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3,6-Dichloro-4-[2-(4-thiamorpholino)-ethanesulfanyl]pyridazine and 3,6-bis(pyrazol-1-yl)-4-[2-(4-thiamorpholino)ethanesulfanyl]pyridazine

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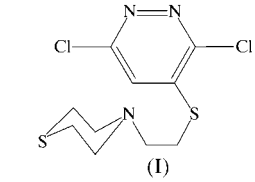
The *trans–trans* conformations adopted by the derivatized bis-(bidentate) chelating N_4-donor ligand 3,6-bis(pyrazol-1-yl)-4-[2-(4-thiamorpholino)ethanesulfanyl]pyridazine, $C_{16}H_{19}N_7S_2$, and an intermediate in its formation, 3,6-dichloro-4-[2-(4-thiamorpholino)ethanesulfanyl]pyridazine, $C_{10}H_{13}Cl_2N_3S_2$, contrast with the *cis–cis* conformation found previously for 3,6-bis(thiophen-2-yl)pyridazine [Ackers, Blake, Hill & Hubberstey (2002). *Acta Cryst*. C**58**, o640–o641], which places all four heteroatoms on the same side of the molecule.

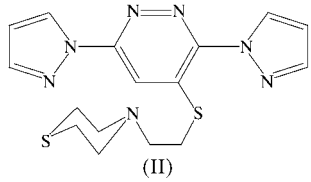
Comment

Pyridazines with N-donor substituents (*e.g.* pyrazole, 2-pyridine, 2-aminopyridine and 2-mercaptopyridine) located in the 3- and 6-positions can act as tetradentate N_4-donor ligands in a bis(bidentate) chelating fashion. These compounds are ideal for the generation of multinuclear coordination complexes with relatively short internuclear separations [$d(M\cdots M) \simeq$ 3.6 Å]. Many dinuclear copper(II) complexes, often with ancillary hydroxide or halide bridges, have been prepared (Chen *et al.*, 1993*a*,*b*; Tandon *et al.*, 1992, 1995; Thompson *et al.*, 1985; Xu *et al.*, 2000; Zhang *et al.*, 1995) because of interest in the magnetic behaviour of these complexes. By using metal centres predisposed to tetrahedral geometries, diverse molecular grids (2×2 and 2×3) have also been generated (Baxter *et al.*, 1997; Youinou *et al.*, 1992). Our own work with these ligands (Hubberstey & Russell, 1995) has concentrated on their use in generating trinuclear copper(I) complexes as small-molecule analogues of the trinuclear active sites in copper proteins, such as ascorbate oxidases and laccases.

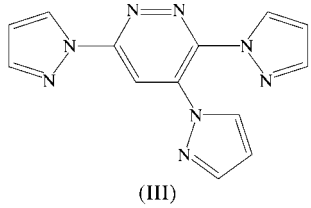
In an effort to develop this chemistry and generate molecules with linked mononuclear and trinuclear sites, as is the case in ascorbate oxidases (Messerschmidt *et al.*, 1989, 1992, 1993) and laccases (Bertrand *et al.*, 2002; Ducros *et al.*, 1998, 2001; Hakulinen *et al.*, 2002), we have attempted to attach potential mononuclear ligating centres to the pyridazine backbone. These can be either mono- or multidentate.



(I)



(II)



(III)

Following Hiller *et al.* (1968), who reported that the 4-position of 3,4,6-trichloropyridazine was much more sensitive to nucleophilic substitution than the 3- or 6-positions, we have been able to add the potentially tridentate chelating moiety 2-(thiamorpholino)ethanesulfanyl to the 4-position of the pyridazine ring and subsequently replace the remaining Cl atoms with pyrazole moieties, forming first 3,6-dichloro-4-[2-(4-thiamorpholino)ethanesulfanyl]pyridazine, (I), and then 3,6-bis(pyrazol-1-yl)-4-[2-(4-thiamorpholino)ethanesulfanyl]-pyridazine, (II).

