

IRTG-Seminar: Non-covalent Interactions

Stefan Grimme
Theoretische Organische Chemie
Universität Münster

13/14. 8. 2008

Introduction and Theory

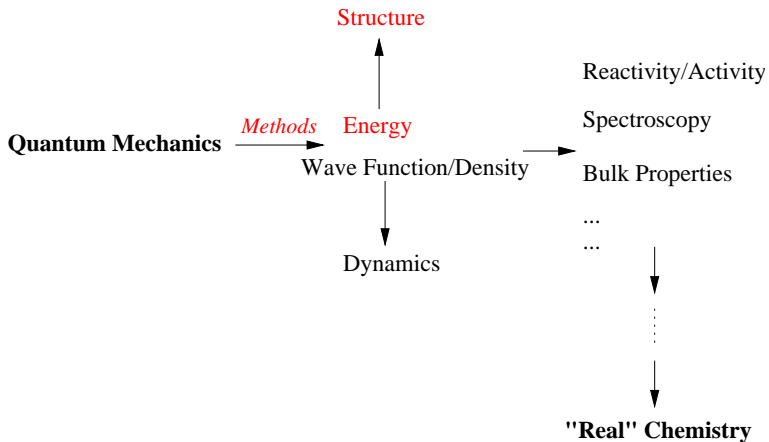
Dispersion Correction (DFT-D)

Van der Waals complexes

Conformations and Folding (Intramolecular Cases)

Supramolecular Structures

What it is all about



Noncovalent Interactions are Important

in many areas of Physics, Chemistry and Biology, e.g.

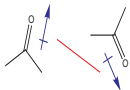
- ▶ Formation of condensed phases (gas→fluid→solid)
- ▶ Aggregation of molecules to clusters
- ▶ Supramolecular Chemistry
- ▶ Protein structure and folding
- ▶ DNA/RNA structure and mechanism
- ▶ Drug-receptor binding
- ▶ ...

Molecular Interactions

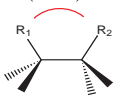
covalent – ionic
"strong"

non-covalent
"weak"

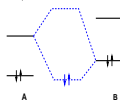
electrostatic
(induction)



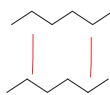
exchange–repulsion
(Pauli)



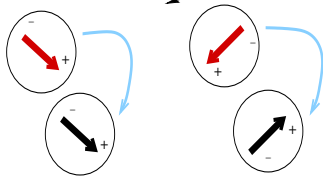
Charge–Transfer
(orbital inter.)



dispersion
(van der Waals)



→ correlated electronic
wave function



Weak? Typical Dissociation (-Interaction) Energies (kcal/mol)

(Ne) ₂	0.1
(CH ₄) ₂	0.5
(Xe) ₂	0.6
(benzene) ₂	2.8
(NH ₃) ₂	3.1
(H ₂ O) ₂	5.0
(HCOOH) ₂	16
G-C bas pair (WC)	28
C ₆₀ @C ₂₄₀	180

The typical distance regime (inter-atomic or center-of-mass) is

250–600 pm

for neutral fragments

Contributions and Distance Dependence

1. Dispersion (van der Waals without repulsive part)



$$E \propto -\frac{C^6}{R^6} - \frac{C^8}{R^8} - \frac{C^{10}}{R^{10}}$$

- ▶ medium (long-range)
- ▶ always present, not very system-dependent

2. Electrostatics

- ▶ short to very long-range
- ▶ very system-dependent

3. Induction (polarization)

- ▶ medium to long range
- ▶ system-dependent

4. Pauli-Exchange Repulsion

- ▶ short-range
- ▶ always present, not very system-dependent

5. Charge-Transfer und orbital-interactions

- ▶ short-range
- ▶ system-dependent, not well-defined

Electrostatics (ES)

Interaction of the unperturbed charge distributions (ρ and nuclei) on A and B:

$$\Delta E = \sum \sum \frac{Z_A Z_B}{R_{AB}} + \int \int \frac{\rho_A(r_1) \rho_B(r_2)}{r_{12}} dr_1 dr_2 - \int \frac{Z_A \rho_B(r_1)}{r_{1A}} dr_1 - \int \frac{Z_B \rho_A(r_1)}{r_{1B}} dr_1$$

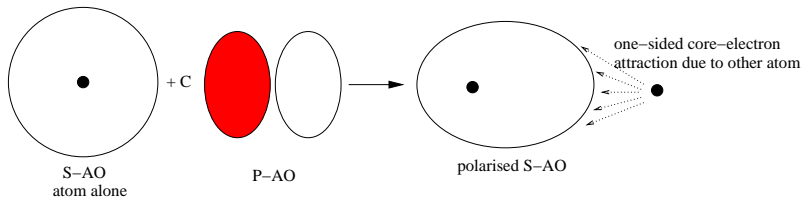
- ▶ almost always attractive
- ▶ multipole-expansion
 - ▶ charge-charge $\frac{1}{R^1}$
 - ▶ charge-dipole $\frac{1}{R^2}$
 - ▶ charge-quadrupole $\frac{1}{R^3}$
 - ▶ dipole-dipole $\frac{1}{R^3}$
 - ▶ dipole-quadrupole $\frac{1}{R^4}$
 - ▶ ...

Induction (Ind)

- ▶ proportional to polarizability α of A and multipole-moment of B
- ▶ $\alpha = \frac{\partial^2 E}{\partial F_{xyz} \partial F'_{xyz}}$
- ▶ requires change of WF (density) of one component (second-order effect)
- ▶ e.g. interaction of a point-charge with the induced dipole moment in a H-Atom

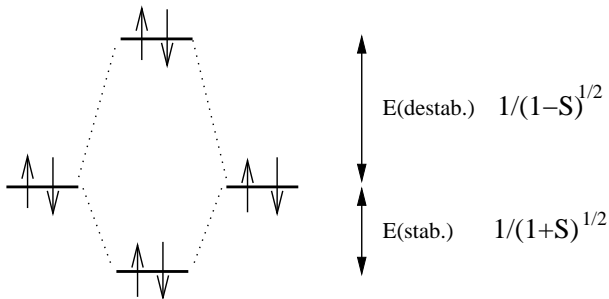
$$\Delta E = -\frac{\alpha}{2R^4}$$

Requires mixing of valence with higher angular momentum functions:

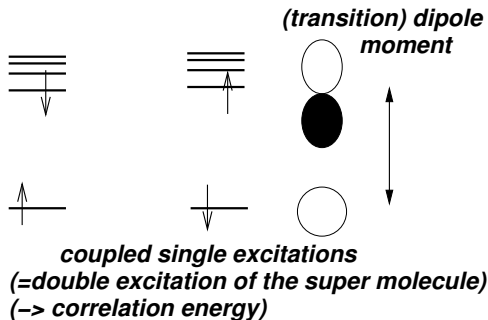


Pauli-Exchange Repulsion (EXR)

- ▶ electrons with same spin can not be at the same position in space (Fermi-hole)
- ▶ these electrons have an *additional* (independent of charge) repulsion
- ▶ it is proportional to the orbital overlap S
- ▶ four-electron (e.g. He_2) model:



London-Dispersion Interactions (disp)



- ▶ many particle effect originating from correlated electron "movements" ("fluctuations")
- ▶ time-independent phenomenon
- ▶ present in *any* many-electron system even if electron-densities are *not* overlapping
- ▶ not accounted for by simple MO theories (e.g. Hartree-Fock and standard KS-DFT)

Symmetry Adapted Perturbation Theory (SAPT)

See e.g.:

R. Podesszwa, R. Bukowski, R., K. Szalewicz J. Phys. Chem. A, 2006, 110, 10345.

A. Heßelmann, G. Jansen and M. Schütz J. Chem. Phys., 2005, 122, 014103.

The word *symmetry* refers to the Fermionic-anti-symmetry of the WF

Partitioning:

$$\hat{H} = \hat{H}(A) + \hat{H}(B) + \hat{V}(AB)$$

Interaction energy:

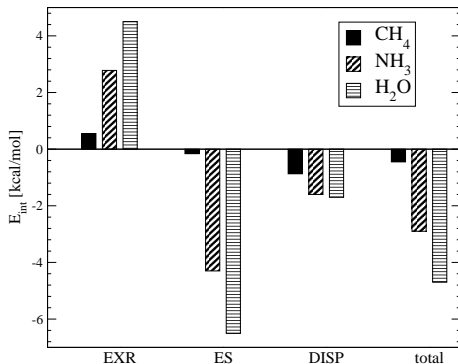
$$\Delta E_{int,AB} = E_{es}^{(1)} + E_{exr}^{(1)} + E_{ind}^{(2)} + E_{exr-ind}^{(2)} + E_{disp}^{(2)} + E_{exr-disp}^{(2)}$$

Condensed to:

$$\Delta E_{int,AB} = E_{exr} + E_{es} + E_{disp}$$

Example: $(\text{CH}_4)_2$, $(\text{NH}_3)_2$, $(\text{H}_2\text{O})_2$

RI-SAPT-DFT(PBE0)/aug-cc-pVTZ at r_e



→ transition from typical vdW complex to a conventional hydrogen-bond

→ even hydrogen-bonded systems benefit significantly from dispersion

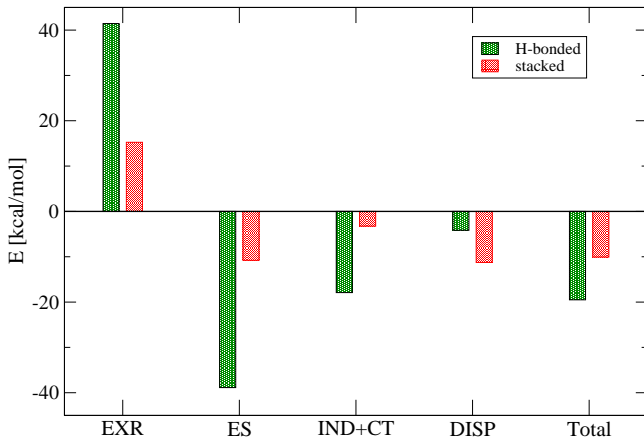
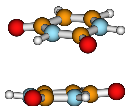
Energy Decomposition Analysis (DFT-D)

urcail dimer

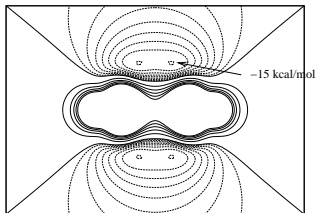
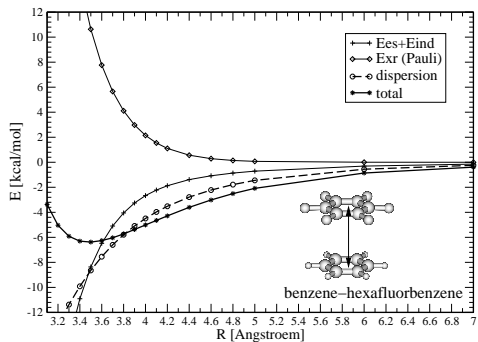
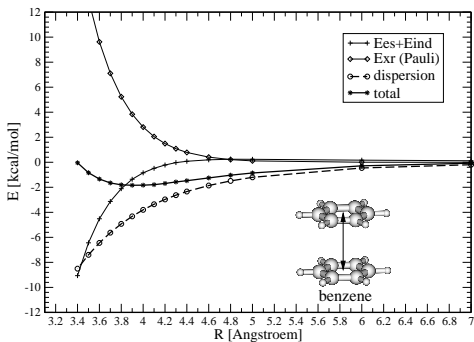
hydrogen bonded (in-plane)



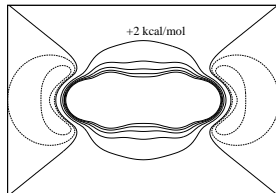
stacked



Energy Decomposition Analysis Distance dependent

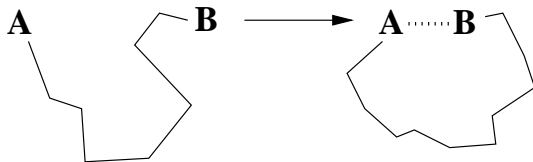
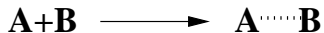


electrostatic potential of benzene



electrostatic potential of hexafluorbenzene

Inter- vs. Intra-Molecular Interactions



- ▶ methods should treat both cases on an equal footing
- ▶ intramolecular case important for biomolecules (e.g. protein-folding)

