PCCP

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c7cp06828j

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

Ziling Luo, Tomislav Friščić and Rustam Z. Khaliullin *

Selective binding of steroid molecules is of paramount importance for designing drugs that can target the biological pathways of only individual steroids. From this perspective, it is remarkable that progesterone (PRO) and pregnenolone (PRE), two structurally similar steroids, demonstrate a dramatically different propensity to interact with aromatic molecules. It has been recently reported that, in solid-state cocrystallization, PRO forms cocrystals with a wide variety of aromatic systems whereas PRE cocrystallizes only with a few. In this work, a simple yet effective computational procedure was developed to explain the fundamental origins of this surprising phenomenon. This procedure enables a direct comparison of the strength of intermolecular binding in the structurally similar cocrystals of PRO and PRE by generating experimentally inaccessible meta-stable cocrystals of PRE that closely resemble those observed for PRO. Direct comparative analysis shows that interactions between the α-face of the steroid and the π-electrons of aromatic molecules, the focus of previous studies, are not sufficiently different to explain the cocrystallization behavior of PRO and PRE. Instead, the observed difference is attributed to the different stabilities of the cocrystals relative to their pure components: organic and steroid crystals. It is calculated that the cocrystallization process is thermodynamically favorable in the case of PRO and unfavorable in the case of PRE. Furthermore, strong hydrogen bonds in the pure PRE crystal appear to be the major factor that makes the cocrystallization of PRE energetically unfavorable for a wide range of aromatic molecules. The fundamental analysis performed in this work has important practical implications for designing new steroid-containing crystals, selective biomolecular steroid receptors, and steroid-specific drugs. It suggests that a strategy for the selective binding of steroids should focus primarily on tuning the strength of hydrogen bonding.

Received 6th October 2017,
Accepted 15th November 2017

DOI: 10.1039/c7cp06828j

rsc.li/pccp

Introduction

Intermolecular interactions of steroid molecules determine their prominent roles in the biochemistry of living organisms.[1,2] Such interactions are key for their transport through the blood by carrier proteins, their function as components of cell membranes and as chemical messengers that regulate gene expression.[3] It is fascinating that despite a similar molecular structure of steroids their intermolecular interactions have been fine-tuned in the process of evolution to control their biomolecular functions (*e.g.* binding to protein receptors) with a high degree of selectivity. Studying the characteristic patterns in the intermolecular binding of steroids to small organic molecules and learning to adjust the energetics of the binding to the desired range can open new opportunities for designing drugs that selectively target the biological pathways of steroids.[4]

This work is motivated by a remarkable recent observation that PRE and PRO, two steroid hormones with similar molecular structures (Fig. 1), demonstrate dramatically different propensities to form cocrystals with aromatic molecules. In a solid-state[5] complexation of the two steroids with 24 molecules representing a wide variety of aromatic systems, PRO was found to form cocrystals with almost all of them (19 out of 24) whereas PRE cocrystallizes only with a few (4 out of 24).[6] Such a high sensitivity of the binding affinity to slight modifications in the steroid molecule raises important fundamental questions about the nature of the interactions of steroids with aromatic molecules and the origins of the observed different behavior. From a practical perspective, answering such questions is important for the development of new steroid-containing crystals[7–10] and for designing selective steroid-binding drugs.

Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, QC H3A 0B8, Canada. E-mail: rustam@khaliullin.com

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7cp06828j

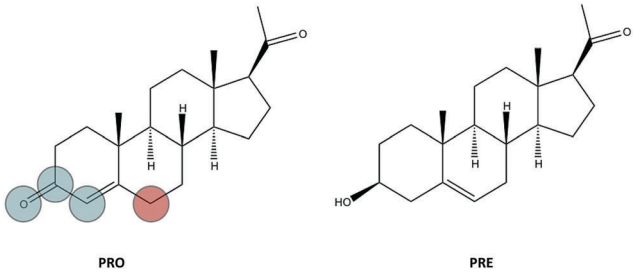


Fig. 1 Structural difference between PRO and PRE. The PRE structure can be obtained from PRO by adding hydrogen atoms at the carbon atoms marked with the blue circles and removing a hydrogen atom at the center marked with the red circle. The downward and upward facing sides of the molecule are called the α- and β-faces, respectively.

