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The formation of paracetamol (acetaminophen) adducts with hydrogen-bond acceptors

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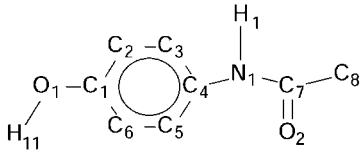
The crystal structures of five hemiadducts of paracetamol with 1,4-dioxane, *N*-methylmorpholine, morpholine, *N*,*N*-dimethylpiperazine and piperazine and a related 1:1 adduct of paracetamol with 4,4′-bipyridine are described. All structures are characterized by the formation of chains of paracetamol molecules, which are linked *via* either OH···O=C interactions [*C*(9) chains in graph-set notation] or NH···O=C interactions [*C*(4) chains], depending on the presence or absence of substituent groups on the guest molecule. In all cases except for the morpholine and bipyridine adducts these chains are connected by hydrogen-bond interactions with the guest molecules, which reside on crystallographic inversion centres. In the bipyridine adduct this linkage also involves a π-stacking interaction; in the morpholine adduct it is formed between the OH groups of two opposed paracetamol molecules. Most adducts (that with 4,4′-bipyridine is an exception) decompose on heating to give monoclinic paracetamol. This is the first systematic study of a series of co-crystals containing paracetamol.

1. Introduction

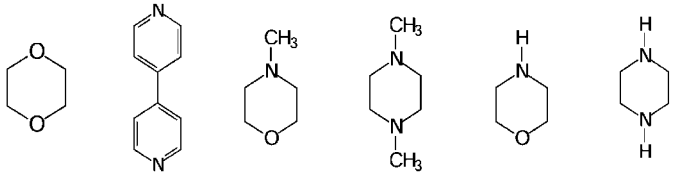
There have been a number of detailed studies on the polymorphic behaviour of paracetamol (acetaminophen, *p*-hydroxylacetanilide or Tylenol). Form I, which is monoclinic, was first characterized by Haisa *et al.* (1976), and has since been shown to be the thermodynamically more stable form. Form II is orthorhombic and was also described by Haisa *et al.* in 1974 (Haisa *et al.*, 1974). The orthorhombic form can be grown using a single orthorhombic crystal as a seed from a super-saturated aqueous solution of paracetamol. This method, however, can result in the crystals changing to the monoclinic form if left in contact with the solution for any length of time (Nichols & Frampton, 1998). The same authors showed that the only method that gives the orthorhombic polymorph reproducibly is growth from the melt. They also showed that this form is stable if dried and stored in a stoppered vial and that neither grinding nor compression induces a transition to the monoclinic form. In a very careful study, Boldyreva *et al.* (2000) have shown that application of hydrostatic pressures up to 4.2 GPa does not induce a transition from the monoclinic to the orthorhombic form. The behaviour of the orthorhombic form is of interest for its ability to undergo plastic deformation when compressed, thereby facilitating the production of tablets of paracetamol.

With the exception of our own recent report of paracetamol trihydrate (McGregor *et al.*, 2002), little structural work appears to have been carried out on solvates or other co-crystals of paracetamol, although a thermochemical study showed the existence of a hemisolvate of paracetamol with

1,4-dioxane (Fachaux *et al.*, 1995). In this report, we describe the preparation and characterization of six new adducts of paracetamol with 1,4-dioxane, 4,4′-bipyridine, *N*-methylmorpholine, *N*,*N*-dimethylpiperazine, morpholine and piperazine (these are referred to as *guest molecules* below; see Schemes). All these molecules, except for morpholine, can be considered to be at least pseudo-centrosymmetric with respect to their hydrogen-bonding properties.



Paracetamol, with atomic numbering scheme.



Guest molecules used to form adducts with paracetamol. Left to right: dioxane, bipyridine, *N*-methylmorpholine, *N*,*N*-dimethylpiperazine, morpholine and piperazine.

2. Experimental

2.1. Synthesis

All starting materials were obtained from Sigma-Aldrich except for 1,4-dioxane (May & Baker) and were used as received.

Paracetamol:0.5 1,4-dioxane. A saturated solution of paracetamol (1.51 g, 10 mmol) in 1,4-dioxane (2 cm^3, 23 mmol) was refluxed and allowed to cool. Colourless crystals were formed overnight at 293 K according to the published procedure (Fachaux *et al.*, 1995).

Paracetamol:4,4′-bipyridine. Paracetamol (0.51 g, 3.40 mmol) was refluxed with an equimolar amount of 4,4′-bipyridine (0.52 g, 3.33 mmol) in ethanol (1 cm^3). Pale-yellow needle-like crystals were formed on standing overnight at room temperature.

Paracetamol:0.5 N-methylmorpholine. Paracetamol (0.43 g, 2.85 mmol) and *N*-methylmorpholine (1 cm^3, 9.11 mmol) were refluxed and allowed to cool. The flask was maintained at 277 K, leading to the formation of colourless rod-shaped crystals.

Paracetamol:0.5 N,N-dimethylpiperazine. Paracetamol (0.55 g, 3.64 mmol) and *N*,*N*-dimethylpiperazine (3 cm^3, 22.2 mmol) were refluxed together and allowed to cool. A large excess of dimethylpiperazine was required to dissolve the paracetamol completely. The flask was maintained at 277 K leading to the formation of colourless rod-shaped crystals.

Paracetamol: 0.5 piperazine. Paracetamol (0.62 g, 4.1 mmol) was refluxed together with piperazine (0.35 g, 4.1 mmol) in ethanol (1 cm^3). Colourless crystals formed on cooling to 293 K.

Paracetamol:0.5 morpholine. Paracetamol (0.57 g, 3.8 mmol) was refluxed with morpholine (0.37 g, 4.3 mmol). Colourless crystals formed directly from the reaction mixture after a week at 277 K.

Ethanol was required in the reactions of paracetamol with piperazine and 4,4′-bipyridine because these compounds are both solids at room temperature.

2.2. Differential scanning calorimetry (DSC)

DSC traces were recorded using a Perkin Elmer Pyris DSC 1. Samples were contained in open aluminium pans and purged with helium during the temperature scans to facilitate the removal of any volatile products of thermal decomposition. Samples were heated from 298 K to 453 K at a rate of 10 K min^{-1}.