The molecular structures of (I) and (II) (Figs. 1*a* and 1*b*, respectively) can be compared with that of the tris(pyrazole)-substituted molecule 3,4,6-tris(pyrazol-1-yl)pyridazine [(III); Fig. 1*c*; Blake *et al.*, 2002]. It is clear that (I), an intermediate in the synthesis of (II), is not a potential ligand, unlike (II) and (III), for which two noteworthy points emerge. Firstly, the pyridazine and pyrazole rings are not coplanar, giving buckled molecules. Secondly, the rings adopt a *trans–trans* conformation, which contrasts with the *cis–cis* conformation adopted when the molecules act as tetradentate N_4-donor ligands in a bis(bidentate) chelating fashion.

The deviation from planarity in (II) is relatively small, as illustrated by the dihedral angles between the planes of the pyridazine ring and the two substituent pyrazole rings [13.5 (2) and 23.3 (1)°]. The molecules of (III) are much more buckled. Although the 6-substituted pyrazole ring is almost coplanar with the pyridazine ring [dihedral angle 5.5 (2)°], the 3- and 4-substituted pyrazole rings are severely bent out of the plane of the pyridazine ring [dihedral angles 40.2 (2) and 51.2 (2)°, respectively]. Although the molecular structure of 3,6-bis(pyrazol-1-yl)pyridazine, (IV), has yet to be investigated in the solid state, it is predicted to be planar by analogy with similar multi-ring species, including 3,6-bis(thiophen-2-yl)-

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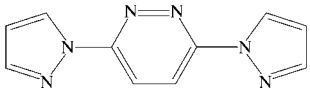
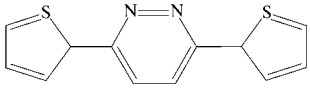
pyridazine, (V) (Ackers *et al.*, 2002), and 2,2′-bipyridine (Howard, 1996). Since detailed calculations on isolated 2,2′-bipyridine molecules show the most stable arrangement to be that with a dihedral angle of 44.9 (2)° between the planes of the aromatic rings (Howard, 1996), the fact that 2,2′-bipyridine adopts a planar *trans* arrangement in the solid state can be attributed to the more favourable packing interactions associated with planar rather than non-planar molecules. Deviation from planarity in (II) and (III) is thus attributed to steric conflict. That in (III) can be attributed to the interactions between the adjacent pyrazole substituents on the 3- and 4-positions of the pyridazine ring. The substituent in the 3-position of (II), 2-(thiamorpholino)ethanesulfanyl, although longer than pyrazole, is much less sterically demanding, leading to a much flatter molecular arrangement.



(IV)

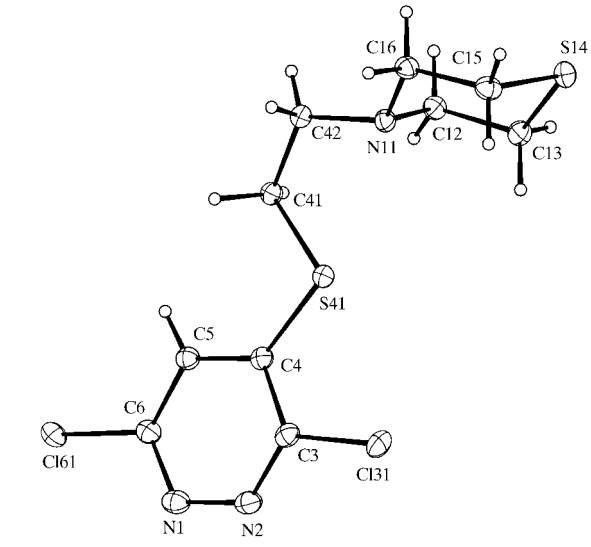


(V)