The structural analysis of PRO cocrystals has shown the persistent appearance of a molecular motif, in which the α-face of PRO molecules is adjacent to the π-electrons of aromatic systems (Fig. 2A). The recurrence of this structural pattern, both in the X-ray studies and in the accompanying computational crystal structure prediction, has led to the recognition of a previously unnoted interaction between the α-face of PRO and the π-electron density, further referred to as the α–π interaction. Moreover, the fact that cocrystals of PRE are few and do not exhibit the same α–π pattern has implied that the α–π interaction is the main driving force behind the cocrystallization and also the origin of the different cocrystallization behavior of steroids. Analysis of the electrostatic potentials of isolated steroid molecules (*i.e.* without considering interactions between molecules in the cocrystals) has suggested that the α–π interaction is mostly of an electrostatic nature and it is the different distribution of charges over the steroid backbone that is responsible for a selective recognition of the π-electron density.[6]

Important implications of this work have motivated us to perform a systematic comparative analysis to examine the fundamental interactions between aromatic and steroid molecules in the cocrystals of PRO and PRE. To make such a comparative examination possible, we designed a simple computational procedure that generates experimentally inaccessible structures of the PRE cocrystals without relying on conventional crystal structure prediction algorithms, which would be unfeasible in this case. Our study reveals that the different cocrystallization propensities of PRO and PRE cannot be attributed solely to the strength of α–π interactions nor to simple electrostatics. The observed phenomenon has more complex origins than previously thought and is a result of a fine balance between steroid–steroid and steroid–aromatic intermolecular interactions in various crystal lattices formed by steroid molecules.

Methodology

Why does not PRE cocrystallize with aromatic molecules despite being structurally similar to PRO? This key question is easier to answer if we can directly compare the interactions of PRO and PRE with aromatic molecules in a similar environment. The main obstacle to performing such a comparative analysis is that most cocrystals of PRE cannot be obtained in experiments and those that can have a packing motif that is different from that of PRO. Therefore, we resorted to computational methods that can generate experimentally inaccessible meta-stable (that is, represented by local minima on the potential energy surfaces) crystal structures. Our assumption that the cocrystals of PRE are meta-stable is reasonable given that the cocrystals of structurally similar PRO (Fig. 1) are stable. As shown below, this assumption is confirmed by calculations.

While conventional crystal structure prediction methods[11] can perform an exhaustive search for stable cocrystals such computationally expensive methods are not ideally suited nor necessary to achieve the goal of this work: generating only those cocrystals of PRE that are structurally similar to the experimentally known, well-characterized cocrystals of PRO. Instead our procedure generates such stable cocrystals of PRE with a sequence of several simple steps. We started with the X-ray structure of a PRO cocrystal and modified the PRO molecules "in-place" (that is, while keeping their lattice positions) to create a reasonable initial guess for the structure of the PRE molecules in the cocrystal. The modifications included: (a) adding a hydrogen atom in all positions marked with blue circles and (b) deleting a hydrogen atom at the atom marked with the red circle in Fig. 1. All hydrogen insertions and deletions were performed randomly: deletion is entirely random; the insertion is performed to produce only chemically reasonable distances and angles with neighbor atoms. The reason for introducing a random element in the insertion and deletion procedure is the ambiguity in the hydrogen position relative to the neighbor molecules. The procedure was repeated to generate several hundred initial candidate structures for the PRE cocrystals (see Computational methods for details). The transformation is performed to guarantee that all molecules in the unit cell are modified in the same way and remain crystallographically equivalent. In the next step, the lattice vectors and atomic positions of the candidates were optimized with the external pressure set to 1 atm to minimize their enthalpy. The potential energy surface for the optimization was generated by using density functional theory (DFT) calculations with the Becke–Lee–Yang–Parr[13] exchange–correlation functional corrected to account for the dispersion interactions with the Grimme D3 method[12] (BLYP + D) and a triple-ζ Gaussian basis set with two sets of polarization functions (TZV2P). The structure with the lowest enthalpy and the correct stereochemistry was selected for further comparative analysis. For a fair comparison, the same optimization procedure was applied to the experimentally known PRO cocrystals.

Molecular structures of PRO and PRE cocrystals with 9-phenanthrol generated by our computational procedure are shown as an example in Fig. 2. It is important to emphasize that the computational procedure described above is not designed to generate the most stable cocrystals of PRE but only those stable PRE cocrystals that resemble the experimentally obtained cocrystals of PRO.

