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Crystal engineering of the composition of pharmaceutical phases

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The carboxylic acid–pyridine supramolecular heterosynthon can be exploited to predictably generate binary crystalline phases involving *rac*-ibuprofen, *rac*-flurbiprofen or aspirin.

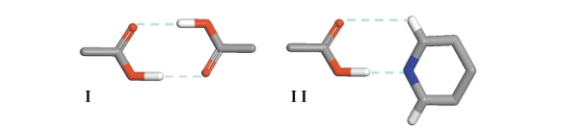
The concept of crystal engineering was originally introduced in the context of stereochemical control of photochemical reactions,[1] but it has subsequently been shown to have wider implications for materials science. In the context of pharmaceuticals, there are important process and intellectual property implications related to control and reproducibility of composition and polymorphism.[2,3] In this contribution, we focus upon how crystal engineering can be applied towards small organic molecules and generation of novel pharmaceutical compositions. This study is premised on the assumption that pharmaceutical molecules are inherently predisposed for such studies since they contain exofunctional supramolecular synthons.[4]

Supramolecular synthons that are based upon hydrogen bonds represent a prototypal tool for crystal engineering[5] and can be readily categorized as illustrated in Scheme 1: 'supramolecular homosynthons' from self-complementary moieties, *e.g.* the dimer formed by carboxylic acids, **I**; 'supramolecular heterosynthons' from two or more components, *e.g.* the dimer formed by pyridines with single or multiple carboxylic acids,[6–10] **II**.

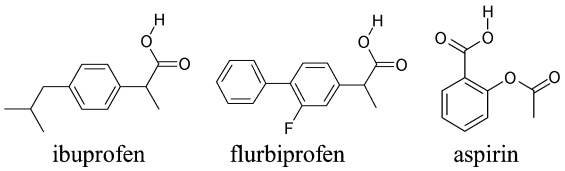
Heterosynthon **II** has previously been exploited for liquid-crystalline materials,[7] two-dimensional beta networks,[7] two-dimensional corrugated sheets[9] and 'ternary supermolecules'[10] and similar heterosynthons have been used as templates for control of solid-state reactions.[11] We herein extend its use to the realm of pharmaceutical molecules by forming novel compositions of ibuprofen,[12] flurbiprofen,[13] and aspirin.[14]

Supramolecular complexes **A**–**D** form when *rac*-ibuprofen, *rac*-flurbiprofen or aspirin are crystallized in the presence of dipyridyls: (ibuprofen)$_2$(4,4′-bipyridine), **A** (Fig. 1); (flurbiprofen)$_2$(4,4′-bipyridine), **B**, (Fig. 2); (flurbiprofen)$_2$ (trans-1,2-bis(4-pyridyl)ethylene), **C** (Fig. 2); (aspirin)$_2$(4,4′-bipyridine), **D** (Fig. 3); **A**–**D** were characterized by FT-IR spectroscopy, XRPD, DSC, TGA and single crystal X-ray diffraction† . The crystal structures of **A**–**D** exhibit the expected 2 : 1 stoichiometries because of heterosynthon **II**. The resulting 3-component adducts are centrosymmetric for **A**–**C** and exhibit herringbone packing patterns of the type seen in the pure phases.[12,13] All hydrogen bonds in **A**–**C** are consistent with expected values,[15–18] including the C–H···O interaction[19,20] that affords rigidity to this supramolecular heterosynthon and helps to explain the similarity between the crystal packing of **A**–**C** and the pure pharmaceutical phases.

