

Electronic supplementary information for the manuscript entitled
“Energy partitioning of pharmaceutical co-crystal structures”

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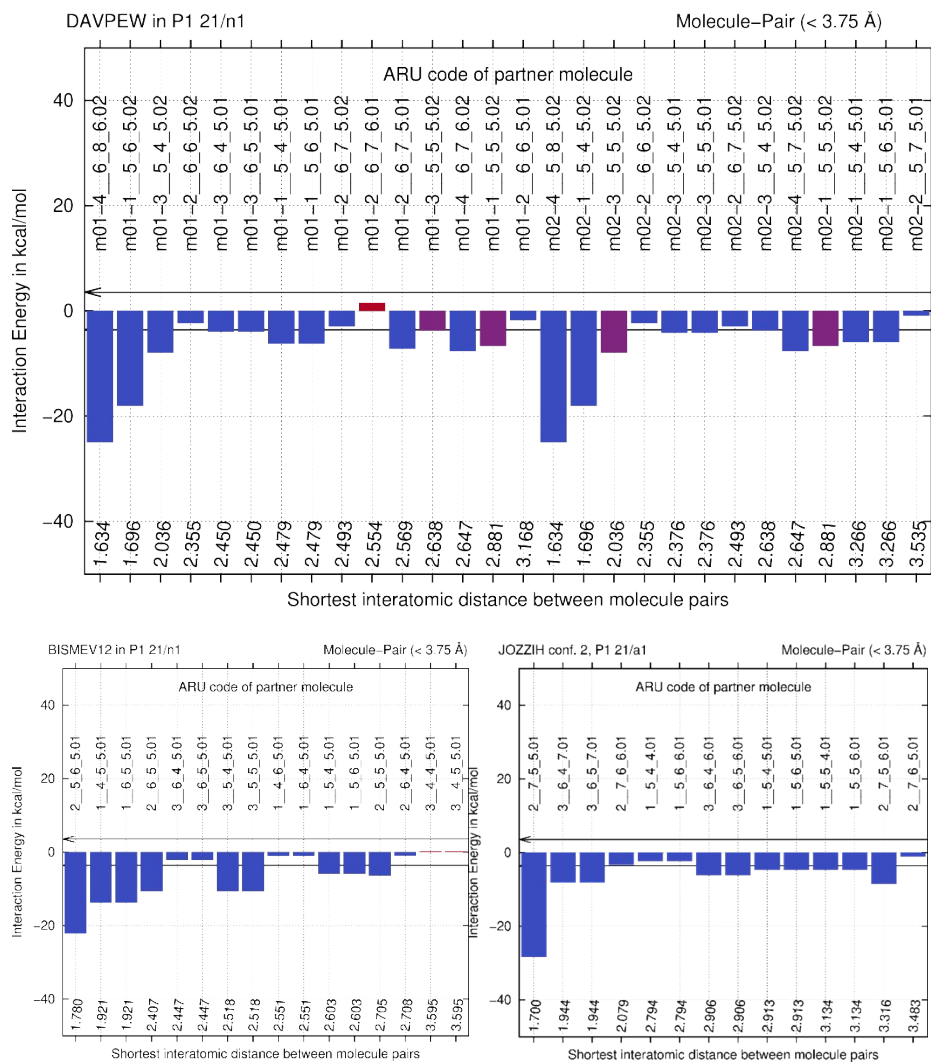
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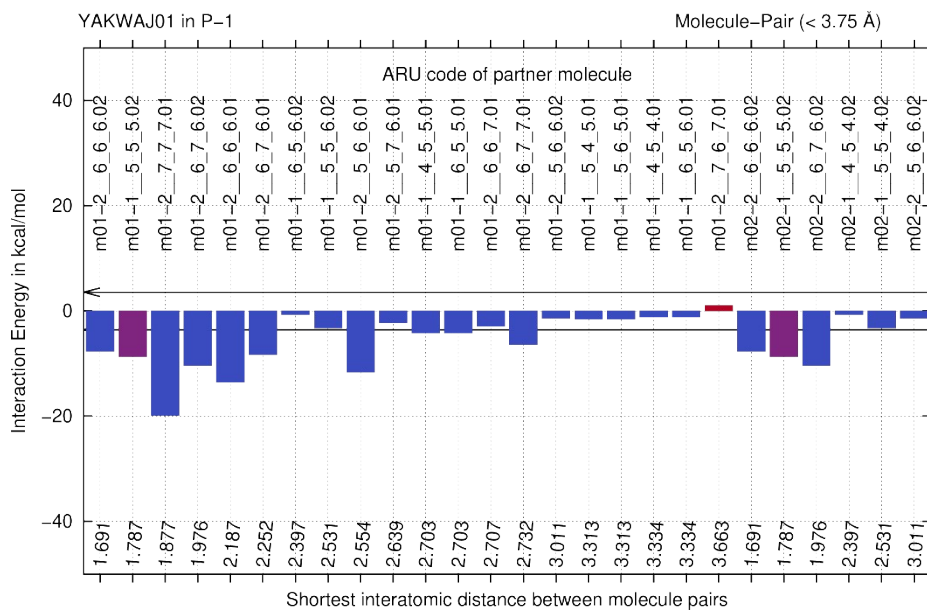
Table 1 ONIOM partitioned molecular energies of piracetam in form II and III, compared to the energy of piracetam in two co-crystals (energy differences ΔE). Cofomer structure dimer energies are also provided. ONIOM MO/MO computations used APFD/6-31G(d,p): APFD/3-21G (or, in brackets B3LYP/6-31G(d,p)/B3LYP/3-21G) and include dispersion correction. We rounded the Hartree energy to four significant figures after the comma for this evaluation and converted Hartree in kcal/mol with a multiplier of 627.507404. wrt=with respect to

