Stacking Interactions

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Do Special Noncovalent π–π Stacking Interactions Really Exist?**

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Noncovalent interactions play an increasingly important role in modern chemical research, and are nowadays considered as cornerstones in supramolecular chemistry, materials science, and even biochemistry.[1] When unsaturated organic groups are involved in noncovalent interactions, the terms "π–π stacking", or more generally "π–π interactions" are often used. As noted recently,[2] this classification has a quite mysterious flavor. For larger structures, π–π stacking is a phenomenon that is theoretically not well understood, although some progress has been made.[3,4]

From many studies of the benzene dimer[5–7] and other complexes involving phenyl rings,[2,8] it can be concluded that the π orbitals do not function as in conventional overlap-driven covalent bonding, although this is not common knowledge.[9] The prototypical benzene dimer is nowadays considered a typical van der Waals complex in which the long-range dispersion interactions (dominant R^{-6} dependence of the interaction energy on interfragment distance[10]) play the major role. As a consequence, the dimer is unbound at uncorrelated Hartree–Fock and many density functional theory (DFT) levels.[11] This more sophisticated view is increasingly replacing Hunter's model[12] of π–π interactions, which (over)emphasises the mainly quadrupole–quadrupole electrostatic component of the interaction in benzene-type systems (see Ref. [13] for recent theoretical work on polar π-systems).

Because van der Waals complexes are formed by almost all neutral, closed-shell molecules, which are considered exclusively herein, what should be so special about the interaction between stacked aromatic units compared to, for example, saturated (hydrogenated) rings of about the same size. This mainly energetic difference is termed herein the π–π stacking effect (PSE). For example, benzene and cyclohexane both exist as fluids at room temperature, which indicates similar intermolecular interactions. According to accurate CCSD(T) computations, the stacked (parallel-displaced, PD) benzene dimer has an even smaller binding energy than the pentane dimer (−2.8 vs. −3.9 kcal mol^{-1}),[2,14] which has the same number of electrons. These observations seem to be incompatible with the assumption of special π–π interactions. On the other hand, it is known that larger polycyclic aromatic hydrocarbons (PAHs) behave differently to large alkanes; for example, PAHs become increasingly insoluble in common organic solvents with increasing size.[15] Thus the magnitude of the intermolecular interactions and possibly also their fundamental character is more strongly size-dependent in aromatic systems than in saturated systems. The clarification of this matter, and the question as to whether the term "π–π interaction" makes sense from a theoretical point of view, is the central topic of the work presented herein.

The linear condensed acenes, from benzene (number of rings $n=1$) to tetracene ($n=4$), and the corresponding perhydrogenated ring systems (*all trans–all anti* stereoisomers) were used as models. Homo-dimers of stacked (aromatic with C_i, except for the PD benzene dimer, which has C_{2h} symmetry, and saturated with C_{2h} symmetry) and T-shaped orientation (aromatic only, C_{2v}) are investigated. The T-shaped forms are important in the crystal packing of aromatic molecules, as analyzed in detail by Desiraju and Gavezzotti.[16] For saturated dimers, no well-defined T-shaped structures could be found. Energy-minimized dimer structures for $n=1$ and $n=4$ are shown as an example in Figure 1.

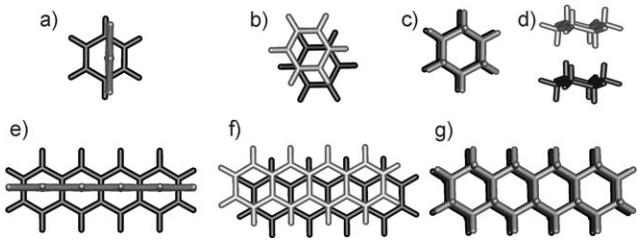

Figure 1. Energy-minimized structures of the benzene dimer: a) T-shaped and b) π–π stacked. c), d) The cyclohexane dimer in two projections. The tetracene dimer: e) T-shaped and f) π–π stacked. g) The octadecahydrotetracene dimer.

