β-Diketone Interactions. Part 11.† The Hydrogen-bonded Adduct 4,6-Dimethylpyrimidin-2-one·Urea (DMP·U) from the Reaction of Pentane-2,4-dione and Urea

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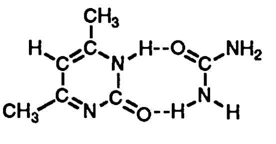
The X-ray crystal structure of the adduct formed between 4,6-dimethylpyrimidin-2-one and urea (DMP·U) shows a compact unit joined through two N–H ··· O=C hydrogen bonds. One of these is remarkably short with $R_{N\cdots O}$ 2.735 Å ($R_{H\cdots O}$ 1.705 Å), and is believed to be among the shortest example of an NHO hydrogen bond between neutral molecules. Its hydrogen-bond energy, estimated from IR data, is *ca.* 75 kJ mol^{-1}.

The reaction of pentane-2,4-dione and urea (U) has been studied several times. Evans, who was the first to investigate it a hundred years ago, reported a puzzling number of products.[1] Since then other workers have identified them.[2–6] Surprisingly, the mechanism whereby the most abundant of these, 4,6-dimethylpyrimidin-2-one (DMP), is formed, has remained unresolved until recently[7] despite the fact that the general reaction between a β-diketone and a urea is of biochemical importance.

Our interest in the reaction arose through one of the products, an adduct between DMP and unchanged urea. This combination has the potential to form a pair of C=O ··· H–N hydrogen bonds, and a structure for this adduct (I) has been proposed.[4] However, its remarkable stability suggested that the hydrogen bonds might be stronger than normal, and it was this which prompted a full X-ray crystal structure, in the hope of finding an unusual N–H ··· O hydrogen bond. That hope has been realised.



(I)

Experimental

Instruments.—IR, Perkin-Elmer 983-G spectrometer; NMR (^{13}C at 62.9 MHz, ^{1}H at 120 MHz) Bruker WM 250 instrument; X-ray, Enraf-Nonius CAD-4 diffractometer.

4,6-*Dimethylpyrimidin*-2-*one.*—Finely ground urea (6 g, 0.1 mmol) was added to a solution of pentane-2,4-dione (12 g, 0.12 mmol) in ethanol (200 cm^3). The suspension was warmed and concentrated HCl (25 cm^3) added. The mixture was heated under reflux for 2 h. On cooling, crystals of 4,6-dimethylpyridinium-2-one chloride were collected. These were dissolved in the minimum of water, neutralised with 10% NaOH solution, and the solution reduced to a third of its volume and left overnight at 0 °C to yield crystals of 4,6-dimethylpyrimidin-2-one that were purified by recrystallization from water and dried at 70 °C *in vacuo.*

The main features of the IR spectrum (KBr disc) that could be linked to the hydrogen bonding in the crystal were bands centred at 3 457m,br (free νNH), 2 820s,vbr (νNH ··· O), 1 639vs (νC=O), 1 313s,br (δNH ··· O), and 957m,br (γNH ··· O) cm^{-1}. ^{1}H NMR δ([$^2H_6$] DMSO solution) 11.67 (br s, 1 H, NH), 613 (s, 1 H, CH), and 2.17 (s, 6 H, CH$_3$).

2,4-*Dimethylpyrimidin*-2-*one–Urea Adduct.*—Urea (3 g, 50 mmol) was added to pentane-2,4-dione (5 g, 50 mmol) in methanol and the solution left at room temperature for several days until small yellow platelets of the adduct had crystallized out of solution (23.8 mg, 43% yield), m.p. 174–178 °C (Found: C, 44.8; H, 6.7; N, 30.0. $C_7H_{12}N_4O_2$ requires C, 45.7; H, 6.5; N, 30.4%).

A direct method of preparing the adduct from its components was less successful. On warming pentane-2,4-dione and urea in methanol both components dissolve, but on cooling, the unchanged urea quickly crystallized out as needles, although small platelets of the adduct could be seen on them. The addition of a small amount of KF (1%) gave an increased yield of the adduct, but again this could not be separated from unchanged urea.

