2813 measured reflections
2813 independent reflections
2438 reflections with $I > 2\sigma(I)$
3 standard reflections
frequency: 20 min
intensity decay: none

Refinement

Refinement on F^2
$R(F) = 0.044$
$wR(F^2) = 0.123$
$S = 1.063$
2813 reflections
307 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0651P)^2 + 0.3922P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.215$ e Å^{-3}
$\Delta\rho_{min} = -0.176$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

S1—O4	1.415 (2)	O1—C3	1.349 (3)
S1—O3	1.423 (2)	O1—C7	1.431 (3)
S1—O2	1.595 (2)	N1—N2	1.237 (3)
S1—C17	1.747 (3)	N1—C1	1.426 (3)
O2—C2	1.413 (3)	N2—C11	1.432 (3)
O4—S1—O3	120.76 (13)	O3—S1—C17	109.82 (13)
O4—S1—O2	104.13 (12)	O2—S1—C17	102.83 (11)
O3—S1—O2	108.69 (11)	N2—N1—C1	114.7 (2)
O4—S1—C17	109.02 (12)	N1—N2—C11	113.8 (2)
C17—S1—O2—C2	−111.1 (2)	N2—N1—C1—C6	17.7 (3)
C1—N1—N2—C11	−175.4 (2)	N1—N2—C11—C16	−179.1 (2)
N2—N1—C1—C2	−167.3 (2)	N1—N2—C11—C12	3.7 (4)

Following a sequence of refinements and difference Fourier syntheses, disordered C9 and C10 atoms were recognized in a 60:40 ratio in the allyl group. Their atomic displacement parameters are only slightly larger than those of the other atoms. A riding model was used for all H atoms at calculated positions with isotropic U_{iso}.

Data collection: *CAD-4 Express* (Enraf–Nonius, 1993). Cell refinement: *CAD-4 Express*. Data reduction: *MolEN* (Fair, 1990). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

The authors wish to acknowledge the use of the CAD-4 diffractometer (purchased under Grant DPT/TBAG1 of the Scientific and Technical Research Council of Turkey) of the Physics Engineering Department, Hacettepe University, Turkey.

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: SK1039). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Methanol Solvate of the 1:1 Molecular Complex of Trimethoprim and Sulfadimidine

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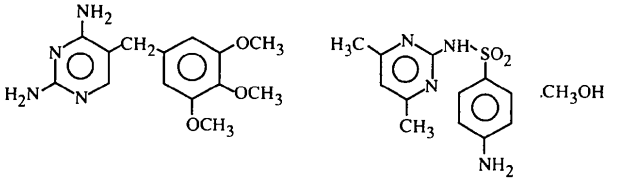
Abstract

In the title complex, $C_{14}H_{18}N_4O_3.C_{12}H_{14}N_4O_2S.CH_4O$, the molecular association between trimethoprim {5-[(3,4,5-trimethoxyphenyl)methyl]pyrimidine-2,4-diamine; TMP} and sulfadimidine [4-amino-*N*-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide; SDMD] is maintained by two N—H···N hydrogen bonds with no proton transfer from the sulfonamide imino N atom to the pyrimidine N atom of TMP. The methanol solvate molecule is linked to an O atom of the sulfonamido group through a strong O—H···O interaction and does not seem to play an important role in the crystal-packing stabilization.

Comment

Complexation of TMP with sulfamethoxazole (Giuseppetti, Tadini, Bettinetti, Giordano & La Manna, 1980; Nakai, Takasuka & Shiro, 1984) and sulfametrole (Giuseppetti, Tadini & Bettinetti, 1994) in the solid state involves a proton transfer from the sulfonamide to the pyrimidine N atom of TMP. In the complex between

TMP, SDMD and methanol described herein, a non-ionic N—H···N interaction is established instead.