In all energy minimizations, a specially designed semilocal density functional with dispersion corrections[17] (B97-D/TZV(2d,2p)) was used, which has been proven to be quite accurate in benchmark studies on many van der Waals complexes.[3,18] For the π–π-stacked complexes, PD orientations that resemble the graphite structure are used, although it is clear that there are a few other possible orientations that are very similar in energy.[4,19] The proper choice of the π–π stacked structure is, however, not expected to have any influence on the final conclusions, and that chosen is best suited for a consistent treatment and convenient analysis of the size dependence. For the stacked saturated complexes, the axial C–H bonds perfectly fit into a CH_2 pocket of the other

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fragment, and other arrangements are energetically unfavorable.

The energy-minimized intermolecular (monomer to monomer center-of-mass) distances R are almost constant in the saturated series (426.2–426.5 pm), whereas they decrease significantly with system size for the aromatic dimers (391.4 [349.4], 383.0 [337.9], 379.4 [333.8], 374.7 [331.4] pm for $n=1$ to 4; interplane distances in brackets). For the T-shaped dimers, even a slight increase from $n=1$ to $n=2$ is found (R values are 491.3, 493.0, 493.5, and 493.4 pm), but for $n=2$–4, the distances are almost constant as in the saturated series. This result indicates that it is not the sheer presence of π orbitals alone that is decisive; the orientation of the monomers also plays an important role.

The intermolecular interaction energies ΔE were computed using the new dispersion corrected double-hybrid density functional B2PLYP-D[20,21] employing the B97-D energy-minimized structures. The B2PLYP-D approach is currently the most accurate quantum chemical method for large systems, reaching in many cases CCSD(T) accuracy, and not only for noncovalent interactions.[21] Total energies from a supermolecular treatment with very large QZV3P atomic orbtital (AO) basis sets are presented in Figure 2 and Table 1. For comparison, (SCS)-MP2[22] wavefunction-based results are also given. They deviate from the DFT results only for the stacked aromatic case (i.e., yielding a more pronounced PSE) but lead qualitatively to the same conclusion; therefore, the B2PLYP-D data are predominantly discussed below.

The B2PLYP-D interaction energies for all three complexes with $n=1$ are very similar (−2.6 to −3.1 kcal mol^{-1}). The ΔE values for the benzene dimers with B2PLYP-D are within 0.1–0.2 kcal mol^{-1} of commonly accepted CCSD(T) or SAPT reference values.[5–7] For naphthalene, ΔE is roughly doubled. The values for the stacked naphthalene dimer (about −7 kcal mol^{-1}) are also in good agreement with estimated CCSD(T) data.[8] The differences between the three binding motifs increase for larger n, but they are still within 10–20% of ΔE for $n=2$, which marks the transition point for the larger stability of the stacked aromatic dimers.

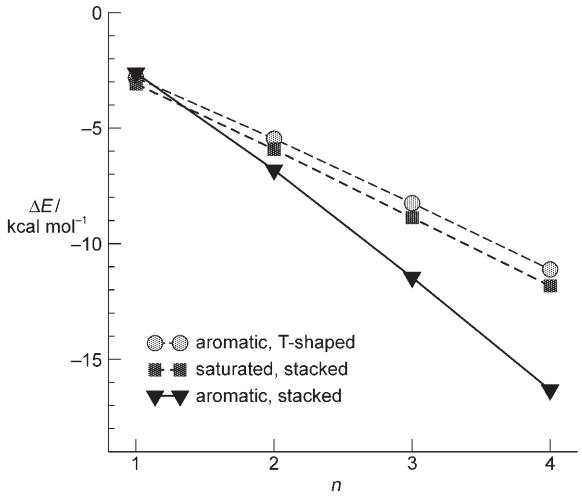

Figure 2. Interaction energies ΔE [B2PLYP-D/QZV3P(1/2CP)] as a function of the number of rings n.