The IR spectrum (KBr disc) showed bands centred at 3 396vs,br (νNH, urea), 3 185s,br, 2 737vs,vbr (νNH), 1 873w, 1 676vs (νC=O), 1 633vs (νC=O), 1 465 + 1 446s,br (δNH ··· O) 1 382s, 1 315s, 1 186m, 1 159m, 1 102w, 987mw, 932m, 795s, 640 + 618s,vbr (γNH ··· O), 556s, 520w, and 352m cm^{-1}.

The adduct is soluble in water but not in organic solvents such as CDCl$_3$, DMSO, acetone, or methanol. Although DMP·U slowly grows from the methanol solution in which it is prepared, this solvent is not capable of dissolving a sufficient concentration to run an NMR spectrum. The ^{1}H NMR spectrum (in D$_2$O) had δ 6.47 (s, 1 H, NH) and 2.36 (s, 6 H, CH$_3$). The NH$_2$ protons of urea were not observed, having exchanged with the solvent which gave an HOD signal at δ 4.87. The ^{13}C NMR spectrum (in D$_2$O) had δ 163.55 (urea CO), 159.75 (DMP CO), 108.71 (CCH$_3$), 106.79 (CH), and 22.58 (CH$_3$). These values differ slightly from those published[6] and they represent a spectrum which is the sum of the two components, DMP and U indicating dissociation in this medium.

Crystallography

Crystal Data.—$C_7H_{12}N_4O_2$, M = 184, monoclinic, space group $P2_1/n$, a = 11.098(1), b = 12.804(1), c = 7.177(1) Å, β =

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† Part 10: J. Emsley, L. Y. Y. Ma, S. A. Karaulov, M. Motevalli, and M. B. Hursthouse, *J. Mol. Struct.*, 1990, **216**, 143.

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for the 4,6-dimethylpyrimidin-2-one–urea adduct.

	x	y	z
N(1)	6 946(4)	2 988(3)	−580(5)
O(1)	6 645(3)	4 638(2)	402(4)
N(2)	5 027(4)	3 699(3)	−1 058(7)
C(1)	6 220(5)	3 801(4)	−372(6)
N(3)	9 082(3)	4 983(3)	1 783(5)
N(4)	10 960(3)	4 208(3)	3 244(5)
O(2)	9 269(3)	3 234(2)	2 061(4)
C(2)	9 542(5)	5 954(4)	2 048(6)
C(3)	10 736(5)	6 063(4)	2 930(7)
C(4)	8 711(6)	6 840(4)	1 311(8)
C(5)	11 410(5)	5 167(4)	3 513(6)
C(6)	12 712(6)	5 227(5)	4 526(8)
C(7)	9 764(5)	4 102(4)	2 370(6)

Table 2. Selected bond lengths and angles for the 4,6-dimethylpyrimidin-2-one–urea adduct.

(*i*) Bond lengths/Å

C(1)–N(1)	1.342(9)	C(1)–O(1)	1.257(8)
C(1)–N(2)	1.329(9)	C(2)–N(3)	1.344(8)
C(7)–N(3)	1.379(8)	C(5)–N(4)	1.327(8)
C(7)–N(4)	1.363(8)	C(7)–O(2)	1.241(8)
C(3)–C(2)	1.363(10)	C(4)–C(2)	1.495(11)
C(5)–C(3)	1.391(10)	C(6)–C(5)	1.491(11)
H(9)–N(1)	1.040(63)	H(10)–N(1)	1.115(50)
H(8)–N(2)	0.972(63)	H(11)–N(2)	0.900(67)
H(12)–N(3)	1.040(62)	H(4)–C(3)	1.017(56)
H(1)–C(4)	0.987(65)	H(2)–C(4)	0.927(66)
H(3)–C(4)	1.055(62)	H(5)–C(6)	0.979(70)
H(6)–C(6)	0.959(65)	H(7)–C(6)	1.045(67)

