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Crystal Structure of Methyl Paraben Polymorph II

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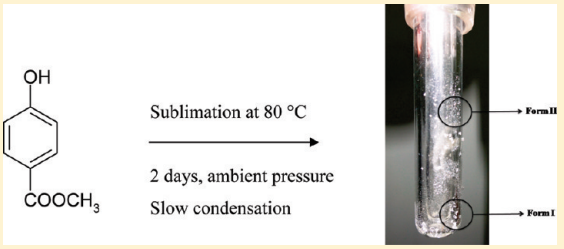
Supporting Information

ABSTRACT: The single crystal X-ray structure of a second polymorph of methyl paraben was determined after 80 years of the indication of its existence. The X-ray crystal structure, calculated powder diffraction lines, molecular packing, and thermal behavior visualized under a hot stage microscope for this second polymorph are distinctly different from those of the reported crystal structure(s). 2D fingerprint plots as Hirshfeld surfaces of these two polymorphs highlight the differences in hydrogen bonding and aromatic interactions. The crystal structure of methyl paraben polymorph II is similar to the layered structure of ethyl and propyl paraben. The X-ray crystal structure of a second polymorph in parabens is reported for the first time.



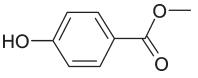
Parabens[1] are a group of alkyl esters of *p*-hydroxybenzoic acid and typically include methyl paraben, ethyl paraben, propyl paraben, butyl paraben, heptyl paraben, and benzyl paraben. The parabens or their salts are widely used as preservatives in cosmetics, toiletries, food, and pharmaceuticals, as they have a broad spectrum of antimicrobial activity. Methyl paraben (MP) (Scheme 1) is particularly important because of its high solubility (2.7 mg/mL in phosphate buffer)[2] compared to higher esters in the series. Methyl paraben is added as a preservative to skin creams, shampoos, and eye makeup to protect users from infections, rashes, and microbial attacks. Approximately 30,000 lbs of methyl paraben is consumed annually in the USA.

Polymorphism in MP was first indicated by Fischer and Stauder in 1930,[3] following which Kofler and Kofler investigated the phenomena and discovered its two modifications (Figure S1).[4] Later, in 1939, Lindpainter described six modifications of MP.[5] We have successfully determined the X-ray crystal structure of the second polymorph of MP 80 years after its discovery. Methyl paraben was called *p*-oxybenzoic acid methyl ester in the older literature.

The single crystal X-ray structures for two modifications of β-cyclodextrin−methylparaben inclusion structures are reported.[6] Cocrystal polymorphs of lamotrigine with methyl paraben were recently published.[7] Methyl paraben also acts as a "molecular hook" for the selective separation of quinidine from its stereoisomer quinine based on its molecular specificity.[8] MP is known to interact with sugar and sugar alcohols.[9]

Three crystal structures of MP are archived in the Cambridge Structural Database[10] (version 1.12, August 2010 update; CSD Refcodes: CEBGOF,[11] CEBGOF01,[12] and CEBGOF02).[13] A new polymorph of MP was claimed by Vujovuc and Nassimbeni[12] in 2006, but this was proved to be the same crystal structure by Threlfall and Gelbrich.[14] The latter authors commented that the shifts in the X-ray powder diffraction (XRPD) lines were due to lattice parameter changes with temperature. Another polymorph of MP with different *c*-axis and β-angle from that for form I was claimed[13] in 2008, but the crystal structure, space group, and *Z* values are the same. There is only one unique crystal structure of methyl paraben in the literature as of early 2011 based on the comparison of unit cell parameters, space group, calculated XRD lines, and molecular packing (see Table S1 and Figures S2 and S3, Supporting Information). These single crystals were obtained by solution crystallization from alcoholic solvents (MeOH, EtOH) at room temperature. We have successfully crystallized a second polymorph of methyl paraben, hereafter form II, and report its X-ray crystal structure and compare the molecular packing, thermal behavior, and Hirshfeld surface plots of the two polymorphic structures. A survey of the CSD suggested that the other parabens, such as ethyl, propyl, allyl, *n*-hexyl, and benzyl, have only one crystal structure report each.

Scheme 1. Molecular Structure of Methyl Paraben (MP)



Commercial methyl paraben was confirmed to be form I by XRPD (Figure S4, Supporting Information). Different techniques were used for polymorph screening, such as crystallization from various solvents at room temperature and low temperature, flash cooling, melting, and sublimation. A second polymorph of

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methyl paraben was obtained in sublimation experiments as thin plate type crystals concomitantly with form I (block crystals) when condensation was allowed to happen slowly over 2 days, as described in the Supporting Information. All other techniques and experiments gave form I.

