# Revealing the Roles of Solvation in D-mannitol's Polymorphic Nucleation

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## Contents of Supporting Information

**Table S1**

TABLE S1. Optimized and experimental lattice parameters of β-D-man by different force fields.

| Lattice parameters | *a*/Å | *b*/Å | *c*/Å |
|---|---|---|---|
| Experimental | 5.5381 | 8.5800 | 16.7950 |
| COMPASS | 5.4952 | 8.3750 | 16.7400 |
| Dreiding | 5.8702 | 8.8912 | 17.0742 |
| Universal | 6.3907 | 9.3883 | 16.9352 |
| cvff | 5.4265 | 8.5740 | 16.8486 |
| pcff | 5.7457 | 8.5957 | 16.9435 |

**Table S2**

Table S2. Mole fraction solubility ($x^{exp}$) of D-man in the water + methanol solvent mixtures at temperature *T* and pressure P = 0.1 MPa. [a]

| $x^0$ | $10^3 x_A{}^{exp}$ | $10^3 x_A{}^{cal}$ |
|---|---|---|
| | *T* = 288.15 K | |
| 0 | 0.119 | 0.118 |
| 0.1 | 0.172 | 0.167 |
| 0.2 | 0.282 | 0.291 |
| 0.5 | 1.305 | 1.322 |
| 0.8 | 5.736 | 5.738 |
| 0.9 | 8.888 | 8.924 |
| 1.0 | 15.051 | 15.084 |
| | *T* = 293.15 K | |
| 0 | 0.163 | 0.166 |
| 0.1 | 0.230 | 0.230 |
| 0.2 | 0.374 | 0.375 |
| 0.5 | 1.669 | 1.683 |
| 0.8 | 7.047 | 7.007 |
| 0.9 | 10.754 | 10.712 |
| 1.0 | 17.506 | 17.454 |

| | | |
|---|---|---|
| | $T$ = 298.15 K | |
| 0 | 0.225 | 0.221 |
| 0.1 | 0.298 | 0.309 |
| 0.2 | 0.501 | 0.484 |
| 0.5 | 2.197 | 2.132 |
| 0.8 | 8.525 | 8.522 |
| 0.9 | 12.798 | 12.819 |
| 1.0 | 20.153 | 20.137 |
| | $T$ = 303.15 K | |
| 0 | 0.286 | 0.284 |
| 0.1 | 0.402 | 0.404 |
| 0.2 | 0.630 | 0.627 |
| 0.5 | 2.671 | 2.689 |
| 0.8 | 10.212 | 10.323 |
| 0.9 | 15.320 | 15.295 |
| 1.0 | 23.113 | 23.166 |
| | $T$ = 308.15 K | |
| 0 | 0.344 | 0.351 |
| 0.1 | 0.530 | 0.518 |
| 0.2 | 0.807 | 0.814 |
| 0.5 | 3.354 | 3.376 |
| 0.8 | 12.499 | 12.458 |
| 0.9 | 18.242 | 18.195 |
| 1.0 | 26.589 | 26.578 |
| | $T$ = 313.15 K | |
| 0 | 0.422 | 0.419 |
| 0.1 | 0.645 | 0.650 |
| 0.2 | 1.052 | 1.059 |
| 0.5 | 4.223 | 4.221 |
| 0.8 | 15.044 | 14.980 |
| 0.9 | 21.486 | 21.586 |
| 1.0 | 30.424 | 30.413 |
| | $T$ = 318.15 K | |
| 0 | 0.483 | 0.483 |
| 0.1 | 0.797 | 0.798 |
| 0.2 | 1.384 | 1.380 |
| 0.5 | 5.260 | 5.255 |
| 0.8 | 17.914 | 17.949 |
| 0.9 | 25.579 | 25.538 |
| 1.0 | 34.708 | 34.711 |

[a]$x^0$is the initial mole fraction of water in binary solvent mixture; $x_A^{exp}$ denotes the experimentally determined solubility; $x_A^{cal}$ denotes the calculated solubility by the modified Apelbat model.