The 3-component supramolecular adduct formed between aspirin and 4,4-bipyridine differs from **A**–**C** in that the 4,4′-bipyridine molecules are twisted with a torsion angle of 39° rather than planar and the planes of the C_6 rings in the aspirin molecules are oriented with a torsion angle of *ca.* 54°. This precludes formation of a centrosymmetric supramolecular adduct and results in dramatically different crystal packing. The crystal packing of adducts of **D** results in a channel inclusion



Scheme 1



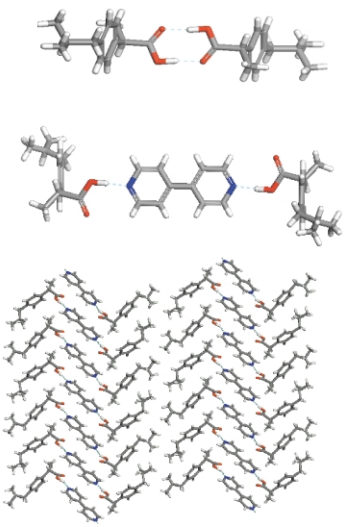


Fig. 1 The 3-component adducts present in pure ibuprofen and **A** (above); the herringbone crystal-packing pattern seen in **A** (below).

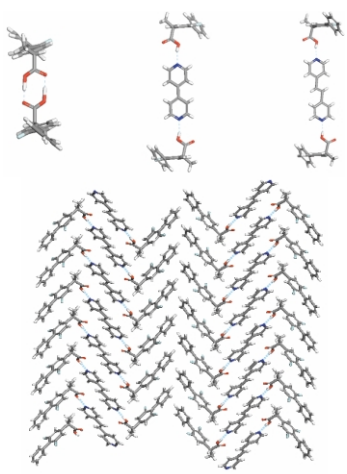


Fig. 2 The 3-component adducts present in pure flurbiprofen, **B** and **C** (above); the herringbone crystal-packing pattern seen in **C**, which is isostructural with **B** (below).

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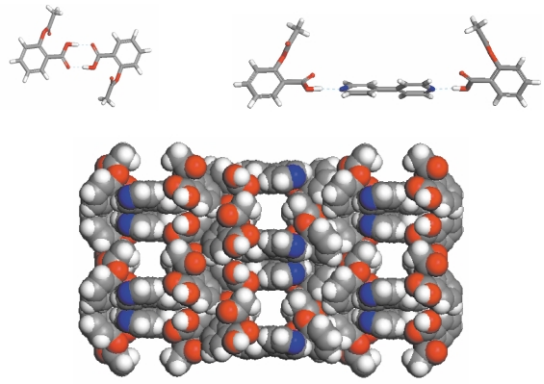

Fig. 3 The 3-component adducts present in pure aspirin and **D** (above); the open framework crystal packing pattern seen in **D** (below). The hourglass channels have effective dimensions as follows: 4.7 Å in height; 2.4 Å wide at the narrowest point (middle); 2.7 Å wide at the widest point (top & bottom).

compound, presumably templated by the presence of hexane during crystallization (Fig. 3). A review of the crystallographic literature revealed that 4,4-bipyridine moieties exhibit torsional flexibility in other circumstances.[15]

In conclusion, supramolecular heterosynthons can be exploited for generation of binary crystals that contain pharmaceutical components and, furthermore, the nature of the non-pharmaceutical component can dramatically affect crystal packing and, therefore, physical properties. For example, the melting points for **A**–**C** are higher than their pure individual components, and the melting point of **D**, a phase that exhibits dramatically different crystal packing, has a lower melting point than its pure individual components.‡

Whereas **A**–**D** should only be regarded as model compounds, we believe that the observations reported herein could have broad implications for the formulation of pharmaceuticals since control of composition can in appropriate circumstances now be regarded as being addressable *via* a supramolecular retrosynthetic[21] approach. Further studies will focus upon multiple component crystalline phases that will be designed and optimized for improved pharmaceutical performance and contain components that are generally regarded as safe (GRAS) by the FDA.[22]