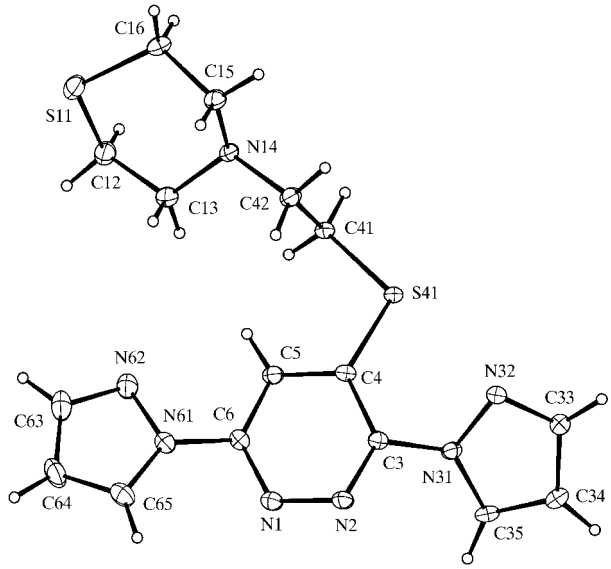
The *trans–trans* conformations adopted by (II) (Fig. 1*b*) and (III) (Fig. 1*c*) contrast with the conformation of (V), in which all four heteroatoms are located on the same side of the molecule, giving a *cis–cis* conformation (Ackers *et al.*, 2002). These apparently conflicting arrangements are, however, consistent with the results of semi-empirical AM calculations using the *PC SPARTAN-Plus* suite of programs (Wavefunction, 2002). These results confirm that the lowest energy conformations of (IV) and (V) are the *trans–trans* and *cis–cis* conformers, respectively. Relative enthalpies of formation are given in Table 1. Interestingly, the stabilization of the *trans–trans* isomer of (IV) over the *cis–cis* form (-32.01 kJ mol^{-1}) is similar to the difference between the enthalpies of formation of the *trans* and *cis* versions of planar 2,2′-bipyridine (32.3 kJ mol^{-1}), for which the *trans* conformer is the more stable (Howard, 1996; see Table 1).

The greater stability of the *trans–trans* conformer of (IV) relative to the *cis–cis* conformer may be attributed to (i) the presence of four intramolecular C—H···N hydrogen bonds in the former and (ii) steric repulsion between the H atoms attached to atoms C4 and C35 and the H atoms attached to atoms C5 and C65 in the latter. Although an explanation for the different behaviour of (IV) and (V) is not immediately obvious, the fact that twice as many intramolecular C—H···N hydrogen bonds occur in the *trans–trans* version of (IV) (four) than in the corresponding conformer of (V) (two) may be significant.

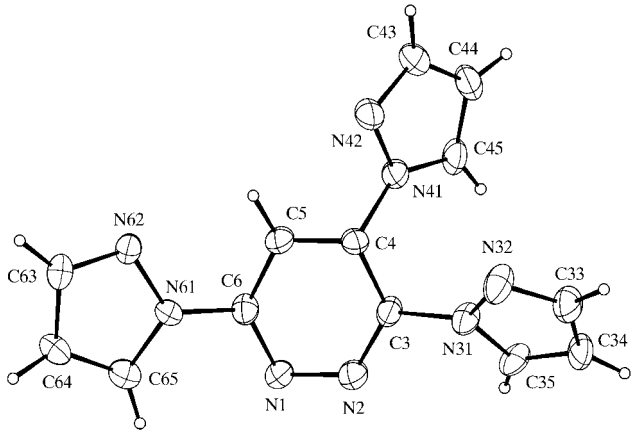
The more favourable packing interactions associated with planar rather than non-planar molecules may be traced to π–π-stacking forces, as the extended structures of both (I) and (II) involve offset face-to-face interactions (Hunter & Sanders, 1990; Hunter *et al.*, 2001). An analysis of the extended structure of (I) reveals a columnar arrangement of



(*a*)



(*b*)



(*c*)

Figure 1
Views of the molecular structures and the atom-numbering schemes of (*a*) compound (I), (*b*) compound (II) and (*c*) compound (III). Displacement ellipsoids have been drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

