in their metal binding properties. For example, the resulting metal complexes often exhibit the enhanced stability typical of macrocyclic systems while showing some degree of the coordination flexibility characteristic of many non-macrocyclic systems [9]. Overall, it has also been well demonstrated that the introduction of appropriate pendant functional donor groups generally enhances the cation-binding capacity of simple macrocycle ligands.

In a previous study we have synthesised the pendant-arm ligand **1**, derived from its parent macrocyclic ring **2** (see Scheme 1) and demonstrated that it is an excellent coordinating agent towards copper(II), zinc(II), cadmium(II), silver(I) and lead(II) [7].



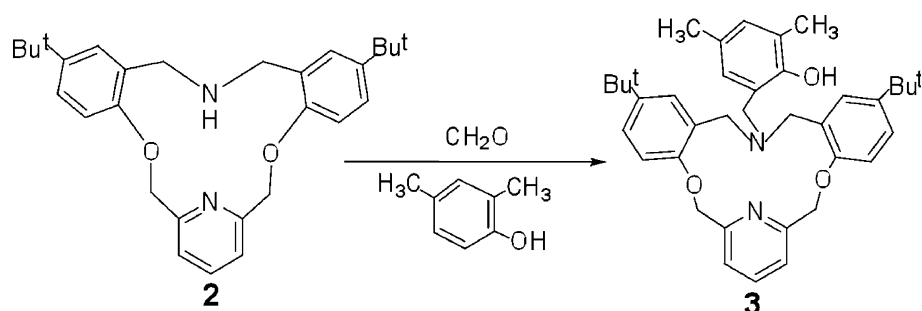
A tribute to the outstanding contribution of Len Lindoy to Inorganic, Macrocyclic and Supramolecular Chemistry.

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Each of these ions forms a 1:1 complex with **1**, with individual log *K* values in 95% methanol (0.1 Et₄ClO₄, 25 °C) ranging from 6.7 (Pb) to >14 (Cu and Ag). In part, these results motivated us to probe the metal ion binding properties of the related 6-methylene-2,4-dimethylphenol pendant-arm macrocycle **3** (also derived from **2**, see Scheme 1). It was anticipated that the singularly charged,

Scheme 1 Synthesis of the 6-methylene-2,4-dimethylphenol pendant-arm macrocycle **3**



deprotonated form of **3** might lead to interesting new metal ion chemistry when reacted with ions such as those mentioned above. Accordingly, the synthesis of **3** was undertaken and a preliminary investigation of its interaction with individual transition and post-transition metals was made.

Experimental

Materials and instrumentation

¹H and ¹³C NMR spectra were recorded in CDCl₃ using a Bruker AC200 spectrometer. Where available, all reagents were of analytical grade and were used without further purification. The synthesis of the precursor macrocycle **2** has been reported previously by us [7].

Synthesis of **3**

Precursor macrocycle **2** (1.3 g, 3 mmol), 2,4-dimethylphenol (0.5 g, 4 mmol) and 37% formaldehyde solution (1 mL) were added to toluene (5 mL) and water (10 mL). The resultant mixture was refluxed with stirring for 24 h and then cooled to room temperature. The crude product (**3**) was extracted with dichloromethane (150 mL × 2). The combined extracts were dried over anhydrous sodium sulfate and evaporated on a rotary evaporator to give a crude powder which was slurried in cold methanol and collected as a white solid (1.15 g, 68%). This was then recrystallised from a mixture of ethanol and dichloromethane (5:1) over 3 days to yield colourless crystals; mp 213–215 °C; a crystal from this batch was used for the X-ray diffraction study. Calc. for C₃₈H₄₆N₂O₃: C, 78.86; H, 8.01; N, 4.58. Found: C, 78.81 H, 7.94; N, 4.58%. ¹H NMR (CDCl₃) δ 1.25 (s, (CH₃)₃, 18 H), 2.19 (s, CH₃–4Ph, 3H), 2.21 (s, CH₃–2Ph, 3H), 3.66 (s, PyCH₂N, 2 H), 3.87 (s, (CH₂N, 4 H), 5.19 (s, CH₂O, 4 H), 6.64 (s, H–3Ph, 1H), 6.84 (d, J = 9 Hz, H–6', 2 H), 7.14 (dd, J = 2, 4 Hz, H–5'), 7.18 (H–5Ph), 7.26 (d, J = 2 Hz, H–3(5), 2 H), 7.34 (d, J = 2 Hz, H–3', 2 H), 7.61 (t, J = 8 Hz, H–4, 1 H); ¹³C NMR (CDCl₃) δ 15.8, 20.4, 31.4, 34.1, 53.6, 57.2, 72.0,

113.8, 121.4, 121.9, 124.8, 126.8, 127.1, 128.8, 130.0, 136.6, 144.1, 153.8, 154.5, 155.4, 156.6.

Structure determination

A full sphere of CCD/area detector diffractometer data was measured (Bruker AXS instrument; monochromatic Mo Kα radiation, λ = 0.71073 Å, ω-scans, 2θ_{max} 58°; T ca. 153 K) yielding 34,166 reflections, these merging to 8,721 independent, after 'empirical'/multiscan 'absorption correction' (μ_{Mo} = 0.071 mm⁻¹; specimen: 0.55 × 0.40 × 0.02 mm; T_{min/max} = 0.79; R_{int} = 0.084) which were used in the full matrix least squares refinements on F² (reflection weights: (σ²(F_o²) + (0.085P)²)⁻¹ (P = (F_o² + 2F_c²)/3)), refining anisotropic displacement parameter forms for the non-hydrogen atoms, hydrogen atom treatment following a riding model, the phenolic hydrogen excepted, which was refined in (x,y,x,U_{iso}). Residuals at convergence were R₁ = 0.065 (3582 reflections, I > 2σ(I)), wR₂ = 0.17; S = 0.86; |Δρ_{max}| was 0.36 eÅ⁻³. Pertinent results are given below and in Fig. 1 which shows non-hydrogen atoms with 50% probability amplitude displacement envelopes, hydrogen atoms having arbitrary radii of 0.1 Å. Neutral atom complex scattering factors were employed within the SHELXL 97 program [10].

