Polymorphism

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Combinatorial Crystal Synthesis: Structural Landscape of Phloroglucinol:1,2-bis(4-pyridyl)ethylene and Phloroglucinol:Phenazine**

*Ritesh Dubey and Gautam R. Desiraju**

Abstract: *A large number of crystal forms, polymorphs and pseudopolymorphs, have been isolated in the phloroglucinol-dipyridylethylene (PGL:DPE) and phloroglucinol-phenazine (PGL:PHE) systems. An understanding of the intermolecular interactions and synthon preferences in these binary systems enables one to design a ternary molecular solid that consists of PGL, PHE, and DPE, and also others where DPE is replaced by other heterocycles. Clean isolation of these ternary cocrystals demonstrates synthon amplification during crystallization. These results point to the lesser likelihood of polymorphism in multicomponent crystals compared to single-component crystals. The appearance of several crystal forms during crystallization of a multicomponent system can be viewed as combinatorial crystal synthesis with synthon selection from a solution library. The resulting polymorphs and pseudopolymorphs that are obtained constitute a crystal structure landscape.*

It is only recently that polymorphism in cocrystals has been systematically observed and recorded.[1] The nature of this polymorphism has also been analyzed in terms of heterosynthon formation,[2] the so-called synthon polymorphism.[3] If one considers the crystal as a supramolecular entity,[4] one may think of the crystallization of cocrystal polymorphs as combinatorial crystal synthesis from a library of supramolecular synthons in solution.[5] We herein illustrate this with reference to the binary systems of phloroglucinol (PGL) with the bases 1,2-bis(4-pyridyl)ethylene (DPE) and phenazine (PHE). This is extended to the logic-driven synthesis of ternary cocrystals based on PGL. Closely allied to such a theme is the notion of a crystal structure landscape,[6] which is a set of low-energy crystal structures of polymorphs and pseudopolymorphs (structures formed in the late stages of crystallization) and their energy relationships.[7] A landscape may also be taken as a library of crystal structures.[8] If crystallization is considered as a supramolecular reaction, there could be a link between synthons in solution and the polymorphic crystal structures that are obtained, although crystallization takes place under supersaturated conditions that could be far from equilibrium.[9]

The appearance of several crystal forms, namely polymorphs and pseudopolymorphs, in cocrystallization experiments of polyhydric phenols with heterocyclic bases is well-documented.[10] We have previously described the landscape of the orcinol:4,4′-bipyridine (ORC:BP) cocrystal.[11] There are five crystal forms that are distinguished by different topologies of the O−H⋯N hydrogen bonds in the representative supramolecular synthons, the chain **A** and the closed tetramer **B** (Figure 1). Only form I contains synthon **A**. Forms II–V have different packing arrangements of the zero-dimensional synthon **B** in their crystal structures and effectively represent a traversing of the landscape. In this study, we examined the PGL:DPE and PGL:PHE systems and found that they are related to ORC:BP. Figure 2 shows that the chain and the tetramer persist, thus showing structural modularity. However, there are some differences in the hydrogen bonding and stacking because PGL has three OH groups, while ORC has only two, and the heterocycles DPE and PHE have a better stacking ability than BP. These factors provide increased competition and interplay between hydrogen-bonded and stacking synthons in PGL:DPE and PGL:PHE, and this possibly results in a greater prevalence of polymorphism.

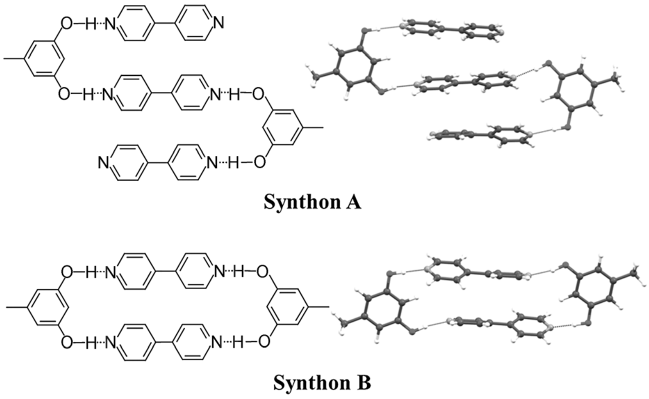

Figure 1. Supramolecular synthons chain **A** and tetramer **B** in the ORC:BP system.

