MS40-03 **A Computational Investigation of the Polymorphophore Concept** Ogaga G. Uzoh[a], Aurora J. Cruz-Cabeza[b] and Sarah L. Price[a] [a]*Chemistry Department, University College London, UK*[b]*Van 't Hoff Institute for Molecular Sciences, University of Amsterdam, The Netherlands*
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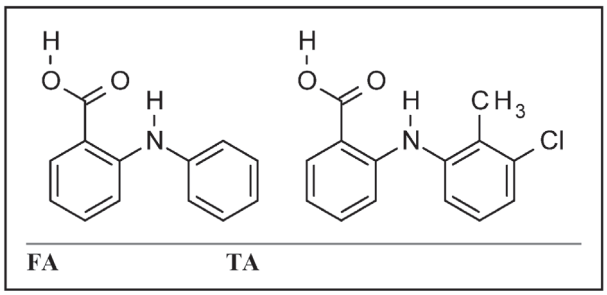
A polymorphophoreis a structural element that, when incorporated into a molecule, favors the observation of polymorphs. The extensive polymorphism observed for the fenamates as well as ROY andcarbamazepine derivatives has been attributed to their main molecularskeleton being a polymorphophore.Despite this, verylittle is understood as to whycertain molecular fragments may favour polymorphism.



We studied why the fenamate fragment appears to be a polymorphophore by contrasting the crystal energy landscapesof fenamic acid (FA) with its derivativetolfenamic acid (TA). TA is a well-studied non-steroidal anti-inflammatory drug and has five known polymorphs with varying Z? .Is the observation of only one form of FA due to insufficient screening (FA is not a drug molecule unlike TA)? The computed crystal energy landscapes for TA and FA revealedthat there are more crystal structures clustered around the global minimum for TA than for FA [5].Since the hypothetical crystal structures generated for FA are very similar to the known forms of TA and those of other fenamates, the difference in the observed polymorphismis due to thefine balance between the intermolecular and intramolecular energies. The difference in the relative energies of the crystal structures is due to the substituents on the fenamate core, but the hydrogen bonded dimer of the fenamate molecules can pack well in a wide range of structures with different conformations.

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Keywords: polymorphophore; crystal structure prediction; polymorphism

MS40-04 **A novel approach to crystal structure determination for organic compounds.** Mark D. Eddleston,[a] Katarzyna E. Hejczyk,[a] Erica G. Bithell,[a] Graeme M. Day[a] and W. Jones,[a] [a]*University of Cambridge, UK*
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A new approach to crystal structure determination for molecular compounds, combining crystal structure prediction and transmission electron microscopy (TEM), has been developed for use with samples which are not suitable for conventional single crystal or powder X-ray diffraction approaches. This crystal structure determination method requires a small number (1 to 3) of experimental electron diffraction patterns to be recorded from a sample, which are then used to identify the corresponding crystal structure from a calculated set of potential low energy crystal structures generated from a global search for structures on the lattice energy surface. Critically, it is possible to obtain these electron diffraction patterns from one crystallite with sub-micron or even nano-sized dimensions, and before significant sample deterioration occurs in the electron beam [1]. This methodology was used to identify a novel crystal phase of the pharmaceutical compound theophylline. The crystal structure of this new polymorph was determined from TEM analysis of a single crystallite with an approximate mass of 3 pg and despite this phase occurring as a minor component in a mixture with a second crystal form of theophylline at an estimated concentration of less than 0.1 %w/w, a value below the limits of detection of analytical methods routinely used for pharmaceutical characterisation.

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Keywords: crystal structure determination; transmission electron microscopy; crystal structure prediction