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Structure of an Adenine–Hydrogen Peroxide Adduct

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Abstract. $C_5H_5N_5.H_2O_2$, $M_r = 169.14$, monoclinic, $C2/c$, $a = 8.939$ (3), $b = 10.697$ (4), $c = 14.920$ (4) Å, $\beta = 102.55$ (2)°, $V = 1392.5$ (7) Å^3, $Z = 8$, $D_x = 1.614$ g cm^{-3}, λ(Mo $K\alpha_1$) = 0.71069 Å, $\mu = 1.209$ cm^{-1}, $F(000) = 704$, $T = 293$ K, final $R = 0.047$ for 1090 observations. Each hydrogen peroxide molecule hydrogen bonds with three adjacent adenine molecules. Hydrogen bonding also occurs between N(9)—H(N9) and N(3) of an inversion related molecule. Molecules from adjacent planes are related by a non-crystallographic inversion center and exhibit strong stacking interactions along the b axis [planar separation 3.283 (3) Å].

Introduction. Hydrogen peroxide (H_2O_2) is a by-product of several metabolic pathways, including the conversion of hypoxanthine to xanthine by xanthine oxidase. H_2O_2 is also produced in the 'respiratory burst' following neutrophil phagocytosis. Significant quantities of H_2O_2 have been detected in whole human blood using a radio-isotopic exchange technique (Varma & Devamanoharan, 1991). It is likely that these concentrations represent a dynamic equilibrium between the amount of H_2O_2 produced and the amount decomposed by catalase.

H_2O_2 may generate highly reactive radicals by any or all three of the following mechanisms: the Fenton reaction, the Haber–Weiss reaction, or the reaction of H_2O_2 with ascorbic acid (Rowley & Halliwell, 1983). Free radicals generated *in vivo* may damage biomolecules, including DNA. Ten modified DNA bases have been identified after treating mammalian cells with H_2O_2 (Dizadaroglu, Nackerdien, Chao, Gajewski & Rao, 1991). Mode I killing of *Escherichia coli* strains by H_2O_2 occurs at physiologically relevant doses and DNA damage appears to be a significant factor in cell death (Cantoni, Brandi, Cerutti, Meyn & Murray, 1987). Alloxan, an agent which exhibits potent diabetogenicity, causes the production of H_2O_2 which is then believed to induce DNA strand breaks, eventually leading to diabetes (Takasu, Asawa, Komiya, Nagasawa & Yamada, 1990).

Recent findings suggest that many biological effects of H_2O_2 in aqueous solution are actually mediated by H_2O_2 adducts; hydrogen-bonded complexes of H_2O_2 and compounds found in biochemical systems (Schubert & Wilmer, 1991). H_2O_2 adducts enhance H_2O_2 stability by decreasing the rate of H_2O_2 decomposition up to several hundredfold. Neutrally charged H_2O_2 adducts appear to cross the cell membrane, thereby carrying extracellular H_2O_2 to intracellular targets. Exchange experiments between glucose, nucleic acid components and H_2O_2 strongly suggest that nucleic acids form H_2O_2 adducts (Schubert & Wilmer, 1991). The base adenine and its nucleoside adenosine appear to form the most stable adducts; however, no structural studies of such compounds have been performed prior to our work. We report here the structure of an adenine–hydrogen peroxide complex, obtained *via* crystallization of adenine from aqueous H_2O_2.

