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Symmetry Constraints, Molecular Recognition and Crystal Engineering. Comparative Structural Studies of Urea–Butanedioic and Urea–*E*-Butenedioic Acid (2:1) Cocrystals

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Abstract

The crystal structures of two urea–dicarboxylic acid (2:1) cocrystals have been determined. Urea–butanedioic acid forms monoclinic crystals, space group $P2_1/c$ (no. 14), with $a = 5.637(4)$, $b = 8.243(3)$, $c = 12.258(3)$ Å, $\beta = 96.80(5)°$, $V = 565.6(8)$ Å^3, $Z = 2$. Urea–*E*-butenedioic acid also forms monoclinic crystals, space group $P2_1/c$ (no. 14), with $a = 5.540(1)$, $b = 8.227(1)$, $c = 12.426(3)$ Å, $\beta = 97.22(3)°$, $V = 561.9(2)$ Å^3, $Z = 2$. The geometry and the conformation of both molecular aggregates and the three-dimensional networks formed are very similar. The two strongest hydrogen-bond interactions are constrained in the formation of the heteroaggregates, the third hydrogen-bond interaction is used to self-associate the heteroaggregates in one-dimensional chains, whereas the next three weaker hydrogen bonds interconnect the chains into well organized three-dimensional networks.

1. Introduction

This crystal structure study is part of a broader program of urea–dicarboxylic acid cocrystal engineering with predesigned crystal building blocks (Videnova-Adrabińska, 1995*a*,*b*, 1996). Despite the misleading structural similarity of the butanedioic (succinic) acid and *E*-butenedioic (fumaric) acids, both compounds display quite different physico-chemical properties, which are to a great extent a result of their molecular packing into three-dimensional crystal structures. Both compounds exhibit two polymorphic forms: room temperature, which is monoclinic with space group $P2_1/c$, and high temperature, which is triclinic with $P\bar{1}$. The structure of the low-temperature phase (β-polymorph) of succinic acids was resolved with X-ray diffraction methods (Morrison & Robertson, 1949; Broadley, Cruickshank, Morrison & Robertson, 1959) and with neutron diffraction methods (Leviel, Auvert & Savariault, 1981). The neutron diffraction study of β-succinic acid carried out at 77 and 300 K yields a monoclinic unit cell (space group $P2_1/c$) with cell dimensions $a = 5.519(2)$, $b = 8.862(6)$, $c = 5.101(2)$ Å, $\beta = 91.59(4)°$, $V = 249.39$ Å^3 at 300 K and $a = 5.464(1)$, $b = 8.766(3)$, $c = 5.004(1)$ Å, $\beta = 93.29°$, $V = 239.31$ Å^3 at 77 K. No low-temperature structural transformation was observed. Although the bond lengths decrease with temperature increase, both the cell dimensions and the volume increase, which is due to the increase of the spacing between the succinic chains [from 3.583 (4) to 3.694 (7) Å] associated with a decrease in the β angle [from 93.29 (3) to 91.59 (4)°]. The translation parameter of the molecule in the hydrogen-bonded chain remains exactly the same [7.619 (2) Å]. It is the same as in α-fumaric acid (along the *a* direction) or in β-fumaric acid (along the *b* direction). β-Succinic acid transforms into a triclinic form $P\bar{1}$ (α-polymorph) on heating to temperatures higher than 423–433 K (Petropavlov & Jarantsev, 1983). Contrary to the room-temperature polymorph of the succinic acid, the room-temperature phase of fumaric acid is termed an α-polymorph and is also monoclinic (space group $P2_1/c$), comprising six molecules of two different kinds [two molecules are centrosymmetric and four molecules are non-centrosymmetric (Brown, 1966)]. Its β-polymorph can be obtained only from sublimation at 403 K and is triclinic [$P\bar{1}$ (Bednowitz & Post, 1966)]. Similar to other dicarboxylic acids, the molecules in both polymorphs are hydrogen-bonded to form long homomeric chains arranged in flat layers. Since all available 'good' donors (Etter, 1990) from the carboxylic groups are already used in the formation of dimer chains, any other interactions between the chains and layers are expected to be very weak. The interchain distances (of 3.04 and 3.12 Å) between the hydroxyl and methyne hydrogens of one chain and the carbonyl and hydroxyl oxygens of the adjacent chain are too long to be considered as 'classic' hydrogen bonds. However, they are directed exactly towards the oxygen lone pair and thus they might have some bonding character stabilizing the two-dimensional layers in the β-polymorph.

The hydrogen bond is well documented to be directional, selective and stoichiometric. It also displays cooperativity features. For this reason it is very suitable for intermolecular synthesis and crystal design (Etter, 1991). The choice and formation of the building blocks (basic structural units) is the first and most important step in crystal engineering (Videnova-Adrabińska, 1996). Their further organization in one-, two- and three-dimensional assemblies [Kitajgoroski Aufbau Principle, KAP (Perlstein, 1994*a,b*)] depends strongly on their recognition properties. Cocrystallization of dicarboxylic acids with urea introduces additional proton donor and acceptor sites in the systems and hence the hydrogen-bonded motifs become different compared with those of the parent acids. The hydrogen-bonded heteroaggregates can be considered as independent units (comolecules) with new chemical properties and recognition features. However, they still inherit some of the chemical and symmetry features of the constituting (parent) molecules (Videnova-Adrabińska, 1996). Bearing in mind the above considerations, the urea and succinic and fumaric acid molecules were deliberately chosen to form 1:1 and 2:1 heteromolecular aggregates. We consequently term these heteromolecular aggregates comolecules, provided that they are stable and the strongest hydrogen-bond interactions are involved in their formation (Videnova-Adrabińska, 1996). Once the comolecules are formed in the solution they develop new recognition features and start to see each other as independent particles. Hence, the heteromeric aggregates formed through the common eight-membered hydrogen-bonded ring motif $R_2^2(8)$ (Etter, McDonald & Bernstein, 1990) can be considered as the building blocks of the whole three-dimensional crystal structure. The next strongest hydrogen-bond interactions should be used to self-associate comolecules in order to form comolecular chains (KAP, stage 1). However, not all comolecules which are close enough to interact are able to form stable nucleus associations. The proper space orientation of the hydrogen-bond sites is a necessary pre-condition for uniform self-assembly, which is further discussed in this paper.

