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Selective solvent inclusion as a tool for mapping molecular properties in crystal structures: a diethylstilbestrol example

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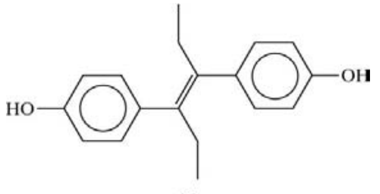
Useful information about hydrogen bonding, the preferred modes of hydrophobic interaction and conformational preferences of a specific molecule can be obtained from cocrystallization of the solute with a selected series of solvent molecules. This method is used in a study of nine different crystal structures of diethylstilbestrol (DES) solvates. It is shown that solvent inclusion results not only in stronger hydrogen bonds, but usually also in a larger number of favorable $C-H\cdots\pi$ interactions between DES molecules. Furthermore, solvent molecules such as DMSO, DMF, acetonitrile and acetone demonstrate important hydrogen-bond donating properties in addition to their more familiar role as hydrogen-bond acceptors. Molecular conformations in the crystal structures compare favorably with results from molecular mechanics calculations.

1. Introduction

The crystal structure of an organic compound gives valuable information on molecular geometry and conformation in the solid phase, but no information about other possible conformations. Similarly, the true significance of the observed types of hydrophobic interactions is highly uncertain and the hydrogen-bond pattern in the crystal may be only one out of a number of plausible candidates. Occasionally the asymmetric unit in the crystal structure contains more than one copy of the molecule of interest ($Z' \geq 2$) or several crystal forms of the same compound (polymorphism) are observed, which provides more comprehensive information about conformation and intermolecular contacts (Bernstein, 1993). Unfortunately, in either case a very small number of alternative structures (usually two) are found. A solution to this shortage of information is crystallization of a series of modified structures, *e.g.* by adding various types of covalently bonded substituents. The Cambridge Structural Database (Allen & Kennard, 1993) is a very powerful tool for studies of conformation and hydrogen bonding in a series of related structures.

Useful as they may be, studies of derivatives have several potential shortcomings when interest is focused on one specific compound. In this article we show that the desired information can be obtained by selective cocrystallization with different solvents, thus obtaining a series of 'pseudopolymorphs' (Nangia & Desiraju, 1999; Threlfall, 1995). It is of course not obvious that the solvent used will be cocrystallized with the solute in the crystal, but at least for large molecules the likelihood of solvate formation is high (Görbitz & Hersleth, 2000). Furthermore, two solvates may be isomorphous and essentially identical in every respect except at the solvent position, in which case little new information is gained about the solute molecule. If solvents of variable sizes are used, however, our own research (Görbitz & Torgersen, 1999) indicates that qualitatively different packing arrangements are often obtained.

trans-Diethylstilbestrol (DES), see (I), is an oestrogen, despite its non-steroidal structure.



(I)

It is orally active and was previously widely used to prevent miscarriages, but is now banned because it has been found to be a potent carcinogen. DES was used as a model compound for the current work for several reasons: it is readily available, a reasonably simple and small organic molecule, and four crystal structures were already known [DES (Weeks *et al.*, 1970), DES·methanol, DES·ethanol and DES·dimethylsulfoxide (Busetta *et al.*, 1973)], which indicated high propensity for solvent inclusion. The latter three structures, however, were of low quality by current standards, with no or limited information on H atoms or hydrogen bonding. Redetermination was therefore included in the project.

2. Experimental

2.1. Preparation

Crystals of the dimethyldisulfoxide (DMSO) solvate (d·dmso), the dimethylformamide (DMF) solvate (d·dmf), the acetone solvate (d·actn), the acetonitrile solvate (d·acn), the 2-propanol solvate (d·2-pr), the ethanol solvate hydrate (d·et·w) and the methanol solvate hydrate (d·met·w) were grown by diffusion of water into 50–150 µl solutions of 1−2 mg of DES in the organic solvents or mixtures between the solvent and water. Diffusion of water into a solution of 1 mg of DES in 150 µl of a water/1-propanol mixture yielded thin plates of the 1-propanol solvate (d·1-pr) for all test tubes, except one which was found to contain needles of the 1-propanol solvate hydrate (d·1-pr·w). Crystals of the *tert*-butanol solvate (d·tbut) were grown by diffusion of *tert*-butanol into a 100 µl acetonitrile solution containing 1 mg of DES. All crystals obtained were stable enough in air to be handled without special precautions. Crystallization attempts with 1-butanol, 2-butanol, isobutanol, ethyl acetate and diethyl ether were unsuccessful, giving microcrystals or amorphous precipitations.

2.2. Data collection

The data collections with *SMART* (Bruker, 1998*a*) covered almost a full sphere of reciprocal space, usually by a combination of five sets of exposures, but only three sets were used for d·tbut and d·actn. Additionally, the first 30 frames of set 1 were always recollected at the end to check for intensity decay. Exposure times ranged from 25 to 65 s.

In view of previous findings (Görbitz, 1999), the rather large crystals obtained for some complexes were not reduced in size prior to data collection in order to maximize diffraction intensities and the number of useful reflections. For data sets with a fairly high $\theta_{\max}$ value around 38°, the data is 95% complete to ~30°.

2.3. Structure determination and refinement

After integration with *SAINT* (Bruker 1998*b*) and absorption correction with *SADABS* (Sheldrick, 1996), the structures were all solved routinely with *SHELXTL* (Sheldrick, 1997). The structure of d·1pr showed several signs of complex disorder and further work with refinement was abandoned when the *R* factor was ~0.17. No further discussion of this structure will be given, but we note that the molecular arrangement appears to be very closely related to that seen in the d·2-pr structure.

The structures of d·dmso, d·dmf, d·acn and d·2-pr are fully ordered and were refined without constraints. Various degrees of disorder are present for the remaining five structures. Occupancies were then constrained to add up to 1.00, except for the water molecule in d·met·w (sum = 0.79).

