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Structural Studies of Analgesics and Their Interactions. V.* The Crystal and Molecular Structure of Metamizol Monohydrate†

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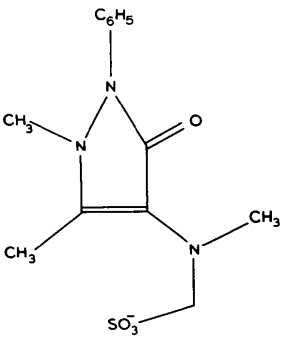
Abstract

Metamizol, $Na[C_{13}H_{16}N_3O_4S]$, $C_{13}H_{16}N_3O_4S^-Na^+$, a sulphonyl derivative of amidopyrine, is perhaps the most widely used non-narcotic analgetic and anti-inflammatory pyrazolone derivative. The monohydrate of the compound crystallizes in the monoclinic space group $P2_1/c$ with eight molecules in a unit cell of dimensions $a = 9{\cdot}143$ (3), $b = 49{\cdot}50$ (2), $c = 7{\cdot}314$ (2) Å and $\beta = 90{\cdot}9$ (1)°. The structure was solved by direct methods and refined to an R value of 0·080 for 4466 observed reflections. The two crystallographically independent molecules in the structure have similar dimensions. The elongated molecules are hydrophobic at one end and hydrophilic at the other with the middle portion partly hydrophobic and partly hydrophilic. The pyrazolone group in the structure has dimensions similar to those found in uncomplexed antipyrine and amidopyrine. The crystal structure can be described as consisting of double layers of metamizol molecules stacked perpendicular to the b axis. The adjacent double layers are separated by a layer of Na ions and water molecules.

Introduction

[(2,3-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-yl)methylamino]methanesulfonic acid (I) sodium salt, $C_{13}H_{16}N_3O_4S^-Na^+$, known variously as metamizol, dipyrone, methampyrazone, novalgin, analgin, *etc.*, is perhaps the most widely used analgetic pyrazolone derivative. Like other non-narcotic anti-inflammatory analgesics, metamizol is also believed to act through the inhibition of prostaglandin biosynthesis (Flower, 1974). As part of a series of X-ray analyses of such analgesics and their crystalline complexes, we report here the crystal structure of metamizol monohydrate.



(I)

Experimental

Needle-like crystals of the compound were grown by the gas-diffusion technique using water as the solvent and ethanol as the precipitant. The space group and unit-cell dimensions were determined from X-ray diffraction photographs and the density was measured by flotation in a mixture of benzene and carbon tetrachloride.

Crystal data

Metamizol monohydrate, $C_{13}H_{16}N_3O_4S^-Na^+.H_2O$, $a = 9{\cdot}143$ (3), $b = 49{\cdot}50$ (2), $c = 7{\cdot}314$ (2) Å, $\beta = 90{\cdot}9$ (1)°, $D_m = 1{\cdot}388$ (5), $D_c = 1{\cdot}409$ Mg m^{-3}, $Z = 8$, $\mu = 2{\cdot}167$ mm^{-1} for $\lambda = 1{\cdot}5418$ Å.

The intensity data were collected on a Picker four-circle diffractometer using graphite-monochromatized Cu $K\alpha$ radiation from a crystal with dimensions 0·30 × 0·26 × 0·42 mm up to a maximum Bragg angle of 60·5°. Of the 4990 independent reflections in this range, the intensities of 4466 had $I > 3\sigma(I)$ and were used for structure determination and refinement. The data were corrected for Lorentz and polarization factors, but not for absorption.

* Part IV: Singh & Vijayan (1977).

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Structure analysis

The phases were determined in a straightforward manner by use of *MULTAN* (Germain, Main & Woolfson, 1971), followed by conventional Fourier techniques. The structure was refined, first isotropically and then anisotropically, to an R value of 0·093 using a modified version of the block-diagonal program *SFLS* written by Professor R. Shiono. The positions of all the H atoms, except those belonging to the water molecules, were fixed at this stage from geometrical considerations by comparison with similar structures and with the aid of a difference Fourier map. These atoms were assumed to have the same isotropic temperature factors as those of the heavier atoms to which they were attached. The H atoms were included in the structure factor calculations in the subsequent *SFLS* cycles, but only the positional and the anisotropic thermal parameters of the non-hydrogen atoms were refined. The refinement was terminated at R = 0·080 when all the least-squares shifts were lower than the corresponding standard deviations. The weighting function used in the final calculations had the form $1/(a + bF_o + cF_o^2)$, where a = 1·0, b = 0·004 and c = 0·0011. The form factors of the non-hydrogen atoms and the H atoms were taken from Cromer & Waber (1965) and Stewart, Davidson & Simpson (1965) respectively. The final positional parameters of the non-hydrogen atoms are given in Table 1.*

