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1,3-Bis(8-chlorotheophyllin-7-yl)propane: a molecule with no intramolecular stacking

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.002 Å
R factor = 0.037
wR factor = 0.098
Data-to-parameter ratio = 12.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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The structure of 1,3-bis(8-chlorotheophyllin-7-yl)propane, $C_{17}H_{18}Cl_2N_8O_4$, which has no acidic H atom for conventional hydrogen bonding, is described. The compound shows only intermolecular stacking, as found in many xanthines, and most importantly it does not show intramolecular stacking, unlike the closely related 1,3-bis(theophyllin-8-yl)propane which has an acidic NH group for conventional hydrogen bonding. The title compound, in addition, exhibits intermolecular Cl···O interactions.

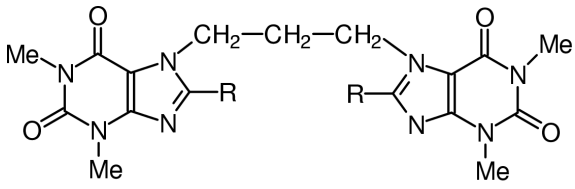
Comment

Interactions between aromatic moieties are known to play an important role in chemistry and biology. They play a significant role in molecular recognition (Hunter, 1994), stabilization of DNA/RNA structures (Hobza & Sponer, 1999) and crystal engineering (Desiraju, 1995). X-ray crystallographic investigations are considered important for studies on stacking interactions between organic molecules as they demonstrate the precise geometry (orientation) resulting from such interactions (Dahl, 1994). Use of a 'trimethylene linker' for studying π–π interactions was pioneered by Leonard in the late sixties (Browne *et al.*, 1968). The use of this linker, along with a closely related isobutyric acid linker, has increased with time for such studies (Pang *et al.*, 1999).

The crystal structure of 1,3-bis(theophyllin-8-yl)propane, (1), determined in 1971, is considered to be the first 'propylene linker' compound which shows unusual intramolecular stacking in addition to intermolecular stacking (Rosen & Hybl, 1971). Recently, we have reported the synthesis of several 'polymethylene linker' compounds derived from pyrazolo[3,4-*d*]pyrimidine, which is isomeric with the purine ring system found in xanthines, as new flexible models for studying aromatic π–π interactions (APPI) (Avasthi *et al.*, 1995, 1998). During these studies, we have deliberately avoided the presence of any acidic protons (*e.g.* OH, NH *etc*.) so that stacking interactions due to APPI could be seen by X-ray crystallography without any complication from stronger conventional hydrogen bonding. Indeed, four of our 'propylene linker' models showed intermolecular and intramolecular stacking (Biswas *et al.*, 1995; Maulik *et al.*, 1998; Avasthi *et al.*, 2001), while the fifth compound, which had an additional methylene group in its linker, showed only intermolecular stacking due to APPI (Maulik *et al.*, 2000).

Compound (1), which crystallizes as a hydrate, shows six intermolecular hydrogen-bonding contacts per molecule, two of which involve the NH group, two involve the water molecule and the remaining two are involved in C—H···O bonding (Desiraju & Steiner, 1999). In addition, owing to disorder in the 'propylene linker', the angle at the central

carbon is unusually large at 121.2 (8)°. For comparison, our four intramolecularly stacked model compounds have no water of crystallization, no NH groups and no disorder in the 'propylene linker'. Our four 'propylene linker' models have angles at the central carbon of 114.1 (2), 115.2 (2), 114.3 (5) and 113.5 (2)°, respectively. In the light of such a comparison, we wondered if the observed intramolecular stacking in compound (1) was due mainly to hydrogen bonding.



(2) R = H
(3) R = Cl

Thus, in order to probe a source of unusual intramolecular stacking in compound (1), we decided to change the 'propylene linker' from the 8,8′-positions to the 7,7′-positions, effectively removing two NH groups capable of intermolecular hydrogen bonding while keeping it isomeric with compound (1). This new compound, (2), was synthesized using a literature method (Itahara & Imamura, 1994), but we were unable to obtain X-ray quality crystals. Therefore, we decided to make the title compound (3), in which two additional Cl atoms are present at the 8,8′-positions. Incorporation of these substituents has two additional advantages: first, the size of chlorine is quite comparable to the methylene groups present in compound (1) at the 8,8′-positions. Secondly, the presence of Cl atoms effectively removes the H atoms present at the 8,8′-positions in compound (2) which are known to take part in C—H···O interactions in xanthine-type compounds (Desiraju & Steiner, 1999), thus making it more similar to compound (1).

This compound easily gave diffraction quality crystals; the conformation of this compound, as determined by X-ray crystallography, is shown in Fig. 1 (the asymmetric unit contains one half of the molecule and the other half is related by twofold rotational symmetry). To our delight, intramolecular stacking is absent while intermolecular stacking is still present, as shown in Fig. 2. The average interplanar distance between the pyrimidine planes is 3.363 Å. The crystal packing also reveals weak intermolecular Cl···O interactions [Cl1···O1($\frac{1}{2}+x, -y, z$) 3.100 (2) Å; Desiraju, 1995]. The value of the angle at the central carbon in the 'propylene linker' is 112.3 (2)°, which is normal. The planes drawn through the theophylline moieties make an angle of 78.49 (3)° with each other. Furthermore, the water of crystallization and the disorder in the 'propylene linker' compound are also absent. In conclusion, the crystallographic results on compound (3), in conjunction with our four 'propylene linker' compounds, strongly suggest the importance of conventional hydrogen bonding involving NH groups and the H_2O molecule for the intramolecular stacking observed in compound (1).

