Heteroaromatic π-stacking Energy Landscapes

Roland G. Huber[+], Michael A. Margreiter[+], Julian E. Fuchs[+], Susanne von Grafenstein[+], Christofer S. Tautermann[#], Klaus R. Liedl[+*], Thomas Fox[#]

[+] Institute of General, Inorganic and Theoretical Chemistry, Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, CCB – Center for Chemistry and Biomedicine, Innrain 80/82, A-6020 Innsbruck, Austria

[#] Computational Chemistry, Lead Identification and Optimization Support, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Straße 65, D-88397 Biberach an der Riss, Germany

Keywords: pi-pi interactions, density functional theory, dispersion correction, drug design, lead optimization, scaffold hopping, potential energy surfaces

* Corresponding Author: klaus.liedl@uibk.ac.at

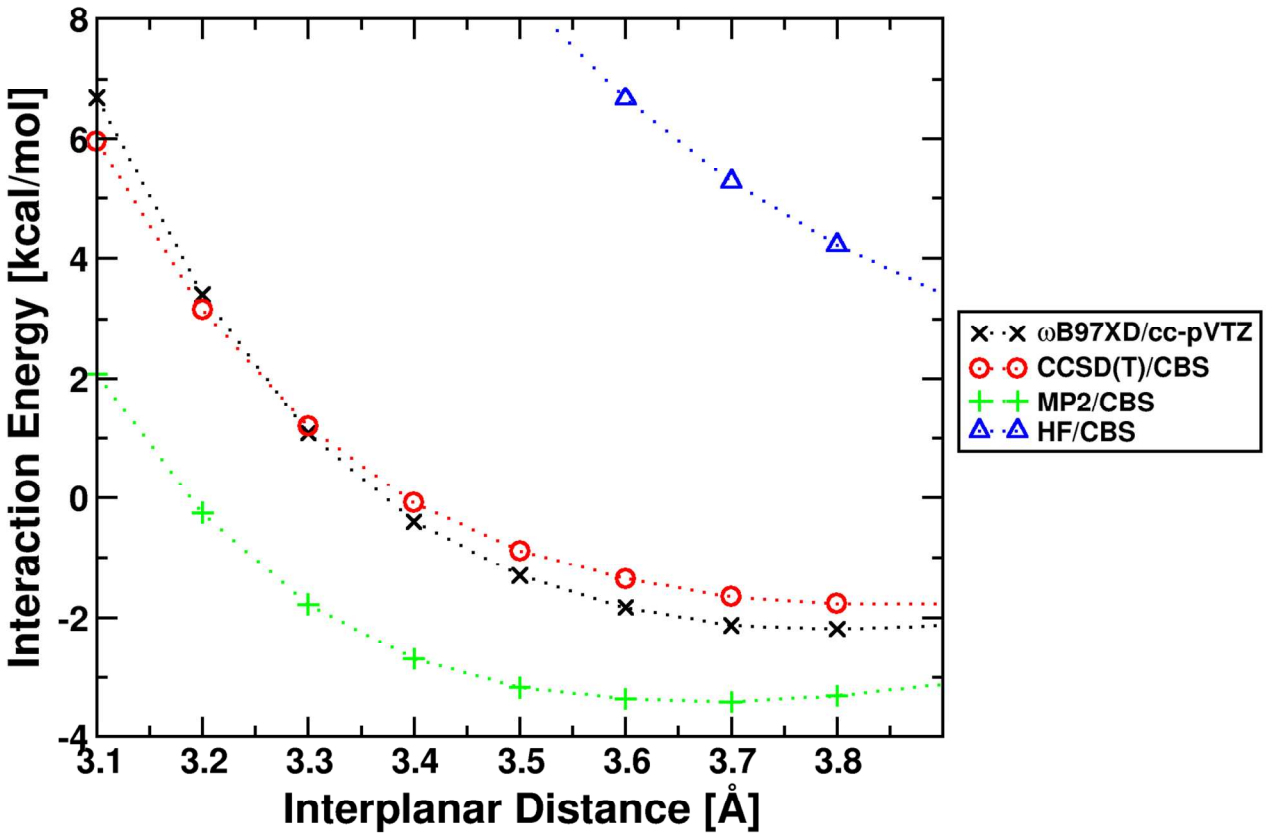

Figure S1. Comparison of stacked energies of the benzene dimer at various distances at the complete basis set limit (CBS) of HF, MP2 and CCSD(T) with ωB97XD/cc-pVTZ. CCSD(T)/CBS results were obtained through extrapolation from MP2/CBS. All observed deviations in the attractive regime between CCSD(T)/CBS and ωB97XD/cc-pVTZ are below 0.5 kcal/mol.

