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2-Hydroxyisophthalic acid: hydrogen-bonding patterns in the monohydrate and the tetraphenylphosphonium salt. An instance of dramatic acidity enhancement by symmetric, internally hydrogen-bonded anion stabilization

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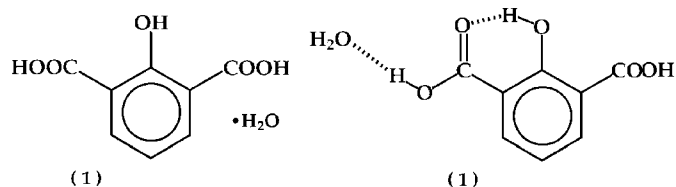
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The monohydrate of the title phenolic diacid ($C_8H_6O_5 \cdot H_2O$, 2-hydroxybenzene-1,3-dioic acid or 3-carboxysalicylic acid) adopts a planar conformation, with the phenol hydrogen internally hydrogen-bonded to the carbonyl of one highly ordered carboxyl, which, in turn, donates a hydrogen bond to the oxygen of water. The second carboxyl is disordered and hydrogen-bonded both to water and to the disordered carboxyl of a centrosymmetrically related neighbor in a static disorder arrangement extending over two full asymmetric units. The water accepts either one or two hydrogen bonds and donates a long bifurcated hydrogen bond shared equally by O atoms of the phenol and the disordered carboxyl. The hydrogen bonding includes no standard carboxyl pairing and is entirely two-dimensional. The resulting planar ribbons stack translationally at a distance of 3.413 (8) Å, in an offset arrangement having non-translational interplanar distances of 0.821 (5) and 2.592 (6) Å. This structure is compared with two previously reported for this compound. The title compound forms a monoanion, whose tetraphenylphosphonium salt is described ($C_{32}H_{25}O_5P$, tetraphenylphosphonium 2,6-dicarboxyphenolate, tetraphenylphosphonium 2-oxidoisophthalic acid or tetraphenylphosphonium 3-carboxyl-*ortho*-salicylate). The phenol oxygen is the site of formal negative charge on the anion, which is stabilized in a planar arrangement by symmetrical hydrogen bonds from both *ortho*-carboxyl groups. The energetics of this arrangement, the phenol and carboxyl acidities, and factors affecting those acidities and providing anion stabilization are discussed.

1. Introduction

Our study of hydrogen-bonding motifs in simple keto-carboxylic acids has included α - and β -keto acids, several examples of which are known to exist predominantly in their enol forms. This has directed our interest towards hydrogen bonding in certain phenolic and enolic analogs (Destro & Marsh, 1984; Roversi *et al.*, 1996; Sugawara *et al.*, 1992; Duncan *et al.*, 2002). For example, the X-ray structures of the monoanionic salts of 2,6-dihydroxybenzoic acid (Smith *et al.*, 1988; Gdaniec & Gilski, 1994) reveal symmetrical, internal hydrogen bonding to the carboxylate by both flanking phenolic H atoms. The resulting anion stabilization presumably accounts for that acid's extraordinarily low pK_a value (1.08–1.3), which is comparable to that of 2,6-dinitrobenzoic acid (pK_a 1.14). Our title diacid (1) is also reported to have a

greatly enhanced first pK_a value (1.6–2.1), which has been attributed to similar cooperative internal hydrogen bonding (Murakami & Martell, 1964). However, no X-ray structure for any monoanionic salt of (1) has been reported and we have undertaken a study in order to examine this possibility.



One structure has been published previously for the monohydrate (1) of the fully protonated phenolic diacid: Cambridge Structural Database (CSD), refcode TOLCAY (Solari *et al.*, 1996); another has been entered separately into the same database: CSD, refcode TOLCAY01 (Mereiter *et al.*, 2001). Our results for (1) agree closely with both these structures in every respect as regards the space group, the cell parameters and the atom positions for C, O and carbon-bound H. However, some discrepancies exist with respect to the placement and the role of the H atoms on the water of hydration. Regarding these differences, the second of the prior references is silent, assigning positions to none of the H atoms in question.

2. Experimental

Compound (1) was prepared from the corresponding cresotic acid by the published oxidation procedure (Todd & Martell, 1973) and recrystallized from acetone–water; the hydrate loses water at or below 373 K and samples not subjected to slow heating melt with decomposition and outgassing at *ca* 525 K. Numerous preparations and trials of various monoanionic alkali, alkaline-earth and other salts of (1) failed to yield usable crystals. The salt (2) was prepared by slow evaporation

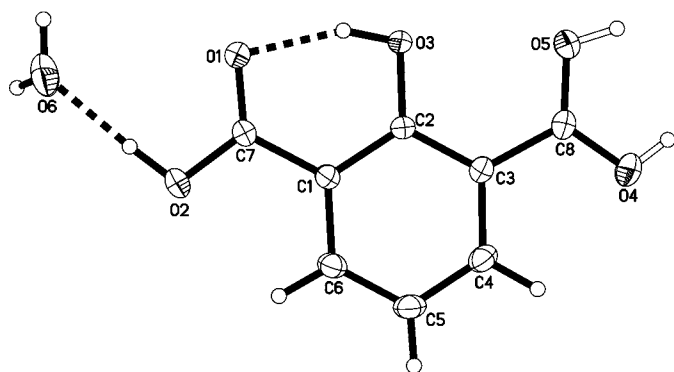


Figure 1

The asymmetric unit of (1) with its numbering scheme. The water molecule has multiple connections but is shown here only in its relationship to the ordered carboxyl group. Except for the water, whose H atoms are shown in idealized positions, all H atoms were found in difference maps and refined as described. The disordered carboxyl is represented as found, with two half-H atoms, connect by ghost O–H bonds. Displacement ellipsoids are set at the 30% probability level.

of HBr from an equimolar ethanolic solution of (1) and tetraphenylphosphonium bromide, using repeated cycles of solvent evaporation and replenishment. Redissolution of the crude solid in ethanol, addition of water and partial evaporation produced pale yellow crystals, which were then recrystallized from methyl acetate, m.p. 446 K.

