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1:1 Molecular Complex of Trimethoprim and Sulfametrole

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Abstract

In the complex between trimethoprim, 5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine, TMP, and sulfametrole, 4-amino-*N*-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide, SMTR, $C_{14}H_{19}N_4O_3^+.C_9H_9N_4O_3S_2^-$, the proton participating in the hydrogen bond between the pyrimidine and sulfonamide N atoms [2.808 (3) Å] is transferred from SMTR to TMP ($NH^+\cdots N^-$). An N—H···O hydrogen bond [2.933 (4) Å] is also established between the 2-aminopyrimidine group of TMP and an O atom of the sulfonamido group of SMTR. The bimolecular complex units are linked in the crystal through N—H···O hydrogen bonds [3.057 (3) Å] between *p*-aminophenyl and sulfonamido groups.

Comment

Trimethoprim (TMP) displays complexing ability with various sulfa drugs present in pharmaceutical antibacterial associations (Bettinetti & Giordano, 1988). The nature of the molecular interactions in solution (Fruttero, Hawkes, Randall, Gasco & Groombridge, 1988) and in the solid state (Giuseppetti, Tadini, Bettinetti, Giordano & La Manna, 1980; Nakai, Takasuka & Shiro, 1984) for the 1:1 TMP:sulfamethoxazole (SMZ) complex has been determined. In the title compound, the $N11^-\cdots H46—N26^+$ [2.808 (3) Å] ionic interaction is established (Figs. 1 and 2) which involves a proton transfer similar to that found in the complex between TMP and SMZ (Nakai, Takasuka & Shiro, 1984). The proton involved is located closer to N26 of TMP [1.02 (3) Å] than to N11 of SMTR [1.79 (3) Å], to which it was originally bound. Moreover, the increase in the pyridine N-atom bond angle in the complex [C20—N26—C25 = 119.2 (3)°] confirms the formation of the TMP cation, since the corresponding angle in unprotonated TMP is 115.5° (Koetzle & Williams, 1976).

The torsion angles necessary to represent the molecular conformations are $\tau_{1,\rm TMP}$ (C22—C24—C27—C28) = −62.1 (4) and $\tau_{2,\rm TMP}$ (C24—C27—C28—C39) = −42.2 (4)° for TMP, and $\tau_{1,\rm SMTR}$ (N11—S8—C5—C4) = −64.8 (2), $\tau_{2,\rm SMTR}$ (C5—S8—N11—C12) = −64.8 (2) and $\tau_{3,\rm SMTR}$ (S8—N11—C12—N18) = 9.2 (4)° for SMTR. The N19—H51···O9 hydrogen-bond interaction [2.933 (4) Å],

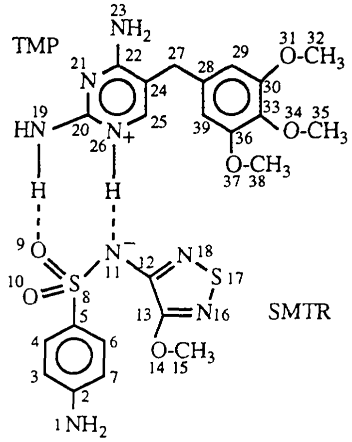

Fig. 1. Structural diagram of the 1:1 trimethoprim:sulfametrole complex with atomic numbering scheme.

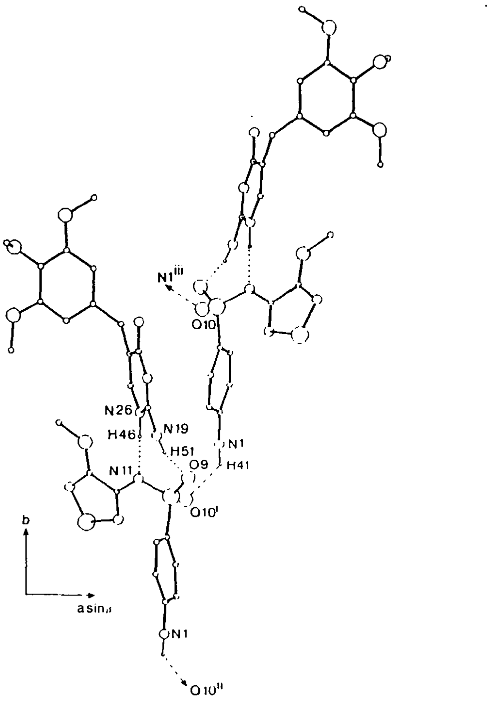

Fig. 2. *ORTEP*II drawing of the 1:1 trimethoprim:sulfametrole complex with intermolecular bonds responsible for molecular packing in the crystal (dashed lines). Symmetry codes: (i) $-x$, $y-\frac{1}{2}$, $-z+\frac{1}{2}$; (ii) x, $y-1$, z; (iii) $-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$.