There are clear differences in the cell parameters of form II and the reported crystal structures (see Table 1) of different Z' values (form I, $Z' = 3$; form II, $Z' = 1$; the ORTEP plot is shown in Figure S5). Among the three different structure reports for form I, we take the crystal data of Vujovuc and Nassimbeni[12] (CEBGOF01) for discussion because it has the lowest R-factor (0.033) and was determined at about the same temperature as our reflections data (113 K, 100 K).

The yield of form II was very low (~1%), and the quality of single crystals was poor compared to that of form I crystals. Both polymorphs crystallized concomitantly on the coldfinger of the sublimation apparatus (Figure 1). Crystals of form II were found to be very unstable. Mechanical handling resulted in crystal deformation or phase change to form I, and hence, analytical measurements such as DSC, XRPD, and ss-NMR could not be carried out on form II.

Table 1. Comparison of Cell Parameters of the Best Reported Crystal Structure of Methyl Paraben Form I with Form II To Highlight the Differences

compd	form II	CEBGOF01
ref	this work	ref 12
space group	$P2_1/c$	Cc
T/K	100	113
a/Å	4.8186(13)	13.006(3)
b/Å	14.630(4)	17.261(4)
c/Å	10.239(3)	12.209(2)
β/deg	99.810(5)	129.12(3)
Z'/Z	1/4	3/12
V/Å^3	711.3(3)	2126.445
D_{calc}/(g cm^{-3})	1.421	1.426
R_1 [$I > 2\sigma(I)$]	0.0801	0.033
reflns collected	7072	
Unique reflns	1370	
observed reflns	1252	
wR_2 [all]	0.1564	
R_{int}	0.0518	

The crystal structure of form I contains zigzag chains of O−H···O hydrogen bonds (1.79 Å, 174.0°; 1.77 Å, 165.3°; and 1.76 Å, 168.5°) along the c-axis, and such chains are connected via C−H···O (2.41 Å, 139.5°; 2.61 Å, 152.4°; and 2.47 Å, 137.8°) and C−H···π (2.70 Å, 134.8°; 2.57 Å, 146.4°; 2.69 Å, 150.7°; and 2.61 Å, 133.8°) interactions (Figure 2d and e). Whereas the molecules are coplanar in a molecular dimer of form II, they are nearly orthogonal in form I (Figure 2a and b). The main synthon in both structures is the O−H···O hydrogen bond from the hydroxyl O−H to the carbonyl oxygen. The sheet structure of form II is sustained by an O−H···O hydrogen bond (1.71 Å, 174.2°) and auxiliary C−H···O interactions (2.35 Å, 167.6°; 2.63 Å, 124.9°). Adjacent layers are stacked at a 3.23 Å distance. There are thus clear differences between the crystal structures of form I (zigzag chain of molecules, 3D packing) and form II (linear chain, lamellar packing), apart from the fact that their space groups, unit cell parameters, and Z' values are different. The calculated XRD lines from the crystal structure show clear differences in peak positions for forms I and II (Figure 3).

Their IR spectra exhibit C═O stretching frequency at different values (form I, 1680 cm^{-1}; form II, 1686 cm^{-1}) (Figure S6, Supporting Information). The crystal structure of form II is similar to the crystal structures of ethyl paraben and propyl paraben[15] (Figure S7, Supporting Information), which has planar sheets with the ester ethyl and propyl groups projecting out of the layer, albeit more so than in the methyl analog. This leads to the following thought:[16] could ethyl and propyl paraben have a polymorphic structure similar to the 3D packing in form I of methyl paraben?

The thermal events were visualized under a hot stage microscopy for both polymorphs. Form II crystals showed changes during heating which started at 68 °C and ultimately melted at 124 °C (Figure 4a), whereas sublimation of form I crystals was observed which started at 100 °C and finally melted at 124 °C (Figure 4b).

