

2-[[Bis(2-pyridylmethyl)amino]-methyl]-6-[(2-hydroxyanilino)methyl]-4-methylphenol: a novel binucleating asymmetric ligand as a precursor to synthetic models for metalloenzymes

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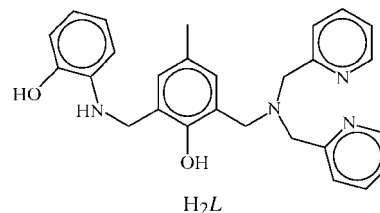
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The title compound (H_2L), $C_{27}H_{28}N_4O_2$, is an asymmetric binucleating ligand with well defined soft (N_3O -donor) and hard (NO_2 -donor) sides. H_2L was designed as a ligand for the preparation of heterodinuclear mixed-valence M^{III}/M^{II} complexes which are models for heterobimetallic active sites of enzymes, principally calcineurin. The molecular structure of H_2L shows a spatial pre-organization of the donor groups for coordination. This conformation is stabilized by bifurcated intra- and intermolecular $O-H\cdots N$ hydrogen bonds involving both phenol groups. The intermolecular hydrogen bonds link molecules of H_2L into chains running parallel to the crystallographic c axis.

Comment

Many enzymes contain bimetallic cores within their catalytic sites and can be classified as either homobinuclear [e.g. catechol oxidase, with its $Cu^{II}Cu^{II}$ centre (Klabunde *et al.*, 1998)] or heterobinuclear [e.g. kbPAP, with its $Fe^{III}Zn^{II}$ centre (Sträter *et al.*, 1995)] metalloenzymes, depending on the nature of the metals present. Recent X-ray crystallographic studies have indicated that, even for homobinuclear sites, the two metal centres usually reside in chemically different environments, an asymmetry that may also involve the coordination numbers and the geometry of the metal centres (Belle & Pierre, 2003). Calcineurin, a phosphatase found predominantly in neural tissues, constitutes an interesting example of total asymmetry in heterobinuclear sites: the metal, coordination number, donor and geometry all exhibit asymmetry. This enzyme contains an $Fe^{III}Zn^{II}$ bimetallic core in its active centre, which comprises an octahedral Fe^{III} nucleus coordinated by one O atom from Asp90, one N atom from His92, an O-bridging carboxylate from Asp118 and three water molecules, one of which acts as an exogenous bridge. On

the other hand, the Zn^{II} centre shows a distorted trigonal-bipyramidal geometry formed by three O atoms from Asp118, Asn150 and the bridging water molecule, and two N atoms from His199 and His281 (Kissinger *et al.*, 1995).



In recent years, the study of models based on simple dinuclear metal complexes has become an important tool for gaining insight into the biological functions of such bimetallic cores. In this context, the design of binucleating ligands capable of providing asymmetric dinuclear complexes is a subject of great interest. It is convenient to classify binucleating ligands by the bridging groups that are used for assembling the two metal ions in close proximity (Gavrilova & Bosnich, 2004). Our research group has extensive experience in the development of asymmetric binucleating ligands containing alkoxide (Rossi *et al.*, 2005) and phenoxide (Mitić *et al.*, 2006) bridging units, which have been used in the synthesis of numerous bimetallic complexes. We report here the structure of a new phenoxide-based binucleating hexadentate ligand, H_2L , which presents donor, geometry and coordination-number asymmetries, thereby constituting a versatile precursor to synthetic models for the active sites of asymmetric metalloenzymes, with a special focus on calcineurin. It should be emphasized that H_2L possesses a softer N_3O -donor side, defined by the tertiary amine, both pyridine rings and the bridging phenolate group, capable of accommodating divalent metal ions, and a harder NO_2 -donor side,

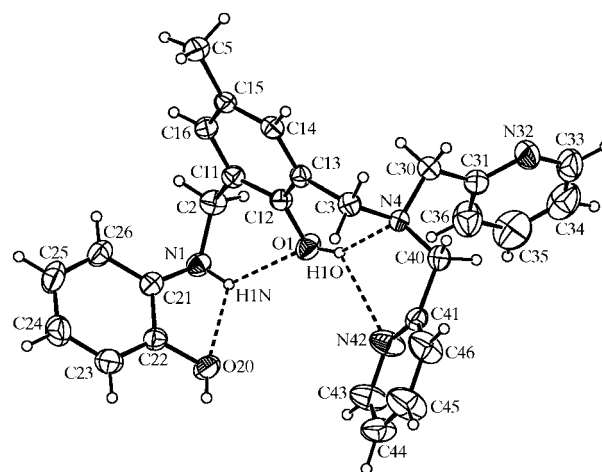


Figure 1
The molecular structure of H_2L , showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 40% probability level. All H atoms are shown and the intramolecular hydrogen bonds are drawn as dashed lines.

comprising the secondary amine and the terminal and bridging phenol moieties, which binds preferentially to trivalent cations. This represents a convenient strategy for the attainment of mixed-valence heterobimetallic systems.

