

N–H...O and C–H...O interaction mimicry in the 1:1 molecular complexes of 5,5-diethylbarbituric acid with urea and acetamide

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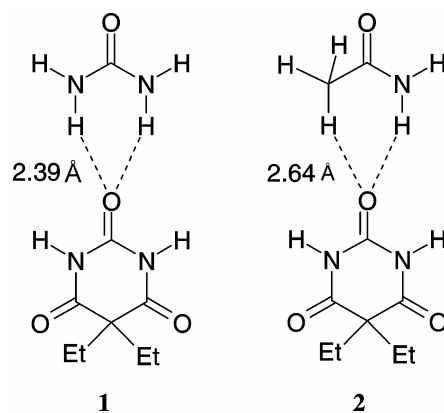
The analogy between N–H...O and C–H...O intermolecular interactions is studied with variable temperature (180–100 K) single crystal X-ray diffraction analysis. 5,5-Diethylbarbituric acid (barbital) forms isostructural molecular complexes (co-crystals) with urea (**1**) and acetamide (**2**) that respectively contain these analogous interactions. The behaviour of these two interactions as a function of temperature is very similar. This indicates that the C–H...O bond in barbital–acetamide plays a similar chemical and structural role as does the N–H...O bond in barbital–urea. The close relationship between these interactions and their comparable nature is further adduced from the formation of a ternary solid solution (**3**) of barbital, urea and acetamide. The fact that the C–H...O interaction in barbital–acetamide is weaker than the N–H...O interaction in barbital–urea is shown by the fact that acetamide is under expressed and urea is over expressed with respect to the quantities of these substances present in solution prior to crystallization of these ternary crystals.

Keywords: Barbital, co-crystal, hydrogen bond, isostructurality, X-ray crystallography.

INTERACTION mimicry, wherein an intermolecular interaction in a crystal structure is substituted by another interaction in the crystal structure of another compound with little other change in the overall packing arrangement, has generally been taken to be an indication of the equivalence of the two interactions^{1,2}. This kind of analogy has been especially helpful in our understanding of hydrogen bonds, for example, the weak C–H...O bond. Hydrogen bonding is an interaction type of major importance and pervasive significance in structural chemistry and biology³. After a century of intensive research into its nature and properties, there is still no sign of any diminution of interest in this subject⁴.

One of the earliest mentioned examples of interaction mimicry are the analogous N–H...O and C–H...O interactions in the pair of isomorphous 1:1 molecular complexes (nowadays referred to as co-crystals in the crystal

engineering literature⁵) formed respectively by 5,5-diethylbarbituric acid (barbital) with urea⁶ and acetamide⁷. Both barbital–urea (**1**) and barbital–acetamide (**2**) take the space group $P2_12_12_1$ with practically identical unit cell parameters. Of note are the equivalent bifurcated–acceptor arrangements which are found respectively in the two crystal structures (Scheme 1). Hsu and Craven⁷ noted that these structures are equivalent but they specifically stated that the C–H...O bond of 2.64 Å in **2**, which replaces the N–H...O bond of 2.39 Å in **1**, is not a hydrogen bond because it is at the ‘normal van der Waals distance’. This interpretation reveals the classical attitude towards hydrogen bonding prevalent during those times⁸. A decade later, Berkovitch-Yellin and Leiserowitz⁹ interpreted this C–H...O geometry in **2** as a hydrogen bond with the following argument. They stated that because **1** and **2** are isostructural, it means that the C–H...O contact of 2.64 Å in **2** plays the same chemical role as does the N–H...O contact of 2.39 Å in **1**. Since the N–H...O contact in **1** is unquestionably a hydrogen bond, this means that the C–H...O contact in **2** is likewise also one. Extensions to this line of thought are to be found elsewhere and interaction analogy continued to be a powerful argument while discussing the nature and role of many weak intermolecular interactions^{10–12}.



Scheme 1. Bifurcated hydrogen bonds in molecular complexes **1** and **2**. An N–H...O bond of 2.39 Å in **1** is replaced by an equivalent C–H...O bond of 2.64 Å in **2**. These interactions distances are taken from the papers of Craven and co-workers (refs 6 and 7).

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However, analogy-based arguments of this kind can be contested. For example, it could be maintained that the C–H...O geometry in **2** is a forced contact and that it is a consequence of all the other interactions in the structure, notably the other N–H...O hydrogen bond that is conserved. If the 2.64 Å C–H...O distance is indeed a forced contact, it could lie in the repulsive region, or even be destabilizing³. It has also been stated that many C–H...O geometries in crystal structures need not be attributed to specific attractive interactions of the hydrogen bond type and that they may be accommodated within the scope of close packing considerations^{13,14}. Beyond a point, none of these arguments that argue in favour of or against a particular C–H...O geometry being a hydrogen bond or a repulsive forced contact, can be proved or disproved by merely observing and comparing isolated crystal structures. However, and in all fairness, there is general consensus that short H...O contacts formed by activated C–H groups have hydrogen bond character. When the C–H group in question is not activated, the matter is ambiguous. The C–H...O contact in **2** is not from an activated C–H group. It is also not so short. Further, it is part of a bifurcated geometry. Accordingly, while it might not exactly be termed as being repulsive, it may also not be particularly attractive or crystal structure determining in nature. Is there a more definitive way of characterizing this interaction?