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where the amino group of TMP acts as a donor, involves the O atom of the sulfonamide group as an acceptor instead of the N18 heteroatom, as one could expect from the pattern found in the TMP:SMZ complex where the acceptor is just the N heteroatom of the isoxazole ring (Giuseppetti, Tadini, Bettinetti, Giordano & La Manna, 1980). This suggests that, in the title compound, the lone-electron pair of N18 is strongly involved in the resonance of the fully planar thiadazole ring. As can be seen in Fig. 2, the bimolecular complex units are linked head-to-tail in the crystal at the N1 *p*-amino and O10 sulfonamido groups, through N1—H41···O10 hydrogen bonds [3.057 (3) Å]. These bonds are remarkably weak when compared to those that combine molecules of TMP and SMTR.

Experimental

Single crystals of the title compound were obtained by recrystallization from 95% ethanol (m.p. 454 K) (Bettinetti & Giordano, 1988).

Crystal data

$C_{14}H_{19}N_4O_3^+.C_9H_9N_4O_3S_2^-$
$M_r = 576.65$
Monoclinic
$P2_1/c$
$a = 14.768$ (3) Å
$b = 15.133$ (4) Å
$c = 12.818$ (3) Å
$\beta = 112.36$ (2)°
$V = 2649.2$ (4) Å^3
$Z = 4$
$D_x = 1.446$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.7107$ Å
Cell parameters from 48 reflections
$\theta = 2$–22°
$\mu = 0.244$ mm^{-1}
$T = 296$ K
Prismatic
0.40 × 0.30 × 0.18 mm
White

Data collection

Philips PW1100 diffractometer
ω–2θ scans
Absorption correction: empirical (North, Phillips & Mathews, 1968)
$T_{\min} = 0.929$, $T_{\max} = 0.995$
3569 measured reflections
3410 independent reflections

2582 observed reflections [$I > 3\sigma(I)$]
$\theta_{\max} = 22°$
$h = -14 \rightarrow 14$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 13$
3 standard reflections
frequency: 180 min
intensity variation: mean 2.0%

Refinement

Refinement on F
$R = 0.0319$
$wR = 0.0524$
$S = 1.823$
2582 reflections
532 parameters
Unit weights applied
$(\Delta/\sigma)_{\max} = 0.212$
$\Delta\rho_{\max} = -0.66$ e Å^{-3}
$\Delta\rho_{\min} = 0.55$ e Å^{-3}

