A study of methanol solvates using the Cambridge structural database

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A search of the Cambridge Structural Database (CSD) yielded a data set of 375 purely molecular structures to be used for study of methanol solvates. Five different hydrogen bond environments of methanol were defined and their occurrence within this data set investigated. Methanol is most commonly found to be either, a proton donor or simultaneously both a donor and single acceptor. Analysis with VISTA and Isogen provided statistical information concerning the hydrogen bond lengths and angles. A common feature of methanol in these structures is that it adopts a hydrogen-bonding motif similar to that found in liquid methanol. A common feature of the host molecules is that they exhibit more acceptor than donor functionality although there is no correlation between the extent of this mismatch and the tendency for methanolate formation. Finally 21 structural pairs in which a single host molecule has both a known solvated and unsolvated form were identified and compared.

Introduction

Crystalline solvates are important from both solid state and solution chemistry perspectives. In the former case there is significant interest in understanding intermolecular interactions through which solvents are incorporated into crystal structures.[1] In the latter case, practical issues of habit modification, polymorph appearance and nucleation rates are often solvent dependant and hence understanding how solvents interact with solutes is of key significance.[2,3] Table 1 compares the relative occurrence of the 10 most common solvates in the CSD for the years 1978[4] and 2008.

In Table 1, water, benzene and toluene, did not change in their relative ranking over 1978 to 2008 time period. Even though hydrates are the most common solvates in both database releases, their relative frequency has decreased. The biggest changes can be seen in the percentages of methanol (increase from 4.7 to 10% taking it from 4th to 2nd place), and dimethyl sulfoxide solvated structures (increase from 0.6 to 5.2%, taking it from 10 to 4th place).

Based on this analysis showing the increasing frequency of methanolates together with the undoubted importance of methanol as a crystallisation solvent, the current paper surveys and analyses the environments of methanol in structures recorded in the CSD 2008 release. This work forms part of a programme aimed at correlating the occurrence of solvates with the solution chemistry and thermodynamics of the crystallisation environment. Of specific interest therefore has been the possibility of comparing methanol environments in crystals with those in solutions and in identifying solvated/unsolvated pairs for possible experimental studies.

Search procedures

The study was carried out on the V5.29 release of the CSD. Search queries aimed at identifying methanolates were defined in version 1.10 of ConQuest. All of the atoms in methanol were drawn explicitly, specifying the number of bonded atoms (defined in Conquest by T_n), in order to limit the results to structures with defined hydrogen positions. The search resulted in 7224 structures. Further restrictions were then applied, so as to include only organic structures having 3-D coordinates without ions, no disorder or errors and R factors ≤ 0.05. Polymeric structures and structures solved from powder data were also excluded. This created a dataset of 375 structures for further investigation. The exclusion of disorder from this dataset was justified on the basis that of the 105 structures in this category, 94% had their disorder associated with the hydrogen bonding network, either with methanol or with oxygen, nitrogen, hydrogen atoms on the host molecule.

These 375 structures were analysed in terms of methanol coordination and the dataset further reduced to include only those structures in which methanol acts both as a donor to

Table 1 A comparison of the 10 most common solvates in the 1978[4] and 2008 CCDC releases

	Structural occurrence (%)			
	1978 release[a]		2008 release	
Water	(1)	70.7	(1)	61.3
Dichloromethane	(2)	6.8	(5)	4.6
Benzene	(3)	5.4	(3)	6.7
Methanol	(4)	4.7	(2)	10.0
Acetone	(5)	3.2	(6)	3.4
Chloroform	(6)	3.2	(7)	3.2
Ethanol	(7)	3.0	(8)	2.3
Tetrahydrofuran	(8)	2.7	(10)	1.5
Toluene	(9)	2.5	(9)	1.8
Dimethyl sulfoxide	(10)	0.6	(4)	5.2

[a] Recalculated from ref. 4 in relation to the 10 most common solvents.