Variable temperature measurements offer a possible means of evaluating weak interactions like the C–H...O hydrogen bond. This is because the hydrogen bond X–H...Y is an electrostatic interaction which may be understood as a screening of negative charges on X and Y by the positively charged H-atom. Accordingly, all true hydrogen bonds will undergo a shortening and also a straightening out when the measurement temperature is lowered. If an X–H...Y contact is a forced one, then it will lengthen and/or take a more distorted nonlinear geometry upon lowering of temperature. Let us consider the case of a hexakis-adduct of C₆₀. The molecule contains >C(CO₂C₂H₅)₂ groups and the crystal structure contains seven distinct sets of C–H...O geometries involving these groups¹⁵. At 270 K, six of these occur in the *D* and θ ranges 3.26–3.60 Å and 125–155° (neutron corrected). The crystal structure was re-determined at 230 K and again at 180 K and it was observed that these six C–H...O geometries became shorter with a decrease in temperature. The decrease in *D* ranged from 0.01 to 0.09 Å while θ remained practically unchanged. As mentioned here, this kind of behaviour is very characteristic of interactions that are both attractive and stabilizing (hydrogen bonds). The seventh interaction was, however, noted to be different. It occurs in a centrosymmetric dimer pattern involving carboxy groups. The values of *D*, *d* and θ at 270 K are 3.49 Å, 2.41 Å and 174°. Upon cooling to 230 K, the values become 3.51 Å, 2.41 Å and 177°. Finally at 180 K, they are 3.56 Å, 2.46 Å and 178°. If the

H-atom positions are corrected, the *d* value is seen to rise from 2.40 to 2.49 to 2.50 Å while the θ value falls from 173° to 154° before rising to 163° at the lowest temperature. These observations are interpreted as being caused by repulsion. In order to further investigate the analogous behaviour of C–H...O and N–H...O hydrogen bonds in the barbital co-crystals, a variable temperature study (from 180 to 100 K) of the crystal structures of **1** and **2** was carried out.

Materials and methods

5,5-Diethylbarbituric acid 99% (Qualigens), urea 99% (BDH) and acetamide 99% (E. Merck) were procured commercially. *n*-Propanol (LR grade), ethanol (AR grade) and cyclohexane (LR grade) were used without further purification.

Sample preparation

Co-crystals **1** and **2** could not be obtained with the literature procedures^{6,7}. Accordingly, the procedures were changed. Barbital (600 mg, ~3.3 mmol) and urea/acetamide (300 mg, ~5.0/5.1 mmol) were hand ground using the solvent drop technique¹⁶ with *n*-PrOH in a mortar and pestle for 10 min and this mixture was then dissolved in 1:1 *n*-PrOH:EtOH (for barbital–urea) and 4:1 *n*-PrOH:cyclohexane (for barbital–acetamide). The solutions were slowly evaporated at room temperature till single crystals of **1** and **2** that were suitable for X-ray diffraction were obtained. Ternary solid solutions **3** were prepared from barbital, urea and acetamide using solvent drop grinding with EtOH. Details of these co-crystal preparations are given in Table 1.

Single-crystal X-ray diffraction

Variable temperature data (180–100 K) were collected for **1** and **2** using a Bruker SMART 4K CCD diffractometer using MoK α X-radiation¹⁷ equipped with an Oxford Cryosystems Cryostream cooling apparatus. Data were processed using the Bruker SAINT package¹⁸ with structure solution and refinement using SHELX97 (ref. 19). Data were collected for co-crystal **3** on a Rigaku Mercury375R/M CCD (XtaLAB mini) diffractometer using graphite monochromated Mo–K α radiation, equipped with a Rigaku low temperature gas spray cooler. In these cases, data were processed with the Rigaku CrystalClear software²⁰. Structure solution and refinements were performed using SHELX97 (ref. 19) using the WinGX suite²¹. All structures were solved by direct methods and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for all non-hydrogen atoms. ORTEP diagrams of **1**, **2** and **3** (at 150 K) are

Table 1. Ternary co-crystals of barbital (B), acetamide (A) and urea (U)

	Molar equivalents of B : A : U taken in solution	Crystallizing solvent ^a	Molar equivalents of B : A : U in co-crystal ^b	N/C–C=O bond length ^c (Å)	Melting point ^d (°C)
1	1 : 0 : 1	EtOH	1 : 0 : 1	1.347(2)	150.3
3a	1 : 1 : 1	EtOH	1 : 0.16 : 0.84	1.416(3)	134.7
3b	1 : 3 : 3	EtOH	1 : 0.24 : 0.76	1.417(2)	132.2
3c	1 : 0.2 : 0.8	EtOH	1 : 0 : 1	1.358(2)	147.3
3d	1 : 0.4 : 0.6	EtOH	1 : 0 : 1	1.349(2)	141.4
3e	1 : 0.5 : 0.5	MeOH	1 : 0.26 : 0.74	1.414(2)	129.8
3f	1 : 0.6 : 0.4	EtOH	1 : 0.33 : 0.67	1.434(2)	128.4
3g	1 : 0.8 : 0.2	EtOH	1 : 0.43 : 0.57	1.471(3)	123.7
2	1 : 1 : 0	EtOH	1 : 1 : 0	1.499(2)	119.5

^aIn all cases, solvent drop grinding was performed by co-grinding the B : A : U mixture with 1–2 drops of EtOH for 15–20 min.

^bThese values were as given by the converged refinements of the positional occupancies of the pertinent N/C atoms of urea/acetamide in the co-crystal.

^cN/C–C=O bond lengths corresponds to 150 K data.

^dRecorded with DSC at a heating rate of 5°C/min.

