**Molecule-in-a-box calculations**

**Methods**

The energy of a single molecule in the PBE-TS optimized crystal structure was calculated as a molecule in a periodic orthorhombic box with periodic PBE-TS using the same cutoff energies and one single k-point in CASTEP. The molecules were kept at their PBE-TS optimized conformations without any optimization. The orthorhombic box was chosen to ensure that a minimum distance (R0) between adjacent copies of the molecules was maintained along every direction. R0 were converged to make sure that any further increase by 2 Å of R0 does not change the absolute energy more than 0.1 kJ/mol, shown in the following table. For polymorphs with Z’ > 1, molecules in the asymmetric unit were set up as Z’ separate calculations, one for each molecule.

|  |  |  |  |
| --- | --- | --- | --- |
|  | 5-fluorouracil | 7-fluoroisatin | FFA |
| R0\* | 20.0 | 20.0 | 17.0 |

\* minimum distance between copies of the molecules in periodic DFT-D calculations. Note the actual unit cells used in the calculations are of lengthes of R0 + molecular dimensions in that direction.

**Periodic PBE-TS intermolecular energies:**

In the following tables, the intermolecular energy were calculated as the difference between the Ecrys/Z and Emol-in-box . When there are Z’ molecules in the asymmetric unit cell, the averaged Emol-in-box is used. Ecrys/Z is the PBE-TS energy of the optimized crystal structure, normalized to one molecule.

5-fluorouracil:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Space grp, Z’ | Emol-in-box /eV | Ecrys/Z /eV | Einter / kJ mol−1 |
| **Experimental forms** | | | | |
| **form I** | P-1, Z’=4 | −2771.890522 | −2773.513996 | −157.41 |
|  |  | −2771.881763 |  |  |
|  |  | −2771.871408 |  |  |
|  |  | −2771.886330 |  |  |
| **form II** | P21/c, Z’=1 | −2771.874382 | −2773.496977 | −156.56 |
| **CSP hypothetical forms Z’=1** | | | | |
| **am64** | P21/c | −2771.910741 | −2773.403427 | −144.02 |
| **fc19** | P21/c | −2771.880125 | −2773.438187 | −150.33 |
| **ak24** | P21/c | −2771.878758 | −2773.437909 | −150.44 |

7-fluoroisatin:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Space grp, Z’ | Emol-in-box /eV | Ecrys/Z /eV | Einter / kJ mol−1 |
| **Experimental forms** | | | | |
| **form I** | P21/c, Z’=1 | −3141.030541 | −3142.475440 | −139.41 |
| **form II** | P-1, Z’=2 | −3141.043217 | −3142.463638 | −136.95 |
|  |  | −3141.045193 |  |  |
| **form III** | P21/c, Z’=2 | −3141.033173 | −3142.451295 | −136.87 |
|  |  | −3141.032333 |  |  |
| **CSP hypothetical forms Z’=1** | | | | |
| **am33** | P21/c | −3141.034169 | −3142.452680 | −136.87 |
| **fc13** | P21/c | −3141.034499 | −3142.496843 | −141.09 |

Flufenamic acid:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Space grp, Z’ | Emol-in-box  (PBE-TS) /eV | Ecrys/Z /eV | Einter / kJ mol−1 |
| **Experimental forms** | | | | |
| form I | P21/c, Z’=1 | −5509.227791 | −5511.14969 | −185.43 |
| form II | P21/c, Z’=1 | −5509.226166 | −5511.18459 | −188.96 |
| form III | C2/c, Z’=1 | −5509.201279 | −5511.18930 | −191.81 |
| form IV | P-1, Z’=3 | −5509.228331 | −5511.12184 | −182.70 |
|  |  | −5509.235157 |  |  |
|  |  | −5509.237035 |  |  |
| form VII | P21/c, Z’=2 | −5509.234681 | −5511.14684 | −184.49 |
|  |  | −5509.243402 |  |  |
| **CSP hypothetical forms Z’=1** | | | | |
| 882 | P-1 | −5509.214869 | −5511.06913 | −178.91 |
| 1129 | P-1 | −5509.213669 | −5511.07851 | −179.93 |
| 1248 | C2/c | −5509.242229 | −5511.03792 | −173.26 |
| 1956 | P-1 | −5509.191139 | −5511.07306 | −181.58 |
| 1173 | P21/c | −5509.225176 | −5511.06394 | −177.41 |
| FFA in TFA-I | P21/c | −5509.212496 | −5511.00996 | −173.43 |
| FFA in TFA-II | P21/c | −5509.220258 | −5511.07897 | −179.34 |
| FFA in MFA-III | P-1 | −5509.247072 | −5510.98070 | −167.27 |