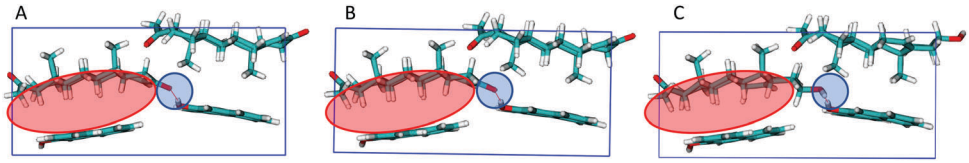


Fig. 2 (A) Structure of PRO-13 obtained with X-ray diffraction analysis, computer generated and optimized using the BLYP + D/TZV2P model structures of (B) PRO-13 and (C) PRE-13. Only half of the molecules in the unit cell are shown for clarity. α–π and hydrogen bonding interactions are highlighted with red and blue colors, respectively.

Generating molecular structures of stable PRE cocrystals *in silico* gives us a unique opportunity to perform a direct comparative analysis of the intermolecular binding in the cocrystals of PRO and PRE. The comparative analysis was done using the same exchange–correlation functional and basis sets that were used in the geometry optimization procedure.

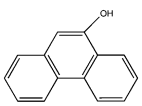
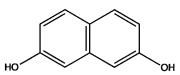
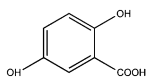
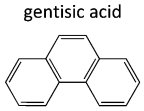
The enthalpies of all solid-state structures analyzed in this work are almost identical to their energies because the pressure–volume terms are negligibly small at 1 atm. Finite temperature effects, such as phonon contributions and the thermal expansion of crystals, were neglected in this work.

Results and discussion

We selected 9-phenanthrol, 2,7-dihydroxynaphthalene, gentisic acid, and phenanthrene, denoted as 13, 14, 15 and 21, respectively, in the previous study[6] and here, as representative aromatic molecules to study the differences in intermolecular interactions between PRO and PRE cocrystals (Table 1).

The optimized structures of the PRO cocrystals agree well with the structures obtained from the X-ray diffraction measurements confirming that the selected dispersion-corrected DFT exchange–correlation functional is appropriate to describe the interactions in the cocrystals. The calculated length of lattice vectors is systematically underestimated leading to a slightly overestimated density of the cocrystals (Table 2). This discrepancy between the calculated and observed structural parameters is expected because we neglect the vibrational motions that typically lead to the expansion of crystals.[14] Zero-point and finite-temperature corrections can certainly improve the agreement between theory and experiment. However, they will have only a minor effect on the comparative analysis of PRE and PRO because these corrections will affect similar cocrystals to approximately the same degree.

Table 1 Result of a solid-state screening for complex formation from ref. 6 ('+' indicates that the organic molecules are able to cocrystallize with steroids, '–' means unsuccessful cocrystallization)

No.	Structure	PRO	PRE
13	 9-phenanthrol	+	–
14	 2,7-dihydroxynaphthalene	+	+
15	 gentisic acid	+	–
21	 phenanthrene	+	–

A visual inspection (Fig. 2) and a detailed comparison of the geometric parameters of the computationally optimized PRO and PRE cocrystals (Table 2) reveal that, for each organic molecule, the two structures are almost identical. For example, the distance between the α-face of a steroid molecule and an organic molecule do not differ by more than 0.05 Å in the PRO and PRE cocrystals. Differences in the β-face-aromatic distances are also insignificant. This observation confirms our hypothesis that PRE and PRO are able to form stable cocrystals with similar molecular packing and bonding patterns. The similarities between the structures of cocrystals allow us to perform a detailed comparative analysis of the intermolecular binding.

To compare the energetic stability of the cocrystals we calculated the energy of the formation of the lattice from isolated (*i.e.* noninteracting) molecules fixed in their lattice geometries as described in Computational methods. These energies, denoted as ΔE_{INT}(PRO) and ΔE_{INT}(PRE), are shown in Fig. 3A as the total height of the column. To facilitate comparison between cocrystals with different numbers of steroid molecules in the unit cell, all energies are reported per one steroid molecule. The height of the columns shows that, for all organic molecules considered in this work, intermolecular interactions are stronger in the PRO than in the PRE cocrystals. The origins of this difference can be understood when the total interaction energy is decomposed further. As reported in the ESI,† the bonding cooperativity of steroid cocrystals is negligible and, therefore, the total interaction energy can be accurately represented as a sum of two-body interaction energies. This allows us to analyze and compare different types of interacting pairs independently. We categorized all two-body interactions as steroid–steroid, organic–organic, and steroid–organic interactions. The latter group was further split into α–π, β–π, hydrogen bonding (HB), neighbor and distant-pair interactions (see the ESI† for a precise definition of each category).

