Polymorphism In 2,6-Dihydroxy And 2,6-Dimethoxy Benzoic Acids

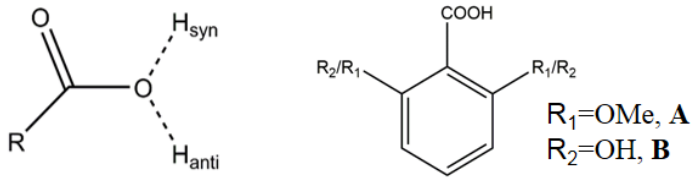
Rumpa Pal,[1] Dylan Jayatilaka,[2] Christian Jelsch,[3] Boris J. Nachtsheim,[1] M. Mangir Murshed,[1] Lorraine A. Malaspina,[1] Alison Edwards,[4] Simon Grabowsky[1]

[1]*University of Bremen, Department 2: Biology/ Chemistry, Bremen, Germany,* [2]*School of Molecular Sciences, The University of Western Australia, Crawley 6009, Australia,* [3]*CRM2, CNRS, Université de Lorraine, Faculte des Sciences et Technologies, Nancy, France,* [4]*Bragg Institute, Australian Nuclear Science and Technology Organisation, Lucas Heights, Australia*

e-mail: rpal @uni-bremen.de

Organic molecules, such as pharmaceuticals, agro-chemicals and pigments exist in several crystallographic forms, known as polymorphs.[1] Due to either change in molecular conformations or 3-dimensional crystal packing in different forms, these polymorphs exhibit entirely different physicochemical properties. Many active pharmaceutical ingredients (APIs) contain carboxylic acid groups and the packing modes of carboxylic acids are one of the most heavily studied systems in crystal engineering.[2]

In a systematic study of *syn vs. anti* carboxylic acids (see Figure 1a) in –OH and –OMe substituted benzoic acid derivatives, we have encountered new polymorphic forms in 2,6-dimethoxy benzoic acid, A, (see Figure 1b). It has previously been reported to be present in both *syn* and *anti* COOH conformation.[3,4] In this study, we have obtained a new *syn* form and a salt formation while attempting to obtain the reported *syn* form from a 1:1 mixture with phenylboronic acid from DMF solution. These polymorphs differ in molecular geometry and 3-dimensional packing arrangements. Along with X-ray diffraction, single crystal neutron diffraction experiments have been carried out to locate the acidic proton accurately. Since not all the forms could be grown as large crystals prerequisite for neutron diffraction, solid state Raman spectroscopic measurements[5] have been performed to investigate the local structure and differences in *syn* and *anti* COOH groups.



(a) (b)

Figure. 1(a) *Syn* and *anti* H Atom Positions in Carboxylic Acids Relative to the Carbonyl Oxygen Atom, (b) model systems

In a CSD database search we see another widely used API, 2,6-dihydroxybenzoic acid, B (see Figure 1b), also exhibits polymorphism having *syn* and *anti* COOH conformations.[6] However, the gas phase and solid state stability reveal that in the gas phase, the *syn* form is more stable in both the compounds, A and B, whereas cohesive energy calculations using the CRYSTAL14 package and in CE model energies using the program CrystalExplorer shows that,

in the crystal phase the stability order gets reversed: the, *anti* form becomes more stable in A, but *syn* remains more stable in B.

Furthermore, the stereochemistry of the lone pair orientations on the oxygen atoms and as well as the H-bond directionalities have been correlated through various chemical bond descriptors,[7] topological parameters at the bond critical points according to Quantum Theory of Atoms in Molecules (QTAIM), natural bond orbital (NBO) descriptors and electron localization methods.

References

1. Bernstein, J. Polymorphism in molecular crystals. Oxford University Press, **2002**, 14.

2. Das, D. ; Desiraju, G. R. *Chem. Asian. J.* **2006**, 1, 231-244.

3. Bryan, R. F.; White, D. H. *Acta Cryst. B* **1982**, 38, 1014-1016.

4. Portalone, G. *Acta Cryst. E* **2011**, 67, o3394 -o3395.

5. Ayala, A. P.; Caetano, M. W. C.; Honorato, S. B.; Filho, J. M.; Siesler, H. W.; Faudone, S. N.; Cuffini, S. L.; Martins, F. T.; Silva, C. C. P. D.; Ellena, J. *J. Raman Spectrosc.*, **2012**, 43, 263-272.

6. Gdaniec, M.; Gilski, M.; Denisov, G. S. *Acta Cryst. C*, **1994**, 50, 1622.

7. Pal, R.; Reddy, M. B. M.; Dinesh, B.; Venkatesha, M. A.; Grabowsky, S.; Jelsch, C.; Row, T. N. G. *J. Phys. Chem. A*, **2018**, 122, 3665-3679.