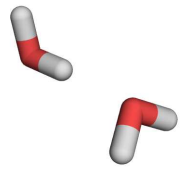
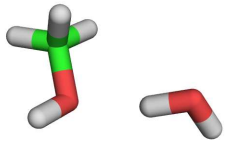
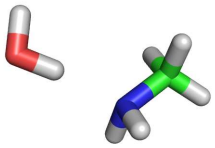
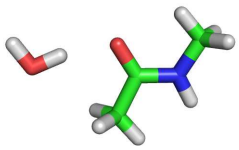
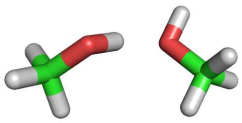
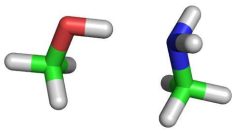
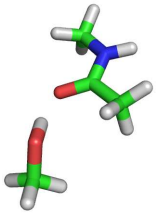
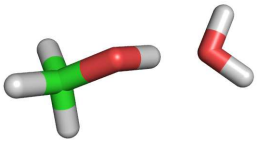
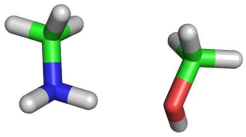
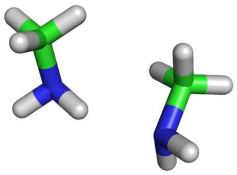
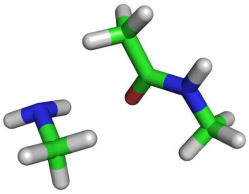
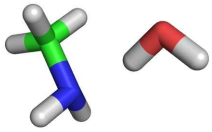
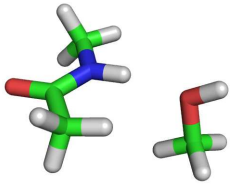
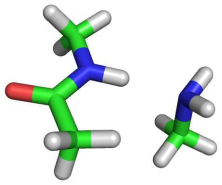
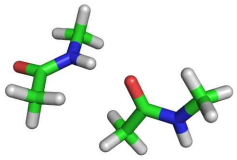
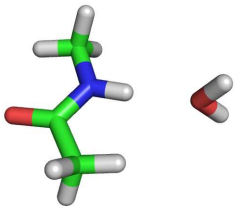
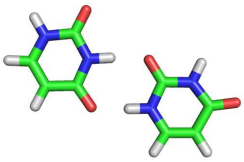
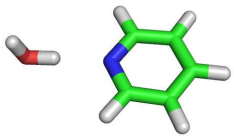
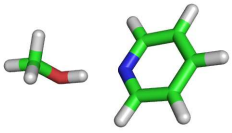
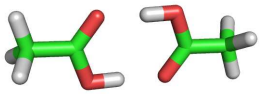
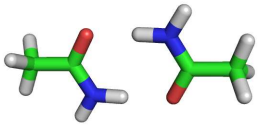
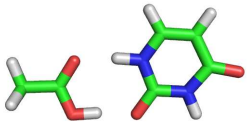
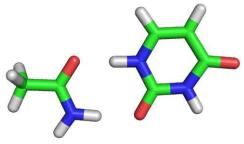
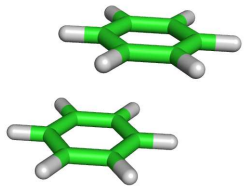
Table S1. *Errors (RMSE relative to average interaction energy in the group, in %) for the separate interaction categories in S66 set. Dispersion interactions are divided further into π-π, aliphatic-aliphatic and π-aliphatic complexes.*