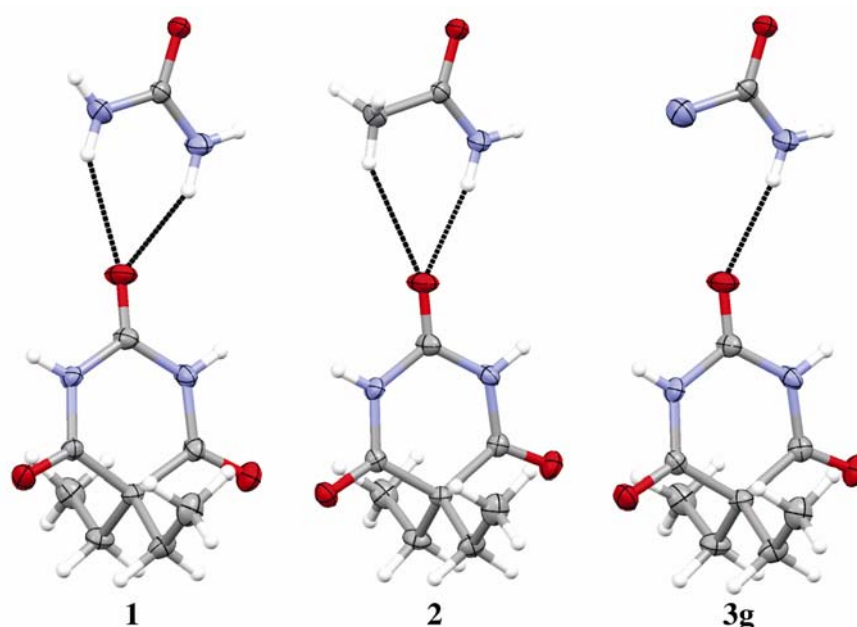


Figure 1. ORTEP diagrams of co-crystals barbital–urea (**1**), barbital–acetamide (**2**) and barbital–acetamide–urea (**3g**) at 150 K (ellipsoids are shown at 50% probability).

given in Figure 1. For **1** and **2**, all the H-atoms on the NH₂ and CH₃ groups were identified on the difference map and refined freely. In **3**, one of the NH₂ groups is partly replaced by a CH₃ group and the relative site occupancies were obtained by modelling the disorder in the C/N-atom positions using EXYZ and EADP constraints. Three *q*-peaks corresponding to the H-atom positions were found in the difference map around the disordered N/C-atom and a Newman projection of these positions is shown in Figure 2. Other H-atoms were placed in calculated positions and refined. Crystal data and details of data collections, structure solutions and refinements for **1** and **2** are summarized in Tables 2 and 3. For the ternary crystals **3**, the crystallographic details are given in Table 4. Extended packing diagrams for **1** and **2** are given in

Figures 3 and 4. Data on hydrogen bonds are given in Tables 5–7.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) data were recorded on a Mettler Toledo DSC 823^o instrument. Heating of the samples was done at a rate of 5°C/min up to 200°C with the purging of dry nitrogen gas (20 mL/min).

Results and discussion

The two isostructural co-crystals **1** and **2** show multiple N–H···O and C–H···O intermolecular contacts forming a

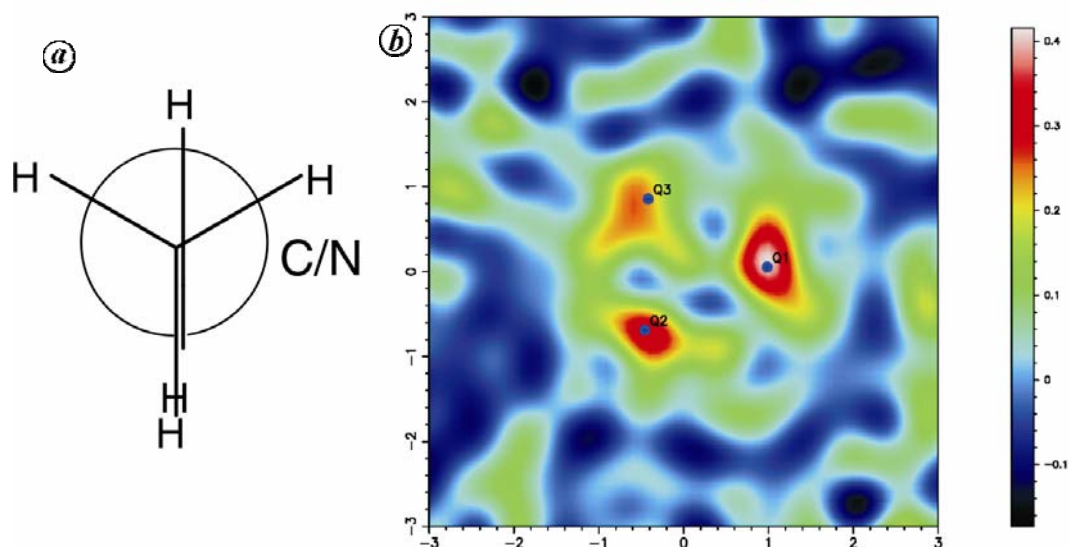


Figure 2. *a*, Newman projection showing H-atom positions for the methyl group of acetamide and the amino group of urea occupying the same site in the B:A:U ternary crystals. *b*, Difference Fourier map showing three *q*-peaks corresponding to the H-atom positions around the disordered N/C-atom.

