New insights into an old molecule: Interaction energies of Theophylline crystal forms

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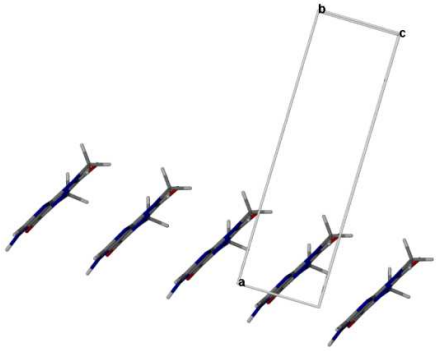
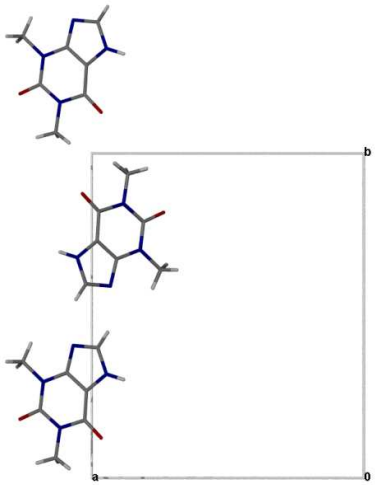
Electronic supporting information

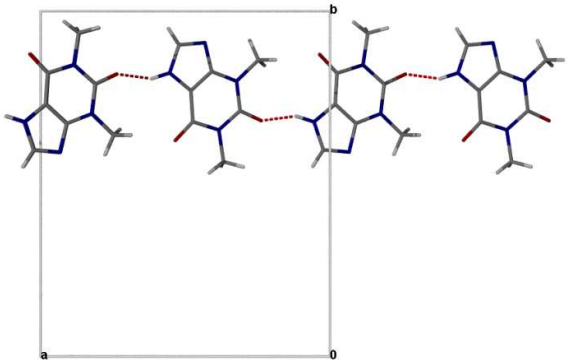
Packing motifs of the theophylline polymorphs