2.3. Crystallography

X-ray diffraction intensities were collected on either a Stoe Stadi-4 diffractometer with Cu $K\alpha$ radiation or a Bruker SMART APEX CCD diffractometer with Mo $K\alpha$ radiation. Both instruments were equipped with Oxford Cryosystems low-temperature devices. An absorption correction for the four-circle data was applied using ψ scans [*SHELXTL* (Sheldrick, 1997*a*), based on the procedure described by North *et al.* (1968)]; the multiscan procedure *SADABS* [(Sheldrick, 1997*b*), based on the procedure described by Blessing (1995)] was applied to the CCD data sets. All structures were in space group $P2_1/c$, except the morpholine adduct, which formed in $P2_12_12_1$. All structures were solved by direct methods and refined by full-matrix least squares against F^2 using all data (*SHELXTL*). H atoms were placed in calculated positions and allowed to ride on their parent atoms; methyl groups were treated with the Sheldrick (1997) rotating rigid group model. H atoms involved in hydrogen bonding were located in difference maps and refined freely. All non-H atoms were modelled with anisotropic displacement parameters.

One of the two crystallographically independent dioxane molecules in the 1,4-dioxane adduct was disordered over two orientations about a crystallographic inversion centre. The occupancies of the two components were fixed at 0.75 and 0.25 after competitive refinement. Similarity restraints were applied to the geometries and displacement parameters of the two components. The program *ROTAX* (Cooper *et al.*, 2002) suggested that the crystal may have been twinned by a twofold rotation about the [100] direct lattice direction. Incorporation of this into the model reduced *R*1 slightly from 7.02% to 6.86%, with a twin scale factor of 2.6 (3)%. This is barely significant, and the twinning is omitted in the model presented here.

In the *N*-methylmorpholine adduct, the *N*-methylmorpholine is disordered over a crystallographic inversion centre with

Table 1
Experimental details.

All data were collected at 150 K.

	1,4-Dioxane adduct	Dimethylpiperazine adduct	*N*-methylmorpholine adduct
Crystal data			
Chemical formula	$2[C_8H_9O_2N][C_4H_8O_2]$	$2[C_8H_9NO_2][C_6H_{14}N_2]$	$2[C_8H_9NO_2][C_5H_{11}NO]$
Chemical formula weight	390.43	416.52	403.47
Cell setting, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$
a, b, c (Å)	12.421 (5), 12.056 (4), 13.396 (3)	10.6970 (9), 11.0240 (9), 9.4896 (8)	10.5749 (8), 11.0221 (8), 9.3894 (7)
β (°)	91.51 (3)	100.684 (2)	101.145 (2)
V (Å^3)	2005.4 (11)	1099.65 (16)	1073.77 (14)
Z	4	2	2
D_x (Mg m^{-3})	1.293	1.258	1.248
D_m (Mg m^{-3})	Not measured	Not measured	Not measured
Radiation type	Cu $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
No. of reflections for cell parameters	80	3488	2729
θ range (°)	20–22	2.5–29	2.5–27.5
μ (mm^{-1})	0.795	0.088	0.090
Temperature (K)	220 (2)	150 (2)	150 (2)
Crystal form, colour	Lath, colourless	Plate, colourless	Rod, colourless
Crystal size (mm)	0.78 × 0.19 × 0.16	0.56 × 0.18 × 0.08	0.34 × 0.09 × 0.07
Data collection			
Diffractometer	Stoe Stadi-4	Bruker SMART APEX CCD	Bruker SMART APEX CCD
Data collection method	ω–θ scans	φ and ω scans	φ and ω scans
Absorption correction	Empirical	Multiscan	Multiscan
T_{min}	0.602	0.833	0.792
T_{max}	0.826	1	0.962
No. of measured, independent and observed reflections	4865, 3499, 2508	7034, 2724, 2512	6517, 2444, 1890
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0532	0.0164	0.0221
θ_{max} (°)	69.79	29.08	27.49
Range of h, k, l	$-15 \rightarrow h \rightarrow 15$ $0 \rightarrow k \rightarrow 14$ $0 \rightarrow l \rightarrow 15$	$-8 \rightarrow h \rightarrow 14$ $-15 \rightarrow k \rightarrow 14$ $-12 \rightarrow l \rightarrow 12$	$-13 \rightarrow h \rightarrow 13$ $-14 \rightarrow k \rightarrow 14$ $-11 \rightarrow l \rightarrow 12$
No. and frequency of standard reflections	3 every 60 min	Not measured	Not measured
Intensity decay (%)	10.9	0	0
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0702, 0.2243, 1.078	0.0525, 0.1339, 1.059	0.0408, 0.1082, 0.973
No. of reflections and parameters used in refinement	3499, 285	2724, 146	2444, 147
H-atom treatment	Riding	Riding/All H-atom parameters refined	Riding/All H-atom parameters refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.125P)^2 + 1.1494P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.069P)^2 + 0.4625P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0658P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.002	0.009	0.000
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.503, −0.260	0.401, −0.193	0.216, −0.220
Extinction method	*SHELXL*	None	*SHELXL*
Extinction coefficient	0.0019 (6)	0	0.008 (3)

	Piperazine adduct	4,4′-Bipyridine adduct	Morpholine adduct
Crystal data			
Chemical formula	$2[C_8H_9NO_2][C_4H_{10}N_2]$	$[C_8H_9NO_2][C_{10}H_8N_2]$	$2[C_8H_9NO_2][C_4H_9O]$
Chemical formula weight	388.46	307.35	389.45
Cell setting, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Orthorhombic, $P2_12_12_1$
a, b, c (Å)	15.893 (5), 5.1664 (17), 12.993 (4)	11.2906 (10), 24.103 (2), 11.5526 (10)	7.2791 (9), 14.6277 (18), 18.303 (2)

the N and O atoms sharing an equivalent site. A composite scattering factor $[0.5f(N) + 0.5f(O)]$ was used for this site; the occupancy of the methyl group was fixed at 0.5.

A consistent numbering scheme was used for the paracetamol molecules in all structures and this is shown in the schemes above. Where there is more than one paracetamol molecule in the asymmetric unit the labels in the schemes are augmented with the letters *A* and *B*. Labels for atoms forming part of the guest molecules carry the letters *S*, *T etc*. A full listing of crystal, data collection and refinement parameters is given in Table 1; a set of hydrogen-bonding parameters is given in Table 2.[1] The figures were produced using *CAMERON* (Watkin *et al.*, 1993). Other analyses utilized the PC version of the program *PLATON* (Spek, 2002; Farrugia, 1999).

3. Results

3.1. Paracetamol

Crystal structures of the monoclinic and orthorhombic polymorphs of paracetamol have been reported several times, but here we have used the structures reported by Nichols & Frampton (1998) [Cambridge Structural Database (CSD; Allen *et al.*, 1983) reference codes HXACAN07 and HXACAN08]. Our motive for discussing them here is to highlight certain features of their graph sets that enable structural relationships to be drawn between them and the adducts that form the subject of the rest of this paper.