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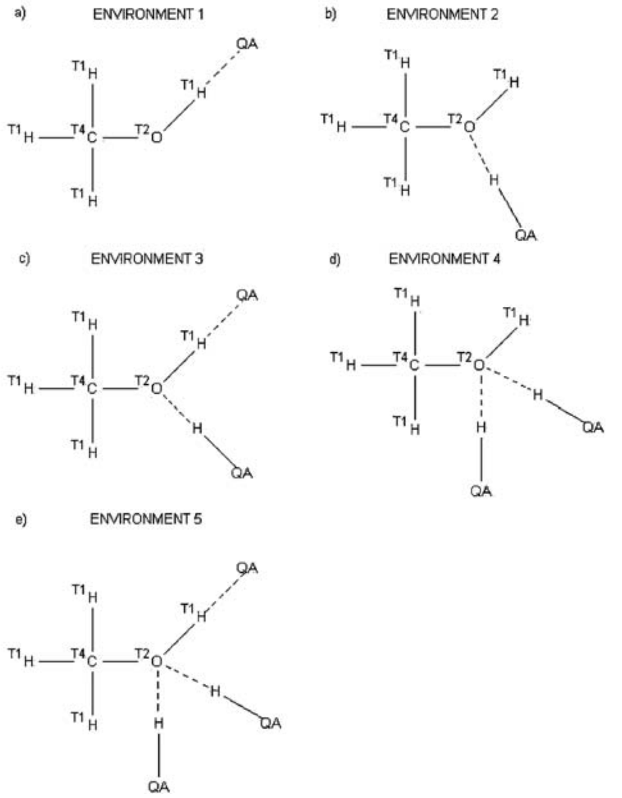

Fig. 1 Five coordination environments for methanol.

oxygen or nitrogen in the host structure and/or an acceptor of OH or NH protons. Sulfur, having a significantly different electronic structure was not included in this study. Structures containing more than two host components were removed manually. Following a previous study[5] five different coordination environments were defined as presented in Fig. 1. These environments vary from 1 and 2, in which methanol forms one hydrogen bond with the surrounding crystal lattice through to environments 3 and 4 with two hydrogen bonds, to environment 5 with three hydrogen bonds.

In analysing the structures within these environments the N–H and O–H bond lengths were normalised to their standard neutron values of 1.009 and 0.983 Å, respectively. H-bonds were defined, using the generally accepted search criterion,[5,6] as close contacts less than the sum of the hydrogen and nitrogen van der Waals radii (2.75 Å). For each environment the search gave the O–H···QA and O···HQA distances and angles for each structure.

The output from the searches was further analysed in terms of the hydrogen bond distance and angle data using VISTA 2.2,[7] and it was visualised as scatter plots using both Microsoft Office Excel 2003 and IsoStar (version 2.0.1) run in IsoGen 2.0.1.[6] In generating IsoStar plots the IsoGen option 'omit atoms' was used to ensure good overlay of the methanol fragment aiding visualisation of the donor and acceptor geometries.

The programs Solvates[8] and the Materials Module of Mercury[9] (CSD version 5.29) were used to identify and compare crystal structures of molecules exhibiting both solvated and non-solvated forms. Donor : acceptor ratios for the 305 structures were assessed by hand, following the methodology and definitions of Desiraju.[10]

Results

Of the subset of 375, the ConQuest searches for the five coordination environments (Fig. 1) accounted for a total of 305 structures. 53 of these (17%) belonged to environment 1, 7 (2%) to environment 2, 214 (70%) to environment 3, 3 (1%) to environment 4, and 28 (9%) to environment 5. The remaining 70 structures could not be classified under any of the defined environments. This was for a number of reasons: no 3D coordinates specified for hydrogen; the search had wrongly included ionic, metallo-organic or disordered structures; the intermolecular distances suggest that methanol acted as a space filler; the heteroatom involved in the hydrogen bond was neither oxygen or nitrogen; structural errors in which, although methanol seemed to act as a donor, no hydrogen bond was present. The subsequent analysis of this reduced dataset focuses on the three most significant environments: 1, 3 and 5. environments 2 and 4 are not considered in detail since the number of structures involved are statistically insignificant, a feature which suggests a reluctance of methanol to crystallise using only its acceptor functionality. However, it is important to recall that this analysis excludes structures involving sulfur and hence may overestimate the occurrence of environments 2 and 4.

Colour coding of figures

In the Fig. 2, 5, 9 blue, red and white are used to represent nitrogen, oxygen and hydrogen, respectively. Thus blue and red crosses represent nitrogen and oxygen acting as acceptors; red–white and blue–white sticks correspond to –O–H and –N–H groups acting as donors; methanol is symbolised by a white–red–black stick.