Table 2 Selected geometric descriptors of cocrystals. Experimental measurements are performed at room temperature, calculation results are for zero-temperature structures

	PRO-13 expt.	PRO-13 comp.	PRE-13 comp.	PRO-14 expt.	PRO-14 comp.	PRE-14 comp.	PRO-15 expt.	PRO-15 comp.	PRE-15 comp.	PRO-21 expt.	PRO-21 comp.	PRE-21 comp.
A (Å)	9.204	8.864	9.039	7.496	7.256	7.272	7.288	7.114	7.192	7.434	7.251	7.260
B (Å)	14.763	14.548	14.208	11.284	11.314	11.453	14.052	13.441	13.703	39.649	38.304	38.805
C (Å)	20.051	20.006	20.200	13.424	12.879	12.975	23.385	23.554	23.948	11.196	11.139	11.350
α (degree)	90.0	90.0	89.8	78.3	79.1	81.7	90.0	90.1	89.8	90.0	90.0	90.2
β (degree)	90.0	90.0	89.9	83.7	84.2	86.4	90.0	90.0	89.8	107.3	106.6	105.5
γ (degree)	90.0	90.1	90.0	74.8	75.2	75.8	90.0	89.9	90.0	90.0	89.9	90.3
Density (g cm^{-3})	1.245	1.314	1.302	1.229	1.313	1.264	1.305	1.387	1.318	1.188	1.263	1.209
Hydrogen bond (Å)	1.89	1.65	1.73	1.88	1.70	1.73	1.93	1.72	1.72	None	None	None
α–π distance[a] (Å)	4.23	4.14	4.15	4.24	4.13	4.13	4.25	4.15	4.14	4.23	4.14	4.19

[a] Definition of the distance between the α face of steroid molecules and the aromatic plane is in the ESI.