Crystal data

C₃₈H₄₆N₂O₃, M = 578.8. Monoclinic, space group P2₁/c (C_{2h}⁵, No. 14), a = 19.028(7), b = 16.675(6), c = 11.049(4) Å, β = 104.148(7)°, V = 3399(2) Å³. D_c (Z = 4) = 1.13₁ g cm⁻³.

Results and discussion

The pendant-arm product **3** was obtained by reaction of the macrocyclic precursor **2** with 2,4-dimethylphenol and formaldehyde in a 'one pot' condensation procedure (Scheme 1). The ¹H and ¹³C NMR spectra (in CDCl₃) as well as the microanalytical data were in accord with the expected structure.

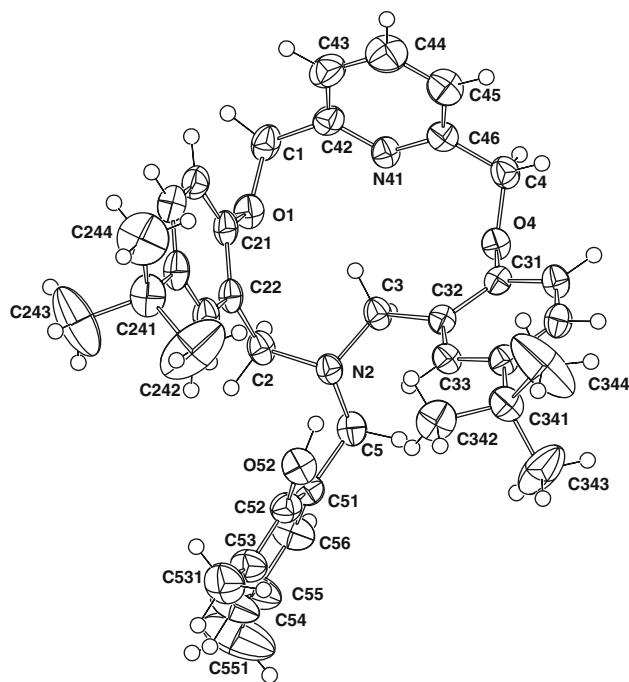


Fig. 1 Molecular projection of **3**, through the macrocycle with crystallographic numbering scheme. O(1)–C(1,21) are 1.429(3), 1.383(3); O(4)–C(4,31) 1.431(3), 1.395(2) Å; C(52)–O(52) is 1.371(3) Å. Intraring angles at C(24,34,53,55) are 116.8(2), 116.6(2), 117.2(2), 117.5(3); angles at O(1,4) are 118.5(2), 116.4(2)°

Despite reports that some other macrocyclic systems bearing appended phenol groups do yield stable complexes with individual transition and post transition metal ions in their phenol-deprotonated forms [11–16], preliminary attempts at obtaining pure complexes of **3** with ions of the type previously employed in the formation of these complexes were unsuccessful. Where solids were obtained they presented as intractable mixtures of metal hydrolysis products, reflecting the basic conditions employed. In the absence of base no products were isolated; we find no other records of structure determinations of ligands or complexes with the skeleton of **3** (i.e., devoid of methyl or *t*-butyl groups) recorded in the Cambridge Structural Database although structures of copper(II), silver(I) and lead(II) have been reported for the same macrocycle with pendant 2-CH₂-C₅H₄N (methyl pyridyl) [5], namely **1** mentioned earlier [7]. The reluctance of **3** to yield isolable pure complexes under neutral or basic conditions was initially surprising and led to a single crystal X-ray study. The structure was consistent with the stoichiometry and connectivity proposed for **3** on the basis of the physical measurements; a single molecule devoid of crystallographic symmetry, and well removed from any potential mirror symmetry as suggested in the representation in Scheme 1, comprises the asymmetric unit for the structure (Fig. 1). Intramolecular geometries are unremarkable and consistent

with the usual norms. A powerful determinant of conformational stereochemistry, bearing on (at the least) local potential coordination characteristics in the vicinity of the phenolic oxygen appears to arise in the form of the strong intramolecular interaction found between the phenolic hydrogen and the nearby pyramidal macrocyclic nitrogen atom, the lone pair of the latter being appropriately directed (N⋯H,O 1.82(3), 2.713(3) Å, angle sum at N 339.6°), a stabilising six-membered ring being thereby formed. An analogous six-membered ring involving an intramolecular phenol-amine hydrogen bond has been reported previously in the solid state structure of a related twenty-membered N₂O₄-donor macrocyclic ligand bearing a substituted methylenephenol pendant group [17].

Conclusion

If the strong hydrogen-bonded arrangement in the neutral ligand is maintained in solution it will clearly inhibit metal binding by the tertiary nitrogen donor in the macrocyclic ring. Such an arrangement will also likely restrict the remainder of the fourteen-membered ring to an unfavourable conformation for metal binding. It appears that strongly basic conditions may be necessary to break this hydrogen bond but, under the conditions employed by us, any complexation behaviour has been accompanied by hydrolysis such that only (insoluble) intractable species could be isolated.

Supplementary material

Crystallographic data for **3** have been deposited with CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, CCDC 733225. Copies of this information can be obtained free of charge on request by e-mail at deposit@ccdc.cam.ac.uk or at <http://www.ccdc.cam.ac.uk>.

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