The solid-state (KBr) IR spectrum of (1) has a single C=O peak at 1697 cm^{-1} , typical for an associated carboxyl. In CHCl_3 solution the principal C=O band appears at 1738 cm^{-1} , suggesting significantly diminished hydrogen bonding, with a minor peak at 1672 cm^{-1} . For (2) the KBr spectrum has an intense C=O peak at 1678 cm^{-1} , consistent with a very strong hydrogen bond, and a minor peak at 1726 cm^{-1} . The O–H stretch does not have the extreme width typical of carboxylic acids, but is confined to a single broadened peak at 3439 cm^{-1} . In CHCl_3 solution the intense C=O peak is found at 1666 cm^{-1} , accompanied by a minor peak at 1622 cm^{-1} . Full experimental details on crystal data, data collection and refinement are given in Table 1¹

3. Results and discussion

3.1. The phenolic diacid (1)

Fig. 1 illustrates an asymmetric unit of (1). The entire system is planar, but the two carboxyl groups are not identical. The phenolic hydrogen is internally hydrogen bonded, in a highly ordered arrangement, to the carbonyl group of one of the carboxyls, which is also strongly ordered, having lengths of 1.219 (2) and 1.3163 (18) Å, respectively, for its double and single C–O bonds. The C–C–O angles are 122.61 (13) and 115.58 (14)°. These distances and angles are comparable to those found in a variety of highly ordered carboxyl situations. Our own survey of 56 keto acid structures that are not acid dimers gives average values of 1.200 (10) and 1.32 (2) Å, and 124.5 (14) and 112.7 (17)°, respectively, for these C–O lengths and C–C–O angles. These values are in accordance with the typical values of 1.21/1.31 Å and 123/112° cited for highly ordered dimeric carboxyls (Borthwick, 1980). This ordered carboxyl in (1) is hydrogen bonded through its own acid hydrogen to a water of hydration [O2···O6 2.694 (2) Å]. The geometry of the six-membered phenolic hydrogen-bonding system includes an internal O–H···O angle of 155 (3)°, and distances of 0.92 (3), 1.70 (3) and 2.5632 (16) Å for O–H, O···H and O···O, respectively.

The second carboxyl group (C8) participates in no internal hydrogen bonding and is disordered with respect to its C–O bond lengths, which are identical within experimental error [1.261 (2) and 1.262 (2) Å]. However, the C–C–O angles display some residual ordering [120.45 (13) and 116.99 (15)°]. Both half-H atoms for this disordered carboxyl were found in difference maps and fully refined positionally, with their temperature factors held constant, to occupancies of 50% and then held at 50%. This carboxyl is hydrogen bonded through

¹ Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA5013). Services for accessing these data are described at the back of the journal.

Table 1
Experimental details.

	(1)	(2)
Crystal data		
Chemical formula	C ₈ H ₆ O ₅ ·H ₂ O	C ₂₄ H ₂₀ P·C ₈ H ₅ O ₅
<i>M_r</i>	200.14	520.49
Cell setting, space group	Triclinic, <i>P</i> $\bar{1}$	Monoclinic, <i>P</i> 2 ₁ / <i>c</i>
<i>a</i> , <i>b</i> , <i>c</i> (Å)	3.6673 (6), 9.7608 (19), 11.8421 (15)	15.287 (5), 8.027 (3), 22.144 (7)
α , β , γ (°)	97.647 (13), 90.219 (13), 100.537 (16)	90.00, 101.15 (2), 90.00
<i>V</i> (Å ³)	412.87 (15)	2665.7 (15)
<i>Z</i>	2	4
<i>D_x</i> (Mg m ⁻³)	1.610	1.297
Radiation type	Mo <i>K</i> α	Mo <i>K</i> α
No. of reflections for cell parameters	24	22
θ range (°)	8.7–19.7	4.1–10.5
μ (mm ⁻¹)	0.14	0.14
Temperature (K)	296 (2)	296 (2)
Crystal form, colour	Square prism, pale yellow	Prism, colourless
Crystal size (mm)	0.40 × 0.30 × 0.20	0.50 × 0.44 × 0.26
Data collection		
Diffractometer	Siemens P4	Siemens P4
Data collection method	2 θ / θ scans	2 θ / θ scans
Absorption correction	Numerical	Numerical
<i>T_{min}</i>	0.95	0.94
<i>T_{max}</i>	0.98	0.97
No. of measured, independent and observed reflections	3409, 2400, 1574	6087, 4707, 2544
Criterion for observed reflections	<i>I</i> > 2 σ (<i>I</i>)	<i>I</i> > 2 σ (<i>I</i>)
<i>R_{int}</i>	0.059	0.031
θ_{max} (°)	30.0	25.0
Range of <i>h</i> , <i>k</i> , <i>l</i>	−1 ⇒ <i>h</i> ⇒ 5 −13 ⇒ <i>k</i> ⇒ 13 −16 ⇒ <i>l</i> ⇒ 16	−18 ⇒ <i>h</i> ⇒ 1 −9 ⇒ <i>k</i> ⇒ 1 −26 ⇒ <i>l</i> ⇒ 26
No. and frequency of standard reflections	3 every 97 reflections	3 every 97 reflections
Intensity decay (%)	Variation < 2.0	Variation < 1.3
Refinement		
Refinement on	<i>F</i> ²	<i>F</i> ²
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.059, 0.186, 1.11	0.063, 0.137, 1.01
No. of reflections	2400	4707
No. of parameters	148	350
H-atom treatment	Mixture of independent and constrained refinement	Mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1001P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0417P)^2 + 0.5629P]$, where $P = (F_o^2 + 2F_c^2)/3$
(Δ/σ) _{max}	0.46	<0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å ⁻³)	0.39, −0.42	0.17, −0.24
Extinction method	SHELXL	SHELXL
Extinction coefficient	0.00 (3)	0.0030 (5)

Computer programs used: XSCANS (Siemens, 1996), SHELXS97 (Sheldrick, 1997), SHELXL97 (Sheldrick, 1997), SHELXP97 (Sheldrick, 1997).

one of its O atoms (O4) to the water molecule in another asymmetric unit [O4···O6' 2.692 (2) Å] and through its other O atom (O5) to the disordered carboxyl of a centrosymmetrically related neighboring molecule [O5···O5' 2.702 (2) Å]. Fig. 1 shows the water of hydration in its relationship to the ordered carboxyl group (C7).