Environment 1

Environment 1 contains 53 structures, in which methanol plays a donor role, as seen in Fig. 2 which shows orthogonal views of the data. The grouping of structures around methanol's OH group is completely as expected in this environment.

Fig. 3 shows the same data as a plot of –O–H···QA distances *vs.* angles. Overall the hydrogen bond lengths in environment 1 vary from 1.52 to 2.72 Å, with the bulk of the

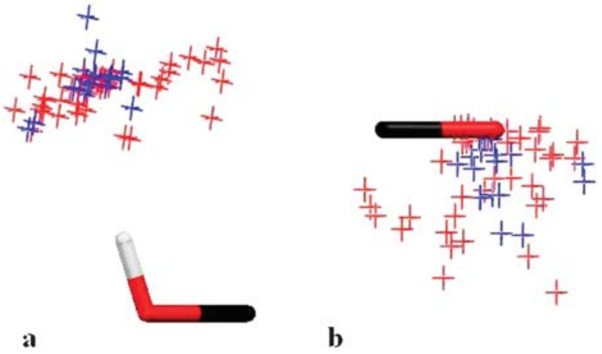

Fig. 2 IsoStar scatter plots of environment 1: (a) the view from the side, (b) viewed along the O–H bond.

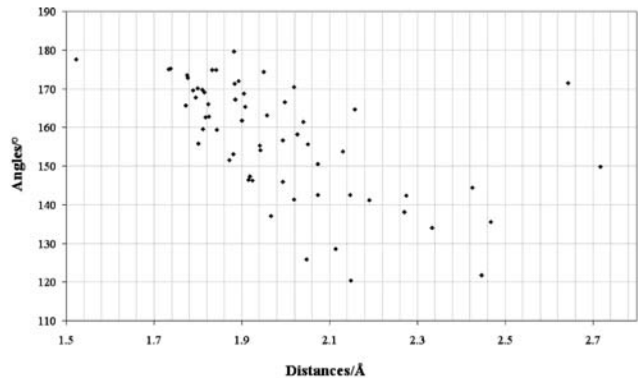

Fig. 3 O–H· · ·QA distance *vs.* angle for environment 1.

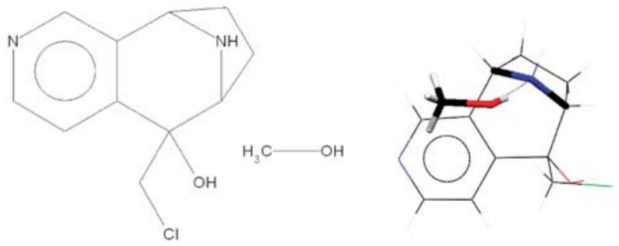

Fig. 4 An example of environment 1: (1*S*,8*R*,9*R*)-8-(chloromethyl)-4,12-diazatricyclo(7.2.1.$0^{2,7}$)dodeca-2,4,6-trien-8-ol–methanol solvate[11] in which methanol acts only as donor.

data clustered in the region between 1.74 and 2.1 Å with angles between 140 and 180°.

An example of environment 1 is (1*S*,8*R*,9*R*)-8-(chloromethyl)-4,12-diazatricyclo(7.2.1.$0^{2,7}$)dodeca-2,4,6-trien-8-ol–methanol solvate, $C_{11}H_{13}ClN_2O{\cdot}CH_4O$ (YARPOX),[11] presented in Fig. 4. Methanol is hydrogen bonded to nitrogen in this structure with a bond length and angle of 1.841 Å and 174.86°.

Environment 3

Environment 3, in which methanol is both a donor and acceptor, is the most populated environment having 214 structures. The IsoGen scatter plots are presented in the Fig. 5(a), (b) and (c). It can be clearly seen that, as expected, the acceptors are situated around the hydroxyl hydrogen of methanol, while the donors are grouped around the oxygen.