Solvent and Other Effects

Experiment: $\Delta G(\text{solv})$

Computed: $\Delta E(\text{gas})$

typically $\Delta G(\text{gas}) \ll \Delta G(\text{solv})$

$$\Delta G \approx \Delta H$$

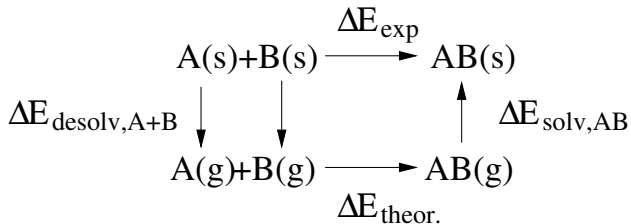
$$\Delta H = \Delta E + \Delta ZPVE + \textit{thermal}(298K)\textit{contributions}$$

$\Delta ZPVE > 0$ (because new internal degrees of freedom are created)
and thus

$$\Delta H > \Delta E$$

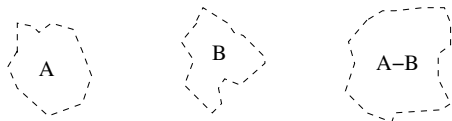
For $(\text{H}_2\text{O})_2$, $\Delta E = -5$ kcal/mol and $\Delta ZPVE \approx 1.2$ kcal/mol

Solvent and Other Effects



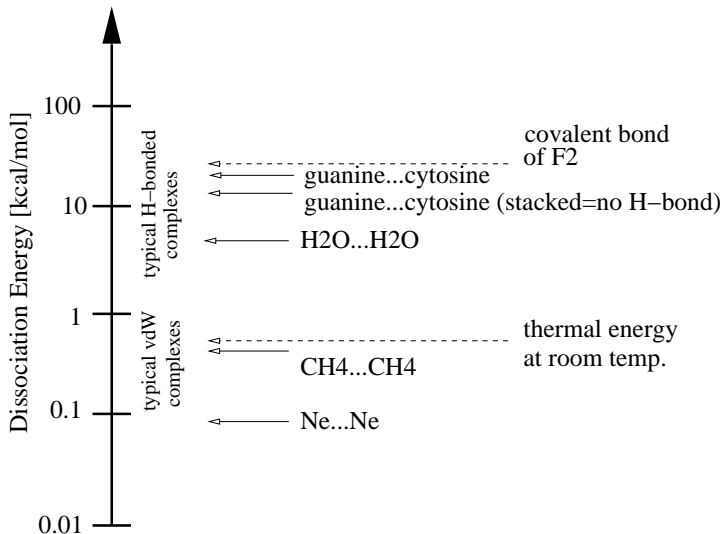
$$\Delta E(s)_{\text{exp}} > \Delta E(g)_{\text{theor.}}$$

$$\text{Reason: } |\Delta E_{\text{desolv,A+B}}| > |\Delta E_{\text{solv,AB}}|$$



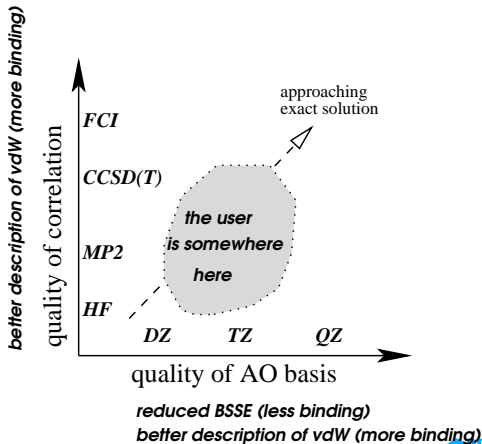
solvent accessible surface of $A+B > A-B$

General Aspects



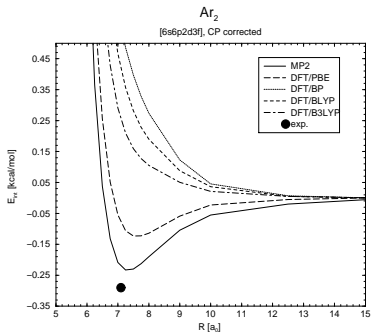
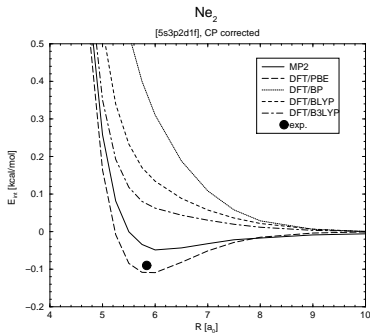
General Methodological Problems

- ▶ weak on a pair-wise basis (but: many small effects may add up!)
- ▶ contributions of different sign
- ▶ error compensation problematic (very system dependent)
- ▶ numerical artefacts
- ▶ basis set truncation

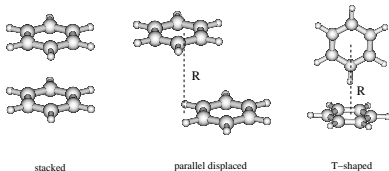


Methods

- ▶ simple MO theory (semiempirical methods, Hartree-Fock, standard DFT) not possible because of lack of dispersion
- ▶ correlated WF-theory (e.g. CCSD(T)) with large basis sets is OK but too costly for large systems
- ▶ force-fields are OK but often too inaccurate (the main problem is ES and ind) and not generally applicable
- ▶ the current standard for large systems is dispersion corrected DFT (called DFT-D)



The benzene dimer: a difficult but quite realistic test



	PD		T	
	R	$-\Delta E$	R	$-\Delta E$
exp.	–	–	496	2.0-2.8
est. CCSD(T) ^a	360	2.8	500	2.8
SCS-MP2/aug-cc-pVTZ	355	2.5	490	2.3
MP2/aug-cc-pVTZ	340	4.7	480	3.5
DFT-B3LYP	not bound			
DFT-B97-D/TZVPP	352	2.8	492	3.0

in pm and kcal/mol. ^a M. O. Sinnokrot and C. D. Sherrill, JPC A, 108 (2004) 10200.

Empirical dispersion correction (DFT-D)

Originally for HF: Scholes et al. Chem. Phys. Lett., 36 (1975) 451.