Figs. 2 and 3 illustrate the packing. The cell contains a centrosymmetrically related pair of asymmetric units belonging to two separate internally hydrogen-bonded layers

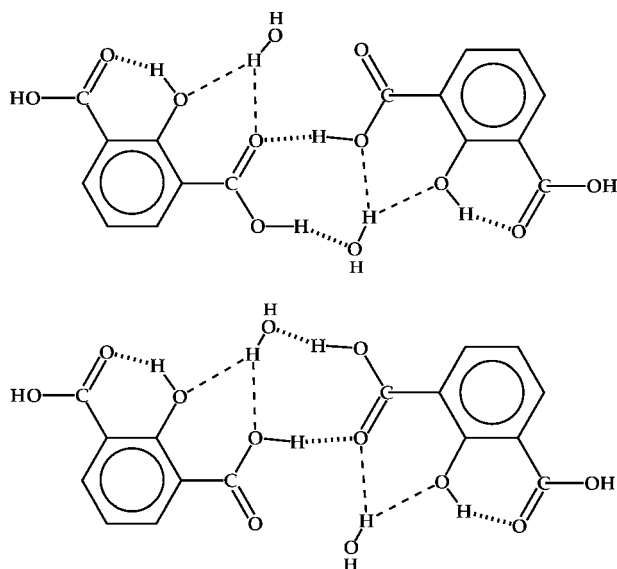
that stack in planes lying at a dihedral angle of 11.8 (3)° relative to the *bc* plane (Fig. 2). The ribbon-like arrangement of hydrogen bonds has width in the *b* dimension, but extends by translation only in the *c* direction (Fig. 3). It includes no standard carboxyl pairing and is entirely two-dimensional, with the greatest deviation from the least-squares plane for all non-H atoms being 0.0968 (16) Å for the carboxyl carbonyl oxygen O1. The extremely short non-translational interplanar distances of 2.592 (6) (Fig. 2) and 0.821 (5) Å are possible only because the alternation of centrosymmetrically related adjacent layers offsets these ribbons so that no molecules or parts of molecules in adjacent layers lie directly over one another in the stacking dimension. These distances represent the interplanar separations for molecules centrosymmetrically related across $\frac{1}{2}, \frac{1}{2}, \frac{1}{2}$ [2.592 (6) Å] and across 0, $\frac{1}{2}, \frac{1}{2}$ [0.821 (5) Å]. The distance between translationally stacked layers lying directly over one another is 3.413 (8) Å, about 93% of the *a* cell dimension. For comparison, the interplanar distance in graphite is 3.354 Å (Nelson & Riley, 1945); in benzene, 3.8 Å (Cox, 1932) and in phenanthrene, 3.55 Å (Trotter, 1963).

We found the distances O6···O3' and O6···O5' to be 3.066 (2) and 3.065 (3) Å, respectively, which is in close agreement with the previous two versions of the structure. These are significantly beyond the usual range for hydrogen bonding in neutral O—H···O systems (2.7 ± 0.2 Å) and seem, from our own experience (Brunskill *et al.*, 1999), to be well beyond even the occasional 'normal' extremes of *e.g.* 2.975 (5) Å. Nevertheless, it appears probable that these spaces contain some version of a

hydrogen bond. Based on difference-Fourier mapping, the structure for (1) published by Solari *et al.* (1996) contains a hydrogen bond from water to the phenol (O6···O3') in this space (with a highly problematic O—H distance of 1.21 Å), but lacks any connection between O6 and O5', albeit these two O···O distances scarcely differ (3.069 *versus* 3.063 Å). These authors also found a second, but disordered, water hydrogen, partly out of the molecular plane and partly involved in a hydrogen bond to O4'. In contrast, we have found no electron

density for water H atoms in either region, but have located them at alternative sites in electron-density difference maps; these positions were refinable, but were not associated with any hydrogen bonding and involved an unrealistic 130° H—O—H angle (Fig. 2). Consequently, we have omitted the water H atoms from our refinement and have used idealized positions for them, found by the computer program *HYDROGEN* (Nardelli, 1999), based on the electrostatic influences of nearby heavy atoms (Figs. 1 and 2). This places one water H equidistant from O3' and O5', at distances of 2.33 and 2.32 Å, respectively (Fig. 4), while the second H is aimed out of the molecular plane and is involved only in even more remote polar interactions. The resulting bifurcated 'hydrogen bond' is thus very long by normal standards and may be better characterized as a 'long polar attraction'.

Fig. 3 shows that wherever its H atoms are placed, water is nevertheless an intimate part of the entire hydrogen-bonding pattern. Each water in Fig. 3 accepts either one or two hydrogen bonds within its own layer and these play a crucial role in stitching together the ribbon structure shown, even without the long bifurcated hydrogen bond assignable to our idealized water H atoms.



