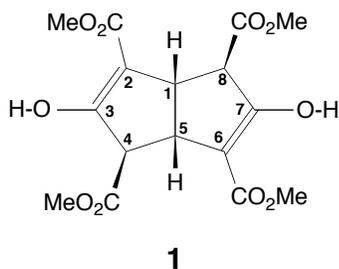


Awkward Shape and the Prediction of Potential Host Molecules?

Roger Bishop, Jiabin Gao and Mohan M. Bhadbhade
School of Chemistry, The University of New South Wales, Sydney, Australia
r.bishop@unsw.edu.au

Many researchers working on clathrate compounds have commented that this inclusion phenomenon is associated with the presence of awkwardly shaped host molecules. In other words, these molecules cannot pack efficiently in a crystal just by themselves and complementary guest molecules are included to achieve higher density and greater packing coefficient values. This behaviour is common, for example, in crystal structures of proteins: though this characteristic is generally played down in light of the much more significant protein molecule information. Amongst low molecular weight hosts, arguably the best exploitation of molecular awkwardness has been that by Edwin Weber in his comprehensive studies into compounds containing multi-aromatic rings.¹ These rings may be combined in a molecule using both edge-edge and edge-face geometries to produce crosswise, V-shape, T-shape, and many other molecular arrangements. Furthermore, functional groups such as triarylmethane provide wheel or propeller geometries. Combination of these various structural elements has provided a huge range of new moderately complex clathrand hosts.

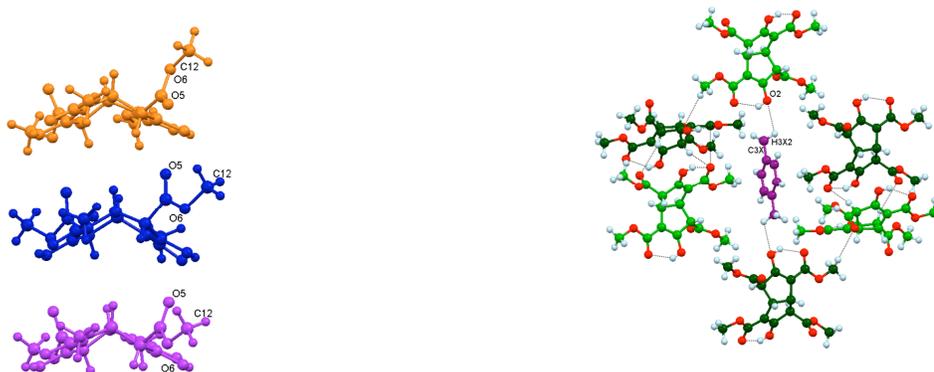
“Molecular awkwardness” is, however, a very ill defined term. Can we recognise this characteristic in very simple organic molecules? To what extent can we, consequently, predict clathrate behaviour for entirely new potential host molecules? Will awkwardness more widely encourage the formation of multiple crystal forms – such as polymorphs, clathrates, hydrates, and hydrogen-bonded cocrystals? This presentation will report on several simple derivatives of the bicyclo[3.3.0]octane ring system in this regard. Just one of these test compounds, the tetraester **1**, is discussed in this abstract.



Crystals of racemic **1** grown from methanol² or acetone³ at room temperature gave identical crystals that were free of solvent in the monoclinic space group $P2_1/n$. The molecule adopts a shape like a shallow dish with a handle. Two molecules of tetraester **1** associate, concave face to concave face, by means of C-H...O weak hydrogen bonding to produce a centrosymmetric double dish unit as illustrated. Repetition of these units generates the net crystal structure. Dishes would normally be expected to pack in a

concave face to convex face manner, and the failure of **1** to do so creates a repeat unit that packs inefficiently with its neighbours.

We therefore identified **1** as an “awkward molecule” and predicted that other crystal forms, very likely involving inclusion behaviour, would be possible. This hypothesis was quickly demonstrated to be correct. Crystallisation from methanol at 0°C yielded a second solvent-free polymorph, this time in the triclinic space group $P\bar{1}$. Furthermore, crystallisation at room temperature from approximately half of the solvents tested produced a family of essentially isostructural clathrate compounds, (host)₂.(guest), in the monoclinic space group $P2_1/c$.⁴



These three crystal forms are accompanied by conformational change in just one of the four ester groups: original structure (brown), low temperature structure (blue), and inclusion structure (magenta). The latter two conformations no longer permit the original concave face to concave face association. The inclusion crystal form contains voids with a roughly rectangular cross-section (*ca.* 6.5 x 8.5 Å) in which the guest molecules reside – as illustrated here for (1)₂.(*p*-xylene). Atom code: O red, H light blue, host C green (opposite enantiomers light or dark), guest C purple.

Identification of the tetraester **1** as an awkward molecule was determined from its published crystal structure, and then successful prediction was made of its inclusion host behaviour. In turn, this allowed us to identify *why* **1** was prone to packing in a concave face to concave face manner in the first place. This knowledge was then applied to identification of other awkward bicyclo[3.3.0]octane derivatives – these conclusions now being based solely on their molecular structures. These additional compounds, which similarly have a strong tendency to produce multiple crystal forms and also to act as inclusion hosts, will be discussed in the oral presentation.

1. Weber E. *Comprehensive Supramolecular Chemistry*, **6**, 535-592 (1996).
2. Djaidi D. *Ph. D. Thesis, University of New South Wales* (2006).
3. Vega A., Donoso-Tauda O., Ibañez A., Escobar C.A. *Acta Crystallogr.*, **E64**, o199 (2008).
4. Gao J., Bhadbhade M. M., Bishop R. *CrystEngComm*, manuscript submitted (2011).