A prospective multidonor ligand: 2,6-bis(thiomorpholino)-*p*-cresol: synthesis, spectroscopic and crystal structure analysis

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An X-ray structure investigation of 2,6-bis (thiomorpholino)-*p*-cresol has been performed. The two thiomorpholino-groups have adopted the chair conformation and the cresol ring has deviated from planarity. The Willgerodt–Kindler reaction has been used to prepare this prospective ligand, having O, N and S donor sites, in a one pot synthesis.

Keywords: multidonor ligand, Willgerodt–Kindler reaction, crystal structure analysis

In the last few years, model studies with reference to the type 3 coppers have addressed mainly ligand environment, its architecture and number and type of donor atoms, which will greatly affect the geometry, spectral, magnetic and redox properties of the resulting complexes.

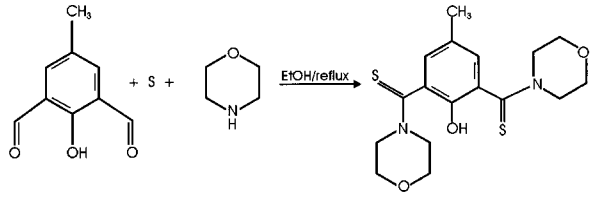
There are two principal strategies used for preparing biomimics; self assembly and total synthesis. The later strategy employs the technique of total synthesis to prepare an organic molecule (ligand) capable of binding the metal ion in a prescribed way. Subsequent addition of metal ion gives the desired complex. The advantage of this approach is that steric, hydrophobic or hydrophilic constraints can be incorporated into the complex; conceptually, the polypeptide loops and linkers in metalloproteins have been replaced by simple organic fragments holding the donors in the desired manner.[1]

Complexes with two metal ions in close proximity can result from the association of two monomeric units via an appropriate bridging group or from the incorporation of two metal ions into a single binucleating ligand. The latter route offers the advantage that the presence of binuclear form in solution is not governed by monomer – dimer equilibrium[2] and majority of the complexes reported so far are based on binucleating ligands.

For the first time, we have applied the Willgerodt–Kindler reaction to 2,6-diformyl-*p*-cresol to construct a novel ligand having O, N and S donor sites in a one pot synthesis. We thought that it is essential to structurally characterise this ligand before it could be exploited for using it as a precursor for designing a synthetic model for metalloenzymes. A lot of complex chemistry has to be done with this new family of multidonor ligands.

Experimental

The title compound was prepared by heating under reflux, 2,6-diformyl-*p*-cresol (1.64g), morpholine (8.7g) and sulfur (6.4g) on steam bath. An exothermic reaction occurred, and the mixture was refluxed for 3h. The resulting dark oil (which sometimes solidifies as red compound) was dissolved in boiling ethanol and the hot solution was filtered from a small insoluble residue. The filtrate on slow evaporation yielded diffraction-grade yellow needles; yield 60%.



Physical measurements: C, H and N were estimated on a Thermoquest CHN analyser. IR spectra were recorded in the 4000–400 cm^{-1} region (KBr disc) on a Nicolet 170 SX FT-IR instrument. The ^1H NMR spectra were obtained in d_6-DMSO on a JEOL AMX-400 NMR spectrometer. ^{13}C NMR spectra were recorded in d_6-DMSO on a JEOL GSX 400 spectrometer. Anal. Calcd (%) for $C_{17}H_{22}N_2O_3S_2$: C, 55.71; H, 6.05; N, 7.64; S, 17.5. Found: C, 55.62; H, 6.1; N, 7.59; S, 17.22. ^1H NMR (DMSO-d_6): 2.2 (s,3H,–CH_3), 6.93(s, 2H, aromatic H adjacent to CH_3), 3.63 and 4.2 (m, morpholine H), 9.1 (s, OH, D_2O exchangeable); ^{13} C NMR (DMSO-d_6): 194.7 (C–S), 141.3 (C–OH), 128–132 (C, aromatic), 38–51 (C, morpholine), 19.7 (–CH_3). IR (KBr discs):3394 cm^{-1} (–OH), 844 cm^{-1} (C=S). UV–Vis. (DMF): 262, 290 nm (π–π*), 382, 439 nm (n -π*).

