

Madhukar Hemamalini,<sup>a</sup>  
Packianathan Thomas  
Muthiah,<sup>a\*</sup> Gabriele Bocelli<sup>b</sup> and  
Andrea Cantoni<sup>b</sup>

<sup>a</sup>Department of Chemistry, Bharathidasan University, Tiruchirappalli 620 024, Tamil Nadu, India, and <sup>b</sup>IMEM-CNR, Palazzo, Chimico-campus, Parco Area delle Scienze 17/a, I-43100, Parma, Italy

Correspondence e-mail:  
tomtrichy@yahoo.co.in

#### Key indicators

Single-crystal X-ray study  
 $T = 293\text{ K}$   
Mean  $\sigma(\text{C}-\text{C}) = 0.002\text{ \AA}$   
 $R$  factor = 0.045  
 $wR$  factor = 0.136  
Data-to-parameter ratio = 17.1

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

## Hydrogen-bonded supramolecular motifs in trimethoprim–terephthalate–terephthalic acid (2/1/1)

In the title compound [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidin-1-ium terephthalate terephthalic acid],  $2\text{C}_{14}\text{H}_{19}\text{N}_4\text{O}_3^+ \cdot \text{C}_8\text{H}_4\text{O}_4^{2-} \cdot \text{C}_8\text{H}_6\text{O}_4$ , the trimethoprim molecule is protonated at one of the pyrimidine N atoms. The terephthalate anion and terephthalic acid molecule are centrosymmetric. The carboxylate groups of the terephthalate anion form double hydrogen bonds of type  $\text{N}-\text{H} \cdots \text{O}$ , resulting in a fork-like interaction with the protonated diaminopyrimidine rings.

#### Comment

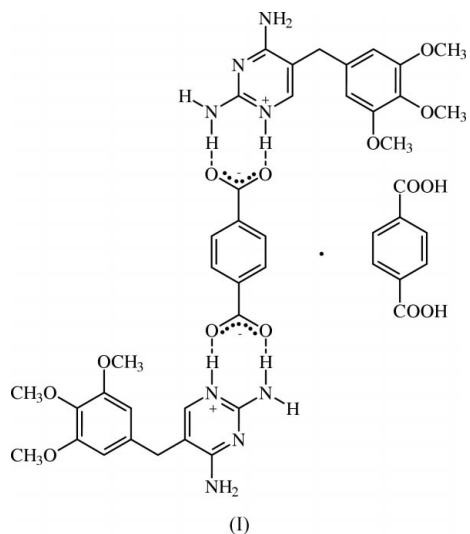
Trimethoprim [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine], TMP, is a well-known antifolate drug. It selectively inhibits the bacterial dihydrofolate reductase (DHFR) enzyme. The present study has been undertaken as part of our research programme to explore hydrogen-bonding patterns involving aminopyrimidine–carboxyl(ate) interactions. Hydrogen bonding plays a key role in molecular recognition (Goswami & Ghosh, 1997) and crystal engineering (Goswami *et al.*, 1998). The design of highly specific solid-state structures is of considerable significance in organic chemistry, due to their important application in the development of new optical, magnetic and electronic systems (Lehn, 1990). Weak  $\text{C}-\text{H} \cdots \text{O}$  interactions are also important in building up the supramolecular organization (Desiraju & Steiner, 1999). The crystal structure of terephthalic acid itself has been reported (Bailey & Brown, 1967). Aminopyrimidine–carboxylate interactions are very important for biological functions. For example, in the DHFR–trimethoprim complex, the protonated diaminopyrimidine ring of the drug makes a pair of  $\text{N}-\text{H} \cdots \text{O}$  hydrogen bonds with the carboxylate group of the enzyme (Hitching *et al.*, 1988). This bimolecular hydrogen-bonded cyclic motif is present in many crystal structures of aminopyrimidine–carboxylate complexes. This hydrogen-bonded motif can self-organize in various ways, leading to a variety of supramolecular architectures (Robert *et al.*, 2001). The crystal structure of aminopyrimidine–terephthalic acid has also been reported (Goswami *et al.*, 1999). Aminopyrimidine–carboxylate interactions are of current interest (Francis *et al.*, 2002). In particular, we are applying crystal-engineering techniques to diaminopyrimidine–carboxylate salts. Some of the hydrogen-bonded supramolecular motifs in diaminopyrimidine–carboxylate salts have been reported recently from our laboratory (Stanley *et al.*, 2002). We have already determined the crystal structures of TMP formate (Umadevi *et al.*, 2002), TMP salicylate monohydrate (Murugesan & Muthiah, 1997), TMP hydrogen maleate (Prabakaran *et al.*, 2001), TMP hydrogen glutarate (Robert *et al.*, 2001), TMP sulfate trihydrate (Muthiah *et al.*, 2001), TMP