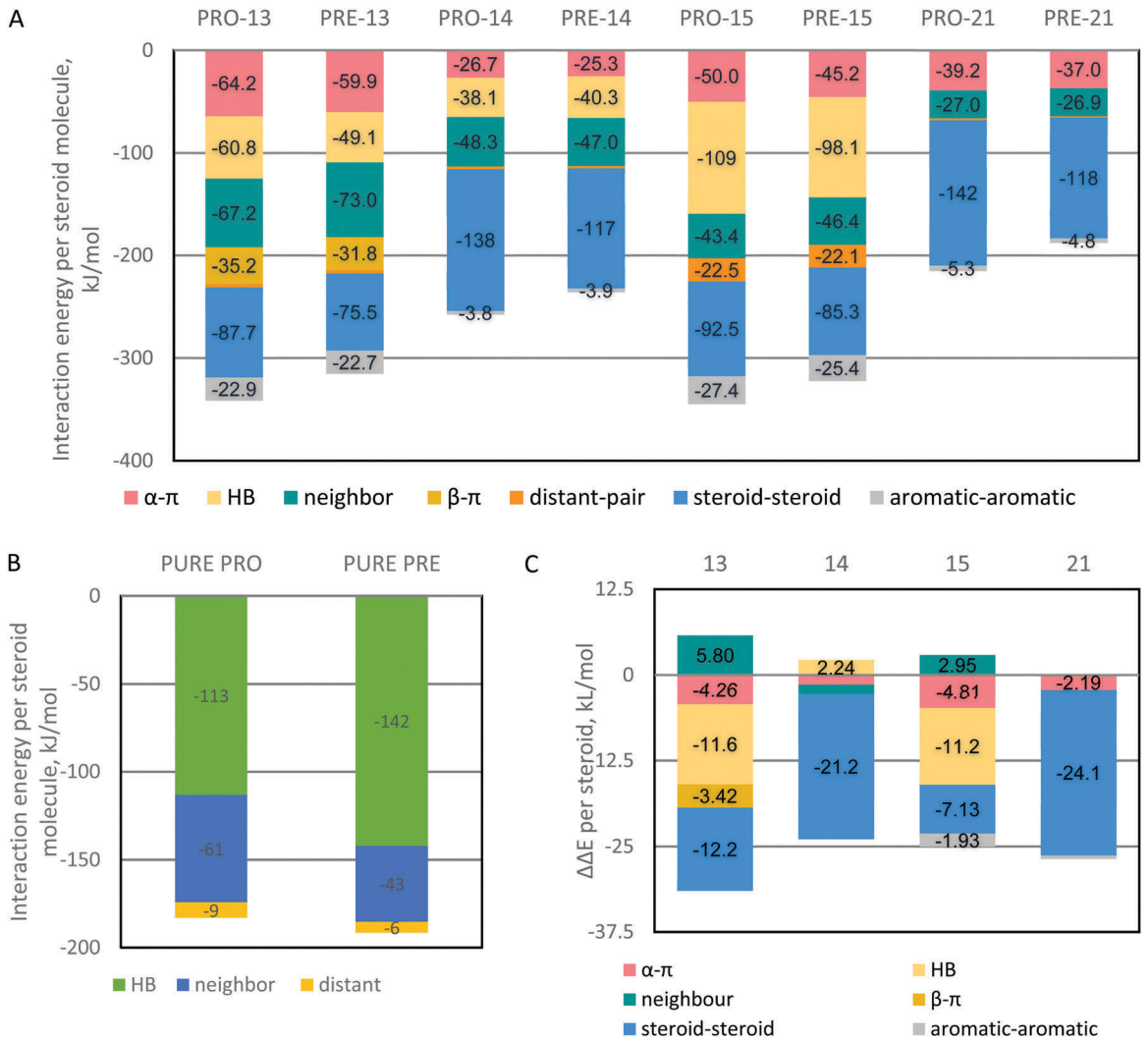


Fig. 3 Analysis of the interaction energies in (A) cocrystals and (B) pure crystals of PRO and PRE. (C) Difference in the total interaction energies of PRO and PRE cocrystals. Negative numbers mean that the interaction is stronger in the PRO cocrystal, positive – in the PRE cocrystal.

The decomposition clearly shows that α–π interactions are a significant component of the overall lattice stabilization (Fig. 3A) and contribute between 10% and 20% to the lattice energy. This strength is a result of the dispersion interactions between the π-electron density and hydrogen atoms of the steroid backbone. If the dispersion component of the exchange–correlation functional is turned off the α–π interactions become repulsive. However, despite the strength of the α–π interactions the difference does not seem significant enough to justify the dramatic difference in the observed behavior of PRO and PRE.

Fig. 3C shows that the difference in α–π interactions is only between 1 and 5 kJ mol^{-1} per steroid molecule. It contributes between 6% and 21% to a typical overall difference of 22–27 kJ mol^{-1} per steroid molecule.

The detailed analysis of the interaction energy difference (Fig. 3C) reveals that it is the steroid–steroid interactions and steroid–organic hydrogen bonding interaction that make the largest contribution to the difference $\Delta\Delta E_{INT} = \Delta E_{INT}(PRO) - \Delta E_{INT}(PRE)$ and make the PRO cocrystals more stable than those of PRE. Other types of interactions also contribute to the relative stabilization but to a lesser degree and not consistently throughout the entire set of the four organic molecules considered here. Thus, our analysis of intermolecular binding shows that, in contrast to previous assumptions, α–π interactions formed by PRO and PRE are very similar in strength and are unlikely to be the origin of the different cocrystallization behavior of PRO and PRE. Instead our calculations demonstrate that the strength of hydrogen bonds formed by PRO and PRE with some aromatic molecules (*e.g.* molecules 13 and 15) can be very different. This observation suggests that a selective binding of steroid molecules may be achieved by fine-tuning the strength of their intermolecular hydrogen bonds.

While our analysis helps understand what interactions contribute to the lattice energy of cocrystals, it remains unclear why the difference of just 22–27 kJ mol^{-1} per steroid molecule makes such a dramatic effect on the cocrystallization behavior. To examine a possible origin of this difference we compared the energy of the formation of cocrystals from their pure components: organic and steroid crystals. This energy, called the cocrystallization energy ΔE_{CC} here, is almost equal to the cocrystallization enthalpy because of the negligible pressure–volume term and, therefore, can be used to describe the thermodynamics of the cocrystallization process at zero temperature. The comparison of the cocrystallization energies reveals an important trend: $\Delta E_{CC}(PRO)$ is lower than $\Delta E_{CC}(PRE)$ by more than 21 kJ mol^{-1} per steroid molecule for all the four organic molecules considered in this work (Fig. 5). Moreover, $\Delta E_{CC}(PRO)$ tends to be slightly negative (3 out of 4 cases) whereas $\Delta E_{CC}(PRE)$ is always positive. Specifically, $\Delta E_{CC}(PRO)$ ranges from −7 to +11 kJ mol^{-1} per steroid molecule and $\Delta E_{CC}(PRE)$ is between +25 and +50 kJ mol^{-1} per steroid molecule. This trend implies that the main reason for the drastically different behavior of the two structurally similar steroids is of a thermodynamic origin: the cocrystallization process is stabilizing for PRO ($\Delta G_{CC}(PRO) < 0$) and destabilizing for PRE ($\Delta G_{CC}(PRO) > 0$).[15] We would like to emphasize that this conclusion is drawn based entirely on the analysis of the structures generated with our simple procedure. While we did not perform an extensive crystal structure search and, therefore, cannot guarantee that the PRE structures correspond to the global minimum our calculations are fully consistent with the experimentally observed fact that PRE indeed rarely forms cocrystals.