X-Ray analysis: The X-ray diffraction data were collected on a Bruker Smart CCD Area Detector System using MoKα (0.71073Å) radiation for the crystal. Intensity data were collected up to a θ max of 27.5° for the compound in the $\omega - \phi$ scan mode. A total of 14021 reflections were collected, resulting in 3563 independent reflections of which the number of reflections satisfying $I>2\ \sigma(I)$ criteria were 2741, and these were treated as observed. The details of crystal data, data collection and the refinement are given in Table 1. Corrections for Lorentz and polarisation effects were applied. The structure was solved by Direct Methods and Difference Fourier synthesis using SHELXS97.[3] The positions of all non-hydrogen atoms were included in the full matrix least-square refinement using SHELXL97.[4] Anisotropic refinement using full matrix least square procedures was carried out for a few cycles until convergence was reached. Then the hydrogen atoms, (a few located in ΔF maps and a few geometrically fixed) were refined isotropically. The R factor after final convergence was 0.0961 and maximum and minimum values of residual electron density were 0.760 and –0.391 $eÅ^{-3}$. Figures were made using the programs ORTEP [5] and Pluton.[6]

Results and discussion

The crystal data are summarised in Table 1. The bond distances, angles and torsion angles are given in Table 2. All non-bonded interactions are tabulated in Table 3. The ORTEP diagram of the molecule is shown in Fig.1.

The planarity calculation of *p*-cresol labelled 'B', shows that the ring is slightly deviated from perfect planarity, which is probably due to the effect of substituents. This is a very common feature observed in methyl substituted benzene derivatives. It may be seen that two thiomorpholino-sulfur atoms S1 and S2 are transpositioned. Torsion angles (C1 – C2 – C16 – S1) = 56.09(2) Å, (C1 – C6 – C17 – S2) = 118.16 (1) Å explain the orientation of the sulfur atoms. The structure is characterised by a strong intramolecular hydrogen bonding (H–O1…S1) = 3.131(1)Å through thiomorpholino-sulfur S1 and

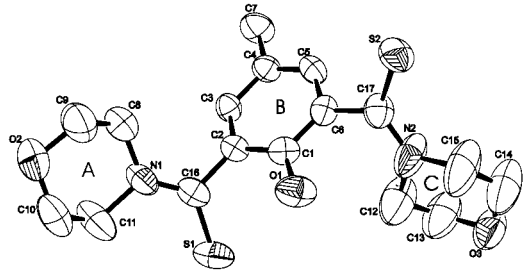


Fig 1. The structure of the title compound, showing 50% probability displacement ellipsoids and the atom numbering scheme.

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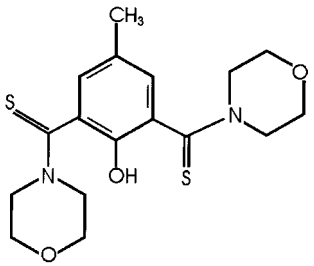
Table 1 Crystal data and structure refinement

Crystal date	
$C_{17}H_{22}N_2O_3S_2$	Mo $K\alpha$ radiation
M_r = 366.51	λ = 0.71073 Å
Monoclinic $P2_1/c$	Cell Parameters from 14021 reflections
a = 9.611 (2) Å	θ = 1.86 – 26.12°
b = 21.935 (5) Å	μ = 0.311 mm^{-1}
c = 9.196 (2) Å	*T* = 293 (2) K
β = 111.693 (4)°	Needle
V = 1801.4 (7) $Å^3$	Yellow
Z = 4	.36 × .26 × .12 mm
D_c = 1.351 Mg m^{-3}	
Data collection	
Bruker SMART CCD area-detector diffractometer	2741 reflections with >2sigma(*I*)
φ and ω scans	R_{int} = 0.0348
Absorption correction: none	θ_{max} = 26.12°
14021 measured reflections	*h* = –11 → 11
3563 independent reflections	*k* = –24 → 27
	l = –11 → 11
Refinement	
Refinement on F^2	$w=1/[\sigma^2(F_O^2) + (0.1038P)^2 + 3.2857P]$ where $P = (F_O^2 + 2F_C^2)/3$
$R(F)$ = 0.096	$(\Delta/\sigma)_{max}$ = 0.716
$wR(F^2)$ = 0.2534	$\Delta\rho_{max}$ = 0.76 e $Å^{-3}$
S = 1.076	$\Delta\rho_{min}$ = 0.391 e $Å^{-3}$
3563 reflections	Extinction correction: none
249 parameters	Scattering factors from *Internationsl Tables* for *Crystallography* (Vol. C)
H atoms treated by a mixture of independent and constrained refinement	



Scheme 1 A prospective multidonor ligand; 2,6-bis(thiomorpholino)-*p*-cresol.

