Noncovalent Interactions

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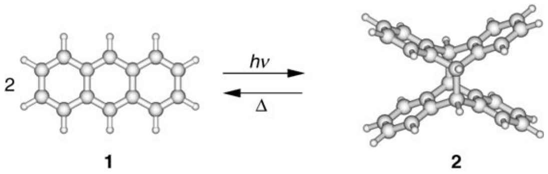
The Importance of Inter- and Intramolecular van der Waals Interactions in Organic Reactions: the Dimerization of Anthracene Revisited**

Stefan Grimme, Christian Diedrich, and Martin Korth*

The van der Waals (also called dispersive) interactions between atoms and molecules play an important role in many chemical systems. They are delicately balanced with electrostatic and exchange/repulsion interactions[1] and together they control, for example, the structures of DNA and proteins, the packing of crystals, the formation of aggregates, host–guest systems, and the orientation of molecules on surfaces or in molecular films.[2] It is generally believed that van der Waals effects are of major importance only for intermolecular situations (for example, weakly bonded complexes), although there are theoretical indications that, for example, protein folding is also significantly influenced by intramolecular van der Waals interactions.[3] It is shown herein for the first time that these effects are also of particular importance for the accurate description of the thermodynamics of "normal" chemical reactions. Furthermore, it will be shown how and why actual implementations of Kohn–Sham density functional theory (DFT)[4] yield a seemingly right answer for the *wrong* reason.

The photodimerization of anthracene (**1**), a clean and reversible reaction that occurs through a [4+4] cycloaddition to yield the covalently bound polycyclic dimer (**2**; Scheme 1), has been known for about 140 years.[5] The dimer is thermally labile at elevated temperatures and reverts back to the monomers, which raised some hopes for its use as a solar energy storage device.

The reaction enthalpy for the dimerization of anthracene has been measured by several methods, under different conditions. 9-Substituted anthracenes have also been investigated (see Ref. [6] and references therein). Experimentally,



Scheme 1.

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[*] Prof. Dr. S. Grimme, Dr. C. Diedrich, M. Korth
Theoretische Organische Chemie
Organisch-Chemisches Institut der Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-33412
E-mail: grimmes@uni-muenster.de

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the dissociation was always found to be exothermic, that is, $\Delta H_D < 0$ for $\mathbf{2} \rightarrow 2 \times \mathbf{1}$. The most reliable experimental data are summarized in Table 1, where for convenience theoretical corrections for thermal and zero-point vibrational contributions (and for substituent effects in the last four cases) have been applied to obtain pure electronic dissociation energies D_e for the parent system. These energies can be better compared with theoretical computations that primarily yield energies instead of enthalpies. The corrected values for the substituted compounds should be considered with some care because of the experimentally relevant electrostatic effects in the condensed phase (see below).

Table 1: Summary of experimental (condensed phase) results [kcal mol^{-1}].[a]

Monomer	Method	ΔH_D	D_e
anthracene	heat of combustion, solid[b]	-13 ± 4	-10
anthracene	DSC, solid/melt (479 K)[c]	-6.9 ± 1.5	-4
9-methoxy-anthracene	heat of combustion, solid[d]	-24	-16
9-decyloxy-anthracene	DSC, tetralin solution (370 K)[e]	-7.1 ± 0.7	$+1$
9-cyanoanthracene	DSC, solid/melt[f]	-20 ± 2	-6
9-decylanthracene	DSC, tetralin solution (392 K)[e]	-6.5 ± 0.7	$+1$
anthracene	average		-6 ± 4

[a] ΔH_D is the reaction enthalpy for dimer dissociation and D_e refers to a pure electronic dissociation energy for the parent system. The ZPVE, thermal, and substituent corrections (in the head-to-tail dimers, the decyl(oxy) group has been replaced by ethyl and methoxy groups, respectively) have been obtained at the DFT-D-PBE/TZV(2d,2p) level. The corrections from E to H are between 2.1 and 2.7 kcal mol^{-1} for the systems considered. [b] Derived from solid-state heats of formation of **1** ($\Delta_f H_s^0 = 30$ kcal mol^{-1-1}) and **2** ($\Delta_f H_s^0 = 73$ kcal mol^{-1}).[8] [c] Differential scanning calorimetry (DSC), Ref. [9]. [d] Ref. [10]. [e] Ref. [6]. [f] Ref. [11].

Although the data show some scatter with relatively large error bars, it is evident that the experimental D_e value for the parent system is negative, probably around -6 kcal mol^{-1} (average) with an estimated uncertainty of ± 4 kcal mol^{-1}.