a) Form I motif 1

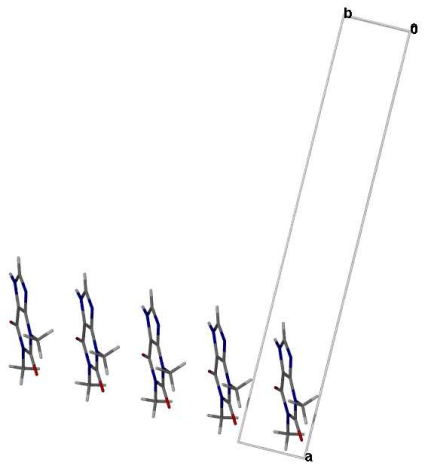


b) Form I motif 2

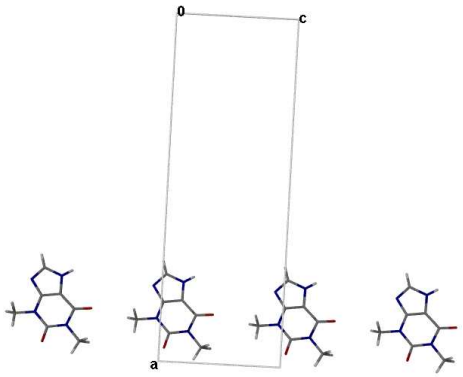


c) Form I motif 3

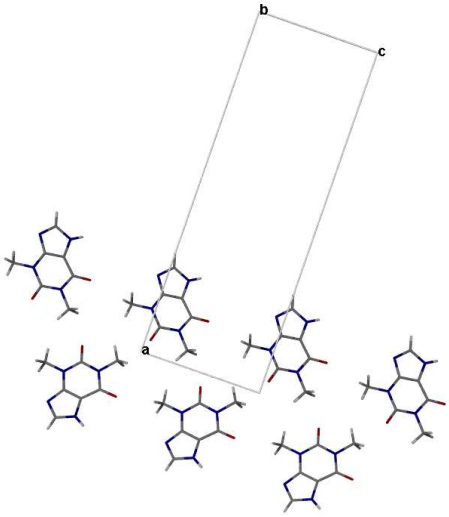
S 1 Packing motifs of THEO form I



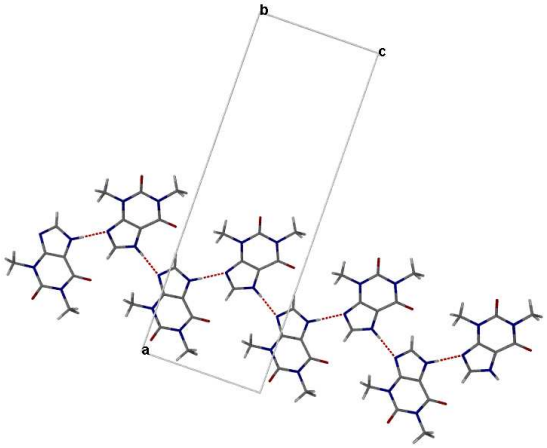
a) Form II motif 1



b) Form II motif 2

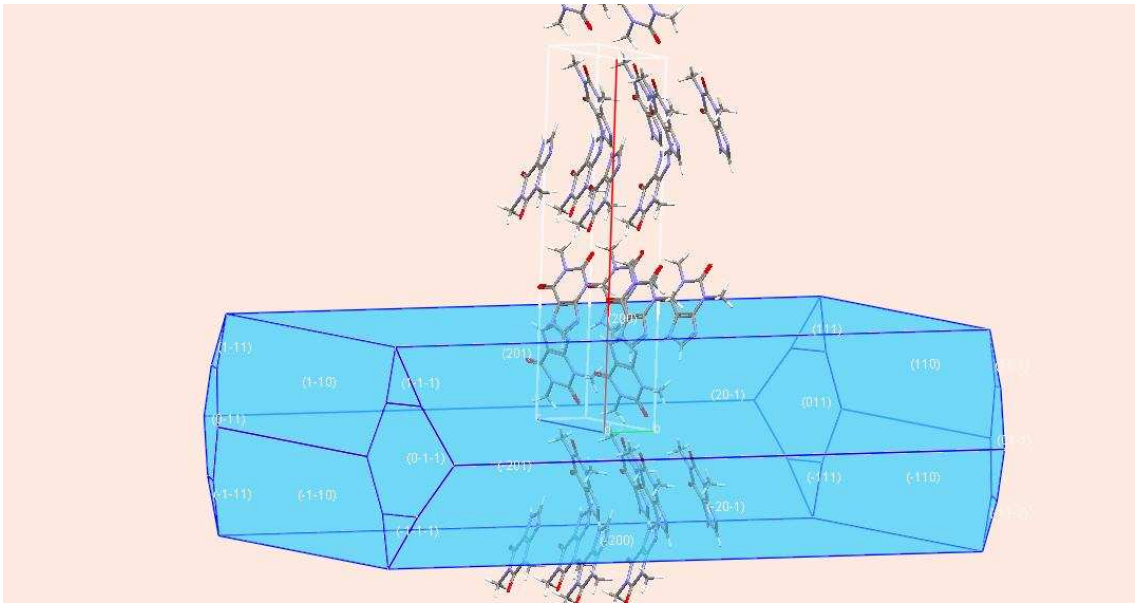


c) Form II motif 3

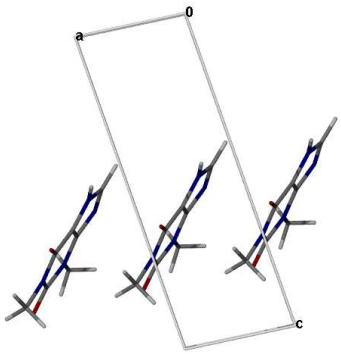


d) Form II motif 4

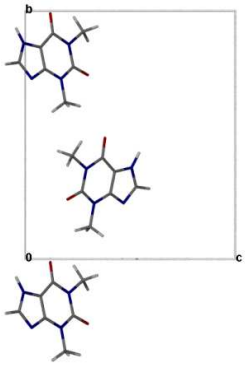
S 2 Packing motifs of THEO form II.



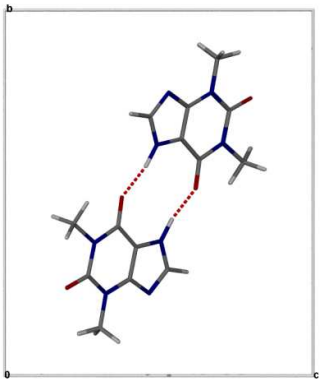
S 3 Orientation of the molecular packing in the crystal. Morphology calculated as BFDH model.