(*ii*) Bond angles/°

O(1)–C(1)–N(1)	121.9(8)	N(2)–C(1)–N(1)	117.3(8)
N(2)–C(1)–O(1)	120.8(8)	C(7)–N(3)–C(2)	122.8(7)
C(7)–N(4)–C(5)	117.8(8)	C(3)–N(3)–N(3)	118.1(8)
C(4)–C(2)–N(3)	117.4(8)	C(4)–C(2)–C(3)	124.5(9)
C(5)–C(3)–C(2)	118.4(8)	C(3)–C(5)–N(4)	123.6(8)
C(6)–C(5)–N(4)	115.0(9)	C(6)–C(5)–C(3)	121.4(8)
N(4)–C(7)–N(3)	119.3(8)	O(2)–C(7)–N(3)	118.7(8)
O(2)–C(7)–N(4)	122.0(8)	H(9)–N(1)–C(1)	106.4(35)
H(10)–N(1)–C(1)	115.8(34)	H(10)–N(1)–H(9)	128.6(50)
H(8)–N(2)–C(1)	116.3(40)	H(11)–N(2)–C(1)	120.9(44)
H(11)–N(2)–H(8)	122.2(59)	H(12)–N(3)–C(2)	123.2(36)
H(12)–N(3)–C(7)	114.0(36)	H(4)–C(3)–C(2)	117.6(35)
H(4)–C(3)–C(5)	123.7(36)	H(1)–C(4)–C(2)	112.6(44)
H(2)–C(4)–C(2)	114.7(46)	H(2)–C(4)–H(1)	105.1(65)
H(3)–C(4)–C(2)	116.2(37)	H(3)–C(4)–H(1)	101.5(55)
H(3)–C(4)–H(2)	105.2(58)	H(5)–C(6)–C(5)	116.3(47)
H(6)–C(6)–C(5)	117.1(42)	H(6)–C(6)–H(5)	89.7(56)
H(7)–C(6)–C(5)	110.7(41)	H(7)–C(6)–H(5)	130.2(61)
H(7)–C(6)–H(6)	83.1(51)		

(*iii*) Hydrogen bonds/Å

N(3)···O(1)	2.735	H(12)···O(1)	1.705
N(1)···O(2)	2.915	H(9)···O(2)	1.877

100.888(9)°, $U = 1\,001.57$ Å^3, $Z = 4$, $D_c = 1.222$ g cm^{-3}, $F(000) = 392$, $\lambda = 1.5718$ Å, μ(Cu-K_α) = 6.90 cm^{-1}.

Data collection. Unit-cell dimensions were determined and intensity data collected at room temperature on a CAD-4 diffractometer using graphite-monochromated Cu-K_α radiation, graphite monochromator, and an ω–2θ scan procedure.[8] A total of 1 886 unique reflections were observed ($3 < 2\theta < 130°$), 1 698 of which were independent. The segment of reciprocal space scanned was: $h(0 \longrightarrow 13)$ $k(0 \longrightarrow 15)$ $l(-8 \longrightarrow 8)$. The reflection intensities were corrected for absorption using the azimuthal-scan method;[9] maximum transmission factor 1.00, minimum 0.815.

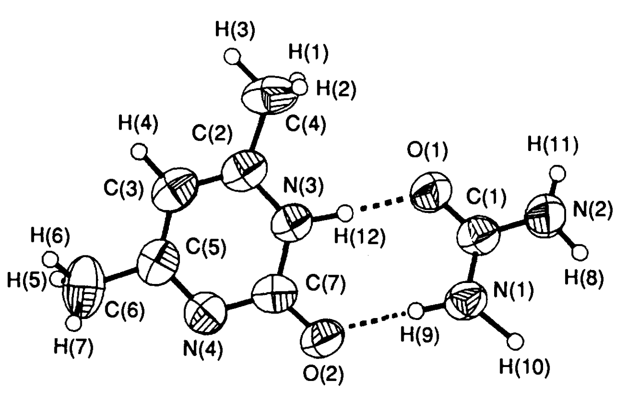

Figure 1. The molecular structure and numbering scheme of the 4,6-dimethylpyrimidin-2-one–urea adduct.

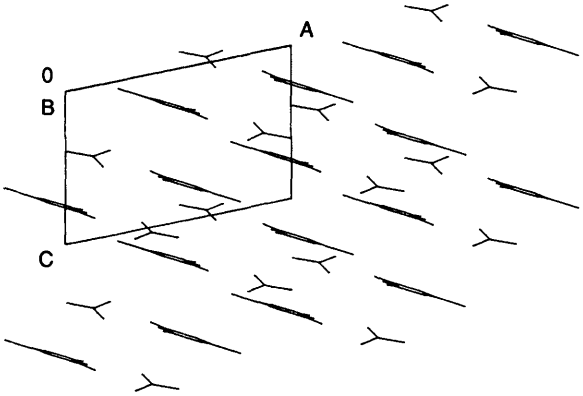

Figure 2. The unit cell of the 4,6-dimethylpyrimidin-2-one–urea adduct viewed along the plane of the DMP molecules.