**Table S3**

Table S3. Predicted Mole fraction solubility ($x$) of D-man in the methanol + water solvent mixtures at temperature $T$ = 268.15 and 278.15 K and pressure P = 0.1 MPa. [a]

| $x^0$ | $10^3 x_A^{cal}$ | |
|---|---|---|
| | T = 268.15 K | $T$ = 278.15 K |
| 0 | 0.019 | 0.054 |
| 0.1 | 0.035 | 0.082 |
| 0.2 | 0.108 | 0.175 |
| 0.5 | 0.466 | 0.783 |
| 0.8 | 2.522 | 3.883 |
| 0.9 | 4.277 | 6.311 |
| 1.0 | 8.220 | 11.261 |

[a]$x^0$is the initial mole fraction of water in binary solvent mixture; $x_A^{cal}$ denotes the calculated solubility by the modified Apelbat models.

**Figure S1**

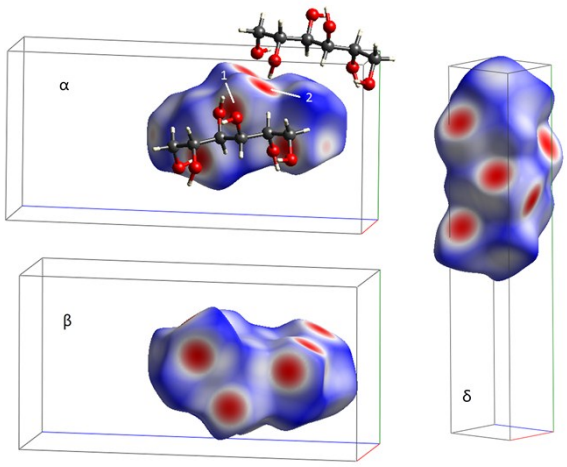


**Figure S1.** Hirshfeld surface of three anhydrous polymorphs mapped with $d_{norm}$. The HB donor is labelled as "1" and HB acceptor is labelled as "2".