REFCODE of structure	High-layer Energy in Hartrees	ΔE (kcal/mol) to lowest energy self-environment
Piracetam form II (BISMEV11, self-environment)	-494.2657 (-494.6835)	+1.19 (+1.07) (wrt. form III)
Piracetam form III (BISMEV12, self-environment)	-494.2676 (-494.6852)	± 0.0 (± 0.0)
Piracetam in piracetam monohydrate (YAKWAJ)	-494.2683 (-494.6858)	-0.44 (-0.38) (wrt. form III)
Piracetam in piracetam monohydrate, (YAKWAJ01, mol. 1)	-494.2684 (-494.6860)	-0.50 (-0.50) (wrt. form III)
Water in myricetin hydrate, NIKLAX	-76.3595 (-76.4200)	± 0.0 (+0.063 wrt. water average for B3LYP, water result same for APFD)
Myricetin without water (NIKLAX, monohyd. env., mol. 1)	-1178.5250 (-1179.4982)	± 0.0 (± 0.0)
Myricetin hydrate (NIKLAX, monohydrate env. with water)	-1254.9002 (-1255.9331)	-9.85 (-9.29)
Water in piracetam monohydrate (YAKWAJ01, molecule 2)	-76.3595 (-76.4202)	± 0.0 (-0.13) wrt. water in NIKLAX monohydrate, water result same for APFD
Piracetam hydrate, ASU energy for both molecules, YAKWAJ01	-570.6417 (-571.1199)	-9.16 (-9.10) (here wrt. to sum of hydrate components)
Piracetam in co-crystal piracetam:myricetin, FIXROV01 molecule 2	-494.2700 (-494.6875)	-1.51 (-1.44) (wrt. form III)
Myricetin in co-crystal piracetam:myricetin FIXROV01 molecule 1	-1178.5268 (-1179.4999)	-1.13 (-1.07) (wrt. myricetin in monohydrate)
Piracetam:myricetin co-crystal, ASU energy for both FIXROV molecules	-1672.8215 (-1674.2119)	-18.14 (-17.88) (wrt. sum of components of self-env.)
p-hydroxybenzoic acid (JOZZIH, self-env.) conformation 1	-495.6609 (-496.0808)	+0.06 (± 0.0) (only known form)
p-hydroxybenzoic acid (JOZZIH, self-env.) conformation 2	-495.6608 (-496.0808)	± 0.0 (± 0.0) (only known form)
Piracetam in co-crystal piracetam:p-hydroxy-benzoic acid, DAVPEW	-494.2687 (-494.6861)	-0.69 (-0.56) (wrt. form III)
p-hydroxy-benzoic acid in DAVPEW co-crystal piracetam:p-hydroxy-benzoic acid	-495.6599 (-496.0798)	+0.56 (+0.63) (wrt. lower energy conformation APFD /above conformations B3LYP)
Piracetam:p-hydroxy-benzoic acid co-crystal, ASU energy for both molecules	-989.9391 (-990.7759)	-6.71 (-6.21) (wrt. sum of components in their self-env.)
Gentisic acid (BESKAL04, self-env.)	-570.8391 (-571.3127)	± 0.0 (± 0.0)
Piracetam in co-crystal piracetam:gentisic acid, DAVPAS molecule 1	-494.2705 (-494.6877)	-1.82 (-1.57) wrt. BISMEV12
gentisic acid in co-crystal piracetam:gentisic acid, DAVPAS molecule 2	-570.8368 (-571.3104)	+1.44 (+1.44)
Piracetam:gentisic acid co-crystal DAVPAS, ASU energy for both molecules	-1065.1179 (-1066.0083)	-7.03 (-6.53) (wrt. sum of components in self-environment)