For d·actn the disorder is comparatively simple with a major [0.893 (4)] and a minor [0.107 (3)] position for one of the two acetone molecules in the asymmetric unit.

The most complex disorder occurs for d·tbut, which has three alternative positions for each of the two solvent molecules [0.515 (5), 0.319 (5) and 0.166 (4)], as well as for the DES molecule [0.451 (4), 0.421 (4) and 0.128 (3), one half is the asymmetric unit]. The DES molecule in d·met·w is the only other example of a disordered solute molecule, confined to one half of the molecule with one very dominating major position [0.924 (3)] with a nearby minor position [0.076 (3)]. The methanol solvent molecule has three different positions with occupancies 0.694 (6), 0.158 (5) and 0.149 (6). A total of five different water positions were identified with a combined occupancy of 0.79. Anisotropy was introduced only at the

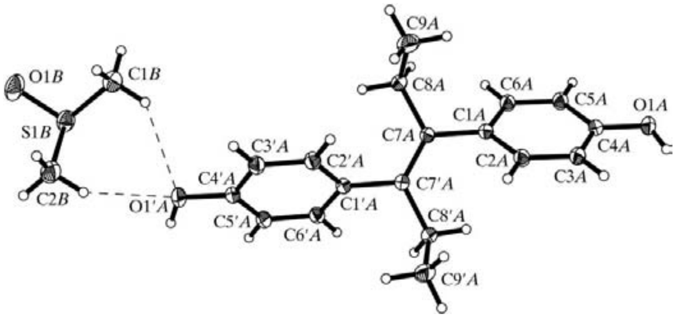


Figure 1
The asymmetric unit of the DES·dmso solvate (d·dmso) with atomic numbering. Thermal ellipsoids are shown at the 50% probability level. H atoms are spheres of arbitrary size. The dashes represent the weak hydrogen bonds between the solute and the solvent molecules.

Table 1
Experimental details.

Computer programs used: data collection: *SMART* (Bruker, 1998*a*); cell refinement and data redeuction: *SAINT* (Bruker, 1998*b*); structure solution, refinement and preparation of material for publication: *SHELXTL* (Sheldrick, 1997).

	d·acn	d·dmso	d·dmf	d·actn	d·2-pr
Crystal data					
Chemical formula	$C_{18}H_{20}O_2.C_2H_3N$	$C_{18}H_{20}O_2.C_2H_6OS$	$C_{18}H_{20}O_2.C_3H_7NO$	$C_{18}H_{20}O_2.C_3H_6O$	$C_{18}H_{20}O_2.C_3H_8O$
Chemical formula weight	309.39	346.47	341.44	326.42	328.43
Cell setting	Triclinic	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	$P\overline{1}$	$P\overline{1}$	$P\overline{1}$	$P\overline{1}$	$P2_1/c$
a (Å)	7.5866 (2)	7.8841 (5)	7.6393 (1)	9.6266 (15)	5.6981 (2)
b (Å)	8.9294 (2)	9.1401 (5)	9.9833 (3)	13.662 (2)	21.1274 (7)
c (Å)	13.4851 (3)	13.6505 (8)	13.3161 (1)	15.365 (2)	16.0891 (6)
α (°)	95.762 (1)	90.975 (2)	91.883 (2)	69.979 (2)	90
β (°)	106.263 (1)	105.924 (2)	104.036 (1)	77.853 (2)	90.914 (2)
γ (°)	101.386 (1)	100.892 (2)	104.311 (1)	83.927 (3)	90
V (Å^3)	847.87 (3)	926.41 (9)	950.00 (3)	1854.9 (5)	1936.66 (12)
Z	2	2	2	4	4
D_x (Mg m^{-3})	1.212	1.242	1.194	1.169	1.126
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073	0.71073
No. of reflections for cell parameters	6167	5718	5987	4011	5942
θ range (°)	2.4–41.1	2.3–37.9	2.1–38.0	1.8–27.8	1.6–30.5
μ (mm^{-1})	0.078	0.189	0.079	0.077	0.074
Temperature (K)	150 (2)	150 (2)	150 (2)	150 (2)	150 (2)
Crystal form	Needle	Needle	Plate	Needle	Needle
Crystal size (mm)	1.25 × 0.45 × 0.20	0.75 × 0.35 × 0.15	0.70 × 0.65 × 0.15	0.75 × 0.30 × 0.15	1.50 × 0.30 × 0.15
Crystal color	Colorless	Colorless	Colorless	Colorless	Colorless
Data collection					
Diffractometer	Siemens SMART CCD	Siemens SMART CCD	Siemens SMART CCD	Siemens SMART CCD	Siemens SMART CCD
Data collection method	Sets of exposures each taken over 0.6°ω rotation	Sets of exposures each taken over 0.3°ω rotation	Sets of exposures each taken over 0.3°ω rotation	Sets of exposures each taken over 0.3°ω rotation	Sets of exposures each taken over 0.6°ω rotation
Absorption correction	Empirical	Empirical	Empirical	Empirical	Empirical
$T_{\min}$	0.907	0.868	0.946	0.943	0.884
$T_{\max}$	0.985	0.972	0.988	0.989	0.988
No. of measured reflections	19 304	14 256	14 448	15 681	24 125
No. of independent reflections	10 110	8871	9040	7676	5850
No. of observed reflections	7526	7444	7209	5236	4661
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
$R_{\rm int}$	0.0149	0.0172	0.0135	0.0265	0.0258
$\theta_{\max}$ (°)	41.15	37.99	38.02	27.89	30.51
Range of h, k, l	$-12 \rightarrow h \rightarrow 13$ $-16 \rightarrow k \rightarrow 15$ $-24 \rightarrow l \rightarrow 24$	$-12 \rightarrow h \rightarrow 13$ $-15 \rightarrow k \rightarrow 15$ $-22 \rightarrow l \rightarrow 23$	$-12 \rightarrow h \rightarrow 12$ $-17 \rightarrow k \rightarrow 16$ $-22 \rightarrow l \rightarrow 22$	$-12 \rightarrow h \rightarrow 11$ $-17 \rightarrow k \rightarrow 17$ $-19 \rightarrow l \rightarrow 19$	$-8 \rightarrow h \rightarrow 7$ $-27 \rightarrow k \rightarrow 30$ $-22 \rightarrow l \rightarrow 22$
Refinement					
Refinement on	F^2	F^2	F^2	F^2	F^2
$R[F^2>2\sigma(F^2)]$	0.0512	0.0404	0.0468	0.0527	0.0491
$wR(F^2)$	0.1600	0.1214	0.1467	0.1336	0.1346
S	1.065	1.065	1.035	1.042	1.044
No. of reflections used in refinement	10 110	8871	9040	7676	5850
No. of parameters used	230	241	251	480	245
H-atom treatment	Mixed	Mixed	Mixed	Mixed	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0811P)^2 + 0.1642P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0658P)^2 + 0.1723P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0839P)^2 + 0.1252P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0426P)^2 + 1.2036P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0624P)^2 + 0.7023P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.011	0.012	0.009	0.010	0.000
$\Delta\rho_{\max}$ (e Å^{-3})	0.686	0.543	0.501	0.394	0.317
$\Delta\rho_{\min}$ (e Å^{-3})	−0.301	−0.322	−0.308	−0.295	−0.267
Extinction method	None	None	None	None	None

