Supporting Information

Polymorph Discrimination using Low Wavenumber Raman Spectroscopy

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S1. Sample Preparation

Acetaminophen (ACM). ACM form I (monoclinic) was obtained from the evaporation of a water solution of ACM (16.75 mg/mL) which was prepared by heating at 80°C and filtering through a 0.45 μm PTFE filter. Orthorhombic form II of ACM was obtained through polymer-induced heteronucleation.[3] A water solution of ACM (10.6 mg/mL) was prepared by heating at 80°C and immediate filtering through a 0.45 μm PTFE filter. Approximately 0.3 mL of this solution was dispensed into the wells of a 96-well polypropylene plate containing Nylon 6/6. The plate was covered loosely, allowing for slow evaporation to yield orthorhombic form 2 of ACM.[1]

Tolfenamic Acid (TA). Form I of TA was obtained as white needles from the evaporation of an acetonitrile solution of TA (14.3 mg/mL) at room temperature. The solution was prepared by heating at 80 °C and subsequently filtered through a 0.45 μm PTFE filter. Form II of TA was obtained as yellow needles by cooling a boiling absolute ethanol solution of tolfenamic acid (13 mg/mL) to room temperature rapidly.[2]

Nabumetone (NB). A saturated solution of NB was prepared by dissolving the material in 2-propanol (20 mg/mL) at 70 °C. The solution was filtered hot through a 0.45 μm PTFE filter and then allowed to evaporate at room temperature yielding form I of NB. An absolute ethanol solution of NB (13.5 mg/mL) was prepared through heating the solution at 70 °C. The solution was filtered hot through a 0.45 μm PTFE filter and was allowed to evaporate under ambient conditions. The evaporation of absolute ethanol solutions yielded form II with the occasional ancillary formation of form I.[3]

Furosemide (FUR). An absolute ethanol solution (12.5 mg/mL) of FUR was prepared at 80°C and the hot solution was filtered immediately with a .45 μm PTFE filter. The solution was allowed to evaporate at room temperature yielding form I of FUR. A saturated solution of FUR was prepared by dissolving commercial FUR in n-butanol (18 mg/ml). The hot solution was filtered through a 0.45 μm PTFE filter and was allowed to evaporate in ambient conditions to yield form II. An acetone solution of FUR (25 mg/mL) was prepared by heating at 50°C. The solution was filtered hot with a 0.45 μm PTFE filter. The solution was then allowed to evaporate in ambient conditions overnight to yield form III of FUR.[4]

Mefenamic Acid (MA). An absolute ethanol solution of MA (12 mg/mL) was prepared by heating at 80 °C and immediately filtering with a .45 μm PTFE filter. The solution was then allowed to evaporate in ambient conditions leading to the formation of pure form I crystals. Form II was obtained through heating 10 mg of MA on a glass slide at a rate of 10ºC/minute and was held at 160ºC for a time of 120 minutes. Heating of sample was done on a Linkam LTS350 hot stage connected to a Linkys32 control processor with the sample underneath a glass cover slip.[5]

Flurbiprofen (FB). Polymer-induced heteronucleation provided a reproducible method to crystallize all three polymorphs of FB. Absolute ethanol (26.5 mg/mL) and methanol (26.5 mg/mL) solutions of FB were prepared through heating the solutions at 70°C and filtering both solutions hot with .45 μm PTFE filters. Approximately 0.3 mL of the prepared solution was added to each well of a 96-well polypropylene

plate containing a few milligrams of a single polymer in each well. The wells containing ethylene/vinyl acetate copolymer in methanol solution yielded form III of FB. The wells containing chorosulfonated polyethylene in methanol solution crystallized form II of FB. The wells containing ethanol solution and nylon 6/12 polymer gave pure FB form I.[6]

Sulfamethazine (SMZ). Crystalline sample of SMZ used for the study was prepared from a crystallization of an absolute ethanol solution of commercial SMZ (15 mg/ml). Amorphous form of SMZ was prepared by melting of commercial SMZ (15 mg) over glass plate at 160 °C on a hot plate and subsequently placing the glass slide on a metal block kept on ice.[7]

Sulindac (SUL). A methanol solution of SUL (16 mg/mL) was prepared by heating the solution to 70°C and filtering hot with a .45 μm PTFE filter. This solution was dispensed over 15 mg of nylon 6/9 polymer and after evaporation at room temperature yielded form I of SUL. The same solution when dispensed over 15 mg of chlorinated polyethylene (42%) and allowed to evaporate in ambient conditions yielded form IV of SUL. An absolute ethanol solution of SUL (16 mg/mL) was prepared by heating the solution at 80°C and immediately filtering with a .45 μm PTFE filter. Through room temperature evaporation of this solution, form II of SUL was obtained.[6]