The reaction was investigated thoroughly by quantum chemical computations in 1999.[6] Quite reasonable agreement with the experimental data was obtained with DFT and Hartree–Fock methods, but even then strikingly different results ($D_e = 20$ kcal mol^{-1}) were obtained from second-order Møller–Plesset (MP2) theory. The better available computer hardware and algorithmic developments in computational quantum chemistry means that it is nowadays possible to push our approximations to the solutions of the electronic Schrödinger equation to a limit, which allows us to resolve this apparent discrepancy. Both **1** and **2** represent quite "normal" organic molecules that lack any apparent complicated electronic structure (for example, biradicalic or extremely unsaturated (metallic) character[12]). Thus, our conclusions have quite important consequences for routine computational modeling studies where similar problems/systems are quite common.

The results of calculated dissociation energies D_e are summarized in Table 2. Systematically improved basis sets up to quadruple-zeta quality (leading to 2140 basis functions for **2**) have been used for the Hartree–Fock (HF) and MP2 methods which allow quite accurate extrapolation to the one-particle basis set limit. One finds from perusing Table 2 that reasonably converged results can be obtained with the cc-pVTZ AO basis. The D_e value at the MP2 basis set limit is estimated to be 20.9 kcal mol^{-1}. Thus, the correlation contribution to the reaction energy is very large (D_e(MP2)$-D_e$(HF) = 42 kcal mol^{-1}), and stabilizing the dimer relative to the two monomers. It is well known, however, that the MP2 method generally overestimates various electron correlation effects,[13] as can be seen from the smaller D_e values at the more reliable QCISD(T) and SCS-MP2 (improved MP2 method, see Ref. [13]) levels. Assuming that MP2 and QCISD(T) have a similar basis set dependence, one can estimate a basis set limit QCISD(T) value of 9.5 kcal mol^{-1} with an estimated uncertainty of about ± 2 kcal mol^{-1}. Strikingly, this value still differs by about 15 kcal mol^{-1} from the experimental value, and even the sign is different (endothermic by theory, exothermic by experiment). This difference prompted us to check the D_e value by an independent, completely different quantum mechanical approach. Diffusion Monte Carlo (DMC) is a stochastic method that allows the electronic Schrödinger equation to be solved directly.[14] Within the fixed-node (FN) approximation, which is necessary to fulfill the Pauli principle, DMC calculations are exact and yield energies including a statistical standard deviation. In our case we get $D_e = 9 \pm 2$ kcal mol^{-1}, which is in perfect agreement with the results from the traditional wave-function methods. We can thus finally state a definite (gas-phase) D_e value that is positive, around 9 kcal mol^{-1}, with a conservative error estimate of ± 3 kcal mol^{-1}.

Table 2: Summary of calculated dissociation energies D_e for the anthracene dimer (**2**).

Method[a]	AO basis	D_e [kcal mol^{-1}]
Hartree–Fock	cc-pVDZ	-15.7
Hartree–Fock	cc-pVTZ	-20.7
Hartree–Fock	cc-pVQZ	-21.1
MP2	cc-pVDZ	24.2
MP2	cc-pVTZ	21.4
MP2	cc-pVQZ	21.0
SCS-MP2	cc-pVTZ	13.4
QCISD	cc-pVDZ	11.9
QCISD(T)	cc-pVDZ	12.7
QCISD(T)	est. cc-pVQZ[b]	9.5
FN-DMC	[c]	9 ± 2
best estimate		9 ± 3
DFT-B3LYP	cc-pVTZ	-25.8
DFT-PBE	TZV(2df,2pd)	-14.5
DFT-D-PBE	TZV(2df,2pd)	-3.7

[a] Single-point calculations using the MP2/TZV(2d,2p) geometry. The effect of full geometry optimization at each theoretical level has been estimated to be ± 1 kcal mol^{-1}. [b] D_e(QCISD(T)/cc-pVDZ) + [D_e(MP2/cc-pVQZ)-D_e(MP2/cc-pVDZ)]. [c] For details see the Methods Section.

We also applied different density functionals to the problem, but found that they all perform in a very similar manner. Representative results with standard functionals (B3LYP[15] and PBE[16]) as well as one with corrections for dispersion interactions (DFT-D[17]), which are notoriously poor with current functionals,[18] are also given in Table 2. If one compares these data with our accurate theoretical reference value one can conclude that standard DFT fails completely, and yields negative D_e values similar to the (uncorrelated) HF method. Particularly striking is the poor performace of the commonly used B3LYP functional that leads to a huge and unacceptable error for D_e of about 35 kcal mol^{-1}. At first sight, however, DFT seems to be in good agreement with experiment (which also yields $D_e < 0$), but as will be shown below this results from error compensation between the neglect of inter- and intramolecular van der Waals interactions in the monomers and dimers, respectively.