Table 1 (continued)

	d·acn	d·dmso	d·dmf	d·actn	d·2-pr
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Computer programs: as above.

	d·tbut	d·et·w	d·1-pr·w	d·met·w
Crystal data				
Chemical formula	$C_{18}H_{20}O_2{\cdot}4C_4H_{10}O$	$C_{18}H_{20}O_2{\cdot}C_2H_6O{\cdot}2H_2O$	$C_{18}H_{20}O_2{\cdot}C_3H_8O{\cdot}2H_2O$	$C_{18}H_{20}O_2{\cdot}CH_4O{\cdot}0.79H_2O$
Chemical formula weight	564.84	350.44	364.47	314.6
Cell setting	Triclinic	Triclinic	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	6.2717 (6)	7.7092 (4)	7.7102 (2)	7.5712 (6)
b (Å)	7.4330 (8)	8.9320 (5)	8.9295 (2)	9.1543 (7)
c (Å)	20.364 (2)	15.3466 (8)	15.4299 (3)	13.5964 (10)
α (°)	85.140 (2)	93.797 (2)	94.337 (1)	73.691 (3)
β (°)	85.031 (2)	100.629 (2)	100.071 (1)	75.460 (3)
γ (°)	82.626 (2)	98.866 (2)	98.291 (1)	80.517 (3)
V (Å^3)	935.34 (17)	1021.32 (9)	1029.46 (4)	870.95 (12)
Z	1	2	2	2
D_x (Mg m^{-3})	1.003	1.140	1.176	1.237
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
No. of reflections for cell parameters	3903	6108	7925	5992
θ range (°)	2.8–25.0	2.6–38.0	1.4–30.5	2.8–38.0
μ (mm^{-1})	0.067	0.081	0.082	0.081
Temperature (K)	150 (2)	150 (2)	150 (2)	150 (2)
Crystal form	Plate	Needle	Plate	Plate
Crystal size (mm)	1.0 × 0.50 × 0.10	1.60 × 0.30 × 0.25	0.60 × 0.30 × 0.10	1.20 × 1.10 × 0.20
Crystal color	Colorless	Colorless	Colorless	Colorless
Data collection				
Diffractometer	Siemens SMART CCD diffractometer	Siemens SMART CCD diffractometer	Siemens SMART CCD diffractometer	Siemens SMART CCD diffractometer
Data collection method	Sets of exposures each taken over 0.3° ω rotation scans	Sets of exposures each taken over 0.3° ω rotation scans	Sets of exposures each taken over 0.6° ω rotation scans	Sets of exposures each taken over 0.3° ω rotation scans
Absorption correction	Empirical	Empirical	Empirical	Empirical
$T_{\rm min}$	0.935	0.878	0.952	0.907
$T_{\rm max}$	0.993	0.980	0.992	0.984
No. of measured reflections	7061	15 807	15 483	13 311
No. of independent reflections	3281	9755	6159	8261
No. of observed reflections	2514	7414	4739	6630
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
$R_{\rm int}$	0.0167	0.0125	0.0203	0.0161
$\theta_{\rm max}$ (°)	25.02	38.03	30.51	38.00
Range of *h*, *k*, *l*	$-7 \rightarrow h \rightarrow 7$ $-8 \rightarrow k \rightarrow 8$ $-24 \rightarrow l \rightarrow 22$	$-11 \rightarrow h \rightarrow 13$ $-14 \rightarrow k \rightarrow 15$ $-25 \rightarrow l \rightarrow 26$	$-11 \rightarrow h \rightarrow 10$ $-12 \rightarrow k \rightarrow 12$ $-22 \rightarrow l \rightarrow 22$	$-13 \rightarrow h \rightarrow 13$ $-15 \rightarrow k \rightarrow 15$ $-22 \rightarrow l \rightarrow 23$
Refinement				
Refinement on	F^2	F^2	F^2	F^2
$R[F^2>2\sigma(F^2)]$	0.0572	0.0463	0.0418	0.0618
$wR(F^2)$	0.1648	0.1465	0.1219	0.1875
S	1.046	1.027	1.048	1.047
No. of reflections used in refinement	3281	9755	6159	8261
No. of parameters used	533	293	294	287
H-atom treatment	Mixed	Mixed	Mixed	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0760P)^2 + 0.2702P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0827P)^2 + 0.1207P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0643P)^2 + 0.1839P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0896P)^2 + 0.2731P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max}$	0.006	0.001	0.005	0.007
$\Delta\rho_{\rm max}$ (e Å^{-3})	0.168	0.539	0.339	0.637
$\Delta\rho_{\rm min}$ (e Å^{-3})	−0.147	−0.341	−0.228	−0.422
Extinction method	*SHELXTL* (Sheldrick, 1997)	None	None	None
Extinction coefficient	0.032 (6)	–	–	–

Table 1 (continued)

	d·tbut	d·et·w	d·1-pr·w	d·met·w
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

dominating position [0.34 (2)]. Disorder for the water and methanol molecules was not discovered for d·met·w in the previous investigation (Busetta *et al.*, 1973).