Table 1: Calculated interaction energies $-\Delta E$ [kcal mol^{-1}].[a]

Method	Number of Rings			
	1	2	3	4
	T-shaped, aromatic			
(SCS)-MP2	2.49	4.98	7.70	10.53
B2PLYP-D	2.82	5.46	8.25	11.12
	stacked, saturated			
(SCS)-MP2	2.48	5.02	7.72	10.48
B2PLYP-D	3.09	5.92	8.88	11.83
	stacked, aromatic			
(SCS)-MP2	2.97	7.77	13.15	18.86
B2PLYP-D	2.62	6.81	11.46	16.33

[a] Counterpoise-corrected (1/2CP) single-point energy calculations using B97-D/TZV(2d,2p) energy-minimized geometries and a QZV3P AO basis set. (SCS)-MP2 refers to MP2 for saturated and SCS-MP2[22] for the aromatic systems, which is currently the best wavefunction approach for large van der Waals complexes.[33]

For $n=3$ and $n=4$, stacked arenes are strongly preferred over the saturated structures (by 3–4 kcal mol^{-1} for $n=4$) that have about the same interaction energies as the T-shaped conformations. In Figure 2 it can be clearly seen that the magnitude of the slope of ΔE with system size is very similar for stacked saturated and T-shaped aromatic dimers, but much larger (numerically smaller) for the π-stacked conformations. This is a clear indication for the existence of a PSE.

Only experimental data up to $n=3$ are available for the thermodynamics of phase change.[23] Whereas benzene and cyclohexane ($n=1$) have about the same heat of vaporization (about 8 kcal mol^{-1}), the value for naphthalene is larger than for decalin (17 vs. 12 kcal mol^{-1}). For $n=3$, the heat of sublimation is also larger for the PAHs (23 vs. 17 kcal mol^{-1}). It is not clear how, for example, long-range interactions in the solid or the dynamics in the liquid phase affect these data. Tentatively, these experimental results can be interpreted such that the intermolecular interactions for $n=2$ and $n=3$ are stronger in the unsaturated than in the saturated system. These considerations are in line with the theoretical results for the interaction energies of the isolated dimers, and together with the presented geometrical data support the common view of special interactions in the π–π stacked arrangement. But what are the reasons, and is the π system directly responsible for it?

Concerning noncovalent interactions, the most special property of unsaturated compared to saturated molecules seems to be the quadrupolar shape of the electrostatic (ES) potential of the former, as illustrated for the monomers with $n=2$ in Figure 3. From these plots, a more favorable ES interaction in the saturated systems and ES repulsion from the regions of negative potential above and below the molecular plane for the stacked π systems would be expected. This interpretation, however, is misleading, and the ES potential is not the answer to our question, as demonstrated by an energy decomposition analysis (EDA) of the interaction energies[11,24] (see Table 2 and Figure 4). The ES component indeed favors the saturated systems (although ES components are only lower by 30%), but this component is counterbalanced by the Pauli exchange repulsion (EXR),

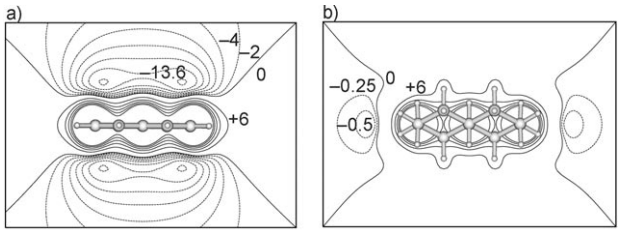

Figure 3. Electrostatic potentials (B97-D/TZV(2d,2p), isosurface values in kcal mol^{-1}) for a) naphthalene and b) decalin.

Table 2: Contributions[a] to the interaction energies (B2PLYP-D/TZV-(2d,p), [kcal mol^{-1}]) from an EDA.[b]