**Figure S2**

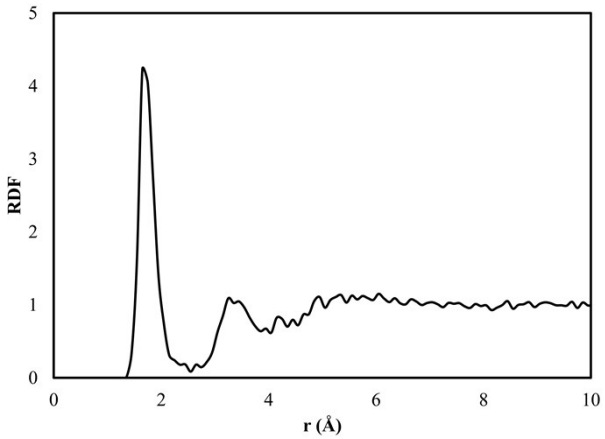


**Figure S2.** RDF between solvent molecules in aqueous solution.

**Figure S3**

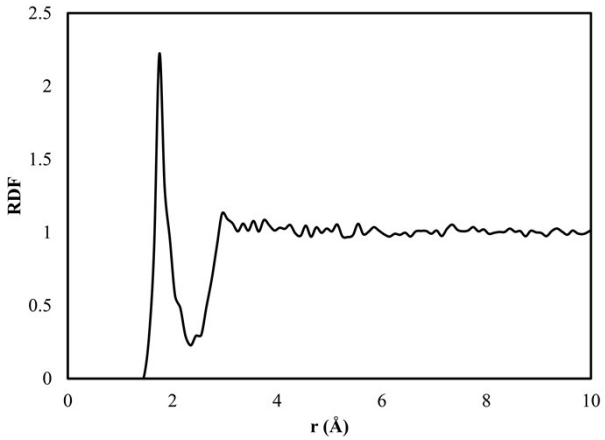


**Figure S3.** RDF between solvent molecules in methanol solution.

**Figure S4**

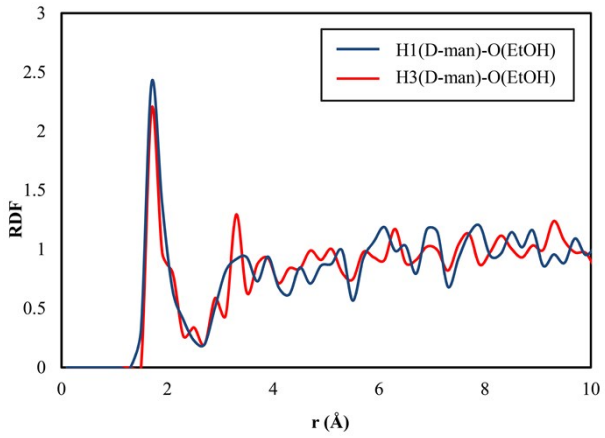


**Figure S4.** RDFs between hydrogen atoms of D-man molecules and oxygen atoms of ethanol molecules in ethanol solution.

**Figure S5**

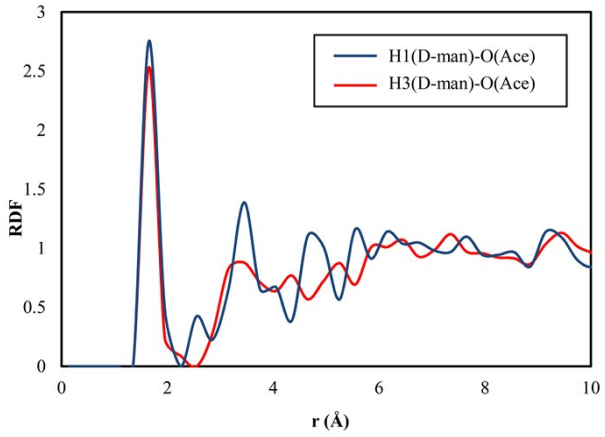


**Figure S5.** RDFs between hydrogen atoms of D-man molecules and oxygen atoms of acetone molecules in acetone solution.

**Figure S6**

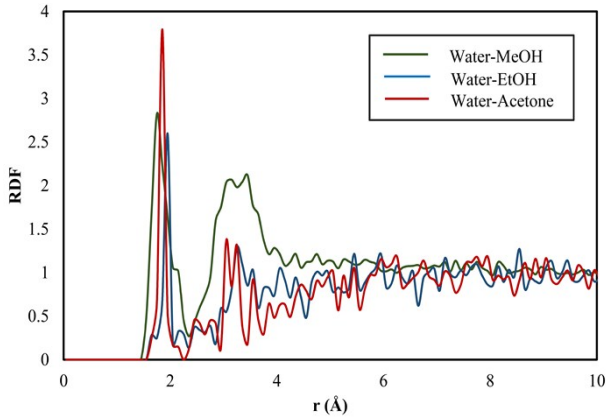


**Figure S6.** RDFs between hydrogen and oxygen atoms of water molecules in water-methanol/ethanol/acetone solutions.

**Figure S7**

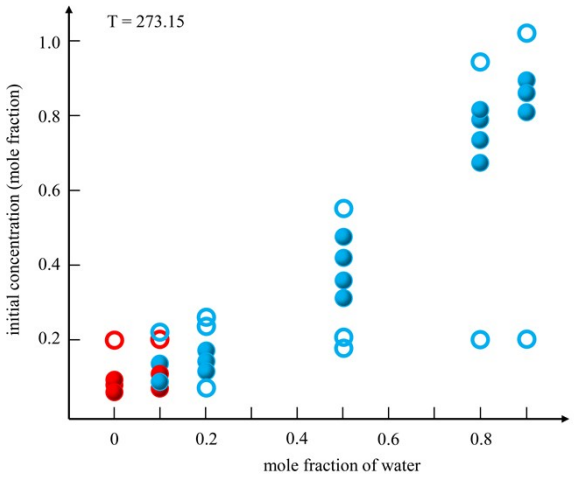


**Figure S7.** Crystallization outcomes in water-methanol solutions with different solvent ratios. The red and blue colors represent the α and δ form respectively. Balls are experimental results transformed from Figure 4, circles represent the crystallization result s from the extra experiments

with extended initial concentrations. Blue and red both appear at the mole ratio of water equals to 0.1, representing a commitment polymorph behavior.