Received 15 November 2002

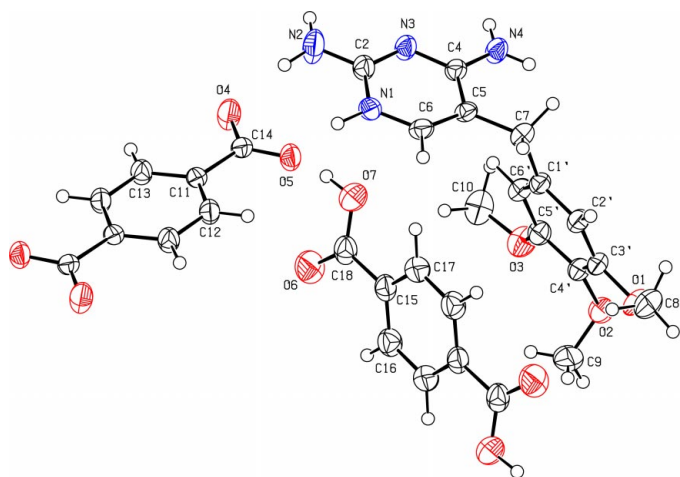
Accepted 22 November 2002

Online 7 December 2002

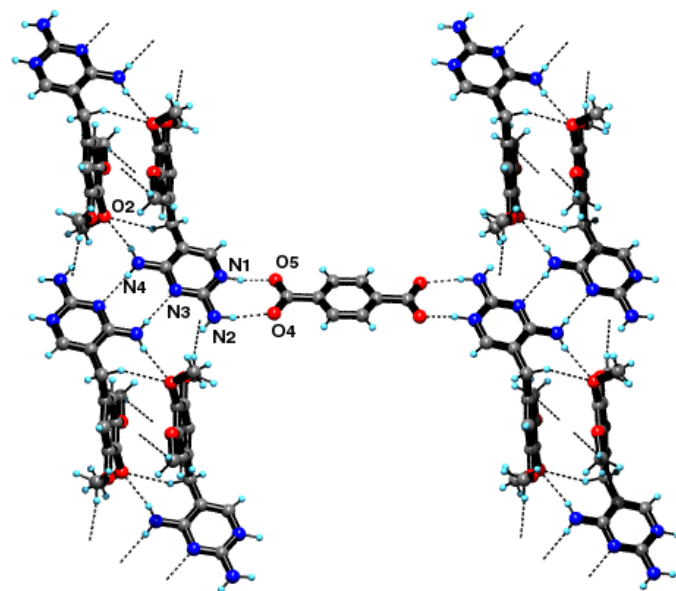
perchlorate (Muthiah *et al.*, 2002), TMP salicylate methanol solvate (Panneerselvam *et al.*, 2002) and TMP trifluoroacetate (Francis *et al.*, 2002). In this paper, the conformation and hydrogen-bonding patterns of trimethoprim–terephthalate–terephthalic acid (2/1/1) (TMPT), (I), are discussed.