Tight-binding DFT: Elstner et al., J. Chem. Phys. 114, 2001, 5149

Generalization: SG, J. Comput. Chem. 25 (2004) 1463, ibid. 27 (2006) 1787.

$$E_{DFT-D} = E_{DFT} + E_{disp}$$

Dispersion term:

$$E_{disp} = -s_6 \sum_{i=1}^{N_{at}-1} \sum_{j=i+1}^{N_{at}} \frac{C_6^{ij}}{R_{ij}^6} f_{dmp}(R_{ij})$$

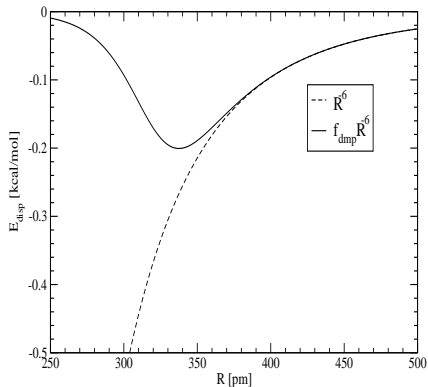
Damping function and composing rule:

$$f_{dmp}(R) = \frac{1}{1 + e^{-\alpha(R/R_0-1)}} \quad C_6^{ij} = \sqrt{C_6^i C_6^j}$$

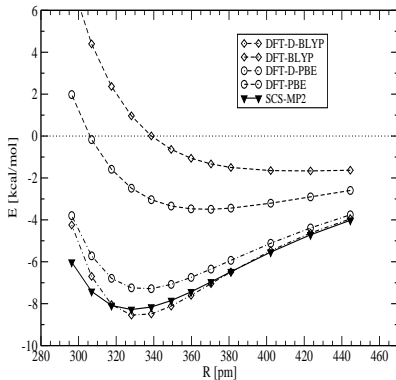
- ▶ Functional dependence accounted for by scaling factor s_6 (B2PLYP: 0.55, PBE: 0.75, BLYP: 1.2)
- ▶ Atomic cut-off radius R_0 at 0.01 a.u. electron density contour
- ▶ Atomic C_6^i parameters for H-Xe available

Damping and Scaling in DFT-D

DFT-D potential for two C-atoms ($s_6 = 1$)



(cytosine)₂ potential curves



Non covalently bound systems: Hobza's S22 test set

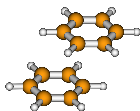
22 complexes, mean D_e of 9 kcal/mol, range: 0.5–21 kcal/mol

- ▶ hydrogen-bridged complexes



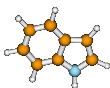
(A-T Watson-Crick)

- ▶ dispersion-dominated complexes

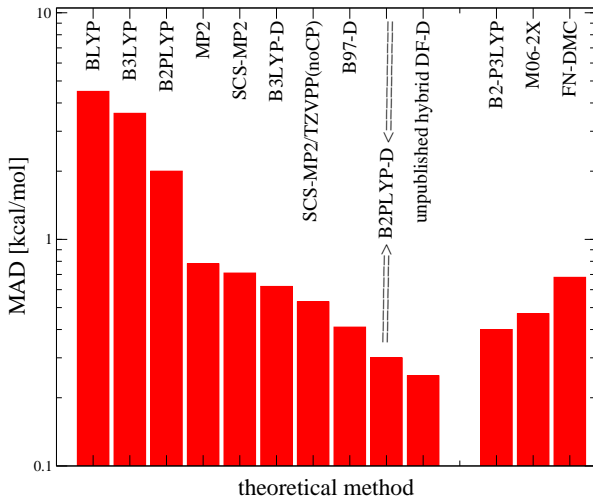


(parallel displaced benzene dimer)

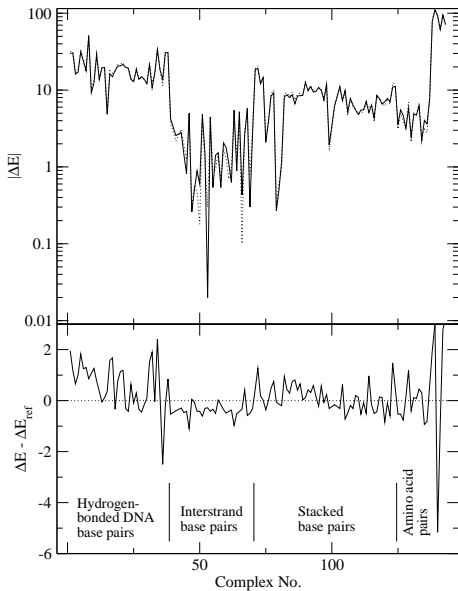
- ▶ mixed-type complexes



(indole-benzene complex)



DFT-D (B97-D/TZVPP) Benchmarks for Biomolecular Complexes



Set and reference data (est. CCSD(T)/CBS) taken from: P. Jurecka, J. Sponer, J. Cerny, and P. Hobza, PCCP, 2006, 8, 1985.

MAD (**143** entries):

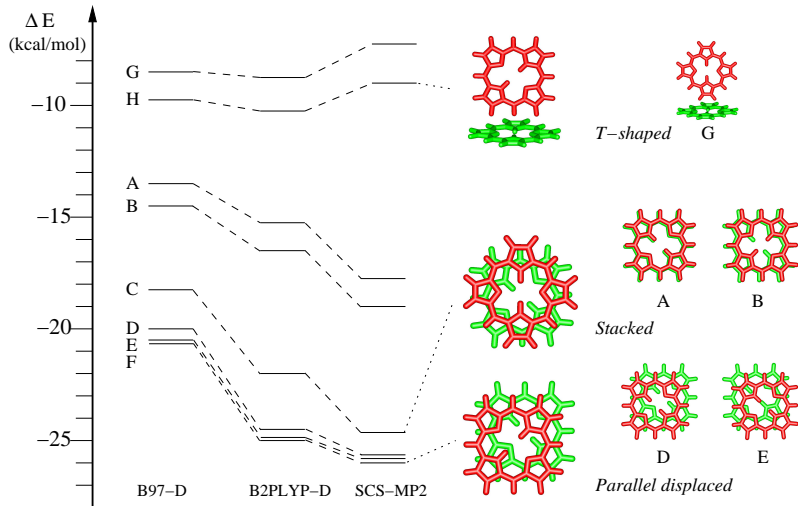
0.5-0.6 kcal/mol (BLYP-D, B97-D)