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Experimental. An adenine–hydrogen peroxide complex preferentially crystallized upon slow evaporation from an equimolar (0.1 *M*) solution of adenine and thymidine in inhibitor-free 30% hydrogen peroxide. The specimen used for data collection measured 0.60 × 0.40 × 0.30 mm and was wedged in a 0.5 mm thin-walled glass capillary. The crystal was bathed in mother liquor to prevent rapid (within 24 h) loss of hydrogen peroxide. Unit-cell parameters were derived from least-squares fits of 19 reflections with $20 < 2\theta < 30°$. Data over one quadrant ($0 \le h \le 10$, $0 \le k \le 12$, $-17 \le l \le 17$) were collected on a refurbished Picker diffractometer to $2\theta = 50°$ [6° min^{-1} in 2θ, 2° peak scan width, $(\sin\theta/\lambda)_{max} = 0.595$ Å^{-1}] using 2θ–θ scans. Of 1399 reflections, 80 were extinct, 84 were redundant ($R_{int} = 0.0117$), and 295 had intensities with $I < 2.33\sigma(I)$, leaving 940 unique reflections with intensities greater than 2.33 standard deviations. Intensities of the standard reflections ($16 < 2\theta < 23.1°$) indicated no measurable decay. Data were not corrected for absorption. *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) gave the location of all non-H atoms. All H atoms were located by inspection of a difference map. 1090 structure factors were used to 0.595 Å^{-1} in $\sin\theta/\lambda$ in the weighted refinement [$w = 1/\sigma^2(F)$] of the positions and thermal tensors of the non-H atoms and the positions and isotropic thermal parameters of the H atoms. Scattering factors came from *International Tables for X-ray Crystallography* (Cromer & Waber, 1974). The highest and lowest peaks in the final difference map were 0.202 and −0.158 e Å^{-3}. The final statistics of refinement were $R = 0.0471$, $wR = 0.0505$, $(\Delta/\sigma)_{max} = 0.453$ and $S = 1.414$. All calculations were performed on a 386 PC using software supplied by the Molecular Structure Center at Indiana University, described elsewhere (Huffman, Lewis & Caulton, 1980).

Discussion. Fractional coordinates and average isotropic temperature factors are given in Table 1;* Fig. 1 shows the atom-numbering scheme and Fig. 2 displays a stereoview viewed approximately normal to the (100) plane. Average bond lengths (Table 2) for C—C [1.396 (3) Å] and C—N [1.349 (3) Å] indicate partial double-bond character typical of aromatic compounds. Atoms of adenine are planar [N(1), C(2), N(3), C(4), C(5), C(6), N(7), C(8), N(9), N(10); average deviation from planarity 0.0145 (22) Å]. Adenine molecules arrange themselves in planes with a separation of 3.283 (3) Å. Molecules from adjacent planes are related by a non-crystallographic inversion center and exhibit strong stacking interactions along the *b* axis. Four hydrogen bonds occur between a hydrogen peroxide [torsion angle H(O1)—O(1)—O(2)—H(O2) −111.94 (3.70)°] and three adjacent adenine molecules (Table 2, Fig. 3). The adenine molecule at *x*, *y*, *z* is related to the second and third adenine molecules by the symmetry operations $x - \frac{1}{2}$, $\frac{1}{2} - y$, $z - \frac{1}{2}$ and $\frac{1}{2} - x$, $\frac{1}{2} - y$, $1 - z$. Average bond angles [164.54 (2.90)°] and donor to acceptor distances [O—H···N 2.763 (3), N—H···O 3.016 (3) Å] indicate strong hydrogen-bonding interactions. Two more hydrogen bonds occur between inversion-related

Table 1. *Atom coordinates* (× 10^4, × 10^3 *for* H *atoms*) *with e.s.d.'s in parentheses and average temperature factors* (Å^2 × 10)

$B_{iso} = \frac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$, where B_{ij} are components of the temperature factor of the form $\exp[-\frac{1}{4}\sum_i\sum_j B_{ij}a_i^*a_j^*h_ih_j]$.