TMP SDMD

The C13—N7—C14 angle of 115.6 (2)° is the same as the corresponding angle in unprotonated TMP (Koetzle & Williams, 1976), while it increases in complexes where TMP is protonated, *i.e.* with sulfametrole [119.2 (2)°; Giuseppetti, Tadini & Bettinetti, 1994] and sulfamethoxazole [118.9 (3)°; Nakai, Takasuka & Shiro, 1984]. We can deduce that SDMD (pK_a 7.4) is too weak an acid compared with sulfamethoxazole (pK_a 5.7) and sulfametrole (pK_a 4.8) to protonate TMP. Moreover, SDMD is present in the amido tautomeric form (*i.e.* a H atom is linked to N1), the N—C sulfonamide bond distance [1.391 (2) Å] being comparable with the corresponding distances in free SDMD [1.406 (3) Å; Basak, Mazumdar & Chaudhuri, 1983; Tiwari, Haridas & Singh, 1984; Maury *et al.*, 1985], its methanol solvate [1.391 (6) Å; Rambaud *et al.*, 1985] and other molecular complexes where no SDMD deprotonation occurs, *e.g.* with 4-aminosalicylic acid [1.397 (4) Å; Caira, 1992], 2-aminobenzoic acid [1.386 (3) Å; Caira, 1991] and salicylic acid [1.379 (4) Å; Patel, Haridas & Singh, 1988]. Distinctly shorter lengths for this bond are displayed by deprotonated SDMD, for example, in the complex with aminacrine [1.355 (5) Å; Ghose, Chakrabarti, Dattagupta, Le Page & Trotter, 1988] and in the SDMD monosodium salt dihydrate [1.366 (6) Å; Hannan & Talukdar, 1992]. Another consequence of the sulfonamido N-atom deprotonation is a shortening of the N—S bond distance, which has values of 1.572 (3) (Ghose, Chakrabarti, Dattagupta, Le Page & Trotter, 1988) and 1.573 (6) Å (Hannan & Talukdar, 1992) in the SDMD anion compared with 1.621 (2) Å in the title compound.

The second link connecting TMP and SDMD in the complex is established between the 2-amino group of TMP and an N atom of SDMD (Fig. 1 and Table 2). This pattern resembles that found in the TMP–sulfamethoxazole complex, where the N atom of the isoxazole ring acts as an acceptor (Giuseppetti, Tadini, Bettinetti, Giordano & La Manna, 1980), while it differs from that in the TMP–sulfametrole complex, where a sulfonamide O atom is the counterpart of the same amino group of TMP (Giuseppetti, Tadini & Bettinetti, 1994).

As far as the interatomic distances and bond angles of the title compound are concerned, those of both the sulfonamide portion and the TMP and SDMD pyrimidine moieties agree well with their equivalents in the structures of free TMP (Koetzle & Williams, 1976) and free SDMD (Basak, Mazumdar & Chaudhuri, 1983; Tiwari, Haridas & Singh, 1984; Maury *et al.*, 1985). The same holds for the torsion angles necessary to represent the molecular conformation of TMP, *i.e.* τ_1(TMP) (C14—C15—C17—C18) of 93.3 (2) and τ_2(TMP) (C15—C17—C18—C19) of −27.1 (3)°,

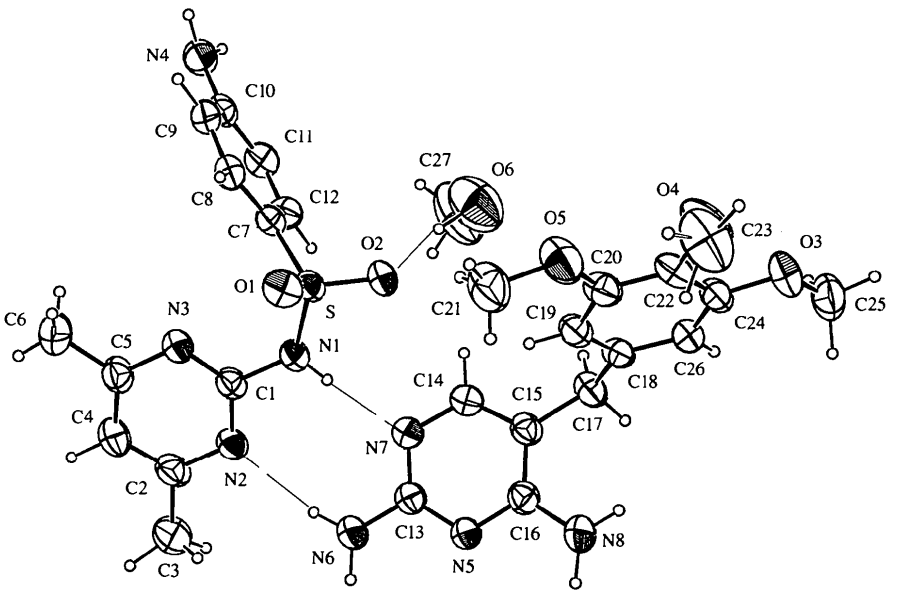


Fig. 1. A perspective view of the title complex with ellipsoids shown at the 30% probability level.

which are within a few degrees of those found in the free molecule (Koetzle & Williams, 1976). Differences in the conformational parameters of SDMD bound to TMP, which are represented by τ_1(SDMD) (C8—C7—S—N1) of 131.2 (2), τ_2(SDMD) (C7—S—N1—C1) of −65.2 (2) and τ_3(SDMD) (N3—C1—N1—S) of 10.5 (2)°, relative to those observed in the free and methanol-solvated SDMD structures, are evident (Rambaud *et al.*, 1985). Significant conformational changes in SDMD on complexation with aromatic carboxylic acids have been noted previously (Patel, Haridas & Singh, 1988; Caira, 1991, 1992).

