Supporting Information:

Extension of an Atom-Atom Dispersion Function to Halogen Bonds and Its Use for Rational Design of Drugs and Biocatalysts

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1 Details of $E^{(2)}_{\text{disp}}$ calculations

The majority of the $E^{(2)}_{\text{disp}}$ values were obtained with SAPT(DFT) method implemented in SAPT2008 program,\textsuperscript{S1} which applied PBE0 functional\textsuperscript{S2,S3} with the Fermi-Amaldi-Tozer-Handy asymptotic correction,\textsuperscript{S4} and the aug-cc-pVTZ basis set,\textsuperscript{S5} supplemented by a 3s3p2d2f set of bond functions with (0.9,0.3,0.1) and (0.6,0.2) exponents for sp and df functions, respectively. The energies for systems from the X40x10\textsuperscript{S6} (training dataset), NBC10ext\textsuperscript{S7} and XB51 Kozuch and Martin\textsuperscript{S8} datasets (test datasets) were calculated with DFT-SAPT\textsuperscript{S9–S11} method implemented in MOLPRO\textsuperscript{S12,S13} (version 2012.1) without density fitting, which applied PBE0 functional and the gradient-regulated asymptotic correction\textsuperscript{S14} and the aug-cc-pVTZ basis set or, in the case of bromine and iodine atoms, the aug-cc-pVTZ-PP\textsuperscript{S15} basis set (accounting for relativistic pseudopotentials). Experimental ionization potential (IP) values, needed for the asymptotic correction, were obtained from Ref. S16. However, OPH\textsubscript{3}, NBS, and NIS monomers from XB51 dataset lacked the experimental IP values in Ref.,\textsuperscript{S16} and for these molecules, present in the following dimers: Br\textsubscript{2} – OPH\textsubscript{3}, FI – OPH\textsubscript{3}, CH\textsubscript{3}I – OPH\textsubscript{3}, NCH – NBS, NH\textsubscript{3} – NBS, PCH – NBS, NCH – NIS, NH\textsubscript{3} – NIS, PCH – NIS, IP values were calculated in Gaussian (version 2016 B-01)\textsuperscript{S17} using the PBE0/aug-cc-pVTZ (including pseudopotentials for bromine and iodine atoms) method.
2 Details of the dispersion fit

The training set used for the determination of $D_{as}^{20}$ parameters, shown in Table S1, consisted of 164 dimers (see Table S2). Geometries of the training set dimers with bromine and iodine atoms were taken from the X40 database, and included four geometries with the center-of-mass (COM) separation ($R$) smaller than at the minimum, and five geometries with the COM separation larger than at the minimum (together yielding ten different configurations for each dimer). Geometries of the remaining dimers were optimized at the second order Moeller-Plesset MP2/aug-cc-pVTZ level of theory (several minimum geometries were obtained from the S22 or NCCE31/05 datasets, as indicated in Table S2). For these dimers, ten different radial geometries corresponding to the same angular configuration were provided. In particular, the minimum geometry was accompanied by two geometries with the COM separation smaller than at the minimum, and seven geometries with the COM separation larger than at the minimum (up to 10Å). Overall, there were 1640 configurations in the training set, and the MUE and MURE errors associated with the obtained $D_{as}^{20}$ values were equal to 0.1 kcal · mol$^{-1}$ and 5.1%, respectively.

The $D_{as}^{20}$ parameters are given in Table S1. The $C_6^x$ and $C_8^x$ coefficients are given in the units of J · nm$^6$ · mol$^{-1}$ and J · nm$^8$ · mol$^{-1}$, respectively. The values of $\beta_x$ are given in bohr$^{-1}$. To obtain the values of $C_6^x$ and $C_8^x$ in atomic units, the corresponding values need to be multiplied by 17.34525495 and 6194.102092, respectively.
Table S1: List of $D_{as}^{20}$ dispersion expression parameters.