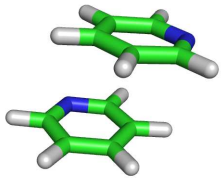
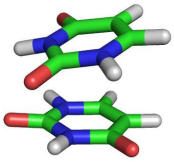
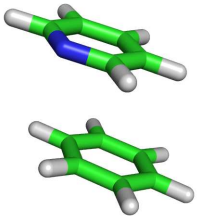
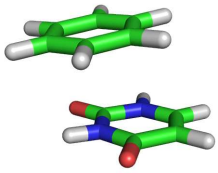
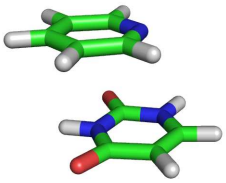
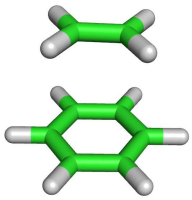
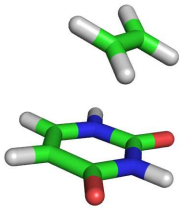
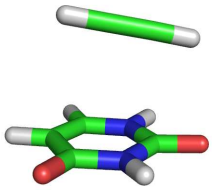
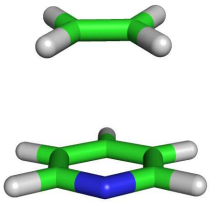
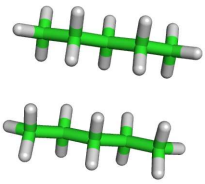
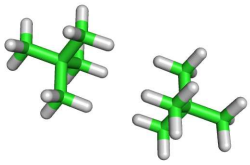
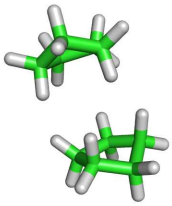
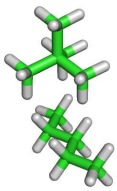
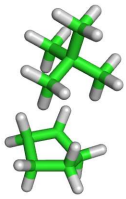
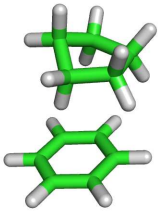
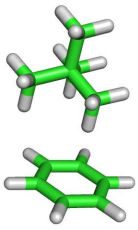
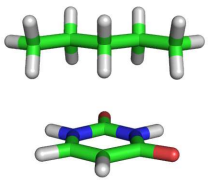
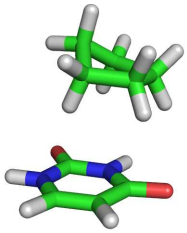
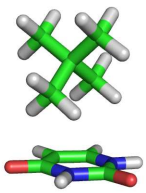
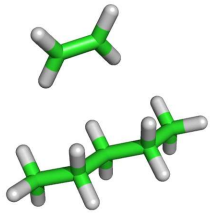
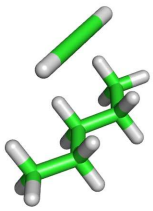
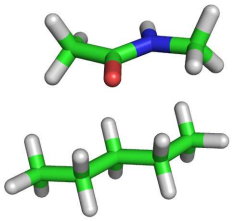
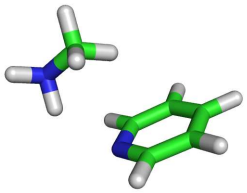
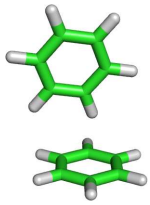
Method	S66 categories			Dispersion subcategories		
	H-bonds	Dispersion	Other	π-π	A-A	π-A
MP2/TZ	12.7	13.7	12.1	12.5	15.0	14.3
MP2/aDZ	11.6	15.1	15.4	15.8	11.5	11.6
MP2/CBS	3.2	9.2	17.5	8.9	9.4	7.8
MP2C/CBS	11.3	12.4	14.3	10.6	6.3	19.7
SCS-MP2/CBS	12.5	19.0	15.4	13.1	21.2	30.9
SCS-MI-MP2/CBS	4.5	10.2	5.5	2.9	11.6	21.4
DW-MP2/CBS	3.7	10.8	6.2	2.4	12.1	23.2
MP3/CBS	3.6	9.0	15.2	5.0	11.9	15.1
MP2.5/CBS	1.0	3.3	3.4	2.2	3.7	5.4
CCSD/CBS	7.2	13.0	15.2	8.8	15.2	20.7
SCS-CCSD/CBS	2.7	4.9	5.3	5.4	2.4	3.2
SCS-MI-CCSD/CBS	1.1	2.1	1.1	0.9	1.7	4.4