Carbamazepine (CBZ). Form I of CBZ was prepared by heating 200 mg of commercial CBZ at 140°C for 3 h in a oven. An absolute ethanol solution of CBZ (48mg/mL) was prepared by heating the solution at 80°C for approximately 15 minutes. The solution was then allowed to cool to room temperature and was filtered using a .45 μm PTFE filter. Once filtered, the solution was further cooled to 5°C for 8 hours leading to the precipitation of CBZ form II crystals. The solution was allowed to evaporate off slowly allowing for the form II needles to be collected. An absolute ethanol solution of CBZ (16 mg/mL) was prepared through heating the solution to 80°C and filtering with a .45 μm PTFE filter. After filtration the solution was allowed to evaporate at room temperature and yielded CBZ form III.[8]

Phenobarbital (PB). Commercial PB contains both form I and form II as a mixture. Form I of PB obtained when the 20 mg of commercial PB taken with 0.5 ml of absolute ethanol on a glass vial and shaken on shakers for 3 days. After 3 days form I was obtained as block-like crystals. Form II of PB prepared from a hot saturated water solution (.25 mg/mL) which was prepared by heating at 80°C was and immediately filtering with a .45 μm PTFE filter. This water solution was then kept inside the refrigerator at 4 °C to yield form II of PB as plate like crystals.[9]

S2. Raman Spectroscopy:

Conventional Raman spectra were collected using a Renishaw inVia Raman microscope equipped with a Leica microscope, RenCam CCD detector, 647 nm Kr^+ laser, 1800 lines/nm grating, and 50 µm slit. Spectra were collected in extended scan mode in the range of 3600-100 cm^{-1} and then analyzed using the Wire 3.1 software package. Calibration was performed using a silicon standard.
Low wavenumber Raman spectroscopy data were collected using a NExT filter accessory configured in a Renishaw inVia Raman microscope with a RenCam CCD detector, 647 nm Kr^+ laser, 1800 lines/nm grating, and 25 µm slit. Calibration was performed using sulfur.

Table S1. Frequency of Raman vibrational modes* (cm^{-1}) for the polymorphs of studied compounds

Carbamazepine			**Phenobarbital**		**Furosemide**		
Form I	Form II	Form III	Form I	Form II	Form I	Form II	Form III
25.2 - S	25.4 - S	29.6 - W	16.0 - S	17.0 - S	22.2 - S	18.2 - W	22.2 - VS
42.9 - W	29.6 - S	39.0 - VS	20.1 - VS	29.6 - S	29.6 - S	29.7 - VS	42.1 - S
73.2 - S	69.3 - S	47.3 - W	29.6 - VS	34.8 - W	36.9 - M	44.4 - S	63.0 - S
86.8 - M	106.9 - VS	65.1 - W	49.4 - M	42.1 - M	62.0 - VS	64.3 - M	97.5 - W
108.8 - VS	164.4 - W	73.5 - W	59.9 - M	53.6 - VS	70.3 - S	80.0 - VS	113.2 - W
165.2 -M	170.7 - W	90.2 - M	77.6 - W	75.5 - VS	86.0 - S	112.5 - M	263.8 - VW
171.5 - W	261.7 - W	104.8 - S	83.9 - W	189.5 - W	216.7 - W	142.8 - W	
262.3 - W	392.4 - VW	119.5 - M	124.7 - M		285.7 - W	218.2 - W	
368.9 - W		125.7 - M	147.7 - W		348.4 - W	259.0 - W	
392.9 - W		139.3 - M				283.2 - VW	
		168.6 - W				359.6 - M	
		183.24 - W					

Acetaminophen		**Nabumetone**		**Mefenamic acid**		**Tolfenamic acid**	
Form I	Form II	Form I	Form II	Form I	Form II	Form I	Form II
20.1 - W	25.4 - W	32.9 - VS	29.7 - S	22.9 - W	22.8 - M	28.9 - S	28.9 - M
32.7 - VS	51.5 - W	43.3 - S	56.9 - M	33.3 - VS	30.1 - S	35.2 - M	35.2 - VS
42.1 - W	71.3 - W	50.7 -S	69.5 - M	48.0 - M	45.8 - VS	41.4 - S	45.6 - W
55.7 - W	122.6- VS	100.9 - S	94.7 - W	85.6 - W	52.1 - VS	70.8 - VS	49.8 - W
63.0 - W		119.8 - W	131.3 - VS	99.2 - W	68.8 - S	104.3 - S	68.7 - M
83.9 - M			143.9 - VS	110.8 - W	84.5 - S	169.2 - W	91.7 - M
90.2 - S					93.9 - M	209.0 - W	95.9 - M
106.9 - W					153.6 - W	234.1 - W	164.0 - W
151.9 - VW						321.0 - W	234.1 - W
214.6 -VW							