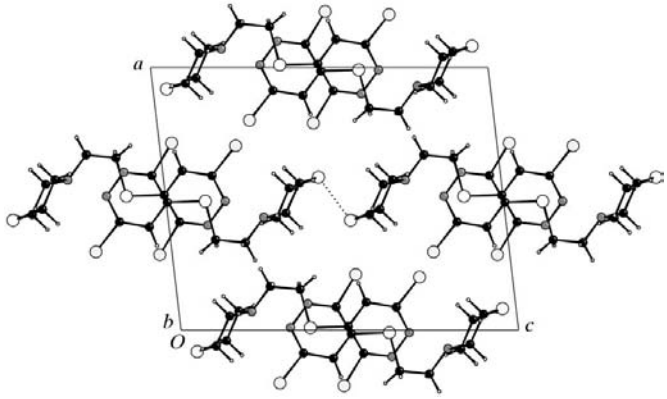


Figure 2
A projection of the structure of (I) on to the (010) plane, showing the π–π-stacking interactions and intermolecular S$\cdots$S contacts (S atoms are large pale-grey circles, Cl are large dark-grey circles, C are intermediate black circles, N are intermediate dark-grey circles and H are small pale-grey circles).

molecules, stacked in the *b* direction and held together by π–π-stacking interactions between their aromatic moieties (Fig. 2). The perpendicular separations between the aromatic moieties, which are crystallographically constrained to be parallel, average 3.43 (3) (range 3.385–3.466 Å) and 3.58 (3) Å (range 3.539–3.620 Å). The columns are linked by very long S$\cdots$S contacts, similar in length [3.973 (2) Å] to those linking the molecules in the extended structure of (V) [3.980 (2) Å; Ackers *et al.*, 2002], to give a two-dimensional architecture parallel to the (001) plane (Fig. 3).

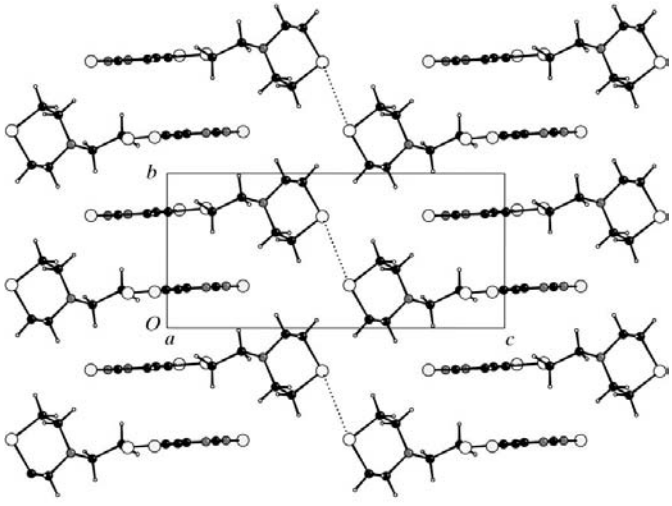


Figure 3
A projection of the structure of (I) on to the (100) plane, showing the π–π-stacking interactions and intermolecular S$\cdots$S contacts. Atom types are represented as in Fig. 2.

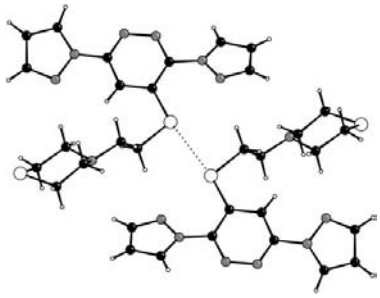


Figure 4
A view of the structure of (II), showing the intermolecular S$\cdots$S contact generating the dimeric arrangement. Atom types are represented as in Fig. 2.

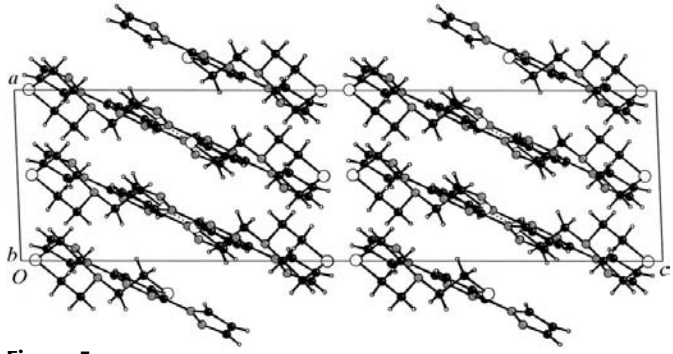


Figure 5
A projection of the structure of (II) on to the (010) plane, showing the stacking of the dimers along the *a* direction. Atom types are represented as in Fig 2.

