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Disappearance of intramolecular stacking due to one-atom movement or increment of a 'propylene linker' in pyrazolo[3,4-*d*]pyrimidine-based flexible models

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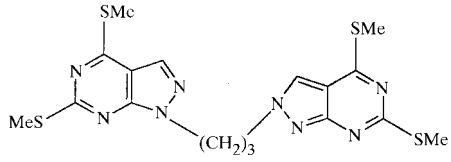
In the crystal structures of 4,6-dimethylthio-1-[3-(4,6-dimethylthio-2*H*-pyrazolo[3,4-*d*]pyrimidin-2-yl)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{17}H_{20}N_8S_4$, and 1-[4-(4-methoxy-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)butyl]-5-methyl-6-methylthio-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one, $C_{18}H_{22}N_8O_2S_2$, only intermolecular stacking due to aromatic π–π interactions between pyrazolo[3,4-*d*]pyrimidine rings is present.

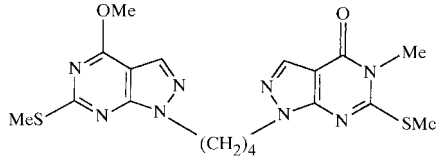
Comment

Interactions between aromatic units play a significant role in chemistry and biology. The use of a 'propylene linker' was first documented by Brown *et al.* (1968) for the promotion of intramolecular aromatic π–π interactions (APPI). Recently, we have reported convenient synthesis, high resolution ^{1}H NMR analysis (Avasthi *et al.*, 1995; Avasthi, Rawat, Chandra & Bhakuni, 1998) and X-ray studies (Biswas *et al.*, 1995; Maulik *et al.*, 1998) of three novel 'propylene linker' compounds: 1,3-bis(4,6-dimethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propane, (1), 1,1′-(1,3-propanediyl)bis(5-methyl-6-methylthio-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one, (2), and 1-[3-(4-methoxy-6-methylthio-1*H*-pyrazolo[3,4-*d*]-pyrimidin-1-yl)propyl]-5-methyl-6-methylthio-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one, (3). These three compounds show inter/intramolecular stacking due to APPI. In this communication, we report the crystal structures of two compounds, (4) and (5), which are very closely related to our earlier flexible models (1)–(3).

4,6-Dimethylthio-1-[3-(4,6-dimethylthio-2*H*-pyrazolo[3,4-*d*]-pyrimidin-2-yl)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, (4), was prepared earlier as a co-product during the synthesis of (1).



(4)



(5)

The conformation of (4) is shown in Fig. 1. The structure does not show any intramolecular stacking [N1′—N2 3.956 (3) Å], although the angle at the centre of the bridge [C8—C9—C10 114.9 (3)°] is quite comparable to the corresponding angle in the structure of (1) (Biswas *et al.*, 1995). This disappearance of intramolecular stacking compared with the structure of (1) may highlight the importance of specific orientation for intramolecular stacking (Hobza & Sponer, 1999). Interestingly, intermolecular stacking due to APPI is still present (Fig. 2), as indicated by an average space of 3.67 (4) Å between two stacked rings [angle between the stacked rings: 6.32 (10)°]. The other compound, 1-[4-(4-methoxy-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)butyl]-5-methyl-6-methylthio-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one, (5), which differs from compound (3) in having an extra methylene group in its linker, has been synthesized by us recently (Avasthi, Rawat, Chandra & Bhakuni, 1998). The conformation of (5) is shown in Fig. 3. Once again, the crystal structure does not show any intramolecular stacking [N1—N1′ 5.249 (2) Å and torsion angle C8—C9—C10—C11 170.3 (2)°] confirming an earlier conclusion drawn on the basis of ^{1}H

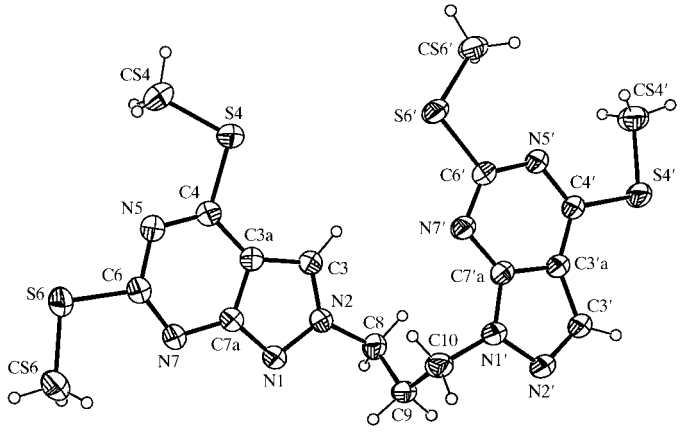


Figure 1
ORTEP (Johnson, 1965) diagram showing the molecular structure of (4) with labelling of the non-H atoms and displacement ellipsoids at the 50% probability level.

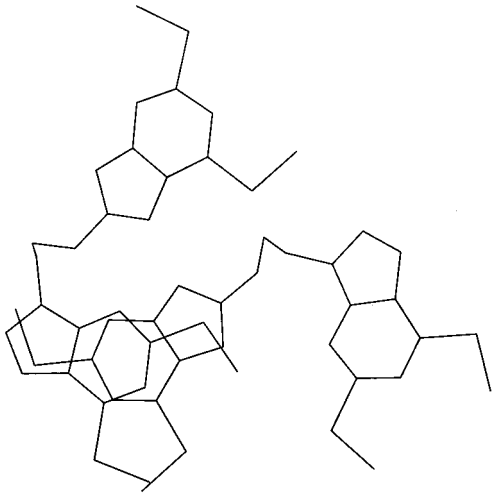


Figure 2
View of the molecules of compound (4) showing the partial overlapping of the rings owing to intermolecular stacking.

