In situ co-crystallisation as a tool for low-temperature crystal engineering†

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Synthesis and single-crystal X-ray diffraction of a series of low-melting co-crystals of pyrazine and *n*-alkyl carboxylic acids demonstrates *in situ* co-crystallisation as a versatile tool for low-temperature crystal engineering.
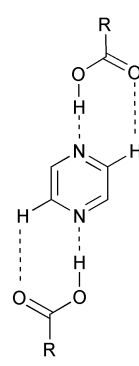
Research in the diverse field of crystal engineering continues to expand at a dramatic rate, with the scope for production of new crystalline and co-crystalline molecular materials seemingly unbounded.[1] Preparation of multi-component molecular crystals represents genuine synthesis on a supramolecular scale, forming non-covalent rather than covalent bonds between molecular components during co-crystallisation. Since the resulting materials exist only in the solid state however, there arises a practical difficulty when studying co-crystals that melt below room temperature. This complicates the synthesis and solid-state characterisation of multi-component crystals of many of the simplest molecules. As a consequence, studies of co-crystalline molecular materials have to date generally been restricted to those that are solid under ambient conditions.

Single-crystal X-ray diffraction analysis of low-melting materials has recently undergone something of a resurgence,[2–5] principally as a result of improvements in equipment and techniques for *in situ* crystal growth.[6,7] While these techniques have become well established for single-component systems, their extension to multi-component systems has not been reported. Successful application of *in situ* techniques to multi-component mixtures should expand dramatically the range of co-crystals that may be prepared and studied by single-crystal X-ray diffraction, presenting new opportunities for study of multi-component crystals that do not exist under ambient conditions. Reported here is the *in situ* synthesis and single-crystal X-ray diffraction analysis of a series of co-crystals containing pyrazine and *n*-alkyl carboxylic acids, all of which melt around or below room temperature. The study demonstrates that *in situ* co-crystallisation may indeed be employed successfully for the synthesis and characterisation of low-melting multi-component crystals, and the technique should prove to be a versatile tool for low-temperature crystal engineering.

Co-crystals **1**–**10** were prepared from 1 : 2 stoichiometric mixtures of pyrazine and the appropriate *n*-alkyl carboxylic acid, the stoichiometry being selected by consideration of the trimeric supramolecular motif shown in Scheme 1, predicted on the basis of the supramolecular synthon approach.[8,9] In the 1 : 2 stoichiometry, the mixtures may be considered to be pure molten co-crystals rather than simply solutions of pyrazine in the respective carboxylic acids. Mixtures **1**–**8**, containing methanoic to octanoic acid respectively, are liquid under ambient conditions (295 K, 1 atm), while mixture **9**, containing nonanoic acid, solidifies slowly at room temperature. A solution of pyrazine in decanoic acid (which is just solid under ambient conditions) was effected by gentle heating, and mixture **10** solidifies on returning to room temperature. Crystals of **1**–**8**

were grown in 0.2 mm diameter glass capillaries at a temperature just below the melting point of the solid, using a simple zone-refinement technique.[4,7] Crystals of **9** and **10** were grown using a slight variation of the technique: the mixture was melted and loaded into a capillary, and the crystal was obtained by temperature cycling of ±1 K around the melting point. It is considerably more difficult to obtain a satisfactory single crystal using this technique. Once grown, all crystals were cooled to 180 K prior to data collection.‡ A certain degree of flexibility is possible in the stoichiometry of the mixture since the zone-refinement technique effectively purifies the co-crystalline product, but the process of obtaining a single crystal becomes considerably more difficult as the stoichiometry deviates from ideal. The melting points of the crystals (Scheme 1) were also determined *in situ* by warming the crystal in the N$_2$ gas stream after data collection — melting is readily detectable by the abrupt loss of the diffraction pattern.[10]

Although the pyrazine–carboxylic acid system was studied primarily as a test for the *in situ* co-crystallisation technique, the resulting materials are of interest in themselves since they form a complete homologous series of co-crystal structures studied at a common temperature. Similar studies of single-component molecular materials have yielded notable insight into the correlation between crystal structures and physical properties, in particular melting points.[2,3] In each co-crystal **1**–**10**, the expected trimeric supramolecular motif is formed *via* an $R_2^2(7)$ hydrogen-bond pattern (Fig. 1), the C–H⋯O interaction providing the driving force for adoption of co-planarity between the carboxyl group and pyrazine ring.[9] In common with the early members of homologous single-component series, the structures of **1**–**6** exhibit considerable variation (Table 1) as a result of the complex balance between competing inter-molecular forces. The structures of **7**–**10**, however, exhibit regularity, with the trimeric moieties arranged in layers similar to those in the *n*-alkanes and *n*-alkyl carboxylic acids (Fig. 2). Both of the latter molecular series display an alternation in their melting points, those members of each series with an odd number of carbon atoms having a relatively lower melting point than those with an even number of carbon atoms. In both cases, this is correlated with alternating crystal density.[2,11] In this respect, it is interesting to note that the densities and melting