Table 2. X-ray crystallographic data for co-crystal **1** ($C_8H_{12}N_2O_3 : CH_4N_2O$, $P2_12_12_1$, $Z = 4$) as a function of temperature

	180 K	160 K	140 K	120 K	100 K
<i>a</i> (Å)	10.078(4)	10.061(5)	10.057(6)	10.029(6)	10.013(6)
<i>b</i> (Å)	10.200(4)	10.184(5)	10.184(7)	10.155(6)	10.141(7)
<i>c</i> (Å)	11.662(5)	11.662(6)	11.682(7)	11.669(7)	11.674(8)
<i>V</i> (Å ³)	1198.8(9)	1195.0(10)	1196.5(13)	1188.4(12)	1185.4(13)
ρ_{calc} (g/cm ³)	1.353	1.358	1.356	1.365	1.369
μ (MoK α) (mm ⁻¹)	0.107	0.108	0.108	0.108	0.109
R_1 [$I > 2\sigma(I)$]	0.0336	0.0352	0.0346	0.0339	0.0336
wR_2	0.0768	0.0815	0.0826	0.0766	0.0767
Goodness-of-fit	1.039	1.025	1.089	1.055	1.023
Unique reflections	2365	2366	2366	2363	2353
Observed reflections	2082	2100	2028	2109	2128

Table 3. X-ray crystallographic data for co-crystal **2** ($C_8H_{12}N_2O_3 : C_2H_5NO$, $P2_12_12_1$, $Z = 4$) as a function of temperature

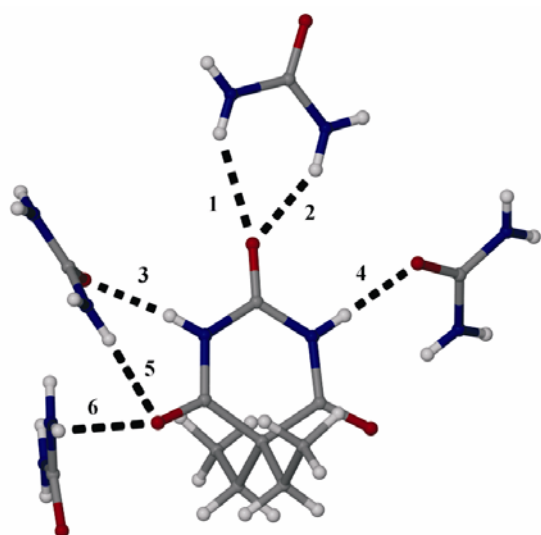
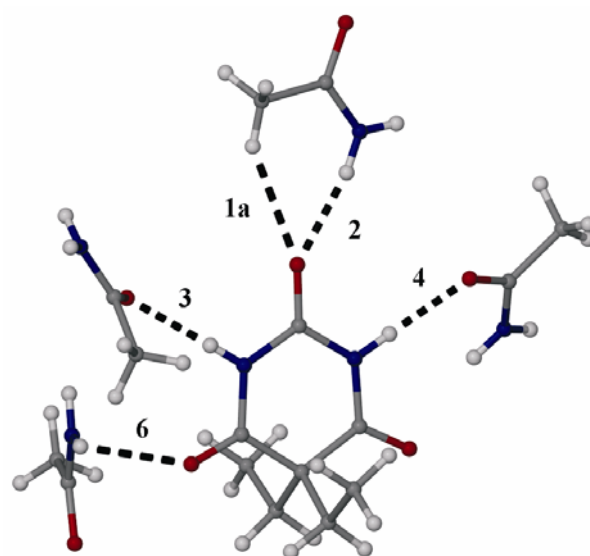
	180 K	160 K	140 K	120 K	100 K
<i>a</i> (Å)	10.516(2)	10.503(2)	10.4836(8)	10.4699(8)	10.4572(9)
<i>b</i> (Å)	10.521(2)	10.516(2)	10.5020(8)	10.4946(8)	10.4921(10)
<i>c</i> (Å)	11.169(2)	11.161(2)	11.1488(9)	11.1399(8)	11.1366(10)
<i>V</i> (Å ³)	1235.8(4)	1232.7(4)	1227.47(17)	1224.06(16)	1221.89(19)
ρ_{calc} (g/cm ³)	1.308	1.311	1.316	1.320	1.322
μ (MoK α) (mm ⁻¹)	0.102	0.102	0.102	0.103	0.103
R_1 [$I > 2\sigma(I)$]	0.0309	0.0299	0.0287	0.0274	0.0290
wR_2	0.0718	0.0718	0.0686	0.0659	0.0608
Goodness-of-fit	1.064	1.061	1.052	1.055	0.963
Unique reflections	2453	2453	2403	2389	2393
Observed reflections	2284	2287	2260	2265	2024

complex 3D hydrogen bond network. Arguments pertaining to whether the C–H...O interaction in crystal **2** is a true hydrogen bond or merely a geometrical construct is addressed by the variable temperature measurements.

Co-crystal 1: Two important types of N–H...O hydrogen bond are observed. The first has urea as an NH-donor and barbital as a bifurcated O-acceptor. In the second, barbital acts as an NH-donor and urea behaves as the

Table 4. Crystallographic and structure refinement details for the binary and ternary co-crystals of barbital, acetamide and urea ($P2_12_12_1$, $Z = 4$). All data were collected at 150 K