Packing in both polymorphs is dominated by the formation of NH···OH and OH···O=C hydrogen bonds (Fig. 1) giving rise to layered two-dimensional networks. Both polymorphs of paracetamol have identical graph sets (Bernstein *et al.*, 1995), in which the

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: AN0622). Services for accessing these data are described at the back of the journal.

Table 1 (continued)

	Piperazine adduct	4,4′-Bipyridine adduct	Morpholine adduct
β (°)	113.633 (5)	96.1484 (16)	90
V (Å^3)	977.4 (6)	3125.8 (5)	1948.9 (4)
Z	2	8	4
D_x (Mg m^{-3})	1.320	1.306	1.327
D_m (Mg m^{-3})	Not measured	Not measured	Not measured
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
No. of reflections for cell parameters	1227	5375	3801
θ range (°)	2.5–29	2–28.5	2.5–24.5
μ (mm^{-1})	0.093	0.087	0.096
Temperature (K)	150 (2)	150 (2)	150 (2)
Crystal form, colour	Plate, colourless	Block, colourless	Block, colourless
Crystal size (mm)	0.77 × 0.28 × 0.11	0.46 × 0.28 × 0.18	0.54 × 0.52 × 0.28
Data collection			
Diffractometer	Bruker Smart Apex CCD	Bruker SMART APEX CCD	Bruker SMART APEX CCD
Data collection method	ω and φ scans	ω and φ scans	φ and ω scans
Absorption correction	Multiscan	Multiscan	Multiscan
T_{min}	0.690	0.830	0.868
T_{max}	1	1	1
No. of measured, independent and observed reflections	5628, 2309, 1778	20270, 7766, 6044	12312, 4733, 4265
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0458	0.0220	0.0308
θ_{max} (°)	28.55	29.18	28.97
Range of h, k, l	$-17 \rightarrow h \rightarrow 21$ $-6 \rightarrow k \rightarrow 6$ $-17 \rightarrow l \rightarrow 16$	$-14 \rightarrow h \rightarrow 14$ $-19 \rightarrow k \rightarrow 31$ $-15 \rightarrow l \rightarrow 15$	$-9 \rightarrow h \rightarrow 7$ $-19 \rightarrow k \rightarrow 18$ $-24 \rightarrow l \rightarrow 22$
No. and frequency of standard reflections	Not measured	Not measured	Not measured
Intensity decay (%)	0	0	0
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0779, 0.1652, 1.179	0.0471, 0.128, 1.038	0.0462, 0.1028, 1.066
No. of reflections and parameters used in refinement	2309, 140	7766, 433	4733, 276
H-atom treatment	Riding/All H-atom parameters refined	Riding/All H-atom parameters refined	Riding/All H-atom parameters refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.052P)^2 + 0.5663P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0676P)^2 + 0.569P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.049P)^2 + 0.2716P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.002	0.001	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.336, −0.447	0.357, −0.246	0.256, −0.270
Extinction method	None	None	*SHELXL*
Extinction coefficient	0	0	0.0031 (7)

Computer programs used: Stoe *DIF*4 (Stoe & Cie, 1990*a*), Stoe *REDU*4 (Stoe & Cie, 1990*b*), Bruker *SMART* (Bruker, 2001), Bruker *SAINT* (Bruker, 2002), *SHELXTL* (Sheldrick, 1997*a*).

OH···O=C and NH···OH hydrogen bonds, respectively, form $C(9)$ and $C(7)$ motifs at the unitary level.[2] In both polymorphs, these are disposed about crystallographic glide planes. In the monoclinic form, the hydrogen-bonded layers are arranged parallel to the (010) planes, which means that the layers are polar: in Fig. 1(*a*) all the molecules have the methyl group on the left. This polarity is reversed in neighbouring layers by crystallographic inversion centres. In the orthorhombic form, glide planes run perpendicular to the layers, so that the layers are non-polar: in Fig. 1(*b*) the methyl groups lie on the left- and right-hand sides of the molecules in alternate $C(9)$ chains.

The angles between mean planes of the amide and phenyl groups in orthorhombic and monoclinic paracetamol are 17.7° and 20.5°, respectively. Analogous angles observed in this work are given in the figure captions and range from 3.03° to 41.72°. pπ-pπ bonding between the phenyl ring and the amide group favours a dihedral angle of zero, and some correlation between this angle and the N—C(phenyl) bond length might have been expected, though none is evident at the precision of these structure determinations. This angle is evidently a rather easily deformed structural parameter, and is presumably at the mercy of crystal-packing forces. As we show in the following sections, hydrogen bonding is the dominant feature in these structures, and the torsion observed is presumably a consequence of the optimization of these interactions.

3.2. The paracetamol:1,4-dioxane adduct

The asymmetric unit in the crystal structure of the dioxane adduct of paracetamol consists of two paracetamol molecules and two half molecules of dioxane. The latter both reside on crystallographic inversion centres. One of the dioxane molecules (labelled *T*/*U* in the tables and supplemental data) is disordered, although both components participate in hydrogen bonding. The occupancy ratio is 0.75:0.25 and in the discussion that follows we have ignored the minor component (*U*). There is some evidence from electron-density difference maps that the other dioxane molecule (labelled *S*) is disordered as well, although, if present, the distinction between the components is at the limit of the resolution of our data set. An ordered model for this part of the structure is therefore presented here. The structure is depicted in Fig. 2. Primary bond lengths and angles are normal and have been deposited; hydrogen-bonding parameters are listed in Table 2.

[2] Note that where no sub- and superscripts appear in the graph-set descriptor, one donor and one acceptor are implied.

The $C(9)$ chains formed by hydrogen bonding between OH···O=C moieties of neighbouring molecules described above with regard to the crystal structures of paracetamol are also observed in the structure of the 1,4-dioxane adduct. In order to accommodate the dioxane molecules these chains are sinusoidal, with the two crystallographically independent paracetamol molecules alternating along the chain. The NH groups point towards the O atoms of dioxane molecules forming NH···O hydrogen bonds. Since both dioxane molecules reside on inversion centres, the space-group symmetry builds up two-dimensional sheets in which chains of paracetamol are linked by dioxane bridges (Fig. 2). In graph-set notation, the bridges can be described as $D_2^2(6)$. The two-dimensional sheets are parallel to the (210) lattice planes, and the rather open structure depicted in Fig. 2 is 'filled in' by symmetry-equivalent sheets parallel to $(2\bar{1}0)$.