	R	m.p. / K
1	H	285
2	CH$_3$	268
3	CH$_2$CH$_3$	252
4	(CH$_2$)$_2$CH$_3$	260
5	(CH$_2$)$_3$CH$_3$	260
6	(CH$_2$)$_4$CH$_3$	272
7	(CH$_2$)$_5$CH$_3$	282
8	(CH$_2$)$_6$CH$_3$	283
9	(CH$_2$)$_7$CH$_3$	295
10	(CH$_2$)$_8$CH$_3$	300

Scheme 1

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Table 1 Crystal system, space group, unit-cell parameters and crystal density at 180 K for **1–10**

			Z^a	a/Å	b/Å	c/Å	α/°	β/°	γ/°	U/Å³	D_c/g cm⁻³
1	Monoclinic	$P2_1/c$	2	3.6994(1)	7.0340(3)	16.1607(9)	90	96.068(2)	90	418.17(3)	1.367
2	Triclinic	$P\bar{1}$	2	5.4869(2)	8.1885(2)	11.9960(4)	70.076(1)	86.667(1)	89.925(2)	505.76(3)	1.315
3	Monoclinic	$P2_1/n$	2	4.8735(2)	5.4384(2)	23.2428(10)	90	93.197(1)	90	615.07(4)	1.232
4	Monoclinic	$P2_1/n$	2	9.8544(7)	5.7127(4)	13.5338(13)	90	109.736(3)	90	717.13(10)	1.187
5	Monoclinic	$P2_1/c$	2	13.2449(1)	5.4022(3)	11.9960(8)	90	105.716(3)	90	826.24(7)	1.143
6	Monoclinic	$C2/c$	4	27.6365(7)	5.4294(1)	12.2322(4)	90	94.639(1)	90	1829.42(8)	1.134
7	Triclinic	$P\bar{1}$	1	5.5106(3)	6.8970(3)	13.7860(8)	76.816(2)	85.697(2)	76.802(2)	496.53(5)	1.139
8	Triclinic	$P\bar{1}$	1	5.4774(2)	6.9086(3)	15.2102(8)	81.541(2)	84.977(2)	76.158(4)	551.95(4)	1.109
9	Triclinic	$P\bar{1}$	1	5.4731(2)	6.8775(2)	16.3824(6)	89.776(1)	82.992(1)	76.091(1)	593.89(4)	1.109
10	Triclinic	$P\bar{1}$	1	5.4573(2)	6.8970(2)	18.0387(6)	80.575(1)	81.940(1)	75.554(2)	645.10(4)	1.093

^{a} Z is the number of trimeric supermolecules in the unit cell.
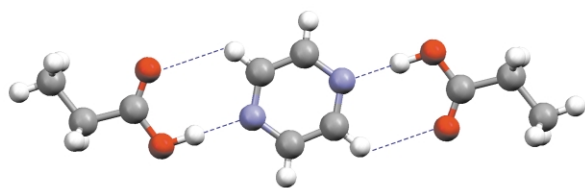

Fig. 1 Trimeric supramolecular moiety in **3** with hydrogen bonds shown as dotted lines. Comparable motifs are observed in the other co-crystals.
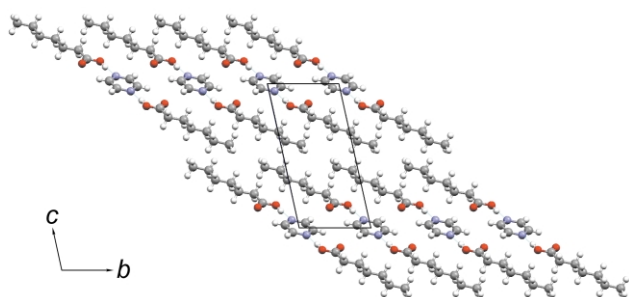

Fig. 2 Projection of **7** along the a direction showing the layered arrangement of the supramolecular moieties. Similar layered structures are adopted by **8–10**.

points of **7–10** appear also to signify the onset of an alternating trend, suggesting that melting point alternation may be a property of this two-component system, as well as of the carboxylic acids themselves.† Studies of the co-crystals of pyrazine with the higher acids, all of which are solid under ambient conditions, are underway in an effort to confirm this observation.