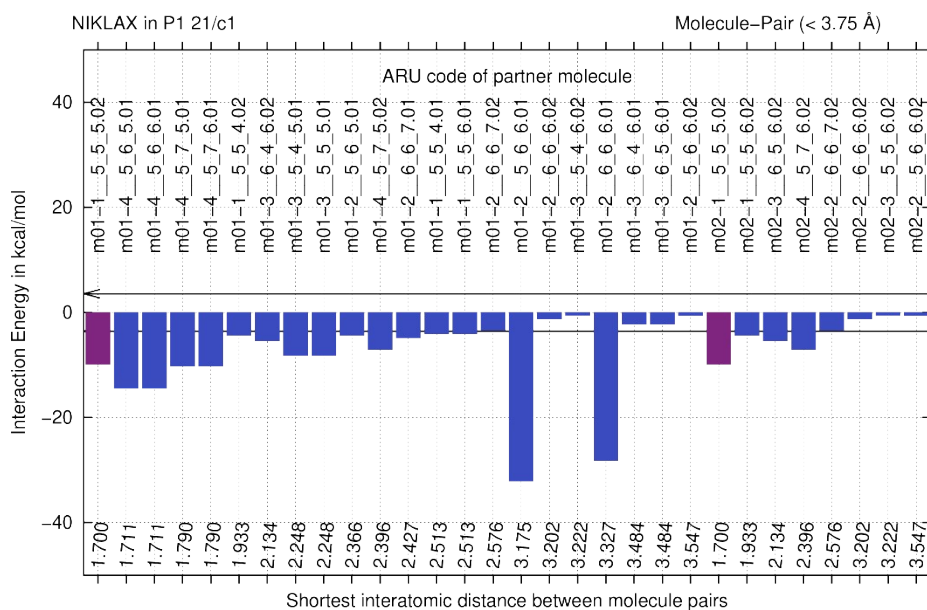
We emphasize that the sum of the ONIOM high-layer energies of the individual molecules is not the same as the energy of the high-layer energy of the combined ASU content. There is thus a pronounced energy gain for ASU dimer formation in these classical hydrogen-bonded systems. As one can see from adding the values given in Table 1 for piracetam and gentisic acid in the co-crystal and subtracting this sum from the energy of both molecules in a bigger cluster generated from the entire ASU content of that structure, this energy gain for the ASU dimer in the cluster of the co-crystal environment is considerable. The same is found for the piracetam p-hydroxybenzoic acid system. Since dimers (in their co-crystal pocket) are considerably more stable than the monomers in their respective self- or co-crystal environment, this finding identifies the main driving force of co-crystal formation from these examples.