Flurbiprofen			Sulfamethazine		Sulindac		
Form I	Form II	Form III	Crystalline form	Amorphous form	Form I	Form II	Form IV
29.7 - VS	13.0 - M	13.0 - M	28.7 - W	28.7 - M	28.7 - VS	32.9 - VS	33.7 - VS
56.9 - S	18.9 - W	30.8 - VS	43.3 - VS	35.0 - VS		132.3 - W	118.3 - W
81.0 - W	33.9 - VS	56.9 - W	80.0 - VW	46.5 - M			207.9 - VW
98.8 - M	60.1 - M	94.6 - W	104.1 - VW	78.94 - W			332.6 - VW
127.1- M	71.6 - W	127.1 -W	120.8 - VW				397.5 - W
150.1 - W	89.4 - W	218.2 - W	137.6 - W				
215.1 -W							
220.3 -W							
238.1 - W							

* VS= Very Strong, S= Strong, M= Medium, W= Weak, VW= Very weak

S3. Packing of Carbamazepine polymorphs.

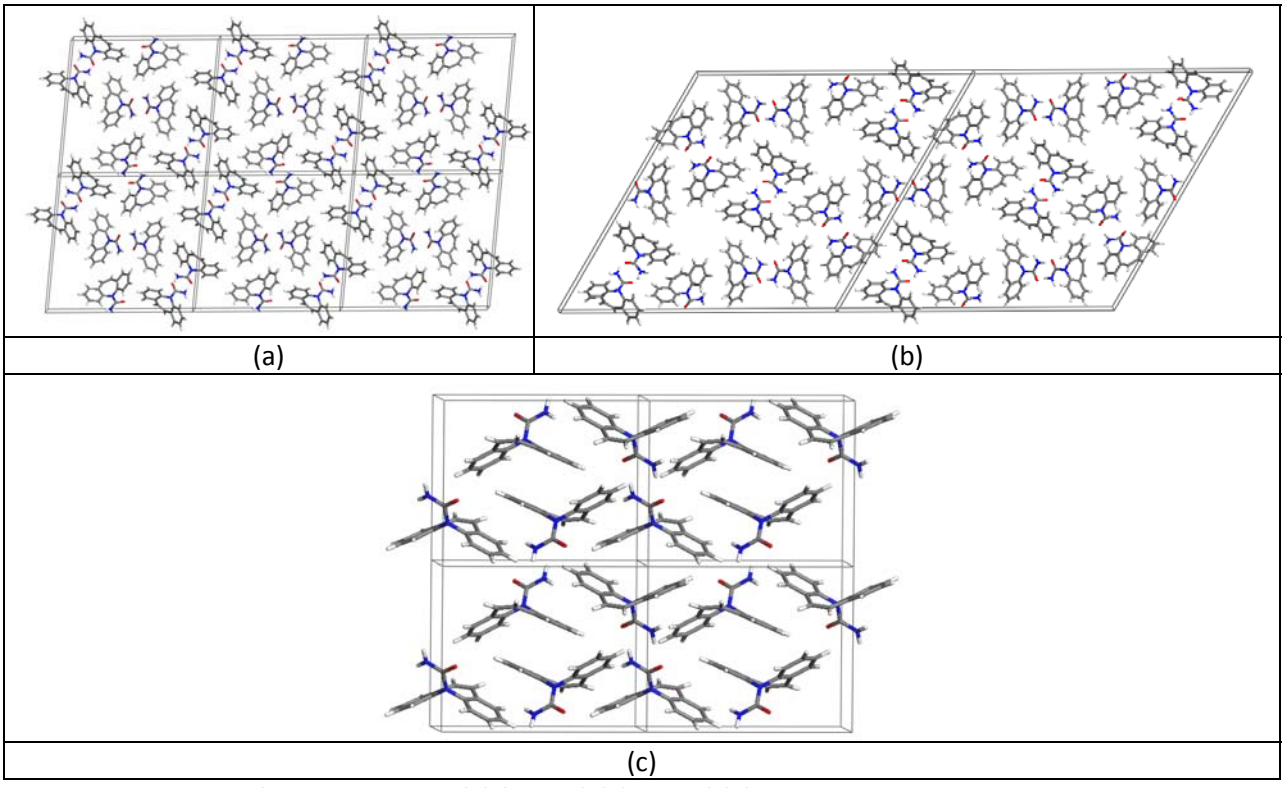


Figure S1. Packing of carbamazepine (a) form I (b) form II (c) form III

S4. Powder X-ray Diffraction of Phenobarbital polymorphs I and II

Powder X-ray diffraction (PXRD) patterns were collected using a Rigaku R-Axis Spider diffractometer with an image plate detector and graphite monochromated Cu-Kα