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Structural Studies on Chemical Models of Enzymatic Catalysis: 2-Acetoxy-3-methylbenzoic Acid

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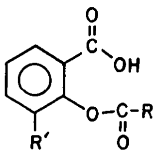
Abstract. $C_{10}H_{10}O_4$, monoclinic, $P2_1/c$, $a = 4{\cdot}910$ (1), $b = 11{\cdot}702$ (2), $c = 17{\cdot}233$ (6) Å, $\beta = 98{\cdot}36$ (2)°, $Z = 4$, $d_c = 1{\cdot}317$ (1) Mg m^{-3}, $R = 0{\cdot}032$ for 615 observed data measured by diffractometer. The carboxyl group is twisted by 11·9 (6)° out of the plane of the aromatic ring, and the acetoxy group is also twisted out of plane by 85·5 (5)°. The ester oxygen atom O(3) lies out of plane of the aromatic ring by 0·17 (1) Å. The carboxyl group is oriented such that its shorter C—O bond is *syn* to the acetoxy group, unlike aspirin in which it is *anti*. The molecule forms dimers with linear, asymmetric hydrogen bonds having O···O 2·627 (3) Å.

Introduction. Intramolecular reactions in which the reacting groups are in close proximity have been proposed as valid models for enzymatic reactions (Fersht & Kirby, 1980; Fife, 1975). Furthermore, intramolecular reactions permit the study of a reaction where there is a defined geometry between the groups. Because of this definition of geometry, pictures of transition-state structures for these reactions can be developed readily. Thus, the study of the structures and dynamics of molecules which undergo intramolecular reactions is quite relevant to both chemistry and biochemistry (Gandour, 1978).

We have been studying the pH dependence of the hydrolysis rates of methyl-substituted 2-acyloxybenzoic acids (Gandour, Mani, Blanco, Wiseman & Williams, 1980). The 3-methyl compound, (1) ($R = CHCl_2$, $R' = CH_3$), shows a significant rate reduction in its hydrolysis when compared to the 4- and 5-methyl compounds.



(1)

In order to develop a clearer understanding of the contribution of steric effects to this rate reduction, an X-ray crystallographic study of 2-acetoxy-3-methylbenzoic acid (3-methylaspirin), (1) ($R = R' = CH_3$), has been completed. The acetoxy compound has been chosen in lieu of the dichloroacetoxy derivative because of its greater stability towards decomposition and for purposes of comparison with aspirin (Wheatley, 1964), (1) ($R = CH_3$, $R' = H$). The results of this structural study form the basis of this report and mark the beginning of a series of structural studies on molecules which contain juxtaposed reacting groups.

Freshly distilled acetyl chloride was added to 2-hydroxy-3-methylbenzoic acid in benzene. The heterogeneous mixture was refluxed with stirring for 5 h producing a yellow solution. Benzene was evaporated and a crude product remained. This product was dissolved in hot ethyl acetate, treated with charcoal and then filtered. Slow evaporation of the cooled filtrate afforded colorless needles m.p. 384·5–385 K uncor. (lit. m.p. 386 K, Anschutz & Scholl, 1909).

Intensity data were obtained from a colorless crystal of dimensions 0·34 × 0·32 × 0·24 mm mounted in random orientation on an Enraf–Nonius CAD-4 automatic diffractometer. One quadrant of data having $4° \leq 2\theta \leq 50°$ was measured using graphite-monochromatized Mo $K\alpha$ radiation ($\lambda = 0{\cdot}71073$ Å). The ω–2θ scans were made at speeds varying from 0·39 to 6·67° min^{-1} in order to measure all significant data with approximately equal precision. Of the 1865 independent data thus measured, 687 had $F_o^2 > 3\sigma(F_o^2)$. After being corrected for background, Lorentz, and polarization effects but not for absorption ($\mu = 0{\cdot}096$ mm^{-1}), these data were used in the refinement.

The structure was solved by routine application of direct methods (Sheldrick, 1976) by program *SHELX* 76. Refinement was accomplished by full-matrix least squares based upon F with weights $w = [\sigma^2(F_o)]^{-1}$. H atoms were located by difference Fourier methods, the acid H appearing as a small peak of density 0·21 e Å^{-3}. Non-H atoms were treated anisotropically. Aromatic ring H atoms were refined with a common isotropic temperature factor. Methyl group C(9) was refined as a rigid body with fixed (1·09 Å) C—H distances and a

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second common isotropic temperature factor for the H atoms. Methyl group C(10) was represented as two half-populated sets of three H atoms rotated 20° with respect to each other in fixed positions. These H atoms were assigned the same temperature factor as those of methyl group C(9). Convergence was achieved with $R = 0{\cdot}032$, $R_w = 0{\cdot}035$, and a difference Fourier map yielded $0{\cdot}12$ e Å^{-3} as its largest residual.