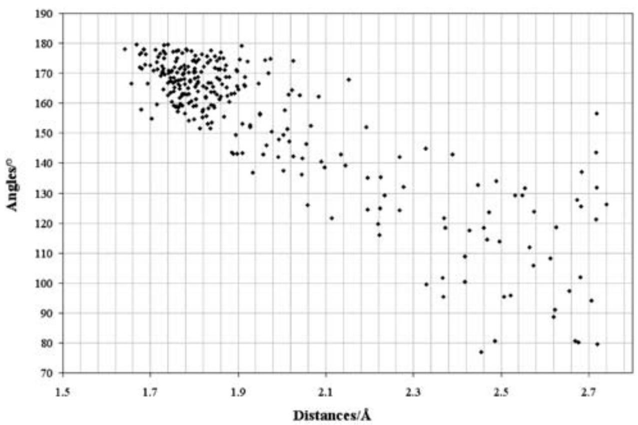

Fig. 6 O–H· · ·QA distance *vs.* angle for environment 3.

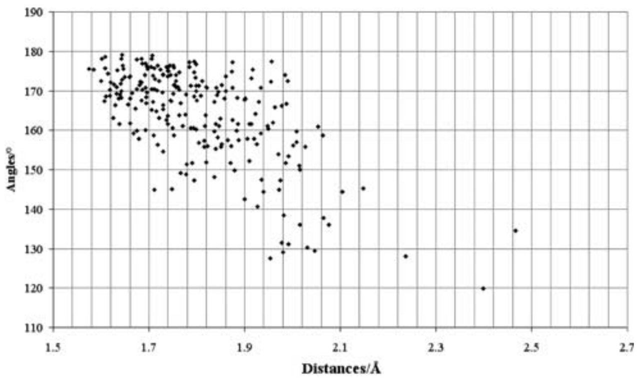

Fig. 7 O· · ·H–QA distance *vs.* angle for environment 3.

As seen in Fig. 6 the hydrogen bond lengths for methanol as a donor in environment 3 vary from 1.65 to 2.74 Å. The cluster in the region which includes distances from 1.65 to 1.9 Å and angles between 150 and 180° comprises 67% of the structures.

When methanol acts an acceptor (Fig. 7) in environment 3 the hydrogen bond distances are in the range of 1.45 Å to 2.5 Å. In this case the majority of structures have distances and angles in the region 1.56 to 2.1 Å and 145 to 180°.

(The apparent symmetry of the QA–H donor group results from the clustering algorithm applied by IsoGen. For each structure a centroid representing the centre of mass of all contact group atoms is calculated. The mirror symmetry

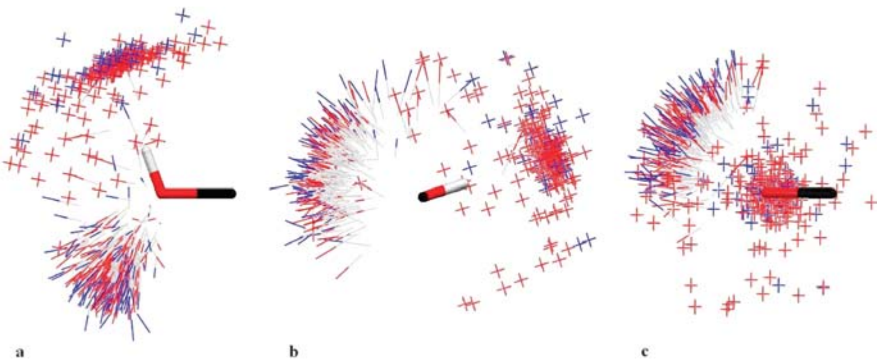

Fig. 5 The IsoStar scatter plots of environment 3: (a) the view from the side, (b) viewed along the C–O bond and (c) viewed along the O–H bond.

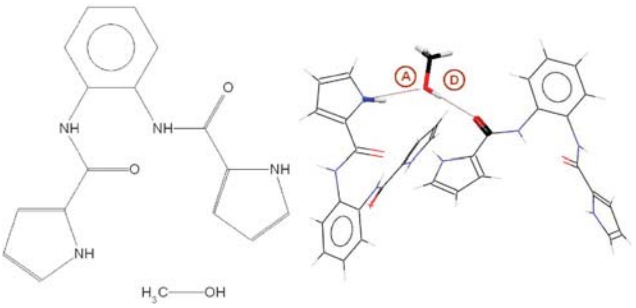

Fig. 8 An example of environment 3, 1,2-bis((pyrrol-2-ylcarbonylamino)benzene–methanol solvate,[12] where methanol acts as A an Acceptor and D a Donor.

present in the methanol group is used when appropriate to cluster the centroids, and the resulting positions of the contact atoms are plotted.)