Extinction correction: Coppens & Hamilton (1970)
Extinction coefficient: 1.51 (4) × 10^{-5}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$B_{\rm eq} = (1/3)\Sigma_i\Sigma_j B_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$
N1	0.0827 (2)	0.1078 (2)	0.5879 (2)	3.94 (9)
C2	0.0825 (2)	0.1914 (2)	0.6292 (2)	2.89 (8)
C3	0.1138 (2)	0.2639 (2)	0.5850 (2)	3.20 (9)
C4	0.1129 (2)	0.3475 (2)	0.6269 (2)	3.02 (8)
C5	0.0807 (2)	0.3605 (1)	0.7143 (2)	2.58 (8)
C6	0.0523 (2)	0.2886 (2)	0.7608 (2)	2.87 (8)
C7	0.0530 (2)	0.2049 (2)	0.7191 (2)	3.13 (9)
S8	0.06908 (4)	0.46834 (4)	0.75887 (5)	2.74 (2)
O9	0.0148 (1)	0.5184 (1)	0.6582 (1)	3.38 (6)
O10	0.0219 (1)	0.4604 (1)	0.8391 (1)	3.58 (6)
N11	0.1730 (1)	0.5147 (1)	0.8109 (2)	2.75 (6)
C12	0.2416 (2)	0.4802 (2)	0.9084 (2)	2.62 (8)
C13	0.3300 (2)	0.5283 (2)	0.9703 (2)	3.20 (8)
O14	0.3439 (1)	0.6085 (1)	0.9346 (1)	4.20 (6)
C15	0.4272 (3)	0.6573 (3)	1.0103 (3)	6.25 (14)
N16	0.3893 (1)	0.4907 (1)	1.0615 (2)	4.16 (8)
S17	0.33626 (6)	0.39743 (5)	1.07365 (6)	4.63 (3)
N18	0.2361 (1)	0.4055 (1)	0.9579 (2)	3.41 (7)
N19	0.1172 (2)	0.6280 (2)	0.5492 (2)	3.88 (8)
C20	0.1462 (2)	0.6990 (2)	0.6164 (2)	2.94 (8)
N21	0.1503 (1)	0.7770 (1)	0.5717 (2)	3.10 (7)
C22	0.1792 (2)	0.8464 (2)	0.6411 (2)	2.97 (8)
N23	0.1796 (1)	0.9240 (1)	0.5935 (2)	3.85 (8)
C24	0.2076 (2)	0.8389 (1)	0.7612 (2)	2.89 (8)
C25	0.2022 (2)	0.7571 (2)	0.7988 (2)	3.03 (8)
N26	0.1720 (1)	0.6866 (1)	0.7282 (2)	2.94 (7)
C27	0.2362 (2)	0.9177 (2)	0.8384 (2)	3.49 (9)
C28	0.3257 (2)	0.9685 (2)	0.8413 (2)	2.95 (8)
C29	0.3257 (2)	1.0594 (2)	0.8485 (2)	3.02 (8)
C30	0.4095 (2)	1.1072 (2)	0.8599 (2)	3.07 (8)
O31	0.4159 (1)	1.1971 (1)	0.8675 (2)	4.16 (7)
C32	0.3282 (2)	1.2446 (2)	0.8477 (3)	4.81 (11)
C33	0.4931 (2)	1.0634 (2)	0.8648 (2)	3.16 (8)
O34	0.5774 (1)	1.1118 (1)	0.8842 (1)	4.36 (7)
C35	0.6025 (3)	1.1228 (3)	0.7896 (3)	6.95 (15)
C36	0.4925 (2)	0.9725 (2)	0.8553 (2)	3.29 (9)
O37	0.5781 (1)	0.9354 (1)	0.8598 (2)	4.88 (7)
C38	0.5826 (3)	0.8434 (3)	0.8543 (3)	6.07 (14)
C39	0.4086 (2)	0.9248 (2)	0.8433 (2)	3.32 (9)

Table 2. *Selected geometric parameters* (Å, °)

N1—C2	1.371 (4)	C20—N26	1.348 (4)
C2—C3	1.393 (4)	N21—C22	1.337 (4)
C2—C7	1.393 (4)	C22—N23	1.324 (4)
C3—C4	1.375 (4)	C22—C24	1.437 (4)
C4—C5	1.388 (4)	C24—C25	1.342 (4)
C5—C6	1.380 (4)	C24—C27	1.503 (4)
C5—S8	1.759 (4)	C25—N26	1.360 (4)
C6—C7	1.376 (4)	C27—C28	1.517 (4)
S8—O9	1.447 (4)	C28—C29	1.379 (4)
S8—O10	1.449 (4)	C28—C39	1.385 (4)
S8—N11	1.585 (4)	C29—C30	1.392 (4)
N11—C12	1.377 (4)	C30—O31	1.366 (4)
C12—C13	1.441 (4)	C30—C33	1.381 (4)
C12—N18	1.314 (4)	O31—C32	1.418 (4)
C13—O14	1.339 (4)	C33—O34	1.382 (4)
C13—N16	1.295 (4)	C33—C36	1.382 (4)
O14—C15	1.447 (4)	O34—C35	1.407 (4)
N16—S17	1.649 (4)	C36—O37	1.363 (4)
S17—N18	1.654 (4)	C36—C39	1.390 (4)
N19—C20	1.341 (4)	O37—C38	1.398 (4)
C20—N21	1.324 (4)		
N1—C2—C7	120.2 (3)	N21—C20—N26	122.9 (3)
N1—C2—C3	121.3 (3)	C20—N21—C22	117.9 (3)
C3—C2—C7	118.5 (3)	N21—C22—C24	122.7 (3)
C2—C3—C4	120.8 (3)	N21—C22—N23	116.5 (3)
C3—C4—C5	120.2 (3)	N23—C22—C24	120.8 (3)
C4—C5—S8	119.9 (3)	C22—C24—C27	122.5 (3)
C4—C5—C6	119.4 (3)	C22—C24—C25	115.2 (3)