In d·et·w and d·1-pr·w crystals the number of alcohol positions is four [0.330 (12) to 0.153 (12)] and three [major = 0.709 (6)], respectively, but with a common location of the hydroxyl group. The seven (O—)H atoms are distributed over 14 positions with occupancy < 1. Four positions have fixed occupancies (0.50), while occupancies at the remaining ten positions were obtained from refinement of four free variables.

Heavy atoms were refined anisotropically, except for atoms with occupancy less than ~0.3 in disordered structures, which were refined isotropically. H atoms bonded to C were placed geometrically and refined with constraints to keep all C—H distances and all C—C—H angles on one C atom the same. Free rotation was permitted for fully occupied methyl groups. Positions for H atoms bonded to O were in general refined, except for a few with occupancy < 0.3 which were introduced in theoretical positions in the direction of the closest acceptor with the bond length O—H 0.85 Å. $U_{\rm iso}$ values for H atoms were constrained to be $1.2U_{\rm eq}$ of the carrier atom, or $1.5U_{\rm eq}$ for methyl groups.

Since we obtained a different ethanol solvate (d·et·w) than reported previously (d·et; Busetta *et al.*, 1973), the d·et structure was examined on a molecular graphics device using *SYBYL*6.6 (Tripos, 1999). It was straightforward to assign approximate positions of the two missing hydroxyl H atoms and thus obtain the complete hydrogen-bond network. All H atom positions had been found in the study of the solvent-free DES crystals (DES; Weeks *et al.*, 1970).

An example of the molecular structure of DES, in d·dmso, is shown in Fig. 1. The same atomic numbering is used throughout this paper (for d·actn the solute molecules are denoted *A* and *B*, and the solvent molecules *C* and *D*). The atom label C6 (and equivalently for C6′) is chosen such that the C6—C1—C7—C7′ torsion angle is in the range 0–180°. Crystal data, experimental conditions and refinement results are summarized in Table 1.[1] For completeness, cell parameters for DES (Weeks *et al.*, 1970), d·et (Busetta *et al.*, 1973) and the abandoned d·1-pr structure are listed in Table 2. Parameters for O—H···*A* and C—H···*A* hydrogen bonds are listed in Tables 3 and 4, respectively.

2.4. Molecular mechanics calculations

Energy minimizations were carried out with the Tripos force field as implemented in the *SYBYL*6.6 program (Tripos, 1999). Atomic charges were calculated with the Gasteiger–Hückel method, the non-bonded cut-off limit was set to infinity, the dielectric constant was 1.0, and a gradient < 0.01 kJ mol^{-1} Å^{-1} was used as the convergence criterion.

3. Results and discussion

3.1. Space groups and unit cells

d·2-pr and d·1-pr crystallize in monoclinic space groups. Other DES complexes crystallize in the space group $P\bar{1}$. All except d·tbut have unit-cell lengths ~7.6 (doubled for d·actn), 9 and 14 Å. One might then suspect that these structures share the same general packing features and that differences are found mainly at the solvent positions. A closer inspection reveals that this is not the case; all structures have unique packing arrangements, as illustrated in Fig. 2 for d·acn and

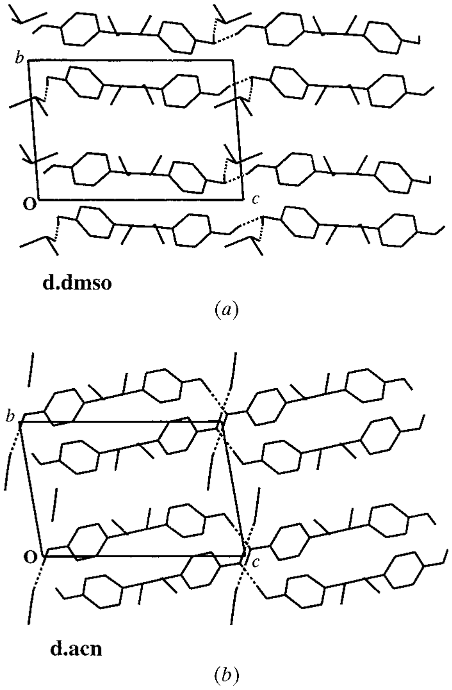


Figure 2
Unit-cell and molecular packing for (*a*) d·dmso and (*b*) d·acn viewed along the *a* axes. In Figs. 2 and 3 O—H···*A* hydrogen bonds are shown as dotted lines. H atoms not involved in such interactions have been removed for clarity.

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[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: OS0062). Services for accessing these data are described at the back of the journal.

Table 2
Cell dimensions for other DES crystals.

	d·1-pr	d·et[(a)]	DES[(b)]
Chemical formula	$C_{18}H_{20}O_2{\cdot}C_3H_8O$	$C_{18}H_{20}O_2{\cdot}C_2H_6O$	$C_{18}H_{20}O_2$
Cell setting	Monoclinic	Triclinic	Orthorhombic
Space group	*Pn*	$P\bar{1}$	*Pbca*
a (Å)	25.993 (2)	9.2941	8.954 (4)
b (Å)	5.6466 (4)	13.841	14.929 (1)
c (Å)	26.065 (2)	7.713	5.291 (1)
α (°)	90.0	71.95	90.0
β (°)	105.905 (9)	80.26	90.0
γ (°)	90.0	98.60	90.0
V ($Å^3$)	3679.2 (3)	907.9	1497.3
Z	8	2	4

References: (*a*) Busetta *et al.* (1973); (*b*) Weeks *et al.* (1970).