The title compound (I) (with labelling of atoms in the asymmetric unit only) is shown in Fig. 1. The asymmetric unit contains one TMP cation, a half of the terephthalate anion and a half of the terephthalic acid molecule. TMP is protonated at N1 of the pyrimidine moiety, which is evident from the increase in the internal angle at N1 (C2–N1–C6) from 115.46 (5)° in neutral TMP (Koetzle & Williams, 1976) to 119.26 (9)° in the present study. This increase of the internal angle has also been observed in many TMP–carboxylate salts (Panneerselvam *et al.*, 2002). The dihedral angle between pyrimidine and phenyl planes is 72.34 (5)°. This value is in the reported range of 69.96 (8)–89.5 (2)° (Giuseppetti *et al.*, 1984; Muthiah *et al.*, 2001; Panneerselvam *et al.*, 2002). The torsion



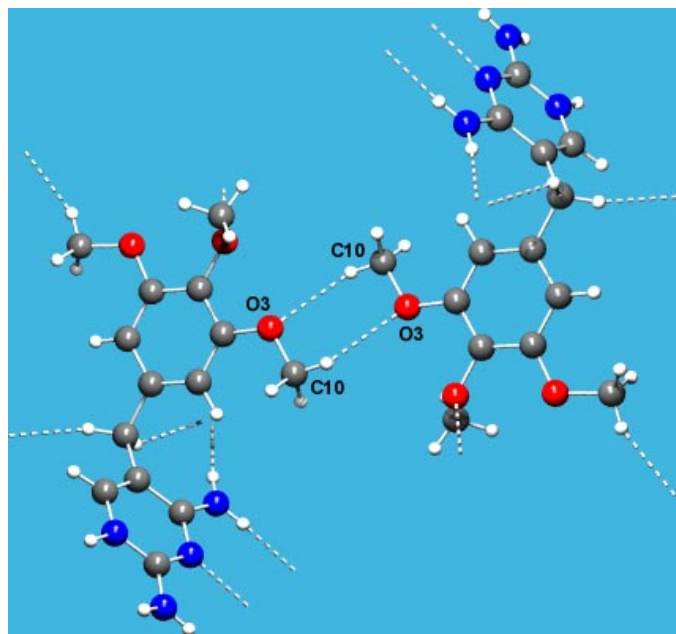
**Figure 1**  
View of the title compound, (I), showing 50% probability displacement ellipsoids.



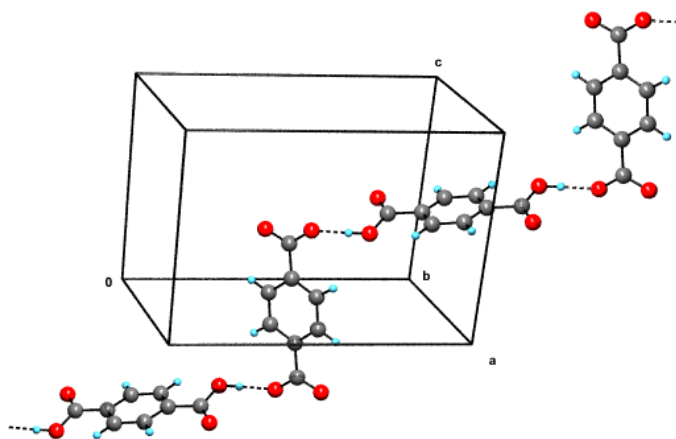
**Figure 2**  
Hydrogen-bonding patterns in (I).