The first hint to the problem of the discrepancy between ab initio theory and experiment/DFT comes from the large dispersion correction obtained from the DFT-D method. Part of the answer to the problem is related to the large size of the molecules (especially the dimer), with many interatomic distances close to those of typical van der Waals minima. When used together with the PBE density functional, the long-range (R^{-6}) dispersion correction lowers the energy of the dimer relative to two separated anthracene molecules by about 11 kcal mol^{-1}, thus leading finally to a much smaller D_e value of -3.7 kcal mol^{-1} (similar results have also been obtained at the DFT-D level with other functionals). Clearly (and ultimately quite understandably), there are strong intramolecular van der Waals interactions in **2**. One can already see clearly from the structure that the four outer benzene rings are in a stacked arrangement (C···C distances from 270 to 450 pm) which should add roughly 5–10 kcal mol^{-1} internal stabilization compared to 2 × **1**. These effects are entirely a result of long-range electron correlation, and are absent in Hartree–Fock and standard DFT, which calculate that the dimer is too unstable ($D_e < 0$). In contrast, all the correlated ab initio methods (SCS-MP2, QCISD(T), FN-DMC) accurately include long-range electron correlation and yield $D_e > 0$.[19]

However, what about the intermolecular van der Waals interactions mentioned in the title? They are of utmost importance under the experimental conditions, namely, in the condensed phase, for which we consider the following model (Figure 1): the first product of the dissociation of **2** is of course not two infinitely separated anthracene molecules (as hitherto considered in the calculations) but rather a van der Waals complex (**3**) that may later dissociate. Since the complex **3** and **2** have about the same spatial dimensions (surfaces), their solvation enthalpy is roughly the same, and thus need not to be considered further. A simple and computationally straightforward condensed-phase correction to the calculated (separated, gas-phase) D_e value is thus the van der Waals dimer binding energy of the stacked complex (**3**; Figures 1 and 2).

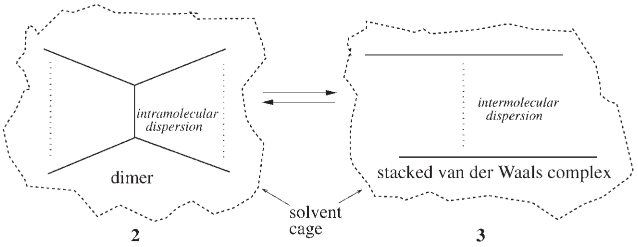

Figure 1. Model for the dimerization of anthracene in the condensed phase.

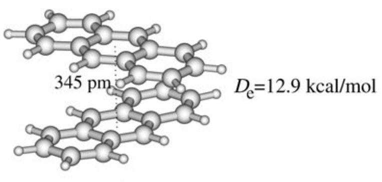

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Figure 2. Crossed (D_{2d}) structure (**3**) of the van der Waals complex of two anthracene molecules. The structure has been optimized at the DFT-D-BLYP/TZV(2d,2p) level, while the interaction energy refers to counterpoise-corrected, single-point SCS-MP2/aug-cc-pVTZ computations. Only slightly higher in energy (about 0.2 kcal mol^{-1}) is a displaced, graphite-like structure with C_i symmetry (not shown).

At the very reliable SCS-MP2/aug-cc-pVTZ level (estimated error ±2 kcal mol^{-1}) we obtain a quite substantial binding energy of 12.9 kcal mol^{-1} for **3**. This result means that when combined with the previous (separated, gas-phase) D_e value of 9 ± 3 kcal mol^{-1} we obtain 2 × **1** as the van der Waals complex that is energetically now *below* **2** (that is, $D_e^{\text{corrected}} = -4 \pm 3$ kcal mol^{-1}). This value is (within the error bars) in reasonable agreement with the experimental findings (exergonic dissociation). The model (which is summarized in Figure 3) is supported by the results of calculations performed for the hydrogenation of **1**. This reaction leads to 9,10-dihydroanthracene, which is electronically similar to **2** (that is, has a saturated inner ring and two outer benzene rings) but lacks the intramolecular dispersion interactions. In this case, all applied theoretical methods are in much better agreement with each other and are also close to the experimental value.[20]

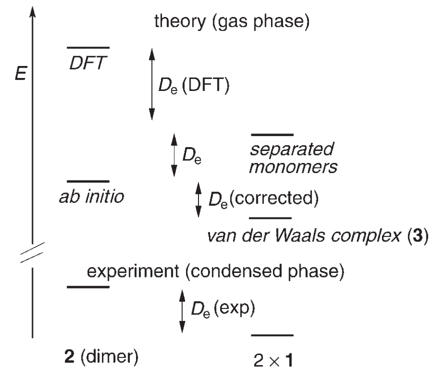

Figure 3. Model to explain the difference between experiment and theory.