The structure of H_2L is shown in Fig. 1, and selected bond lengths and angles are given in Table 1. The bond distances and angles for the aromatic and heteroaromatic rings are not significantly different from those found in similar compounds containing these groups, for example, 2,6-bis-[(2-hydroxyphenyl)(2-pyridylmethyl)amino]methyl-4-methylphenol (Campbell *et al.*, 1993) and 4-*tert*-butyl-2,6-bis[(4-methylpiperazin-1-yl)methyl]phenol (Shanmuga Sundara Raj *et al.*, 1994). An interesting trend in the three-dimensional arrangement of the molecule is that H_2L shows a self-induced spatial pre-organization of the donor groups for coordination: with the exception of atom N32, all donor atoms point towards bridging atom O1. The respective O20...O1 and N42...O1 distances are 3.622 (3) and 3.310 (4) Å, very similar to the values observed for a hydroxo-bridged $Fe^{III}Zn^{II}$ complex [3.950 (8) and 3.354 (8) Å, respectively] of the asymmetric ligand 2-[bis(2-pyridylmethyl)aminomethyl]-6-[(2-hydroxybenzyl)(2-pyridylmethyl)amino]methyl-4-methylphenol (Neves *et al.*, 2007).

The molecular conformation is influenced by intra- and intermolecular hydrogen bonds involving both phenol groups (Table 2). Within each molecule, the N1—H1N donor interacts with the acceptors O1 [N...O = 2.896 (3) Å] and O20 [N...O = 2.662 (3) Å], although the latter only achieves a less favourable five-membered ring. The bridging phenol acts as an acceptor in the N1—H1N...O1 interaction, and as a donor in

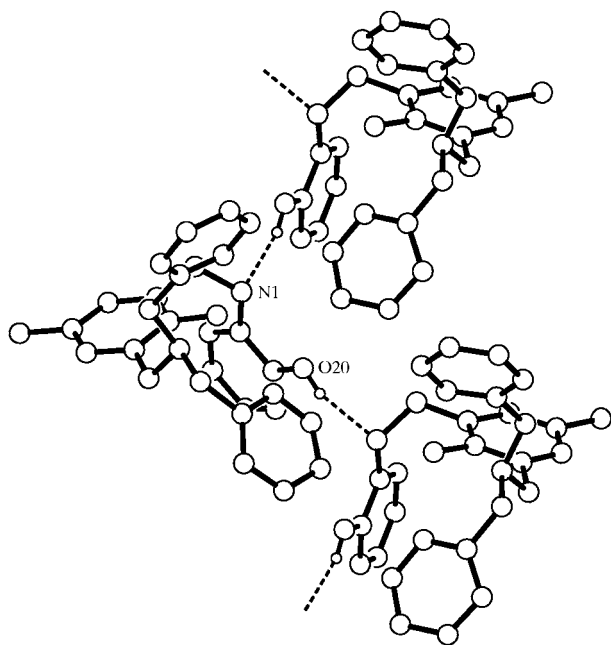


Figure 2

A view of H_2L , showing the hydrogen-bonding network. Intermolecular hydrogen bonds are drawn as dashed lines.

a second bifurcated hydrogen bond involving the interactions O1—H1O...N4 [moderate, O...N = 2.758 (3) Å] and O1—H1O...N42 [weak, O...N = 3.309 (4) Å]. It is interesting to note that the shorter component of this bifurcated hydrogen bond is associated with a narrower angle [N4—C3—C13 = 112.7 (2)°] compared with N1—C2—C11 [116.1 (2)°].

The title ligand has a direct linkage between the terminal phenolic ring and the secondary amine, allowing the formation of a more rigid five-membered chelate during the complexation process. The constriction induced in the complexes by going from a six-membered to a five-membered ring can give rise to modified spectroscopic and electrochemical properties. This was observed by Neves *et al.* (1992) for a mononuclear Mn^{III} complex with the ligand *N,N'*-bis(2-hydroxybenzyl)-*N,N'*-bis(2-methylpyridyl)ethylenediamine. As far as we know, there is only one previous example in the literature of a phenoxide-bridging ligand with such a structural feature (Campbell *et al.*, 1993).

Moderate intermolecular hydrogen bonds (Table 2) of the type O20—H20O...N1ⁱ [2.814 (3) Å; symmetry code: (i) $x, \frac{1}{2} - y, z - \frac{1}{2}$] link the molecules of H_2L into zigzag chains (Fig. 2) which run parallel to the crystallographic *c* axis.

