

Electronic Supplementary Information

Ionized Form of Acetaminophen with Improved Compaction

Properties

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S1. Synthetic procedure for **1**.

Figure S1. X-Ray difference Fourier map in the region of the atoms O(7) and O(100) in the crystal structure of **1**.

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Table S1. X-Ray crystal data and structure refinement for **1**.

Table S2. X-Ray crystal data and structure refinement for **2**.

References

S1. Synthesis of 1: Acetaminophen (ACM, 302mg) was dissolved in Con.HCl (1.6mL) with slight heating then cooled to room temperature. Single crystals of **1** suitable for structure determination by X-ray diffraction method were formed within 30 min. An X-ray difference Fourier map reveals that the site of protonation is the amide oxygen, O(7) (Figure S1), which is consistent with the observation made in literature (Refs 4 and 7 in the paper).

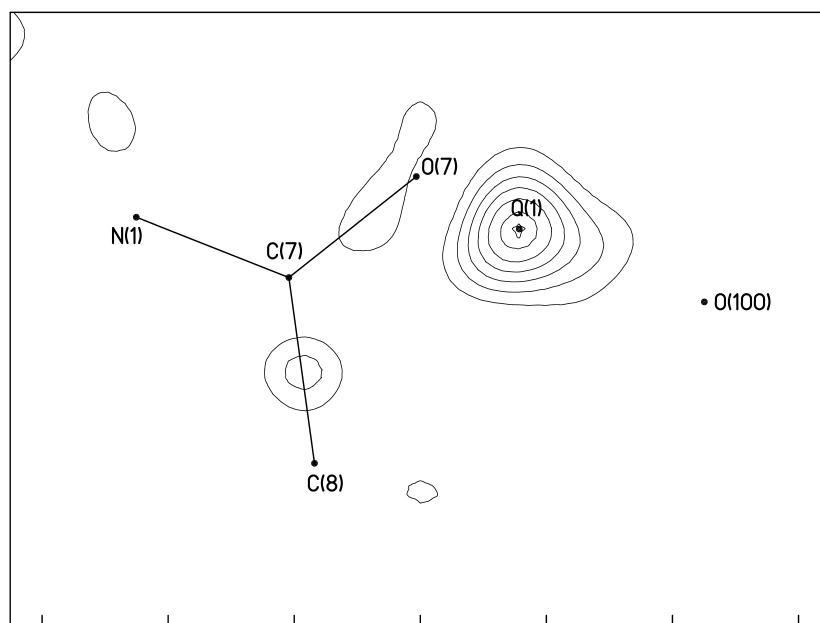


Figure S1. X-Ray difference Fourier map in the region of the atoms O(7) and O(100) in the crystal structure of **1**. The single maximum of $0.63 \text{ e} \text{ \AA}^{-3}$ near the atom O7 corresponds to protonated hydrogen; its distance from O(7) is 0.89 \AA , and its distance from O(100) is 1.61 \AA .

We prepared bulk powders of **1** by either linearly scaling up the above-mentioned reaction or by suspending ACM (15 g) in Con.HCl (75 mL) at room temperature for 12 hours. If prolonged heating is applied, crystals of **2** are produced (Figure S2).

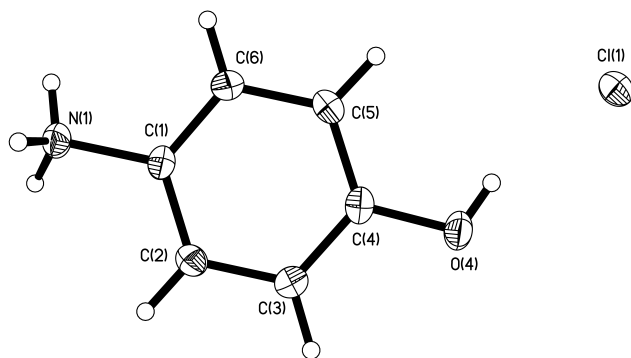


Figure S2. ORTEP diagram of asymmetric unit of **2**.

S2. Mechanical properties determined by nanoindentation

Crystal hardness, H , were determined using a nanoindenter (TriboIndenter TI-900, Hysitron Inc., MN, USA) with a Berkovich diamond indenter tip. Before nanoindentation testing, the tip area function was derived from a series of indentations on a fused quartz standard. The nanoindentation experiments were performed under the displacement control mode. The rates of loading and unloading were both 100 nm/s and a 10 s holding was applied at the maximum indentation depth of 500 nm. Nanoindentation data were analyzed following the standard procedure.^{S1} Representative nanoindentation data for ACM Form **I** and **1** are shown in Figure S3.