An analysis of the extended structure of (II) shows the formation of dimers through relatively short S$\cdots$S interactions [3.246 (2) Å; Fig. 4]. The dimers, facing alternate directions, stack along the *a* direction (Fig. 5), utilizing weak offset face-to-face π–π interactions between pyridazine rings [perpendicular separation = 3.7 (2) Å and range = 3.43–3.95 Å].

As the three rings in the structure of (II) depart only marginally from coplanarity, it is anticipated that (II) will be able to act as a bis(bidentate) chelating ligand in much the same way as the non-derivatized species (IV). However, owing to the severe buckling of the structure of (III), which results from steric repulsion between the 3- and 4-substituted pyrazole rings, it will probably not be possible for (III) to act in a similar manner. Consequently, our future efforts to generate small-molecule analogues of multinuclear copper proteins will concentrate on the use of (II) rather than (III).

Experimental

For the preparation of (I), potassium carbonate (0.21 g, 1.54 mmol) was added to a stirred solution of 2-(thiamorpholino)ethanethiol (0.5 g, 3.07 mmol), which was previously synthesized by treatment of ethylene sulfide with thiamorpholine, in degassed MeCN (50 ml). After 15 min, 3,4,6-trichloropyridazine (0.56 g, 3.07 mmol) was added and the mixture was heated at reflux for 20 h. The white precipitate that appeared on cooling was removed by filtration, washed with water and recrystallized from ethanol as pale-yellow columns (yield 0.69 g, 2.22 mmol, 72%). Analysis found: C 38.20, H 4.05, N 13.10%; calculated for $C_{10}H_{13}Cl_2N_3S_2$: C 38.70, H 4.20, N 13.55%. IR (KBr disc, ν, cm^{-1}): 3069 (*m*), 2929 (*m*), 2808 (*s*), 2772 (*m*), 1518 (*s*), 1420 (*m*), 1373 (*s*), 1339 (*s*), 1319 (*s*), 1296 (*s*), 1289 (*s*), 1227 (*m*), 1201 (*m*), 1164 (*m*), 1138 (*s*), 1115 (*s*), 1076 (*m*), 1048 (*m*), 981 (*s*), 963 (*m*), 943 (*m*), 886 (*m*), 868 (*m*), 840 (*s*), 748 (*m*), 662 (*m*), 579 (*s*), 424 (*m*). ^{1}H NMR ($CDCl_3$, p.p.m.): 2.67–2.84 (*m*, 10H), 3.10 (*t*, 2H), 7.29 (*s*, 1H). EI MS (*m*/*z*) 309 $[C_{10}H_{13}Cl_2N_3S_2]^+$. For the preparation

of (II), sodium hydride (0.071 g, 2.96 mmol) was added to a solution of pyrazole (0.120 g, 1.76 mmol) in pre-dried tetrahydrofuran (50 ml). After stirring the mixture for 20 min, (I) (0.275 g, 0.89 mmol) was added and the mixture was heated at reflux for 4 h. After cooling to room temperature, the solvent was removed, and the resultant solid was dissolved in dichloromethane (50 ml) and washed with water (3 × 50 ml). The organic layer was dried over magnesium sulfate and the solvent was removed to give a thick pale-brown oil; this oil was recrystallized from ethanol to yield colourless plates (yield 0.070 g, 0.187 mmol, 21%). Analysis found: C 50.95, H 5.00, N 25.85%; calculated for $C_{16}H_{19}N_7S_2$: C 51.45, H 5.15, N 26.25%. IR (KBr disc, ν, cm^{-1}): 2899 (*m*), 1561 (*s*), 1518 (*s*), 1449 (*s*), 1392 (*s*), 1262 (*m*), 1200 (*m*), 1108 (*s*), 1091 (*s*), 1034 (*s*), 1018 (*s*), 950 (*m*), 932 (*s*), 875 (*m*), 825 (*s*), 805 (*s*), 765 (*s*), 634 (*m*), 606 (*m*), 534 (*m*). ^{1}H NMR ($CDCl_3$, p.p.m.): 2.69–2.86 (*m*, 10H), 3.18 (*t*, 2H), 6.57 (*m*, 2H), 7.81 (*q*, 1H), 7.88 (*q*, 1H), 8.23 (*s*, 1H), 8.49 (*q*, 1H), 8.74 (*q*, 1H). FAB MS (*m*/*z*) 374 $[C_{16}H_{19}N_7S_2 + H]^+$.