An example of environment 3 is 1,2-bis((pyrrol-2-ylcarbonylamino)benzene–methanol solvate; $C_{16}H_{14}N_4O_2{\cdot}CH_4O$ (IBOYAA)[12] shown in Fig. 8. The hydrogen–oxygen distance is 1.791 Å and angle 167.640° for methanol acting as a donor and the hydrogen–nitrogen distance 1.852 Å and angle 156.450°, when methanol is an acceptor.

Environment 5

Environment 5 is the third most common environment revealed in the searches. In this environment methanol acts as a donor and at the same time it accepts two protons, each from a different donor atom. In the Fig. 9(a) and (b), the IsoStar plots of environment 5 are presented and demonstrate, in contrast to environment 3, that both donor and acceptor sites are accessed symmetrically.

Fig. 10 illustrates that when methanol acts as a donor in environment 5 the H-bond distances vary from 1.68 to 2.72 Å. The most highly populated region has distances and angles between 1.68 and 1.94 Å and 150 to 180°.

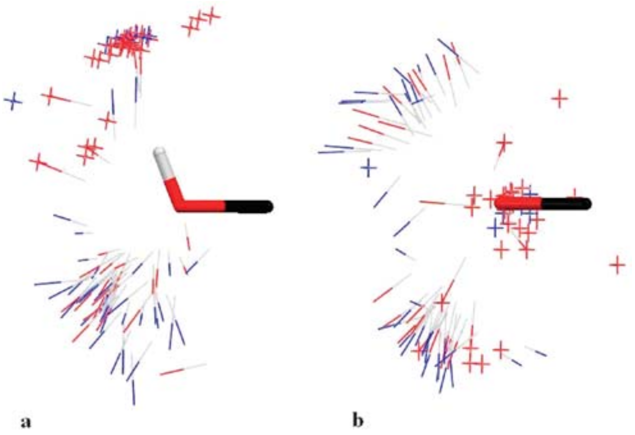

Fig. 9 The IsoStar scatter plots of environment 5: (a) viewed from the side and (b) viewed along the O–H bond.

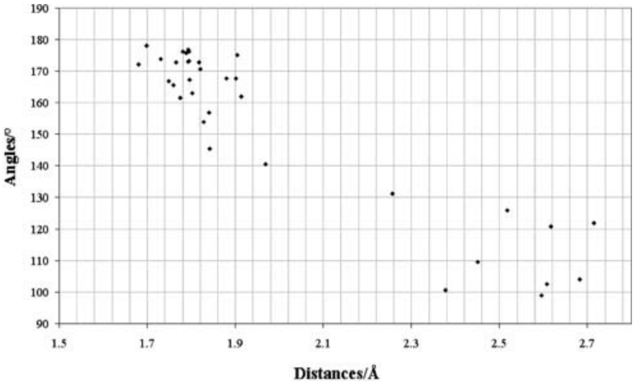

Fig. 10 O–H· · ·QA distance *vs.* angle for environment 5.

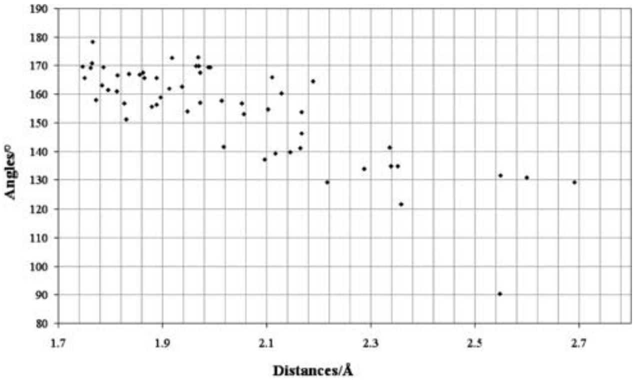

Fig. 11 O· · ·H–QA distance *vs.* angle for environment 5.