2. Experimental

Both cocrystals were synthesized in a stoichiometric ratio from water–methanol (5:1) solution. The starting compounds were purchased from Aldrich (urea 99%, succinic acid 99% - gold label - and fumaric acid 99% - gold label) and used without any further purification. After threefold recrystallization, high quality transparent cocrystals were obtained. Both stoichiometric forms 1:1 ($T_{\rm melt} = 419$–421 K) and 2:1 ($T_{\rm melt} = 423$–425 K) urea–succinic acid were obtained. The IR and solid-state NMR spectra for both cocrystals were measured and compared with those of the starting materials. Repeated attempts to synthesize the urea–fumaric acid (1:1) cocrystal resulted in formation of only the 2:1 cocrystal ($T_{\rm melt} = 428$–430 K). This is probably the only stable aggregate which can be formed on energetical, stereochemical and topochemical grounds.

2.1. *X-ray structure determination of the 2:1 cocrystals*

The intensity of three standard reflections remained constant throughout the data collection, indicating crystal and electronic stability. Lorentz, polarization and secondary extinction corrections were made. The structures were solved by direct methods with *MITHRIL* (Gilmore, 1984) and *DIRDIF* (Buerkens, 1984) and refined by least-squares procedures. In both crystal structures the non-H atoms were refined with anisotropic displacement parameters. The H atoms in urea–succinic acid were refined isotropically, except for the H atoms of the methyl group which were included in the structure-factor calculation and placed in idealized positions with assigned isotropic displacement parameters $B = 1.2 \times B$ of the atoms to which they are bonded. All H atoms for urea–fumaric acid were found in a difference-Fourier map and refined without any constraints and restraints. Refinement was based on wF using *TEXSAN* (Molecular Structure Corporation, 1985) for the first crystal and on wF^2 using *SHELXL*93 (Sheldrick, 1993) for the second crystal. Scattering factors were taken from Cromer & Waber [1974 (urea–succinic acid cocrystal)] and *International Tables for Crystallography* [1992 (urea–fumaric acid cocrystal]. Reflections with $I > 2\sigma(I)$ were considered 'observed'. Table 1 contains the crystal data and the refinement parameters for the title cocrystals. The atomic parameters are listed in Tables 2 and 3 and the interatomic distances and angles are collected in Table 4.* A comparison between the bond lengths and angles observed in the investigated cocrystals and those from the parent compounds is presented in Tables 5 and 6. Drawings were made using *ORTEP*II (Johnson, 1976) and *PLUTO* (Motherwell & Clegg, 1978). Figs. 1(*a*) and (*b*) depict *ORTEP* presentations of the urea–succinic acid and the urea–fumaric acid comolecules, whereas Fig. 2 presents a stereoview of the unit-cell packing in urea–fumaric acid (2:1) cocrystal.

3. Discussion

Among all differently oriented comolecules which happen to be in close proximity in the solution, the 1:1 comolecule will be able to recognize and hydrogen bond only that which is related to it through a screw axis. Figs. 3 and 4 demonstrate the logical consequences of symmetry-constrained molecular recognition of 1:1 and 2:1 comolecules, based on prior ranking the hydrogen-bond donating abilities (Etter, 1990), which results in one-dimensional self-assemblies as stable mesoforms of three-dimensional

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* Lists of atomic coordinates, anisotropic displacement parameters, complete geometry and structure factors have been deposited with the IUCr (Reference: AB0345). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Experimental details*