Table 1. *Final positional coordinates* (×10⁴)

The estimated standard deviations are given in parentheses.

	x	y	z
N(1)	5312 (10)	1537 (1)	4129 (11)
N(2)	5924 (9)	1489 (1)	5860 (11)
C(3)	6348 (9)	1215 (2)	5838 (12)
C(4)	6134 (9)	1110 (2)	4151 (12)
C(5)	5550 (10)	1317 (2)	2974 (12)
C(6)	5021 (13)	1588 (2)	7356 (13)
C(7)	6975 (11)	1086 (2)	7507 (14)
O(8)	5279 (9)	1317 (1)	1345 (9)
N(9)	6551 (7)	848 (1)	3561 (10)
C(10)	8077 (10)	835 (2)	3003 (17)
C(11)	5546 (10)	729 (2)	2269 (12)
S(12)	5137 (2)	382 (1)	2719 (3)
O(13)	4466 (7)	369 (1)	4505 (9)
O(14)	4160 (9)	308 (1)	1239 (10)
O(15)	6513 (8)	233 (1)	2693 (10)
C(16)	5026 (7)	1805 (1)	3514 (9)
C(17)	3886 (20)	1843 (3)	2283 (19)
C(18)	3572 (26)	2109 (3)	1710 (25)
C(19)	4383 (32)	2316 (3)	2294 (29)
C(20)	5564 (24)	2274 (3)	3503 (28)
C(21)	5869 (18)	2013 (2)	4166 (22)
Na(22)	7273 (4)	38 (1)	9912 (5)
W(23)	6730 (8)	261 (1)	7105 (10)
N(31)	337 (4)	1542 (1)	7207 (5)
N(32)	863 (9)	1489 (2)	5429 (11)
C(33)	1336 (9)	1220 (2)	5506 (13)
C(34)	1305 (9)	1126 (2)	7236 (13)
C(35)	694 (12)	1336 (2)	8384 (13)
C(36)	−139 (13)	1578 (2)	3975 (14)
C(37)	1842 (11)	1079 (2)	3832 (14)
C(38)	518 (12)	1341 (2)	10039 (10)
N(39)	1849 (8)	880 (1)	7866 (11)
C(40)	3401 (11)	845 (2)	7950 (20)
C(41)	1000 (11)	741 (2)	9235 (14)
S(42)	299 (2)	430 (1)	8357 (3)
O(43)	−566 (7)	497 (2)	6741 (9)
O(44)	−583 (7)	319 (1)	9824 (9)
O(45)	1547 (6)	260 (1)	7952 (9)
C(46)	61 (7)	1815 (1)	7735 (9)
C(47)	−1046 (7)	1854 (1)	8999 (8)
C(48)	−1290 (31)	2126 (4)	9532 (27)
C(49)	−554 (33)	2339 (3)	8791 (30)
C(50)	570 (27)	2290 (3)	7609 (28)
C(51)	860 (20)	2028 (2)	7013 (23)
Na(52)	2468 (4)	84 (1)	5198 (5)
W(53)	560 (12)	266 (2)	3531 (13)

Discussion

Molecular geometry

Almost all the bond lengths and angles in the two crystallographically independent molecules are the same within experimental error and their average values are given in Fig. 1. Four valency angles in the methylaminomethanesulphonate group, however, differ by more than 3° (σ = 0·7°) and, hence, their individual values are given.

Metamizol is a sulphonate derivative of amidopyrine (which in turn is a dimethylamino derivative of antipyrine) and it is of interest to compare the dimensions of the two molecules. As will be seen later, the carbonyl group is involved neither in metal coordination nor in hydrogen bonding, as in the structure of free amidopyrine (Singh & Vijayan, 1976), and hence the geometry of the pyrazolone group could be expected to

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34062 (27 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

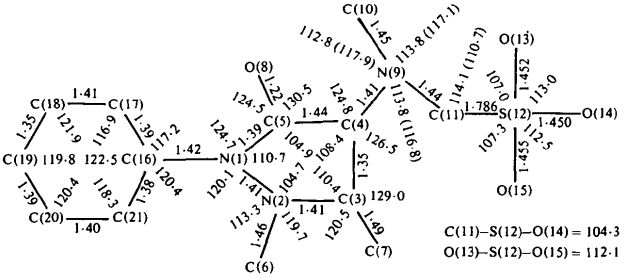

Fig. 1. Average bond lengths (Å) and angles (°). Individual values are given for four angles (see text). The estimated standard deviations are 0·01 Å for bond lengths (0·005 Å for lengths involving the S atom) and 0·5° for bond angles.