The methanol molecule is strongly involved in a hydrogen-bonding interaction with a sulfonamido O atom (Fig. 1 and Table 2). This structural feature is reflected in the unusual high desolvation temperature of about 419 K recorded by differential-scanning calorimetry and thermogravimetry under standard experimental conditions (Bettinetti & Giordano, 1988). A similar hydrogen bond was displayed by the solvent molecule in the SDMD methanol solvate (Rambaud *et al.*, 1985), though the desolvation temperature (about 358 K) was distinctly lower (Maury *et al.*, 1985).

Besides van der Waals forces, the crystal packing is stabilized by an extensive hydrogen-bond network involving the *p*-aminophenyl and amino groups as proton donors and the sulfonamido O and pyrimidine N5 atoms as proton acceptors (Table 2). All the above interactions are relatively weaker than those displayed by the molecular species in the complex. The methanol molecules, strongly hydrogen bonded to the sulfonamido groups, do not seem to play an important role in the crystal-packing stabilization; they are stacked in channels down the **a** direction.

Experimental

Single crystals of the title compound were prepared by recrystallization of 2.84 g of an equimolar mixture of TMP and SDMD from 100 ml of methanol.

Crystal data

$C_{14}H_{18}N_4O_3.C_{12}H_{14}N_4O_2S.CH_4O$
M_r = 600.69
Triclinic
$P\bar{1}$
a = 7.812 (1) Å
b = 12.000 (1) Å
c = 17.161 (1) Å
α = 78.92 (2)°
β = 84.32 (2)°
γ = 72.23 (2)°
V = 1502.0 (3) Å^3
Z = 2
D_x = 1.3282 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 25 reflections
θ = 34–38°
μ = 1.373 mm^{-1}
T = 293 (3) K
Prism
0.58 × 0.54 × 0.28 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (North, Phillips & Mathews, 1968)
T_{min} = 0.581, T_{max} = 0.681
7113 measured reflections
5542 independent reflections
5269 reflections with $I > 3\sigma(I)$
R_{int} = 0.007
θ_{max} = 70°
h = −9 → 9
k = −14 → 14
l = −3 → 20
3 standard reflections
every 300 reflections
intensity decay: 1.7%

Refinement

Refinement on F
R = 0.042
wR = 0.041
S = 0.632
5269 reflections
532 parameters
H-atom coordinates refined
Unit weights applied
$(\Delta/\sigma)_{max}$ = 0.01
$\Delta\rho_{max}$ = 0.289 e Å^{-3}
$\Delta\rho_{min}$ = −0.041 e Å^{-3}
Extinction correction: Zachariasen (1963)
Extinction coefficient: 2.537 × 10^{-6}
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Table 1. *Selected geometric parameters (Å, °)*

