Keywords: Ranella Olerea , mollusc shell, combined analysis.

MS15. Structure property relationships

Chairs: Kari Rissanen, Martin Bremholm

MS15-P1 Crystal Math – When numerical algorithms meet black magic

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Determining the three-dimensional structure of small drug-like molecules is an inevitable process in the design of novel potential drugs in both the industrial as well as the academic domain. The most commonly used method is structure determination by X-ray diffraction, which requires either crystalline powder or a tightly packed single crystal of a compound. When it comes to growing the latter, the optimal conditions differ from case to case and are usually determined by a chemist's experience combined with a practical trial-and-error approach. For our in-house structure elucidation service, we have devised a standard procedure of subsequent crystallization experiments that every compound undergoes. The results from these standardized experiments are stored in an Oracle database accessible via a graphical user interface and have been recorded for the past four years.

In order to further increase our understanding of the conditions and the process of crystallization by solvent evaporation, we conducted several statistical analyses on the abovementioned crystallization database. This includes a first assessment and substitutions of the solvents used in the standard experiments, as well as statistical correlation analysis of compound similarity, solubility and crystallinity, based on molecular fingerprints. Identified correlations in the database were then used to guide rational machine learning approaches.

Machine learning is a collective term for numerous algorithmic approaches that can be used to find regularities and correlations in multi-dimensional data, premised on mathematical models[1]. These models can subsequently be used for classification or predicting properties of previously unknown data points. Applications in pharmaceutical research divisions worldwide include the prediction of a drug's activity, side effects, metabolism and physicochemical properties such as solubility, melting points or transmembrane permeability. However, only few approaches have attempted to amalgamate machine learning techniques with predicting small molecule crystallization[2,3].

We present here preliminary results of our efforts to build a machine learning model that is able to distinguish whether a compound will form a crystal under certain conditions. Our aim is to train this model on our in-house data and then use it to predict optimal crystallization conditions for previously unseen compounds.

Keywords: crystallisation, statistical analysis, crystallisation database, machine learning

MS15-P2 Substituent effects in nitro derivatives of carbazole investigated by XRD studies and DFT calculations

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Carbazole and its derivatives have attracted significant attention owing to their applications in pharmacy. These compounds are considered also to be potential candidates for electronic applications such as colour displays, organic semiconductors, laser and solar cells as they demonstrate electroactivity and luminenscence. In the last years, cross-linked polycarbazole have been widely employed as electron donors in materials for organo-electronic applications as organic light emitting diodes (OLEDs) [1]. The crystal structure of 9*H*-carbazole (I, Fig. 1a), has been re-determined at low temperature for use as a reference structure in a comparative study with the structures of 1-nitro-9*H*-carbazole (II, Fig. 1b), and 9-nitrocarbazole (III, Fig. 1c). All three solid-state structures are slightly nonplanar, the dihedral angles between the planes of the arene and pyrrole rings ranking from 0.40(7)° in (III) to 1.8(2)° in (II). Nevertheless, a density functional theory (DFT) study predicts completely planar conformations for the isolated molecules. To estimate the influence of nitro-group substitution on aromaticity, the HOMA (Harmonic Oscillator Model of Aromaticity) [2,3] descriptor of π-electron delocalization has been calculated. The HOMA indices for the isolated and solid-state molecules are relatively consistent and decrease in value for aromatic rings that are substituted with a π-electron-withdrawing nitro group. Substitution of the arene ring influences the π-electron delocalization in the ring only weakly, showing strong resistance to a perturbation of its geometry, contrary to what is observed for nitro substitution of the five-membered heterocyclic pyrrole ring. In (II), the molecules are arranged in near-planar dimers connected to each other by strong N-HO hydrogen bonds that stack parallel to the crystallographic *b* axis. A similar stacking arrangement is observed in (III), although here the stacked structure is formed by stand-alone molecules [4]. References: [1] Shirota Y, Kageyama H, (2007) Chem. Rev. 107, 953–1010 [2] Krygowski TM (1993) J. Chem. Inf. Comput. Sci. 33, 70-78 [3] Krygowski TM, Cyrański MK (1996) Tetrahedron 52, 10255-10264 [4] Gajda K, Zarychta B, Kopka K, Daszkiewicz Z, Ejsmont K (2014) *Acta Cryst.* C70, 987-991.

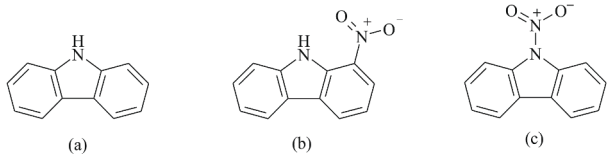

Figure 1. The chemical schemes of nitro derivatives of carbazole

Keywords: carbazole, substituent effect, DFT calaculations, HOMA index