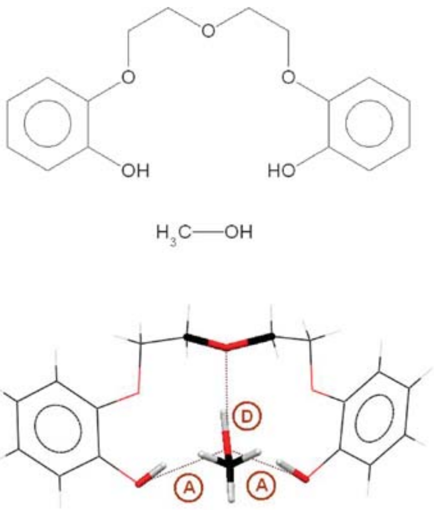

Fig. 12 Environment 5 for YOKCOQ, bis(2-(2-hydroxyphenoxy)ethyl) ether–methanol solvate,[13] where methanol acts as A an acceptor and D a donor.

In environment 5 where methanol acts as a double acceptor, the data shown in the Fig. 11 refer to the entire dataset, with no attempt to separate them according to the stereochemistry of the acceptor environment. The hydrogen bond distances range from 1.75 to 2.69 Å. The most populated region lies between 1.75 to 2.2 Å and 150 to 175°.

A representative structure of environment 5 is bis(2-(2-hydroxyphenoxy)ethyl) ether–methanol solvate, $C_{16}H_{18}O_5{\cdot}CH_4O$ (YAKCOQ[13]) shown in Fig. 12. The hydrogen–oxygen distance is 2.450 Å and angle 109.674° for methanol acting as a donor and

1.784, 1.826 Å and angles of 163.086, 156.716°, respectively when methanol is an acceptor.

Discussion

For each of the above environments the choice of the van der Waals radii search criterion gives H-bond distances up to 2.74 Å. This upper limit may be considered somewhat long for a hydrogen bond (–H···AQ distance) which is often assumed to have a value closer to 2.0 Å.[14] An examination of the distance/angle data given in Fig. 3, 6, 7, 10 and 11 suggests that in general[14] there is a continuum of dimensions, only Fig. 7 and 10 show evidence of two populations. Here a distance of *ca.* 2.1 Å might be considered a boundary with distances greater than this representing 'outliers' for which, the long distance is often associated with an angle lower than 150°. Individual examination of these outlier structures indicated that the long distances occurred in structures having two or three methanol molecules in the asymmetric unit or in which there was a possibility of simultaneous choice of two distances, both meeting the van der Waals criterion.

Table 2 gives the mean distances and angles in each environment for the entire dataset.

From these median data it is clear that when methanol is a donor the H-bond distances and angles become shorter and more nearly linear on inclusion of acceptor groups in environments 3 and 5. The related acceptor hydrogen bond distances and angles in these two environments increase and decrease, respectively with the number of acceptors. This is consistent with the enhanced steric effect as the environment changes from 3 to 5.

Using the final subset of 305 methanolate structures identified in Conquest, 21 molecules were found for which at least one unsolvated structure was also reported in the CSD (in some cases the unsolvated structure was polymorphic). The appropriate environment was identified for the solvated form (Table 3) and it is evident that the pairs identified had methanol bound only in environments 1, 3 and 5, reflecting the common occurrence of these environments in the total data set. Some of the unsolvated structures did not have 3D coordinates available (CORTMS, HADVOY and RUXLIF), while KOYNOB is highly disordered and NUMVEW01 is a methanolate of a hydrate. These factors made subsequent analysis impossible and these structures are not included in Table 3. The crystal packing similarity was calculated for the remaining pairs of solvated and unsolvated structures using Mercury 2.0 which compares a cluster of 15 molecules from the reference unsolvated structure with the entire solvated structure. It is clear from the remaining 20 unsolvated/solvated couples, that in general and unsurprisingly, methanol incorporation significantly changes the packing, leaving few structural similarities. Only two molecules, $C_{18}H_{26}NO_6$, &Qj; (Jacobine) and $C_{38}H_{69}NO_{13}$, (Clarithromycin), show significant packing similarities between the unsolvated and solvated pairs. In the former case, the positions of 9 out of 15 molecules overlay, resulting from an –N···H–O··· hydrogen bonded chain of host molecules which is a common feature of both structures. In the latter, 15 molecules from both structures show a good match due to retention of a common chain of –O–H···O··· bonded host molecules and the existence of voids into which the methanol molecule fits.