	1	3a	3b	3c	3d	3e	3f	3g	2
a (Å)	10.081(3)	10.300(2)	10.297(4)	10.408(2)	10.415(1)	10.306(2)	10.239(1)	10.124(4)	10.483(3)
b (Å)	10.203(3)	10.320(2)	10.306(4)	10.431(2)	10.444(1)	10.313(1)	10.334(1)	10.242(4)	10.506(3)
c (Å)	11.656(4)	11.375(2)	11.397(4)	11.249(2)	11.343(1)	11.380(2)	11.578(1)	11.595(4)	11.152(3)
V (Å ³)	1198.9(7)	1209.1(4)	1209.5(8)	1221.3(4)	1233.8(2)	1209.5(3)	1225.1(2)	1202.3(8)	1228.2(6)
ρ_{calc} (g/cm ³)	1.353	1.329	1.329	1.313	1.301	1.327	1.324	1.349	1.316
μ (MoK α) (mm ⁻¹)	0.107	0.106	0.106	0.104	0.103	0.105	0.105	0.107	0.102
R_1 [$I > 2\sigma(I)$]	0.0293	0.0318	0.0440	0.0482	0.0380	0.0339	0.0374	0.0314	0.0336
wR_2	0.0784	0.0890	0.1079	0.1202	0.1040	0.0951	0.0919	0.0877	0.0754
Goodness-of-fit	1.127	1.114	1.097	1.031	1.111	1.126	1.090	1.186	1.066
Reflections collected	12425	12409	12921	12771	13004	12612	12927	11401	13029
Unique reflections	2726	2764	2773	2789	2818	2767	2797	2733	2810
Observed reflections	2668	2699	2419	2265	2611	2650	2382	2558	2571
CCDC No.	767622	767625	767624	767630	767629	767628	767627	767626	767623

**Figure 3.** N–H...O hydrogen bond network in the barbital–urea co-crystal **1**. The numbering of hydrogen bonds corresponds to the numbers in Table 5.**Figure 4.** N–H...O and C–H...O hydrogen bond network in the barbital–acetamide co-crystal **2**. The numbering of hydrogen bonds corresponds to the numbers in Table 6.

O-atom acceptor. This is shown in Figure 3 and Scheme 2. These hydrogen bonds are shown in Scheme 2 using the synthon nomenclature²².

The two N...O distances (D) in the N–H...O bonds in synthon **II** shorten from 2.767 to 2.757 Å and from 2.802 to 2.796 Å as the temperature is lowered. The hydrogen bonds in synthon **I** are expectedly longer but they too shorten from 3.115 to 3.090 Å and from 2.937 to 2.925 Å as the temperature is lowered. These changes in distance are outside the standard deviations (3σ) and so they are significant. The hydrogen bond angles in both synthons hardly change with temperature. All these N–H...O bonds show the classical behaviour of true hydrogen bonds—they become shorter upon cooling with a very slight increase of the angles (Table 5). Especially in synthon **I**, a change in angle with temperature is not expected because

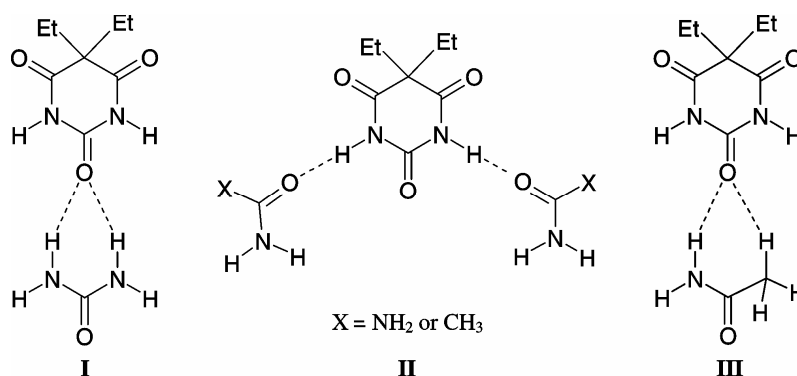
of geometrical constraints inherent in a bifurcated geometry.

Co-crystal **2**: In this case too, synthon **II** is seen but synthon **I** is modified to **III** because the relevant NH₂ group (in urea) is replaced by the CH₃ group of acetamide (Scheme 2). The H-atom of the methyl group makes a contact with the O-atom of barbital and it is noted that the relevant C–H bond is coplanar with the rest of synthon **III** – an indication that the C–H...O contact (indicated by the numerical 1a in Figure 4) is indeed a hydrogen bond.

As expected, the N–H...O bonds in the crystal structure shorten upon cooling. Of crucial importance, however, is the variable temperature behaviour of the C–H...O contact. On lowering the temperature from 180 to 100 K, it was found that this C–H...O contact shows a consistent and regular shortening from 3.464 to 3.447 Å while the

Table 5. Geometrical parameters of N–H...O hydrogen bonds in co-crystal **1** as a function of temperature. The number in parentheses for each hydrogen bond corresponds to that given in Figure 3

X–H...A	Temperature (K)	X–H (Å)	H...A (Å)	X...A (Å)	∠X–H...A (°)
N–H...O(1)	180	0.86(2)	2.38(2)	3.115(3)	144(2)
	160	0.83(3)	2.37(3)	3.107(3)	147(3)
	140	0.89(2)	2.37(3)	3.101(3)	139(2)
	120	0.83(2)	2.39(2)	3.097(3)	143(2)
	100	0.83(2)	2.38(2)	3.090(3)	145(2)
N–H...O(2)	180	0.85(2)	2.15(2)	2.937(2)	155(2)
	160	0.86(2)	2.12(2)	2.936(3)	158(2)
	140	0.89(2)	2.09(2)	2.931(3)	158(2)
	120	0.87(2)	2.11(2)	2.930(2)	156(2)
	100	0.88(2)	2.10(2)	2.925(2)	156(2)
N–H...O(3)	180	0.87(2)	1.89(2)	2.767(2)	175(2)
	160	0.87(2)	1.90(2)	2.765(2)	176(2)
	140	0.91(2)	1.86(2)	2.764(2)	173(2)
	120	0.86(2)	1.90(2)	2.761(2)	172(2)
	100	0.84(2)	1.92(2)	2.757(2)	172(2)
N–H...O(4)	180	0.87(2)	1.93(2)	2.799(2)	177(2)
	160	0.87(2)	1.93(2)	2.798(2)	176(2)
	140	0.85(2)	1.95(2)	2.802(2)	173(2)
	120	0.86(2)	1.94(2)	2.797(2)	175(2)
	100	0.85(2)	1.94(2)	2.796(2)	177(2)
N–H...O(5)	180	0.86(2)	2.40(3)	3.229(3)	161(2)
	160	0.87(2)	2.40(2)	3.217(3)	158(2)
	140	0.83(2)	2.42(2)	3.215(3)	160(2)
	120	0.85(2)	2.38(2)	3.195(3)	160(2)
	100	0.85(2)	2.39(2)	3.186(3)	158(2)
N–H...O(6)	180	0.81(2)	2.44(2)	3.060(2)	134(2)
	160	0.85(2)	2.40(2)	3.051(3)	134(2)
	140	0.83(2)	2.41(2)	3.053(3)	134(2)
	120	0.83(2)	2.38(2)	3.040(3)	137(2)
	100	0.85(2)	2.35(2)	3.033(3)	138(2)