Notes and references

‡ Crystal systems, space groups, unit-cell parameters and crystal densities for **1–10** are listed in Table 1. All data were collected at 180 K. *Crystal data for* **1**: $C_6H_8N_2O_4$, $M = 172.14$, μ(Mo-Kα) = 0.116 mm⁻¹. Of 2895 reflections measured, 760 were unique ($R_{int} = 0.1556$) and were used in all calculations. The final $wR2 = 0.1925$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0723, and goodness-of-fit on F^2, $S = 1.11$ (CCDC 192849). *Crystal data for* **2**: $C_8H_{12}N_2O_4$, $M = 200.20$, μ(Mo-Kα) = 0.106 mm⁻¹. Of 5274 reflections measured, 2287 were unique ($R_{int} = 0.0719$) and were used in all calculations. The final $wR2 = 0.1499$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0518, and goodness-of-fit on F^2, $S = 1.06$ (CCDC 192850). *Crystal data for* **3**: $C_{10}H_{16}N_2O_4$, $M = 228.25$, μ(Mo-Kα) = 0.096 mm⁻¹. Of 1845

reflections measured, 891 were unique ($R_{int} = 0.1186$) and were used in all calculations. The final $wR2 = 0.2189$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0749, and goodness-of-fit on F^2, $S = 1.25$ (CCDC 192851). *Crystal data for* **4**: $C_{12}H_{20}N_2O_4$, $M = 256.30$, μ(Mo-Kα) = 0.089 mm⁻¹. Of 3855 reflections measured, 1245 were unique ($R_{int} = 0.0363$) and were used in all calculations. The final $wR2 = 0.1154$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0448, and goodness-of-fit on F^2, $S = 1.04$ (CCDC 192852). *Crystal data for* **5**: $C_{14}H_{24}N_2O_4$, $M = 284.35$, μ(Mo-Kα) = 0.084 mm⁻¹. Of 4881 reflections measured, 1374 were unique ($R_{int} = 0.1216$) and were used in all calculations. The final $wR2 = 0.1962$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0726, and goodness-of-fit on F^2, $S = 1.09$ (CCDC 192853). *Crystal data for* **6**: $C_{16}H_{28}N_2O_4$, $M = 312.40$, μ(Mo-Kα) = 0.081 mm⁻¹. Of 8015 reflections measured, 2092 were unique ($R_{int} = 0.0443$) and were used in all calculations. The final $wR2 = 0.1318$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0475, and goodness-of-fit on F^2, $S = 1.06$ (CCDC 192854). *Crystal data for* **7**: $C_{18}H_{32}N_2O_4$, $M = 340.46$, μ(Mo-Kα) = 0.080 mm⁻¹. Of 5160 reflections measured, 2210 were unique ($R_{int} = 0.0383$) and were used in all calculations. The final $wR2 = 0.1192$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0436, and goodness-of-fit on F^2, $S = 1.07$ (CCDC 192855). *Crystal data for* **8**: $C_{20}H_{36}N_2O_4$, $M = 368.51$, μ(Mo-Kα) = 0.076 mm⁻¹. Of 4435 reflections measured, 2441 were unique ($R_{int} = 0.0786$) and were used in all calculations. The final $wR2 = 0.2571$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0882, and goodness-of-fit on F^2, $S = 1.10$ (CCDC-192856). *Crystal data for* **9**: $C_{22}H_{40}N_2O_4$, $M = 396.56$, μ(Mo-Kα) = 0.075 mm⁻¹. Of 6194 reflections measured, 2652 were unique ($R_{int} = 0.0648$) and were used in all calculations. The final $wR2 = 0.1489$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0533, and goodness-of-fit on F^2, $S = 1.05$ (CCDC 192857). *Crystal data for* **10**: $C_{24}H_{44}N_2O_4$, $M = 424.61$, μ(Mo-Kα) = 0.073 mm⁻¹. Of 4697 reflections measured, 2235 were unique ($R_{int} = 0.0417$) and were used in all calculations. The final $wR2 = 0.1324$ (all data), $R1$ [$F^2 > 2\sigma(F^2)$] = 0.0470, and goodness-of-fit on F^2, $S = 1.10$ (CCDC 192858). See http://www.rsc.org/suppdata/cc/b2/b208904a for crystallographic data in CIF format.

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10 The temperature at the sample was calibrated by measuring the melting points of the series of pure *n*-alkyl carboxylic acids from heptanoic to decanoic acid, comparing these with literature values (see ESI).
11 A. D. Bond, manuscript submitted.