Table 2 Median hydrogen bond lengths and angles for environments 1, 3 and 5

	Median bond lengths/Å		Median bond angles/°	
Environment	QA···H	QA–H···O (MeOH)	QA···H	QA–H···O (MeOH)
1	1.92	—	159.29	—
3	1.84	1.77	163.16	167.53
5	1.82	1.97	165.62	157.82

Finally, the donor–acceptor ratios (D/A) for the 305 solvated structures are shown in Fig. 13. These mirror the earlier result found with hydrates,[10] in that the host molecules share a common feature of exhibiting more acceptor than donor functionality. However, there appears to be no direct relationship between values of D/A and the tendency to form a methanolate, since decreasing D/A is not associated with an increase in the number of methanolates, rather the solvates appear to be randomly distributed. This point is reinforced by the recent detailed statistical analysis of van de Streek and Motherwell[15] which showed that, at least for hydrates, the D/A imbalance of hosts (0.63) was less pronounced than in a random sample of unsolvated structures (0.28) hence invalidating previous suggestions that hydrate formation was associated with low D/A values.[10] The existence of the solvated/unsolvated pairs allows further detailed exploration of this feature.

Thus, Table 3 provides for each pair the numbers and utilisation of host donors and acceptors in the unsolvated form compared with the same data for the solvated structures. In this way it is possible to explore the extent to which methanol is utilised to satisfy previously unused hydrogen bonding capability in the host. The key parameter here is $X/(Y + Z)$ which is the ratio of the number of satisfied donors and acceptors for the host in the unsolvated structure (X) to the total number of satisfied donors and acceptors for the host in the solvated structure. The latter has been partitioned into those satisfied by the host (Z) and those satisfied by methanol (Y). For each X, Y and Z value the constituent number of donors and acceptors are also given in parenthesis. If this ratio is equal to 1 then the host experiences no change in its hydrogen bond utilisation while for values less than 1, the inclusion of methanol allows more hydrogen bonding to the host, and for values greater than 1, less hydrogen bonding. For the three pairs which have two molecules in the asymmetric each molecule has been treated separately. It is now evident that within these pairs 20% experience a reduction in hydrogen bond utilisation on solvation while 25% show no hydrogen bonding advantage. The highest fraction (55%) is for those having an increase in their hydrogen bonding uptake and we note that in those structures (7 in this dataset) where methanol has a choice between oxygen and nitrogen as acceptors, it always chooses nitrogen. For the two molecules for which the hydrogen bonding environment decreases it is important to note that in one case this is only true for one of the molecules in the asymmetric unit (NODTUV) while in the other case it is true only for one of the unsolvated polymorphs

Table 3 Donor/acceptor analysis for solvated/unsolvated pairs ((1) and (2) for YUTCEV, NODTIJ and LUDYAK refer to the different molecules in the asymmetric unit)

Unsolvated structures					Solvated structures				
Ref. code	No. D	No. A	D/A ratio	No. D or A satisfied by host molecules (*X*)	Ref. code	Enviro-nment	D or A satisfied by MeOH (*Y*)	D or A satisfied by host molecules (*Z*)	*X*/(*Y* + *Z*)
ADAJUK/ ADAJUK01	1	4	0.25	2 (1A, 1D)	ADAKOF	1	1 (1A)	0	2
CHBZOA20/ CHBZOB20	0	8	0	0	CHBZOC01	1	1 (1A)	0	0
JACOBN	1	7	0.143	2 (1A, 1D)	CIMLIT	1	1 (1A)	0	0.5
HEHLOV10	0	6	0	0	IWUFOV	1	1 (1A)	0	0
AMEPOX	2	5	0.4	2 (1A, 1D)	AMEPUD	3	2 (1A, 1D)	2 (1A, 1D)	0.5
ESTTRD	2	2	1	4 (2A, 2D)	BEQJIQ	3	2 (1A, 1D)	0	2
SLFNMD01	3	6	0.5	4 (2A, 2D)	COVXIU	3	2 (1A, 1D)	0	2
SLFNMD10	3	6	0.5	2 (1A, 1D)	COVXIU	3	2 (1A, 1D)	0	1
DALJUW	2	6	0.333	4 (2A, 2D)	DALKAD	3	2 (1A, 1D)	2 (1A, 1D)	1
DAYHIU	2	9	0.222	2 (1A, 1D)	DAYHOA	3	2 (1A, 1D)	1 (INTER)	0.667
YUTCEV (1)	3	5	0.6	6 (3A, 3D)	FIVMIG10	3	2 (1A, 1D)	4 (2A, 2D)	1
YUTCEV (2)	3	5	0.6	4 (2A, 2D)	FIVMIG10	3	2 (1A, 1D)	4 (2A, 2D)	0.667
BTCOAC	3	6	0.5	6 (3A, 3D)	IYUQIC	3	2 (1A, 1D)	4 (2A, 2D)	1
NODTIJ (1)	3	5	0.6	5 (2A, 3D)	NODTUV	3	2 (1A, 1D)	2 (1A, 1D)	1.25
NODTIJ (2)	3	5	0.6	3 (2A, 1D)	NODTUV	3	2 (1A, 1D)	2 (1A, 1D)	0.75
NAVSUY	3	13	0.231	2 (1A, 1D)	WANNUU	3	2 (1A, 1D)	2 (1A, 1D)	0.5
BEFZES	1	4	0.25	2 (1A, 1D)	WARFIN	3	2 (1A, 1D)	0	1
LUDYEO (1)	4	8	0.5	5 (3A, 2D)	LUDYAK (1)	5	0	7 (4A, 3D)	0.714
LUDYEO (2)	4	8	0.5	3 (2A, 1D)	LUDYAK (2)	5	1 (1A)	4 (2A, 2D)	0.6
XODPUB	2	2	1	0	XODPOV	5	2 (1A, 1D)	0	0