Table 2
Hydrogen-bonding parameters.

Standard uncertainties are omitted in the case of the dioxane adduct because the H-atom positions were calculated and not refined. N—H and O—H distances were normalized to 1.009 Å and 0.983 Å, respectively, to aid comparison with Cambridge Structural Database search results (Fig. 7).

Adduct	Donor	Acceptor	Observed distance (Å)	Normalized distance (Å)	Typical normalized distance (Å)
1,4-Dioxane	N1*A*—H1*A*	O1*S*	2.03	1.90	1.96
	O1*A*—H11*A*	O2*B*	1.82	1.67	1.78
	O1*B*—H11*B*	O2*A*^{i}	1.86	1.71	1.78
	N1*B*—H1*B*	O1*U*	1.92	1.77	1.96
	N1*B*—H1*B*	O1*T*	2.13	2.00	1.96
4,4′-Bipyridine	O1*A*—H11*A*	O2*B*	1.755 (19)	1.68	1.78
	N1*A*—H1*A*	N10*S*	2.047 (18)	1.92	1.96
	O1*B*—H11*B*	O2*A*^{ii}	1.81 (2)	1.71	1.78
	N1*B*—H1*B*	N1*T*^{iii}	2.100 (18)	2.01	1.96
N,*N*-dimethylpiperazine	N1—H1	O2^{iv}	1.98 (2)	1.84	1.92
	O1—H11	N1*S*^{v}	1.81 (2)	1.82	1.82
N-methylmorpholine	O1—H11	O1*S*/N1*S*^{vi}	1.88 (2)	1.81	1.81/1.82
	N1—H1	O2^{vii}	1.925 (16)	1.80	1.92
Piperazine	O1—H11	N1*S*	1.79 (3)	1.74	1.82
	N1—H1	O2^{viii}	2.14 (3)	2.06	1.92
	N1*S*—H1*S*	O1^{viii}	2.30 (3)	2.21	2.03
Morpholine	O1*A*—H11*A*	O1*B*^{ix}	1.97 (2)	1.76	1.87
	N1*A*—H1*A*	O2*B*^{x}	2.033 (18)	1.87	1.92
	O1*B*—H11*B*	N4*S*^{xi}	1.79 (3)	1.69	1.82
	N1*B*—H1*B*	O2*A*^{xii}	2.061 (19)	1.86	1.92

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

3.3. The paracetamol:4,4′-bipyridine adduct

The O atoms in 1,4-dioxane formally have two lone pairs of electrons, each of which could potentially act as a hydrogen-bond acceptor. In practice, however, motifs in which ethers act as double hydrogen-bond acceptors occur rarely, and so for practical crystal-packing purposes it can be considered to be a centrosymmetric molecule containing two hydrogen-bond acceptors. 4,4′-Bipyridine is similar, although a torsion about the central C—C bond breaks the inversion symmetry. Recrystallization of paracetamol from a solution of 4,4′-bipyridine in ethanol yields a 1:1 co-crystal rather than the hemisolvate obtained with dioxane, a possible effect of the greater basicity of bipyridine.

The crystal structure of paracetamol:bipyridine contains two independent molecules each of paracetamol and bipyridine. Primary bond lengths and angles are normal and have been deposited; hydrogen-bonding parameters are listed in Table 2. As in the dioxane adduct, the paracetamol molecules form $C(9)$ chains through OH···O=C hydrogen bonds (Fig. 3). The two crystallographically independent paracetamol molecules alternate along the chain. The disposition of the molecules within the chains is rather similar to that in orthorhombic paracetamol, except that alternate molecules are rotated through 180° about the chain axis in order to accommodate the bipyridine molecules.

The NH bonds of paracetamol act as hydrogen-bond donors to the aromatic N atoms of the bipyridine molecules, forming a discrete (D) graph set. However, since this crystal is a 1:1 adduct there are insufficient hydrogen-bond donors for the number of acceptors present, and only one of the two N atoms in each bipyridine acts as an acceptor. The result is that there are no hydrogen-bonded pathways connecting the $C(9)$ paracetamol chains. The structure thus consists of a paracetamol backbone with attached bipyridine molecules. These motifs are interconnected by π-stacking between the bipyridine molecules, building up sheets than run parallel to the $(10\bar{1})$ planes.

3.4. The paracetamol adducts with *N*-methylmorpholine and *N*,*N*-dimethylpiperazine

N,*N*-dimethylpiperazine and *N*-methylmorpholine are closely related to 1,4-dioxane by the substitution of one or both O atoms by N—Me; paracetamol forms 2:1 adducts with both compounds, as it does with dioxane. The *N*,*N*-dimethylpiperazine adduct consists of one crystallographically independent paracetamol molecule with the *N*,*N*-dimethylpiperazine residing on a crystallographic inversion centre. The *N*-methylmorpholine adduct is isostructural with this, with the guest molecule disordered about the inversion centre. Primary bond lengths and angles are unremarkable and have been deposited; hydrogen-bonding parameters are listed in Table 2

The crystal structures are similar to those of the dioxane and bipyridine adducts in that the packing can be described with reference to chains of paracetamol molecules. However, rather than $C(9)$ motifs formed through OH···O=C H bonds, the paracetamol molecules define a $C(4)$ graph set through NH···O=C bonds (Fig. 4). The NH moiety of the para-

cetamol now fulfils the role of the OH groups in the dioxane structure, and *N*,*N*-dimethylpiperazine and *N*-methylmorpholine are similar to dioxane with regard to their hydrogen-bonding properties. Therefore, although the nature of the paracetamol chain differs from that of the dioxane adduct, the roles of the *N*-methylmorpholine and dimethylpiperazine molecules are similar, and both act to link paracetamol chains *via* the $D_2^2(6)$ graph set. Overall, this structure consists of a two-dimensional network, although the sheets formed have a corrugated or zigzag appearance in cross section. Alternate regions of the network are approximately parallel to the (310) and (3$\bar{1}$0) planes. Just as in the dioxane adduct, the open structure of Fig. 4 is filled in by symmetry-equivalent networks.