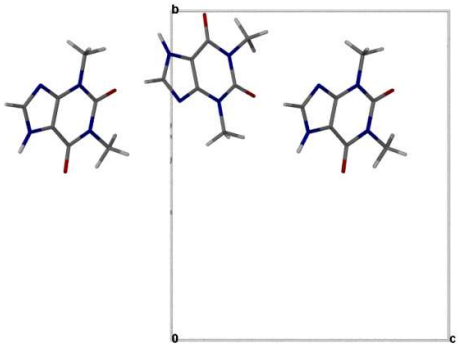
a) Monohydrate motif 1



b) Monohydrate motif 2



c) Monohydrate motif 3



d) Monohydrate motif 4

S 4 Packing motifs of THEO monohydrate.

PACHA energy calculations

Form I

SE_{mol} = -272.6 kJ mol^{-1}

Stacking in (0 0 1) (motif 1)

SE_{stack} = -268.5 kJ mol^{-1} (Z = 1)

$\Delta SE = SE_{mol} - SE_{stack}$ =272.6 – 268.5 = +4.1 kJ mol^{-1}

Stacking along *n* glide plane (motif 2)

$SE_{motif\ 2}$ = -580.0 kJ mol^{-1} (Z = 2)

$\Delta SE = (2*SE_{motif\ 1} – SE_{motif\ 2})/2$ = (2*268.5 – 580.0)/2 = -21.5 kJ mol^{-1}

Stacking in hydrogen bonded chains (motif 3)

$SE_{motif\ 3}$ = -614.0 kJ mol^{-1} (Z = 2)

$\Delta SE = (2*SE_{motif\ 1} – SE_{motif\ 3})/2$ = -38.5 kJ mol^{-1}

Correction for stacking interactions (stacking like motif 3 but without hydrogen bonds, motif 4)

$SE_{motif\ 4}$ = -559.8 kJ mol^{-1} (Z = 2)

$\Delta SE = (2*SE_{motif\ 1} – SE_{motif\ 4})$ = -14.6 kJ $mopl^{-1}$

Hydrogen bond = -38.5 + 14.6 = -23.9 kJ mol^{-1}

Form II

SE_{mol} = -274.1 kJ mol^{-1}

Stacking in (0 1 0) (motif 1)

$SE_{motif\ 1}$ = -266.3 kJ mol^{-1} (Z = 1)

$\Delta SE = SE_{mol} – SE_{motif\ 1}$ = 274.1 – 266.3 = +7.8 kJ mol^{-1}

Stacking along (0 1 0) and (0 0 1) (motif 2)

$SE_{motif\ 3}$ = -277.1 kJ mol^{-1} (Z = 1)

$\Delta SE = SE_{motif\ 1} – SE_{motif\ 3}$ = -10.8 kJ mol^{-1}

Stacking along *a* glide plane (motif 3)

$SE_{motif\ 2}$ = -551.8 kJ mol^{-1} (Z = 2)

$\Delta SE = (2* SE_{motif\ 1} – SE_{motif\ 2})/2 = -9.6$ kJ mol^{-1}

Hydrogen bonded stacks (motif 4)

$SE_{motif\ 4} = -581.5$ kJ mol^{-1} (Z = 2)

$\Delta SE = (2*SE_{motif\ 1} – SE_{motif\ 4})/2 = -24.6$ kJ mol^{-1}

Correction for stacking

Hydrogen bond = -24.6 + 10.8 = -13.7 kJ mol^{-1}

Monohydrate 120K

$SE_{THEO} = -270.9$ kJ mol^{-1}

$SE_{H2O} = -210.0$ kJ mol^{-1} (H2W)

$SE_{H2O} = -240.5$ kJ mol^{-1} (H3W)

Water interaction

$SE_{water} = -1035.0$ kJ mol^{-1} (Z = 4)

$\Delta SE = (2*210.0 + 2*240.5 – 1035.0)/4 = -33.5$ kJ mol^{-1}

Theophylline interactions

Stacking of THEO along (1 0 0) (motif 1)

$SE_{motif\ 1} = -272.3$ kJ mol^{-1} (Z = 1)

$\Delta SE = SE_{THEO} – SE_{motif\ 1} = -1.4$ kJ mol^{-1}

Stacking of motif 1 along (0 1 0) (motif 2)

