

Why pregnenolone and progesterone, two structurally similar steroids, exhibit remarkably different cocrystallization with aromatic molecules

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Supplementary Information

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Overlay comparison between experimental and computed PRO-13 cocrystals

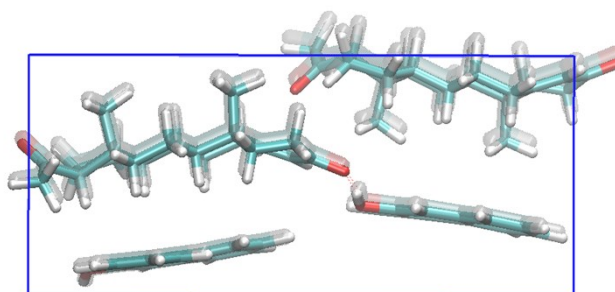


Figure 1. Overlaid image of the PRO-13 cocrystal structure obtained experimentally (transparent) and computationally at the BLYP+D3/TZV2P level (solid). Lattice parameters of experimental PRE-13 were used to make the overlaid image clear.

Contribution of many-body interactions into the lattice energy of cocrystals

Table 2 Comparison of the total interaction energy and the many-body energy term. All energies are per 1 mole of steroid molecules.

Cocrystals	ΔE_{MB} , kJ/mol	ΔE_{INT} , kJ/mol	Error %
PRO-13	9.282	-335.4	2.8
PRE-13	7.949	-309.5	2.6
PRO-14	7.538	-254.2	3.0
PRE-14	2.741	-230.9	1.2
PRO-15	7.311	-327.8	2.2

PRE-15	0.7731	-307.9	0.25
PRO-21	13.35	-210.7	6.3
PRE-21	9.726	-181.6	5.3

Definition of the distance of α - π contacts

α atoms are defined as the hydrogen atoms of the α face of a steroid molecule. π atoms of an α atom are those atoms of an aromatic molecule that lie within 5 Å of this α atom. The distance of α - π contacts in cocrystals is defined as the average over distances between pairs of all α atoms and their corresponding π atoms.

Categories of interacting molecular pairs

Steroid-aromatic pairs:

α - π (β - π) molecular pairs are those where the α -face (β -face) of a steroid molecule and the plane of an aromatic molecule are adjacent to each other. Such pairs can be unambiguously determined upon visual inspection of cocrystals.

Among all other pairs we identified hydrogen-bond pairs. A pair is called hydrogen-bond pair if there exists a hydrogen bond between the molecules. Hydrogen bond exists if the distance between an electronegative atom ($X = \text{C}, \text{O}, \text{N}$) and a hydrogen atom is less than 2.4 Å and the hydrogen bond angle ($\text{Y-H}\cdots\text{X}$) is less than 30 degrees.

All remaining molecular pairs are subdivided into neighbor pairs and distant pairs. If the distance between the nearest atoms of the two molecules is less than 6 Å then the pair is neighbor pair. Otherwise, it is classified as distant pair.

Steroid-steroid pairs:

All pairs are categorized into hydrogen-bond, neighbor, and distant pairs according to the criteria described above.

Aromatic-aromatic pairs:

Are not divided into categories.