	Urea–succinic acid (2:1)	Urea–fumaric acid (2:1)
Crystal data		
Chemical formula	$C_6H_{14}N_4O_6$	$C_6H_{12}N_4O_6$
Chemical formula weight	238.20	236.18
Cell setting	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (Å)	5.637 (4)	5.540 (1)
b (Å)	8.243 (3)	8.227 (1)
c (Å)	12.258 (3)	12.426 (3)
β (°)	96.80 (5)	97.22 (3)
V (Å^3)	565.6 (8)	561.9 (2)
Z	2	2
D_x (Mg m^{-3})	1.399	1.396
Radiation type	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073
No. of reflections for cell parameters	48	25
θ range (°)	10.05–22.35	6.0–15.0
μ (mm^{-1})	0.116	0.125
Temperature (K)	297	294
Crystal form	Prism	Prism
Crystal size (mm)	0.60 × 0.50 × 0.40	0.48 × 0.39 × 0.25
Crystal colour	Colourless	Colourless
Data collection		
Diffractometer	Enraf–Nonius CAD-4	Kuma KM-4
Data collection method	ω–2θ scans	ω–2θ scans
Absorption correction	None	None
No. of measured reflections	2364	1783
No. of independent reflections	1187	1632
No. of observed reflections	817	919
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.035	0.022
$\theta_{\max}$ (°)	25.95	30.0
Range of h, k, l	$0 \rightarrow h \rightarrow 6$ $-8 \rightarrow k \rightarrow 9$ $-14 \rightarrow l \rightarrow 13$	$-8 \rightarrow h \rightarrow 0$ $0 \rightarrow k \rightarrow 13$ $-19 \rightarrow l \rightarrow 20$
No. of standard reflections	3	3
Frequency of standard reflections	60 min	Every 50 reflections
Refinement		
Refinement on	F	F^2
R*	0.057	0.041
wR	0.069†	0.088‡
S	1.75	1.04
No. of reflections used in refinement	817	919
No. of parameters used	94	98
H-atom treatment	See text	See text
Weighting scheme	$w = 4F_o^2/\sigma^2(F_o^2)$	$w = 1/[\sigma^2(F_o^2) + (0.0658P)^2 + 0.0555P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.001	0.011
$\Delta\rho_{\max}$ (e Å^{-3})	0.42	0.21
$\Delta\rho_{\min}$ (e Å^{-3})	−0.41	−0.7
Extinction method	*TEXSAN* (Molecular Structure Corporation, 1985)	*SHELXL*93 (Sheldrick, 1993)
Extinction coefficient	0.27511×10^{-3}	0.031 (9)
Source of atomic scattering factors	Cromer & Waber (1974)	*International Tables for Crystallography* (1992, Vol. C)

* $R = \sum(|F_o| - |F_c|)/\sum|F_o|$. † $wR_1 = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$. ‡ $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4]^{1/2}$.

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for urea–succinic acid (2:1)*

$$B_{\text{eq}} = (1/3)\textstyle\sum_i\sum_j B_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
O1	0.4327 (4)	0.7909 (3)	1.0448 (2)	4.3 (1)
O2	0.2595 (4)	0.8588 (3)	0.8792 (2)	4.3 (1)
C1	0.2687 (5)	0.8646 (3)	0.9787 (2)	3.0 (1)
C2	0.0953 (5)	0.9573 (4)	1.0381 (2)	3.4 (1)
O10	0.7535 (4)	0.6309 (3)	0.9641 (2)	4.3 (1)
N12	0.9336 (5)	0.4864 (4)	0.8427 (3)	4.2 (1)
N11	0.5911 (7)	0.6259 (5)	0.7880 (3)	6.3 (2)
C10	0.7585 (5)	0.5816 (4)	0.8675 (2)	3.6 (1)

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for urea–fumaric acid (2:1)*

$$U_{\text{eq}} = (1/3)\textstyle\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O1	0.5672 (2)	0.2050 (2)	−0.0375 (1)	0.062 (1)
O2	0.7487 (2)	0.1454 (2)	0.1271 (1)	0.062 (1)
C1	0.7361 (3)	0.1360 (2)	0.0293 (1)	0.046 (1)
C2	0.9104 (3)	0.0406 (2)	−0.0260 (1)	0.052 (1)
O10	0.2519 (2)	0.3724 (2)	0.0381 (1)	0.063 (1)
N11	0.4075 (4)	0.3742 (3)	0.2140 (1)	0.085 (1)
N12	0.0668 (3)	0.5208 (2)	0.1546 (1)	0.062 (1)
C10	0.2430 (3)	0.4220 (2)	0.1333 (1)	0.053 (1)

Table 4. *Intramolecular distances (Å) and angles (°) with e.s.d.'s in parentheses*

Urea-succinic acid (2:1)		Urea-fumaric acid (2:1)	
Urea subunit		Urea subunit	
C10=O10	1.255 (3)	C10=O10	1.258 (2)
C10—N11	1.325 (4)	C10—N11	1.327 (2)
N11—N1N11	0.90 (4)	N11—H1N11	0.93 (3)
N11—H2N11	0.76 (4)	N11—H2N11	0.83 (3)
C10—N12	1.324 (4)	C10—N12	1.323 (2)
N12—H1N12	0.83 (4)	N12—H1N12	0.89 (2)
N12—H2N12	0.80 (3)	N12—H2N12	0.82 (2)
Succinic acid subunit		Fumaric acid subunit	
C1—O1	1.305 (3)	C1—O1	1.301 (2)
O1—H1O1	1.03 (5)	O1—H1O1	0.96 (3)
C1=O2	1.216 (3)	C1=O2	1.210 (2)
C1—C2	1.496 (4)	C1—C2	1.479 (2)
C2—C2^{i}	1.512 (6)	C2—C2^{ii}	1.299 (3)
Urea subunit		Urea subunit	
C10—N11—H1N11	120 (2)	C10—N11—H1N11	119 (2)
C10—N11—H2N11	121 (3)	C10—N11—H2N11	120 (2)
H1N11—N11—H2N11	119 (4)	H1N11—N11—H2N11	121 (2)
C10—N12—H1N12	115 (2)	C10—N12—H1N12	116 (1)
C10—N12—H2N12	117 (2)	C10—N12—H2N12	118 (1)
H1N12—N12—H2N12	126 (4)	H1N12—N12—H2N12	125 (2)
O10—C10—N11	120.7 (3)	O10—C10—N11	120.7 (2)
O10—C10—N12	120.6 (3)	O10—C10—N12	120.3 (1)
N11—C10—N12	118.6 (3)	N11—C10—N12	119.0 (1)
Succinic acid subunit		Fumaric acid subunit	
C1—O1—H1O1	112 (2)	C1—O1—H1O1	112 (2)
O1—C1—O2	123.2 (3)	O1—C1—O2	124.0 (1)
O1—C1—C2	113.1 (2)	O1—C1—C2	113.2 (1)
O2—C1—C2	123.7 (3)	O2—C1—C2	122.8 (1)
C1—C2—C2^{i}	113.3 (3)	C1—C2—C2^{ii}	123.0 (2)