Experimental

H_2L was synthesized from the precursor compound 3-[*N,N*-bis(2-pyridylmethyl)aminomethyl]-5-methylsalicylaldehyde (bpmamff), which was prepared as described by Uozumi *et al.* (1998) by nucleophilic substitution of bis(2-pyridylmethyl)amine in 3-chloromethyl-5-methylsalicylaldehyde. A methanolic solution (10 ml) of 2-aminophenol (0.32 g, 2.9 mmol) was added dropwise to a stirred solution of bpmamff (1.0 g, 2.9 mmol) in methanol–tetrahydrofuran (1:1, 20 ml) and the mixture was left to react for 30 min. A strong orange colour appeared progressively due to the formation of the Schiff base. Reduction of the imine was performed by the addition, in portions, of $NaBH_4$ (0.11 g, 2.9 mmol) in an ice bath. The pH of the medium was then carefully adjusted to 6.0–7.0 with 4 M HCl, and the solvent was evaporated to half of its initial volume. The solution was then filtered to eliminate any undesirable precipitate. After a few hours, crystals of H_2L suitable for X-ray determination were isolated by filtration, washed with small amounts of cold methanol and diethyl ether, and dried *in vacuo* (yield 0.56 g, 44%; m.p. 416 K). Analysis found: C 73.56, H 6.33, N 12.55%; calculated for $C_{27}H_{28}N_4O_2$: C 73.61, H 6.41, N 12.72%.

Crystal data

$C_{27}H_{28}N_4O_2$
 $M_r = 440.53$
 Monoclinic, $P2_1/c$
 $a = 12.651$ (1) Å
 $b = 21.071$ (5) Å
 $c = 9.262$ (1) Å
 $\beta = 106.09$ (1)°
 $V = 2372.2$ (7) Å³

$Z = 4$
 $D_x = 1.233$ Mg m⁻³
 Mo $K\alpha$ radiation
 $\mu = 0.08$ mm⁻¹
 $T = 293$ (2) K
 Irregular block, pale yellow
 $0.46 \times 0.30 \times 0.23$ mm

Data collection

Enraf–Nonius CAD-4
 diffractometer
 $\omega/2\theta$ scans
 4338 measured reflections
 4142 independent reflections
 2138 reflections with $I > 2\sigma(I)$

$R_{int} = 0.039$
 $\theta_{max} = 25.1^\circ$
 3 standard reflections
 every 200 reflections
 intensity decay: 1%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.056P)^2 + 0.792P]$
$R[F^2 > 2\sigma(F^2)] = 0.053$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.155$	$(\Delta/\sigma)_{\max} < 0.001$
$S = 1.02$	$\Delta\rho_{\max} = 0.23 \text{ e } \text{Å}^{-3}$
4142 reflections	$\Delta\rho_{\min} = -0.18 \text{ e } \text{Å}^{-3}$
305 parameters	Extinction correction: <i>SHELXL97</i>
H atoms treated by a mixture of independent and constrained refinement	(Sheldrick, 1997)
	Extinction coefficient: 0.0072 (11)

Table 1
Selected geometric parameters (Å, °).

O1—C12	1.374 (3)	N4—C40	1.465 (4)
O20—C22	1.362 (3)	N4—C30	1.466 (4)
N1—C21	1.408 (4)	N4—C3	1.475 (4)
N1—C2	1.474 (4)	C2—C11	1.511 (4)
C21—N1—C2	119.0 (3)	C30—N4—C3	110.2 (2)
C40—N4—C30	111.0 (2)	N1—C2—C11	116.1 (2)
C40—N4—C3	109.6 (2)	N4—C3—C13	112.7 (2)

Table 2
Hydrogen-bond geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
N1—H1N \cdots O1	0.86 (1)	2.32 (2)	2.896 (3)	124 (2)
N1—H1N \cdots O20	0.86 (1)	2.22 (3)	2.662 (3)	113 (2)
O1—H1O \cdots N4	0.82	2.04	2.758 (3)	145
O1—H1O \cdots N42	0.82	2.68	3.309 (4)	134
O20—H20O \cdots N1 [†]	0.82	2.03	2.813 (3)	160

Symmetry code: (i) $x, -y + \frac{1}{2}, z - \frac{1}{2}$.

The phenol hydroxyl H atoms were found from ΔF maps and were then refined as part of rigid rotating groups, with O—H = 0.82 Å and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{O})$. The amine H atom was found in a ΔF map and thereafter refined with N—H restrained to 0.86 (1) Å. The remaining H atoms were added in their geometrically calculated positions and refined with C—H = 0.93 Å (0.96 Å for methyl groups) and $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$, with the H atoms on C5 being treated as an idealized methyl group equally disordered over two orientations separated by a rotation of 60°. The slightly high displacement parameters observed for atoms N42, C43, C44, C45 and C46 indicate possible disorder of this aromatic ring, but the ΔF peaks near C45 and C46 are small, and no valid disorder model could be developed. We therefore accepted the ordered model with high U values.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *SET4* in *CAD-4 EXPRESS*; data reduction: *HELENA*

(Spek, 1996); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM3018). Services for accessing these data are described at the back of the journal.

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