of the host (SLFNMD01). Thus not only is there no general correlation between the D/A ratio and the numbers of methanolates but it is clear from the pairs that as far as the host molecules are concerned methanolate formation does not necessarily lead to an improved utilisation of H-bonding sites of the host molecule.

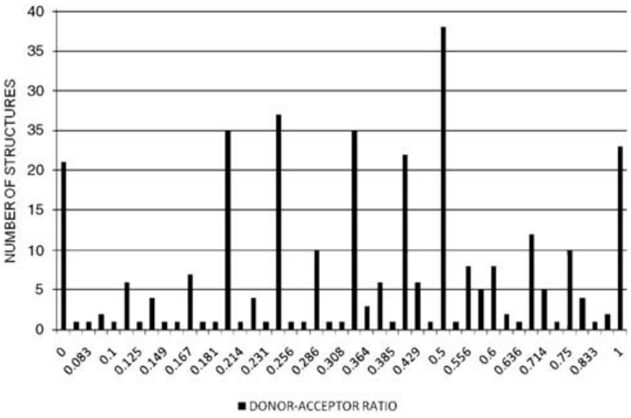

Fig. 13 Methanolate occurrence in relation to host donor/acceptor ratios.

Conclusions

The searches made in ConQuest resulted in 305 methanolate structures which were analysed in terms of their methanol hydrogen bonding environment (defined in Fig. 1), the existence of solvated and unsolvated pairs and the similarity of host packing in such pairs. The IsoStar and scatter plots summarise the totality of the geometric data and indicate that with increasing acceptor usage, when methanol is involved not only as an H-bond donor, but also in accepting two protons from other molecules, steric restrictions lead to longer and less linear H-bonds.

The most uncommon environments are 2 and 4 with less than 3.5% of the total number of structures. In these groups methanol is acting only as an acceptor. The most significant environments are 3, 1 and 5 with occupancies 70, 17 and 9% of all structures, respectively. The most common environment was that in which the methanol hydroxyl group acts as both a donor and acceptor (environment 3). Interestingly this is the motif it adopts in the orthorhombic form of solid methanol[16] with an O–H···O distance of 1.75 Å. Existing computational[17] and experimental data[18,19] on the coordination of methanol in its pure liquid state indicate that a similar motif exists here also. Alcohol molecules are held in short H-bonded chains in which, most commonly, each methanol molecule forms two hydrogen bonds with its neighbours. We may infer from this that within these crystal structures methanol has a tendency to replicate its liquid phase environment.

Unsurprisingly, the existence of solvated/unsolvated structural pairs has made it clear that in the majority of cases the incorporation of methanol significantly impacts on the packing of the host molecules. While all the methanolates considered here involve host molecules having an excess of acceptors over donors this factor is evidently not correlated with solvate formation. Within the solvate/unsolvated pairs there is an approximate balance between the number of structures in which methanol enhances the hydrogen bond environment of the host and those in which it either does not change or is reduced.

Acknowledgements

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