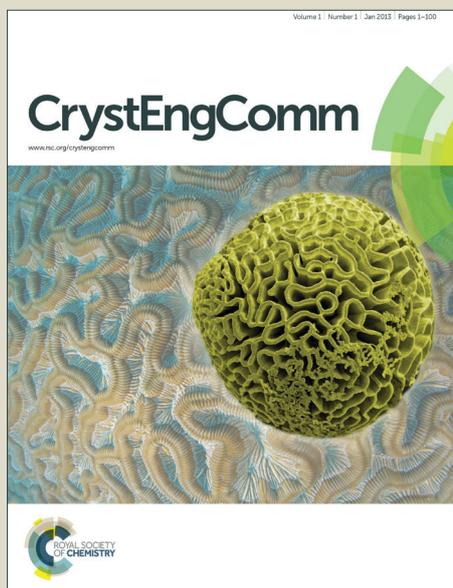


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Combinatorial crystal synthesis of ternary solids based on 2-methylresorcinol

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Cocrystallization experiments of 2-methylresorcinol with several N-bases were performed to identify selective and preferred crystallization routes in the relevant structural landscapes. These preferred supramolecular synthon based crystallization routes were further enhanced by using carefully chosen cofomer combinations to synthesize stoichiometric ternary solids. The exercise consists of modular selection and amplification of supramolecular synthons from single through two- to three-component molecular solids, and is equivalent to solid state combinatorial synthesis.

Alternative crystal packings for a given organic molecule can occur within say, a 2 kcal/mol energy window and include polymorphs,¹ pseudopolymorphs² and high Z' crystal structures,³ all of which together may be taken as a *crystal structure landscape* of a compound.⁴ The landscape is a manifestation of the presence of different crystallization routes and the real time isolation of multiple crystal forms is a consequence of this.⁵ We have shown that the concept of the landscape is equally well applicable to multi-component molecular crystals⁶ as it is to a single component crystal.^{7,8} A related idea pertains to whether or not cocrystal⁹ formation of a polymorphic substance decreases the likelihood of occurrence of polymorphism. This matter has been commented upon previously by Aakeröy et al.,¹⁰ Almarsson and Zaworotko,¹¹ and more recently by Dubey and Desiraju.¹² A two component crystal derived from a polymorphic substance may have a lesser tendency to be obtained in polymorphic forms and analogously, a three component crystal that is obtained from a polymorphic two component crystal would be even less likely to exist in multiple forms, in other words the formation of a higher component entity is a convergent process.¹² In an extension of this argument, this paper summarizes the further manipulation of modular supramolecular synthons¹³ in the landscape to isolate ternary molecular solids,¹⁴ an arguably difficult task in crystal engineering.

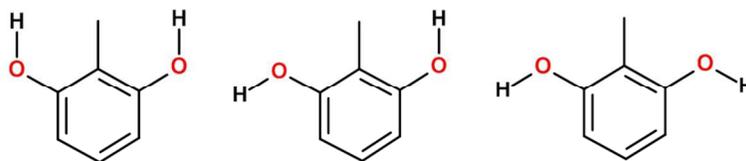


Fig. 1: Molecular conformations in 2-methylresorcinol, MRE: *syn-syn* (left), *syn-anti* (middle), and *anti-anti* (right). The relative stabilities of the three conformations are respectively 2.03, 0.10, and 0.00 kcal/mol.

2-Methylresorcinol (MRE) is the starting point in the present crystal engineering exercise. This crystal structure has $Z' = 3$ which is shown in Fig. 2. All the three molecules exist in the most stable *anti-anti* conformation. This crystal structure is held together with $\text{O-H}\cdots\text{O}$ hydrogen bonds and obviously MRE acts both as a hydrogen bond donor and acceptor in these interactions. These hydrogen bonds are not identical in their strength (Fig. 2). Whether or not this lack of interaction degeneracy is characteristic of low symmetry clusters in high Z' structures is a matter of conjecture and is not explored here. In the context of the present work, what is important is that it might be possible to exploit this lack of degeneracy in the bond metrics towards the synthesis of cocrystals. Appreciating the fact that many $\text{O-H}\cdots\text{N}$ hydrogen bonds are stronger than $\text{O-H}\cdots\text{O}$ bonds, and that accordingly phenol-pyridine cocrystals are formed easily,¹⁵ we undertook cocrystallization experiments of MRE with heterocyclic bases. We obtained 15 two-component and six three-component crystals, which are now described.