Table S1. Comparison of stacked energies of the benzene dimer at various distances at the complete basis set limit (CBS) of HF, MP2 and CCSD(T) with ωB97XD/cc-pVTZ. CCSD(T)/CBS results were obtained through extrapolation from MP2/CBS. Energies are given in kcal/mol. All observed deviations in the attractive regime between CCSD(T)/CBS and ωB97XD/cc-pVTZ are below 0.5 kcal/mol.

dZ (Å)	**3.1**	**3.2**	**3.3**	**3.4**	**3.5**	**3.6**	**3.7**	**3.8**	**3.9**
HF/CBS	22.99	17.77	13.78	10.74	8.42	6.66	5.27	4.23	3.42
MP2/CBS	2.08	-0.25	-1.78	-2.69	-3.17	-3.36	-3.41	-3.31	-3.12
CCSD(T)/CBS	5.96	3.15	1.20	-0.08	-0.88	-1.35	-1.65	-1.77	-1.77
ωB97XD/cc-pVTZ	6.68	3.40	1.08	-0.40	-1.30	-1.83	-2.13	-2.19	-2.14

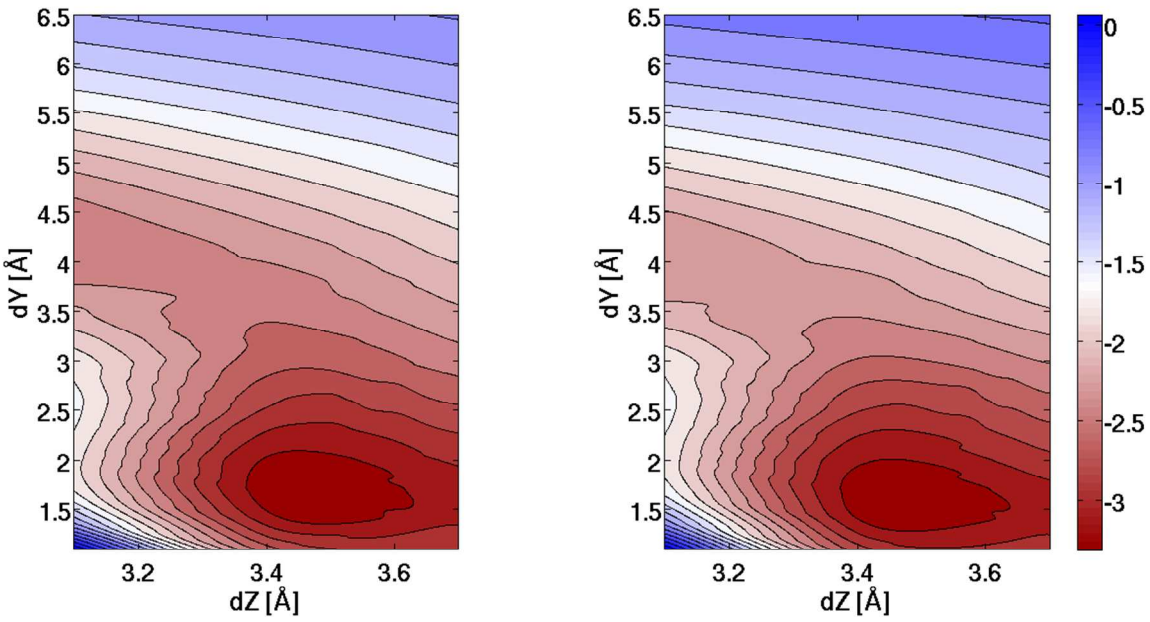

Figure S2. Comparison of parallel-displaced energy surfaces for the benzene dimer at the CCSD(T)/cc-pVTZ (left) and wB97XD/cc-pVTZ (right) levels of theory. Energies are given in kcal/mol.

Table S1. Minimum interaction energies with benzene and dipole moments calculated at ωB97XD/cc-pVTZ level of theory for the investigated heterocyclic systems.

5-Membered	Minimum Energy [kcal/mol]	Dipole Moment [Debye]	6-Memberd	Minimum Energy [kcal/mol]	Dipole Moment [Debye]
Furan	-3.34	0.56	Benzene	-3.56	0.00
Thiophene	-3.52	0.55	Pyridine	-4.07	2.21
Thiazole	-3.86	1.54	Pyridazine	-4.93	4.16
Isothiazole	-4.06	2.44	Pyrimidine	-4.72	2.31
Oxazole	-3.80	1.57	Pyrazine	-4.49	0.00
Isoxazole	-4.05	2.93	S-Triazine	-4.51	0.00
1,3,4-Thiadiazole	-4.47	3.31			

Table S2. Positions of the stacked and parallel-displaced minima for all investigated sytems. These positions are used in the definition of the X' axis as outlined in Figure 2. The slope of the X' axis is also given for all systems.

Heterocycle	dZ stacked [Å]	dX parallel-displaced [Å]	dZ parallel-displaced [Å]	dX' Slope
Benzene	3.80	1.60	3.46	-0.21
Pyridine	3.70	1.50	3.37	-0.22
Pridazine	3.70	1.40	3.36	-0.24
Pyrimidine	3.70	1.40	3.36	-0.24
Pyrazine	3.70	1.50	3.36	-0.23
s-Triazine	3.60	1.30	3.27	-0.25
Furan	3.70	1.50	3.36	-0.23
Thiophene	3.80	1.60	3.46	-0.21
Thiazole	3.80	1.50	3.47	-0.22
Isothiazole	3.80	1.50	3.46	-0.23
Oxazole	3.70	1.30	3.36	-0.21
Isoxazole	3.70	1.30	3.36	-0.21
1,3,4-Thiadiazole	3.70	1.30	3.37	-0.21