Discussion. Positional parameters for heavy atoms are given in Table 1.* Bond distances are depicted in Fig. 1 and bond angles are given in Fig. 2.

Table 1. *Fractional coordinates* ($\times 10^4$) *and equivalent isotropic temperature factors for non-*H *atoms with e.s.d.'s in parentheses*

$$U_{eq} = \tfrac{1}{3}\textstyle\sum_i\sum_j U_{ij}a_i^*a_j^*\,\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq} (Å^2)
C(1)	1632 (8)	4064 (3)	3255 (2)	0·054 (3)
C(2)	3596 (7)	3241 (3)	3166 (2)	0·051 (3)
C(3)	4028 (7)	2824 (3)	2442 (2)	0·056 (3)
C(4)	2439 (9)	3291 (4)	1787 (2)	0·067 (3)
C(5)	528 (9)	4140 (4)	1848 (2)	0·069 (3)
C(6)	118 (8)	4520 (3)	2576 (3)	0·061 (3)
C(7)	1048 (8)	4471 (4)	4028 (2)	0·061 (3)
C(8)	4750 (9)	1932 (4)	4204 (2)	0·064 (3)
C(9)	6870 (9)	1693 (4)	4897 (2)	0·089 (3)
C(10)	6118 (9)	1899 (4)	2379 (2)	0·072 (3)
O(1)	1942 (6)	3984 (2)	4652 (2)	0·078 (3)
O(2)	−515 (6)	5362 (2)	4005 (2)	0·088 (3)
O(3)	5416 (5)	2883 (2)	3822 (1)	0·058 (3)
O(4)	2731 (7)	1387 (2)	3993 (2)	0·088 (3)

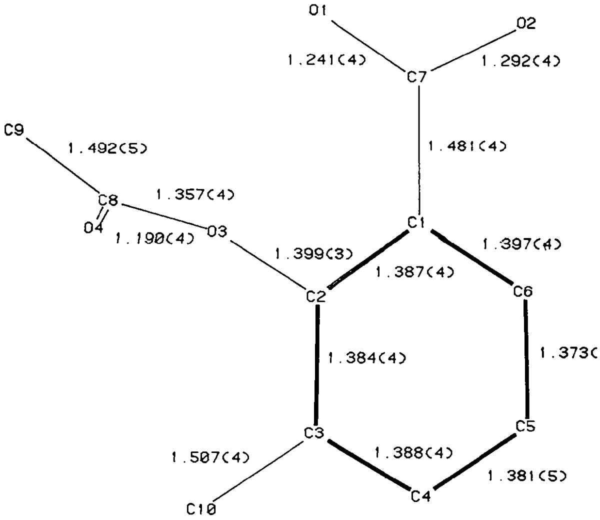

Fig. 1. Observed bond lengths (Å).

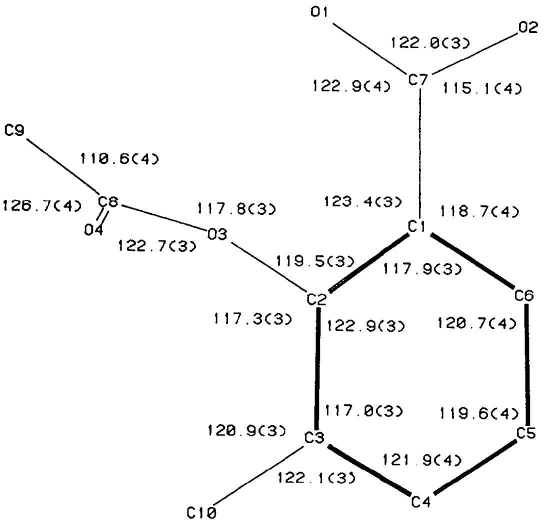

Fig. 2. Observed bond angles (°).

Three notable differences exist when comparing the crystal structures of aspirin (Wheatley, 1964) and 3-methylaspirin: (*a*) Whereas in aspirin, the carboxyl group has its shorter C—O bond C(7)—O(1) *anti* to the carbon atom C(2) bearing the acetoxy group, it is *syn* in 3-methylaspirin, (*b*) methyl substitution at C(3) changes the torsion angles involving the substituents at C(1) and C(2) significantly, and (*c*) the oxygen atom O(3) attached to the benzene ring in 3-methylaspirin lies 0·17 (1) Å out of the plane of the aromatic ring, compared to 0·06 (1) Å in aspirin.