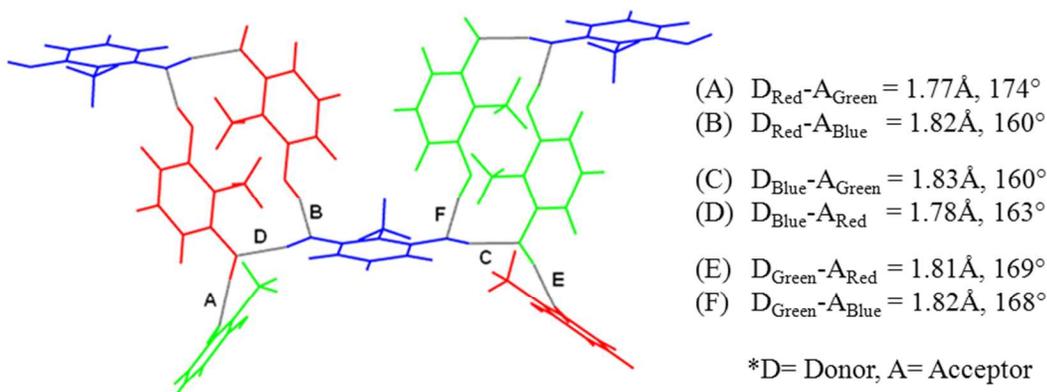


Fig. 2: 2-Methylresorcinol ($P2_1/n$, $Z'=3$) crystal structure to show six independent $\text{O-H}\cdots\text{O}$ hydrogen bonds. Color coding indicates symmetry independent molecules. All the molecules take the *anti-anti* conformation. Normalized metrics are given.

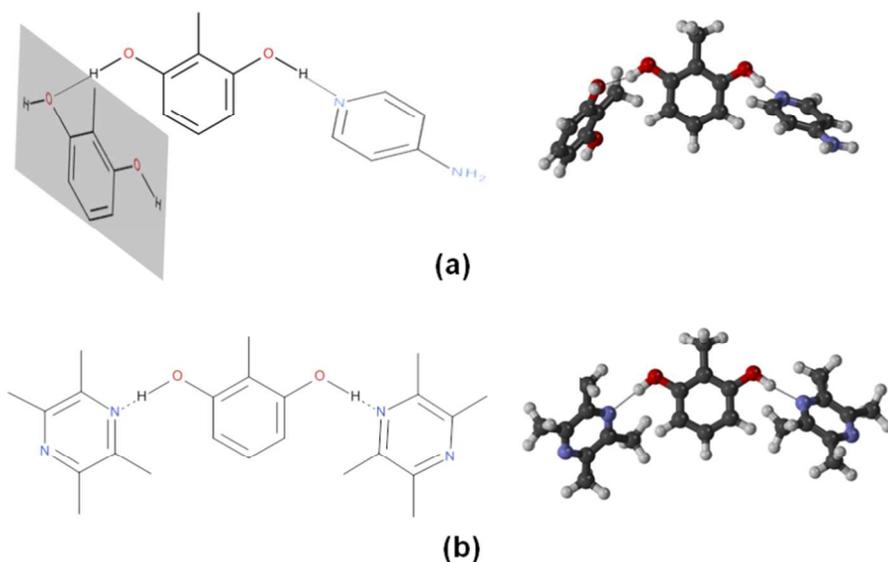


Fig. 3: Representative supramolecular synthons in binary MRE cocrystals. (a) Mixed O–H···O and O–H···N based synthon **A** in 1:1 MRE:4-aminopyridine cocrystal; (b) O–H···N based synthon **B** in 1:1 MRE:tetramethylpyrazine cocrystal.

Table 1: List of binary cocrystals in this study

Synthon A based		Synthon B based
4-Phenylpyridine (4AP)	2,2'-Bipyridine (22BP)	Tetramethylpyrazine (TMP)
Benzo[<i>h</i>]quinoline (BZQL)	1,10-Phenanthroline (110PHE)	4,4'-Azopyridine (44AP)
Acridine (ACR)	Phenazine (PHE)	1,2- <i>bis</i> (4-Pyridyl)ethylene (DPE-I)
Quinoxaline (QUXL)	2,3-Dimethylquinoxaline (DMQX)	1,2- <i>bis</i> (4-Pyridyl)ethane (DPE-II)
4-Aminopyridine (4AP)	4-Dimethylaminopyridine (4DMAP)	Acridine (ACR)

The cocrystal screen involved 14 heterobases and all of them gave binary solids with MRE. There are two possibilities for binary cocrystal formation and these are illustrated in Fig. 3 and Table 1. These hydrogen bonding arrangements in the cocrystals may be interpreted based on two individual supramolecular synthons (synthon **A** and synthon **B**); synthon **A** consists of two MRE molecules and one coformer molecule while synthon **B** contains one MRE molecule and two coformer molecules. The heterocyclic bases provide additional synthon possibilities in the prenucleation events and allow the selection of kinetically preferred O–H···N rather than O–H···O hydrogen bonds from the virtual synthon libraries in solution. These representative selections are illustrated by 4-aminopyridine (4AP) and tetramethylpyrazine (TMP) coformer based MRE cocrystals (Fig. 3). Both types of crystal structures are supported by auxiliary C–