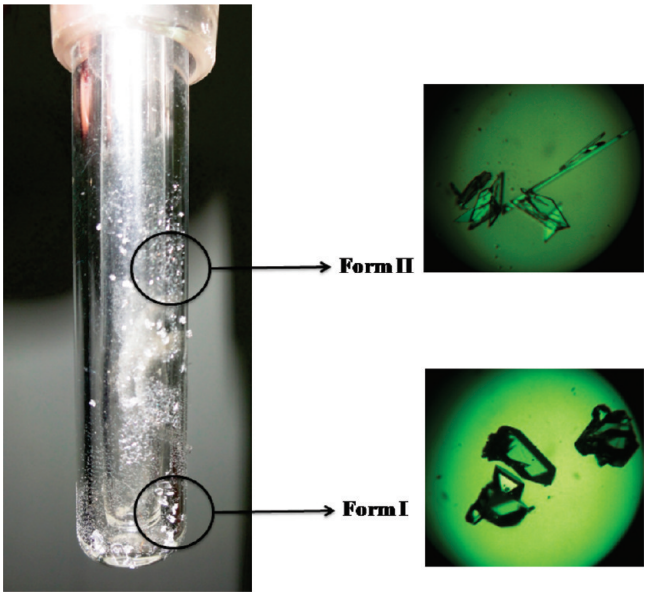

Figure 1. Concomitant crystallization of form I and form II of methyl paraben by sublimation on the coldfinger.

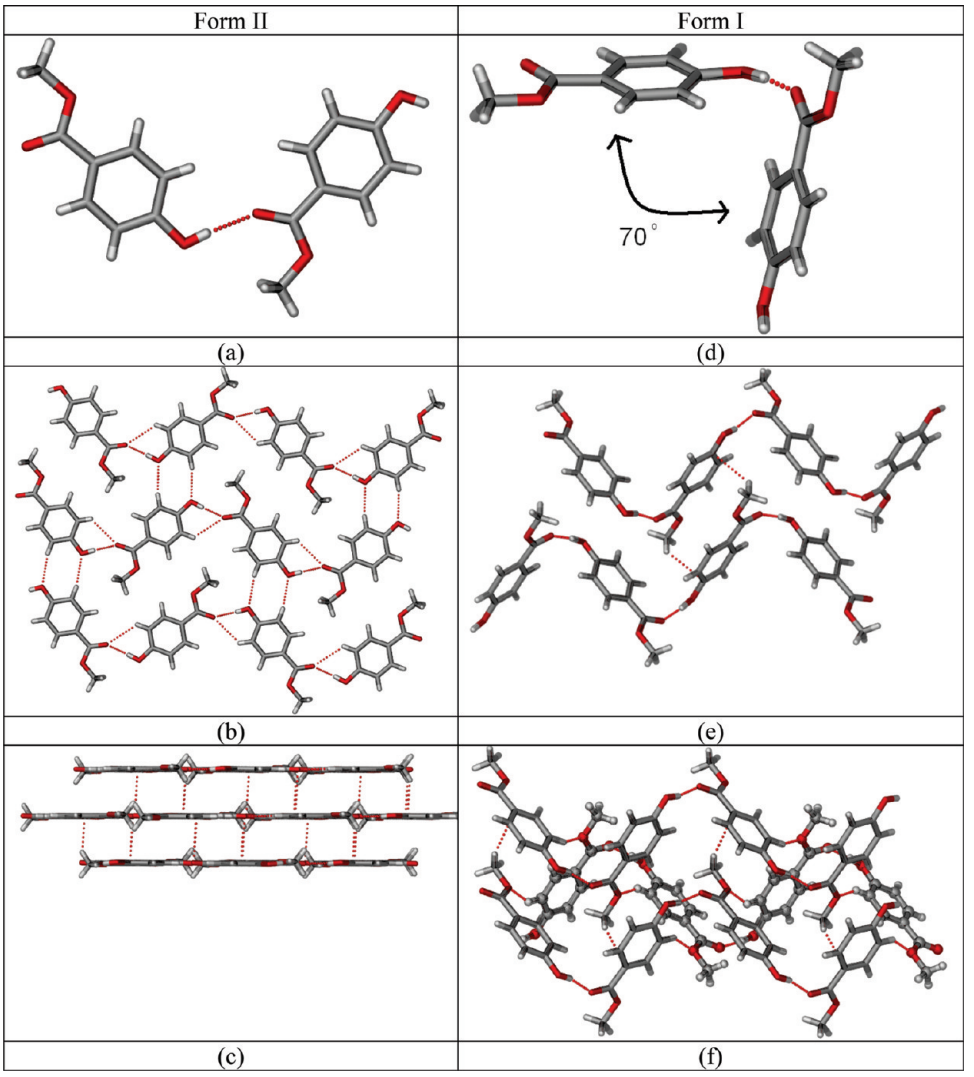

Figure 2. Hydrogen bonding and molecular packing in the crystal structures of MP: form I (right panel) and form II (left panel).