Table S2. *Errors in the S66x8 set. Relative errors for geometries with intermolecular distance shorter and longer than equilibrium are listed separately (the equilibrium geometry and the 5% displacements from it are excluded).*

Method	S66x8 RMSE kcal/mol	S66x8 short RMSE %	S66x8 long RMSE %
MP2/TZ	0.59	21	13
MP2/aDZ	0.67	28	11
MP2/CBS	0.67	23	9
SCS-MP2/CBS	0.71	31	15
SCS-MI-MP2/CBS	0.32	13	5
DW-MP2/CBS	0.36	16	6
MP3/CBS	0.56	26	9
MP2.5/CBS	0.14	5	3
CCSD/CBS	0.61	29	10
SCS-CCSD/CBS	0.21	7	4
SCS-MI-CCSD/CBS	0.07	3	1

Figure S1. *Structures of the complexes in the S66 dataset.Type of the complex is indicated by color: hydogen bond (blue), dispersion (red), other (green).*

 Water…Water	 Water...MeOH	 Water...$MeNH_2$	 Water...Peptide
 MeOH...MeOH	 MeOH...$MeNH_2$	 MeOH...Peptide	 MeOH...Water
 $MeNH_2$...MeOH	 $MeNH_2$...$MeNH_2$	 $MeNH_2$...Peptide	 $MeNH_2$...Water
 Peptide...MeOH	 Peptide...$MeNH_2$	 Peptide...Peptide	 Pepttide...water
 Uracil...Uracil (BP)	 Water...Pyridine	 MeOH...Pyridine	 AcOH...AcOH
 $AcNH_2$...$AcNH_2$	 AcOH...Uracil	 $AcNH_2$...Uracil	 Benzene...Benzene (π- π)

 Pyridine...Pyridine (π- π)	 Uracil...Uracil (π- π)	 Benzene...Pyridine (π- π)	 Benzene...Uracil (π- π)
 Pyridine...Uracil (π- π)	Ben zene ...Et hen e 	 Uracil...Ethene	 Uracil...Ethyne
 Pyridine...Ethene	 Pentane...Pentane	 Neopentane...Neopentane	 Cyclopentane...Cyclopentane
 Pentane...Neopentane	 Neopentace...Cyclopentane	 Benzene...Cyclopentane	 Benzene...Neopentane
 Uracil...Pentane	 Uracil...Cyclopentane	 Uracil...Neopentane	 Ethene...Pentane
 Ethyne...Pentane	 Peptide...Pentane	 $MeNH_2$...Pyridine	 Benzene...Benzene (TS)

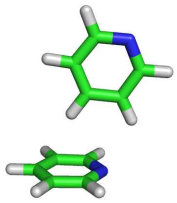
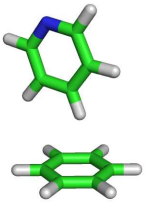
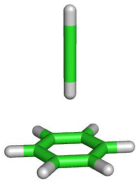
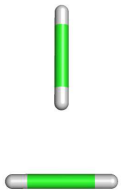
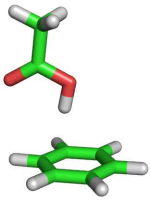
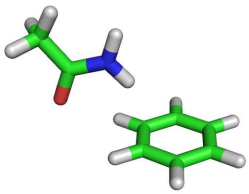
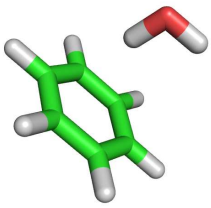
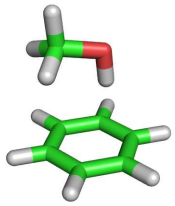
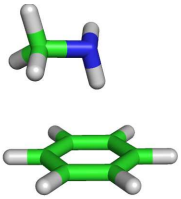
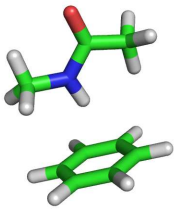
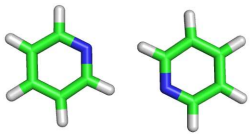
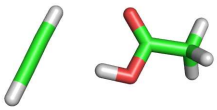
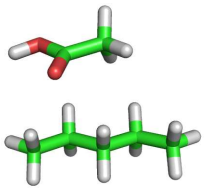
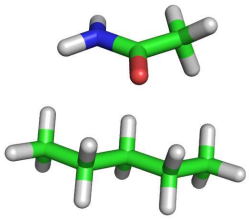
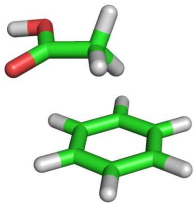
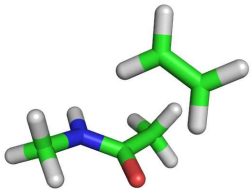
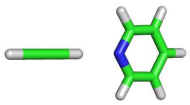
 Pyridine...Pyridine (TS)	 Benzene...Pyridine (TS)	 Benzene...Ethyne (TS)	 Ethyne...Ethyne (TS)
 Benzene...AcOH (OH-π)	 Benzene...$AcNH_2$ (NH-π)	 Benzene...Water (OH-π)	 Benzene...MeOH (OH-π)
 Benzene...$MeNH_2$ (NH-π)	 Benzene...Peptide (NH-π)	 Pyridine...Pyridine (CH-N)	 Ethyne...Water (CH-O)
 Ethyne...AcOH (OH-π)	 Pentane...AcOH	 Pentane...$AcNH_2$	 Benzene...AcOH
 Peptide...Ethene	 Pyridine...Ethyne (CH-N)		