**Scheme 2.** Sketch of hydrogen bonded synthons discussed in this paper.

hydrogen bond angle remains practically unchanged (Figure 5 and Table 6). Once again, these changes are outside the standard deviations (3σ). From this observation, it is clear that this particular C–H...O geometry corresponds to a genuine hydrogen bond. Being somewhat weak (long, bifurcated, unactivated donor), this contact may not be crystal structure determining but rather just supportive: but a true hydrogen bond it certainly is. The

rest of the intermolecular contacts also show a shortening of distances with the hydrogen bond angles tending towards linearity at lower temperatures.

An interesting sidelight to the crystal packing of co-crystal **2** is that it is the weaker of the two N–H...O hydrogen bonds in the bifurcated synthon **I** in co-crystal **1** (3.115 Å, 144°; 2.937 Å, 155° at 180 K) that is replaced by the C–H...O bond when urea is replaced by acetamide.

Table 6. Geometrical parameters of N–H...O and C–H...O hydrogen bonds in co-crystal **2** as a function of temperature. The number within parentheses for each hydrogen bond corresponds to that given in Figure 4

X–H...A	Temperature (K)	X–H (Å)	H...A (Å)	X...A (Å)	∠X–H...A (°)
C–H...O(1a)	180	0.92(2)	2.66(2)	3.464(2)	146(2)
	160	0.94(2)	2.63(2)	3.458(2)	147(2)
	140	0.96(2)	2.61(1)	3.455(2)	147(1)
	120	0.93(2)	2.64(2)	3.449(2)	145(1)
	100	0.96(2)	2.63(2)	3.447(2)	143(1)
N–H...O(2)	180	0.83(2)	2.12(2)	2.946(2)	169(2)
	160	0.84(2)	2.12(2)	2.944(2)	169(2)
	140	0.84(2)	2.11(2)	2.941(2)	168(2)
	120	0.84(2)	2.11(2)	2.937(2)	169(2)
	100	0.83(2)	2.06(2)	2.933(2)	167(2)
N–H...O(3)	180	0.83(2)	1.98(2)	2.809(2)	177(2)
	160	0.85(2)	1.96(2)	2.804(2)	176(2)
	140	0.84(2)	1.96(2)	2.800(2)	178(2)
	120	0.82(2)	1.98(2)	2.795(2)	176(2)
	100	0.88(2)	1.91(2)	2.794(2)	179(2)
N–H...O(4)	180	0.86(2)	1.98(2)	2.835(2)	175(2)
	160	0.88(2)	1.96(2)	2.832(2)	173(2)
	140	0.89(2)	1.95(2)	2.828(2)	173(2)
	120	0.91(2)	1.92(2)	2.826(2)	173(2)
	100	0.92(2)	1.91(2)	2.825(2)	171(2)
N–H...O(6)	180	0.84(2)	2.43(2)	3.031(2)	129(2)
	160	0.86(2)	2.41(2)	3.023(2)	128(2)
	140	0.87(2)	2.38(2)	3.014(2)	131(2)
	120	0.85(2)	2.38(2)	3.008(2)	131(2)
	100	0.85(2)	2.38(2)	3.003(2)	131(1)

One might well ask if it is this lack of degeneracy in these two N–H...O bonds in **1** that disposes this system to an isomorphous co-crystal formation. Is the longer of these bonds (interaction 1 in Figure 3) the ‘weakest’ link in the structure thereby rendering it capable of replacement and modification? Alternatively, one might ask if co-crystal formation with acetamide could have been achieved if the two N–H...O bonds had been more comparable in strength. This last question is perhaps easier to answer. Given that the variable temperature measurements indicate that the C–H...O bond in **2** (interaction 1a in Figure 4) is a true hydrogen bond, and also given the fact that acetamide competes effectively with urea for barbituric acid (see the following experiment), the driving force for the formation of a C–H...O based co-crystal is always real, in the presence of acetamide. It would not matter whether or not the two N–H...O segments in the bifurcated arrangement in urea–barbital are of equal strengths or not—the co-crystal between acetamide and barbital will always be formed. A further and more delicate point is that it is not known what the N–H...O bond lengths would have been in a symmetrical bifurcated arrangement for co-crystal **1**.