To understand the factors that contribute to the different sign of the cocrystallization energies, we computed the energy of all crystals relative to a common reference – the energy of the relaxed gas phase molecules. This shows (Fig. 4) that the stronger intermolecular interactions in PRO cocrystals is only

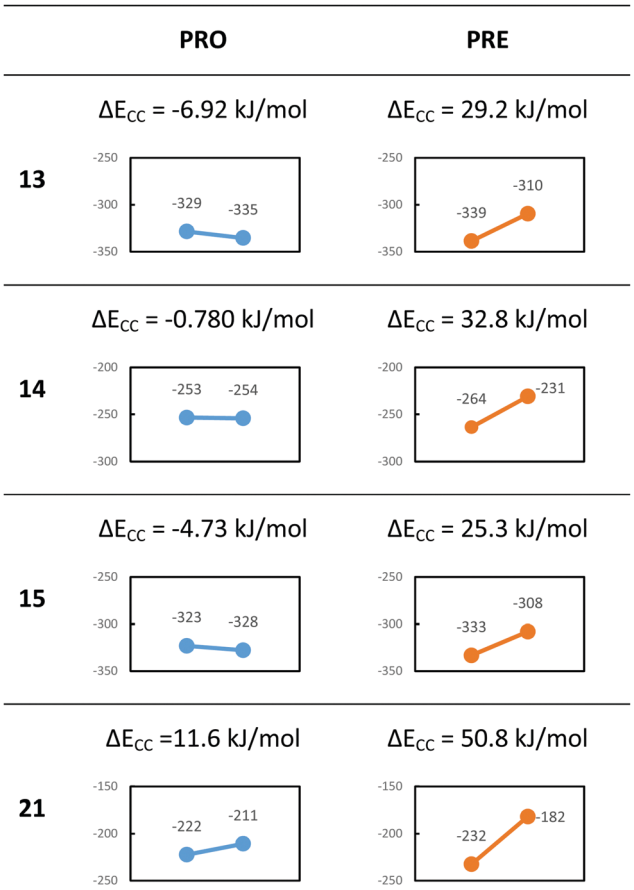


Fig. 4 Energy change for the formation of cocrystals (right point) from pure steroid and organic crystals (left point) for PRO (left panels) and PRE (right panels). All energies are relative to the relaxed gas-phase molecules in kJ mol^{-1} per steroid molecule.

one factor that determines the sign of ΔE_{CC}. Another contributing factor is the stronger intermolecular binding in pure PRE crystals (compare the energies of pure PRO and PRE crystals in Fig. 5 and the lattice energies in Fig. 3B). This is important because the latter factor is independent of the nature of the aromatic molecule and helps explain why a different cocrystallization behavior is observed for a wide range of molecules with π-electrons.

Fig. 3B shows that stronger intermolecular hydrogen bonding is a plausible reason for the higher stability of the pure PRE crystal compared to the pure PRO crystal. However, it is difficult to isolate the exact energetic contribution of a hydrogen bond to the total interaction energy of the two large steroid molecules. A close look at the nature and positions of atoms involved in hydrogen bonding is sufficient to support this argument. The hydrogen bond in the PRE crystal is between the hydrogen of the hydroxyl group and the oxygen of the keto group. Hydrogen bonding of this type tends to be stronger than the typical C–H···O=C hydrogen bonds in the pure PRO crystal. Furthermore, the length of the hydrogen bond in the PRE crystal is typically 1.68 Å while the hydrogen bond in the PRO crystal is elongated to 2.30 Å and is most likely weakened.