typical error 5% of ΔE

J. Antony and SG, PCCP, 8 (2006) 5287

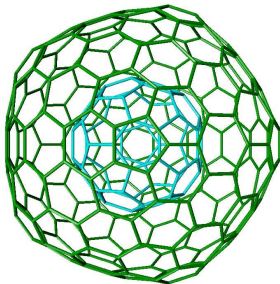
A large vdW complex: the porphine dimer

C. Mück-Lichtenfeld and SG, Mol. Phys. 105, (2007), 2793.



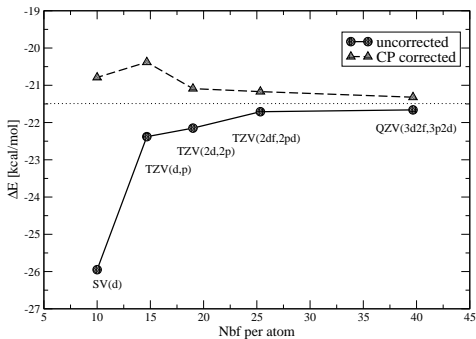
Even Larger: Multi-shell(hyper) Fullerenes, Fullerene Complexes and Graphite

- ▶ Stacking of very large π -systems, accuracy of DFT-D with system-independent C_6 ?
- ▶ Interaction energies for two sheets of graphite not accurately known (exp.: -35 ± 15 meV/atom, -43 meV/atom, -55 ± 5 meV/atom)
- ▶ Also for hyperfullerenes, only empirical or LDA data have been reported

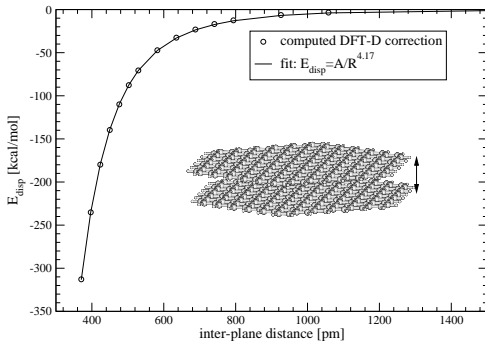


Some Technical Tests

basis set convergence for coronene dimer

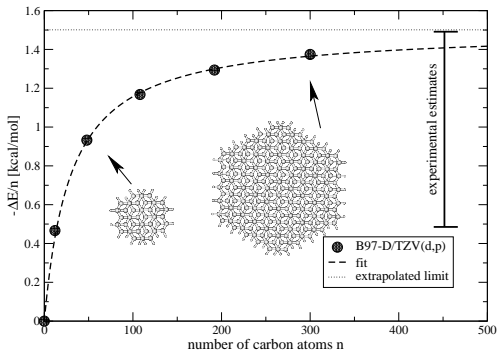


distance dependence of dispersion energy



Results for Graphene/Graphite

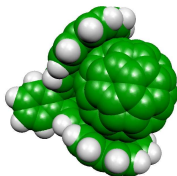
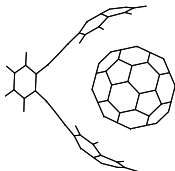
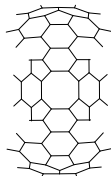
J. Phys. Chem. C 111, (2007), 11199



method	$(C_{150}H_{30})_2$ kcal mol $^{-1}$	$C_{60}@C_{240}$ kcal mol $^{-1}$	graphite meV/atom
B97-D	-206	-184	-66
LDA	-110	-92	-32
PBE	35	1	—
BLYP	109	51	—

A Bucky-Catcher

Experiments: Sygula et al., JACS 129 (2007) 3842.

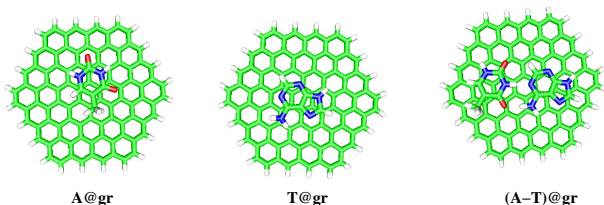


Shortest inter-molecular CC distance:	3.13 Å (exp., disordered) 3.08 Å (B97-D/TZV(2d,p))
Complexation energy	-42 kcal mol ⁻¹ (B97-D/TZV(2d,p)) (66% of graphene sheet)
Fragment deformation energies	2 kcal mol ⁻¹

NA-base-graphene stacking interactions and cooperativity

J. Antony & SG, PCCP in press.

- ▶ Stacking energies on graphene (base1@gr, base2@gr)
- ▶ Hydrogen bond energies of WC pairs (base1-base2)



Results:

- ▶ short inter-plane distances (2.9-3.0 Å)
- ▶ $\Delta E(A@gr) = -20.6$, $\Delta E(T@gr) = -19.9$,
 $\Delta E(C@gr) = -19.2$, $\Delta E(G@gr) = -26.3$
free base-pairs: $\Delta E(A - T) = -17.7$, $\Delta E(G - C) = -32.3$
- ▶ small anti-cooperativities (5-10%)

Are special non-covalent $\pi - \pi$ stacking interactions really existing?

and if yes, what are the reasons?

SG, Angew. Chem. Int. Ed., 47 (2008) 3430-3434.

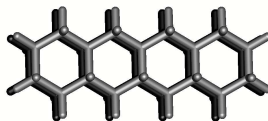
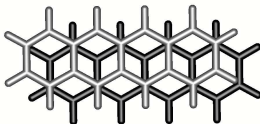
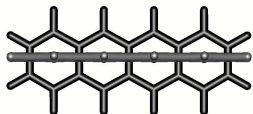
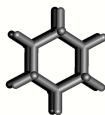
- ▶ Benzene and cyclohexane are fluid at RT (both $\Delta H_{vap} \approx 8$ kcal/mol)
- ▶ Interaction energy (CCSD(T)) of benzene dimer (-2.8 kcal/mol) smaller(!) than that of pentane dimer (-3.9 kcal/mol)
- ▶ C_6 dispersion coefficients very similar for PAH and alkanes
- ▶ But: large PAH are almost unsoluble in normal organic solvents (opposed to large alkanes)

Model systems

Linear acenes (benzene, naphthalene, anthracene tetracene),
 π -stacked and T-shaped

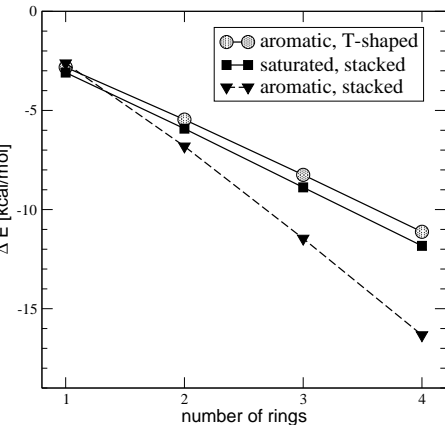
vs.

perhydrogenated acenes (cyclohexane, decaline, ...), stacked



Yes, there is a $\pi - \pi$ stacking effect!