Table 3
O—H···*A* hydrogen-bond distances (Å) and angles (°).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
d·acn				
O1*A*—H1*A*···N1*B*$^{\rm i}$	0.970 (17)	1.935 (17)	2.9037 (14)	176.8 (15)
O1′*A*—H1′*A*···O1*A*$^{\rm ii}$	0.915 (18)	1.950 (18)	2.8515 (10)	168.4 (16)
d·dmso				
O1*A*—H1*A*···O1*B*$^{\rm iii}$	0.869 (16)	1.738 (16)	2.6004 (10)	171.2 (16)
O1′*A*—H1′*A*···O1*A*$^{\rm iv}$	0.889 (17)	1.852 (17)	2.7191 (9)	164.6 (15)
d·dmf				
O1*A*—H1*A*···O1*B*$^{\rm v}$	0.934 (15)	1.671 (15)	2.6009 (9)	173.6 (14)
O1′*A*—H1′*A*···O1*A*$^{\rm vi}$	0.890 (17)	1.836 (18)	2.7032 (10)	164.2 (16)
d·actn				
O1*A*—H1*A*···O11*D*$^{\rm vii}$	0.87 (3)	1.91 (3)	2.767 (3)	167 (3)
O1′*A*—H1′*A*···O1*A*$^{\rm viii}$	0.93 (3)	1.84 (3)	2.763 (2)	170 (2)
O1*B*—H1*B*···O1′*B*$^{\rm vii}$	0.86 (3)	1.84 (3)	2.689 (2)	172 (3)
O1′*B*—H1′*B*···O1*C*	0.85 (3)	1.82 (3)	2.663 (2)	173 (3)
d·2-pr				
O1*A*—H1*A*···O1*B*$^{\rm ix}$	0.90 (2)	1.71 (2)	2.6115 (13)	171.0 (17)
O1′*A*—H1′*A*···O1*A*$^{\rm x}$	0.86 (2)	1.84 (2)	2.6817 (13)	170.1 (19)
O1*B*—H1*B*···O1′*A*$^{\rm xi}$	0.818 (19)	1.95 (2)	2.7457 (13)	165.1 (18)
d·tbut				
O1*A*—H1*A*···O11*C*$^{\rm xii}$	0.96 (3)	1.65 (3)	2.590 (9)	169 (2)
O11*B*—H1*B*···O1*A*	0.82 (3)	1.97 (3)	2.798 (9)	177 (2)
O11*C*—H1*C*···O11*B*	0.82 (3)	1.86 (3)	2.678 (14)	168 (3)
d·et·w				
O1*A*—H1*A*···O1*C*$^{\rm xiii}$	0.79 (2)	1.87 (2)	2.6469 (14)	168 (2)
O1′*A*—H1′*A*···O1*B*	0.82 (3)	1.89 (3)	2.6998 (12)	168 (3)
O1*B*—H1*B*···O1*B*$^{\rm xiv}$	0.94 (3)	1.82 (3)	2.7494 (19)	172 (3)
O1*C*—H11*C*···O1*D*$^{\rm vii}$	0.81 (3)	1.99 (3)	2.7942 (15)	170 (2)
O1*C*—H12*C*···O1*B*	0.85 (3)	1.94 (3)	2.7843 (14)	170 (2)
O1*D*—H11*D*···O1*A*$^{\rm ii}$	0.80 (2)	1.92 (2)	2.7130 (13)	170 (2)
O1*D*—H12*D*···O1*D*$^{\rm xv}$	0.86 (3)	1.86 (3)	2.7195 (19)	175 (3)
O1*D*—H13*D*···O1′*A*	0.81 (4)	1.92 (4)	2.7302 (13)	175 (2)
d·met·w				
O1*A*—H1*A*···O1′*A*$^{\rm ii}$	0.83 (3)	1.95 (3)	2.7760 (18)	170 (3)
O1′*A*—H1′*A*···O11*B*$^{\rm xvi}$	0.87 (2)	1.82 (2)	2.683 (3)	170 (2)
O11*B*—H11*B*···O11*C*$^{\rm xvii}$	0.85	1.83	2.677 (12)	179
O11*C*—H11*C*···O1*A*$^{\rm iv}$	0.85	2.20	3.055 (10)	179

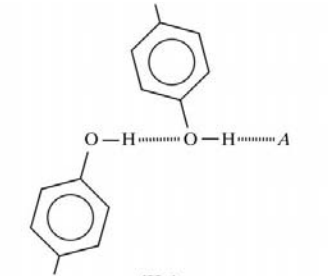
Symmetry codes: (i) $x, y-1, z-1$; (ii) $x, y, 1+z$; (iii) $x-1, y, 1+z$; (iv) $x, y, z-1$; (v) $1+x, y-1, 1+z$; (vi) $x-1, y, z-1$; (vii) $x, 1+y, z$; (viii) $x, y-1, z$; (ix) $-x, -y, -z$; (x) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (xi) $x, \frac{1}{2}-y, z-\frac{1}{2}$; (xii) $x-1, y, z$; (xiii) $1-x, 1-y, 1-z$; (xiv) $-x, 1-y, 2-z$; (xv) $-x, -y, 2-z$; (xvi) $1-x, 2-y, -z$; (xvii) $1-x, 1-y, -z$.

d·dmso. The exception is d·et·w and d·1-pr·w, which are essentially identical structures. The 11 structures (not counting d·1-pr) in Tables 1 and 2 thus provide information about DES in ten different crystallographic environments.

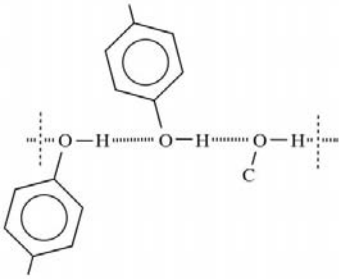
3.2. Intermolecular contacts

The hydrogen-bond pattern in DES (Weeks *et al.*, 1970) contains a single O—H···O—H··· infinite chain. Since the molecule has a center of symmetry, the first-level graph set (Etter *et al.*, 1990; Bernstein *et al.*, 1995, Grell *et al.*, 1999, 2000) is then **C**(2). The hydrogen bonds are almost linear, but O···O distances are comparatively long at 3.026 Å.