Co-crystals 3a–h: To further deploy our argument that the C–H...O contact is a real hydrogen bond rather than just a van der Waals contact, we co-crystallized sev-

eral mixtures of barbital, urea and acetamide. In all cases, we obtained isostructural ternary complexes **3**, whose crystal structures showed slightly different occupancies of urea and acetamide in the crystal. Table 1 gives the preparation conditions for these co-crystals and Table 4 gives the crystallographic details.

Evidence for the presence of acetamide in the ternary co-crystals arises in the following ways: (i) A comparison of the crystal structures of **1**, **2** and **3** at the same temperature (150 K) shows that the values of cell parameters, cell volume, intramolecular dimensions and intermolecular interactions in **3** lie between those of **1** and **2**. This is given in Tables 4 and 7. Most notably the intramolecular C–N distance in **1** is 1.347 Å, while the equivalent C–C distance in **2** is 1.499 Å. The corresponding distances in **3a** through **3g** lie in the range 1.349–1.471 Å enabling one also to estimate the relative amounts of urea and acetamide in these ternary crystals. (ii) The difference map shows evidence for the presence of three peaks corresponding to H-atoms around the pertinent N/C atom in ternary co-crystals **3a**, **3b** and **3e–g**. Among these three peaks, one of them corresponds to the overlapping H-atoms between one NH₂ position and one CH₃ position (found stable on H-atom assignment in refinements). Two other positions correspond to the two other CH₃ positions (Figure 2) detectable only in ternary compositions with a

Table 7. Geometrical parameters of N–H...O and C–H...O hydrogen bonds found in the binary (**1** and **2**) and ternary (**3a–g**) co-crystals of barbitol, acetamide and urea determined at 150 K. The interactions (numbered) correspond to those given in Figures 3 and 4

B : A : U	Interaction	X–H (Å)	H...A (Å)	X...A (Å)	∠X–H...A (°)
1	1	0.85(2)	2.40(2)	3.116(2)	143(2)
	2	0.90(2)	2.10(2)	2.937(2)	155(2)
	3	0.84(2)	1.93(2)	2.763(1)	174(1)
	4	0.85(2)	1.95(2)	2.794(1)	178(1)
	5	0.85(2)	2.42(2)	3.229(2)	159(2)
	6	0.84(2)	2.44(2)	3.058(2)	131(2)
3a	1/1a	–	–	3.294(3)	–
	2	0.80(3)	2.16(3)	2.936(3)	162(3)
	3	0.92(2)	1.86(2)	2.774(2)	174(2)
	4	0.83(2)	1.99(2)	2.817(2)	176(2)
	5	–	–	3.414(3)	–
	6	0.90(3)	2.36(3)	3.038(3)	132(2)
3b	1/1a	–	–	3.300(2)	–
	2	0.83(2)	2.14(2)	2.933(2)	160(2)
	3	0.88(2)	1.90(2)	2.777(2)	175(2)
	4	0.83(2)	1.98(2)	2.809(2)	175(2)
	5	–	–	3.410(2)	–
	6	0.87(2)	2.39(2)	3.043(2)	131(2)
3c	1	0.87(2)	2.40(2)	3.157(2)	144(2)
	2	0.87(2)	2.11(2)	2.931(2)	158(2)
	3	0.83(2)	1.94(2)	2.767(2)	174(2)
	4	0.82(2)	1.99(2)	2.805(2)	176(2)
	5	0.85(3)	2.46(3)	3.267(2)	159(2)
	6	0.81(2)	2.45(2)	3.063(2)	133(2)
3d	1	0.86(3)	2.49(3)	3.213(3)	143(2)
	2	0.88(2)	2.13(2)	2.959(2)	156(2)
	3	0.83(2)	1.96(2)	2.788(2)	175(2)
	4	0.78(2)	2.04(2)	2.818(2)	177(2)
	5	0.94(4)	2.48(4)	3.355(3)	156(3)
	6	0.82(3)	2.54(3)	3.102(2)	127(2)
3e	1/1a	–	–	3.296(2)	–
	2	0.84(2)	2.14(2)	2.935(2)	160(2)
	3	0.90(2)	1.88(2)	2.778(2)	173(2)
	4	0.80(2)	2.01(2)	2.809(2)	174(2)
	5	–	–	3.413(2)	–
	6	0.88(2)	2.40(2)	3.042(2)	131(2)
3f	1/1a	–	–	3.369(2)	–
	2	0.77(2)	2.20(2)	2.953(2)	164(2)
	3	0.85(2)	1.96(2)	2.802(2)	174(2)
	4	0.82(2)	2.01(2)	2.824(2)	172(2)
	5	–	–	3.495(3)	–
	6	0.83(3)	2.49(3)	3.071(2)	128(2)
3g	1/1a	–	–	3.383(4)	–
	2	0.77(3)	2.18(3)	2.940(3)	168(3)
	3	0.80(2)	1.99(2)	2.789(3)	172(2)
	4	0.87(3)	1.96(3)	2.825(3)	172(3)
	5	–	–	3.514(4)	–
	6	0.85(3)	2.38(3)	3.033(3)	133(3)
2	1a	0.93(2)	2.64(2)	3.454(2)	147(2)
	2	0.85(2)	2.10(2)	2.939(2)	168(2)
	3	0.82(2)	1.99(2)	2.802(2)	179(2)
	4	0.87(2)	1.96(2)	2.826(2)	176(2)
	5	–	–	3.568(2)	–
	6	0.82(2)	2.44(2)	3.016(2)	127(2)