C6—C5—S8	120.5 (3)	C25—C24—C27	122.3 (3)
C5—C6—C7	120.5 (3)	C20—N26—C25	119.2 (3)
C5—S8—N11	110.4 (3)	C24—C27—C28	116.2 (3)
C5—S8—O10	106.6 (3)	C27—C28—C39	121.0 (3)
C5—S8—O9	106.6 (3)	C27—C28—C29	119.1 (3)
O10—S8—N11	112.8 (3)	C29—C28—C39	119.8 (3)
O9—S8—N11	105.3 (3)	C28—C29—C30	120.2 (3)
O9—S8—O10	115.0 (3)	C29—C30—C33	120.0 (3)
S8—N11—C12	118.4 (3)	C29—C30—O31	124.0 (3)
N11—C12—N18	127.2 (3)	O31—C30—C33	116.0 (3)
N11—C12—C13	120.6 (3)	C30—O31—C32	117.3 (3)
C13—C12—N18	112.2 (3)	C30—C33—C36	119.8 (3)
C12—C13—N16	116.7 (3)	C30—C33—O34	118.8 (3)
C12—C13—O14	119.5 (3)	O34—C33—C36	121.3 (3)
O14—C13—N16	124.7 (3)	C33—O34—C35	115.0 (3)
C13—O14—C15	115.8 (3)	C33—C36—C39	120.2 (3)
C13—N16—S17	106.3 (3)	C33—C36—O37	115.6 (3)
N16—S17—N18	98.4 (3)	O37—C36—C39	124.3 (3)
C12—N18—S17	107.3 (3)	C36—O37—C38	118.0 (3)
N19—C20—N26	117.7 (3)	C28—C39—C36	119.9 (3)
N19—C20—N21	119.5 (3)		

Lattice parameters were measured with Philips *LAT* routine. Scan speed was 0.05° s^{-1} with a scan width of 2.0° (intensities negligible at $\theta > 22°$). Corrections for Lorentz–polarization effects were applied. The structure was solved by direct methods (*MULTAN*80: Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Coordinates of H atoms were calculated with geometrical considerations (*XANADU*; Roberts & Sheldrick, 1979), confirmed by a final ΔF synthesis and included in the last refinement. Refinement included anisotropic non-H atoms, isotropic H atoms, a scale factor and a secondary-extinction parameter. A locally modified version of *ORFLS* (Busing, Martin & Levy, 1962) and the program *PARST* (Nardelli, 1983) were used. Fig. 2 was drawn with *ORTEP*II (Johnson, 1976).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1061). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Molecular Co-Crystals of Carboxylic Acids. 16.[†] 1:1 Adduct of 3-Nitrobenzoic Acid with 3-Amino-1*H*-1,2,4-triazole

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Abstract

The structure of the 1:1 molecular adduct of 3-nitrobenzoic acid with the herbicide amitrole (3-amino-1*H*-1,2,4-triazole), 3-amino-1*H*,4*H*$^+$-1,2,4-triazolium 3-nitrobenzoate, $C_2H_5N_4^+.C_7H_4NO_4^-$, [(3-AT)(3-NBA)], has been determined by X-ray diffraction. There are two independent but similar cyclic hydrogen-bonded hetero-dimers in the crystallographic asymmetric unit, with hydrogen bonds involving the carboxyl O atoms of the acid and both a heterocyclic N atom and an amine N atom of an amitrole [O···N 2.677–2.951 (3) Å]. The dimers also form into a ribbon-chain polymer structure.

Comment

In a series of studies of the formation of molecular adducts of commercially important herbicides and pesticides with suitable donor or acceptor molecules, amitrole (3-amino-1*H*-1,2,4-triazole, or 3-AT; CA Registry No. 61-82-5) has proved useful, complexing with certain nitro-substituted benzoic acids. The structures of co-crystals of 3-AT with 3,5-dinitrobenzoic acid, [(3-AT)(DNBA)$(H_2O)_2$] (Lynch, Smith, Byriel & Kennard, 1992), and 4-nitrobenzoic acid, [(3-AT)(4-NBA)] (Byriel, Kennard, Lynch, Smith & Thompson, 1992), are known. 3-Nitrobenzoic acid

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[†] Part 15: Lynch, Smith, Byriel & Kennard (1994).

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