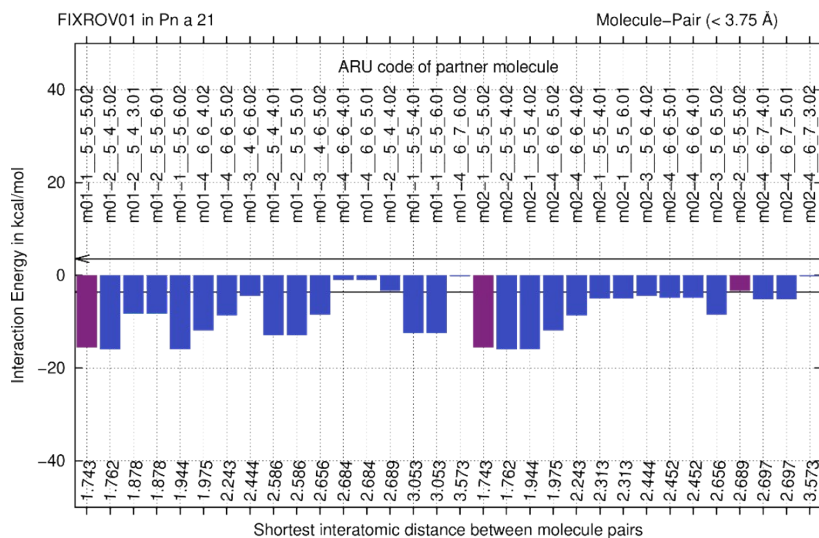
Supplementary Figure 1 E(MPIE) analysis of molecule-pair interaction energies in crystal structure with CCDC recode DAVPAS compared to BISMEV12 and JOZZIH conformer 2, showing that the sum of the strongest interactions occurs between coformer and API, and not between API-API or coformer-coformers.



Supplementary Figure 2 E(MPIE) analysis of molecule-pair interaction energies in hydrate crystal structure with CCDC refcode YAKWAJ01 compared to BISMEV12 (see above). A difference between hydrates and cocrystal structures is that for hydrates the strongest interactions occur between API and API, and not between API and water. Seen from the perspective of the water molecule, the statement still holds: The important interactions for the water m02 are all with molecules with ARU code ending with .02 and not with itself, molecules ending with .01.



Supplementary Figure 3 E(MPIE) analysis of molecule-pair interaction energies in hydrate crystal structure with CCDC refcode YAKWAJ01 compared to BISMEV12 (see above). A difference between hydrates and cocrystal structures is that for hydrates the strongest interactions occur between API and API, and not between API and water. Seen from the perspective of the water molecule, the statement still holds: The important interactions for the water m02 are all with molecules with ARU code ending with .02 and not with itself, molecules ending with .01.



Supplementary Figure 4 E(MPIE) analysis of molecule-pair interaction energies in crystal structure with CCDC refcode FIXROV01 compared to BISMEV12 and NIKLAX (for both see above), showing that the sum of the strongest interactions occurs between coformer and API, and not between API-API or coformer-coformer.

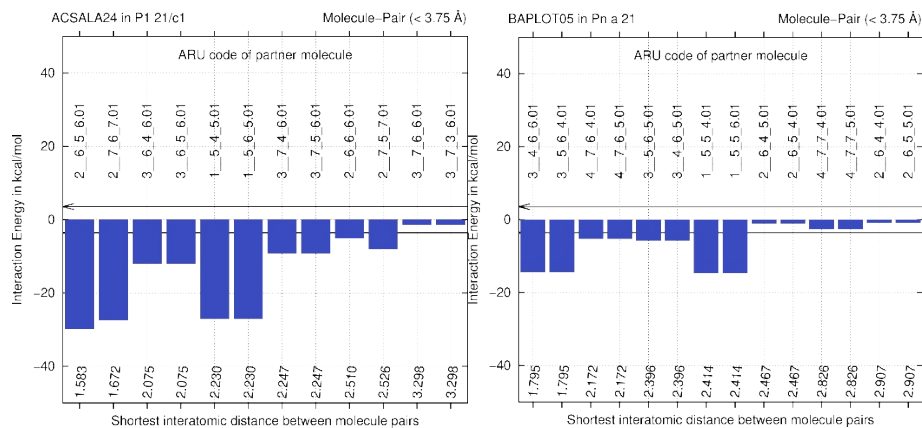
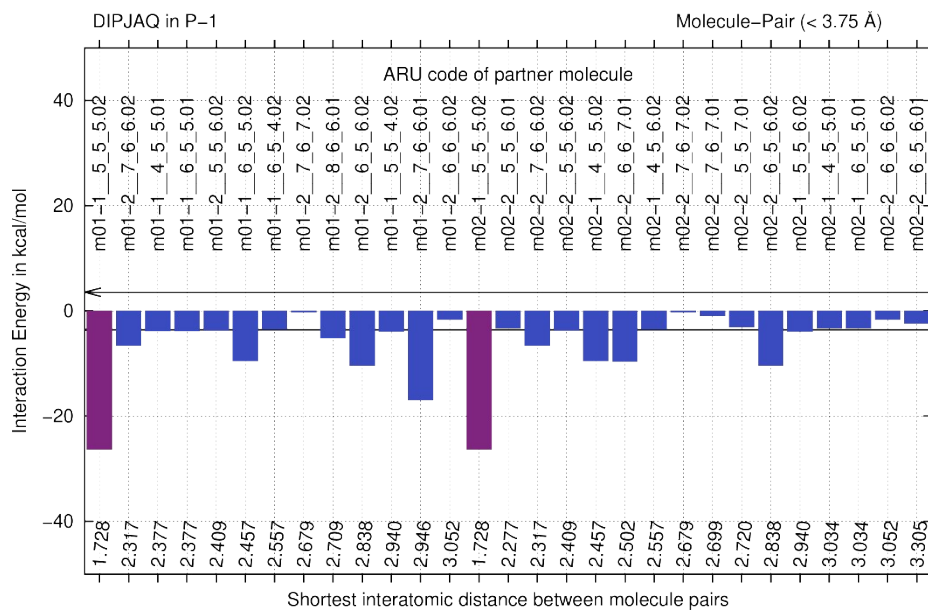
Energies in supplementary Table 2 are provided in a similar manner to the piracetam systems in supplementary Table 1, starting with self-environments on ONIOM partitioned energies for saccharin and piroxicam. Followed by these values are the energies of the molecules and the whole ASU content in the co-crystal.