angles  $\tau_1(\text{C4–C5–C7–C1}')$  and  $\tau_2(\text{C5–C7–C1'–C2}')$  are  $-86.89(13)$  and  $-153.81(10)^\circ$ , respectively. This TMP conformation plays a very important role in DHFR selectivity (Hitching *et al.*, 1988). The carboxylate group of the terephthalate anion interacts with protonated atom N1 and the 2-amino group of the pyrimidine moiety through a pair of N–H···O hydrogen bonds, forming a fork-like interaction. This can be designated by graph-set notation (Etter, 1990; Bernstein *et al.*, 1995)  $R_2^2(8)$ . This motif has been observed in DHFR–TMP complexes (Kuyper, 1990) and it is one of the 24 most frequently observed cyclic hydrogen-bonded motifs in organic crystal structures (Allen *et al.*, 1998). The TMP cations are centrosymmetrically paired through a pair of N–H···N hydrogen bonds involving the 4-amino group and one of the nitrogen atoms (N3) of the pyrimidine moiety, with graph-set notation  $R_2^2(8)$  (Fig. 2). This type of pairing has been observed in the crystal structures of trimethoprim hydrogen glutarate (Robert *et al.*, 2001), trimethoprim perchlorate (Muthiah *et al.*, 2002), trimethoprim salicylate methanol solvate (Panneerselvam *et al.*, 2002) and trimethoprim trifluoroacetate (Francis *et al.*, 2002). These TMP pairs are self-organized through N–H···O and C–H···O hydrogen bonds, leading to the formation of hydrogen-bonded supramolecular double chains. Here, the H atoms of the 4-amino and methylene ( $-\text{CH}_2$ ) groups are hydrogen bonded with one of the methoxy O atoms (O2) of the phenyl moiety, leading to a seven-membered ring (bifurcated acceptor). This can be designated by graph-set notation  $R^1_2(7)$ . Two such hydrogen-bonded supramolecular double chains are linked by fork-like hydrogen-bonded motifs.

One can consider the pyrimidine moiety as the head and trimethoxy phenyl group as the tail portion. Interestingly, the tail portions are centrosymmetrically paired through a pair of C–H···O hydrogen bonds involving a methyl group (C10) and atom O3, with graph-set notation  $R_2^2(6)$  (Fig. 3).



**Figure 3**  
C—H...O hydrogen bonds are responsible for the TMP pair in (I).



**Figure 4**  
Carboxyl-carboxylate interactions in (I).

The carboxyl groups of the terephthalic acid molecules and the carboxylate groups of the terephthalate anions are hydrogen bonded through O—H...O hydrogen bonds, leading to the formation of a step-like arrangement of a hydrogen-bonded supramolecular chain (Fig. 4). This type of carboxyl-carboxylate interaction has recently been reported in the crystal structures of TMP-hydrogen glutarate (Robert *et al.*, 2001) and pyrimethamine hydrogen glutarate (Stanley *et al.*, 2002). This chain can be designated by graph-set notation  $C_2^2(18)$ .

## Experimental

A hot ethanolic solution of trimethoprim (obtained as a gift from Shilpa Antibiotics Ltd) and terephthalic acid (Merck) were mixed in a 1:1 molar ratio and warmed for half an hour over a water bath. On slow evaporation, plate-shaped crystals of (I) were obtained.

## Crystal data

$2C_{14}H_{19}N_4O_3^+ \cdot C_8H_4O_4^{2-} \cdot C_8H_6O_4$   
 $M_r = 912.90$   
 Triclinic,  $P\bar{1}$   
 $a = 8.438(2) \text{ \AA}$   
 $b = 10.760(3) \text{ \AA}$   
 $c = 12.538(3) \text{ \AA}$   
 $\alpha = 90.26(3)^\circ$   
 $\beta = 98.22(2)^\circ$   
 $\gamma = 109.54(3)^\circ$   
 $V = 1060.1(5) \text{ \AA}^3$

$Z = 1$   
 $D_x = 1.430 \text{ Mg m}^{-3}$   
 Mo  $K\alpha$  radiation  
 Cell parameters from 1010 reflections  
 $\theta = 1.6\text{--}32.0^\circ$   
 $\mu = 0.11 \text{ mm}^{-1}$   
 $T = 293(2) \text{ K}$   
 Plate, colourless  
 $0.22 \times 0.22 \times 0.14 \text{ mm}$

## Data collection

Bruker SMART diffractometer  
 $\omega$  scans  
 Absorption correction: none  
 16182 measured reflections  
 6741 independent reflections  
 4992 reflections with  $I > 2\sigma(I)$

$R_{int} = 0.019$   
 $\theta_{max} = 32.4^\circ$   
 $h = -12 \rightarrow 12$   
 $k = -15 \rightarrow 15$   
 $l = -18 \rightarrow 18$

## Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.045$   
 $wR(F^2) = 0.136$   
 $S = 1.04$   
 6741 reflections  
 395 parameters

All H-atom parameters refined  
 $w = 1/[\sigma^2(F_o^2) + (0.084P)^2]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{max} < 0.001$   
 $\Delta\rho_{max} = 0.29 \text{ e \AA}^{-3}$   
 $\Delta\rho_{min} = -0.24 \text{ e \AA}^{-3}$

**Table 1**

Selected geometric parameters ( $\text{\AA}$ ,  $^\circ$ ).