n	E_{EXR}	E_{ES}	E_1	E_{ind}	E_{PT2}^{disp}	$E_{DFT\text{-}D}^{disp}$
T-shaped, aromatic						
1	9.4	−7.8	1.6	−1.0	−1.8	−2.0
2	17.5	−14.1	3.4	−1.8	−3.7	−3.9
3	25.7	−20.4	5.3	−2.6	−5.9	−5.9
4	34.2	−26.9	7.3	−3.4	−8.1	−8.0
stacked, saturated						
1	19.9	−14.7	5.2	−1.5	−2.8	−4.1
2	37.5	−27.5	10.0	−3.0	−5.6	−7.6
3	55.1	−40.3	14.8	−4.6	−8.4	−11.3
4	72.2	−52.8	19.4	−6.1	−11.2	−14.9
stacked, aromatic						
1	12.0	−8.6	3.5	−0.8	−2.9	−2.6
2	27.6	−20.3	7.4	−2.0	−6.9	−5.8
3	44.2	−33.0	11.2	−3.1	−11.2	−9.2
4	62.6	−46.6	16.0	−4.7	−15.9	−12.9

[a] EXR: Pauli exchange repulsion, ES: classical electrostatics, first-order energy: $E_1 = E_{EXR} + E_{ES}$, ind: induction (polarization), disp: dispersion. [b] Counterpoise-uncorrected single-point energy calculations using B97-D/TZV(2d,2p) energy-minimized geometries.

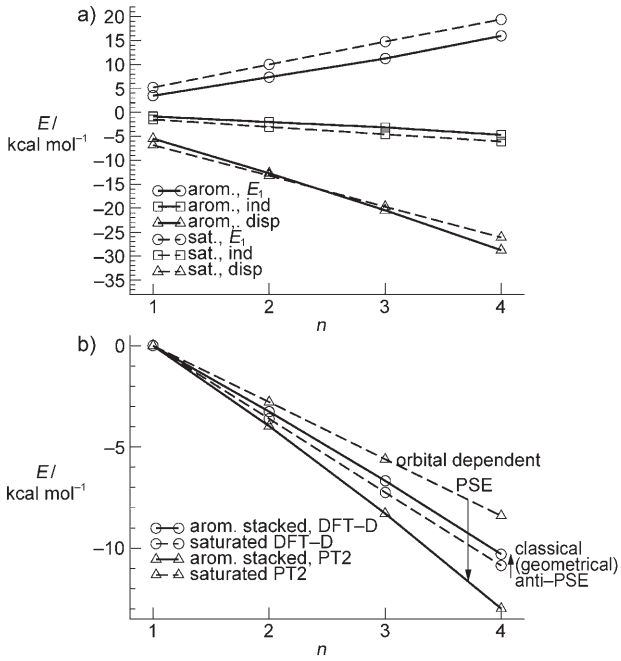

Figure 4. Contributions to the interaction energies (B2PLYP-D/TZV-(2d,p)) from an EDA. a) Total first-order (E_1), induction (ind) and dispersion (disp) contributions. b) Change of orbital-dependent (PT2) and classical (DFT-D) parts of the dispersion energy relative to the cases with $n = 1$, which are set to zero.

which is larger (more positive) for the saturated dimers, owing to the many electron pairs that come close when the saturated rings come together. As a result, the sum of both terms, the first-order interaction energy E_1[25] is in fact slightly smaller (less repulsive) for the aromatic complexes (see also Figure 4). Even more important, however, is the very similar slope of the two E_1 curves, which thus cannot explain the much better binding of the larger aromatic dimers. The same holds for the induction component, which is thus also ruled out as an explanation.

A very important result that can be deduced from Figure 4 is that the increasing stability of the larger π-stacked dimers can be attributed almost exclusively to the dispersion component. In B2PLYP-D, E_{disp} can be further separated into an orbital-dependent part, E_{disp}^{PT2}, and a classical part that comes from the long-range (atom pairwise) R_{AB}^{-6} dispersion correction, $E_{disp}^{DFT\text{-}D}$. These two contributions are shown in Figure 4b, where for convenience the values for $n = 1$ are set to zero. It can be clearly seen that the $E_{disp}^{DFT\text{-}D}$ term, which in this case mainly depends on geometrical parameters (intermolecular distances), cannot account for the PSE: it even yields a small "anti-PSE". The other half of the dispersion contribution results from the orbital-dependent E_{disp}^{PT2} part, and in fact it is this contribution that is predominantly responsible for the PSE. Although E_{disp}^{PT2} is influenced by the decreasing intermolecular distances in the π–π-stacked complexes with increasing number of rings compared to almost constant distances in the saturated dimers, the reason for the PSE must be rooted in special electron correlations in the aromatic system.