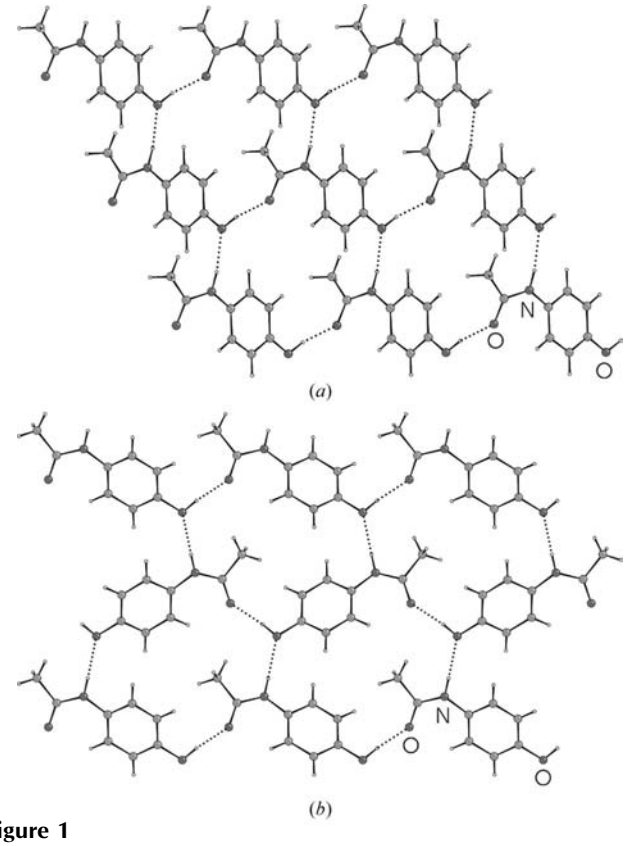


Figure 1
(*a*) Monoclinic paracetamol (Form I) viewed along the *b* axis; the *c* axis runs diagonally from top left to bottom right, so that the *C*(9) chains are established by the *n*-glide. (*b*) Orthorhombic paracetamol (Form II) viewed along the *c* axis; the *a* axis runs horizontally, the *b* axis runs from top to bottom. The *C*(9) chains referred to in the text run from left to right and the *C*(7) chains run approximately vertically. [Colour versions of this and the other figures are available in the online edition of this journal.]

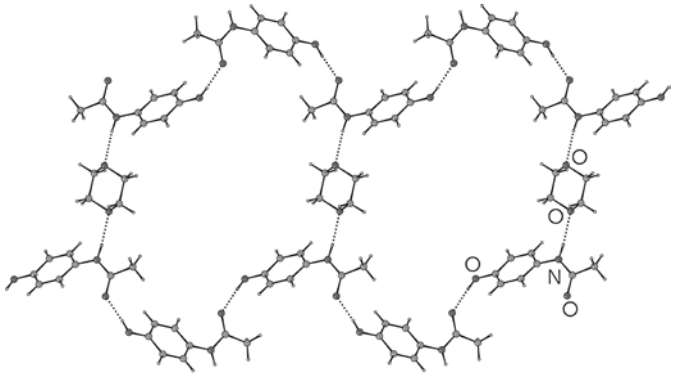


Figure 2
Paracetamol:1,4-dioxane adduct viewed perpendicular to (210); the *c* axis runs horizontally. The *C*(9) chains referred to in the text run from left to right and are linked together by dioxane molecules. The dihedral angles between the amide and phenyl mean planes in the two independent paracetamol molecules are 41.72 (15)° and 39.37 (14)° for molecules *A* and *B*, respectively.

3.5. The paracetamol:morpholine adduct

Morpholine is related to *N*-methylmorpholine by the substitution of the methyl group for hydrogen, and it is unique in this series because the hydrogen-bonding characteristics of the two hetero-centres are not the same: the NH group is a donor and acceptor, the ether O atom potentially a double, but more usually a single, acceptor. The asymmetric unit of the morpholine hemiadduct consists of two crystallographically independent paracetamol molecules (labelled *A* and *B*) and one molecule of morpholine (labelled *S* in the tables). Primary bond lengths and angles are normal and have been deposited; hydrogen-bonding parameters are listed in Table 2.

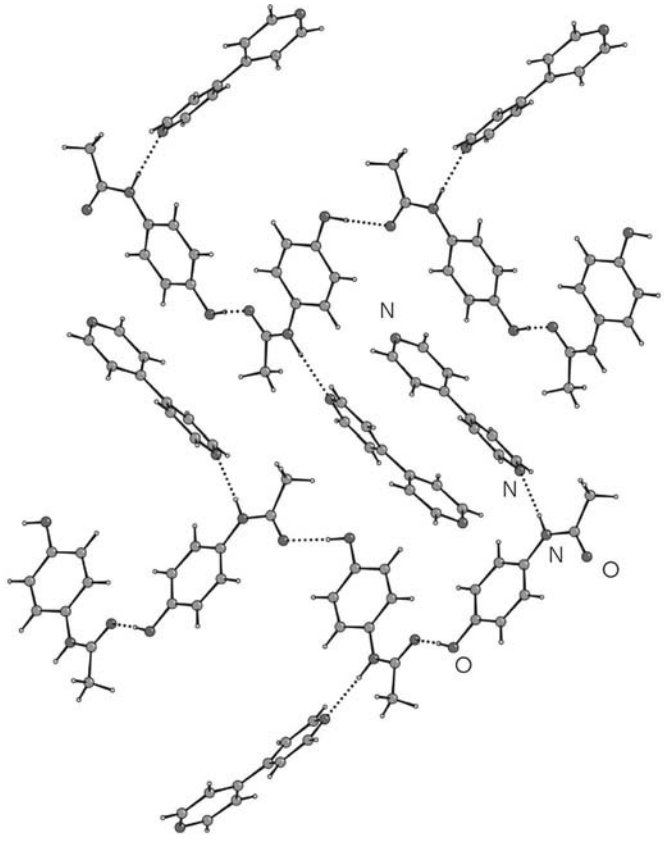


Figure 3
Paracetamol:4,4-bipyridine viewed perpendicular to (10$\bar{1}$); the *b* axis runs from top to bottom. The *C*(9) chains referred to in the text run from left to right and are linked together by a pair of π-stacked bipyridine molecules. The dihedral angles between the amide and phenyl mean planes in the two independent paracetamol molecules are 14.68 (8)° and 13.27 (9)° for molecules *A* and *B*, respectively.

The crystallographically independent paracetamol molecules alternate in the pattern ...*ABABAB*... along a chain formed by ···HNCO···NHCO··· linkages between neighbouring amide groups. Because these molecules are crystallographically independent, these hydrogen bonds formally constitute discrete graphs at the unitary level, although it is clear from Fig. 5 that they are closely related to the *C*(4) graphs observed in the crystal structures of the *N*-methylmorpholine and *N*,*N*-dimethylpiperazine adducts described above. For consistency we continue to use this designation, although it is not formally correct [the binary graph $C_2^2(8)$ takes proper account of symmetry].