Symmetry codes: (i) $-x, 2-y, 2-z$; (ii) $2-x, -y, -z$.

crystal structures. The twofold rotation axis primarily inherent in the urea molecule (Prior & Sanger, 1970) is lost in the new 1:1 comolecular formations, however, it is retained in the one-dimensional chain associations. The inversion centre in the central C—C (C=C) chemical bond of the parent acid molecules is also lost in the 1:1 comolecule, but is present in the chain mesoform. However, the inversion centre is preserved in the 2:1 comolecular units, which further self-associate through inversion relations into one-dimensional chains, whereas the 1:1 comolecules self-associate through screw translations. Therefore, the symmetry operators governing the recognition process between the comolecular units should be quite different for the two stoichiometric cocrystal forms. There are only inversion centres imposed on the 2:1 chain mesoforms, whereas combined inversion centres and twofold symmetry axes are imposed on the 1:1 chains. A generic atom labelling (see Figs. 3 and 4), consistent for all urea-dicarboxylic acid cocrystal structures, is used here in order to enable further parallel studies of bond and angle geometry and intermolecular interactions in both cocrystals. According to this labelling convention, the urea protons *syn*-positioned toward the urea oxygen are assigned with H_p and H_q, whereas those *anti*-positioned are assigned as H'_p and H'_q. The O atoms are assigned as O_o for urea and O_a and O_b for the hydroxyl and carbonyl oxygens of the carboxylic group. C_o belongs to the urea subunit, C_a to the carboxylic group and C_f to the acid chain.

According to the expectations, the urea-succinic and urea-fumaric acid cocrystals are isostructural. The hydrogen-bond connectivity patterns are the same in both (*cf.* Figs. 5*a* and *b*). The comolecules consist of two urea subunits symmetrically arranged *via* the strongest hydrogen-bond interaction $O_a—H_a\cdots O_o$

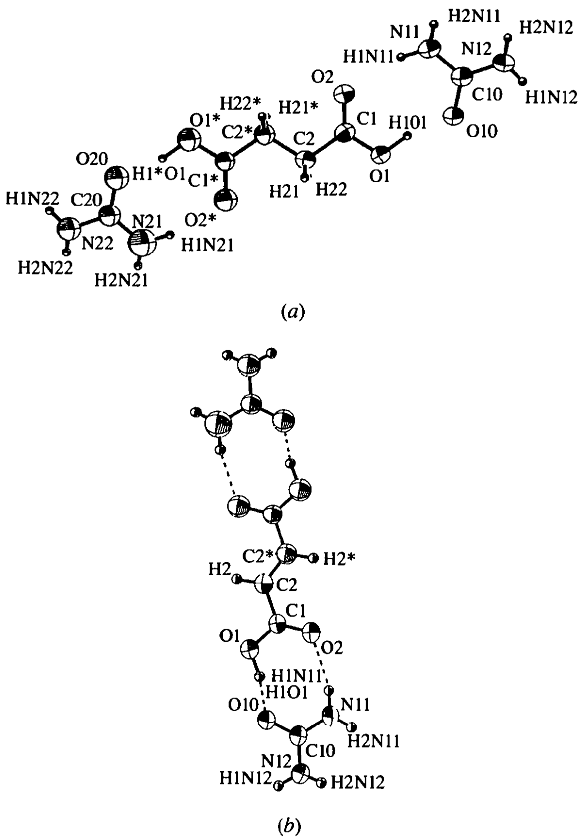

Fig. 1. An *ORTEPII* (Johnson, 1976) diagram of the (*a*) urea-succinic acid (2:1) unit and (*b*) urea-fumaric acid (2:1). Displacement elipsoids are depicted at 50% probability. Dashed lines indicate hydrogen bonds.

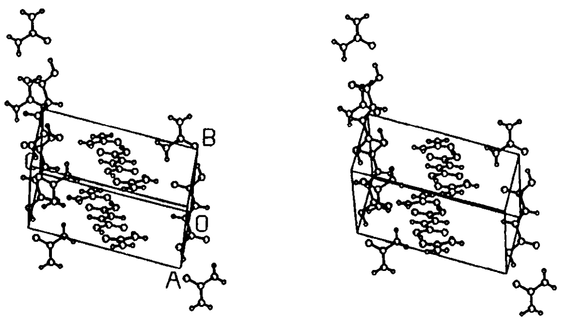

Fig. 2. A stereoview of the unit-cell packing of urea-fumaric acid (2:1) cocrystal.