phenolic oxygen O1. O1 also acts as an acceptor by forming an intermolecular contact (C3 – H3 …O1) = 3.575(1) Å. 144.33(1)° . This intramolecular hydrogen bonding may be the cause of the shortening of the distance (C1–O1) =1.361(5) Å and the lengthening of (C16 – S1) =1.668(5) Å as compared with normal expected values[7] (C-OH) =1.41 Å and also observed in 2-hydroxy-5-methyl benzoic acid,[8,9] (C = S) =1.66(1)Å. The (C4 – C5) distance in the cresol ring is also shortened (1.377(6) Å) and similar observations were made, for example, in the structures of salicylic acid,[10] 2,4-dihydroxy benzophenone,[11] 2,5-dihydroxy benzoic acid[8] and other related compounds. The orientation of S1 and O1 is evident from the torsion angles (S1 – C16 – C2 – C1) = 56.09 Å and (O1 – C1 – C2 – C16) = 5.64 Å. The morpholino-groups adopt chair conformation as reported earlier.[12] The nitrogen atom was found to have a nearly planar conformation with mean exocyclic C–N–C angle 123 ° and with very short exocyclic N–C distances 1.315(6) Å and 1.323(6)Å. This may be seen in two other reported structures where the nitrogen atom of the morpholino-group was bonded to C=S [13] and –C=O.[14]

The total puckering amplitude[15] of the morpholino ring 'A' is QT = 0.5173(2) Å, and the value of the lowest displacement asymmetry parameter[16] ΔC_2 (N1–C11) = 0.0140(1) Å are indicative of chair conformation. The plane calculation shows that the atoms C8 and C10 deviate from the mean plane C9 / O2 / C11 / N1 constituting the ring by 0.5953(1) Å and –0.6088(1)Å respectively, indicating that the conformation of the ring is chair, with the atom C8 at the apex and C10 below. In the case of morpholino-ring labelled 'C' in Fig.1, the total puckering amplitude, QT = 0.4638(2) Å, and the value of the lowest displacement asymmetry parameter ΔC_2 (C14–C15) = 0.0030(1) are indicative of the chair conformation. A mean plane calculation shows that the atoms N2 and O3 deviate from the mean plane, C12 / C13 / C14 / C15 constituting the ring by 0.5804(1) Å and –0.5571(1) Å respectively, indicating that the conformation of the ring is chair with the atom N2 at the apex and O3 below. The torsion angles of both the morpholino-rings indicate these chair conformation.

The packing of the molecules viewed down the 'a' axis is shown in Fig. 2. The molecular packing is stabilised by intermolecular C–H…O hydrogen bonds. O1 atom of the hydroxyl group and O2 atoms of the morpholino-group are involved in these interactions by acting as the acceptor atoms. Out of four intermolecular interactions listed the (C11 – H11 A… O1) interaction is considered as a prominent one, whose donor acceptor distance is 3.466(1) Å. On the whole, the crystal packing is stabilised by hydrogen bonding between polar groups and van der Waals interaction between nonpolar groups.

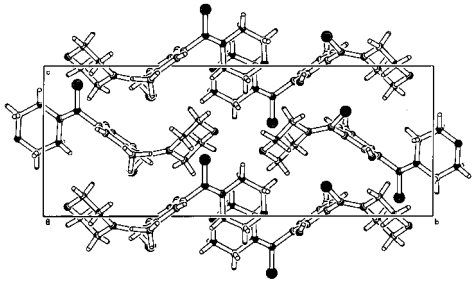


Fig 2. The molecular packing in the title compound, viewed down the *a* axis.

Supplementary material

Crystallographic data for the structure reported in this paper has been deposited with the Cambridge data centre. The deposition number is CCDC 221231.

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Table 2 Bond length (Å), Bond angle (°) and torsion angle (°) for non hydrogen atoms with esd's in parenthesis (°)