S—O1	1.431 (2)	N2—C1	1.332 (3)
S—O2	1.448 (1)	N2—C2	1.341 (2)
S—N1	1.621 (2)	N3—C1	1.332 (3)
S—C7	1.748 (2)	N3—C5	1.346 (2)
O3—C24	1.372 (2)	N4—C10	1.384 (3)
O3—C25	1.428 (3)	N5—C13	1.344 (3)
O4—C22	1.375 (3)	N5—C16	1.344 (2)
O4—C23	1.389 (4)	N6—C13	1.344 (2)
O5—C20	1.374 (3)	N7—C13	1.337 (3)
O5—C21	1.423 (3)	N7—C14	1.351 (2)
O6—C27	1.366 (6)	N8—C16	1.351 (3)
N1—C1	1.391 (2)		
N1—S—C7	107.0 (1)	N3—C5—C4	121.4 (2)
O2—S—C7	108.4 (1)	N3—C5—C6	116.2 (2)
O2—S—N1	103.3 (1)	S—C7—C12	119.3 (2)
O1—S—C7	108.9 (1)	S—C7—C8	119.9 (2)
O1—S—N1	111.8 (1)	N4—C10—C9	120.8 (2)
O1—S—O2	116.8 (1)	N4—C10—C11	120.2 (2)
C24—O3—C25	117.4 (2)	N6—C13—N7	116.7 (2)
C22—O4—C23	118.1 (2)	N5—C13—N7	125.7 (2)
C20—O5—C21	117.6 (2)	N5—C13—N6	117.6 (2)
S—N1—C1	124.3 (1)	N7—C14—C15	124.4 (2)
C1—N2—C2	116.0 (2)	N8—C16—C15	121.9 (2)
C1—N3—C5	115.3 (2)	N5—C16—C15	122.2 (2)
C13—N5—C16	116.8 (2)	N5—C16—N8	115.8 (2)
C13—N7—C14	115.6 (2)	O5—C20—C19	123.6 (2)
N2—C1—N3	127.8 (2)	O5—C20—C22	115.7 (2)
N1—C1—N3	117.9 (2)	O4—C22—C20	123.5 (2)
N1—C1—N2	114.3 (2)	O4—C22—C24	117.4 (2)
N2—C2—C4	120.7 (2)	O3—C24—C22	114.8 (2)
N2—C2—C3	117.6 (2)	O3—C24—C26	124.6 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—HN1···N7	0.83 (2)	1.97 (3)	2.787 (2)	168 (3)
N6—HN6*B*···N2	0.81 (2)	2.23 (3)	3.038 (3)	170 (2)
O6—HO6···O2	1.18 (2)	1.76 (3)	2.931 (3)	174 (2)
N4—HN4*A*···O2^{i}	1.03 (2)	2.40 (3)	3.387 (2)	162 (2)
N4—HN4*B*···O1^{ii}	0.80 (3)	2.42 (3)	3.096 (2)	143 (3)
N6—HN6*A*···O4^{iii}	0.89 (2)	2.35 (2)	3.085 (2)	140 (2)
N8—HN8*A*···O3^{iv}	0.90 (2)	2.36 (3)	3.046 (3)	133 (2)
N8—HN8*B*···N5^{v}	0.98 (2)	2.05 (3)	3.022 (3)	178 (3)

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

All the H atoms were experimentally positioned and their positional parameters refined. The displacement parameters of the acidic H atoms were refined isotropically. Unit weights kept $\Sigma w(\Delta F)^2$ uniform over ranges of $\sin\theta/\lambda$ and $|F_o|$.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CELDIM* in *CAD-4 Software*. Data reduction: *MolEN* (Fair, 1990). Program(s) used to solve structure: *MULTAN*80 (Main *et al.*, 1980). Program(s) used to refine structure: *MolEN*. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

This work was partially supported by a grant from CNR to GPB.

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: SK1047). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1997). C**53**, 597–599

Absolute Configuration of the Double Salt of *cis*-4-Amino-5-chloro-*N*-{1-[3-(4-fluorophenoxy)propyl]-3-methoxypiperidin-1-ium-4-yl}-2-methoxybenzamide Tartrate (Cisapride Tartrate)†

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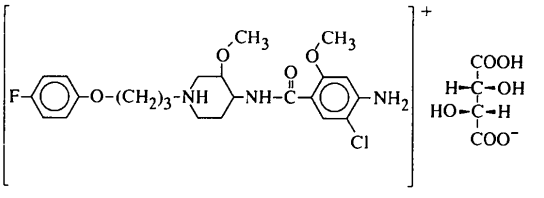
Abstract

The structure determination of cisapride (+)-tartrate, $C_{23}H_{30}ClFN_3O_4^+.C_4H_5O_6^-$, from X-ray diffraction data of crystals obtained from an ethanol solution, showed that the diastereomers [(3*R*,4*S*)(2*R*,3*R*)] and [(3*S*,4*R*)-(2*R*,3*R*)] crystallized as a double salt in a 1:1 ratio.

Comment

The crystal structure of the gastrokinetic drug cisapride (R51619) was determined by Collin *et al.* (1989). It is a 3,4-*cis* racemate, wherein the piperidine ring adopts a chair conformation with the nitrogen substituent and the benzamide function in equatorial positions and the methoxy group in an axial position. To separate cisapride into its enantiomeric forms, it is treated with (+)-tartaric acid and crystallized from ethanol, (I). As the diastereomers could not be resolved, the formation of a double salt in the crystal was supposed.



(I)

To check this hypothesis, the crystal structure and absolute configuration of R53929 has been determined. The asymmetric unit contains the two diastereomers [(3*R*,4*S*)(2*R*,3*R*)] and [(3*S*,4*R*)(2*R*,3*R*)]. The corresponding bond lengths, angles and absolute values of the torsion angles do not differ significantly between the two

† Internal code of the Janssen Research Foundation: R53929.