The disordered hydrogen-bonding connection between the carboxyl O4 atom and the water extends over two full asymmetric units (Fig. 4), both contributors to which are illustrated in the accompanying scheme. As there appears to be no reasonable dynamic mechanism by which these two disorder contributors might interconvert, we conclude that this disorder is static, requiring that some of the waters accept a single hydrogen bond while others accept two. Furthermore, because only one type of water was found in the asymmetric unit, we must conclude that the distribution of the disorder contributors is random. Additional close intermolecular H...O contacts within the 2.7 Å distance we standardly employ as our criterion

(Steiner, 1997; Steiner & Desiraju, 1998) involve O1 [2.37 (3) Å to H3] and O2 [2.68 (3) Å to H6] to centrosymmetrically related molecules, respectively, within the same layer and in an adjacent layer.

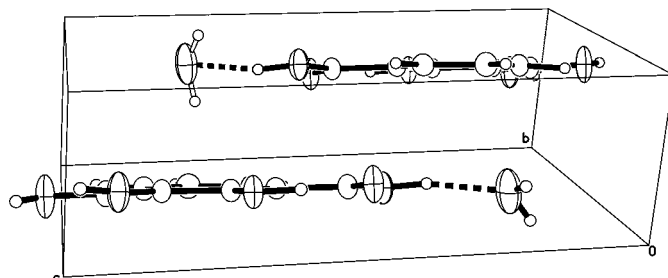


Figure 2

A packing diagram for (1), illustrating the $11.8(3)^\circ$ dihedral angle of the molecular plane relative to the bc plane. The two asymmetric units shown have an interplanar separation of $2.592(6)$ Å. Open bonds on the water at upper left are used to illustrate the hydrogen positions refined from experimental electron densities. The water at lower right, with solid bonds, shows the idealized H positions used in the other figures. Displacement ellipsoids are set at the 30% probability level.

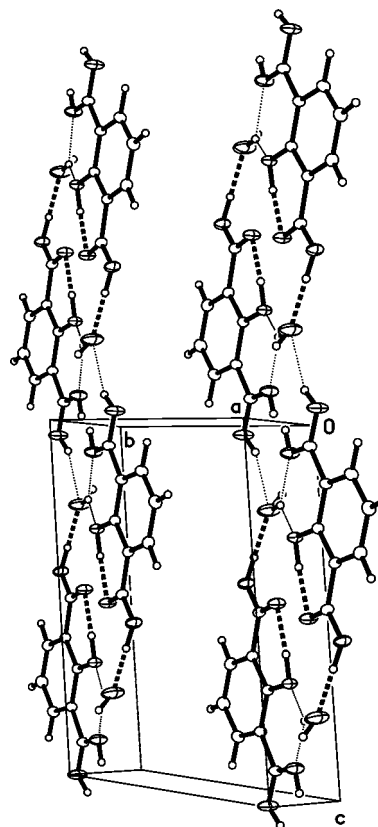
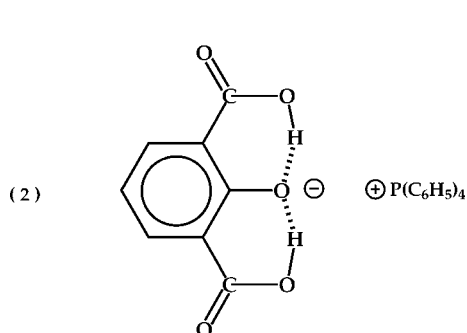


Figure 3

A packing diagram for (1), showing the planar, ribbon-like hydrogen-bonding arrangement extending in the c direction; the water H atoms are shown in idealized positions. Displacement ellipsoids are set at the 20% probability level.



3.2. The tetraphenylphosphonium salt (2)

Fig. 5 shows an asymmetric unit for the tetraphenylphosphonium salt (2) of the singly charged anion of the title compound. The cationic portion of this salt is unremarkable, with the phenyl rings in a conformationally asymmetric arrangement. If the four rings are designated numerically by the four C atoms attached directly to phosphorus, the dihedral angles describing the angular relationships of the rings are as follows: $9/15 = 113.93 (9)^\circ$, $9/21 = 120.39 (8)^\circ$, $9/27 = 99.96 (12)^\circ$, $15/21 = 103.12 (11)^\circ$, $15/27 = 101.85 (8)^\circ$ and $21/27 = 116.53 (10)^\circ$. The tetrahedral angles around phosphorus range in size from $108.04 (16)^\circ$ (C9–P1–C27) to $112.89 (16)^\circ$ (C9–P1–C21).

The anion present is highly planar [mean least-squares deviation for all non-H atoms of $0.022 (12) \text{ \AA}$] and, with only very small departures, symmetrical about the O3–C2–C5 axis. Both carboxyl groups have slight tilts relative to the aromatic plane: $4.7 (7)^\circ$ for the C7 carboxyl and $0.9 (3)^\circ$ for the C8 carboxyl. It seems likely that the slight asymmetries in the anion may safely be attributed to the observed asymmetry in its surrounding field. Fig. 6 illustrates the inherent asymmetry of this environment with a single planar monoanion of (2), surrounded by the cations closest to it in the packing arrangement, shown as bare P atoms. These O3...P distances are $4.803 (3) \text{ \AA}$ to P1 (within the asymmetric unit) and

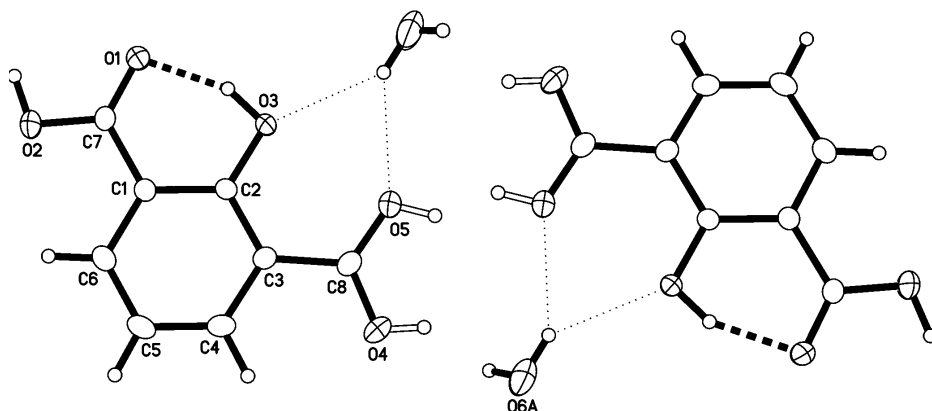


Figure 4

A pair of asymmetric units illustrating the disordering arrangement for (1), with the water H atoms shown in idealized positions. Displacement ellipsoids are set at the 30% probability level.