| Element | $C_{6x}^a$ | $C_{8x}^b$ | $\beta_x^c$ |
|---------|------------|------------|------------|
| H-H     | 0.199730   | 0.010225   | 1.898977   |
| H-B     | 0.625058   | 0.004286   | 2.022739   |
| H-C     | 0.216319   | 0.002841   | 1.737714   |
| H-N     | 0.117956   | 0.012842   | 1.456906   |
| H-O     | 0.155250   | 0.003195   | 1.623847   |
| H-F     | 0.028773   | 0.005962   | 1.618463   |
| H-Al    | 0.984668   | 0.060477   | 1.828202   |
| H-Si    | 0.957855   | 0.011257   | 1.627960   |
| H-P     | 0.338996   | 0.296480   | 0.589819   |
| H-S     | 0.405991   | 0.011234   | 1.416878   |
| H-Cl    | 0.095880   | 0.008433   | 1.660460   |
| H-Br    | 0.185489   | 0.020926   | 1.386093   |
| H-I     | 0.185411   | 0.045112   | 1.310652   |
| He      | 0.071774   | 0.004783   | 2.225149   |
| B       | 0.003104   | 0.264031   | 1.695239   |
| C$_{sp}^1$ | 1.297139   | 0.171713   | 1.951721   |
| C$_{sp}^2$ | 0.914964   | 0.268786   | 1.658960   |
| C$_{sp}^3$ | 0.461576   | 0.235496   | 1.780635   |
| N       | 1.427069   | 0.070811   | 2.396253   |
| O       | 0.723590   | 0.052314   | 2.368908   |
| F       | 0.900101   | 0.015629   | 2.458106   |
| Ne      | 0.261125   | 0.028508   | 2.132240   |
| Al      | 0.415583   | 0.900131   | 1.133178   |
| Si      | 0.009433   | 0.894086   | 2.726511   |
| P       | 0.890484   | 2.415552   | 1.634346   |
| S       | 4.793738   | 0.825826   | 2.279597   |
| Cl      | 6.254113   | 0.691238   | 1.643112   |
| Ar      | 3.331510   | 0.509268   | 1.843843   |
| Br      | 9.995193   | 1.169732   | 1.572187   |
| I       | 21.167203  | 2.745814   | 1.463387   |

*In units of $J \cdot nm^6 \cdot mol^{-1}$. Multiply by 17.34525495 to obtain $C_{6x}^a$ in atomic units.

*In units of $J \cdot nm^8 \cdot mol^{-1}$. Multiply by 6194.102092 to obtain $C_{8x}^b$ in atomic units.

*In units of bohr$^{-1}$. 

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Table S2: Monomers used for the fit of $D_{20}^{\infty}$ parameters to the benchmark $E_{\text{disp}}^{(2)}$ energies. Dimers denoted in blue, red or green overlap with the S22, NCCE31/05 or both of these test sets, respectively.

| A       | B                        |
|---------|---------------------------|
| AlCl₃   | Ar, He, Ne                |
| AlF₃    | AlF₃, Ar, He, Ne          |
| AlH₃    | AlH₃, Ar, He, Ne          |
| Ar      | Ar, C₂H₂, C₂H₆, CH₃OH, CH₄, CO₂ |
| BCl₃    | Ar, BCl₃, He, Ne          |
| BF₃     | Ar, BF₃, He, Ne           |
| BH₃     | Ar, BH₃, He, Ne           |
| C₂H₂    | C₂H₂, C₂H₆, CH₃OH, H₂O, NH₃ |
| C₂H₄    | Ar, C₂H₄, CH₄, F₂, H₂O, NH₃ |
| C₂H₆    | C₂H₂, C₂H₆, CH₃OH, NH₃, Ne |
| C₆H₆    | Ar, C₆H₆*, CF₃Br, CF₃I, CH₄, H₂O, He, Ne |
| CH₃Br   | C₆H₆, CH₂O                |
| CH₃I    | C₆H₆, CH₂O                |
| CH₃OH   | CH₃OH, CH₄, H₂O, HBr, HI, Ne, NH₃ |
| CH₄     | Br₂, C₂H₂, C₂H₆, CH₄, I₂, Ne, NH₃ |
| CO₂     | C₂H₄, C₂H₆, CH₃OH, CH₄, CO₂ |
| H₂      | Ar, H₂, H₂O, He, Ne       |
| H₂O     | Ar, C₂H₂, C₂H₆, CH₄, ClF, CO₂, H₂O |
| H₂S     | Ar, C₂H₂, C₂H₆, CH₃OH, CO₂, H₂O, HF, H₂S |
| HCl     | Ar, CH₃OH, CH₄, CO₂, H₂O, H₂S, HCl, He |
| HCONH₂  | HCONH₂                    |
| HCOOH   | HCOOH                     |
| HF      | Ar, C₂H₂, CH₃OH, CH₄, CO₂, H₂O, HF, N₂ |
| He      | Ar, C₂H₆, CH₃OH, CH₄, CO₂, H₂O, H₂S, HF, He |
| NH₃     | Ar, ClF, H₂S, He, Ne, NH₃, CO₂, H₂O |
| Ne      | Ar, CO₂, H₂O, H₂S, HCl, HF, Ne |
| PCl₃    | Ar, He, Ne, PCl₃          |
| PF₃     | Ar, He, Ne, PF₃           |
| PH₃     | Ar, He, Ne, PH₃           |
| pyrazine| pyrazine                  |
| SiCl₄   | Ar, He, Ne                |
| SiF₄    | Ar, He, Ne, SiF₄          |
| SiH₄    | Ar, He, Ne, SiH₄          |