Figure 2 is a schematic representation of the synthons that lead to the crystal forms in PGL:DPE. We were able to isolate six crystal forms: two anhydrates, a dihydrate, a hexahydrate, a methanolate, and a formamide solvate (Figure 3). All six forms are characterized by either or both the chain (**A**) and

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[*] R. Dubey, Prof. G. R. Desiraju
Solid State and Structural Chemistry Unit
Indian Institute of Science
Bangalore 560 012 (India)

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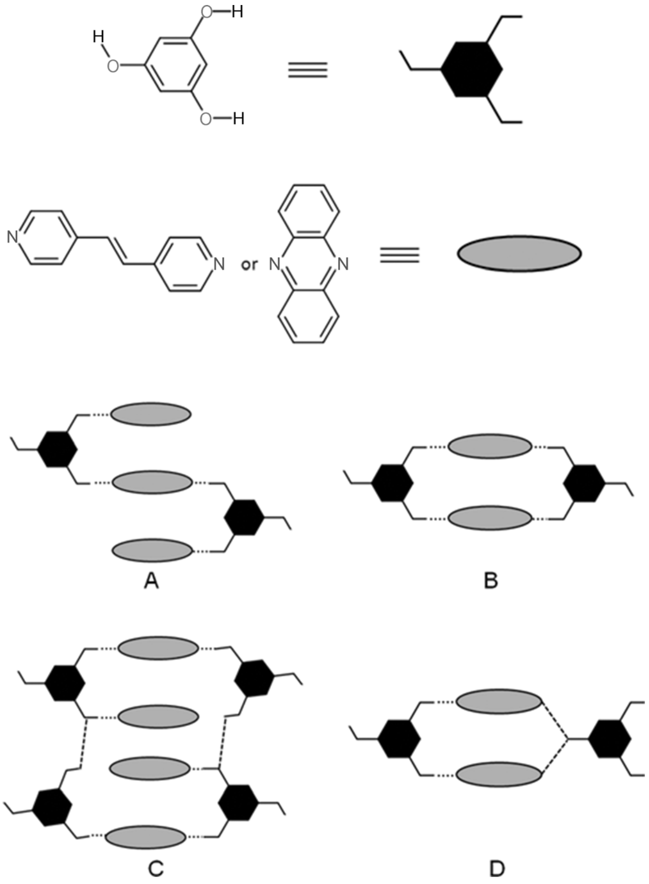

Figure 2. Supramolecular synthons in the PGL:DPE and PGL:PHE systems. Synthons **A**–**D** all have extra hydrogen-bonding capability, relative to ORC:BP, through their "hook" OH groups. Synthons **A** and **B** are analogous to those in ORC:BP, thus showing structural modularity. Synthons **C** and **D** are found in PGL:PHE, but not in ORC:BP and PGL:DPE.

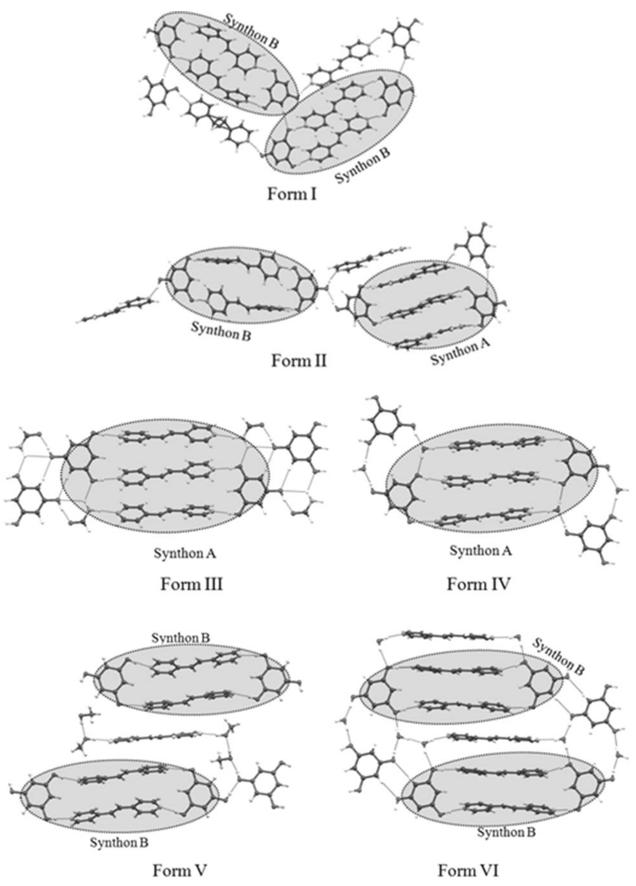

Figure 3. Crystal forms in the PGL:DPE system. The gray ellipses highlight the preferred supramolecular synthons.