Both crystal structures exhibit the expected carboxylic acid hydrogen-bonded dimer formation. This hydrogen bond in aspirin has an O···O distance of 2·645 (3) Å, a result quite similar to that in 3-methylaspirin [2·627 (3) Å]. A major difference is the relative conformation of the carboxyl [see (*a*) above]. Similar conformations are also seen in the crystal structures of salicylic (Cochran, 1953) and 3-methylsalicylic (Gupta & Prasad, 1971) acids. The bond lengths in the carboxyl group of 3-methylaspirin, 1·241 (4) and 1·292 (4) Å, are indicative of a considerable contribution from resonance and are virtually identical to those of aspirin, 1·235 (4) and 1·287 (4) Å. These bond lengths are 1·241 (9) and 1·333 (9) Å in salicylic acid (Cochran, 1953), and 1·275 (30) and 1·309 (25) Å in 3-methylsalicylic acid (Gupta & Prasad, 1971).

Certain torsion angles shown in Table 2 reveal conformational changes brought about by 3-methyl substitution. The O(1)—C(7)—C(1)—C(2) angle shows not only the reversal of the hydrogen-bonding structure discussed above, but also the 10·1° larger deviation from coplanarity of the carboxyl group and the aromatic ring of 3-methylaspirin. The acetoxy group is nearly orthogonal to the aromatic ring in both compounds. The carbonyl oxygen atom O(4) is tilted

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* Lists of structure factors, anisotropic thermal parameters and H atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36022 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

slightly towards the carboxyl in aspirin and slightly away from it in 3-methylaspirin. There does not appear to be any interaction between the carboxyl and the acetoxy group in either aspirin or 3-methylaspirin. The distance from C(8) to the nearest O in the carboxyl is identical in both structures [2·934 (4) *vs* 2·928 (4) Å], and the C(8)—O(4) distances are also the same, 1·190 (4) Å for 3-methylaspirin and 1·183 (5) Å for aspirin. Thus, it is not likely that the longer C—O bond in the carboxyl on the side of the acetoxy for aspirin arises from an interaction between an electronegative O and the electropositive carbonyl carbon C(8). That an interaction might exist is supported by the known nucleophilic character of the carboxyl towards the proximate acyl group (Kirby & Fersht, 1971).

Fig. 3 shows the displacement of O(3) from the plane of the aromatic ring [0·17 (1) Å]. A similar but smaller displacement [0·06 (1) Å] is seen in aspirin (Wheatley, 1964).

Table 2. *Selected torsion angles in aspirin and 3-methylaspirin* (°)

	Aspirin*	3-Methylaspirin
O(1)–C(7)–C(1)–C(2)	−178·2 (5)	−11·9 (5)
C(1)–C(2)–O(3)–C(8)	+85·5 (5)	+94·9 (5)
C(2)–O(3)–C(8)–C(9)	−178·1 (5)	−178·5 (5)
C(7)–C(1)–C(2)–O(3)	−3·0 (5)	−9·6 (5)

* Torsion angles for aspirin have been computed using inversion-related coordinates from the original work.

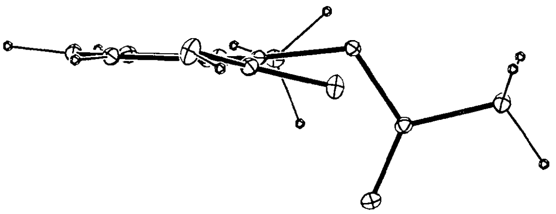

Fig. 3. A view of the 2-acetoxy-3-methylbenzoic acid molecule which emphasizes the displacement of O(3) out of the plane of the aromatic ring.

The structural changes brought about by 3-methyl substitution likely result from a compression of the distance between the carboxyl and acetoxy groups. The C(7)—O(3) distance in aspirin is 2·988 (4) Å whereas in 3-methylaspirin it is 2·898 (4) Å. The atoms of nearest contact between the two groups are O(3) and O(2) [2·674 (4) Å] in aspirin and O(3) and O(1) [2·706 (4) Å] in 3-methylaspirin. Thus, in 3-methylaspirin rotation of the carboxyl out of the plane of the aromatic ring and displacement of O(3) below the plane lengthens the nearest contact distance between the two functional groups.

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