O1–C1	1.361 (5)	N2–C12	1.493 (8)
O3–C13	1.404 (8)	C6–C5	1.380 (6)
O3–C14	1.429 (9)	C6–C1	1.394 (6)
N1–C16	1.315 (6)	C6–C17	1.496 (6)
N1–C8	1.459 (7)	C5–C4	1.377 (6)
N1–C11	1.480 (6)	C3–C4	1.379 (6)
O2–C9	1.394 (7)	C16–S1	1.668 (5)
O2–C10	1.404 (8)	C4–C7	1.506 (6)
C2–C3	1.389 (6)	C17–S2	1.657 (5)
C2–C1	1.395 (6)	C10–C11	1.474 (9)
C2–C16	1.488 (6)	C9–C8	1.461 (9)
N2–C17	1.323 (6)	C14–C15	1.363 (10)
N2–C15	1.465 (8)	C12–C13	1.343 (9)
C13–O3–C14	110.3 (5)	C4–C3–C2	122.5 (4)
C16–N1–C8	125.7 (4)	N1–C16–C2	118.4 (4)
C16–N1–C11	121.9 (5)	N1–C16–S1	123.8 (3)
C8–N1–C11	112.2 (5)	C2–C16–S1	117.7 (4)
C9–O2–C10	109.0 (5)	C5–C4–C3	117.3 (4)
C3–C2–C1	118.6 (4)	C5–C4–C7	121.9 (4)
C3–C2–C16	121.4 (4)	C3–C4–C7	120.7 (4)
C1–C2–C16	119.8 (4)	N2–C17–C6	117.4 (4)
C17–N2–C15	123.7 (5)	N2–C17–S2	124.0 (4)
C17–N2–C12	125.7 (5)	C6–C17–S2	118.6 (3)
C15–N2–C12	110.4 (5)	O2–C10–C11	113.6 (6)
C5–C6–C1	119.3 (4)	O2–C9–C8	114.2 (6)
C5–C6–C17	120.2 (4)	N1–C8–C9	110.7 (5)
C1–C6–C17	120.5 (4)	N1–C11–C10	110.8 (5)
O1–C1–C2	123.0 (4)	C15–C14–O3	116.7 (7)
O1–C1–C6	117.3 (4)	C14–C15–N2	112.6 (7)
C2–C1–C6	119.7 (4)	C13–C12–N2	112.3 (6)
C4–C5–C6	122.4 (4)	C12–C13–O3	116.2 (7)
C13–O3–C14–C15	–49.24 (2)	C12–N2–C15–C14	–47.11 (2)
C14–O3–C13–C12	51.21 (2)	C17–N2–C12–C13	–135.58 (2)
C8–N1–C16–C2	0.73 (2)	C15–N2–C12–C13	49.03 (2)
C8–N1–C16–S1	178.54 (1)	C5–C6–C1–O1	177.34 (1)
C11–N1–C16–C2	–173.09 (1)	C5–C6–C1–C2	–0.17 (2)
C11–N1–C16–S1	4.72 (2)	C17–C6–C1–O1	–0.18 (2)
C16–N1–C8–C9	137.47 (2)	C17–C6–C1–C2	–177.69 (1)
C11–N1–C8–C9	–48.20 (2)	C1–C6–C5–C4	2.62 (2)
C16–N1–C11–C10	–137.79 (1)	C17–C6–C5–C4	–179.85 (1)
C8–N1–C11–C10	47.62 (2)	C1–C6–C17–N2	–59.09 (2)
C9–O2–C10–C11	58.20 (2)	C1–C6–C17–S2	118.16 (1)
C10–O2–C9–C8	–59.40 (2)	C5–C6–C17–N2	123.41 (2)
C3–C2–C1–O1	–179.70 (1)	C5–C6–C17–S2	–59.34 (2)
C3–C2–C1–C6	–2.34 (2)	C6–C5–C4–C3	–2.38 (2)
C16–C2–C1–O1	5.64 (2)	C6–C5–C4–C7	178.13 (1)
C16–C2–C1–C6	–177.00 (1)	H5–C5–C4–C3	–178.51 (2)
C1–C2–C3–C4	2.61 (2)	H5–C5–C4–C7	2.01 (3)
C16–C2–C3–C4	177.19 (1)	C2–C3–C4–C5	–0.29 (2)
C1–C2–C16–N1	–125.97 (2)	C2–C3–C4–C7	179.21 (1)
C1–C2–C16–S1	56.09 (2)	O2–C10–C11–N1	–53.31 (2)
C3–C2–C16–N1	59.51 (2)	O2–C9–C8–N1	55.31 (2)
C3–C2–C16–S1	–118.43 (1)	O3–C14–C15–N2	49.45 (2)
C15–N2–C17–C6	–8.79 (2)	N2–C12–C13–O3	–52.97 (2)
C12–N2–C17–C6	–6.50 (2)		
C12–N2–C17–S2	176.41 (1)		
C17–N2–C15–C14	137.39 (2)		

Table 3 Non-bonded interactions and possible hydrogen bonds (Å,°)

Interactions	D-H	D…A	H…A	D-H…A
Intramolecular				
O1–H1 …S1	0.608	3.131(0)	2.577	153.2
Intramolecular				
C3–H3 …O1^{i}	0.889	3.575(1)	2.815	144.33
C11–H11A …O1^{i}	0.970	3.466(1)	2.846	122.59
C13–H13A …O2^{i}	0.970	3.575(1)	2.989	120.07
C10–H10A …O2^{ii}	1.055	3.576(1)	2.741	136.00

Symmetry corresponds to the symmetry site of the acceptor atom
(i) *x*,-*y*+1/2,+*z*-1/2
(ii) -*x*+1,-*y*,-*z*+2

D=donor, A=acceptor, H=hydrogen.

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