the closed tetramer (**B**). It may be noted that while there is an extra hydrogen-bonding donor functionality here compared to ORC:BP, the structural modularity[12] is not compromised, in that equivalents of synthons **A** and **B** are also present here. All the forms have a close correspondence to structures in the ORC:BP family, but the additional hydroxy group provides a "hook" for further structural development. This third hydroxy group invariably links to another molecule of the heterocycle to generate a two-dimensional network. In the 2:3 anhydrate (form I), synthon **B** is connected through its hooks to a third DPE molecule so that the overall stoichiometry is 2:3. Curiously, different segments of the structure are ordered and disordered, as has been observed in other metastable kinetic structures.[13] In the 4:5 anhydrate (form II), the hook hydroxy group in synthon **B** donates a hydrogen bond to a linker DPE, as in form I, but additionally accepts a hook hydroxy group from another synthon **A** module to form an O–H···O hydrogen bond. This admixture of structural domains suggests a combinatorial selection from a library of synthons in solution.

The other PGL:DPE forms are pseudopolymorphic. Form III has a 2:3 stoichiometry and is a formamide solvate; a chain synthon **A** module consisting of two PGL molecules and three DPE molecules is capped at both ends by N–H···N hydrogen bonds from formamide. This capping role is played by water in the 2:3 dihydrate, form IV. Form V with 4:5 stoichiometry is based on synthon **B** and shows capping by O–H···N hydrogen bonds from methanol. In the hexahydrate (form VI), four hook hydroxy groups from two synthon **B** modules are stitched together with water into an intricate pattern of cooperative O–H···O and C–H···O bonds.

We now discuss the phloroglucinol-phenazine system (PGL:PHE). This consists of seven crystal forms, four of which (I, II, III, IV) have been previously reported,[14] and the other three of which (V, VI, VII) are reported herein. These new forms are illustrated in Figure 4. All the forms may be rationalized in terms of a combinatorial synthon library. Figure 5 is a schematic representation of the seven structures. Forms I and V are closely related: they are anhydrates and have 2:3 stoichiometry. Both are constituted with chain synthon **A** consisting of two PGL and three PHE molecules capped with the hook hydroxy group of an adjacent synthon **A** module. Forms II, VI, and VII are built with tetramer synthon **B**. Form VII is a simple linking of synthon **B** modules with a third PHE molecule and resembles form I of PGL:DPE. In forms II and VI, the extra hydrogen-bond functionalities (hook hydroxy group, N atom) are capped with solvent. Synthon **C** may be considered as arising from two **B** synthons. It is expressed in form III with a 4:7 stoichiometry,