Structural solution and refinements. The structure was solved by the application of routine direct methods (SHELXS 86),[10] and refined by full-matrix least-squares (SHELX 76).[11] All non-hydrogen atoms were refined anisotropically; hydrogen atoms were refined isotropically. The final residuals R and R_w were 0.0529 and 0.0460, respectively, for the 141 variables and 873 data for which $F_o > 6\sigma(F_o)$. The function minimised was $\Sigma w(|F_o| - |F_c|)^2$ with the weight, $w = 1/[\sigma^2(F_o)]$.

Atomic scattering factors and anomalous scattering parameters were taken from refs. 12 and 13, respectively. All computations were made on an Inmos T800 transputer hosted by an IBM/AT. Table 1 lists the atomic co-ordinates, Table 2 the bond lengths and angles including the hydrogen bonds. The structure of the adduct is shown in Figure 1 and a unit-cell packing diagram in Figure 2.*

Discussion

The X-ray crystal structure of the yellow crystals of composition $C_7H_{12}N_4O_2$ that are obtained from the reaction of pentane-2,4-

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* Tables of isotropic and anisotropic temperature factors, hydrogen fractional atomic co-ordinates, full list of bond lengths and angles and selected non-bonded distances have been deposited at the Cambridge Crystallographic Data Centre. For details of the CCDC deposition scheme see 'Instructions for Authors (1990),' *J. Chem. Soc., Perkin Trans. 2*, 1990, issue 1.

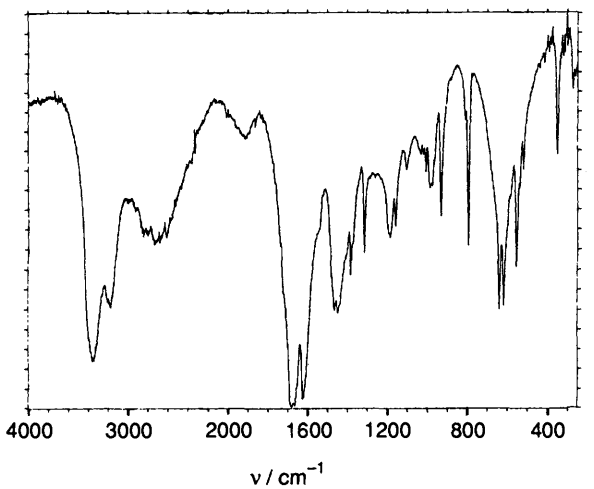

Figure 3. The IR spectrum of the 4,6-dimethylpyrimidin-2-one–urea adduct.

dione and urea shows a hydrogen-bonded adduct, DMP•U, as proposed by Birtwell.[4] Its stability as an adduct may even derive from the strength of the intermolecular hydrogen bonding. One of the bonds, in which the N–H bond of the ring is the donor and the urea carbonyl the acceptor, is only 2.735 Å (N ··· O). The other is 2.915 Å. Together these link the DMP and urea into a recognizable entity in the crystal lattice, although there are weaker hydrogen bonds between the DMP•U entities (Figure 2). The short hydrogen bond is even less than that reported recently for an acid sulphonamide, which at 2.780 Å was thought worthy of comment.[14]

N–H ··· O=C hydrogen bonding is particularly important since it is to be found in biological systems and structures, such as nucleosides and nucleotides,[15] amino acids,[16] and barbiturates.[17] Hundreds of structures have been recorded in which this kind of bonding is present, and the hydrogen bond lengths have been analysed and correlated with other parameters.[18–20] Many systems have three-centred hydrogen bonds, some even have four-centred bonds,[20] and this makes it difficult to discuss the hydrogen bond length in terms of the commonly used distance, $R_{N \cdots O}$. Instead it has become the rule to discuss this kind of hydrogen bonding in terms of the H ··· O distance.