	x	*y*	*z*	B_{iso}
N(1)	6778 (2)	1650 (2)	6344 (1)	25
C(2)	8181 (3)	1152 (2)	6427 (2)	27
N(3)	8807 (2)	643 (2)	5787 (1)	26
C(4)	7812 (2)	636 (2)	4965 (2)	22
C(5)	6336 (2)	1102 (2)	4779 (2)	21
C(6)	5815 (2)	1657 (2)	5513 (1)	21
N(7)	5651 (2)	924 (2)	3855 (1)	24
C(8)	6722 (3)	364 (2)	3521 (2)	26
N(9)	8047 (2)	172 (2)	4150 (1)	25
N(10)	4438 (2)	2183 (2)	5427 (2)	27
O(1)	1706 (2)	1952 (2)	2913 (1)	36
O(2)	3167 (2)	2474 (2)	3397 (1)	37
H(C2)	882 (3)	117 (2)	704 (2)	31
H(C8)	664 (3)	10 (2)	286 (2)	32
H(N9)	896 (4)	−17 (3)	407 (2)	41
H(N10*a*)	421 (3)	248 (3)	590 (2)	35
H(10*b*)	387 (3)	224 (3)	485 (2)	40
H(O1)	164 (5)	247 (4)	231 (3)	84
H(O2)	385 (4)	173 (4)	343 (3)	76

Table 2. *Bond distances* (Å), *bond angles* (°) *and hydrogen-bond geometry* (Å,°) *with e.s.d.'s in parentheses*

N(1)—C(2)	1.343 (3)	C(5)—C(6)	1.411 (3)
N(1)—C(6)	1.348 (3)	C(5)—N(7)	1.395 (3)
C(2)—N(3)	1.325 (3)	C(6)—N(10)	1.334 (3)
N(3)—C(4)	1.349 (3)	N(7)—C(8)	1.315 (3)
C(4)—C(5)	1.380 (3)	C(8)—N(9)	1.359 (3)
C(4)—N(9)	1.371 (3)	O(1)—O(2)	1.4592 (26)

C(2)—N(1)—C(6)	118.95 (20)	C(6)—C(5)—N(7)	132.56 (20)
N(1)—C(2)—N(3)	128.94 (23)	N(1)—C(6)—C(5)	117.36 (19)
C(2)—N(3)—C(4)	111.07 (20)	N(1)—C(6)—N(10)	118.82 (21)
N(3)—C(4)—C(5)	126.40 (21)	C(5)—C(6)—N(10)	123.83 (21)
N(3)—C(4)—N(9)	127.58 (20)	C(5)—N(7)—C(8)	103.72 (19)
C(5)—C(4)—N(9)	106.02 (20)	N(7)—C(8)—N(9)	113.83 (21)
C(4)—C(5)—C(6)	117.24 (20)	C(4)—N(9)—C(8)	106.22 (19)
C(4)—C(5)—N(7)	110.21 (19)		

D—H···*A*	*D*—H	H···*A*	*D*···A	*D*—H···*A*
O(2)—H(O2)···N(7)	1.000 (40)	1.812 (40)	2.736 (3)	152.03 (3.25)
N(10)—H(N10*b*)···O(2)	0.900 (31)	2.137 (32)	3.011 (3)	163.49 (2.52)
N(9)—H(N9)···N(3^{i})	0.924 (31)	2.027 (31)	2.926 (3)	163.74 (2.61)
O(1)—H(O1)···N(1^{ii})	1.051 (42)	1.744 (43)	2.790 (3)	173.14 (3.46)
N(10^{iii})—H(N10*a*)···O(1)	0.836 (31)	2.195 (32)	3.022 (3)	170.29 (2.68)

Symmetry code: (i) $1-x$, $-y$, $1-z$; (ii) $x-\frac{1}{2}$, $\frac{1}{2}-y$, $z-\frac{1}{2}$; (iii) $\frac{1}{2}-x$, $\frac{1}{2}-y$, $1-z$.

* Lists of anisotropic thermal parameters, bond angles and distances involving H atoms, least-squares planes, and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55211 (8 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CR0391]

molecules involving atoms N(9)—N(N9)···N(3^{i})* (Table 2). Crystals of the complex become opaque and non-diffracting upon prolonged exposure to the air. Infrared spectra demonstrate that the adenine–peroxide complex slowly loses its peroxide upon drying to become pure amorphous adenine.

A comparison was made between the title compound and adenosine, a structure containing a typical neutral adenine ring (Lai & Marsh, 1972).