B2PLYP-D/QZV(3d2f,2p1d)//B97-D/TZ2P

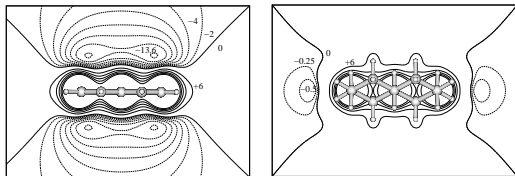


but it is not very significant for the systems for which it is typically discussed!

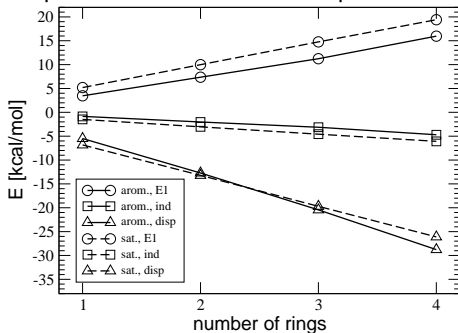
π -systems in T-shaped orientation behave like saturated dimers!

Analysis I

- ▶ no significant π -orbital overlap
- ▶ ES effects favor saturated complexes

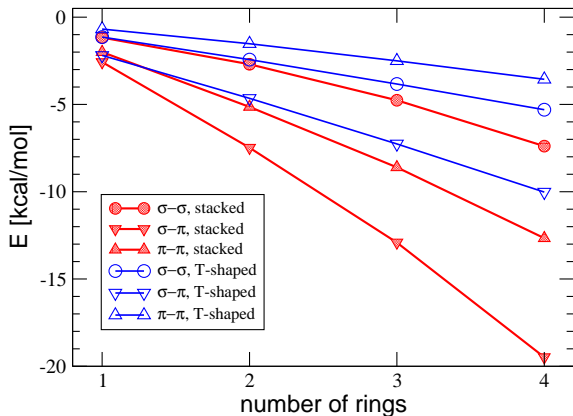


- ▶ Dispersion interactions are important



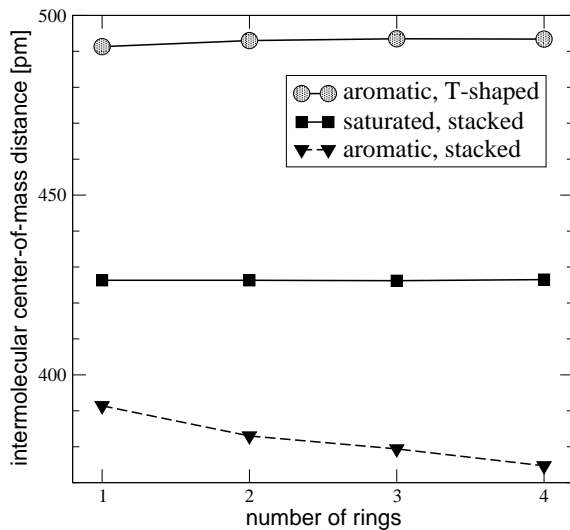
Analysis II

Decomposition into orbital pair correlation energies (SCS-LMP2/TZV(2d,p))
aromatic stacked vs. T-shaped dimers:



Analysis III

Structures



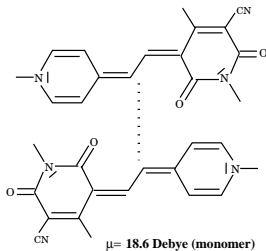
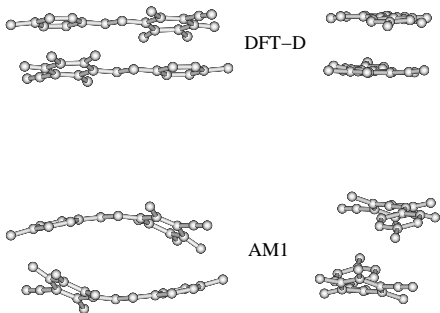
$\pi - \pi$ stacking interactions: Conclusions

- ▶ the term makes sense only for *large* systems
- ▶ depends on the orientation and not only on the presence of π -electrons
- ▶ non-local (orbital-dependent) dispersion effect
- ▶ cooperativity of 'softer' Pauli-exchange repulsion wall and
- ▶ stronger intermolecular $\pi - \pi$ and $\sigma - \pi$ electron correlations in the stacked orientation
- ▶ different behavior of aromatic and saturated systems not accounted for by simple DFT-D treatment

Structures: Dimers of Polar Dyes

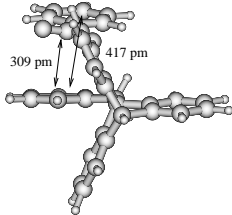
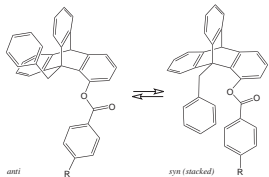
exp.: Würthner et al. JACS 126 (2004) 8336.

first ECD related work on dimeric dyes: T. Mori, Y. Inoue, SG, JOC 71 (2006) 9797.