Are the effects in the stacked PAH characteristic for the monomers, or is it a result of the π–π stacking? The data for the T-shaped structures seem to be compatible with the second view. To put this important point on a more solid basis, we computed orientationally averaged molecular dispersion coefficients C_6 for an interaction between the same two monomers quantum mechanically for the saturated and for the aromatic monomers (see Figure S1 in the Supporting Information). These values can be used to calculate asymptotically the dispersion energy according to the equation $E_{disp} = -C_6/R^6$. Interestingly, the C_6 coefficients are even slightly larger for the saturated monomers than for the aromatic monomers. This means that for the same large intermolecular distances in the aromatic and saturated complexes, the latter would benefit more from a better dispersion energy, which eventually even leads to an anti-PSE (which is consistent with the analysis of the $E_{disp}^{DFT\text{-}D}$ term; see above).

These findings again point to a specical role of the π system in the stacked orientation. This is further supported by a separation of the electron correlation contribution to the interaction energy into intramolecular and intermolecular σ–σ, σ–π and π–π parts based on (SCS)-MP2 computations using localized molecular orbitals (LMO). This partitioning technique has recently been used to analyze the correlation effects in alkane isomerizations.[26] As expected for van der Waals

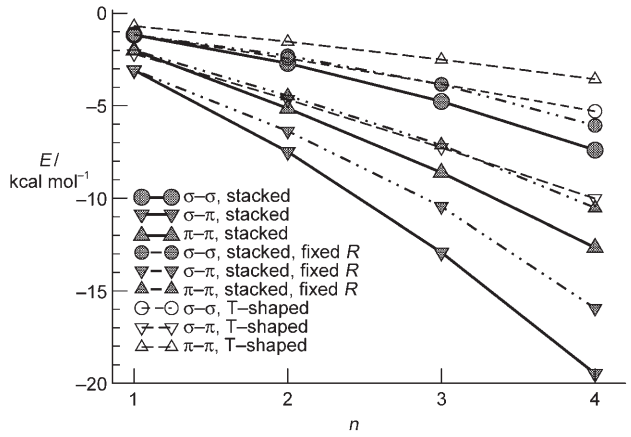

Figure 5. Correlation contributions to the interaction energies (counterpoise-uncorrected SCS-LMP2/TZV(2d,p)) for stacked arenes (——: fully energy-minimized complexes; –•–•: fixed interplane distance of 349 pm) and T-shaped complexes (-----).

complexes, the binding is dominated by the intermolecular correlation energy (the intramolecular part is only about 10% of ΔE in all cases) which is plotted in Figure 5. Evidently both σ–π and π–π contributions distinguish the stacked aromatic orientation from the T-shaped orientation, whereas the σ–σ part is very similar in both.

The nonlinearity of the curves in the stacked case (i.e., increasing attraction per carbon atom) is also present for model complexes with a fixed interplane distance (the value of 349 pm of the benzene dimer), which rules out pure geometrical reasons as an explanation, as already noted above. The PSE can thus be definitely considered as a nonlocal electron correlation effect that only occurs in systems with spatially close-lying π orbitals. This important result also has methodological consequences.[27]

Regarding the question we initially posed, all the results presented above lead to the following general conclusions:

1. The interaction energies of the smaller dimers ($n = 1$–2) are very similar in all three binding motifs studied. Because molecules of similar size, such as stacked nucleobases, are common in chemical or biological systems, caution is required not to overestimate the effect of the π system. Interactions with and between saturated fragments of this size will be similarly strong, and thus also important for structure formation.[28] The stronger interactions for stacked aromatic dimers (the PSE) becomes very significant for more than 10–15 carbon atoms.
2. It is the binding mode (geometrical arrangement of the fragments), and not only the presence of π electrons, that determines the character of the interaction. The aromatic molecules in a T-shaped orientation show a very similar decrease of the interaction energy with system size as the saturated molecules. Also the dependence of the intermolecular distances on system size is similar for T-shaped and for stacked saturated dimers, but is different in the π-stacked mode, for which a substantial shortening is observed for larger values of n.
3. The dominating factor for the PSE is the more favorable dispersion component in the stacked π systems. The electrostatic term acts in the opposite direction, and favors saturated complexes even more. The unfavorable electrostatic effects in the π–π-stacked arrangement are minimized by parallel displacement. As few filled orbitals then overlap, the Pauli exchange repulsion is also quite small, leading overall to an even slightly better first-order interaction energy.
4. According to the results of partitioning the dispersion component to binding, the final answer to the title question is "yes". Special nonlocal electron correlations between the π electrons in the two fragments at small interplane distances are responsible for the PSE. In the aromatic T-shaped complexes, such electron correlations are insignificant because of the larger average distances (about 500 pm). There is also an additional indirect influence of the π system on the PSE through the special shape of the π–π-stacked complexes that allows a closer contact of the monomers (i.e., maximizing the attractive dispersion component) without too much concomitant Pauli exchange repulsion. For geometrical reasons, this is not possible in the analogous arrangement of saturated molecules (or in the T-shaped structures), and thus in these cases interaction components are additive. Because the Pauli exchange repulsion wall in the π-π-stacking mode is softer than in any other intermolecular orientation, the dispersion force can act more freely there towards tighter binding, leading overall to cooperative π effects.

This picture, however, is significantly more complicated than and different from the commonly held view that incorrectly assumes either notable π-orbital overlap or emphasizes electrostatic effects. In summary, we recommend using the term "π–π interactions" in the discussion of noncovalent binding between neutral closed-shell systems with care. For systems with about ten carbon atoms or less, there is little theoretical evidence for a special role of the π orbitals. This view is supported by experimental phase-change data for hydrocarbons, and even extreme cases, such as intramolecular π–π stacking in cyclophanes,[29] fit in. Thus, the term "π-π stacking" should be used as a geometrical descriptor of the interaction mode in unsaturated molecules and to understand π–π interactions as a special type of electron correlation (dispersion) effect that can only act in large unsaturated systems when they are spatially close, which is only possible in the stacked orientation. It is hoped that these results and conclusions lead to a deeper understanding of this important type of noncovalent binding motif, and that it stimulates new experimental investigations, for example, into intramolecular π–π stacking of large PAH fragments, or even "saturated stacking" cases which should be observable already for cyclohexane units.

Methods

The DFT-D and (SCS)-MP2 calculations were performed with slightly modified versions of the TURBOMOLE suite of programs.[30] As AO basis, triple-zeta (TZV) and quadruple-zeta (QZV) sets of Ahlrichs et al.[31] have been employed. The structures were energy-minimized at the RI-B97-D/TZV(2d,2p) level,[17] and subsequent

single-point calculations were performed with B2PLYP-D,[20,21] MP2, and SCS-MP2[22] methods. Further details are given in the Supporting Information.

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[25] One should be careful when interpreting Pauli-exchange repulsion and electrostatic components separately, because they are derived from an nonphysical state of the system that is not antisymmetric with respect to interchange of electron coordinates. This does not hold for E_1, which is thus mainly discussed.

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[27] The dispersion-corrected DFT-D methods without the PT2 part (almost independent of the actual density functional used), although being quite accurate for the absolute interaction energies of the aromatic systems, fail on the correct discrimination of the larger aromatic versus saturated stacked dimers (see Figure 2 in the Supporting Information). However, only small consequences arise for, for example, the computed structures with B97-D that are accurate to within a few pm for the intermolecular distances, even if a somewhat deficient dispersion energy is used. In the conventional DFT-D approach, further improvement can only be achieved by hybridization-specific atomic (i.e., sp^2 vs. sp^3 carbon) C_6 parameters.

[28] One simple reason why stacking of saturated systems is not so frequently observed is that lateral displacement (as for example, forced by the surroundings) leads directly to a strong distortion of the interlocked saturated structure, whereas the aromatic fragments can more easily slide against each other. This effect also leads to unfavorable entropies.

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