It is now clear why the DFT approaches seemingly give the right answer when compared to the experimental results: the neglected intermolecular (monomers) and intramolecular (dimer) van der Waals effects are both of the same magnitude, appear on either side of the reaction equation, and thus their effects fortunately cancel. Note, that our arguments also hold for the data derived from, for example, heats of combustion experiments in the solid state (entry 1, Table 1), where one should consider the lattice energies of the reactants as a correction.[21]

In summary, the results of our studies have two major consequences. First, we encourage experimental chemists to conduct gas-phase experiments (or accurate (gas-phase) heat of formation determinations for **2**) to check our theoretical results. We are, however, very sure that our (gas-phase, $R=\infty$) value of $D_e = 9 \pm 3$ kcal mol^{-1} is correct and thus suggest this system as an important benchmark for approximate quantum chemical methods, including dispersion (especially new density functionals). Secondly, we believe that a delicate balance between inter- and intramolecular dispersion effects is a quite general phenomenon for larger molecules that must be considered more carefully in the future. These often so-called "weak interactions" are intuitively underestimated by most chemists,[22] but may sum up to significant effects even in medium-sized molecules. Another good example is the photodimer of C_{60}, where intramolecular dispersion apparently also leads to a change in the sign of D_e.[23]

Methods Section

The (SCS-)MP2 and DFT calculations were performed with the TURBOMOLE suite of programs,[24] and the RICC code developed in our laboratory was used for the QCISD/QCISD(T) treatments. The triple-zeta sets of Ahlrichs and co-workers (TZV[25]) or the correlation consistent sets of Dunning (cc-pVXZ, X = D, T, Q[26]) were employed as the AO basis. In the (SCS-)MP2 and QCISD/QCISD(T) treatments the RI approximation for the two-electron integrals were used.[27] The geometries of **1** and **2** were optimized at the MP2/TZV(2d,2p) level, while the structure of **3** refers to a DFT-D-BLYP/TZV(2d,2p) calculation.[17] Corrections from enthalpies to energies and the substituent effects were obtained from harmonic frequency calculations at the DFT-D-PBE/TZV(2d,2p) level.

FN-DMC calculations were carried out with Amolqc, a QMC program by Lüchow et al.[28] We used guiding functions of the Slater–Jastrow type, with a B3LYP Kohn–Sham determinant and a Schmidt–Moskowitz type correlation function; Kohn–Sham determinants have proven their usefulness for FNDMC in the past.[29,30] Correlation parameters were optimized by variance minimization. To further improve the efficiency of the calculations, we used soft-ECPs developed by Lester and co-workers[31] for carbon atoms. The error introduced by the ECPs (core-valence polarization) was estimated at the Hartree–Fock level to be about 0.4 kcal mol^{-1} for D_e. The orbitals were expanded in GTO triple-ζ valence basis sets. For carbon atoms, they were fully optimized in atomic Hartree–Fock calculations with the ECPs and were augmented by 2d polarization functions from the Dunning cc-pVTZ basis set. For hydrogen atoms we used an optimized triple-ζ basis (contracted from a 611 primitive) set with 2p and 1d polarization functions also taken from the cc-pVTZ basis. The time-step dependence of the results was checked by performing calculations with steps of 0.005 E_h^{-1} and 0.003 E_h^{-1}, respectively, which yielded differences <1 kcal mol^{-1} for D_e.

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[19] There is an additional correlation effect arising from the formal conversion of four π electrons in **1** into two σ bonds in **2** which is also not accounted for accurately by DFT.

[20] The experimental dissociation energy for 9,10-dihydroanthracene→**1**+H_2 (derived from experimental heats of formation[7] and vibrational DFT-PBE corrections) is 23 ± 2 kcal mol^{-1}. At MP2/cc-pVTZ, SCS-MP2/cc-pVTZ, QCISD(T)/cc-pVDZ, PBE/cc-pVTZ, and B3LYP/cc-pVTZ theoretical levels (MP2/TZV(2d,2p) geometry) one obtains 21.0, 21.2, 23.5, 17.9, and 16.2 kcal mol^{-1}, respectively.

[21] The lattice enthalpy of **1** (the difference in heats of formation in the gas phase and the solid state) is 25 kcal mol^{-1}.[7] If we assume the same value for **2** we can estimate its gas-phase heat of formation to be 98 kcal mol^{-1}, which leads to an experimental estimate for ΔH_D of about 12 kcal mol^{-1}. The thus obtained endothermicity of the dissociation is in full agreement with our theoretical results.

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