Plasticity in zwitterionic drugs: the bending properties of Pregabalin and Gabapentin and their hydrates

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Pregabalin (SPG) and Gabapentin (GP) were purchased from Flourochem. Methanol was purchased from the Sigma-Aldrich and Milli-Q water was used for the experiments.

**Crystallization of SPG:** SPG crystals were obtained from the commercially available SPG that was dissolved in methanol to saturation and left it at room temperature for 2 days.

**Crystallization of SPGH1:** SPG was dissolved in pure water and crystallized at 280 K for 3-5 days to get the good quality crystals.

**Crystallization of GP:** GP and its hydrate crystals are reproduced by following the same procedure mentioned in the reported publications.¹,²

**S1. Experimental Details:**

**Optical microscopy:** SPGH I and GP hydrate crystals were bent with tweezers and a needle, the images have captured using Olympus IX53 microscope under a 4× magnification.

**IR Spectroscopy:** IR spectra for SPG and SPGH I have been collected on a PerkinElmer Spectrum 100 FT-IR Spectrometer equipped with a PerkinElmer Universal ATR Sampling Accessory.

![Figure S1](image-url)  IR spectra for SPG (blue) and SPGH I (red).

**Raman Spectroscopy:** Raman spectra for SPG and SPGH I have been collected on a Horiba Jobin Yvon LabRam Aramis spectrometer with a 532 nm laser source. The spectrometer was coupled with an Olympus BX40 confocal microscope with a CCD camera cooled by a thermoelectric Peltier device. Raman maps were processed using the LabSPEC 5 software package.
**Figure S2**  Raman spectra for SPG (blue) and SPGH I (red).

**Powder X-ray diffraction (PXRD):** PXRD data were collected on Empyrean diffractometer (PANalytical, Philips) using Cu Kα\(_{1,2}\) radiation (λ = 0.1541 nm) at room temperature operated at 40 kV and 40 mA. The samples were scanned over a range of 4-40° 2θ using a step size of 0.02° 2θ and a scan speed of 0.02° 2θ/s.

**Figure S3**  PXRD data for SPGH I: experimental (blue) and theoretical (red), green arrow indicates the traces of SPG.
Figure S4  PXRD data for SPG (commercial): experimental (blue) and theoretical (red).

Figure S5  Theoretical PXRD comparison for SPG (blue), SPGH I (red) and SPGH II (black).
Differential Scanning Calorimetry: calorimetric measurements of SPG and SPGH I were performed on a DSC 214 Polyma, NETZSCH instrument. Typically, 3-5 mg of sample was accurately weighed into a hermetically sealed aluminium pan and heated to 250 °C with 10 °C min$^{-1}$ heating rate, under nitrogen gas flow 50 mL min$^{-1}$.

Figure S7  DSC data for SPG (red) and SPGH I (Green)
Thermogravimetric Analysis: Thermograms of SPG and SPGH I were measured with a Perkin-Elmer TGA 4000 with a heating rate of 10 °C min\(^{-1}\) under a nitrogen stream of 50 mL min\(^{-1}\).

**Figure S8** TGA data for SPGH I

**Figure S9** TGA data for SPG
**X-ray Crystallography:** Single crystal data for SPGH I were collected at ambient temperature using a three circles Bruker D8 Quest with sealed tube Mo anode, $\text{K}\alpha$ radiation = 0.71073 Å, and a Photon 100 detector. Single crystal data for SPGH I were collected at 150 K under a nitrogen-flow (Oxford Cryosystem) using a three circles Bruker D8 Quest with microfocus Cu anode, $\text{K}\alpha$ radiation = 1.5418 Å, and a Photon 100 detector.

The data were integrated and corrected for absorption with the Bruker Apex Suite of programs. The structure solution was obtained by direct methods and refined against all $F^2$ with the SHELX software interfaced though X-Seed. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated positions refined using idealized geometries (riding model) and assigned fixed isotropic displacement parameters.

**Figure S10** Crystallographic interactions in the $p$-Hydroxybenzoic acid: anhydrous (top) and hydrate (bottom).
**Figure S11** Crystallographic interactions in the Uric acid: anhydrous (left) and hydrate (right).

**Figure S12** Crystal packing and interactions in Theophylline: anhydrous (left) and hydrate (right).

**S2. References:**

1. H. A. Reece and D. C. Levendis, Polymorphs of gabapentin. Acta Crystallogr. Sect. C 2008, 64, o105-o108.

2. Y. Wang, S. Du, S. Wu, L. Li, D. Zhang, B. Yu, L. Zhou, H. K. Bekele and J. Gong, Thermodynamic and molecular investigation into the solubility, stability and self-assembly of gabapentin anhydrate and hydrate. The Journal of Chemical Thermodynamics 2017, 113, 132-143.