Table 2 ONIOM partitioned molecular energies and energy differences ΔE of piroxicam/saccharin co-crystal dimers in the cluster compared to the sum of energies of saccharin and piroxicam in the self-environment. ONIOM MO/MO computations used the APFD/6-31G(d,p): APFD/3-21G (or, in brackets B3LYP/6-31G(d,p)/B3LYP/3-21G) functionals that include dispersion correction.

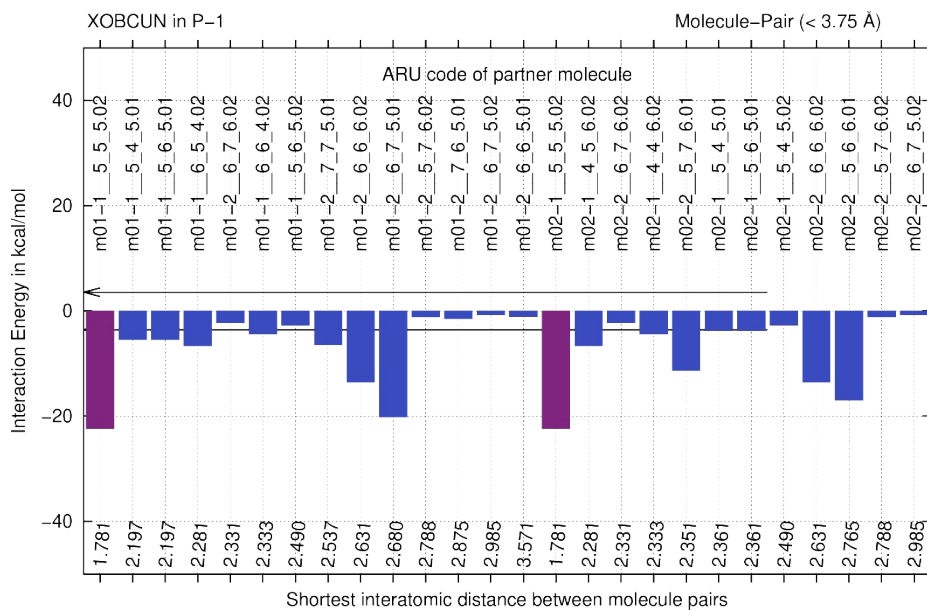
Structure (REFCODE)	High-layer Energy in Hartrees	ΔE (kcal/mol) to lowest energy self-env.
Saccharin (SCCHRNO7, self-environment)	-947.7780 (-948.3461)	± 0.0 (± 0.0)
Piroxicam (BIYSEH11, form III self-env.)	-1441.8221 (-1442.8206)	± 0.0 (± 0.0)
Piroxicam (BIYSEH14, form I self-env.)	-1441.8213 (-1442.8198)	+0.50 (+0.50) (wrt. form III)
Piroxicam (BIYSEH13, form I self-env.)	-1441.8216 (-1442.8198)	+0.19 (+0.50) (wrt. form III)
Piroxicam (BIYSEH12, form IV mol. 1, zwitterion self-env.)	-1441.8018 (-1442.7998)	+12.74 (+13.05) (wrt. form III)
Piroxicam (BIYSEH12, form IV mol 2, uncharged self-env.)	-1441.8169 (-1442.8157)	+3.26 (+3.07) (wrt. form III)
Piroxicam (BIYSEH12, form IV mol 3, uncharged self-env.)	-1441.8177 (-1442.8161)	+2.76 (+2.82) (wrt. form III)
Piroxicam (BIYSEH12, form IV mol 4, uncharged self-env.)	-1441.8199 (-1442.8186)	+1.38 (+1.26) (wrt. form III)
Piroxicam (BIYSEH12, form IV mol 5, uncharged self-env.)	-1441.8177(-1442.8158)	+2.76 (+3.01) (wrt. form III)
Saccharin in piroxicam:saccharin co-crystal YANNEH01	-947.7766 (-948.3446)	+0.88 (+0.94) (wrt. SCCHRNO7)
Piroxicam in piroxicam:saccharin co-crystal (zwitterion) YANNEH01	-1441.8003 (-1442.7990)	+13.68 (+13.55) (wrt. form III)
Piroxicam:saccharin co-crystal, ASU energy for both molecules (YANNEH01)	-2389.5831 (-2391.1750)	-10.67 (-5.21) (wrt. sum of components in their self-env.)
Piroxicam:saccharin co-crystal, ASU energy for both molecules, "different" dimer (relative saccharin position)	-2389.5845 (-2391.1748)	-9.79 (-5.08) (wrt. sum of components in their self-env.)