be largely unaffected by intermolecular influences. It turns out that the dimensions of the pyrazolone group and the phenyl ring, and their mutual orientation are similar in the two compounds. Therefore, the discussion presented when dealing with the molecular geometry of amidopyrine (Singh & Vijayan, 1976) is also relevant to the present structure. The main difference between the molecular dimensions of the two compounds pertains to the valency angles around the amino N(9) atom. In amidopyrine these angles are nearly tetrahedral. The attachment of the sulphonate group to one of the methyl C atoms in metamizol has the effect of enhancing these angles presumably to accommodate the resulting steric interactions. These angles are, however, enhanced to different extents in the two crystallographically independent metamizol molecules probably because of differences in the environment of the methanesulphonate group in the two molecules.

The conformations of the two crystallographically independent molecules are also similar except for the small differences in the methylaminomethanesulphonate group, as can be seen from their perspective views shown in Fig. 2. The two hetero N atoms in the pyrazole ring are pyramidal with the attached phenyl and methyl groups lying on opposite sides of the five-membered ring. The dihedral angle C(6)–N(2)– N(1)–C(16), which defines the mutual orientation of the two groups, is 60·8 and 60·9° in molecules *A* and *B* respectively. The N(1) atom deviates from the plane of the three neighbouring atoms by −0·17 Å in molecule *A* and −0·18 Å in molecule *B*. The corresponding value for N(2) is 0·39 Å in both molecules. The phenyl ring and the pyrazole ring are oriented with respect to each other at 42·5 and 44·5° in molecules *A* and *B* respectively.

The orientation of the methylaminomethane group with respect to the five-membered ring can be defined by the dihedral angles C(5)–C(4)–N(9)–C(10) and C(5)–C(4)–N(9)–C(11). These are 89·3 and −42·2° in molecule *A* and 104·6 and −43·0° in molecule *B*. The differences in the magnitudes of the two dihedral angles are perhaps a reflection of the difference in the sizes of the methyl and the methylene groups. The dihedral angle C(4)–N(9)–C(11)–S(12), which defines the position of the sulphonate group, is −135·6° in molecule *A* and −115° in molecule *B*. The steric interaction between the sulphonate group and the pyrazole ring and its substituents could be expected to be most favourable when this angle is about 180°. However, at this value of the dihedral angle, the sulphonate group would be too close to the methyl group attached to N(9). In fact, the steric interaction between these two groups would be a minimum when the dihedral angle has a much lower magnitude. The observed value of the dihedral angle appears to correspond primarily to a compromise between the two contending steric influences. As the sulphonate group is involved in metal coordination and hydrogen bonding, these interactions are also likely to have had some effect in determining this conformation. The conformation of the sulphonate group is normal with the O atoms assuming an ethane-like conformation about the C(11)–S(12) bond.

As can be seen from Fig. 2, the molecules of metamizol are elongated in shape. The sulphonate end of the molecule is hydrophilic whereas the phenyl end is hydrophobic. The middle portion of the molecule, which consists primarily of the pyrazolone group, has both hydrophilic and hydrophobic regions.

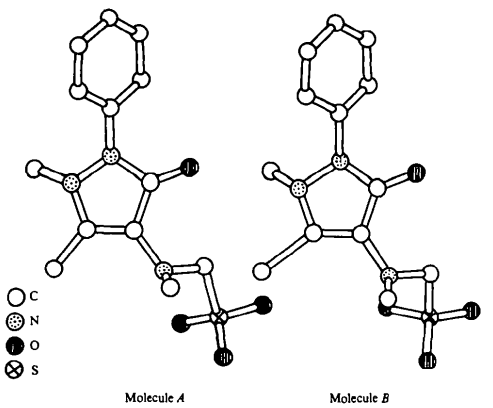

Fig. 2. Perspective views of the two crystallographically independent molecules as viewed along the normals to the respective pyrazolone groups.