Experimentally available structural data shows that the steroid molecules do not form hydrogen bonds with each other in

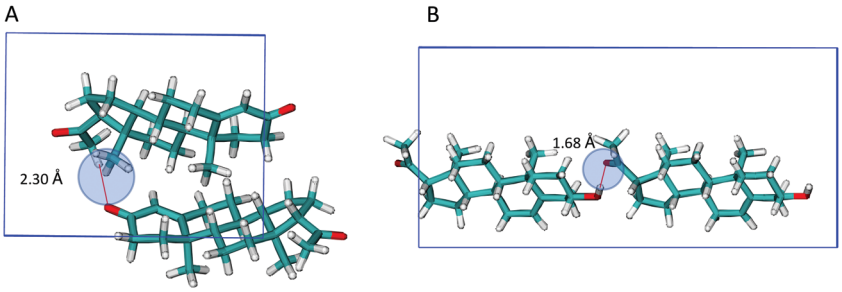


Fig. 5 Hydrogen bond in pure (A) PRO and (B) PRE steroid crystals. Only two hydrogen-bonded molecules in the unit cell are shown for clarity.

cocrystals. Thus, if a PRE molecule does not find a way to form strong bonds with aromatic molecules it "loses" the only stabilizing factor upon cocrystallization, making the process energetically unfavorable.

Conclusions

In summary, this work explains the origins of the dramatically different cocrystallization of aromatic molecules with two structurally similar steroids – progesterone and pregnenolone. To overcome the limitations of the previous computational study of this phenomenon, we designed a simple and inexpensive procedure that generates stable but experimentally unobtainable cocrystals of PRE closely resembling those obtained for PRO. This enabled us to directly compare the strength of typical interactions that control the binding in both cocrystals. Our analysis showed that dispersion interactions between the α-face of steroid and π-electrons of aromatic molecules contribute significantly to the overall stabilization of the cocrystals, as proposed earlier. However, they are not sufficiently different to explain the different cocrystallization behaviors of PRO and PRE. Instead we found that the observed difference can be explained by the stability of the cocrystals relative to the pure organic and steroid crystals. The cocrystallization process tends to be thermodynamically favorable in the case of PRO and always unfavorable in the case of PRE. This key difference is a result of two effects: stronger intermolecular binding in the PRO cocrystals (products) and stronger intermolecular binding in the pure PRE crystals (reactants). While the physical origins of the former effect vary depending on the nature of the organic molecule, the latter effect is entirely due to strong hydrogen bonds between molecules in pure PRE crystals. Since it does not dependent on the nature of the aromatic molecule, we suggest that the overly stable PRE crystal is the main reason for its inability to cocrystallize with a wide range of aromatic molecules. Thus, this fundamental study shows how subtle structural modifications of biologically active molecules lead to their drastically different behavior. It has important practical implications for designing steroid-binding drugs and biomolecular receptors that can selectively interact with steroids. It also suggests that a strategy for designing selective binding of steroids should focus primarily on tuning the strength of hydrogen bonding.

Computational methods

Density functional theory calculations

All calculations were performed using DFT as implemented in the CP2K software package.[16] The energies of crystals were evaluated using periodic boundary conditions whereas the energies of gas-phase molecules were calculated using the non-periodic approach. CP2K relies on the mixed Gaussian and plane-wave representation of the electronic degree of freedom.[17] The localized atom-centered Gaussian basis sets were used for constructing molecular orbitals and the plane waves were used to construct the Kohn–Sham matrix efficiently. The Becke–Lee–Yang–Parr generalized gradient approximation[13] corrected to account for dispersion interactions with the D3 method of Grimme[12] was used as the exchange–correlation functional. All calculations employed Goedecker–Teter–Hutter pseudopotentials[18] and a triple-ζ Gaussian basis set with two sets of polarization functions. The high energy cutoff of 600 Ry was used to define the plane-wave basis set. The integration over the Brillouin zone was performed using the Monkhorst–Pack *k*-point mesh, the density of which was chosen to converge the energy to 1 kJ mol^{-1} per atom.

Crystal structure generation

This procedure was designed to generate cocrystals of PRE that are structurally similar to the experimentally known cocrystals of PRO. The X-ray structures of PRO cocrystals were used as starting points and all PRO molecules were modified while keeping their lattice positions. The modifications included: (a) random deletion of one of the two hydrogen atoms at the carbon atom marked with the red circle in Fig. 1, (b) random insertions of a hydrogen atom in all positions marked with blue circles in Fig. 1. The hydrogen atoms were inserted randomly in chemically reasonable positions using the following restrictions: the distance between the inserted atom and the original atom is between 1.4 and 3.0 Å, the distances between the inserted atom and all neighbor atoms are larger than 1.4 Å. The atomic positions of 432 generated candidates were optimized while keeping the lattice parameters constant. Then only the lowest-lying structures were selected for a more accurate optimization of cell parameters and atomic positions with a larger *k*-point mesh for the Brillouin zone sampling. The same optimization procedure was applied to the experimental X-ray structures of PRO cocrystals.