Table 5. *Bond distances in the urea–succinic (2:1) and urea–fumaric acid (2:1) cocrystals compared with the bond distances of the parent compounds*

Compound bond lengths (Å)	Urea–succinic acid (2:1)	Urea–fumaric acid (2:1)	β-Succinic acid (Leviel, Auvert & Savariault, 1981)		α-Fumaric acid (Brown, 1966)		β-Fumaric acid (Bednowitz & Post, 1966)
α, ω-Dicarboxylic acid subunit			Neutron diffraction $T = 300$ K	$T = 77$ K	Centrosymmetric molecule	Non-centrosymmetric molecule	
C_a-O_a	1.305 (3)	1.301 (2)	1.305 (2)	1.321 (1)	1.287	1.293	1.289 (5)
O_a-H_a	1.03 (5)	0.96 (3)	0.995 (4)	1.005 (2)			
$C_a=O_b$	1.216 (3)	1.210 (2)	1.222 (2)	1.227 (1)	1.233	1.224	1.228 (4)
C_a-C_f	1.496 (4)	1.479 (2)	1.499 (2)	1.503 (1)	1.460	1.473	1.490 (5)
$C_f-C_{f'}$	1.512 (6)	1.299 (3)	1.508 (2)	1.520 (2)	1.361	1.334	1.315 (7)
C_f-C_c						1.462	
$C_c=O_d$						1.214	
O_c-H_c							
C_c-O_c						1.298	
$O_a\cdots O_b$			2.678 (2)	2.672 (1)	2.685	2.684	2.673 (4)
$H_a\cdots O_b$			1.687 (3)	1.670 (2)			
$O_c\cdots O_d$						2.682	
$H_c\cdots O_d$							
Urea subunit			Urea (Prior & Sanger, 1970)		Urea (Swaminathan, Craven & McMullan, 1984)		
$C_o=O_o$	1.255 (3)	1.258 (2)	1.260		1.265		
C_o-N_p	1.325 (4)	1.327 (2)	1.352		1.350		
$N_p-H_{p,\text{syn}}$	0.90 (4)	0.93 (3)	0.998		1.000		
$N_p-H'_{p,\text{anti}}$	0.76 (4)	0.83 (3)	1.003		0.991		
C_o-N_q	1.324 (4)	1.323 (2)					
$N_q-H_{q,\text{syn}}$	0.83 (4)	0.89 (2)					
$N_q-H'_{q,\text{anti}}$	0.80 (3)	0.82 (2)					
$N-H_{\text{syn}}\cdots O_o$	2.944 (4)	2.925 (2)	2.978		2.998 (1)		
$H_{\text{syn}}\cdots O_o$	2.13 (4)	2.04 (2)			2.009 (2)		
$N-H_{\text{anti}}\cdots O_o$			3.035		2.960 (1)		
$H_{\text{anti}}\cdots O_o$					2.067 (2)		

Table 6. *Bond angles in the urea–succinic (2:1) and urea–fumaric acid (2:1) cocrystals compared with the bond angles of the parent compounds*

Compound bond angle (°)	Urea–succinic acid (2:1)	Urea–fumaric acid (2:1)	β-Succinic acid		α-Fumaric acid		β-Fumaric acid
α, ω-Dicarboxylic acid subunit			$T = 300$ K	$T = 77$ K	Centrosymmetric molecule	Non-centrosymmetric molecule	
$C_a-O_a-H_a$	112 (2)	112 (2)	111.99 (22)	111.26 (1)	112.2	109.9	114 (9)
$O_a-C_a-O_b$	123.2 (3)	124.0 (1)	122.93 (13)	123.49	124.3	125.5	124.4 (7)
$O_a-C_a-C_f$	113.1 (2)	113.2 (1)	113.28 (10)	112.95	116.7	115.4	116.0 (6)
$O_b-C_a-C_f$	123.7 (3)	122.8 (1)	123.78 (11)	123.96	119.0	119.1	119.5 (6)
$C_a-C_f-C_{f'}$	113.3 (3)	123.0 (2)	112.47 (10)	112.45	122.8	124.0	122.5 (8)
$O_c-C_c-C_f$						114.2	
$O_d-C_c-C_f$						121.5	
$O_d-C_c-O_c$						124.3	
$C_c-O_c-H_c$						110.8	
$O_a-H_a\cdots O_b$			173.72 (29)	174.27 (12)			
Urea subunit			Urea (Prior & Sanger, 1970)		Urea (Swaminathan, Craven & McMullan, 1984)		
$O_o-C_o-N_p$	120.7 (3)	120.7 (2)	121.7		121.4		
$O_o-C_o-N_q$	120.6 (3)	120.3 (1)					
$N_q-C_o-N_p$	118.6 (3)	119.0 (1)			117.2		
$C_o-N_p-H_p$	120 (2)	119 (2)	119.0		119.2		
$C_o-N_p-H'_p$	121 (3)	120 (2)	120.2		120.7		
$H'_p-N_p-H_p$	119 (4)	121 (2)			120.1		
$C_o-N_q-H_q$	115 (2)	116 (1)					
$C_o-N_q-H'_q$	117 (2)	118 (1)					
$H_q-H_q-H'_q$	126 (4)	125 (2)					
$N-H_{\text{syn}}\cdots O$					166.8		
$N-H_{\text{anti}}\cdots O$					147.6		

(ranked as 1), which is additionally stabilized by $N_p-H_p\cdots O_b$ (ranked as 3) to form two eight-membered hydrogen bond rings on both sides of the parent acid subunits. These two hydrogen-bonds are undoubtedly the strongest bonding interactions in the whole three-dimensional network, cementing the subunits into stable comolecular units (see Table 7) and therefore they can be considered as intra-unit bonds.