O1—C3'	1.3694 (14)	O4—C14	1.2601 (15)
O1—C8	1.423 (2)	O5—C14	1.2420 (15)
O2—C4'	1.3873 (15)	N1—C6	1.3552 (15)
O2—C9	1.419 (2)	N1—C2	1.3549 (15)
O3—C5'	1.3640 (17)	N2—C2	1.3256 (19)
O3—C10	1.4174 (19)	N3—C2	1.3342 (15)
O6—C18	1.202 (2)	N3—C4	1.3425 (15)
O7—C18	1.3196 (18)	N4—C4	1.3380 (14)
C3'—O1—C8	116.60 (11)	N3—C4—N4	116.50 (10)
C4'—O2—C9	114.79 (11)	O2—C4'—C5'	121.08 (12)
C5'—O3—C10	117.69 (11)	O2—C4'—C3'	119.28 (10)
C2—N1—C6	119.26 (10)	O3—C5'—C6'	123.57 (11)
C2—N3—C4	117.84 (10)	O3—C5'—C4'	116.23 (11)
N2—C2—N3	119.99 (11)	N1—C6—C5	121.86 (10)
N1—C2—N3	122.78 (11)	O6—C18—C15	122.35 (13)
N1—C2—N2	117.22 (11)	O7—C18—C15	114.06 (13)
O1—C3'—C4'	115.62 (10)	O6—C18—O7	123.59 (14)
O1—C3'—C2'	124.05 (12)	O4—C14—O5	123.07 (10)
N3—C4—C5	122.30 (10)	O4—C14—C11	119.36 (10)
N4—C4—C5	121.20 (10)	O5—C14—C11	117.57 (10)

**Table 2**

Hydrogen-bonding geometry ( $\text{\AA}$ ,  $^\circ$ ).

$D\text{---}H\text{---}A$	$D\text{---}H$	$H\text{---}A$	$D\text{---}A$	$D\text{---}H\text{---}A$
N1—H1...O5 <sup>i</sup>	0.992 (17)	1.702 (17)	2.6832 (14)	169.3 (15)
N2—H2A...O4 <sup>i</sup>	0.909 (19)	2.000 (19)	2.9017 (17)	171.4 (16)
N4—H4A...O2 <sup>iii</sup>	0.852 (17)	2.287 (17)	3.1260 (17)	168.3 (15)
N4—H4B...N3 <sup>iii</sup>	0.884 (16)	2.210 (16)	3.0843 (16)	169.9 (15)
O7—H7...O4	0.94 (2)	1.62 (2)	2.5499 (17)	176 (2)
C7—H7A...O6 <sup>iv</sup>	0.974 (17)	2.439 (17)	3.3754 (19)	161.2 (13)
C7—H7B...O2 <sup>ii</sup>	1.056 (17)	2.540 (16)	3.3355 (17)	131.6 (12)
C8—H8B...O5 <sup>v</sup>	0.91 (2)	2.493 (19)	3.353 (2)	157.7 (16)
C10—H10A...O3 <sup>vi</sup>	0.93 (3)	2.53 (2)	3.336 (2)	145.0 (17)

Symmetry codes: (i)  $1 - x, 1 - y, 1 - z$ ; (ii)  $2 - x, 2 - y, -z$ ; (iii)  $2 - x, 2 - y, 1 - z$ ; (iv)  $1 + x, y, z$ ; (v)  $1 + x, y, z - 1$ ; (vi)  $1 - x, 2 - y, -z$ .