Crystal structure

The crystal structure of metamizol monohydrate is illustrated in Fig. 3. The structure can be described as being made up of double layers of metamizol molecules stacked perpendicular to the *b* axis. These double layers are centred at *b*/4 and 3*b*/4. The two layers in each double layer are related to each other by a *c* glide perpendicular to the *b* axis and are held together by van der Waals interactions involving exclusively the phenyl rings. Interactions among molecules in each layer involve van der Waals forces, water bridges and metal coordination. Adjacent double layers are connected

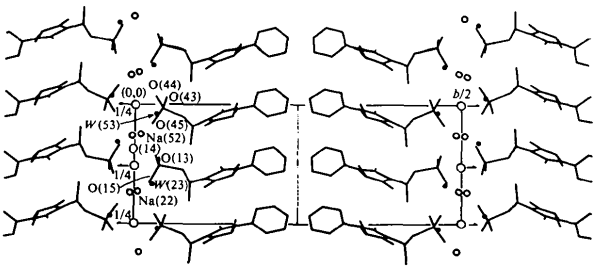

Fig. 3. Crystal structure as viewed along the *c* axis. Only atoms involved in hydrogen bonding or metal coordination are numbered.

exclusively through Na ions and water molecules. Only the sulphonate O atoms are involved in these interactions. Thus the interface between two adjacent double layers is hydrophilic whereas that between the layers in each double layer is hydrophobic.

Metal coordination and hydrogen bonding

The dimensions pertaining to metal coordination and hydrogen bonding in the structure are given in Table 2. Both Na ions have a rather unusual fivefold coordination. In each case, the coordination polyhedron made up of sulphonate and water O atoms could be described as a distorted square pyramid. It may be noted that the environments of the two Na ions are different in detail; so are the environments of the water molecules. The two water molecules are involved in two hydrogen bonds each. However, $W(23)$ is coordinated to Na(22) as well as Na(52) whereas $W(53)$ is coordinated only to Na(52). Consequently the Na ions and the water molecules present dissimilar environments to the sulphonate groups belonging to the two crystallographically independent molecules.

Table 2. *Dimensions pertaining to metal coordination and hydrogen bonding*

Na(22)–O(14)^e	2·31 (1) Å	O(14)^e–Na(22)–O(15)^c	116·3 (4)°
Na(22)–O(15)^c	2·37 (1)	O(14)^e–Na(22)–W(23)^a	85·4 (4)
Na(22)–W(23)^a	2·38 (1)	O(14)^e–Na(22)–O(45)^f	91·5 (5)
Na(22)–O(45)^f	2·40 (2)	O(15)^c–Na(22)–W(23)^a	119·6 (5)
Na(22)–O(44)^b	2·40 (2)	O(15)^c–Na(22)–O(45)^f	80·0 (5)
		O(15)^c–Na(22)–O(44)^b	92·2 (5)
Na(52)–W(53)^a	2·30 (1)	W(23)^a–Na(22)–O(44)^b	82·4 (4)
Na(52)–O(45)^a	2·36 (2)	O(45)^f–Na(22)–O(44)^b	90·9 (6)
Na(52)–O(13)^a	2·37 (1)		
Na(52)–O(15)^e	2·38 (1)	W(53)^a–Na(52)–O(45)^a	91·7 (5)
Na(52)–W(23)^e	2·52 (1)	W(53)^a–Na(52)–O(13)^a	103·5 (3)
		W(53)^a–Na(52)–W(23)^e	98·0 (4)
W(23)···O(43)^b	2·75 (1)	O(45)^a–Na(52)–O(13)^a	104·3 (5)
W(23)···O(13)^a	2·84 (1)	O(45)^a–Na(52)–O(15)^e	80·4 (5)
W(53)···O(43)^a	2·82 (1)	O(13)^a–Na(52)–O(15)^e	103·7 (4)
W(53)···O(44)^d	2·90 (2)	O(13)^a–Na(52)–W(23)^e	91·6 (3)
		O(15)^e–Na(52)–W(23)^e	82·6 (4)

Symmetry code: (*a*) x,y,z; (*b*) $x+1,y,z$; (*c*) $x,y,z+1$; (*d*) $x,y,z-1$; (*e*) $1-x,-y,1-z$; (*f*) $1-x,y,2-z$.

As indicated earlier, only the sulphonate O atoms and the water molecules are involved in metal coordination and hydrogen bonding. In particular, it is interesting to note that the carbonyl group in the pyrazolone ring does not take part in such interactions. It may be recalled that interactions involving this group led to considerable changes in the molecular geometry and electronic structure of antipyrine (Singh & Vijayan, 1973, 1974). However, the attachment of a dimethylamino group at the 4-position, as in amidopyrine, made the molecule more resistant to changes in its dimensions resulting from interactions at the carbonyl group (Singh & Vijayan, 1976). The elucidation of the effect of an interaction at the carbonyl group on the molecular structure of metamizol should await the X-ray analysis of an appropriate crystalline complex involving that compound.

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