Note the significant difference between our perception of the urea-succinic acid (2:1) comolecule and that of the molecular complex presented in the paper of Wiedenfeld & Knoch (1990). These authors consider the molecular complex to be formed by hydrogen bonds from the urea N—H protons (corresponding to $N_p—H'_p\cdots O_b$ and $N_q—H'_q\cdots O_b$ in our generic convention and ranked as the fourth and sixth strongest hydrogen bonds, respectively), which are *anti*-positioned towards the carbonyl oxygen. They do not discuss other hydrogen bonds which obviously exist. The fragment shown in Fig. 2 in their paper does not present the comolecule, but depicts parts of three different comolecular units belonging to different chains as it will be clear from the discussion below.

The second strongest hydrogen bond (ranked as 2) plays the role of an extramolecular (interunit) inter-

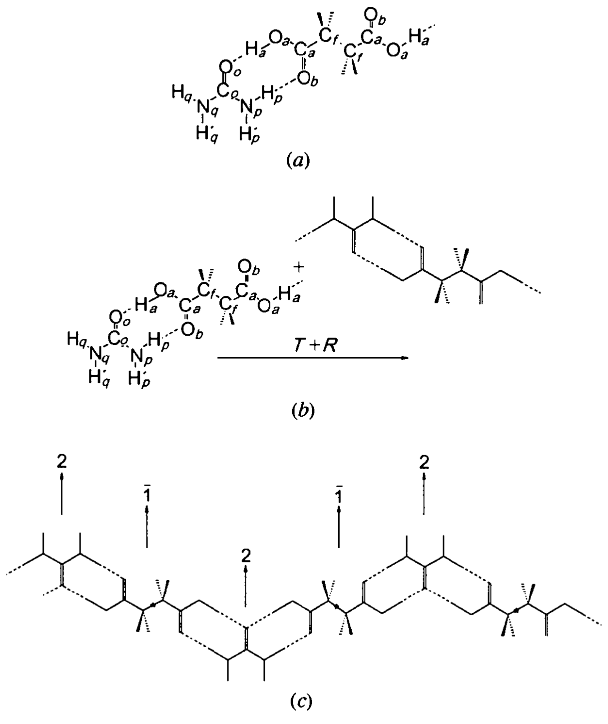

Fig. 3. (*a*) A generic form of the urea-succinic (fumaric) acid (1:1) comolecular unit. There is no any symmetry element imposed on it. (*b*) The hydrogen-bond recognition process between the comolecules is governed by a screw axis. Among all possible comolecules which are close enough to interact, only those with properly oriented hydrogen-bond sites will recognize and further self-assemble. (*c*) The postulated one-dimensional chain self-assembly of urea-succinic acid comolecules (as a *meso* form of the three-dimensional crystal organization). Both symmetry elements (twofold rotation axis and inversion centre) primarily inherent to the parent molecules are alternatively imposed on the chains. The still unused hydrogen-bond donors in *anti* positions ($N—H'_p$ and $N—H'_q$) and the unsatisfied hydrogen-bond acceptors (O_a and O_b lone pairs in *anti* positions) may enable further hydrogen-bond controlled organization.

Table 7. *Hydrogen-bond geometry (Å)*

$D—H\cdots A$	$D\cdots H$	$H—A$	$D\cdots A$
Urea–succinic acid (2:1)			
$O_a—H_a\cdots O_o^{i}$	1.03 (5)	1.52 (5)	2.533 (3)
$N_q—H_q\cdots O_o^{ii}$	0.83 (4)	2.13 (4)	2.944 (4)
$N_p—H_p\cdots O_b^{i}$	0.90 (4)	2.11 (4)	2.988 (5)
$N_q—H'_q\cdots O_b^{iii}$	0.80 (3)	2.24 (4)	2.998 (4)
$N_p—H'_p\cdots O_a^{iv}$	0.76 (4)	2.50 (4)	3.086 (4)
$N_p—H'_p\cdots O_b^{v}$	0.76 (4)	2.57 (4)	3.188 (5)
Urea–fumaric acid (2:1)			
$O_a—H_a\cdots O_o^{i}$	0.96 (3)	1.55 (3)	2.499 (2)
$N_q—H_q\cdots O_o^{vi}$	0.89 (2)	2.04 (2)	2.925 (2)
$N_p—H_p\cdots O_b^{i}$	0.93 (3)	2.06 (3)	2.966 (2)
$N_q—H'_q\cdots O_b^{vii}$	0.82 (2)	2.18 (2)	2.960 (2)
$N_p—H'_p\cdots O_b^{vii}$	0.83 (3)	2.50 (2)	3.172 (2)
$N_p—H'_p\cdots O_a^{viii}$	0.83 (3)	2.54 (3)	3.171 (2)

Symmetry codes: (i) x, y, z; (ii) $2-x, 1-y, 2-z$; (iii) $1-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iv) $x, \frac{3}{2}-y, z-\frac{1}{2}$; (v) $1-x, y-\frac{1}{2}, \frac{3}{2}-z$; (vi) $-x, 1-y, -z$; (vii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (viii) $x, \frac{1}{2}-y, \frac{1}{2}+z$.