Incorporation of solvent in d·dmso, d·dmf, d·actn and d·acn results in a finite chain with two hydrogen bonds, see (II*a*).



(II*a*)



(II*b*)

Compared to DES there is, despite the loss of hydrogen-bond cooperativity (Jeffrey & Saenger, 1991), a substantial reduction in the O(φ)—H···O(φ)—H hydrogen bond length (φ = phenyl) to ~2.70 Å for the first three structures, Table 3. For d·acn the bond is a little longer, 2.8515 (10) Å, since there is less polarization in the system with the weaker acetonitrile acceptor.

The main hydrogen-bond pattern in d·2-pr, with a hydrogen-bond donating solvent molecule, is switched to an infinite chain with hydrogen-bond cooperativity, see (II*b*), in the shape of a helix with pseudo-threefold symmetry and third-level graph set $\mathbf{C}_3^3(6)$ [third level = three crystallographically independent H atoms are involved in the pattern, superscript = number of acceptors, subscript = number of donors, (*n*) shows the number of atoms in the repeating unit (the degree of the pattern)]. The O(φ)—H···O(φ)—H hydrogen bond length is 2.6817 (3) Å, the shortest observed in the structures investigated. An almost identical chain is observed in d·tbut, but with one φ-OH substituted with an alcohol-OH, Fig. 3. In d·et (Busetta *et al.*, 1973) two repeating units in (II*b*) form a homodromic cyclic system (Saenger, 1979) with the third-level graph set $\mathbf{R}_6^6(12)$. A further deviation is found for d·met·w where an extra water molecule is inserted into the chain as an acceptor for the methanol-OH [fourth-level graph set $\mathbf{C}_4^4(8)$].

The two-dimensional hydrogen-bond network in d·et·w, without O(φ)—H···O(φ)—H interactions, is shown in Fig. 4.

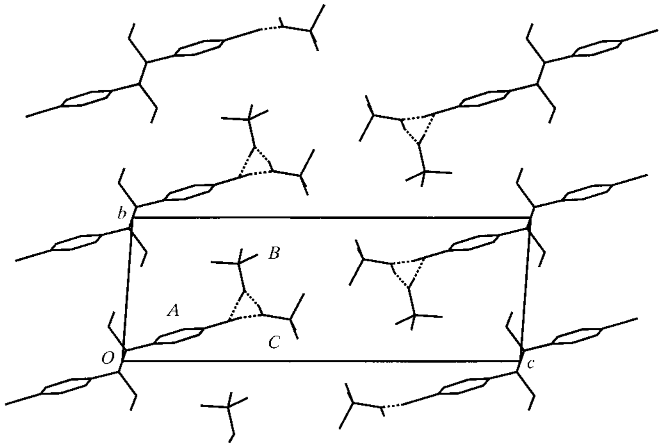


Figure 3
Crystal packing of d·tbut viewed along the *a* axis. The DES molecule (*A*) has inversion symmetry, and there are two solvent molecules (*B* and *C*) in the asymmetric unit.

For each hydroxylic H atom there are two or even three alternative positions, while there are three and four alternative H-atom positions for water molecules *C* and *D*, respectively. This intriguing disorder is reminiscent of the disorder in ice I_h and I_c (Savage, 1986), but with occupancies ranging from 0.128 (17) to 0.872 (17). Four positions are confined by symmetry to have occupancy 0.5. For each O···O distance with two H-atom positions, Table 3 lists only the proton with the highest occupancy. Interactions for d·1-pr·w, which have not been given in Table 3, are similar, but slightly longer (0.01–0.05 Å) than the corresponding interactions in d·et·w.

Apart from the strong O—H···O hydrogen bonds, the presence of numerous weaker C—H···π and C—H···O interactions in DES structures is of considerable interest. Table 4 lists such contacts with C—H···*A* distances < 2.8 Å. The distance criterion has been used to limit the extent of the table and not because longer contacts are unimportant, as will be evident from the discussion below. Two important results appear from Table 4:

(i) Short interactions frequently involve solvent molecules. As has been shown recently by Nangia & Desiraju (1999), DMSO and DMF have a high probability of being included in crystal structures. In addition to their role as hydrogen-bond acceptors, they also invariably form C—H···O hydrogen bonds, as seen in d·dmso, see Fig. 1. Table 3 furthermore shows that methyl groups in acetone (d·actn) and acetonitrile (d·acn) are donors in hydrogen bonds, with at least one H···O distance ≤ 2.61 Å with a O(φ)—H group as an acceptor.