The chains are formed by 2_1 operations parallel to *c*, leading to a pairwise alternation of the centres of the paracetamol molecules above and below the chain. This pattern is reminiscent of the structures of the *N*-methylmorpholine and *N*,*N*-dimethylpiperazine adducts, except that in these cases the alternation applies to single molecules. The potential for this arrangement to lead to some steric hindrance between the phenyl groups of neighbouring molecules is avoided by adjacent molecules veering slightly away from each other and an increase in the torsional angle between the phenyl group and amide group from 3.04 (3)° in molecule *B* to 36.03 (6)° in molecule *A*.

Lattice translation along the *b* direction generates further *C*(4) chains, and these are linked together by discrete [*D*] hydrogen bonds in which an OH group from an '*A*' molecule in one chain acts as a donor to an OH group of a '*B*' molecule in a neighbouring chain. This is the only structure in the series in which pairs of paracetamol molecules interact *via* their hydroxyl moieties.

The two sets of hydrogen bonds described above – the *C*(4) chains and the *D* links between chains – form a grid-like network parallel to the (100) planes. The morpholine molecules fit into the cavities of the grid. As in the *N*-methylmorpholine adduct, the amine N atom acts as an acceptor to the OH group of one of the paracetamol molecules (*B*), but this is the only hydrogen-bonding interaction formed by the morpholine. The NH group of the morpholine is in an axial position to accommodate this interaction.

This scheme satisfies all the hydrogen-bonding potential of the two paracetamol molecules, with the exception of the hydroxyl acceptor of molecule *A*. The weakest acceptor in the system (the ether function of the morpholine) does not

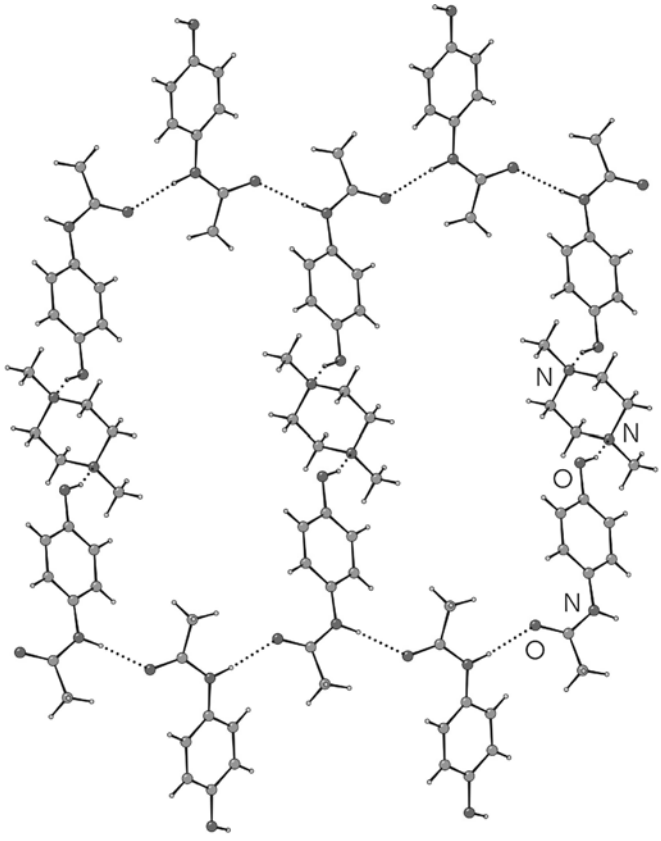


Figure 4
Paracetamol:*N*,*N*-dimethylpiperazine adduct (isostructural to the *N*-methylmorpholine adduct) viewed along the *a* axis; the *c* axis runs from left to right and the *b* axis from top to bottom. The *C*(4) chains referred to in the text run from left to right and are linked together by *N*,*N*-dimethylpiperazine molecules. The dihedral angles between the amide and phenyl mean planes in the paracetamol molecules are 33.75 (7)° and 34.11 (6)° in the *N*,*N*-dimethylpiperazine and *N*-methylmorpholine adducts, respectively.

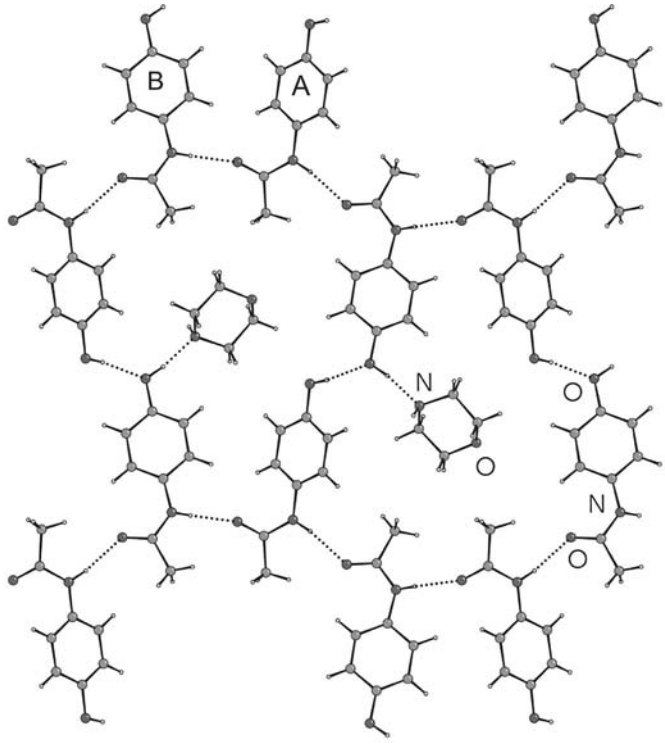


Figure 5
Paracetamol:morpholine adduct viewed along the *a* axis. The *c* direction runs from left to right, the *b* direction up and down. The labels *A* and *B* refer to the crystallographically independent paracetamol molecules referred to in the text. The *C*(4) chains referred to in the text run from left to right and are linked together by hydrogen bonds between opposed OH groups. This forms a grid-like array with the morpholine molecules residing in the grid cavities. The dihedral angles between the amide and phenyl mean planes in the two independent paracetamol molecules are 36.03 (6)° and 3.04 (3)° for molecules *A* and *B*, respectively.

participate in hydrogen bonding at all. A rather surprising feature of this structure, given the excess of acceptors present, is that the NH donor functionality of the morpholine amine moiety is also unsatisfied. However, this is consistent with the relatively long NH···OH hydrogen bonds observed in the piperazine adduct (which is described in the next section) and the generally poor hydrogen-bond-donor ability of secondary amines (see below).