NMR data comparison (Avasthi, Rawat, Chandra & Bhakuni, 1998) with monomeric model compounds (Avasthi, Rawat & Bhakuni, 1998). Intermolecular stacking, due to APPI, however, is still present (Fig. 4), as revealed by the average intermolecular spacing of 3.64 (3) Å [angle between the stacked rings: 0.68 (12)°]. Thus, the crystal structures of (4) and (5) are stabilized mainly by intermolecular APPI and van der Waals forces.

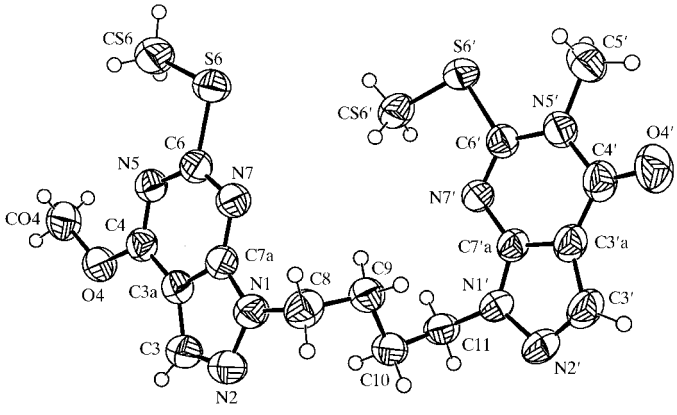


Figure 3
ORTEP (Johnson, 1965) diagram showing the molecular structure of (5) with labelling of the non-H atoms and displacement ellipsoids at the 50% probability level.

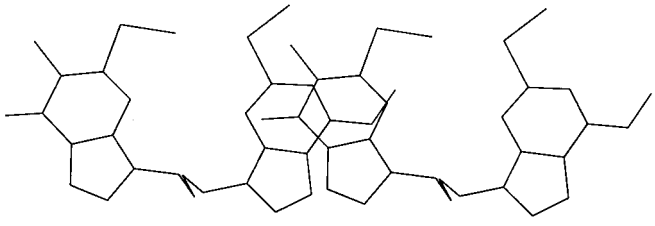


Figure 4
View of the molecules of compound (5) showing the partial overlapping of the rings owing to intermolecular stacking.

We believe that the addition of these two new members, (4) and (5), to an already existing group of three pyrazolo-[3,4-*d*]pyrimidinyl compounds, (1)–(3), isomeric with biologically important purines, constitutes a unique family of five compounds demonstrating very strong conformational (topological) preferences due mainly to APPI.

Experimental

The synthesis of compound (4) was achieved by alkylation of 4,6-dimethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine with 1,3-dibromopropane in the presence of potassium carbonate in dimethylformamide (Avasthi *et al.*, 1995). The synthesis of compound (5) was carried out by treatment of 1,4-bis(4,6-dimethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)butane with aqueous alkali followed by methylation (Avasthi, Rawat, Chandra & Bhakuni, 1998). Diffraction quality crystals of both compounds were obtained by slow evaporation of ethyl acetate/chloroform mixtures at room temperature.

Compound (4)

Crystal data

$C_{17}H_{20}N_8S_4$
M_r = 464.65
Monoclinic, $P2_1/n$
a = 7.620 (2) Å
b = 10.411 (2) Å
c = 26.813 (5) Å
β = 97.92 (2)°
V = 2106.8 (8) Å^3
Z = 4
D_x = 1.465 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 42 reflections
θ = 4.7–13.1°
μ = 0.473 mm^{-1}
T = 293 (2) K
Rhombohedral, colourless
0.5 × 0.5 × 0.5 mm

Data collection

Siemens $P4$ diffractometer
ω scans
Absorption correction: ψ scan (local program; Karcher, 1981)
T_{min} = 0.749, T_{max} = 0.778
3697 measured reflections
3697 independent reflections
2893 reflections with $I > 2\sigma(I)$
θ_{max} = 25.00°
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 12$
$l = -31 \rightarrow 31$
3 standard reflections
every 97 reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.142
S = 0.804
3684 reflections
267 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1195P)^2 + 1.4563P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.50 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0066 (12)

Compound (5)

Crystal data

$C_{18}H_{22}N_8O_2S_2$
M_r = 446.56
Monoclinic, $C2/c$
a = 31.736 (7) Å
b = 8.308 (2) Å
c = 17.467 (4) Å
β = 115.12 (2)°
V = 4169.8 (17) Å^3
Z = 8
D_x = 1.423 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 39 reflections
θ = 4.9–12.8°
μ = 0.289 mm^{-1}
T = 293 (2) K
Trapezoidal, colourless
0.8 × 0.6 × 0.5 mm

Data collection

Siemens *P*4 diffractometer
ω scans
Absorption correction: ψ scan (local program; Karcher, 1981)
T_{min} = 0.772, T_{max} = 0.835
3616 measured reflections
3616 independent reflections
3189 reflections with $I > 2\sigma(I)$
θ_{max} = 25.01°
$h = 0 \rightarrow 37$
$k = 0 \rightarrow 9$
$l = -20 \rightarrow 18$
3 standard reflections
every 97 reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.121$
$S = 1.054$
3616 reflections
276 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0685P)^2 + 1.3387P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0068 (5)

For both compounds, data collection: *XSCANS* (Siemens, 1992); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993) for compound (4), *SHELXL*97 (Sheldrick, 1997) for compound (5). For both compounds; molecular graphics: *NRCVAX* (Gabe *et al.*, 1989); software used to prepare material for publication: *SHELXL*93 for compound (4), *SHELXL*97 for compound (5).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: VJ1110). Services for accessing these data are described at the back of the journal.

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