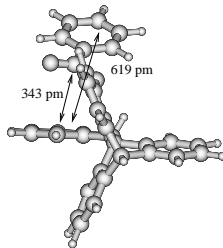


Structures: π -Stacking in Triptycene Derivatives

exp. Reich et al. J. Org. Chem. 70 (2005) 3641



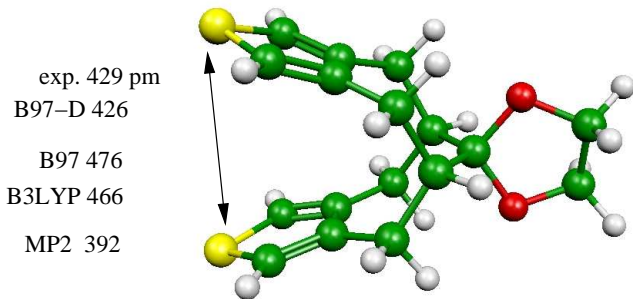
DFT-D



DFT without D-correction

Structures: π -Stacking in Bicyclic Bis-thiophenes

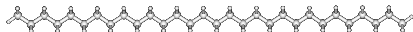
exp. Collard et al. JACS, 128 (2006) 13680



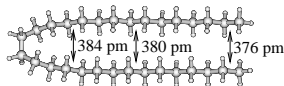
TZV(2d,2p) AO basis

A Simple Model of Folding

SG, J. Antony, T. Schwabe, C. Mück-Lichtenfeld, *Org. Biomol. Chem.* 5 (2007) 741 .



linear



folded

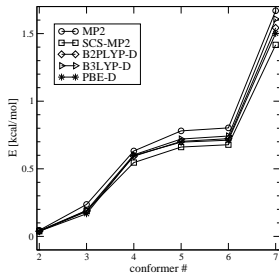
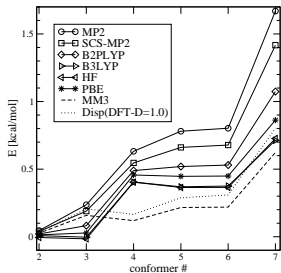
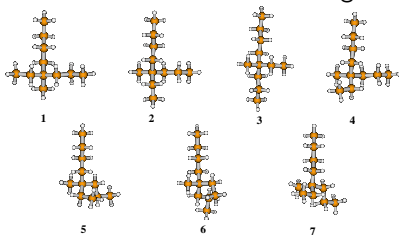
Energy difference^a between linear and folded forms

method	$\Delta E_{LF} (kcal/mol)$		
	C ₁₄ H ₃₀	C ₂₂ H ₄₆	C ₃₀ H ₆₂
HF ^b	-8.9	-23.8	-30.6
BLYP ^b	-6.9	-16.5	-20.8
B3LYP ^c	-7.5	-18.0	-22.9
BLYP-D ^b	-1.4	6.8	12.7
B2PYLP-D ^b	-2.6	3.4	8.2
MP2 ^c	-2.2	3.6	8.8

^a BLYP-D/TZV(d,p) optimized. ^b TZVP(2df,2pd). ^c aug-cc-pVTZ.

Alkane Conformational Energies

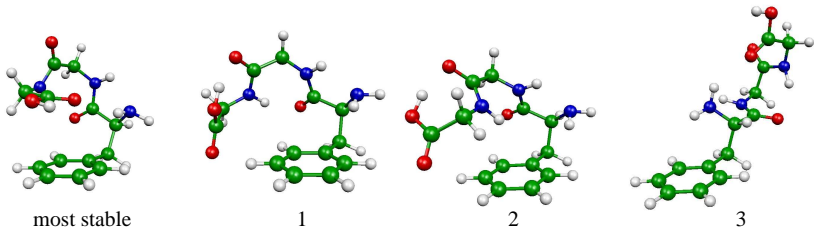
The smallest chiral alkane with a stereogenic center



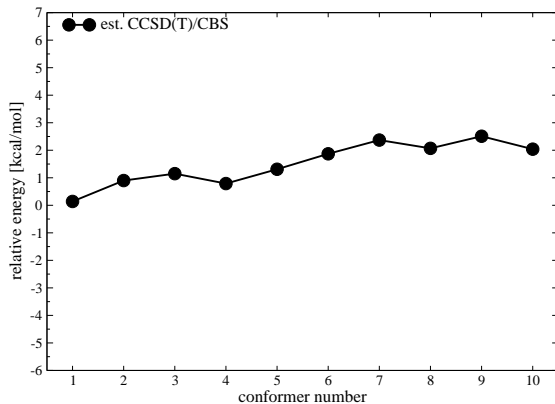
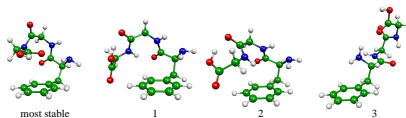
Tripeptide Conformational Energies

T. Schwabe and SG, PCCP, 9 (2007) 3397

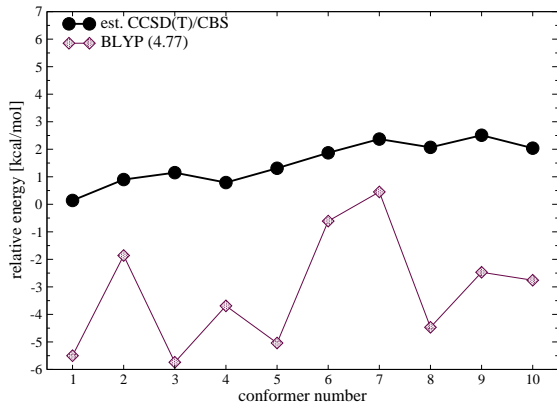
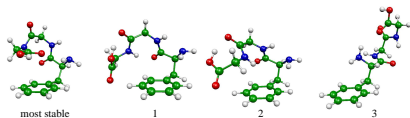
Phenylalanyl-glycyl-glycine benchmark taken from: Hobza et al., Chem. Eur. J. 11 (2005) 6803



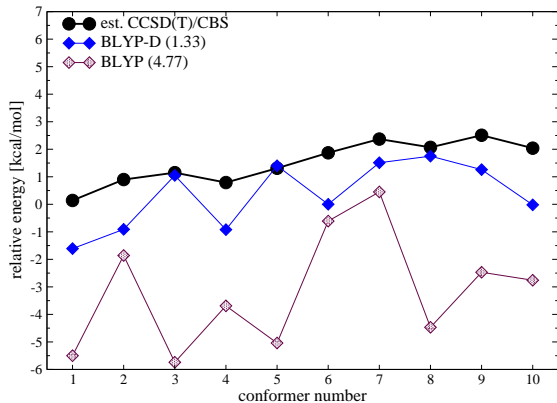
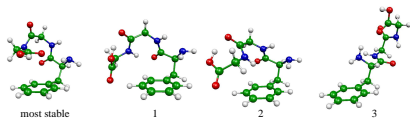
Tripeptide Conformational Energies



