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Unusual molecular conformation in dissymmetric propylene-linker compounds containing pyrazolo-[3,4-*d*]pyrimidine and phthalimide moieties[1]

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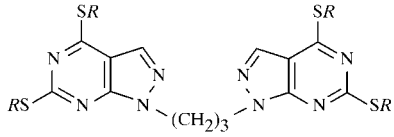
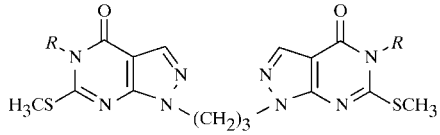
The crystal structure of 4,6-bis(methylsulfanyl)-1-phthalimidopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{18}H_{17}N_5O_2S_2$, (VI), reveals an unusual folded conformation due to an apparent intramolecular C—H$\cdots\pi$ interaction between the 6-methylsulfanyl and phenyl groups. However, the closely related compound 6-methylsulfanyl-1-phthalimidopropyl-4-(pyrrolidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{21}H_{22}N_6O_2S$, (VII), exhibits a fully extended structure, devoid of any intramolecular C—H$\cdots\pi$ or π–π interactions. The crystal packing of both molecules involves intermolecular stacking interactions due to aromatic π–π interactions. In addition, (VI) exhibits intermolecular C—H$\cdots$O hydrogen bonding and (VII) exhibits dimerization of the molecules through intermolecular C—H$\cdots$N hydrogen bonding.

Comment

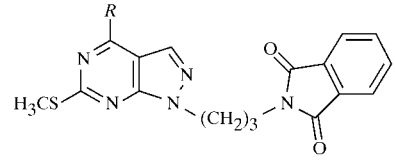
Interactions between aromatic units play significant roles in chemistry (Hunter *et al.*, 2001; Tsuzuki *et al.*, 2002), crystal engineering (Desiraju, 1995) and drug development (Meyer *et al.*, 2003). The use of the 'propylene linker' for the promotion of intramolecular stacking among nucleic acid bases was first introduced by Browne *et al.* (1968), and earlier literature has been reviewed by Leonard (1979). We have reported previously the synthesis (Avasthi *et al.*, 1995) and X-ray structure determination (Biswas *et al.*, 1995) of (I), which is based on the pyrazolo[3,4-*d*]pyrimidine core and is isomeric with the biologically important purine system. X-ray crystallographic analysis of (I) not only confirmed the intramolecular stacking but also revealed intermolecular stacking. Similar results were obtained for the ethyl analogue, (II), *via* ^{1}H NMR spectroscopy and X-ray crystallography (Avasthi, Rawat *et al.*, 2001). Subsequently, the syntheses of another three related compounds, *viz*. (III)–(V), which are derived from (I), were reported by Avasthi *et al.* (1998); a comparison of the ^{1}H NMR spectroscopic data indicated intramolecular stacking. X-ray structure determinations of (III)–(V) also showed inter- and intramolecular stacking (Maulik *et al.*, 1998; Avasthi, Aswal & Maulik, 2001; Avasthi *et al.*, 2002). In short, X-ray crystallography for the five symmetrical compounds (I)–(V) showed an unusual 'U' motif, formed by intramolecular aromatic π–π interactions.



(I) R = CH_3
(II) R = C_2H_5



(III) R = CH_3
(IV) R = C_2H_5
(V) R = Benzyl



(VI) R = SCH_3
(VII) R = pyrrolidin-1-yl

In this communication, we report the X-ray structure determinations of two dissymmetric 'propylene-linker' compounds, (VI) and (VII), which are based on the same pyrazolo[3,4-*d*]pyrimidine core, with a phthalimide ring system replacing one of the pyrazolo[3,4-*d*]pyrimidine moieties of (I). The phthalimide group was chosen because (*a*) it is known to exhibit intermolecular stacking (Barrett *et al.*, 1995), (*b*) it is a bicyclic system, like pyrazolo[3,4-*d*]-*c*) it contains a phenyl ring, which is an important π-acceptor, and (*d*) it contains an available N atom for linker connection. The effect of the substitution on the stacking interactions was examined by ^{1}H NMR spectroscopy and X-ray crystallography.