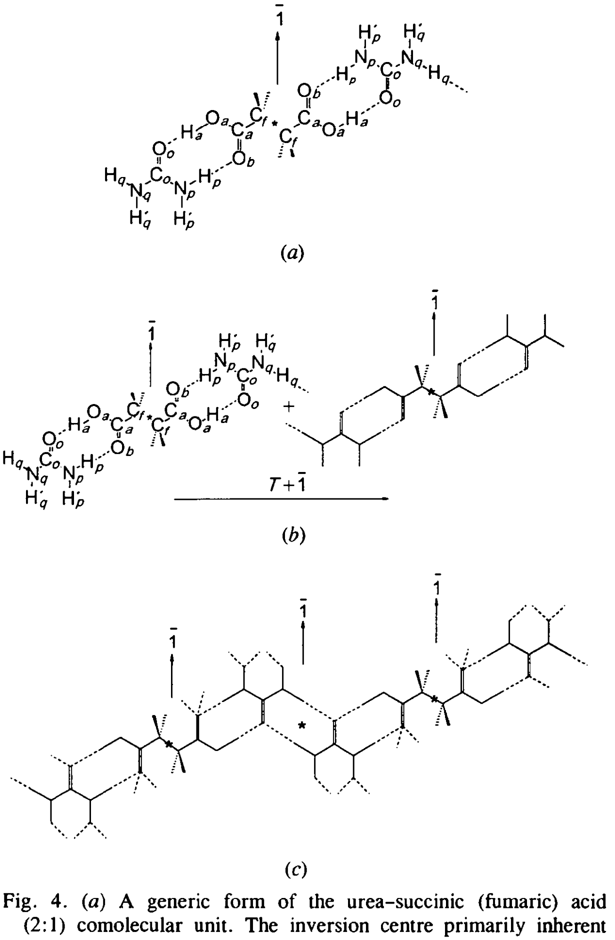

Fig. 4. (*a*) A generic form of the urea-succinic (fumaric) acid (2:1) comolecular unit. The inversion centre primarily inherent for the parent acid subunit is also retained in the comolecular unit. (*b*) The symmetry controlled self-assembly process also requires an inversion relation between the comolecular units in order to form chain *meso* forms. (*c*) Contrary to the case of urea-succinic acid (1:1), the chain assembly of urea-succinic acid (2:1) exhibits only one symmetry element: the inversion centre is imposed in the middle of the C—C (C=C) bonds and also between the comolecular units. The twofold axis is completely lost.

action and is used for comolecular self-association. Thus, the two *syn*-planar oxygen lone pairs and the two N—H *syn*-protons of urea are involved in heteromeric chain formation (*via* hydrogen bonds assigned as 1, 2 and 3). Two eight-membered hydrogen-bonded ring motifs with the same graph set $R_2^2(8)$ notation, but with different internal symmetries (1 and $\bar{1}$), are used in the formation of the connectivity patterns of the one-dimensional chains. These mesoforms are further organized through simple translation relations into two-dimensional comolecular layers held together through van der Waals forces (Fig. 5; KAP, stage 2). Unlike the case of urea–glutaric acid cocrystal (Videnova-Adrabińska, 1995*a*) the three-dimensional networks of the presented cocrystals do not contain independent two-dimensional hydrogen-bonded substructures (layers, Figs. 6 and 7). The *anti*-positioned urea protons (the double proton donor $N_p—H'_p$ and $N_q—H'_q$) are used to doubly cross-link two different comolecular chains in different directions. The three-dimensional structure can also be considered as interpenetrating van der Waals layers interlocked through the hydrogen bonds $N—H_{anti}\cdots O$ (ranked as 4, 5 and 6), which are significantly weaker compared with the $O_a—H_a\cdots O_o$ and $N—H_{syn}\cdots O_b$ and $N—H_{syn}\cdots O_o$ hydrogen bonds responsible for the primary formation of comolecules and chains. Hence, the additional hydrogen-bond donating capabilities of urea (the N—H *anti*-positioned proton donors) are exploited to form the three-dimensional networks (KAP, stage 3).

The hydrogen-bond lengths and contact distances for all six different hydrogen-bond interactions are collected in Table 7. A comparison between the bond distances and bond angles observed in the cocrystals and those of the parent compounds is presented in Tables 5 and 6, which clearly show that the heteromolecular hydrogen-bond contacts $O_a—H_a\cdots O_o$ [2.533 (3) Å for urea–succinic acid and 2.499 (2) Å for urea–fumaric acid] between the

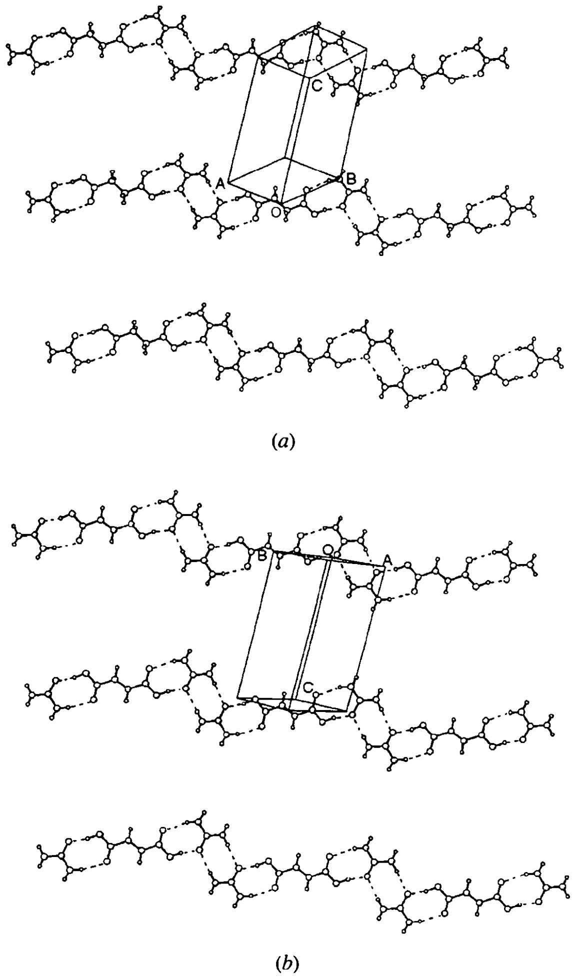

Fig. 5. The hydrogen-bond connectivity patterns in (*a*) urea–succinic acid (2:1) and (*b*) urea–fumaric acid (2:1) cocrystals. The two-dimensional comolecular formations can be considered as consisting of hydrogen-bonded comolecular chains which are further organized by van der Waals interactions and translation relations to form flat comolecular layers.