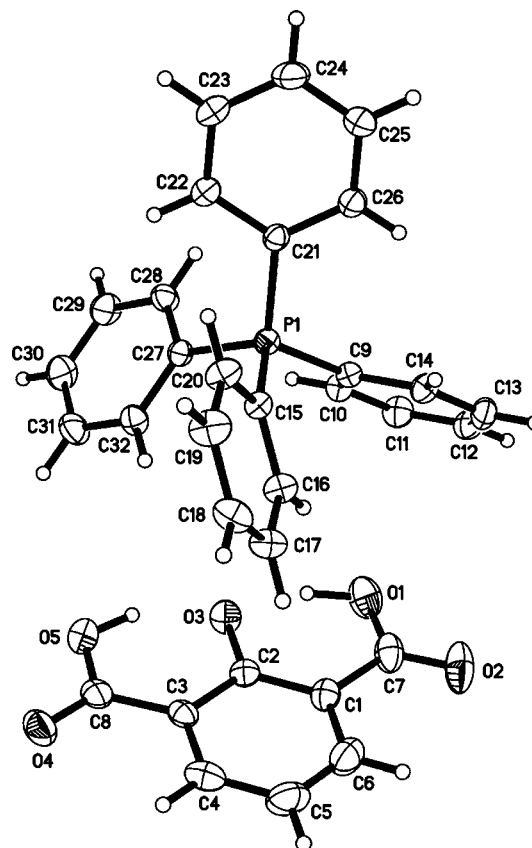


Figure 5

An asymmetric unit of (2) with its numbering scheme. Displacement ellipsoids are set at the 20% probability level.

$7.175 (3)$, $7.440 (3)$ and $6.892 (3) \text{ \AA}$ to the P atoms marked P1A, P1B and P1C, respectively.

Fig. 7 is a full packing diagram, showing complete tetraphenylphosphonium species. The closest C–H...O contacts present are 2.47 (O2...H26A), 2.54 (O3...H18A), 2.59 (O4...H23A), 2.34 (O4...H28A) and 2.39 \AA (O4...H29A), each to a different cation. Although the ion pair chosen as the asymmetric unit has the closest O3...P distance, within this asymmetric unit there are, somewhat surprisingly, no C–H...O contacts up to the 2.7 \AA limit we employ (Steiner, 1997). Using compiled data for a large number of such contacts, Steiner & Desiraju (1998) have found significant statistical directionality even as far out as 3.0 \AA and conclude that these contacts have a greater contribution to packing forces than simple van der Waals attractions.

3.2.1. The hydrogen-bonding structure of the anion.

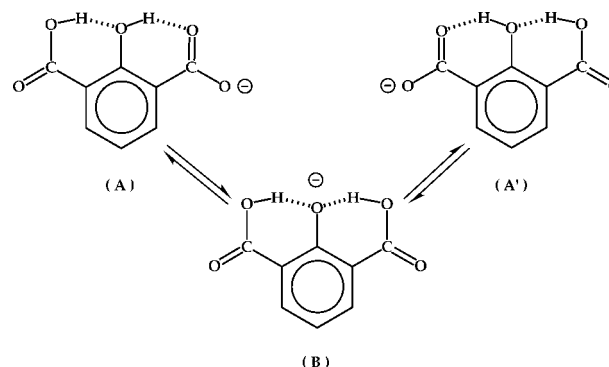
The two residual acidic H atoms of the monoanion, shown in Figs. 5, 6 and 7, were both found in difference maps and fully refined positionally with their temperature factors held constant, revealing that both carboxyl groups are protonated at normal distances

and angles, and that the site of formal charge is therefore the phenol oxygen. Both carboxyl groups participate in stabilizing this phenolate anion by hydrogen bonding, involving entirely typical non-bonded O...H distances of 1.54 (4) and 1.59 (4) Å for H1A and H5A, respectively [the O...H distance for the internal hydrogen bond in (1) is 1.70 (3) Å], while the bonded O—H distances are 1.00 (4) and 0.94 (4) Å, respectively [*cf.* 0.92 (3) Å for (1)] and the O—H...O angles are 154 (3) and 153 (3)°. Although the O...O distances involved [2.477 (4) Å for O3...O1 and 2.464 (4) Å for O3...O5] both lie within the limits suggested by Catti & Ferraris (1976) for 'very short' hydrogen bonds, there is no indication here of any 'symmetric' sharing of the H atoms.

The arrangement found requires the *transoid* (*s-trans*) conformation in both carboxyls, which would normally be energetically disfavored for each group by amounts estimated variously at 8.5–16.5 kJ mol⁻¹ (Leiserowitz, 1976) and 6.5–23 kJ mol⁻¹ (Gandour, 1981). Since the energies usually cited for a hydrogen bond are larger (21–33.5 kJ mol⁻¹ to *neutral* acceptor atoms), the net result can be stabilizing, as it obviously is in observed instances of internal hydrogen bonding (Rychlewska & Gdaniec, 1977; Coté *et al.*, 1996). Although portions of the formally full negative charge on oxygen in (2) are distributed elsewhere by resonance, including onto the carboxyls themselves, the resulting hydrogen bonds should actually be significantly stronger than those typical for neutral acceptor atoms. This would be consistent with the relatively short O...O distances here (see above), which have been suggested to correlate with hydrogen-bond strength (Jeffrey, 1997).