Further complexity arises among N–H ··· O=C bonds because both the donor and the acceptor may carry formal charges, which naturally enhance their mutual attraction. Averages show that for donors the order of $R_{H \cdots O}$ is: $R_3NH^+ < R_2NH_2^+ < RNH_3^+ < NH_4^+ < NH_4^+ < RCONH_2$; and for acceptors the order is $RCO_2^- < RCONH_2 < RCO_2CO$. Thus the average $R_{H \cdots O}$ for R_3NH^+/RCO_2^- is expected to be short and is 1.722 Å, while for $RCONH_2/RCONH_2$ the average is a more typical 1.934 Å.[18–20] In DMP•U the shorter hydrogen bond has $R_{H \cdots O}$ 1.705 Å, which we believe is notable as one of the shortest N–H ··· O=C bonds between neutral molecules. It is even shorter than the average for N–H ··· O=C hydrogen bonds between ions of opposite charge.

The IR spectrum of DMP•U (Figure 3) clearly shows two carbonyl bands, $\nu_{(C=O)}$ at 1 676 cm^{-1} arising from urea, and 1 633 cm^{-1} representing the pyrimidone. These are little changed from the positions in the pure compounds, which in any case are also involved in extensive hydrogen bonding. More characteristic are the NH bands, of which there are three: 3 396, 3 185, and 2 737 cm^{-1}, characterised by their broadness.

The stretching vibrations of those NHs of the urea that are not involved in the adduct are at 3 396 cm^{-1}, these are involved in much weaker hydrogen bonding throughout the crystal. The DMP•U hydrogen bonds give rise to bands at 3 185 and 2 737 cm^{-1}. The NH stretching mode of the longer hydrogen bonds can be identified with the band at 3 185 cm^{-1}. In uracil derivatives a band at 3 200 cm^{-1} corresponds to the N–H ··· O=C hydrogen bonding,[21] and this is the expected part of the spectrum for it to occur. The stretching vibration of the shorter hydrogen bond is associated with the band at 2 737 cm^{-1}.

The shift in the NH stretching frequency on the formation of a hydrogen bond can be a guide to the strength of the bond. This requires a knowledge of ν_{NH} for the free DMP molecule, which should come at *ca.* 3 400 cm^{-1},[21] and which can be identified as a band at 3 457 cm^{-1}. The structure of urea–salicylic acid reveals a non-hydrogen bonding NH group that can be identified with a similar band at 3 476 cm^{-1} in the spectrum.[22] Assuming that the free NH bond of DMP has a similar stretching frequency, then its shift on hydrogen bonding is *ca.* 700 cm^{-1} for the stronger bond.

The shift which occurs in the IR for the N–H ··· O=C hydrogen bonded dimer of butyrolactam is 250 cm^{-1} corresponding to a bond energy of 29 kJ mol^{-1},[23] and for caprolactam is 213 cm^{-1} for an energy of 23 kJ mol^{-1}.[24] On a *pro rata* basis the shift in the IR frequency for the shorter N–H ··· O=C bond of DMP•U would then correspond to a hydrogen bond energy of *ca.* 75 kJ mol^{-1}. If this is so then the hydrogen bonding in DMP•U can be classed as strong, *i.e.* > 50 kJ mol^{-1},[25] and it is undoubtedly much stronger than that found in other systems with N–H ··· O=C bonds, where it is *ca.* 20–30 kJ mol^{-1}.

Normally such weak hydrogen bonding for ordinary N–H ··· O=C bonds has its appeal; *en masse* it is strong enough to determine macromolecular structure, but individually it offers no insurmountable energy barrier to reorganization or reactivity. However at 75 kJ mol^{-1} it cannot be so lightly dismissed. Whether natural systems have found a use for this stronger version remains to be seen.

A very strong hydrogen bond is one that exceeds 100 kJ mol^{-1}.[25] Very strong OHO hydrogen bonds are well known and those which qualify as such have $R_{O \cdots O}$ less than 2.45 Å, which represents a decrease of 0.55 Å below the sum of the van der Waals radii of two oxygen atoms.[26] Applying the same yardstick to a very strong NHO hydrogen bond we would require it to have $R_{N \cdots O} < 2.50$ Å. Recently an intramolecular NHO bond of 2.465 Å has been reported between an imidazole ring and a carboxylic acid group which are attached as 2,3-substituents of a pyridine ring.[27] In this molecule the coplanarity of the two rings and the carboxylic acid group bring the nitrogen and oxygen atoms into close proximity to provide the necessary environment for a short hydrogen bond.

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