

Co-crystallization - The Supramolecular Synthesis

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Co-crystallization of different components represents *the* supramolecular synthesis, where weak interactions link molecules. This is in contrast to organic synthesis which is based on the formation or cleavage of covalent bonds. For pharmaceutical products we expect an increasing importance in the design of modified drugs based on known agents as it is for polymorphs today. Co-crystals are distinct different from solid solutions or mixed crystals, and can be considered as molecular complexes.¹

The design of co-crystals seems to be straight forward because donor and acceptor functionalities can be brought together more easily than with single component systems because the partners are more accessible to arrange themselves into an optimal geometry, leading to favourable intermolecular interactions. On the other hand, the success of this supramolecular synthesis is governed by the problem that either component might prefer to crystallize

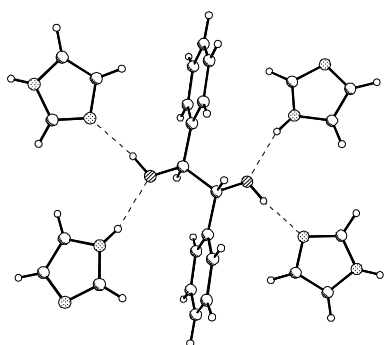
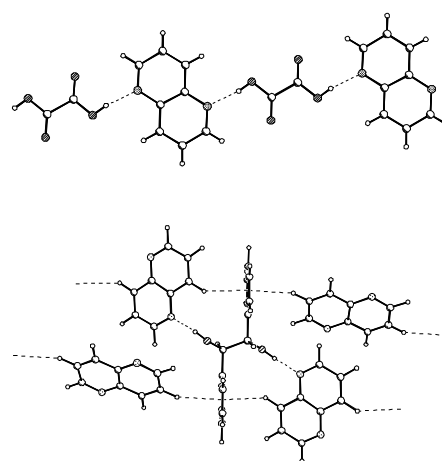


Figure 3

N) can be used alone to form molecular complexes, and we successfully co-crystallized pyrazine and *p*-diethynylbenzene or ethynylbenzene. (Figure 4). Surprisingly, the reverse of the donor-acceptor systems with *p*-diethynylbenzene and pyridine could never be co-crystallized. An explanation gives the calculation of the solid state lattice energies of the single components, the complex found and the hypothetical complex, which is too high so the pure components are crystallized only.

Co-crystals of small molecules have the advantage that the steric influence of a large molecular backbone is avoided. Probably one of the most interesting molecules in terms of weak intermolecular interactions is acetylene. It forms two molecular complexes with acetone, a 1:2 and a 1:1 complex with geometries, where the expected tetrahedral surrounding of oxygen is not fulfilled in both cases (Figures 5,6).⁴



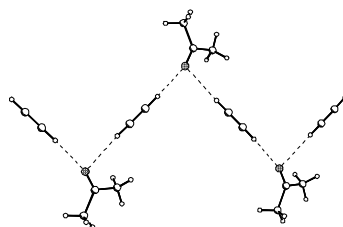
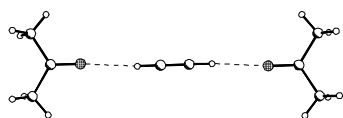
as a neat compound instead of the formation of a molecular complex. **Figures 1,2**

Using O-H...N interactions, we were able to produce numerous co-crystals formed from *meso*-diols or diacids and diaza-compounds such as diazanaphthalene (Figures 1,2).² With imidazole, co-crystals were found where the hydroxyl group serves a proton donor and the oxygen as a C-H acceptor (Figure 3) to stabilize the structure.

In the absence of strong hydrogen bridges, also much weaker intermolecular interactions such as C-H...X (X=O,



Figure 4



Figures 5,6

Even for C-H... π interactions, the geometries remain unpredictable. We were able to co-crystallize acetylene with benzene (Figure 7),⁵ m-xylene or mesitylene, but we were unable to get a molecular complex from acetylene and toluene. In the prior case, the acetylene molecule fulfils a precession-like movement even at temperatures of 120K.

The unexpected geometries underline the electrostatic character of the hydrogen bond, and make it even more difficult to predict the packing of molecular complexes because of the low directionality of the bond. Therefore much experience and intuition is needed to have reasonable approaches to supramolecular synthesis.

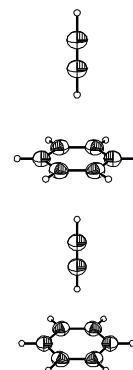


Figure 7

References

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