At least two previous studies have touched on the question of the structure of this monoanion. The authors of one of these (Murakami & Martell, 1964) appear to have considered only the asymmetric structure (A)/(A') (see scheme below). The second study (Brzezinski *et al.*, 1987), carried out in anhydrous acetonitrile and relying principally on IR data, concludes that the correct structure for the tetrabutylammonium mono-salt

of (1) is a rapidly equilibrating one [(A) ⇌ (B) ⇌ (A')], in which the symmetric species (B) plays the major role, with 'considerable' contributions from (A)/(A'), especially at temperatures below ambient.



Any arrangement other than (B) for the two residual acidic protons would necessarily be asymmetric and would therefore require either a dynamic tautomerism or static positional disordering in order to account for the very high degree of symmetry we have observed experimentally in (2). However, the geometries found for the carboxyl groups in (2) indicate disordering that is negligible to non-existent, with lengths and angles of 1.206 (5)/1.318 (5) Å and 122.7 (5)/116.3 (4)°, respectively, for the C7 carboxyl and 1.209 (4)/1.315 (5) Å and

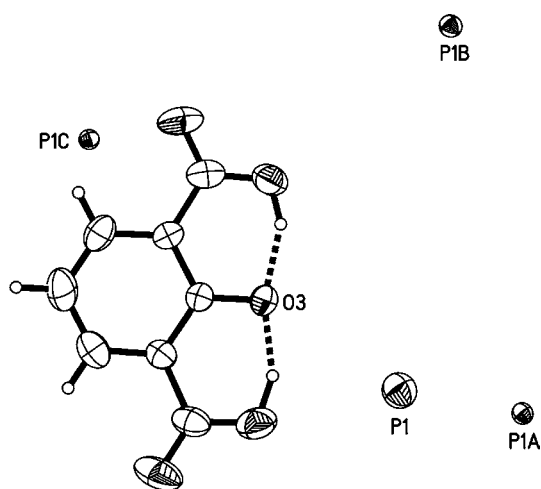


Figure 6
A single monoanion of (2) surrounded by the P atoms closest to O3, illustrating the inherent asymmetry in the environment of the phenolate. Displacement ellipsoids are set at the 30% probability level.

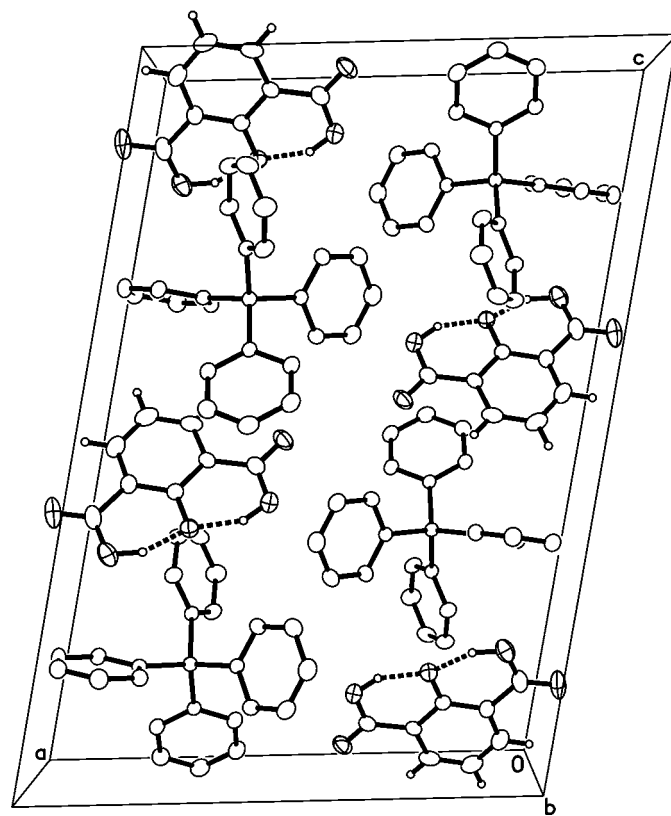


Figure 7
A packing diagram for (2), with all H atoms in the cation removed for clarity. Displacement ellipsoids are set at the 20% probability level.

123.0 (5)/116.5 (4)°, respectively, for the C8 carboxyl. In addition, although both carboxyl H atoms were found in difference maps, we were not able to find any significant electron density at positions nearer the phenolic oxygen, which would be required for averaging of asymmetric structures. Perhaps the strongest single piece of evidence against any such disordered alternative is the phenolic C—O distance, which is 2.6% shorter in (2) than in (1), 1.310 (4) *versus* 1.3456 (15) Å.

Resonance structures indicate strong stabilization for (B) by the distribution of its charge over three O atoms and three ring-C atoms without the necessity of any movement of nuclei. An asymmetric species (A), on the other hand, can distribute charge over two of its carboxyl O atoms by resonance but must undergo a tautomeric shift in order to distribute its charge any further and can place charge directly on the ring only by induction; access to resonance structures that place negative charge directly on the ring is available only through (B).

3.2.2. Models for the anion. Acidity models: Whether or not such resonance arguments are persuasive in favor of (B), the observed structure of (2) appears nevertheless extraordinary in the light of the simplest acidity models, since benzoic acid itself (pK_a 4.20) is more acidic than phenol (pK_a 10.0) by a factor approaching 10^6 . Because the measured first pK_a value for (1) is in the range of 2.0 (see below), when we conclude that the site of formal negative charge in (2) is actually the phenolic oxygen, such models imply an enhancement of phenol acidity by *ca* 10^8 , accompanied by an increase in carboxyl acidity not much greater than 10^2 . Hydrogen-bonding arrangements aside, in resonance terms, the major source of this preferential enhancement must reflect the fact that phenoxides relay their charge into the ring, whereas carboxylates cannot. The general result may be seen in the acidity enhancement achieved upon *para*-nitration for phenol (pK_a 10.0 \rightarrow 7.15) *versus* that for benzoic acid (pK_a 4.20 \rightarrow 3.42).