$SE_{motif\ 2} = -546.5$ kJ mol^{-1} (Z = 2)

$\Delta SE = (2*SE_{motif\ 1} – SE_{morif\ 2})/2 = -1$ kJ mol^{-1}

Stacking of hydrogen bonded dimers along (0 1 0) (motif 3)

$SE_{motif\ 3} = -576.9$ kJ mol^{-1} (Z = 2)

$\Delta SE = ((2*SE_{motif\ 1} – SE_{motif\ 3})/2) – \Delta SE_{motif\ 2} = -15.2$ kJ mol^{-1}

Stacking of motif 1 along (0 0 1) (motif 4)

$SE_{motif\ 4}$ = -552.2 kJ mol^{-1}

$\Delta SE = (SE_{motif\ 1} - SE_{motif\ 4})/2$ = -2.9 kJ mol^{-1}

Water-THEO interactions

Stacking of THEO/H2O (H2W) along (0 1 0) (THEO motif 2 with water)

$SE_{THEO\ H2W}$ = -1007.1 kJ mol^{-1} (Z = 2)

$\Delta SE = (SE_{motif\ 2} + 2*SE_{H2O} - SE_{THEO\ H2W})/2$ = -20.3 kJ mol^{-1}

Stacking of THEO/H2O (H3W) along (0 1 0) (THEO motif 2 with water)

$SE_{THEO\ H3W}$ = -1073.8 kJ mol^{-1} (Z = 2)

$\Delta SE = (SE_{motif\ 2} + 2*SE_{H2O} - SE_{THEO\ H3W})/2$ = -23.2 kJ mol^{-1}

Monohydrate 20K

$SE_{network}$ = -2420.7 kJ mol^{-1} (Z = 4)

SE_{THEO} = -295.2 kJ mol^{-1}

SE_{H2O} = -209.5 kJ mol^{-1} (H2W)

SE_{H2O} = -216.8 kJ mol^{-1} (H3W)

$\Delta SE = (4*295.2 + 2*209.5 + 2*216.8 - 2420.7)/4$ = -96.8 kJ mol^{-1}

Water interaction

SE_{water} = -1006.9 kJ mol^{-1} (Z = 4)

$\Delta SE = (2*209.5 + 2*216.8 - 1006.9)/4$ = -38.6 kJ mol^{-1}

Theophylline interactions

Stacking of THEO along (1 0 0) (motif 1)

$SE_{motif\ 1}$ = -297.1 kJ mol^{-1} (Z = 1)

$\Delta SE = SE_{THEO} - SE_{motif\ 1}$ = -1.9 kJ mol^{-1}

Stacking of motif 1 along (0 1 0) (motif 2)

$SE_{motif\ 2}$ = -595.7 kJ mol^{-1} (Z = 2)

$\Delta SE = (2*SE_{motif\ 1} - SE_{morif\ 2})/2$ = -0.8 kJ mol^{-1}

Stacking of hydrogen bonded dimers along (0 1 0) (motif 3)

$SE_{motif\ 3}$ = -650.0 kJ mol^{-1} (Z = 2)

$\Delta SE = ((2*SE_{motif\ 1} - SE_{motif\ 3})/2) - \Delta SE_{motif\ 2}$ = -27.1 kJ mol^{-1}

Stacking of motif 1 along (0 0 1) (motif 4)

$SE_{motif\ 4}$ = -602.6 kJ mol^{-1}

$\Delta SE = (SE_{motif\ 1} - SE_{motif\ 4})/2$ = -4.2 kJ mol^{-1}

Water-THEO interactions

Stacking of THEO/H2O (H2W) along (0 1 0) (THEO motif 2 with water)

$SE_{THEO\ H2W}$ = -1059.9 kJ mol^{-1} (Z = 2)

$\Delta SE = (SE_{motif\ 2} + 2*SE_{H2O} - SE_{THEO\ H2W})/2$ = -22.6 kJ mol^{-1}

Stacking of THEO/H2O (H3W) along (0 1 0) (THEO motif 2 with water)

$SE_{THEO\ H3W}$ = -1074.0 kJ mol^{-1} (Z = 2)

$\Delta SE = (SE_{motif\ 2} + 2*SE_{H2O} - SE_{THEO\ H3W})/2$ = -22.4 kJ mol^{-1}