Table S3. *Definitions of the coordinate used to displace the complexes forming the S66x8 dataset. Information is provided only for the complexes where the coordinate is not the vector connecting centers of mass of the molecules. Here, the vector is defined by one or more atoms in each molecule. If more atoms are used, their center of mass is used in all cases with the exception of averaging of multiple H-bonds (as indicated in the table) where unit weighting is applied.*

System #	Atoms in monomer A	Atoms in monomer B	Remark
1	3	4	
2	3	4	
3	3	4	
4	3	9	
5	2	7	
6	2	7	
7	2	12	
8	2	7	
9	2	8	
10	2	8	
11	2	13	
12	1	9	
13	8	13	
14	8	13	
15	8	18	
16	8	13	
17	2,4	22,24	average of H-bonds
18	3	4	
19	2	7	
20	2,4	10,12	average of H-bonds
21	2,4	11,13	average of H-bonds
22	2,4	18,20	average of H-bonds
23	2,4	19,21	average of H-bonds
40	1-12	25	T-shape
47	1-12	14	T-shape
48	1-11	18	T-shape
49	1-12	19	T-shape
50	1-12	14	T-shape
51	1,3	6	
52	11	13	T-shape
53	1,11	16	T-shape
57	1-12	20	T-shape
58	1,3	12,22	average of H-bonds
59	2	5	
60	1,3	8	
63	1-12	17	
65	1	15	
66	2	8	

Table S4. *Comparison of interaction energies (in kcal/) in ten small model complexes. The CCSD(T)/CBS scheme used for the S66 dataset is compared to a benchmark value obtained by extrapolation of the CCSD(T) calculations in aug-cc-pVTZ and aug-cc-pVQZ basis sets.*

	ΔE Benchmark	**ΔE S66**	**Error**	**Error, %**
Ammonia ... N_2	-0.683	-0.680	0.003	0.41
Ammonia dimer	-3.147	-3.098	0.049	1.57
Acetylene dimer	-1.532	-1.524	0.008	0.55
Formic acid ... water	-10.828	-10.621	0.207	1.91
Methane ... N_2	-0.349	-0.350	-0.001	-0.29
Methane ... water	-0.973	-0.949	0.024	2.46
Methane dimer	-0.528	-0.527	0.001	0.17
Water ... ammonia	-6.440	-6.347	0.094	1.45
Water ... N_2	-1.186	-1.174	0.012	0.99
Water dimer	-5.012	-4.918	0.094	1.87
Average abs. err			0.049	1.17
Max. abs. error			0.207	2.46
RMSE			0.080	1.39