3.6. The paracetamol:piperazine adduct

Piperazine is related to *N*,*N*-dimethylpiperazine by substitution of the two methyl groups by hydrogen. The asymmetric unit of the piperazine adduct, in common with the *N*,*N*-dimethylpiperazine adduct, consists of one paracetamol molecule and a molecule of piperazine on a crystallographic inversion centre. Primary bond lengths and angles are normal and have been deposited; hydrogen-bonding parameters are listed in Table 2. There are *C*(4) chains, consisting of NH···O=C hydrogen bonds, linked *via* $D_2^2(6)$ motifs consisting of OH···N bonds (Fig. 6). Piperazine is a weak hydrogen-bond donor as well as an acceptor, and the extra NH-donor moiety is satisfied by rotating alternate paracetamol molecules about the *C*(4) chain axis, leading to *D*-type NH···OH hydrogen bonds. This rotation produces ribbons that run parallel to the *b* axis rather than the infinite two-dimensional networks.

3.7. Differential scanning calorimetry

Decomposition of a co-crystal of paracetamol is a potential strategy for the production of the orthorhombic polymorph. In all cases except for the 4,4′-bipyridine adduct, DSC traces exhibited thermal events attributable to loss of the guest molecule followed by a strong endotherm, corresponding to melting, at 438–444 K. The melting point of monoclinic paracetamol is 442 K (Nichols & Frampton, 1998). The same authors showed that DSC traces for orthorhombic paracetamol show either melting at 430 K or a phase transition to the monoclinic form at the same temperature, depending on the method of preparation. The DSC traces observed in this study can therefore be interpreted in terms of decomposition leading to formation of the monoclinic polymorph.

Thermal decomposition temperatures follow the trend that might be predicted on the basis of the boiling points of 1,4-dioxane (374 K), *N*-methylmorpholine (388 K), morpholine (401 K), *N*,*N*-dimethylpiperazine (404 K) and piperazine (419 K). Two exotherms were observed for the dioxane solvate at 299 K and 338 K, in agreement with the previous study (Fachaux *et al.*, 1995). This is plausibly interpreted as sequential loss of the two crystallographically independent dioxane molecules. Dioxane is readily lost at room temperature from a crystalline sample of this adduct, and the DSC trace of a sample that had been allowed to stand for 10 min showed only one exotherm with an onset temperature of 330 K. Decomposition of the morpholine, *N*-methylmorpholine and *N*,*N*-dimethylpiperazine adducts occur as broad exotherms with onsets at approximately 327, 335 and 373 K, respectively. The DSC trace of the piperazine adduct showed one endotherm at 413 K.

4,4′-Bipyridine sublimes at 578 K under ambient pressure, and it is the least volatile compound to have been studied in this work. The DSC trace of the co-crystal exhibits a weak endotherm at 399 K followed by a strong endotherm at 402 K; no thermal event attributable to the melting of pure paracetamol was observed. The strong endotherm occurs at a similar temperature to the decomposition events observed for the other adducts, and it is likely to correspond to a melting process forming paracetamol solvated by liquid bipyridine (m.p. 374–377 K). Unlike the other solvents studied here, bipyridine is not lost to leave pure paracetamol, because its boiling point is well beyond the temperature of adduct decomposition. It is likely that the small peak corresponds to a phase transition.

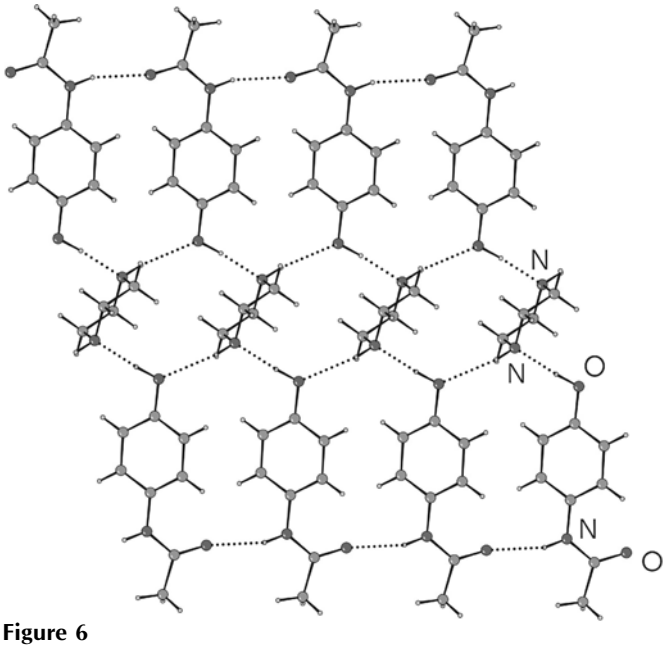


Figure 6
Paracetamol:piperazine adduct viewed perpendicular to (302); the *b* axis runs from left to right. The *C*(4) chains referred to in the text run from left to right and are linked together by piperazine molecules. The latter also act as weak hydrogen-bond donors. The dihedral angles between the amide and phenyl mean planes in the paracetamol molecule is 33.21 (14)°.

4. Discussion and conclusions

This paper has described the formation of five new paracetamol hemiadducts with 1,4-dioxane, *N*,*N*-dimethylpiperazine, *N*-methylmorpholine, morpholine and piperazine and a 1:1 adduct with 4,4′-bipyridine. This is the first such systematic study of paracetamol co-crystals to have been undertaken. As is to be expected, the crystal structures of all adducts are dominated by hydrogen-bond formation, and comparisons between them were much facilitated by the use of graph-set analysis in the form described in the illuminating review by Bernstein *et al.* (1995).