* Symmetry code: (i) $1-x, -y, 1-z$.

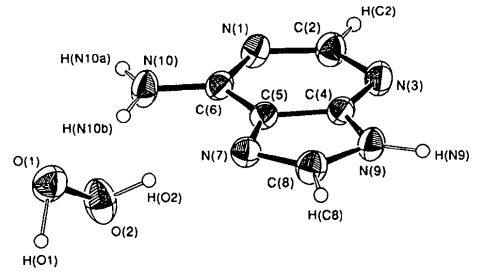

Fig. 1. *ORTEP* (Johnson, 1970) drawing showing the atom-numbering scheme. Ellipsoids represent the 50% probability level for the non-H atoms.

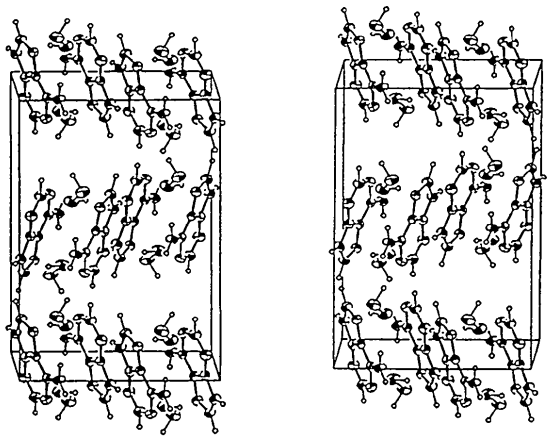

Fig. 2. A stereoview of the contents of one unit cell viewed normal to the (100) plane. Adenine bases stack along the *b* axis.

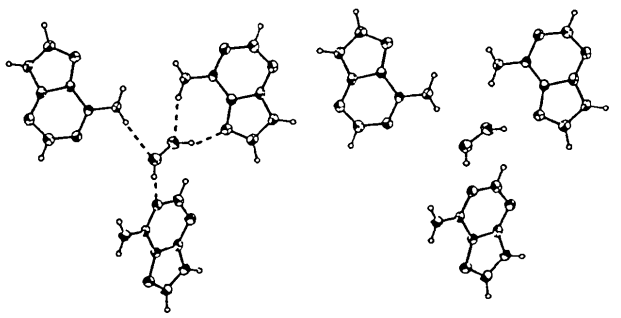

Fig. 3. A stereoview showing the hydrogen bonds about one hydrogen peroxide molecule.

Average C—C and C—N bond lengths were nearly identical; however, C(5)—N(7) and N(7)—C(8) were more than 2σ (0.006 Å) longer in the peroxide complex than in adenosine. Over half the angles which describe the non-H atoms of adenine differed by more than 2σ (0.4°). Notably, the angle C(5)—C(6)—N(10) is compressed [123.8 (2)°] when compared with the same angle in adenosine [124.5 (2)°]. Also, the angle H(N10*a*)—N(10)—H(N10*b*) is significantly larger in the peroxide complex. These differences are most likely owing to the presence of H_2O_2 and the formation of favorable hydrogen bonds in the crystalline structure.

Hydrogen bonding of H_2O_2 to N(7) and one H atom of N(10) may have physiological significance. In nucleic acids N(9) is in an *N*-glycosidic linkage with a sugar residue and is not available for hydrogen bonding. In DNA N(1) and one H atom of N(10) are involved in the formation of Watson–Crick base pairs; therefore, only N(7) and N(10), which are positioned in the major groove of DNA, are readily accessible. A hydroxyl radical generated at this site could lead to DNA damage. It has been previously shown that the hydroxyl radical must be generated at or close to its site of formation owing to its high reactivity (Ward, Blakely & Joner, 1985; Goldstein & Czapski, 1986; Halliwell, 1987).