Table 3 ONIOM partitioned molecular and dimer energies of aspirin co-crystals with theophylline and saccharin in the cluster compared to the energy of the constituents in their self-environments. ONIOM MO/MO computations used the method/basis set combination APFD/6-31G(d,p): APFD/3-21G (or, in brackets B3LYP/6-31G(d,p)/B3LYP/3-21G) with dispersion correction.

Structure (REFCODE or internal code, omitted if new structure reported here)	High layer energy in Hartrees	Energy difference (in kcal/mol) to lowest energy self-env.
Saccharin (SCCHR07, self-environment)	-947.7780 (-948.3461)	±0.0 (±0.0)
Theophylline form I (BAPLOT05, self-env.)	-640.5770 (-641.1115)	±0.0 (±0.0)
Theophylline form II (BAPLOT06, self-env.)	-640.5759 (-641.1105)	+0.69 (+0.63)
Theophylline form IV molecule 1 (BAPLOT03, self-env.)	-640.5767 (-641.1112)	+0.19 (+0.19)
Theophylline form IV molecule 2 (BAPLOT03, self-env.)	-640.5764 (-641.1110)	+0.38 (+0.31)
Aspirin polymorph I, (ACSALA14, self-env.)	-648.1957 (-648.7427)	-0.03 (+0.06)
Aspirin polymorph II, (ACSALA15, self-env.)	-648.1947 (-648.7417)	+0.60 (+0.69)
Aspirin pol. III, mol. 1 (ACSALA24, self-env.)	-648.1963 (-648.7435)	±0.0 (±0.0) (average of both molecules, -648.19565 (-648.7428))
Aspirin pol. III, mol. 2 (ACSALA24, self-env.)	-648.1950 (-648.7421)	±0.0 (±0.0) (average of both molecules)
Theophylline in aspirin:theophylline DIPJQA co-crystal	-640.5760 (-641.1106)	+0.63 (+0.56)
Aspirin in aspirin:theophylline DIPJQA co-crystal	-648.1977 (-648.7446)	-1.29 (-1.13)
Theophylline in theophylline:saccharin XOBGUN co-crystal	-640.5773 (-641.1119)	-0.19 (-0.25) wrt. BAPLOT05
Saccharin in XOBGUN theophylline:saccharin co-crystal	-947.7791 (-948.3472)	-0.69 (-0.69) wrt. SCCHR07
Aspirin:theophylline DIPJQA co-crystal, ASU energy for both molecules	-1288.8156 (-1289.8967)	-26.95 (-26.60)
Theophylline:saccharin XOBGUN co-crystal, ASU energy for both molecules	-1588.3920 (-1589.4947)	-23.22 (-23.28)