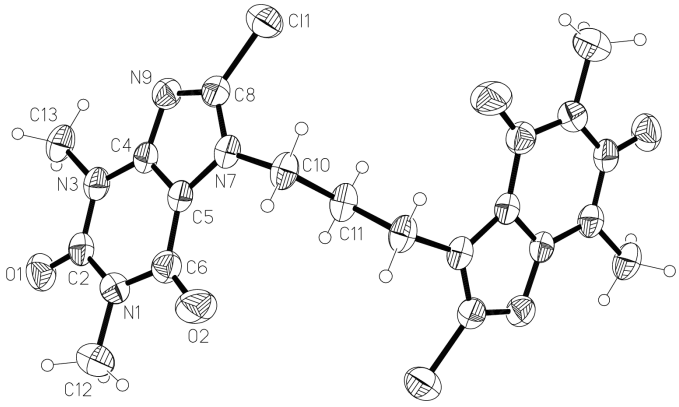


Figure 1
Displacement ellipsoid plot of (3) at the 30% probability level for the non-H atoms. Only one half of the molecule has been labelled, the other half is related by twofold rotational symmetry.

Experimental

Compound (3) was synthesized (Avasthi, K., unpublished) by the reaction of 7-(3-bromopropyl)-8-chlorotheophylline with 8-chlorotheophylline in DMF in the presence of anhydrous K_2CO_3. Diffraction quality crystals were obtained by slow evaporation of an ethyl acetate solution at room temperature.

Crystal data

$C_{17}H_{18}Cl_2N_8O_4$
M_r = 469.29
Monoclinic, $I2/a$
a = 19.929 (1) Å
b = 4.3417 (2) Å
c = 22.788 (2) Å
β = 91.40 (1)°
V = 1970.8 (2) Å^3
Z = 4
D_x = 1.582 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 35 reflections
θ = 5.2–12.5°
μ = 0.38 mm^{-1}
T = 293 (2) K
Block, colourless
0.35 × 0.25 × 0.14 mm

Data collection

Bruker $P4$ diffractometer
θ–2θ scans
2379 measured reflections
1724 independent reflections
1436 reflections with $I > 2\sigma(I)$
R_{int} = 0.014
θ_{max} = 25.0°
$h = -23 \rightarrow 23$
$k = -5 \rightarrow 1$
$l = -27 \rightarrow 1$
3 standard reflections
every 97 reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.098
S = 1.07
1724 reflections
143 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0508P)^2 + 0.8204P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

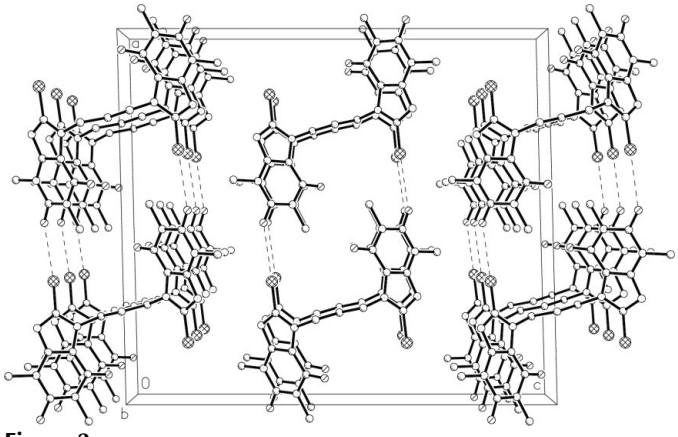


Figure 2
Molecular packing diagram for (3) showing the intermolecular Cl···O interactions as dashed lines.

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

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References

Avasthi, K., Chandra, T. & Bhakuni, D. S. (1995). *Indian J. Chem. B*, **34**, 944–949.
Avasthi, K., Rawat, D. S., Chandra, T. & Bhakuni, D. S. (1998). *Indian J. Chem. B*, **37**, 754–759.
Avasthi, K., Rawat, D. S., Maulik, P. R., Sarkhel, S., Broder, C. K. & Howard, J. A. K. (2001). *Tetrahedron Lett.* **42**, 7115–7117.
Biswas, G., Chandra, T., Avasthi, K. & Maulik, P. R. (1995). *Acta Cryst.* C**51**, 2453–2455.
Browne, D. T., Eisinger, J. & Leonard, N. J. (1968). *J. Am. Chem. Soc.* **90**, 7302–7323.
Bruker (1997). *SHELXTL-NT*. Version 5.1. Bruker AXS Inc., Madison, Wisconsin, USA.
Dahl, T. (1994). *Acta Chem. Scand.* **48**, 95–116.
Desiraju, G. R. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 2311–2327.
Desiraju, G. R. & Steiner, T. (1999). *The Weak Hydrogen Bond in Structural Chemistry and Biology*, pp. 29–121. Oxford University Press.
Hobza, P. & Sponer, J. (1999). *Chem. Rev.* **99**, 3247–3276.
Hunter, C. A. (1994). *Chem. Soc. Rev.* pp. 101–109.
Itahara, T. & Imamura, K. (1994). *Bull. Chem. Soc. Jpn*, **67**, 203–209.
Maulik, P. R., Avasthi, K., Biswas, G., Biswas, S., Rawat, D. S., Sarkhel, S., Chandra, T. & Bhakuni, D. S. (1998). *Acta Cryst.* C**54**, 275–277.
Maulik, P. R., Avasthi, K., Sarkhel, S., Chandra, T., Rawat, D. S., Logsdon, B. & Jacobson, R. A. (2000). *Acta Cryst.* C**56**, 1361–1363.
Pang, Y. –P., Miller, J. L. & Kollman, P. A. (1999). *J. Am. Chem. Soc.* **121**, 1717–1725.
Rosen, L. S. & Hybl, A. (1971). *Acta Cryst.* B**27**, 952–960.
Siemens (1996). *XSCANS*. Version 2.21. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.