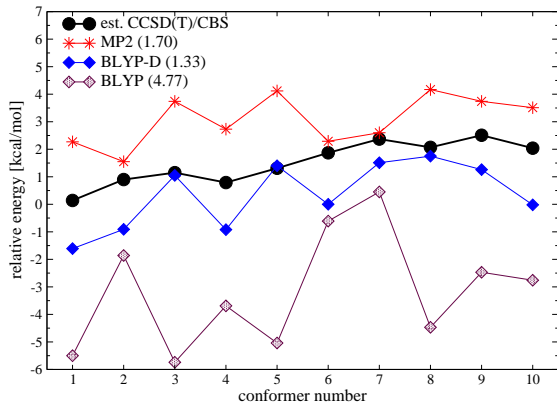
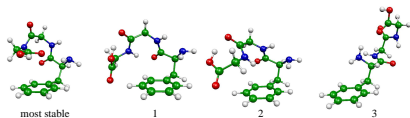
Tripeptide Conformational Energies



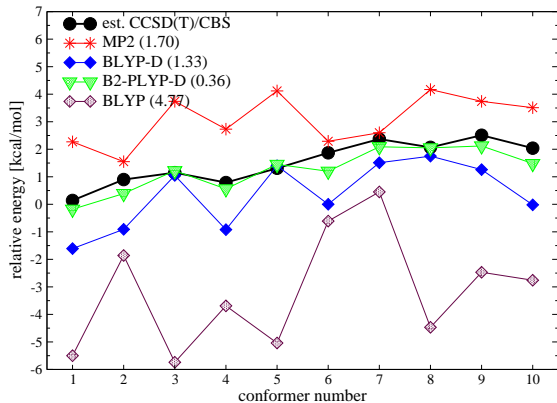
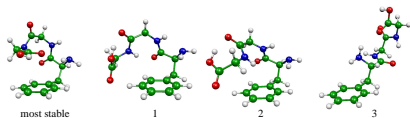
Tripeptide Conformational Energies



Tripeptide Conformational Energies



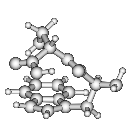
Tripeptide Conformational Energies



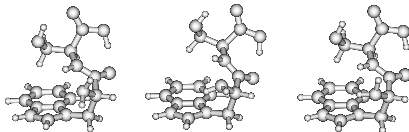
Application: Tryptophane-Serine Conformational Energies

T. Häber, K. Seefeld, G. Engler, SG, K. Kleinermanns, PCCP, 10 (2008) 2844.

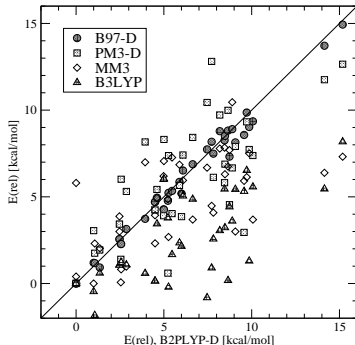
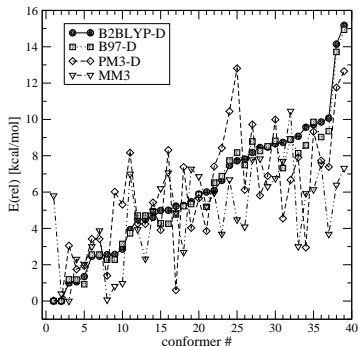
Exp. observed conf. A and B in infrared-UV double-resonance spectra



E=0



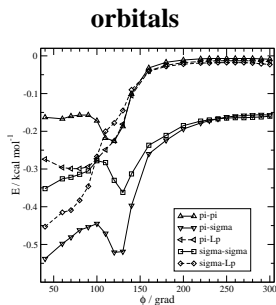
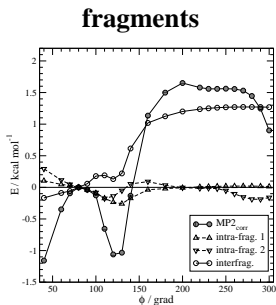
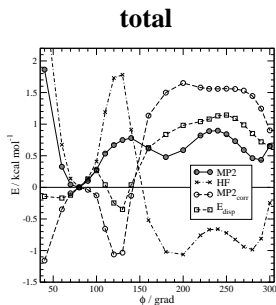
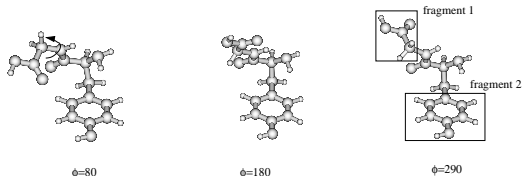
E=1.0–1.4 kcal/mol



LMO-Analysis of Tyrosine-Glycine Conformational Energies

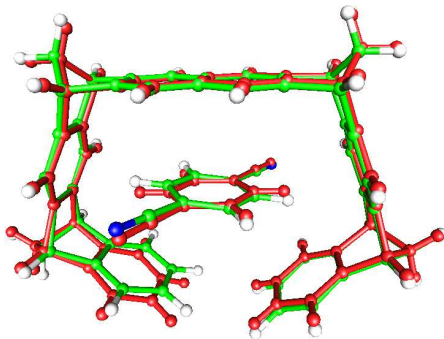
SG, C. Mück-Lichtenfeld, J. Antony, PCCP 10 (2008) 3327.

Example taken from T. van Mourik, Mol. Phys., 2006, 104, 559.



Encapsulation of molecules

First study of Klärner's tweezer and clip complexes: M. Parac, M. Etinski, M. Peric, S. Grimme, J. Chem. Theory Comput. 1, (2005), 1110.

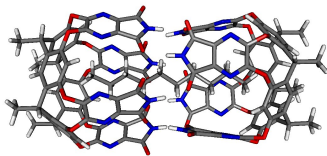


Comparison of BLYP-D/TZVP (green) and experimental (red) structures

Encapsulation of molecules

The example of a resorcinarene dimer: T. Heinz, D. Rudkevich and J. Rebek, Nature, 394, (2000), 764-766.

Encapsulated decane, B97-D/TZVP optimized structure.



Binding energies (B97-D/TZVP in kcal/mol) with and without dispersion correction.

guest	DFT-D	DFT
NONE (formation)	-50.1	-31.6
methane	-6.1	4.2
decane	-44.8	30.6
tetradecane	-47.1	59.8

Hydrogen storage inside C_{60}

Inclusion of up to 20 H_2 molecules in a C_{60} cage was considered. PBE/SVP optimized structures.