The 2D fingerprint plots as a Hirshfeld surface[17] for the two polymorphs display clear differences in the interactions even as the main structure governing the O−H···O hydrogen bond is the same in both structures, which shows up as a pair of sharp spikes in the plots. The planar structure of form II is depicted by the red region in the center of the plot, which is due to a C═O group residing just above the phenyl ring (bond midpoint to ring centroid = 3.67 Å), whereas the light red shade for the three molecules of form I suggests the absence of stacking interactions. The C−H···π interactions in form I show up as wings in A and C molecule plots (C−H···π 2.70 Å and 2.61 Å). The wings are not prominent for the B molecule because the interaction is long (3.09 Å). The absence of a C−H···π interaction in the lamellar structure of form II means that the wings are absent in its fingerprint 2D plot (Figure 5). The relative contributions of each interaction to the Hirshfeld surface are depicted in Figure 6. The form II structure has less O···H and C···H contacts and more H···H contacts compared to form I. From the crystal structure and also from the Hirshfeld fingerprint plot, it is evident that there is lower contribution of C···H contacts in the form II crystal structure compared to form I.

The densities of MP polymorphs are very similar (Table 1). From visual observation of crystal behavior upon manual handling,

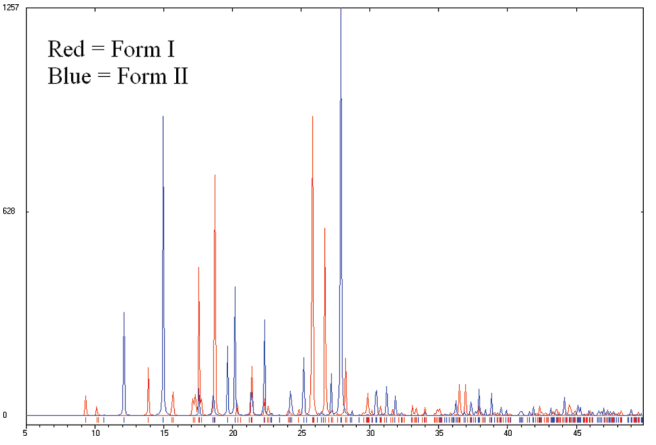

Figure 3. Calculated XRPD pattern of form I (red) and form II (blue).

it is clear that form II is metastable. Lattice energy calculations[18] indicate the greater stability of form I compared to form II (Compass: −24.95, −24.90; Dreiding: −33.65, −31.22). The energy difference is larger in Dreiding calculations because this

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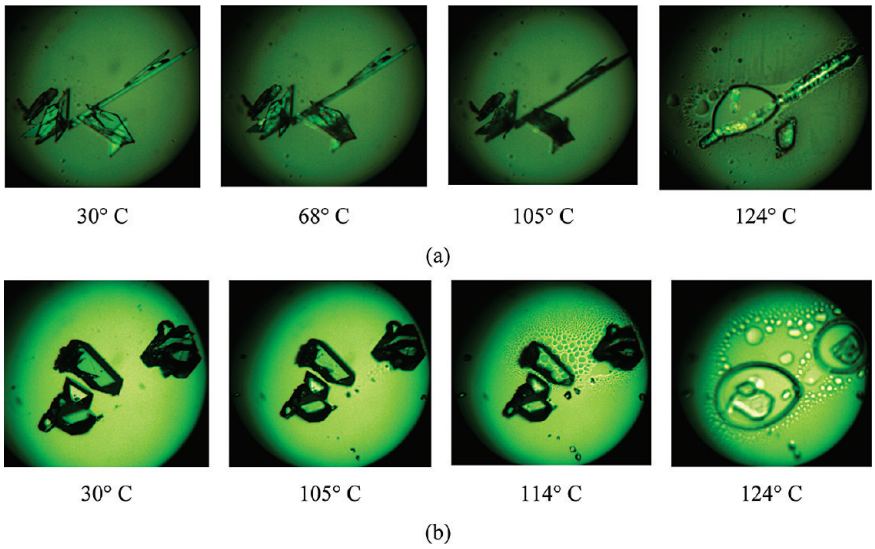

Figure 4. Hot stage microscopy images: (a) form II crystals show changes (transparent to opaque nature) at about 68 °C; (b) form I crystals begin sublimation at about 100 °C and then become liquid state at 124 °C.