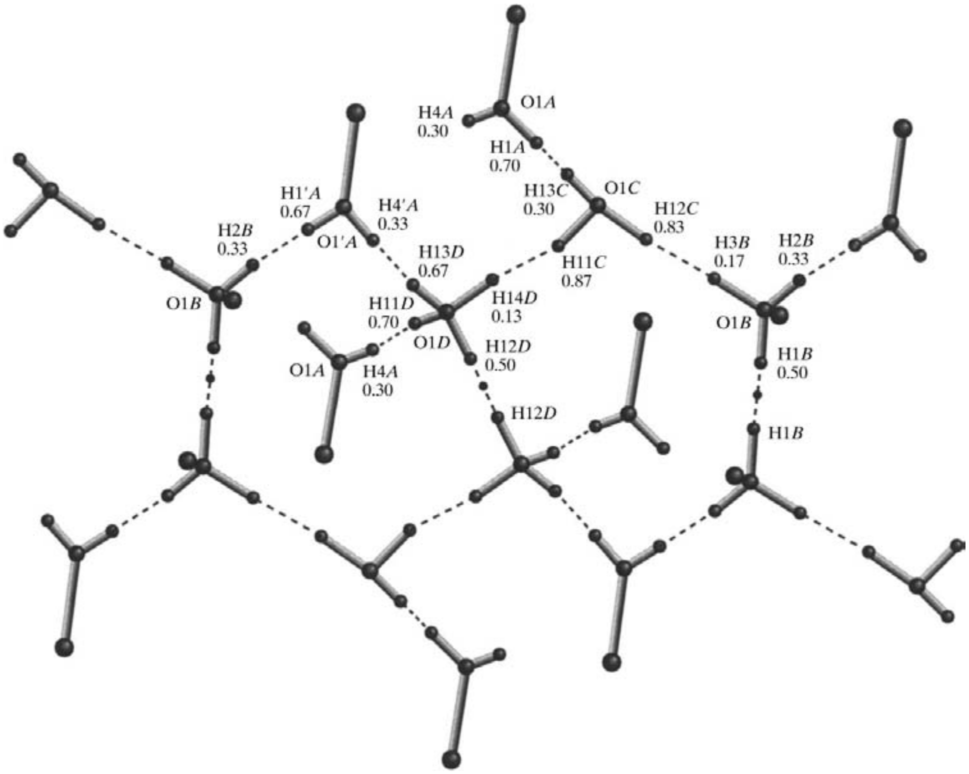


Figure 4
Hydrogen-bond pattern in the d·et·w structure with occupancies for each of the 14 different H-atom positions taken by the seven H atoms bonded to O. Inversion centers have been indicated with ● (dot).

(ii) The two structures with $\mathbf{C}_3^3(6)$ chains have no (d·2-pr) or few entries (d·tbut) in Table 4. The explanation for these observations is associated with differences in molecular packing. Fig. 2 show columns of DES molecules in the d·dmso and d·acn structures (four copies for each). Similar columns are observed in all structures except DES, d·2-pr and d·tbut. Moving down one of these columns, consecutive DES molecules related by inversion symmetry (except in d·actn where there is only pseudo-inversion symmetry) are interconnected with a large number of weak C—H···π interactions, Fig. 5, between aromatic rings at angles between 60.9° for d·actn to 73.1° for d·dmso. There are four donors in each half of the molecule; two adjacent C(ar)—H groups, one —CH$_2$— group and one in the terminal —CH$_3$ group. The accepting π-electrons are usually associated with the aromatic rings, but also with the central C═C

Table 4
C—H···A contacts with H···A distance < 280 Å.

D—H···A	D—H	H···A	D···A	D—H···A
d·acn				
C5A—H5A···O1′$A^{\rm i}$	0.98	2.74	3.5422 (11)	139
C5A—H5A···N1$B^{\rm ii}$	0.98	2.76	3.4826 (12)	131
C′A—H5′A···O1$A^{\rm iii}$	0.96	2.76	3.4395 (9)	128
C2B—H23B···O1′$A^{\rm iv}$	0.99	2.61	3.3632 (14)	133
C8A—H82A···C6′$A^{\rm i}$	0.98	2.78	3.6532 (10)	148
d·dmso				
C3A—H3A···O1$B^{\rm v}$	0.97	2.67	3.3238 (10)	125
C1B—H12B···O1′A	0.96	2.57	3.3492 (12)	138
C1B—H13B···O1$B^{\rm vi}$	0.96	2.56	3.4848 (14)	163
C2B—H23B···O1′A	0.95	2.50	3.2858 (11)	141
d·dmf				
C3A—H3A···O1$B^{\rm vii}$	0.97	2.79	3.4231 (9)	124
C2B—H22B···O1′A	0.90	2.48	3.3716 (14)	171
C3B—H32B···O1$B^{\rm viii}$	0.97	2.65	3.4131 (13)	136
C3B—H32B···O1$B^{\rm viii}$	0.97	2.65	3.4131 (13)	136
C3B—H33B···C5$A^{\rm ix}$	0.97	2.76	3.4924 (13)	133
d·actn				
C5A—H5A···O11$D^{\rm x}$	0.98	2.48	3.170 (4)	128
C5B—H5B···O1′$A^{\rm xi}$	0.98	2.73	3.610 (3)	149
C3′B—H3′B···O1C	0.97	2.59	3.266 (3)	127
C2C—H22C···O1′$A^{\rm ix}$	0.97	2.71	3.676 (3)	177
C3C—H32C···O1$B^{\rm xii}$	0.96	2.59	3.293 (3)	130
C21D—H23D···O1′$A^{\rm xiii}$	0.96	2.74	3.658 (2)	162
C8′B—H84B···C6$B^{\rm xiv}$	0.98	2.74	3.656 (3)	155
C2C—H23C···C4′$B^{\rm xv}$	0.97	2.76	3.533 (3)	138
d·tbut				
C31A—H31A···O11$C^{\rm xvi}$	0.95	2.77	3.392 (8)	124
C41B—H43B···O1A	0.98	2.72	3.433 (6)	130
d·met·w				
C5A—H5A···O1′$A^{\rm iii}$	0.95	2.74	3.4230 (13)	129
C5′A—H5′A···O11$B^{\rm xvii}$	0.95	2.58	3.2683 (18)	129
C8A—H82A···C6′$A^{\rm xviii}$	0.99	2.76	3.6644 (14)	152

Symmetry codes: (i) $1-x, -y, 1-z$; (ii) $x, y-1, z-1$; (iii) $x, y, z+1$; (iv) $1-x, 1-y, 2-z$; (v) $x-1, y, z+1$; (vi) $2-x, 1-y, -z$; (vii) $x+1, y-1, z+1$; (viii) $-x, 2-y, -z$; (ix) $-x, 1-y, 1-z$; (x) $x, y+1, z$; (xi) $1-x, 2-y, 1-z$; (xii) $x-1, y-1, z$; (xiii) $1-x, 1-y, 1-z$; (xiv) $1-x, 2-y, 2-z$; (xv) $-x, 1-y, 2-z$; (xvi) $x-1, y, z$; (xvii) $1-x, 2-y, -z$; (xviii) $-x, 2-y, 1-z$.