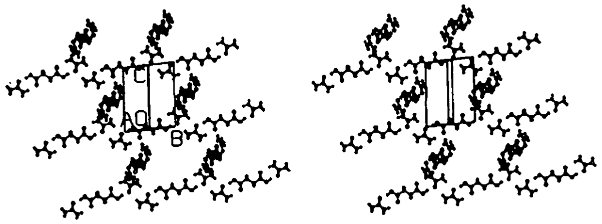

Fig. 6. A stereoview of the urea–succinic acid (2:1) cocrystal. The three-dimensional crystal structure consists of two independent hydrogen-bonded comolecular chains which are packed in a three-dimensional crystal structure through translation operations. Another way to consider the three-dimensional crystal packing patterns is as consisting of two independent monolayer systems (see Fig. 5) interlocked by weaker hydrogen bonds (assigned as 4, 5 and 6 in Table 7). The picture visualizes one comolecular monolayer crossed by six different chains (which are parts of other monolayers).

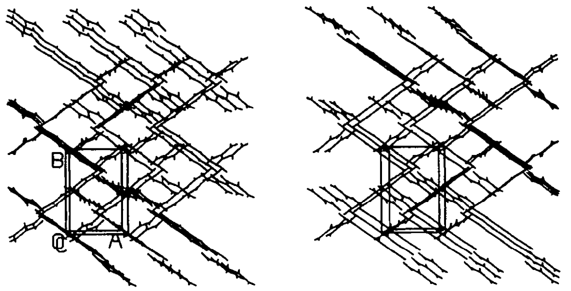

Fig. 7. A stereoview of the three-dimensional crystal structure of urea–fumaric acid (2:1) cocrystal vizualizing the mutual interpenetrating of two-dimensional comolecular layers interlocked by hydrogen-bond interactions.

carboxylic oxygen and the urea oxygen are shorter than the homomolecular contacts $O_a—H_a\cdots O_b$ [2.678 (2) Å for succinic acid and 2.685 Å for fumaric acid] and $N—H_{syn}\cdots O_o$ [2.998 (1) Å for urea], which means that the urea–urea or acid–acid interactions are less preferable than the urea–acid interactions. This leads to a stable comolecular unit formation. In other words, the heteromolecular self-association is energetically and topologically more favourable compared with homomolecular self-associations. Also the relatively weak homomolecular hydrogen-bond interactions along the urea dipolar C=O axis are interrupted in favour of the interactions between urea and the carboxylic groups. The geometrical proximity of the urea oxygen is modified and it is accessible only for the $N—H_{syn}$ protons and only in a *syn*-planar position along the lone-pair lobes (compared with the crystal structure of urea where both *syn*- and *anti*-planar connections between urea are realized in three dimensions). No *anti*-planar approach to the urea oxygen is observed in any of the resolved cocrystal structures. These results demonstrate the significance of the symmetry factors for the recognition process between the molecular units during their three-dimensional crystal arrangement. So, the effective molecular recognition, considered as a dynamical selective process, based on the stereochemical, stereoelectronic, geometrical and functional complementarity of the molecular units in the solution, should be additionally considered as a toposelective and symmetry constraint process in the solid-state organization.

An interesting fact is that by adding two urea molecules on both sides of the parent acid, the crystal packing of the heteroaggregates is in the same space group ($P2_1/c$) as for the parent acid. The number of comolecules per unit cell remains unchanged (two) for the succinic acid crystal and for the urea–succinic acid (2:1) cocrystal. The only significant difference in the crystal lattice parameters is the doubling of the *c*-lattice constant [from 5.101 Å for succinic acid to 12.258 (3) Å for the cocrystal] with *a* and *b* remaining almost the same. The monoclinic angle β opens a little more in the cocrystal structure. The comparative study of the intramolecular distances of the cocrystals and the parent molecules shows that the main deviations from the geometry occur in the hydrogen-bond sites, which is reasonable and expected. The bond distances are slightly changed in the urea-dicarboxylic acid cocrystal compared with the parent acid: $C_a—O_a$ slightly elongates (in urea–fumaric cocrystal), whereas the $C_a{=}O_b$ bond contracts and becomes of more double-bond character (in both cocrystals). This new connectivity pattern in the cocrystal reflects the changes of the electron density around the O atoms. The $C_f{=}C_f$ bond is significantly shorter and has more double-bond character in the cocrystal than in fumaric acid. Also the intermolecular distances change reasonably from homomeric to heteromeric association.

Since the hydrogen-bonded urea–dicarboxylic comolecular units, defined and discussed in this paper, are very stable independent formations with modified recognition capabilities we can finally conclude that they can be considered as stable building blocks for crystal design. Clever use of the van der Waals interactions and additional weaker hydrogen-bond interactions should give rise to a variety of higher level comolecular organizations (Desiraju, 1989). Predesigned structural building blocks of actual shapes and geometries and with suitably arranged recognition sites are the fundamental platform for the crystal engineering in a broad sense.

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