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Structure of *p*-Hydroxybenzoic Acid and *p*-Hydroxybenzoic Acid–Acetone Complex (2/1)

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Abstract. *p*-Hydroxybenzoic acid, $C_7H_6O_3$, M_r = 138.1, monoclinic, $P2_1/a$, a = 18.508 (7), b = 5.228 (2), c = 6.342 (3) Å, β = 93.22 (3)°, V = 612.7 (4) Å^3, Z = 4, D_m(295 K) = 1.525 (10), D_x = 1.497 (1) g cm^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, μ = 0.11 mm^{-1}, F(000) = 288, T = 295 K, R = 0.041 for 1043 unique reflections. *p*-Hydroxybenzoic acid–acetone (2/1), $2C_7H_6O_3.C_3H_6O$, M_r = 334.3, monoclinic, $P2_1/a$, a = 24.093 (8), b = 7.232 (2), c = 9.699 (2) Å, β = 92.47 (2)°, V = 1688 (1) Å^3, Z = 4, D_m(294 K) = 1.308 (10), D_x = 1.315 (1) g cm^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, μ = 0.11 mm^{-1}, F(000) = 704, T = 295 K, R = 0.054 for 2183 unique reflections. Pairs of *p*-hydroxybenzoic acid molecules form cyclic hydrogen-bonded dimers in the pure acid and in the acetone complex. The carboxyl H atom is disordered in the pure *para* isomer. The dimers are centrosymmetric in the pure acid and involve two crystallographically distinct molecules in the acetone complex. In the pure acid, the dimers are linked together through hydrogen-bonded phenolic groups; these bonds spiral around the twofold screw axes to make up layers of dimers parallel to (401). In the acetone complex, a pair of dimers is linked through hydrogen-bonded phenolic groups, and the acetone molecule is hydrogen bonded to one of the phenolic groups; these bonds spiral around the twofold screw axes to form chains of dimers approximately parallel to (201). The monoclinic *p*-hydroxybenzoic acid crystals appeared to be the lower temperature phase with a melting point of 488.0 (2) K and enthalpy of fusion (ΔH_f) of 30.99 (8) kJ mol^{-1}. In the calorimetric studies, a second peak was sometimes detected approximately 1 K above the melting point of the monoclinic *para* isomer. The structure of the high-temperature phase of *p*-hydroxybenzoic acid was not resolved; however, the high-temperature structure is expected to contain no dimers.

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Introduction. There is considerable interest in the structure and thermodynamic properties of the monosubstituted phenols owing to their technical importance. However, the crystallographic characterization of these compounds is incomplete, and the purity of the chemicals is often questionable since the data are quite old and since these compounds are notoriously difficult to purify, as they complex with many solvents and are easily oxidized (Ebisuzaki, Askari, Bryan & Nicol, 1987; Perrin, Armarego & Perrin, 1980). The crystal structure of *p*-hydroxybenzoic acid has not previously been reported (Steinmetz, 1914), although that of the monohydrate has been published (Colapietro, Domenicano & Marciante, 1979; Fukuyama, Ohkura, Kashino & Haisa, 1973). As part of our research on the monosubstituted phenols, we report on the structure of pure *p*-hydroxybenzoic acid and on the structure of the 2/1 acetone complex.

Experimental. Commercial *p*-hydroxybenzoic acid (Aldrich) was recrystallized several times and the solvent pumped off. Crystals of *p*-hydroxybenzoic acid employed in the melting experiment and in the structural study were grown both by vacuum sublimation from solid which had undergone six to eight previous sublimations, and from ethanol–*m*-xylene (1:1 to 1:20 ratio) solutions. Colorless crystals of *p*-hydroxybenzoic acid were grown from ethanol–xylene solution saturated at 313 K and slowly cooled. All crystals were stored in sealed Pyrex tubes.

A calibrated Perkin Elmer differential scanning calorimeter (DSC) (Ebisuzaki, Askari, Bryan & Nicol, 1987) was employed in searching for solid–solid phase transitions within the two instrument ranges (173–292 and 320–490 K) and for measuring the enthaply of fusion (ΔH_f). The two temperature ranges result from an instrument peculiarity, and the