H atoms of one of the two methylsulfanyl groups of (VI) appeared at a higher field in the ^{1}H NMR spectrum; this behaviour is similar to that of (I), thus indicating the closeness of these H atoms to the phenyl portion of the phthalimide moiety. In the spectrum of (VII), the methylsulfanyl H atoms appeared at a comparable higher field.

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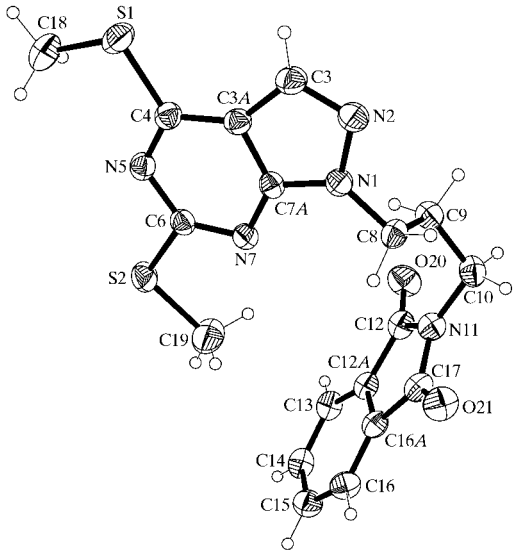

Figure 1
A displacement ellipsoid plot (30% probability level) of the molecule of (VI), showing the atomic labelling scheme.

In order to determine the exact orientation of the unusual upfield shift of the methysulfanyl H atom [*i.e.* parallel mode, as observed for compounds (I)–(V), or another mode], crystallographic structure determination was necessary. The conformations of (VI) and (VII), as determined by X-ray crystallography, are shown in Figs. 1 and 2, respectively. Compound (VI) shows an unusual folded conformation, in which the two planar moieties are close to perpendicular and one methylsulfanyl group is brought close to the phenyl ring of the phthalimide unit, apparently as a result of an intramolecular C—H$\cdots\pi$ interaction. Atoms C12*A* and C13 of the phthalimide moiety are closest to atom C19 [3.578 (3) and 3.609 (4) Å, respectively], while the average distance between the phenyl moiety and atom C19 is 3.851 (4) Å. Although C—H$\cdots\pi$ interactions are now well established (Nishio *et al.*, 1998; Desiraju & Steiner, 1999; Jennings *et al.*, 2001), to the best of our knowledge, the formation of a folded conformation in a flexible 'propylene-linker' compound that also involves a single methyl group not directly attached to an aromatic moiety is unprecedented.

Compound (VII) was synthesized only in order to investigate the robustness of the unusual conformation formed in (VI) as the result of the intramolecular C—H$\cdots\pi$ interaction. Interestingly, (VII) shows a fully extended open conformation, which permits efficient packing without any intramolecular C—H$\cdots\pi$ interaction.

Compounds (VI) and (VII) are a unique and unprecedented pair of compounds, in which the remote substitution of a pyrrolidine moiety for a methylsulfanyl group changes the folded conformation to an extended one in the solid state. The similar behaviour of the methylsulfanyl H atoms in the ^{1}H NMR spectra of these compounds clearly indicates a folded conformation for both (VI) and (VII); however, as a result of the very weak nature of the C—H$\cdots\pi$ interaction (Desiraju, 2002), the folded conformation is not observed in the solid state for (VII) because of competing packing forces.