Supplementary Figure 5 E(MPIE) analysis of molecule-pair interaction energies in crystal structure with CCDC refcode DIPJAQ compared to ACSALA24 and BAPLOT05, showing that the sum of the strongest interactions occurs between cofomer and API, and not between API-API or cofomer-cofomer.



Supplementary Figure 6 E(MPIE) analysis of molecule-pair interaction energies in crystal structure with CCDC refile XOBCUN compared to BAPLOT05 and SCCHR07 (for the latter two plots, see above), showing that the sum of the strongest interactions occurs between coformer and API, and not between API-API or coformer-coformer.

Table 5 VASP full solid-state optimizations and lattice energies of all co-crystal, API and coformer structures relevant for the discussion. VASP was used with a PBE/D3 DFT functional with dispersion correction.

REFCODE	E(kcal/mol/atom)	No. of ASU atoms	SG	a	b	c	alpha	beta	gamma
ACSALA14	-153.12880321498957	21	P2_1/c	11.3305	6.54974	11.40309	90	96.26319	90
ACSALA15	-153.1294371958214	21	P2_1/c	12.1479	6.45759	11.46211	90	111.2822	90
ACSALA24	-153.05669178246504	42	P2_1/c	16.7668	4.78073	23.51771	90	111.1324	90
BAPLOT03	-155.65367293047609	42	P2_1/c	7.80708	12.9698	15.90172	90	104.3773	90
BAPLOT05	-155.60731505069924	21	Pna2_1	12.9672	15.6997	3.933330	90	90	90
BAPLOT06	-155.64727435688874	21	Pna2_1	23.9811	3.86943	8.450861	90	90	90
BESKAL04	-154.89394473180019	17	P2_1/n	5.70242	4.80477	23.45583	90	92.49646	90
BISMEV11	-142.59552002780268	20	P-1	6.42322	6.56040	8.331441	81.10020	78.39854	90.08167
BISMEV12	-142.5944469611448	20	P2_1/n	6.49746	6.43051	16.12559	90	91.84614	90
BIYSEH11	-154.0250766708312	36	P-1	7.80935	10.1496	10.44595	80.74681	71.10988	69.83255
BIYSEH12	-154.03846252259012	180	P-1	12.7411	14.7228	20.58969	85.08347	74.41714	85.17456
BIYSEH13	-154.02158425100254	36	P2_1/c	7.08794	15.0850	13.92085	90	96.37619	90
DAVPAS	-148.31768763241371	37	C_2/c	27.9113	5.12818	19.73289	90	102.0103	90
DAVPEW	-148.01240383056719	36	P_2_1/n	14.3887	5.54070	17.38268	90	108.8243	90
DIPJAJ	-154.37940768086793	42	P-1	7.01732	10.1419	12.04756	104.7154	94.36336	102.6399
FIXROV01	-153.30333249781765	53	Pna2_1	22.9257	11.7721	7.105886	90	90	90
JOZZIH2	-154.58510678049029	16	P2_1/a	19.5110	4.99825	6.203123	90	92.19963	90
NIKLAH	-156.009472471881	36	P2_1/c	6.78099	14.6894	13.18371	90	97.81751	90
SCCHR07	-155.75127033055682	17	P2_1/c	9.43281	6.85886	12.05615	90	104.1877	90
XOBCUN	-155.71281774247359	38	P-1	8.55875	8.80041	11.71180	73.18451	75.11128	65.99831
YANNEH01	-154.6689012	53	P-1	9.63080	10.43135	12.68418	66.97746	71.22074	89.03942
YAKWAJ01	-138.97837065329423	23	P-1	7.07338	7.27280	9.126904	97.28905	102.7984	117.4717