H \cdots O, C–H \cdots N and C–H \cdots π interactions. The underlying theme is that the original O–H \cdots O hydrogen bonds in the parent crystal structure can be bypassed by incorporating competing O–H \cdots N hydrogen bonds. In the context of the *crystal structure landscape*, formation of the synthon **A** based structures is therefore significant because these structures lie somewhere in between the path selection between the native MRE structure (purely O–H \cdots O based) and the synthon **B** (purely O–H \cdots N based) cocrystals. Thus the path selection in synthon **A** (mixture of O–H \cdots O and O–H \cdots N) based cocrystals offers a hint about the accessibility of the possible hydrogen bonds and their distinctive combinations.

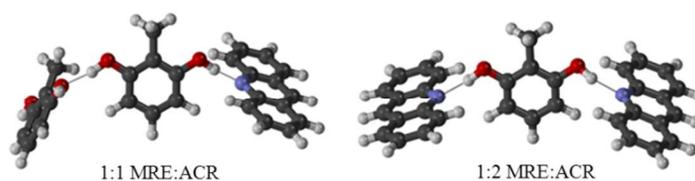


Fig. 4: Cocrystal polymorphism. Supramolecular synthons in 1:1 and 1:2 MRE:ACR cocrystals; synthon **A** (left) and synthon **B** (right).

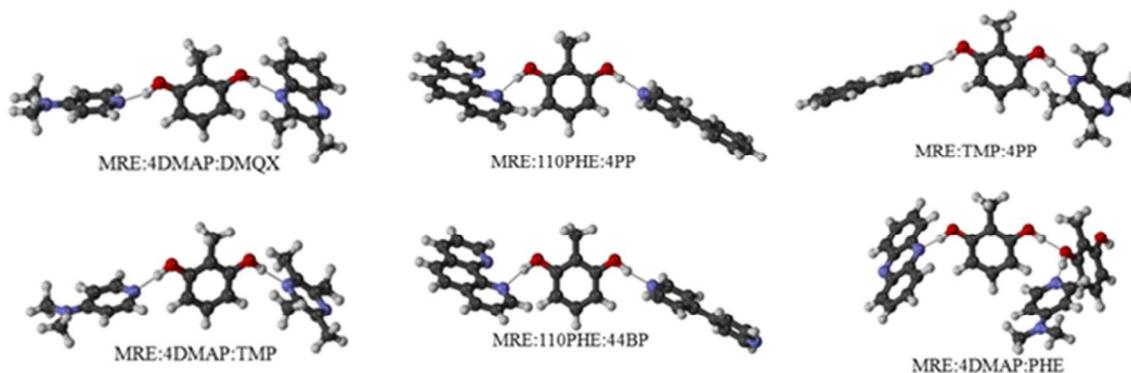


Fig. 5: Ternary cocrystals in this study. Note the robust selection of symmetrical synthon **B** in five cases. In MRE:4DMAP:PHE, there is the exceptional occurrence of synthon **A**.

In one exceptional case, namely acridine (ACR), both synthon **A** and synthon **B** based crystal structures are obtained, completing the picture. The synthon **A** based structure is found in the 1:1 MRE:ACR cocrystal (Fig. 4, left). The synthon **B** based structure is seen in the 1:2 cocrystal (Fig. 4, right). The MRE:ACR system is the only one among the compounds we studied in which both pseudopolymorphs are isolated experimentally. DSC shows that the 1:1 MRE:ACR crystal form provides a clean endotherm at $\sim 200^\circ\text{C}$ while 1:2 MRE:ACR undergoes an enantiotropic

phase transition at $\sim 125^\circ\text{C}$ that finally ends in a broad endotherm at $\sim 200^\circ\text{C}$ hinting at the existence of polymorphism (Supporting Information). In summary, the *anti-anti* based cocrystal landscape provides an understanding of molecular and supramolecular features and their probabilistic role for the development of higher molecular assemblies. All these molecular and supramolecular preferences and their accessibility in the crystal structures enable one to better exploit the kinetic events in the crystallization process.