The crystal packing of (VI) reveals the presence of intermolecular stacking due to aromatic π–π interactions among the six-membered rings. The molecule of (VI) forms an interesting 'fourfold' arrangement of phthalimide–pyrimidine–pyrimidine–phthalimide stacked rings (the minimum C$\cdots$C distance is 3.555 Å between phthalimide and pyrimidine rings, and 3.510 Å between pyrimidine rings), with each phthalimide group 'capped' by methylsulfanyl groups and a head-to-tail arrangement of the molecules in the case of phthalimide–pyrimidine stacking (Fig. 3). The crystal packing further shows that the molecules are connected by intermolecular C—H$\cdots$O hydrogen bonds (Table 1). In (VII), on the other hand, the intermolecular stacking interactions appear to be entirely 'segregated'. As can be seen in Fig. 4, phthalimide rings only stack with other phthalimide rings

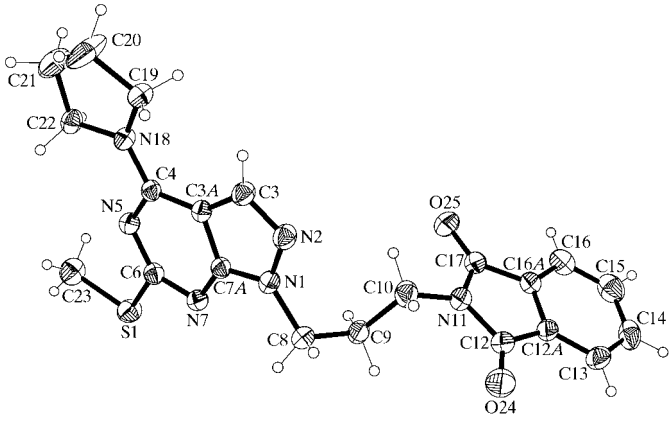

Figure 2
A displacement ellipsoid plot (30% probability level) of the molecule of (VII), showing the atomic labelling scheme.

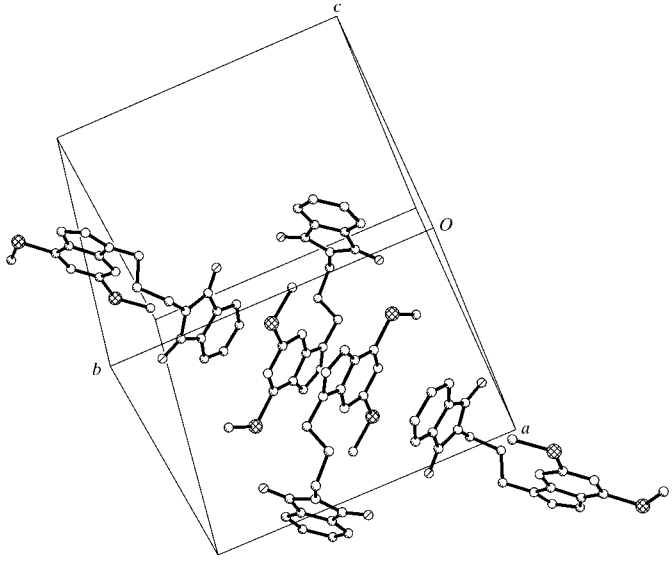

Figure 3
A view of the molecules of (VI), showing the intermolecular phthalimide–pyrimidine–pyrimidine–phthalimide stacking.

(minimum C···C distance = 3.462 Å) and pyrimidine rings only stack with other pyrimidine rings (minimum C···C distance = 3.725 Å). The molecules are further connected by C—H···N hydrogen bonding (Table 2), leading to the dimerization of the molecules. In conclusion, the new dissymmetrical compounds (VI) and (VII), formed by the replacement of one pyrazolo[3,4-*d*]pyrimidine moiety with a phthalimide group, do not show the 'U' motif seen in the symmetrical compounds (I)–(V) in the solid state.