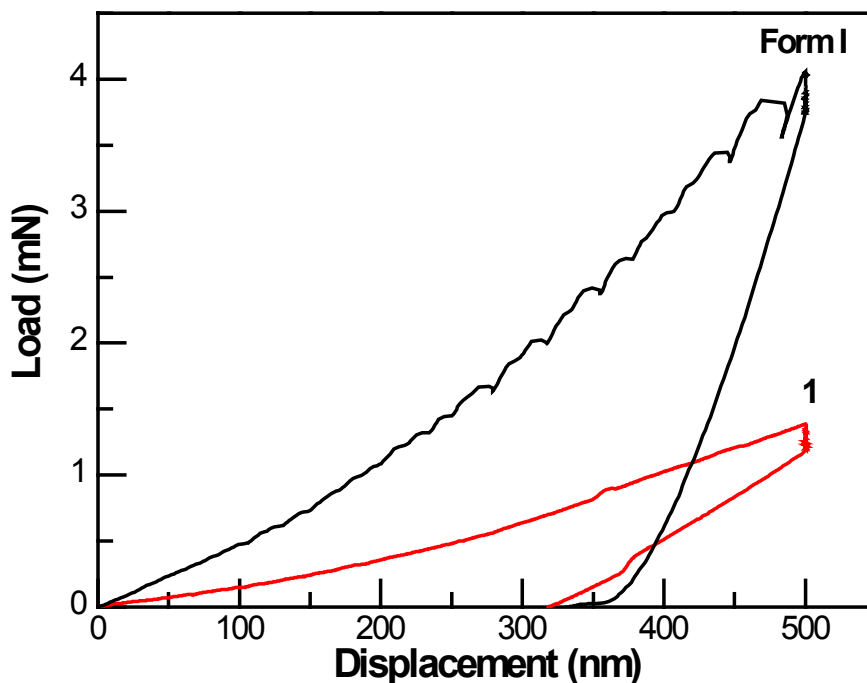


Figure S3. Nanoindentation load-unload curves of ACM Form I and **1**. A much lower force is required to make an indent of the same size on **1** than on ACM.

S3. Powder compaction

A material testing machine (model 1485, Zwick/Roell, Kennesaw, GA) was used to perform compaction study of bulk powder of **1** at a loading rate of 1 mm/s. Powder was grinded in a mortar using a pestle to reduce particle size before compaction studies at pressures ranging from 25 to 350 MPa, where a die (round, 8 mm diameter) and flat-faced punches lubricated with magnesium stearate were employed. Tablets were relaxed under ambient environment for 24 h before measuring diametrical breaking force using a texture analyzer (TA-XT2i, Texture Technologies Corp., Scarsdale, NY). Tablet tensile strength was calculated from the breaking force and tablet dimensions following standard procedure.^{S2}

S4. Powder X-ray diffractometry

X-Ray powder diffractogram was obtained on a wide-angle diffractometer (D5005, Bruker AXS). CuK_α radiation was used. The voltage and current applied were 45 kV and 40 mA respectively. The measurement was performed with a step size of 0.02° from 5° to 35° two theta and a dwell time of 1s. PXRD data were analyzed using a commercial software (JADE, Materials Data Inc., Livermore, CA). Aside from the different peak intensities, which is attributed to the phenomenon of preferred orientation, experimental PXRD pattern of the bulk powder used for compaction matches well with the calculated PXRD pattern (Figure S4).