Definition of the interaction energy

The interaction energy of molecules in a crystal ΔE_{INT} is defined as

$$\Delta E_{INT}(\text{crystal}) = E_{cell}(\text{crystal}) - \Sigma_k^M E_k$$

where E_{cell}(crystal) is the energy of the crystal per unit cell, E_k is the energy of an isolated molecule fixed in its crystal geometry, and M is the number of molecules in the unit cell. We approximated ΔE_{INT}(crystal) with a sum of all pair interaction energies:

$$\Delta E_{INT}(\text{crystal}) = \Sigma_k^M \Sigma_j^\infty \Delta E_{kj} + \Delta E_{MB} \approx \Sigma_k^M \Sigma_j^\infty \Delta E_{kj}$$

where $\Delta E_{kj} = E_{kj} - E_j - E_k$, is the interaction energy between a pair of atoms and ΔE_{MB} is a small neglected many-body term.

Definition of the cocrystallization energy

The cocrystallization energy is defined as the energy of the formation of cocrystals from their pure components normalized per 1 mole of steroid molecules:

$$\text{Steroid} + m/n \text{ aromatic} \leftrightarrows 1/n \text{ steroid}_n\text{aromatic}_m$$

$$\Delta E_{CC} = 1/nE_{cell}^*(\text{cocrystal}) - m/nE_{cell}^*(\text{aromatic}) - E_{cell}^*(\text{steroid})$$

The asterisk indicates that the energy of the periodic systems is expressed relative to the energies of relaxed gas-phase molecules. This reference is used because it is the same for all of the systems studied in the work and facilitates comparison between different aromatic molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The research was funded by the Natural Sciences and Engineering Research Council of Canada (NSERC) through Discovery Grants (RGPIN-2016-0505 and RGPIN-2017-06467). TF would also like to acknowledge receipt of a NSERC E. W. R. Steacie Memorial Fellowship (SMFSU 507347-17). The authors are grateful to Compute Canada and, in particular, the McGill HPC Centre for computer time.

References

1 P. Wallimann, T. Marti, A. Fürer and F. Diederich, *Chem. Rev.*, 1997, **97**, 1567–1608.
2 A. W. Norman, M. T. Mizwicki and D. P. G. Norman, *Nat. Rev. Drug Discovery*, 2004, **3**, 27–41.
3 C. K. Mathews and K. E. Van Holde, *Biochemistry*, Benjamin/Cummings, Redwood City, 1990.
4 A. D. Rohira and D. M. Lonard, *Biochem. Pharmacol.*, 2017, **140**, 1–7.
5 A. M. Belenguer, T. Friščić, G. M. Day and J. K. M. Sanders, *Chem. Sci.*, 2011, **2**, 696–700.
6 T. Friščić, R. W. Lancaster, L. Fábián and P. G. Karamertzanis, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 13216–13221.
7 P. A. Williams, J. Cosme, D. M. Vinković, A. Ward, H. C. Angove, P. J. Day, C. Vonrhein, I. J. Tickle and H. Jhoti, *Science*, 2004, **305**, 683–686.
8 A. Anthony, M. Jaskolski and A. Nangia, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2000, **56**, 512–525.
9 L. Fábián, G. Argay, A. Kálmán and M. Báthori, *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.*, 2002, **58**, 710–720.
10 B. Chand, *J. Chem. Crystallogr.*, 2011, **41**, 1901–1926.
11 (*a*) S. L. Price, *Acc. Chem. Res.*, 2009, **42**, 117; (*b*) T. S. Thakur, R. Dubey and G. R. Desiraju, *Annu. Rev. Phys. Chem.*, 2015, **66**, 21; (*c*) *Modern methods of crystal structure prediction*, ed. A. R. Oganov, Wiley-VCH, Weinheim, 2010.
12 S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Chem. Phys.*, 2010, **132**, 154104.
13 (*a*) A. D. Becke, *Phys. Rev. A: At., Mol., Opt. Phys.*, 1988, **38**, 3098–3100; (*b*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, **37**, 785–789.
14 Y. N. Heit and G. J. Beran, *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.*, 2016, **72**, 514–529.
15 H. C. S. Chan, J. Kendrick, M. A. Neumann and F. J. J. Leusen, *CrystEngComm*, 2013, **15**, 3799–3807.
16 CP2K code and reference material is available at the project web page: http://www.cp2k.org/.
17 J. Hutter, M. Iannuzzi, F. Schiffmann and J. VandeVondele, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2014, **4**, 15–25.
18 S. Goedecker, M. Teter and J. Hutter, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1996, **54**, 1703–1710.