Ternary cocrystals are molecular solids that contain three discrete solid organic compounds in the basic chemical unit. In this paper, the term “ternary cocrystal” does not refer to a multi-component crystal in which one or more of the components is a solvent used for crystallization, or water. Crystal synthesis of ternary solids is a difficult exercise but some progress is being seen in recent times.^{12,14} Such a synthetic endeavour requires not only comprehensive kinetic information about crystallization for the given system, but also a good control over the experimental conditions that are needed to realize this information. In this context, the idea of the *crystal structure landscape* is again relevant. Utilizing the lack of degeneracy in hydrogen bonds, and with a further understanding of synthon preferences **A** and **B**, one can plan a possible route to three-component solids based on MRE. Our strategy was based on the synthon **B** pattern, and to start with, we supplied two bases TMP and 4DMAP in the cocrystallization experiment with MRE, using the three compounds in the expected 1:1:1 proportion. The ternary cocrystal shows the expected synthon **B** based pattern with the central MRE molecule forming O–H \cdots N hydrogen bonds with both TMP and 4DMAP. Other examples of ternary solids obtained by the same method are shown in Fig. 5 and this is indicative of the generality of the synthetic strategy. It is noteworthy that in almost all these cases, the proportion of ternary solids was very high with only minor contamination by binary cocrystals. It was also heartening note a relatively high success rate (20%) with which ternary cocrystals were obtained in crystallization experiments involving three solid components from a large number of solvents and solvent mixtures (see Supporting Information for unsuccessful trials). The combination of 4DMAP and PHE is exceptional in that cocrystallization with MRE in a 1:1:1 proportion gave a 2:1:1 MRE:4DMAP:PHE ternary cocrystal in which synthon **A** rather than synthon **B** is present. No other ternaries were obtained in this structure type. It is curious that the synthon **A** based packing is more common in the binary cocrystals we obtained while the synthon **B** based alternative is

favoured for the ternary solids. The circumstantial evidence is that several synthon precursors for one-, two- and three-component crystals exist together in solution. As the number of chemical components in the solid increases, the process becomes more selective and structurally specific but the synthons are still related, from MRE crystal structure to synthon **A** based binary structures and finally to synthon **B** based ternary solids. These examples highlight the utility of the *crystal structure landscape* in the mapping of crystallization kinetics towards more complex supramolecular architectures. This exercise also argues for the combinatorial nature of the crystallization process (Fig. 6).^{12,14e}

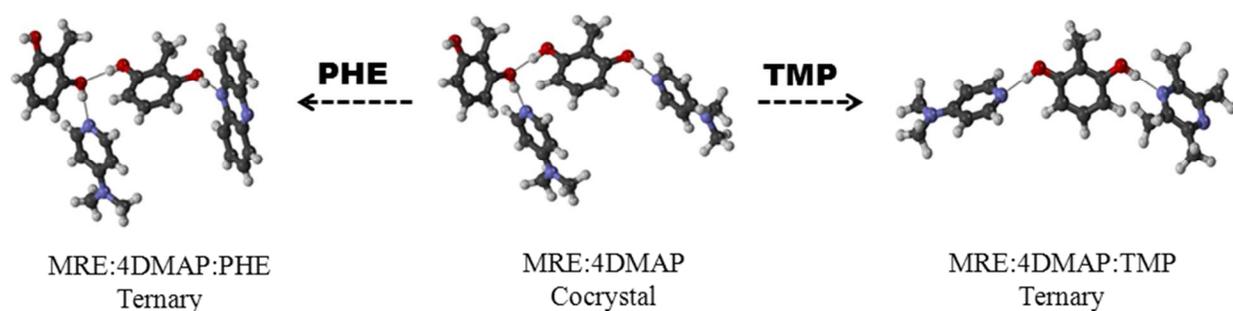


Fig. 6: Combinatorial nature of crystal synthesis. The MRE:4DMAP cocrystal (centre) offers selective synthon amplification i.e. synthon **A** in MRE:4DMAP:PHE and synthon **B** in MRE:4DMAP:TMP ternary solids, by careful selection of template molecules.

In conclusion, the isolation of MRE based ternary solids demonstrates a combinatorial and convergent design strategy that is based on synthon selection from a solution library.^{12,14e} There could be another way of looking at these phenomena. There are subtle differences among nominally equivalent hydrogen bonds in the crystal structure of the native MRE. These hydrogen bonds are templates for the introduction of new chemical entities, in this case heterocyclic bases. The MRE crystal structure also has $Z' = 3$. Is there any significance in the fact that a $Z' = 3$ structure is the starting point for a ternary solid? Three chemically identical but crystallographically distinct molecules in the native MRE crystal structure are transformed into a cocrystal structure in which two of them are replaced by new molecules. One could ask if in an analogous strategy, a four component crystal could be designed from a starting structure in which $Z' = 4$, and so on. To conclude, symmetrically independent molecules in $Z' > 1$ crystal structures might be considered as precursors in the synthesis of higher component molecular crystals. However, any conclusions in this regard must await further experimentation with a

statistically significant number of 1,3-dihydric phenols with both $Z' = 1$ and $Z' > 1$ crystal structures.

NAM thanks DST for the DST-Young scientist fellowship. RD thanks the IISc for a senior research fellowship. ST thanks the IISc for research associate fellowship. GRD thanks the DST for the award of a J. C. Bose fellowship.

These authors equally contributed to this article.

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