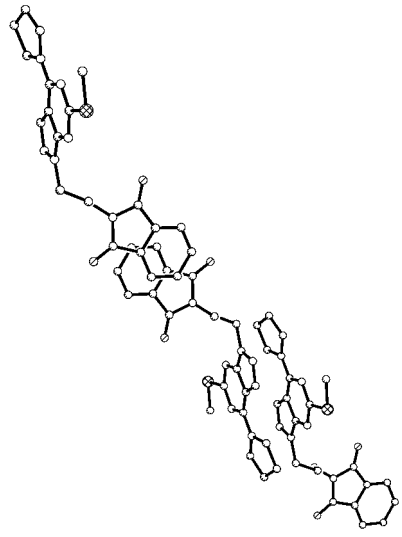

Figure 4
A view of the molecules of (VII), showing the intermolecular stacking between pyrimidine rings and between phthalimide rings due to aromatic π–π interactions.

Experimental

The reaction of commercial 3-bromopropylphthalimide with 4,6-bis(methylsulfanyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine gave a good yield of (VI). Compound (VII) was prepared by refluxing a solution of (VI) with pyrrolidine in benzene. Diffraction-quality crystals of (VII) were prepared from a solution in a mixture of chloroform and ethyl acetate by slow evaporation at room temperature.

Compound (VI)

Crystal data

$C_{18}H_{17}N_5O_2S_2$
M_r = 399.49
Monoclinic, $P2_1/n$
a = 10.471 (1) Å
b = 13.1323 (11) Å
c = 14.0516 (12) Å
β = 102.19 (1)°
V = 1888.7 (3) Å^3
Z = 4
D_x = 1.405 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 40 reflections
θ = 4.8–14.8°
μ = 0.31 mm^{-1}
T = 293 (2) K
Rectangle, colourless
0.38 × 0.31 × 0.26 mm

Data collection

Bruker *P*4 diffractometer
θ–2θ scans
4279 measured reflections
3327 independent reflections
2566 reflections with $I > 2\sigma(I)$
R_{int} = 0.026
θ_{max} = 25.0°
$h = -12 \rightarrow 1$
$k = -15 \rightarrow 1$
$l = -16 \rightarrow 16$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.092
S = 1.02
3327 reflections
247 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.027P)^2 + 0.7345P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0189 (10)

Table 1
Hydrogen-bonding geometry (Å, °) for (VI).

D—H···A	D—H	H···A	D···A	D—H···A
C3—H3···O21^{i}	0.93	2.54	3.367 (3)	149

Symmetry code: (i) $\frac{3}{2} - x, -\frac{1}{2} + y, \frac{1}{2} - z$.

Compound (VII)

Crystal data

$C_{21}H_{22}N_6O_2S$
M_r = 422.51
Triclinic, $P\overline{1}$
a = 7.5993 (6) Å
b = 9.3968 (7) Å
c = 15.376 (2) Å
α = 80.684 (8)°
β = 82.48 (1)°
γ = 72.685 (6)°
V = 1030.54 (19) Å^3
Z = 2
D_x = 1.362 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 49 reflections
θ = 5.1–12.5°
μ = 0.19 mm^{-1}
T = 293 (2) K
Block, colourless
0.28 × 0.20 × 0.16 mm

Data collection

Bruker *P*4 diffractometer
θ–2θ scans
4402 measured reflections
3580 independent reflections
2420 reflections with $I > 2\sigma(I)$
R_{int} = 0.063
θ_{max} = 25.0°
$h = -8 \rightarrow 1$
$k = -11 \rightarrow 10$
$l = -18 \rightarrow 18$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.171
S = 1.06
3580 reflections
273 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0734P)^2 + 0.6332P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.37 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.024 (4)

Table 2
Hydrogen-bonding geometry (Å, °) for (VII).

D—H···A	D—H	H···A	D···A	D—H···A
C3—H3···N2^{ii}	0.93	2.58	3.351 (4)	140

Symmetry code: (ii) $-x, 1 - y, 1 - z$.

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL* (Bruker, 1997); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE1208). Services for accessing these data are described at the back of the journal.

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