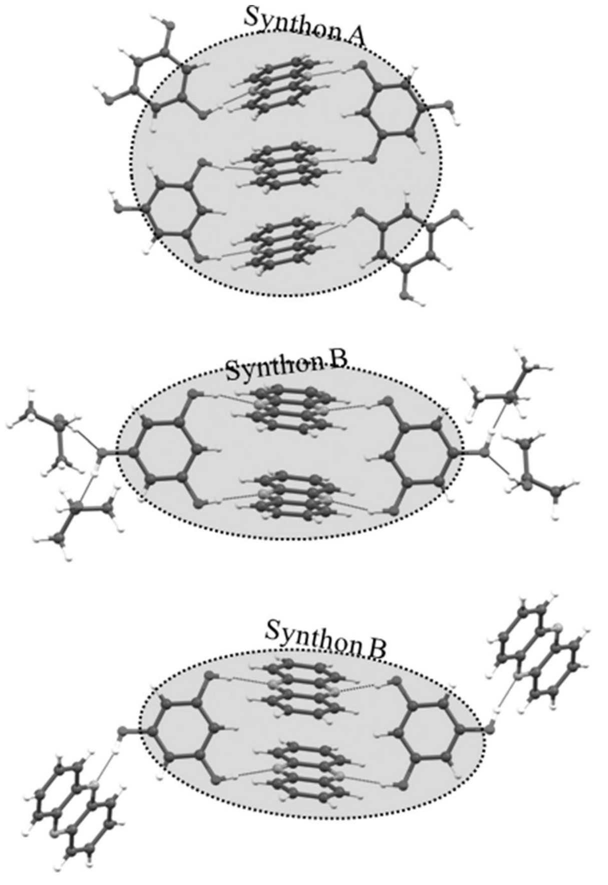

Figure 4. Crystal forms V–VII in the PGL:PHE system. The gray ellipses highlight the preferred supramolecular synthons.

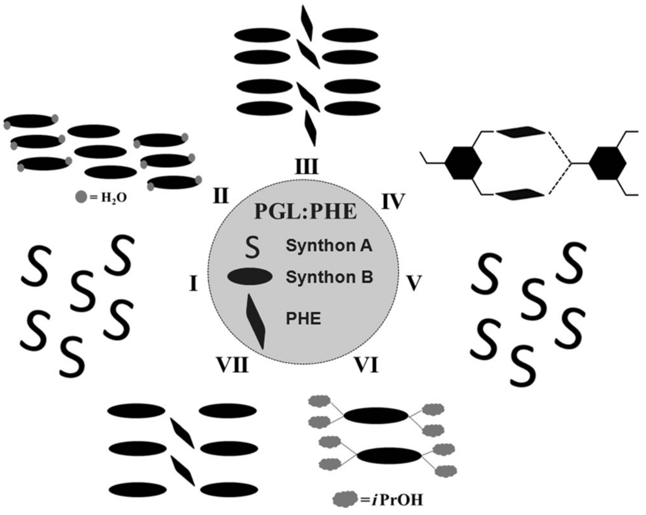

Figure 5. Schematic representation of seven crystal forms in the PGL:PHE system.

where the close approach of neighboring **B** modules causes bifurcation and a consequent lengthening of an O–H···N bond (d 2.892 Å; θ 151.71°) by the presence of an O–H···O bond, such that the latter interaction actually dominates (d 2.571 Å; θ 122.41°). Form IV is unusual, in that the hook hydroxy group is disordered across a mirror plane and behaves like a mimic of the 1,3-dihydroxy fragment of PGL itself (in its ability to act as a hydrogen bond donor), thus defining synthon **D**. Synthons **C** and **D** suggest the idea of synthon virtuality.[15] They may well be present in solution in the ORC:BP and PGL:DPE cases, but they do not show up in any of the isolated crystals under the present laboratory conditions. In effect, these synthons are isolated in PGL:PHE, but are virtual in ORC:BP and PGL:DPE (the crystallographic details of these crystal structures are given in the Supporting Information).

Using the knowledge obtained from the two binary landscapes above, we proceeded to the design of ternary solids, which is a challenging synthetic exercise in crystal engineering.[16] Statistical sampling of molecules has been used to make ternary solids. For example, if there are two related or isomorphous cocrystals ($A{:}B_1$ and $A{:}B_2$) in which the chemical nature of B_1 and B_2 are similar, then any system $A{:}\{(B_1)_x(B_2)_{1\text{-}x}\}$ would formally constitute a ternary solid. This has been noted by Nangia and co-workers in an acid–base system[17] and by MacGillivray and co-workers in a phenol–base system,[18] which is also closely related to the compounds in the present study. Whether these solids can be termed cocrystals or solid solutions is another question.[19] Making a stoichiometric ternary cocrystal from three substances that are all solids under ambient conditions is far more difficult and demands a good knowledge of the interaction preferences.[20] Given that both the PGL:DPE and PGL:PHE landscapes yield many stable crystal forms, the question is whether a good strategy to make a ternary cocrystal from these landscapes would be one which restricts the synthon possibilities during molecular recognition (geometrical based on shape and size, or chemical based on interactions and synthons) so as to cause convergence into a particular structure, which is both modular and robust.[21] In effect, the possibility of isolating one member of the crystal structure library (desired ternary solid) is sought to be amplified.