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Notes and references

† *Synthesis and data:* A–C were prepared by dissolving the pharmaceutical and bipyridine molecules in a 2 : 1 ratio in acetone and slow evaporation. D was prepared by dissolving aspirin and 4,4′-dipyridyl (2 : 1) in hexane and addition of diethyl ether. FT-IR spectra confirmed that deprotonation did not occur. Single crystal X-ray diffraction data for A–D were collected on a Bruker SMART-APEX CCD Diffractometer. Diffracted data were corrected for absorption using the SADABS[23] program. SHELXTL[24] was used for the structure solution and refinement was based on $|F|^2$. All non-hydrogen atoms were refined anisotropically. Carboxylic acid protons were located and refined with isotropic thermal parameters whereas the remaining hydrogen atoms were fixed in idealized positions and refined isotropically with thermal parameters based upon the corresponding carbon atoms [U (H) = 1.2 Ueq (C)]. In B and C the fluorine atom was disordered between the 2 and 6 positions of the benzene ring with the major component having ~70% occupancy. Calculated and experimental XRPD patterns for A–D are consistent with single crystals being representative of the bulk phases.

Crystal data for **A**: $C_{36}H_{44}N_2O_4$, M = 568.73, triclinic, space group $P\bar{1}$; a = 5.759(3), b = 11.683(6), c = 24.705(11) Å, α = 93.674(11), β = 90.880(10), γ = 104.045(7)°, U = 1608.3(13) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.076 mm^{-1}, D_c = 1.174 Mg m^{-3}, λ = 0.71073 Å^3, F(000) = 612, $2\theta_{max}$ = 23.29°. 5208 reflections measured, 3362 unique (R_{int} = 0.0826). Final residuals for 399 parameters were R_1 = 0.0964, wR_2 = 0.2510 for $I > 2\sigma(I)$, and R_1 = 0.1775, wR_2 = 0.2987 for all 3362 data . *Crystal data* for **B**: $C_{40}H_{34}F_2N_2O_4$, M = 644.69, monoclinic $P2_1/n$; a = 5.860(4), b = 47.49(3), c = 5.928(4) Å, β = 107.382 (8)°, U = 1574.3(19) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.096 mm^{-1}, D_c = 1.360 Mg m^{-3}, λ = 0.71073 Å^3, F(000) = 676, $2\theta_{max}$ = 21.69°. 4246 reflections measured, 1634 unique (R_{int} = 0.0677). Final residuals for 226 parameters were R_1 = 0.0908, wR_2 = 0.2065 for $I > 2\sigma(I)$, and R_1 = 0.1084, wR_2 = 0.2209 for all 1634 data.

Crystal data for **C**: $C_{42}H_{36}F_2N_2O_4$, M = 670.73, monoclinic $P2_1/n$; a = 5.8697(9), b = 47.357(7), c = 6.3587(10) Å, β = 109.492(3)°, U = 1666.2(4) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.093 mm^{-1}, D_c = 1.337 Mg m^{-3}, λ = 0.71073 Å^3, F(000) = 704, $2\theta_{max}$ = 21.69°. 6977 reflections measured, 2383 unique (R_{int} = 0.0383). Final residuals for 238 parameters were R_1 = 0.0686, wR_2 = 0.1395 for $I > 2\sigma(I)$, and R_1 = 0.1403, wR_2 = 0.1709 for all 2383 data.

Crystal data for **D**: $C_{28}H_{24}N_2O_8$, M = 516.49, orthorhombic $Pbcn$; a = 28.831(3), b = 11.3861(12), c = 8.4144(9) Å, U = 2762.2(5) Å^3, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.092 mm^{-1}, D_c = 1.242 Mg m^{-3}, λ = 0.71073 Å^3, F(000) = 1080, $2\theta_{max}$ = 25.02°. 12431 reflections measured, 2433 unique (R_{int} = 0.0419) Final residuals for 202 parameters were R_1 = 0.0419, wR_2 = 0.1358 for $I > 2\sigma(I)$, and R_1 = 0.0541, wR_2 = 0.1482 for all 2433 data.

CCDC 188913–188916. See http://www.rsc.org/suppdata/cc/b2/b208574g/ for crystallographic files in CIF or other electronic format.

‡ *Melting points* (°C): **A**: 117–120; **B**: 155–160; **C**: 153–158; **D**: 91–96; aspirin: 133–135; ibuprofen: 77–78; flurbiprofen: 113–114; 4,4′-bipyridine: 111–114; trans-1,2-bis(4-pyridyl)ethylene: 150–153.

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