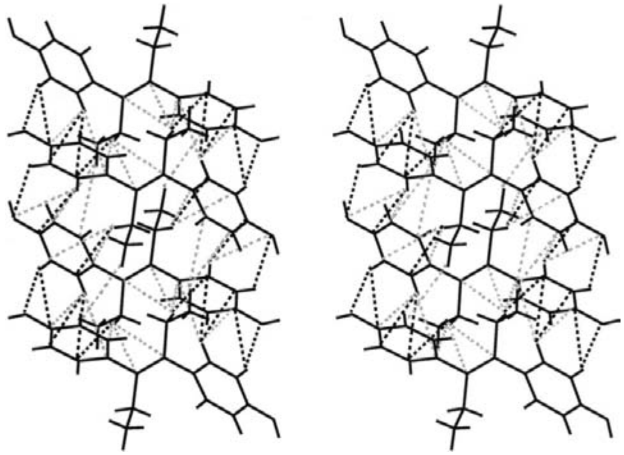


Figure 5
Stereo drawing of a column of DES molecules in the d·dmso structure. C—H···O/C distances < 3.0 Å are indicated with black dots, contacts in the range 3.0–3.2 Å with grey dots.

bond. There may also, as in d·dmso, be additional C(ar)—H···O(φ) interactions, Fig. 5.

In the DES structure the number of C—H donors is the same as in the columnar structures, but the favorable positioning of one (C—)H atom almost directly above the phenyl ring of the neighboring molecule, as seen for d·dmso in Fig. 5, is missing. For unsolvated DES the formation of columns is evidently incompatible with keeping the required $\mathbf{C}(2)$ hydrogen-bonded chain. In d·2-pr, d·tbut and d·et·w the number of C—H···π interactions is reduced, and the remaining interactions are comparatively long. It appears that the lack of interactions between the solvent and the solute, other than the strong hydrogen bonds involving the hydroxyl groups, and the weaker interactions between DES molecules are compensated by the favorable formation of the cooperative $\mathbf{C}_3^3(6)$ hydrogen-bond chains as discussed above.

3.3. Molecular conformation

The molecular mechanics calculations identified only two energy minima, the global minimum $T1$ with twofold symmetry at the central C═C bond, and the local minimum $T2$ with inversion symmetry only 0.85 kJ mol^{-1} higher in energy. All structures with non-crystallographic twofold symmetry have conformations close to $T1$, Fig. 6, while $T2$ is very similar to the conformation observed in DES (with crystallographic inversion symmetry). The conformation in d·tbut is related to, but significantly different from, $T2$. If energy minimizations are carried out with a value which is too high for the energy gradient as the convergence criterion (say 0.1 kJ mol^{-1} Å^{-1}), an apparent third minimum structure

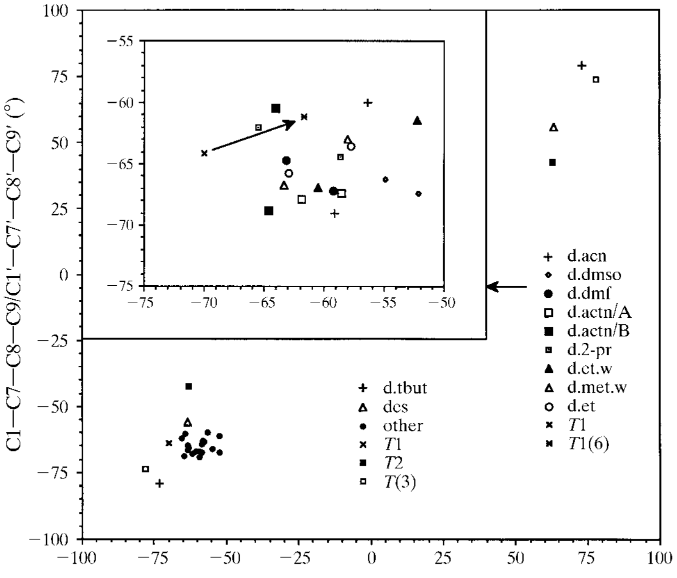


Figure 6
Distribution of the C2—C1—C7—C7′/C2′—C1′—C7′—C7 and C1—C7—C8—C9/C1′—C7′—C8′—C9′ torsion angles for DES in the crystal structures. d·1-pr·w is essentilly identical to d·et·w and has not been included. The arrow in the top left-hand frame (shown at larger scale) indicates movement of the theoretical structure as neighboring molecules are included in the computation.

called $T(3)$ is found 2.8 kJ mol^{-1} above $T1$. As can be seen from Fig. 6, the false $T(3)$ minimum is actually close to the d·tbut conformation. The conformations of DES in the crystal structures thus nicely mirror the fairly simple theoretical calculations.

The value for the C2—C1—C7—C7′ torsion angle (and C2′—C1′—C7′—C7) is −70.0° for $T1$, while the average for the nine crystal structures in the group is −59.6°. To investigate if this difference is associated with the crystal stacking of DES molecules into columns as discussed above, DES hexamers were extracted from various crystal structures. Subsequent energy minimizations always converged at the same molecular structure for the hexamer. In the central pair of DES molecules the C2—C1—C7—C7′ torsion angle is −61.7° [$T1(6)$ in Fig. 6], which is very close to the crystal structure average. This shows how molecular stacking, with the introduction of C—H$\cdots\pi$ interactions, slightly shifts the position of the conformational global energy minimum on the DES energy surface.

4. Conclusions

This investigation of various DES solvates illustrates the usefulness of obtaining crystal structures of several different solvates with different crystal packing patterns. Different molecular conformations can be studied, recurring patterns in hydrophobic aggregation, including C—H$\cdots\pi$ interactions, can be discussed, and the inclusion of a solvent can be rationalized on the basis of observations of the hydrogen bonds found in the crystal structures.

For diethylstilbestrol (DES) we can see that stronger hydrogen bonds are formed in solvates than in the structure of DES alone, and that solvent inclusion enables DES molecules to form well defined columns where molecules are interconnected by strong C—H$\cdots\pi$ interactions.

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