Forms I and II in the PGL:DPE system are the starting points in the crystal-engineering exercise. In both forms, there are regions in which the DPE molecule has a planar conformation and those where the DPE molecules are twisted (Figure 3). These regions are connected to each other through C–H···O and O–H···O bonds, respectively. In form I, both regions are composed of synthon **B**. In form II, there are **A** and **B** regions; the latter contains the twisted conformation of DPE. The very fact that there are so many crystal forms in the PGL:PHE system hints that there are regions of the crystal in which different interaction possibilities exist. If the design strategy for the ternary crystal removes this variability, the system could precisely select the most robust member of the synthon library, thereby resulting in structural convergence into a unique stoichiometric ternary cocrystal.

The essence of the strategy is shown in Figure 6. In both forms I and II of PGL:DPE, synthon **B** is connected with a heterocyclic linker which is identical to DPE itself. In forms II, VI, and VII of PGL:PHE, the heterocycles are stacked. PHE is a flat molecule and provides better stacking behavior than DPE. In our ternary design, we cocrystallized a 2:1:1 mixture of PGL, DPE, and PHE. We utilized this stacking feature of PHE and anticipated that synthon **B**

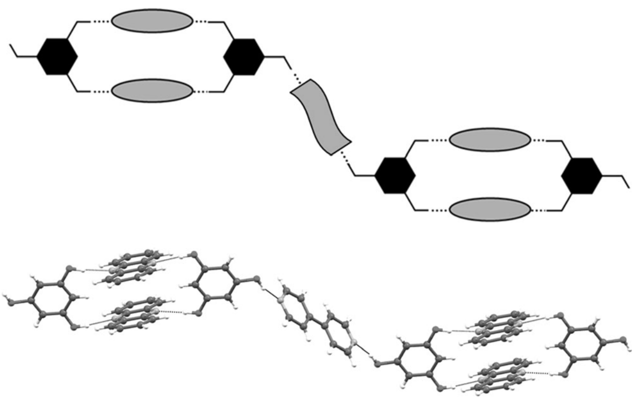

Figure 6. Schematic representation of the ternary cocrystals in this study. The same gray color but different shapes of the heterocycle coformers represent their synthon similarity and shape dissimilarity.

would be constituted with PGL and PHE, while the linking function would be taken over by DPE. Our expectation was justified, and we obtained a 2:2:1 stoichiometric solid in which there is no disorder and where the conformation of DPE is planar. This ternary solid predominates in the crystallized material. Clearly, the formation of a ternary moiety has removed some of the structural "confusion" that was inherent to the binary PGL:DPE solids (forms I and II) that led to convergence. Satisfyingly, the generality of this strategy was shown in the isolation of the corresponding stoichiometric ternary cocrystals in which 1,2-bis(4-pyridyl)ethane, 4,4′-azopyridine, and 4,4′-bipyridine replace DPE. The third component directs crystallization in a more precise manner. Some similarities exist in the idea of structural mimicry expressed many years ago by Jones et al.,[22] and more recently in the idea of pseudoseeding expressed by Friščić and MacGillivray.[23] The crystallographic details of the ternary solids are provided in the Supporting Information.

Several conclusions may be drawn from this study, and are likely to be of further interest: 1) The concept of a supramolecular combinatorial library[14] can be profitably extended to the crystallization process, with supramolecular synthons being the constituents of such a library. 2) This library is virtual both with respect to the molecular conformations selected in synthon construction (PGL is found in only one conformation in all the crystal structures described here) and with respect to more complex distorted synthons which manifest in the final crystal structure but are probably only of transient existence in solution (such as synthons **C** and **D** in PGL:PHE). 3) There are two libraries that need to be considered. The first is a synthon-based library in solution prior to nucleation. The second is a library of crystal structures that constitute the structural landscape. The results herein point to a causal relationship between these libraries, but more definitive conclusions will have to await experimental detection of the synthons in solution. 4) The formation of a specific ternary cocrystal in a system where there are many binary possibilities shows structural convergence during the binary → ternary progression, thereby hinting that such a convergence might also exist in the single-component → two-component progression, in other words that the likelihood of polymorphism is indeed less in cocrystals than in single-component crystals. 5) Polymorphs and pseudopolymorphs are actually much closer to each other in the context of crystallization, and the term "pseudopolymorph" is perhaps well justified. Both of them occur in the crystal structure landscape.

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