Experimental first-acidity constants for (1) have been reported at least twice in the literature. The numbers themselves [pK_a 1.6 (Dunn & Bruice, 1970), 2.1 (Murakami & Martell, 1964)] do not, of course, specify the site of deprotonation or the structure of the resulting anion. The latter authors assume that in aqueous solution (1) has two internal hydrogen bonds and argue that the site of *kinetic* deprotonation in (1) should be the 'exocyclic' hydrogen not involved in the internal hydrogen bonding. Our data for (1) actually cast some doubt on the structural assumption involved, since our hydrate is at least partly 'aqueous' and yet lacks the maximum possible internal hydrogen bonding. However, this does not negate the idea that kinetic deprotonation involves predominantly exocyclic H atoms. In any event, in attempting to understand the structure of (2) in terms of experimental acidity models, the site of kinetic deprotonation is not pertinent, since the measured acidities of the available models and of (1) itself are all equilibrium values. However, significant caution is required in attempts to relate the observed structure to known equilibrium pK_a values: (2) is an anhydrous species, while all the pK_a values used for comparison represent

measurements in aqueous media, where ubiquitous hydrogen bonding by and to the medium undoubtedly plays important roles.

Indeed, pK_a measurements from non-aqueous media, *e.g.* DMSO, often vary quite significantly (even as to order) relative to those from aqueous media (Bordwell, 1988). One view of the hydrogen bonding in (2) is that it amounts to internal solvation, which must replace the external solvation as (2) crystallizes from the aqueous solution that produced it. Hence, it is entirely possible that the anionic structure in (2) does not even correspond to the predominant solution species.

Of the two alternative structures theoretically available for the monoanion, each carrying two internal hydrogen bonds, two different semi-empirical molecular-modeling methods, PM3 and AMI (Wavefunction, 2001), returned consistently lower energies and greater solvation-stabilization for the symmetrical structure actually observed, (B), than for (A). The calculated energy differences (gas phase, 13.4–16.3 kJ mol⁻¹; aqueous, 21.8–25.9 kJ mol⁻¹) would correspond to phenol *versus* carboxyl acidity differences of the order 2.5 pK_a units for the gaseous species and 4.0 for the aqueous ones. These values also suggest that the loss of hydration during crystallization is more disadvantageous to (B), although not enough to reverse its stability relative to (A). The reliability of these numerical values for (1) and (2) is unclear, but certainly, for a solventless salt, the gaseous values would seem the more appropriate ones.

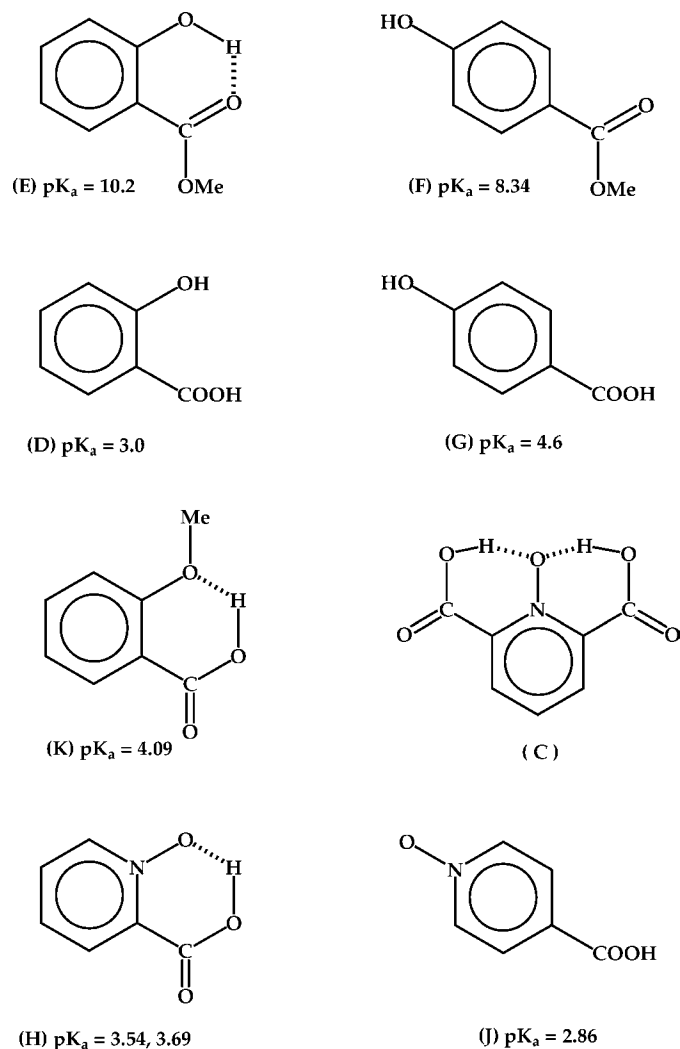
There is one experimental model that not only renders the structure of our anion reasonable but also lends it a tempting, but perhaps illusory, sense of inevitability. The *N*-oxide (C) of dipicolinic acid is isoelectronic with the anion in (2) and its X-ray structure is reported to be highly planar, with two internal hydrogen bonds that match those in (2) within narrow limits as to lengths and angles (Rychlewska & Gdaniec, 1977). In fact, the anion in (2) and (C) match closely in all the essential details except for those directly related to the N atom and its charge. The carboxyl groups of (C) even have slight tilts (1.3, 2.1, 2.8 and 3.5° for the two molecules in the asymmetric unit), similar to those found in (2). The most obvious isoelectronic difference, however, is exactly what makes (C) unfruitful as an acidity model: (C) requires no deprotonation and therefore tells us little about the acidities in (1).