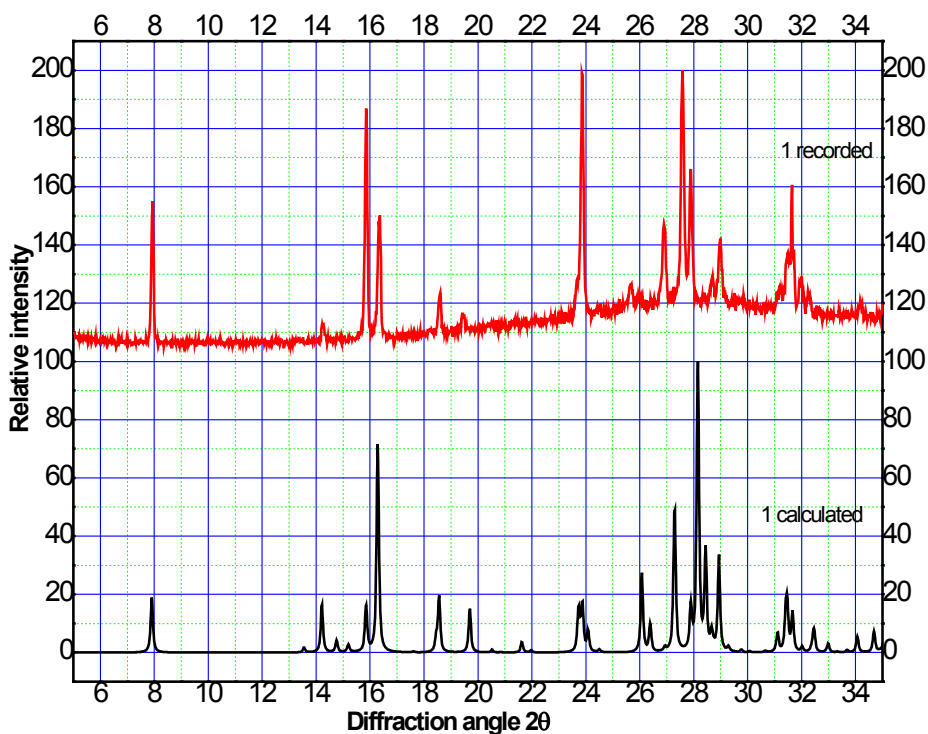


Figure S4. Calculated and measured PXRD patterns of **1** for bulk powder.

S5. X-Ray crystallographic data collection strategy and refinement

Suitable single crystal was placed onto the tip of a 0.1 mm diameter glass fiber and mounted on a Bruker Apex II CCD area detector diffractometer for data collection at 173(2)K using MoK α radiation (graphite monochromator).^{S3} Data processing was accomplished with the SAINT processing program. The structure was solved using Bruker SHELXTL and refined using Bruker SHELXTL.^{S4} A direct-methods solution was calculated, which provided most non-hydrogen atoms from the *E*-map. Full-matrix least squares/difference Fourier cycles were performed, which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located from the difference Fourier map and allowed to ride on their parent atoms in the refinement cycles. Key crystal data and data collection parameters are summarized in Table S1 and S2 for **1** and **2** respectively. Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, S146 Kolthoff Hall, Department of Chemistry, University of Minnesota.

Table S1. X-Ray crystal data and structure refinement for **1**.

Empirical formula	C ₈ H ₁₂ Cl N O ₃	
Formula weight	205.64	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.2761(6) Å	α = 90°.
	b = 22.345(2) Å	β = 97.2570(10)°.
	c = 6.8833(7) Å	γ = 90°.
Volume	957.56(16) Å ³	
Z	4	
Density (calculated)	1.426 Mg/m ³	
Absorption coefficient	0.374 mm ⁻¹	
F(000)	432	
Crystal size	0.36 x 0.26 x 0.16 mm ³	
Theta range for data collection	1.82 to 26.84°.	
Index ranges	-7 ≤ h ≤ 7, -28 ≤ k ≤ 28, -8 ≤ l ≤ 8	
Reflections collected	10318	
Independent reflections	2043 [R(int) = 0.0248]	
Completeness to theta = 26.84°	99.6 %	
Max. and min. transmission	0.9426 and 0.8772	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2043 / 0 / 166	
Goodness-of-fit on F ²	1.060	
Final R indices [I > 2σ(I)]	R1 = 0.0272, wR2 = 0.0734	
R indices (all data)	R1 = 0.0306, wR2 = 0.0760	
Largest diff. peak and hole	0.193 and -0.243 e.Å ⁻³	

Table S2. Crystal data and structure refinement for **2**.

Empirical formula	C ₆ H ₈ Cl N O	
Formula weight	145.58	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.4919(6) Å	α = 90°.
	b = 6.1159(6) Å	β = 90.0320(10)°.
	c = 16.8700(16) Å	γ = 90°.
Volume	669.80(11) Å ³	
Z	4	
Density (calculated)	1.444 Mg/m ³	
Absorption coefficient	0.480 mm ⁻¹	
F(000)	304	
Crystal size	0.19 x 0.16 x 0.15 mm ³	
Theta range for data collection	2.41 to 27.56°.	
Index ranges	-8 ≤ h ≤ 8, 0 ≤ k ≤ 7, 0 ≤ l ≤ 21	
Reflections collected	1682	
Independent reflections	1542 [R(int) = 0.0000]	
Completeness to theta = 27.56°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9315 and 0.9143	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	1542 / 0 / 116	
Goodness-of-fit on F ²	1.097	
Final R indices [I > 2σ(I)]	R1 = 0.0226, wR2 = 0.0658	
R indices (all data)	R1 = 0.0228, wR2 = 0.0660	
Extinction coefficient	0.017(3)	
Largest diff. peak and hole	0.271 and -0.207 e.Å ⁻³	

References:

- (S1) W.C. Oliver, G.M. Pharr, *J. Mater. Res.* **1992**, *7*, 1564-1583
- (S2) J. T. Fell, J. M. Newton, *J. Pharm. Sci.* **1970**, *59*, 688-691.
- (S3) Bruker (**2007**). APEX2, SADABS and SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
- (S4) G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112–122.