Supplementary Information

Salification-driven strategy toward the hydrophobic molecular salt of antifungal drug 5-fluorocytosine and protocatechuic acid with triple-helix structure offers an innovative insight for conquering adverse drug reactions†

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Contents

Section 1. The definition and formulas related to topology analysis

Following the AIM concept, the critical points (CPs) are defined as the point where the gradient mode of the actual space function equals zero.[1] Specifically, the CPs at (3,+1) are the first saddle point of the electron density function, which commonly occurs in circular systems.[2] Emphatically, the CPs at (3,-1), that is, bond critical points (BCPs), as the second saddle point of the electron density function, are ordinarily distributed at bond path (3,-1) between two atoms bonding with non-covalent peculiarity. Herein, the topology research mainly concentrates on the AIM analysis at BCPs, namely the CPs at (3,-1), because it can supply certain pivotal clews utilizing relevant parameters to explore the intermolecular hydrogen bonds in strength. Lu has published reliable computational formulas (1) and (2) for quantitatively evaluating the hydrogen bond strength by analyzing and verifying the wave function for many hydrogen bond systems using the electron density at the BCPs.The formula is as follows:[3]

$$\Delta E = -233.08 \times \rho(\mathrm{r}) + 0.7423 \quad (1)$$

$$\Delta E = -332.34 \times \rho(\mathrm{r}) - 1.0661 \quad (2)$$

Where ΔE denotes the hydrogen bond energy, ρ(r) represents the electron density at BCPs. Of particular note, equation (1) applies to the neutral system, and formula (2) is appropriate for ionic system. Noticeably, the intensity of hydrogen bond interaction serves as a decisive character in physicochemical properties due to these crucial topology parameters being closely related to crystal stacking patterns and structural characteristics. Hence, it is adequately necessary to build an interrelation between the microcosmic structure and the macroscopic property of the molecular salt system.

References

[1] J. H. Li, W. J. Huang, T. Xu, S. R. Kirk and S. Jenkins, *Int. J. Quantum Chem.*, 2018, e25847.
[2] R. G. Parr, P. W. Ayers and R. F. Nalewajski, *J. Phys. Chem. A*, 2005, **109**, 3957-3959.
[3] S. Emamian, T. Lu, H. Kruse and H. Emamian, *J. Comput. Chem.*, 2019, **40**, 2868-2881.

Section 2. Supplementary table

Table S1 Main FT-IR bands (cm^{-1}) for FYT, PCA and molecular salt FYT-PCA.

FYT	PCA	FYT-PCA	Assignment
3133	-	-	ν(NH)
-	-	3179	$\nu(NH^+)$
3406	-	3410	$\nu(NH_2)$
1687	-	1730	ν(C=O)
-	1683	-	ν(COOH)
-	-	1539	$\nu_{as}(COO^-)$
-	-	1364	$\nu_s(COO^-)$
-	3332	3291	ν(-OH)
1338	-	-	ν(-N=C-)

Section 2. Supplementary figures

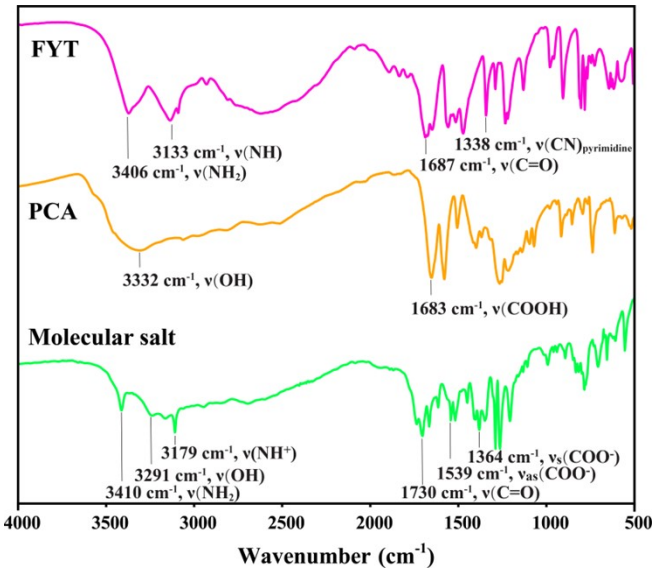

Fig. S1 FT-IR spectra of FYT, PCA and molecular salt FYT-PCA.

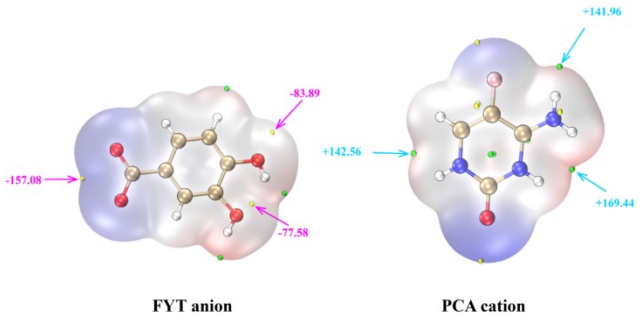

Fig. S2 The MEP draws for FYT and PCA ions, where the yellow and green balls represent the L_{max} and L_{min} points, and mark their corresponding quantitative values indicated by the arrow. The unit is in kcal·mol^{-1}.