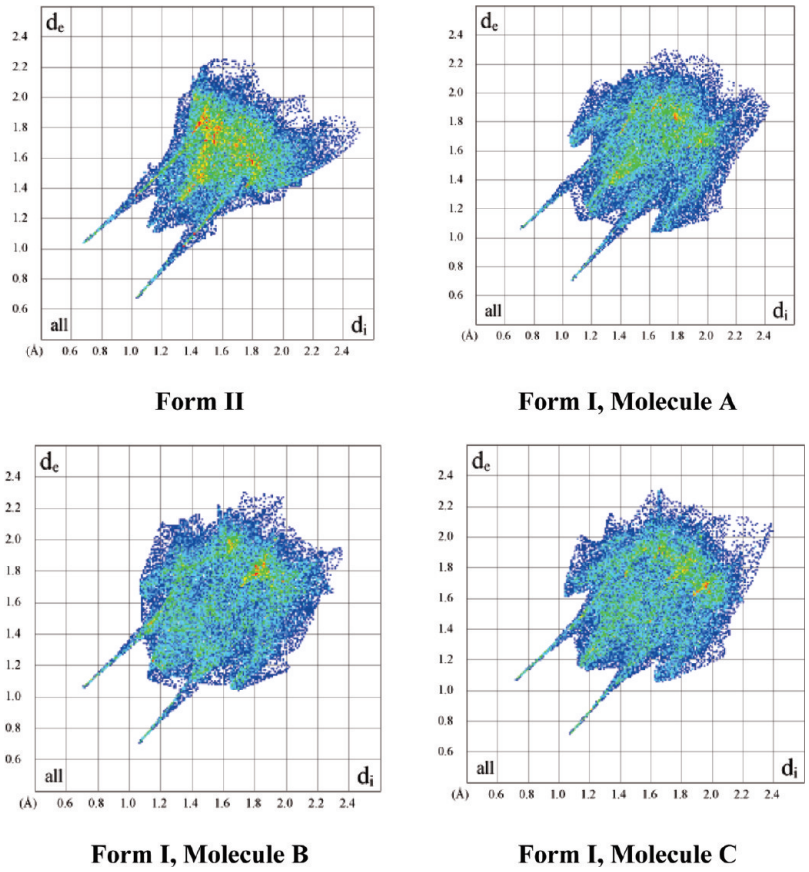

Figure 5. 2D fingerprint plots of form II and three molecules of form I (A, B, and C).

force field explicitly accounts for the hydrogen bond energy component whereas Compass calculates hydrogen bonds as an overall electrostatic term. Attempts to seed a saturated solution of MP in diethyl ether with a few form II crystals at −10 °C were not successful. XRPD of the resulting material did not show any evidence of form II (Figure S8).

An essential, daily use bulk chemical methyl paraben afforded single crystals of a second polymorph under specially optimized sublimation conditions of slow condensation. This polymorph is metastable compared to the well-known and commercial crystalline material. The pair of methyl paraben structures adds to the now growing number of polymorph sets[19] wherein the stable

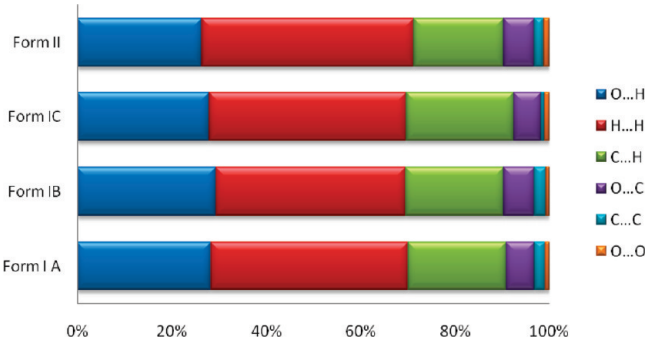

Figure 6. Relative contribution of different interactions to the Hirshfeld surface.

crystal structure has multiple molecules in the asymmetric unit. This preliminary result naturally suggests a search for polymorphism in alkyl esters of *p*-hydroxybenzoic acid.

■ ASSOCIATED CONTENT

Supporting Information. Sublimation experiment, crystallographic data, and packing diagrams, and crystallographic .cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

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