Compound (I)

Crystal data

$C_{10}H_{13}Cl_2N_3S_2$
M_r = 310.26
Monoclinic, $P2_1/n$
a = 12.097 (3) Å
b = 7.021 (2) Å
c = 15.425 (4) Å
β = 96.645 (5)°
V = 1301.2 (6) Å^3
Z = 4
D_x = 1.584 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3123 reflections
θ = 2.7–28.1°
μ = 0.80 mm^{-1}
T = 150 (2) K
Triangular plate, colourless
0.27 × 0.25 × 0.06 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.721, T_{max} = 0.928
8156 measured reflections
3042 independent reflections
2250 reflections with $I > 2\sigma(I)$
R_{int} = 0.046
θ_{max} = 28.7°
$h = -10 \rightarrow 15$
$k = -9 \rightarrow 9$
$l = -20 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.089
S = 0.96
3042 reflections
154 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.054P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Compound (II)

Crystal data

$C_{16}H_{19}N_7S_2$
M_r = 373.50
Monoclinic, $I2/a$
a = 8.0944 (8) Å
b = 13.9838 (14) Å
c = 30.482 (3) Å
β = 92.292 (2)°
V = 3447.5 (6) Å^3
Z = 8
D_x = 1.439 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3172 reflections
θ = 2.5–26.7°
μ = 0.32 mm^{-1}
T = 150 (2) K
Column, pale yellow
0.30 × 0.11 × 0.09 mm

Data collection

Bruker SMART1000 CCD area-detector diffractometer
ω scans
13 401 measured reflections
4084 independent reflections
2588 reflections with $I > 2\sigma(I)$
R_{int} = 0.056
θ_{max} = 28.8°
$h = -10 \rightarrow 10$
$k = -18 \rightarrow 17$
$l = -40 \rightarrow 35$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.119
S = 0.99
4084 reflections
226 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.059P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.35 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Table 1
Calculated enthalpies of formation (kJ mol^{-1}) of the planar conformers of (IV) and (V); relative values.

Conformer	(IV)	(V)
cis–cis	0.00	0.00
cis–trans	−17.07	+4.60
trans–trans	−32.01	+9.25

In (I), H atoms were located from ΔF syntheses and refined positionally, with U_{iso} values of 1.2U_{eq}(C). In (II), H atoms were first located from ΔF syntheses, then placed in idealized positions and refined using a riding model, with aromatic and aliphatic C—H distances constrained to 0.96 and 0.99 Å, respectively, and with U_{iso}(H) values of 1.2U_{eq}(C).

For both compounds, data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT* and *SHELXTL* (Bruker, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: TY1000). Services for accessing these data are described at the back of the journal.