radiation (1.5406 Å). Samples were mounted on a CryoLoop™ and images were collected for five minutes while rotating the sample about the ϕ-axis at 10°/sec, oscillating ω between 120° and 180° at 1°/sec and with χ fixed at 45°. Images were integrated from 5° to 40° with a 0.05° step size using the AreaMax software. Powder patterns were processed in Jade Plus[10] to calculate peak positions and intensities.

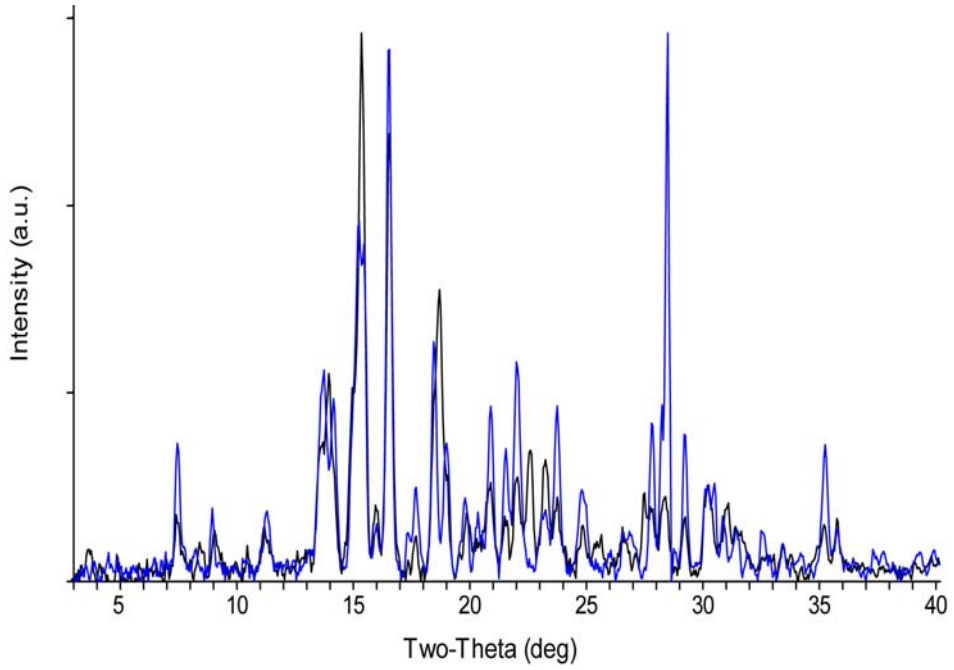


Figure S2. Powder X-ray diffraction profile of phenobarbital form I (black) and form II (blue) suggest similar packing arrangements.

S5. Differential Scanning Calorimetry of Phenobarbital polymorphs I and II

Thermograms of the samples were recorded on a TA Instruments Q10 DSC. The thermal behavior of the samples, placed in sealed aluminum pans, was studied under nitrogen purge with a heating/cooling rate of 5 °C min^{-1} covering the temperature range 35 °C to 200 °C. The instrument was calibrated with an indium standard.