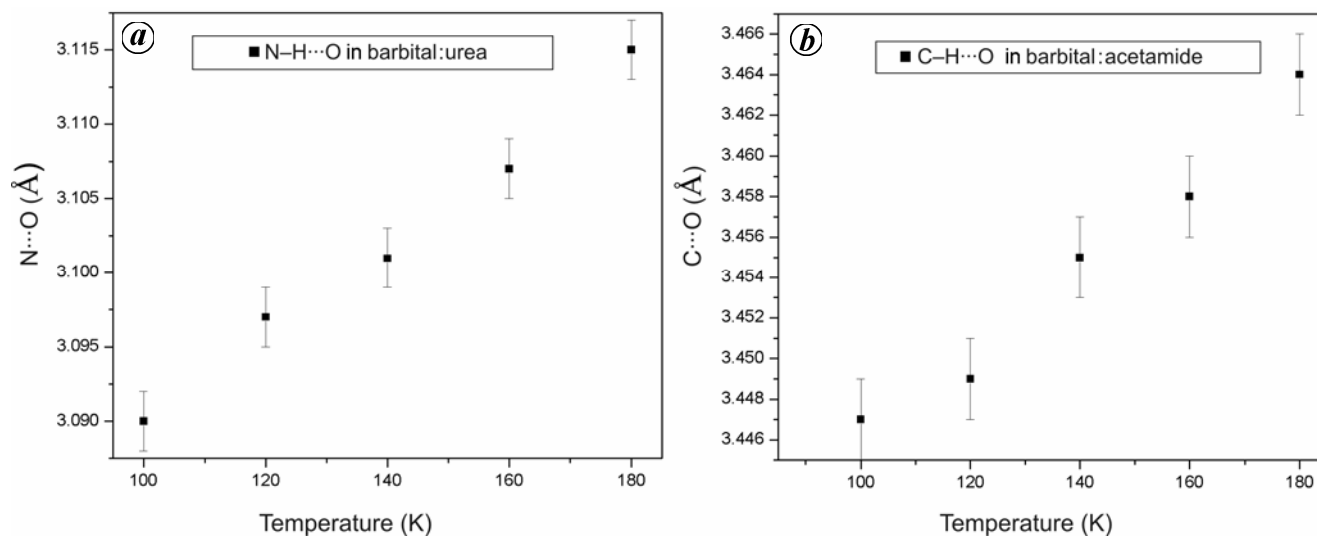


Figure 5. Temperature variations in N...O and C...O distances in the N-H...O (**1**) and corresponding C-H...O (**1a**) interactions in co-crystals **1** and **2**. Interaction numbers **1** and **1a** refer to Figures 3 and 4.

high acetamide ratio (**3a**, **3b** and **3e-g**). (iii) The DSC for the ternary crystals **3** shows melting endotherms in the range 123–147°C (Table 1) and the melting temperature gives a very nice indication of the amount of acetamide in the co-crystal because the extremes of this melting range correspond to the melting points of the binary co-crystals **2** and **1**.

The formation of these ternary solid solutions is a sure sign of structural and chemical mimicry between urea and acetamide. If the C-H...O contact in **2** was a forced one, it is difficult to imagine how acetamide could be incorporated into the co-crystal of urea and barbital in the crystals of **3**. Tables 1 and 7 provide more insights into the relative strengths of the N-H...O and C-H...O bonds. The relative amounts of acetamide and urea in the various samples of **3** were compared with the relative amounts taken for co-crystallization. If the ratios are the same in solution and the crystal, then the two equivalent interactions may be taken to be equi-energetic. In the present case, the amounts of urea are always slightly over-expressed in the ternary co-crystals, showing that the N-H...O interaction (in **1**) is stronger than the corresponding C-H...O interaction (in **2**) although not by a great deal, for when acetamide and urea are taken in a 1 : 1 equimolar ratio in solution, they are incorporated roughly in a 1 : 2 ratio in the co-crystal (Table 1). In co-crystals **3c** and **3d**, the amounts of acetamide are estimated to be less than 10%, which is undetectable in the structure. These small amounts are revealed through differences in the melting point relative to **1**. The refinement in these cases was performed by considering them as binary co-crystals of barbital and urea.

Equivalence of two crystal structures is merely suggestive of interaction equivalence. But ternary solid solution formation in which a C-H...O interaction is able to

replace a stronger N-H...O interaction is more direct evidence of the reality of the weaker interaction¹.

Conclusions

The very similar temperature-dependent behaviour of the C-H...O contact in synthon **III** in the acetamide–barbital co-crystal **2**, and the analogous N-H...O contact in synthon **I** in the urea–barbital co-crystal **1** shows that this particular C-H...O bond is a genuine hydrogen bond. Firm evidence that this C-H...O bond is a physical reality is provided by the isolation of ternary co-crystals in the formation of which acetamide is able to compete effectively with urea for limited amounts of barbital. Significantly, the C-H...O bonds in this study are not very strong in the general C-H...O context³. Generally, C-H...O bonds formed by activated donors (ethynyl, H-atoms α to EWGs) are accepted as hydrogen bonds by most workers. It is bonds formed by weaker to marginal donor groups that excite comment. And, in the end, this is the context in which the present result is of interest.

Supplementary information

For details of the crystal structures, refer to the following CCDC deposition numbers in the Cambridge Crystallographic Data Centre: barbital–acetamide, **1**: 748298 (100 K), 748299 (120 K), 748300 (140 K), 748301 (160 K), 748302 (100 K), 767622 (150 K); barbital–urea, **2**: 748303 (100 K), 748304 (120 K), 748305 (140 K), 748306 (160 K), 748307 (180 K), 767623 (150 K); solid solution, **3a-g** (150 K): 767625, 767624, 767630, 767629, 767628, 767627, 767626. See <http://www.ccdc.cam.ac.uk/products/csd/request/>

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