References

Ackers, B., Blake, A. J., Hill, S. J. & Hubberstey, P. (2002). *Acta Cryst.* C**58**, o640–o641.
Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1993). *J. Appl. Cryst.* **27**, 435.
Baxter, P. N. W., Lehn, J.-M., Kneisel, B. O. & Fenske, D. (1997). *Angew. Chem. Int. Ed. Engl.* **36**, 1978–1981.
Bertrand, T., Jolivalt, C., Briozzo, P., Caminade, E., Joly, N., Madzak, C. & Mougin, C. (2002). *Biochemistry*, **41**, 7325–7333.
Blake, A. J., Hubberstey, P. & Mackrell, A. D. (2002). *Acta Cryst.* E**58**, o1408–o1410.
Bruker (1997). *SHELXTL.* Version 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (1998). *SMART.* Version 5.624. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2001). *SAINT.* Version 6.02a. Bruker AXS Inc., Madison, Wisconsin, USA.
Chen, L., Thompson, L. K. & Bridson, J. N. (1993*a*). *Inorg. Chem.* **32**, 2938–2943.
Chen, L., Thompson, L. K. & Bridson, J. N. (1993*b*). *Inorg. Chim. Acta*, **214**, 67–76.
Ducros, V., Brzozowski, A. M., Wilson, K. S., Brown, S. H., Ostergaard, P., Schneider, P., Yaver, D. S., Pedersen, A. H. & Davies, G. J. (1998). *Nat. Struct. Biol.* **5**, 310–316.

Ducros, V., Brzozowski, A. M., Wilson, K. S., Ostergaard, P., Schneider, P., Svendson, A. & Davies, G. J. (2001). *Acta Cryst.* D**57**, 333–336.
Hakulinen, N., Kiiskinen, L. L., Kruus, K., Saloheimo, M., Paananen, A., Koivula, A. & Rouvinen, J. (2002). *Nat. Struct. Biol.* **9**, 601–605.
Hiller, A., Avata, B. & Ozolin, C. (1968). *Latv. PSR Zinat. Akad. Vestis*, pp. 348–352.
Howard, S. T. (1996). *J. Am. Chem. Soc.* **118**, 10269–10274.
Hubberstey, P. & Russell, C. E. (1995). *J. Chem. Soc. Chem. Commun.* pp. 959–960.
Hunter, C. A., Lawson, K. R., Perkins, J. & Urch, C. J. (2001). *J. Chem. Soc. Perkin Trans.* 2, pp. 651–669.
Hunter, C. A. & Sanders, J. K. M. (1990). *J. Am. Chem. Soc.* **112**, 5525–5534.
Messerschmidt, A., Ladenstein, R., Huber, R., Bolognesi, M., Avigliano, L., Petruzzelli, R., Rossi, A. & Finazziagro, A. (1992). *J. Mol. Biol.* **224**, 179–205.
Messerschmidt, A., Leucke, H. & Huber, R. (1993). *J. Mol. Biol.* **230**, 997–1014.
Messerschmidt, A., Rossi, A., Ladenstein, R., Huber, R., Bolognesi, M., Gatti, G., Marchesini, A., Petruzzelli, R. & Finazziagro, A. (1989). *J. Mol. Biol.* **206**, 513–529.
Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Tandon, S. S., Thompson, L. K. & Hynes, R. C. (1992). *Inorg. Chem.* **31**, 2210–2214.
Tandon, S. S., Thompson, L. K., Manuel, M. E. & Bridson, J. N. (1995). *Inorg. Chem.* **34**, 2356–2366.
Thompson, L. K., Woon, T. C., Murphy, D. B., Gabe, E. J., Lee, F. L. & Page, Y. (1985). *Inorg. Chem.* **24**, 4719–4725.
Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*. Chemical Crystallography Laboratory, Oxford, England.
Wavefunction (2002). *PC SPARTAN-Plus.* Wavefunction Inc., 18401 Von Karman Avenue, Irvine, CA 92715, USA.
Xu, Z. Q., Thompson, L. K., Matthews, C. J., Miller, D. O., Goeta, A. E., Wilson, C., Howard, J. A. K., Ohba, M. & Okawa, H. (2000). *J. Chem. Soc. Dalton Trans.* pp. 69–77.
Youinou, M., Rahmouni, N., Fischer, J. & Osborn, J. (1992). *Angew. Chem. Int. Ed. Engl.* **31**, 733–735.
Zhang, Y. S., Thompson, L. K., Bridson, J. N. & Bubenik, M. (1995). *Inorg. Chem.* **34**, 5870–5877.