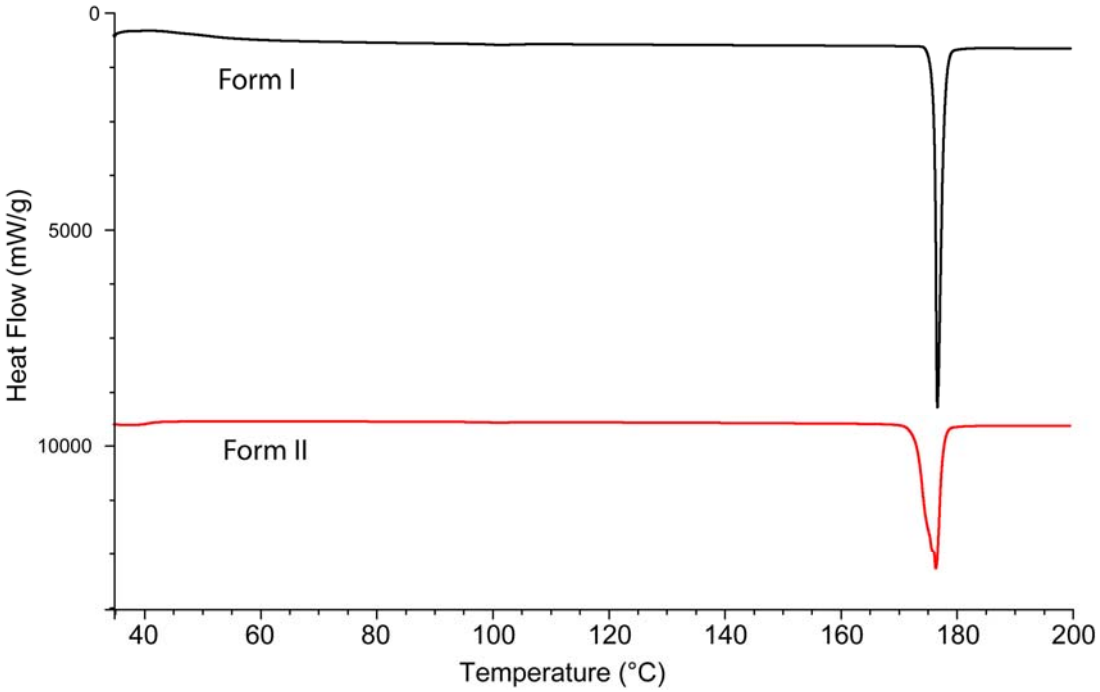
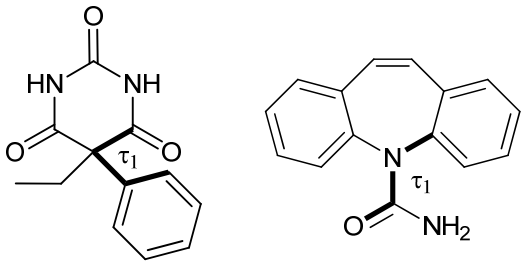


Figure S3. DSC profiles of phenobarbital form I (black) and form II (red).

S6. Conformational Analysis of Carbamazepine and Phenobarbital polymorphs

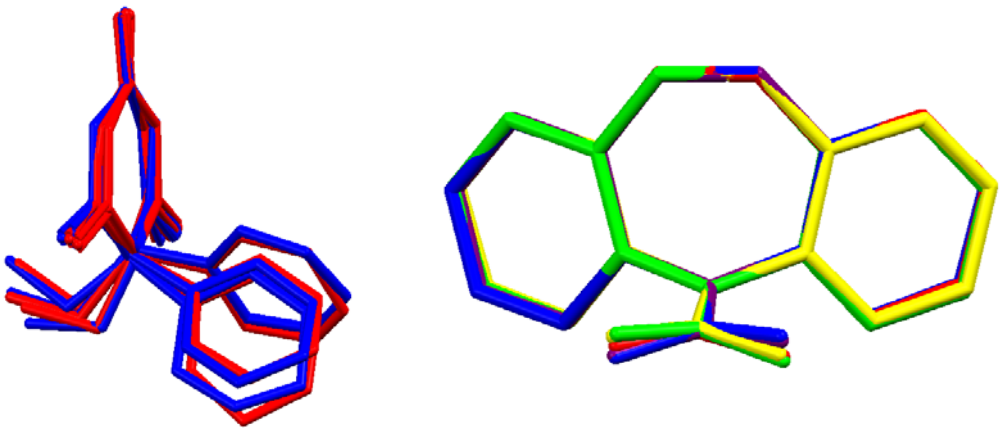


Phenobarbital Carbamazepine

Figure S4. Molecular structure of Phenobarbital and Carbamazepine. Flexible torsions are marked in bold.

Table S2. Torsion angles (τ_1) among the different symmetry independent molecules of phenobarbital and carbamazepine polymorphs.

Polymorph	Molecules	Torsion Angles
		τ_1
Carbamazepine Form I	Molecule 1	168.15°
	Molecule 2	163.66°
	Molecule 3	163.66°
	Molecule 4	161.52°
Carbamazepine Form II	Molecule 1	166.60°
Phenobarbital Form I	Molecule 1	30.34°
	Molecule 2	21.78°
	Molecule 3	11.51°
Phenobarbital Form II	Molecule 1	19.04°
	Molecule 2	22.17°
	Molecule 3	15.18°



(a) (b)

Figure S5. Molecular overlay of symmetry independent molecules from (a) phenobarbital form I and form II conformers and (b) carbamazepine form I and form II conformers. Hydrogen atoms are omitted for clarity.

References

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