Although ether oxygen can potentially act as a double acceptor, it rarely does so, and so with the exception of

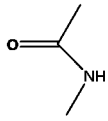
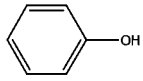
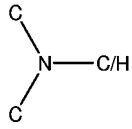
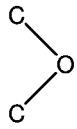
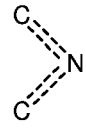
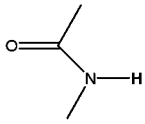
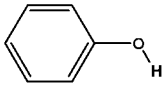
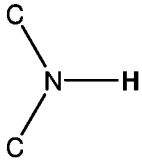
	Acceptor (O or N in each case)					
Donor (NH or OH)						
	Sample size	1250	14	11	31	40
	Max NH..A /Å	(2.2) *	2.14	2.17	2.19	2.19
	Min NH..A /Å	1.73	1.79	1.80	1.83	1.81
	Mean NH..A /Å	**1.92**	**2.01**	**1.96**	**2.03**	**1.96**
	Sample size	49	256	49	53	76
	Max OH..A /Å	2.19	2.20	2.19	2.20	2.18
	Min OH..A /Å	1.60	1.67	1.66	1.62	1.53
	Mean OH..A /Å	**1.78**	**1.87**	**1.82**	**1.90**	**1.81**
	Sample size	5	1 (HOLZOD)	12	4	Not applicable
	Max NH..A /Å	2.17	-	2.20	2.18	
	Min NH..A /Å	2.08	-	2.00	2.11	
	Mean NH..A /Å	**2.13**	**2.03**	**2.14**	**2.13**	

Figure 7
Summary of the results of searches of the CSD (Version 5.23, April 2002) for typical distances (in Å) in hydrogen-bonded systems containing identical functional groups to the paracetamol adducts studied. The distances to H atoms were normalized to typical neutron distances (C—H 1.803, N—H 1.009 and O—H 0.983 Å). Only 'organic' structures where the *R* factor is less than 0.05 with no errors or disorder were included, and ionic or polymeric structures were excluded. The C atoms attached to the amine moieties were specified to be sp^3 hybridized. The donor-H-to-acceptor distance was specified to be 1.50–2.20 Å. The asterisk denotes the limit of search.

morpholine all the guest molecules studied are at least pseudo-centrosymmetric with respect to their hydrogen-bonding properties. The dioxane, *N*-methylmorpholine, *N*,*N*-dimethylpiperazine and piperazine adducts all consist of hydrogen-bonded chains of paracetamol molecules linked together by the guest molecules, which all reside on crystallographic inversion centres. In the bipyridine adduct the chains are linked *via* a pair of π-stacked pyridine rings, though the structure as a whole is still centrosymmetric. The morpholine adduct does not conform to this pattern, although chains of paracetamol are still present. The arrangements of paracetamol chains described in this paper tend to lend themselves to the formation of centrosymmetric crystal structures, and this seems to favour adduct formation in the centrosymmetric guest molecules. It is perhaps significant that we have been unable to prepare an adduct with 1,3,5-trioxane, a molecule closely related to dioxane but which lacks inversion symmetry.

The donor groups that appear in this series are amidic NH, phenol OH and secondary amine NH; the acceptors are amidic O, phenolic O, secondary or tertiary amine N, ether O, and pyridine N. The results of searches of the CSD for typical hydrogen-bond geometries involving these functionalities are shown in Fig. 7; searching criteria are given in the legend to that figure. The pattern of adduct formation observed in this study is quite consistent with the data in Fig. 7 if the reasonable assumption is made that the hydrogen-bond strength is related to the average donor-hydrogen—acceptor distance. The donor group O—H or N—H to acceptor distances observed in this study were normalized to typical neutron values (O—H 0.983 Å and N—H 1.009 Å) to aid ready comparison with typical H-to-acceptor distances derived from our CSD search, and this comparison is made in Table 2. Our hydrogen-bond distances agree tolerably well with typical values; they are often on the short side, as might be expected with low-temperature data.

The strongest hydrogen bonds in Fig. 7 are formed between phenolic OH (as donor) and amide O (as acceptor). These are observed in the $C(9)$ chains formed in structures of both polymorphs of paracetamol. In pure paracetamol, hydrogen bonds are formed between the remaining NH donor and OH acceptor to form $C(7)$ chains, but on adduct formation with 1,4-dioxane and 4,4′-bipyridine it is these, weaker, interactions that break to accommodate the guest molecules, preserving the strongly bound $C(9)$ chains and forming hydrogen bonds between the amide NH of paracetamol and either the ether O or the pyridyl N atoms of the guest molecule. These observations are consistent with the results obtained in the variable-pressure study of monoclinic paracetamol by Boldyreva *et al.* (2000), where the NH···O contacts were found to be more compressible than the OH···O contacts.

Neither dioxane nor bipyridine has any group attached to the donor O or N atoms. All of the other molecules studied carry either hydrogen or methyl groups in these positions, and reference to Fig. 2 or Fig. 3 shows that a structure based on the $C(9)$ paracetamol chains would suffer some steric crowding

between these groups and either the phenyl or the methyl group attached to the amide moiety. In order to avoid steric overcrowding in the morpholine, piperazine, *N*,*N*-dimethylpiperazine and *N*-methylmorpholine adducts, the paracetamol utilizes its NH group as a donor. Fig. 7 shows that the most effective acceptor for this group is amide CO and this explains the formation of *C*(4) paracetamol chains in all four of these structures.

In the structures of *N*-methylmorpholine and *N*,*N*-dimethypiperazine, hydrogen bonds are formed between the OH group of paracetamol and the N or O of the guest molecule. In morpholine and piperazine, both the OH group of paracetamol and the NH group(s) of the guest could act as either donors or acceptors. Fig. 7 shows that secondary aliphatic amines are particularly poor hydrogen-bond donors, and so the hydroxyl group acts as the donor in both cases. In fact, so poor a donor is secondary amine NH that it is left unsatisfied in the morpholine adduct, even in the presence of excess acceptor functions. The weakness of these NH$\cdots$N hydrogen bonds relative to OH$\cdots$O or NH$\cdots$O systems may be a consequence of the size of N relative to O, a feature recently emphasized by Brown (2002). However, in piperazine the NH groups do act as weak donors, and this induces a change in conformation of these *C*(4) chains relative to the *N*,*N*-dimethylpiperazine adduct that condenses the sheets into ribbons.

In the case of morpholine, the *C*(4) chains are linked by the OH group of a paracetamol molecule in one chain acting as a hydrogen-bond donor to a similar group in a neighbouring chain. On the basis of the structures of the other adducts, the role might have been expected to be fulfilled by the ether moiety of the morpholine. Fig. 7 shows that these interactions are of rather similar strength, and this might explain the apparently anomalous behaviour observed in this adduct.

In the 1,4-dioxane adduct, alternate *C*(9) paracetamol chains have reversed polarity. In the adducts based on *C*(4) chains, the resemblance to orthorhombic paracetamol is less obvious, although inspection of Fig. 1(*b*) shows that removal of alternate molecules along the *C*(7) graph followed by a small displacement would yield NH$\cdots$O=C *C*(4) chains. Viewed in this light, desolvation might have been predicted to yield the orthorhombic polymorph of paracetamol, although in practice it was shown by DSC that in all cases except for paracetamol:bipyridine (for which we did not observe desolvation at all) the thermodynamically more stable monoclinic polymorph was formed.

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