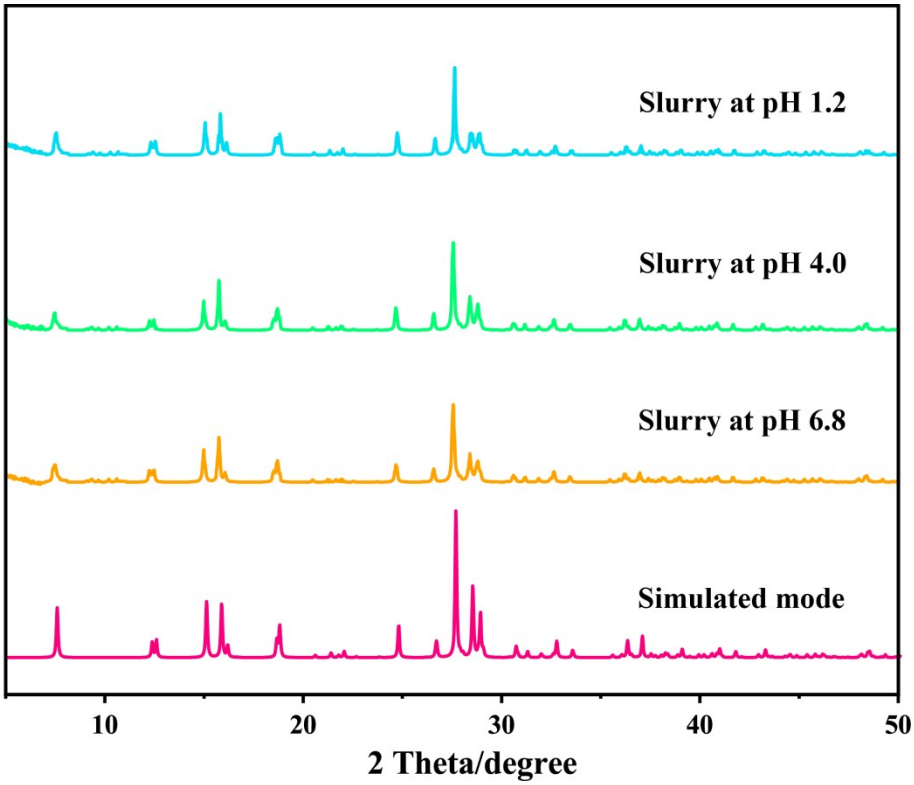

Fig. S3 PXRD comparison of the molecular salt's simulated pattern and the residual solids after the powder dissolution measurements.

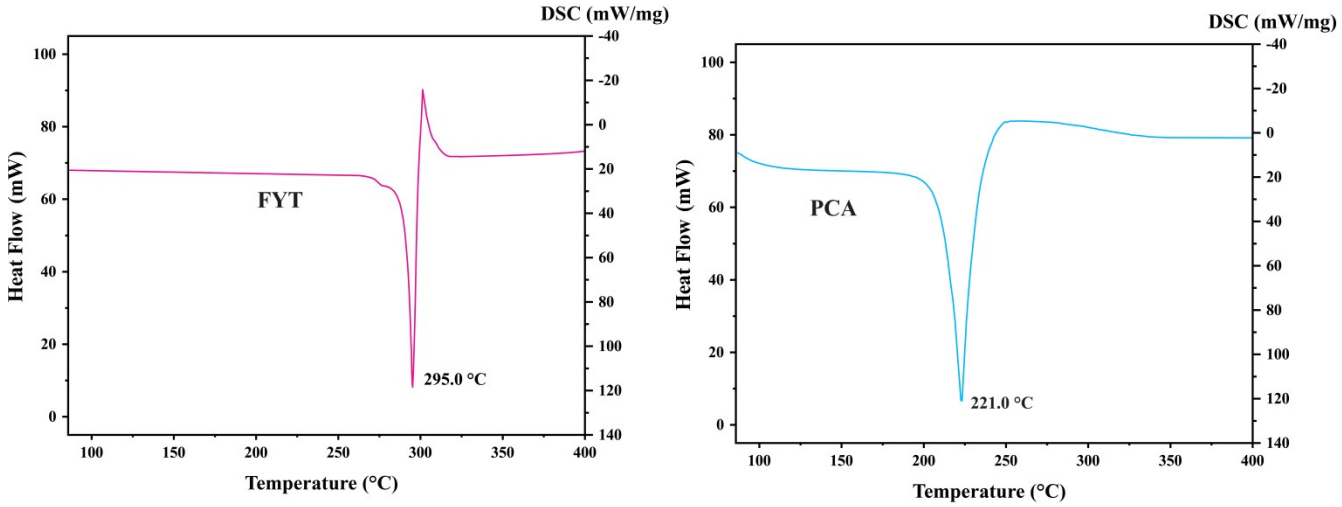

Fig. S4 The DSC curves of FYT and PCA raw material.