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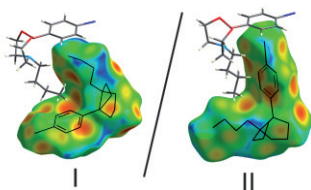
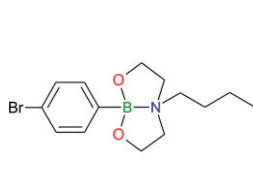
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Polymorphism of a model arylboronic azaester – combined experimental and computational studies

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Arylboronic acids and their esters are very important reagents in synthetic chemistry and in medicine. Protection of boronic acids with appropriate diethanolamines leads to so-called azaesters, and enables their further functionalization. Azaesters of arylboronic acids exhibit anti-cancer, anti-hyperlipidemic, anti-inflammatory and anti-neoplastic activities. Recently azaesters of arylboronic acids were found to show anti-microbial activity against *Streptococcus mutants* mainly responsible for tooth decay.



We have performed combined ¹³C CP/MAS solid-state NMR, single-crystal X-ray diffraction and theoretical studies of two polymorphic structures of model arylboronic azaester (form **I** and **II**). It has been shown that the crystallization conditions determine the phase which is formed. Clear differences are visible in the solid-state NMR spectra, where the chemical shifts for the carbon atoms of form **I** are systematically shifted to higher frequency values, in comparison to form **II**. This can be correlated with the overall crystal field strength suggesting that structure **I** is more compact. This is confirmed by the X-ray diffraction results including crystal structure analysis (packing and Hirshfeld surfaces). Molecular geometries of both forms are fairly similar. Some discrepancies have been found in the conformations of the bicyclic moieties, especially for the lengths of the B–N bonds. The most striking differences between the molecules of different polymorphic forms are observed in Hirshfeld surfaces and fingerprint plots. Thermal-expansion tensor and multi-temperature unit-cell X-ray analysis show significant differences between the forms **I** and **II**. This is especially clear when comparing the thermal expansion of crystals in different crystal directions. Our analysis of molecular dipole moments in crystals provides a clear picture of differences for both polymorphs, however, according to computations the dispersion contributions play a very important role. Theoretical calculations, using *PLXEL* and *CRYSTAL09* programs, are in perfect agreement. They show that the proper handling of the dispersion correction is extremely important for molecular crystals. Calculated lattice energies suggest that the form **I** is slightly more stable than the form **II**. This is also reflected in the crystallization kinetics and melting point temperatures. The higher lattice energy in form **II** seems to be partially compensated by the lower conformational energy of the independent molecules in this form.

[1] K. Durka, A.A. Hoser, R. Kamiński, S. Luliński, J. Serwatowski, W. Koźmiński, K. Woźniak, *Cryst. Growth&Design*, **2011**, accepted.

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Crystal structure of the drug diethylcarbamazine and a new maleate salt

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The Drugs for Neglected Diseases Initiative (DNDi) was created to improve the quality of life for people affected by disease such as lymphatic filariasis (LF). Although the drugs used to treat this disease were developed long ago, little is known about their mechanisms of action. Diethylcarbamazine (DEC-CIT) citrate is one of the most widely used drugs in the treatment of LF. However, very little information about its solid-state characteristics can be found in the literature^[1–3]. In a previous study we crystallized and analyzed DEC-CIT by thermal methods, vibrational and X-ray diffraction, revealing three phase transitions at low temperatures, resulting in changes in its molecular structure^[4]. In the current study, we crystallized and analyzed the solid state properties of DEC in its pure form and in a new salt form with maleic acid, in order to establish relationships concerning their behavior under different molecular crystals arrangements.

DEC crystallizes in the monoclinic space group $P2_1/n$ with four molecules per unit cell. The pattern of molecular interactions is composed only of weak interactions of types C–H...O and C–H...N, forming trimers, unlike what occurs for the citrate salt (DEC-CIT), where citrate molecules form strong bonds with the drug molecules and each other. These weak interactions result in a low density arrangement, which dissolves as the temperature increases. Studies of single crystal X-ray diffraction at different temperatures showed the absence of phase transitions. Above 250K the crystal diffraction stops due to a slow amorphization process that leads to a loss of crystallinity, and evolves into a completely amorphous state at room temperature. DSC experiments confirmed the fusion of DEC around 320K, while the one for DEC-CIT was around 410K. IR and Raman spectra were recorded and were consistent with the structural features shown by DSC.

Diethylcarbamazine maleate (DEC-M) crystallizes in the triclinic space group $P-1$ with two very similar conformations of DEC molecule and two molecules of maleic acid per asymmetric unit. In this new salt, we observed a *cis* conformation for both ethyl chains of the DEC molecules at room temperature. This conformation was only observed in DEC-CIT under 100K, and are *anti* related in the other structures. The crystal structure is stabilized by N–H...O interactions between the DEC and maleic acid molecules. Besides these interactions, there is a complex network of C–H...O interactions, which stabilize the compound in a sandwich-like arrangement, interspersed with layers of DEC over bilayers of maleic acid. This new arrangement keeps the compound stable at room temperature. Studies as function of temperature by DSC, IR and Raman spectroscopy confirmed the absence of phase transitions as observed for DEC-CIT. Although solubility tests are still necessary, it is believed that the new crystal packing releases DEC molecules more quickly in solution, making this new compound a strong candidate for active pharmaceutical ingredient (API), while the weak interactions and low melting point disqualify the DEC in its pure form as an API.

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