The completeness of the reflection data is only 88.7%, because the crystal was of poor quality. All the H atoms were located in difference Fourier maps and refined with isotropic displacement parameters. The C–H, N–H and O–H bond lengths are 0.91 (2)–1.056 (17), 0.852 (17)–0.992 (17) and 0.94 (2) Å, respectively.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINTE* (Bruker, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1997) and *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *PLATON*.

## References

- Allen, F. H., Raithby, P. R., Shields, G. P. & Taylor, R. (1998). *Chem. Commun.* pp. 1043–1044.
- Bailey, M. & Brown, C. J. (1967). *Acta Cryst.* **22**, 387–391.
- Bernstein, J., Davis, R. E., Shimon, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
- Bruker (1997). *SAINTE*, *SMART* and *SHELXTL-NT*. Bruker AXS Inc., Madison, Wisconsin, USA.
- Desiraju, G. R. & Steiner, T. (1999). *The Weak Hydrogen Bond in Structural Chemistry and Biology*. Oxford: Oxford University Press.
- Etter, M. C. (1990). *Acc. Chem. Res.* **23**, 120–126.
- Francis, S., Muthiah, P. T., Bocelli, G. & Righi, L. (2002). *Acta Cryst.* **E58**, o717–o719.
- Giuseppetti, G., Tadini, C., Bettinetti, G. P., Giordano, F. & La Manna, A. (1984). *Acta Cryst.* **C40**, 650–653.
- Goswami, S. P. & Ghosh, K. (1997). *Tetrahedron Lett.* **38**, 4503–4506.
- Goswami, S. P., Mahapatra, A. K., Ghosh, K., Nigam, G. D., Chinnakali, K. & Fun, H.-K. (1999). *Acta Cryst.* **C55**, 87–89.
- Goswami, S. P., Mahapatra, A. K., Nigam, G. D., Chinnakali, K. & Fun, H.-K. (1998). *Acta Cryst.* **C54**, 1301–1302.
- Hitching, G. H., Kuyper, L. F. & Baccanari, D. P. (1988). *Design of Enzyme Inhibitors as Drugs*, edited by M. Sandler and H. J. Smith, p. 343. New York: Oxford University Press.
- Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
- Koetzle, T. F. & Williams, G. J. B. (1976). *J. Am. Chem. Soc.* **98**, 2074–2078.
- Kuyper, L. F. (1990). *Crystallographic and Modeling Methods in Molecular Design*, edited by C. E. Bugg and S. E. Ealick, pp. 56–79. New York: Springer Verlag.
- Lehn, J. M. (1990). *Angew. Chem. Int. Ed. Engl.* **29**, 1304–1319.
- Murugesan, S. & Muthiah, P. T. (1997). *Acta Cryst.* **C53**, 763–764.
- Muthiah, P. T., Umadevi, B., Stanley, N., Bocelli, G. & Cantoni, A. (2002). *Acta Cryst.* **E58**, o59–o61.
- Muthiah, P. T., Umadevi, B., Stanley, N., Shui, X. & Eggleston, D. S. (2001). *Acta Cryst.* **E57**, o1179–o1182.
- Panneerselvam, P., Stanley, N. & Muthiah, P. T. (2002). *Acta Cryst.* **E58**, o180–o182.
- Prabakaran, P., Murugesan, S., Muthiah, P. T., Bocelli, G. & Righi, L. (2001). *Acta Cryst.* **E57**, o933–o936.
- Robert, J. J., Raj, S. B. & Muthiah, P. T. (2001). *Acta Cryst.* **E57**, o1206–o1208.
- Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
- Spek, A. L. (1997). *PLATON*. University of Utrecht, The Netherlands.
- Stanley, N., Sethuraman, V., Muthiah, P. T., Luger, P. & Weber, M. (2002). *Cryst. Growth Des.* **2**, 631–635.
- Umadevi, B., Prabakaran, P. & Muthiah, P. T. (2002). *Acta Cryst.* **C58**, o510–o512.