It would be particularly useful to be able to dissect out the several different effects operating in this remarkable acidity enhancement. The most evident contributors to the phenol acidity are

- (i) the strongly electron-withdrawing groups at both *ortho* positions;
 - (ii) the internal hydrogen bonding observed for the anion.
- For the carboxyl groups, the effects on carboxyl acidity of
- (iii) an *ortho*-hydroxy substituent and
 - (iv) a *meta*-carboxy substituent

are well documented. It is also imaginable that *transoid* carboxyl conformations might have some bearing on carboxyl acidity. However, the structure found for (1) makes it at least uncertain that the fully protonated (aqueous) species contains any such *transoid* arrangements. It is consequently also

unclear exactly what net change in their number occurs on deprotonation, but presumably there must be a gain of at least one, possibly appearing only after deprotonation, when the internally hydrogen-bonded anion structure is established.



In estimating acidities for the phenol and carboxyl groups, certainly the latter is the easier to assess. The effect of neighboring hydroxy groups is well documented and salicylic acid [*ortho*-hydroxybenzoic acid (*D*)] has a pK_a value of 3.0; this structure, like (1), allows deprotonation without the sacrifice of an internal hydrogen bond. Another effect we may estimate with considerable accuracy for each carboxyl group is the effect on its acidity of the other carboxyl at its *meta*-position, for which the clear model is isophthalic acid (pK_a 3.54). The latter pK_a value includes a built-in factor of 2 for the presence of two acidic groups. Assuming additivity, these effects taken together suggest a carboxyl acidity for (1) around pK_a 2.3, almost to within the range of the reported first pK_a of (1).

In modeling the phenol acidity of (1), it would be desirable to separate the resonance effects of the flanking *ortho* substituents from their hydrogen-bonding contribution. The most obvious model for the acidity in a phenol resembling (1),

but lacking the internal hydrogen bonding of (2), might seem to be a diester of (1). However, serious complications arise with such a model, in part because an endocyclic hydrogen bond would be lost in the deprotonation, which should thus be significantly disfavored relative to the case of (1) or even of phenol itself. Such a *net* loss of an endocyclic hydrogen bond is, indeed, energetically costly, as shown by the pK_a of methyl salicylate [(*E*), 10.2], which is actually less acidic than either phenol (pK_a 10.0) or its own corresponding *para* isomer [(*F*), pK_a 8.34].

The second problem arising with ester models is that when deprotonation removes all the internal hydrogen bonding, ring coplanarity with the flanking group may well also be lost or diminished. A preferable model for phenol acidity in (1) might therefore be 2,6-dicyanophenol, which has linear substituents and lacks any internal hydrogen-bonding capacity. It is true that by some measures (*e.g.* Hammett constants) a cyano function appears significantly stronger in electron-withdrawing power than other carboxylic acid derivatives. However, studies of some compounds substituted with $-\text{CN}$ versus $-\text{CO}_2\text{Et}$ have found acidities within 0.6–0.8 pK_a units of one another (Bordwell & Fried, 1981), while enforced coplanarity in carbonyl species, as is present in (2), has been shown to enhance acidity by amounts at least as large (Bordwell & Fried, 1991; Zhang & Bordwell, 1994).

2,6-Dicyanophenol is a known material for which, unfortunately, no pK_a appears ever to have been reported. However, the pK_a for *ortho*-cyanophenol is reliably known to be in the range of 7.0 (6.9, 6.97, 7.22). Assuming an additive acidity enhancement of 3.0 pK_a units for each *ortho* nitrile then suggests a pK_a value for 2,6-dicyanophenol in the range of 4.0. To the extent that 2,6-dicyanophenol is an adequate model, this leaves a shortfall of *ca* 2–2.5 pK_a units (*ca* 11.4–14.2 kJ mol^{-1}) between this estimate and the observed experimental pK_a values for (1) of 1.6–2.1. It thus appears that the phenol acidity of (1) cannot be accounted for by resonance effects alone. However, on the basis of the pK_a values reported for several *ortho* versus *para* isomer examples, this gap does appear to be one that might easily be bridged by the stabilization conferred by two internal hydrogen bonds.

Hydrogen-bonding models: Beyond the data cited above for the *ortho*- versus *para*-carbomethoxyphenols, an estimate of the stabilization contributed by such internal hydrogen bonding is offered by other *ortho/para* isomer pairs exhibiting the same trend, *e.g.* salicylic acid [(*D*), pK_a 3.0] versus *para*-hydroxybenzoic acid [(*G*), pK_a 4.6] and the *N*-oxide of 2-carboxypyridine [(*H*), pK_a 3.54, 3.69] versus that of 4-carboxypyridine [(*J*), pK_a 2.86]. The *ortho/para* differences embodied in such pairs represent the net difference between endo- and exocyclic hydrogen bonding, *i.e.* the energy advantage of the entropically favored internal hydrogen bond relative to external hydrogen bonding with water. It is not clear whether the size of such an energy difference bears a significant relation to the *origin* of the hydrogen involved in the hydrogen bond (a phenol H in the case of the carbomethoxyphenols versus a carboxyl H in the *N*-oxides.) Another instructive acidity difference is that between *ortho*-

anic (*ortho*-methoxybenzoic) acid [(*K*), pK_a 4.09] and salicylic (*ortho*-hydroxybenzoic) acid [(*D*), pK_a 3.00]. In the former case deprotonation removes all endocyclic hydrogen bonding, which can persist in the latter. All these examples suggest a net stabilization probably in excess of one pK_a unit ($> 5.7 \text{ kJ mol}^{-1}$) apiece for such endocyclic hydrogen bonds.

3.2.3. Conclusions regarding the anion. Our conclusion, therefore, is that the high phenol acidity in (1) is due not only to the more obvious ring resonance and the electron-withdrawing effects of the flanking carboxyl groups, but, critically, to the oxyanion stabilization provided by the observed internal hydrogen bonding, which probably contributes a total stabilization equivalent to 2–2.5 pK_a units (*ca* 11.4–14.2 kJ mol^{-1}).

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