*Benzene dimer in sandwich configuration.*
3 Detailed numerical results

Table S3: $E^{(2)}_{\text{disp}}$, $D_{\text{as}}$ and D3 correction energies\(^a\) calculated for excluded metal complexes at equilibrium distances\(^b\).

| Dimer                  | $E^{(2)}_{\text{disp}}$ | $D_{\text{as}}$ | D3(NS)\(^c\) | D3BJ(HF)\(^d\) |
|------------------------|-------------------------|-----------------|--------------|----------------|
| Ar – BeH\(_2\)        | -0.8                    | -0.8            | -0.7         | -0.7           |
| Ar – BeO               | -0.9                    | -0.5            | -0.5         | -0.5           |
| Ar – Li\(_2\)O        | -0.6                    | -1.0            | -6.1         | -2.6           |
| Ar – LiH               | -0.5                    | -0.9            | -6.0         | -2.8           |
| Ar – MgH\(_2\)        | -1.0                    | -0.8            | -1.2         | -1.2           |
| Ar – MgO               | -1.6                    | -1.1            | -0.9         | -0.8           |
| Ar – Na\(_2\)O        | -0.4                    | -0.7            | -1.9         | -1.4           |
| Ar – NaH               | -0.5                    | -0.3            | -2.1         | -1.7           |
| Be – Be                | -7.6                    | -7.1            | -17.3        | -9.3           |
| BeH\(_2\) – BeH\(_2\) | -17.3                   | -16.6           | -70.4        | -8.7           |
| BeO – BeO              | -7.3                    | -8.6            | 86.6         | -3.9           |
| H\(_2\) – BeH\(_2\)   | -1.0                    | -1.0            | -0.5         | -0.9           |
| H\(_2\) – BeO          | -1.2                    | -0.8            | -0.8         | -0.7           |
| H\(_2\) – Li\(_2\)O   | -3.0                    | -2.3            | 53.5         | -3.4           |
| H\(_2\) – LiH          | -0.5                    | -0.9            | 56.4         | -2.5           |
| H\(_2\) – MgH\(_2\)   | -1.7                    | -1.6            | 9.2          | -2.2           |
| H\(_2\) – MgO          | -1.9                    | -1.4            | -1.2         | -1.0           |
| H\(_2\) – Na\(_2\)O   | -6.3                    | -4.1            | 51.3         | -4.0           |
| H\(_2\) – NaH          | -0.8                    | -0.3            | -0.2         | -0.3           |
| He – BeH\(_2\)        | -0.1                    | -0.1            | -0.1         | -0.1           |
| He – BeO               | -0.1                    | -0.1            | -0.1         | -0.1           |
| He – Li\(_2\)O        | -0.2                    | -0.5            | -2.9         | -0.9           |
| He – LiH               | -0.2                    | -0.4            | -1.5         | -0.9           |
| He – MgH\(_2\)        | -0.1                    | -0.1            | -0.1         | -0.1           |
| He – MgO               | 0.0                     | 0.0             | 0.0          | 0.0            |
| He – Na\(_2\)O        | 0.0                     | 0.0             | -0.1         | 0.0            |
| He – NaH               | -0.1                   | -0.1            | -0.2         | -0.2           |
| Li\(_2\)O – Li\(_2\)O | -7.3                    | -6.8            | -192.5       | -13.4          |
| LiH – LiH              | -9.8                    | -2.3            | -92.3        | -7.0           |
| Li – Li                | -0.8                   | -0.8            | -1.2         | -1.1           |
| MgH\(_2\) – MgH\(_2\) | -5.2                    | -2.9            | -9.9         | -3.8           |
| Mg – Mg                | -2.9                    | -2.7            | -4.5         | -3.7           |
| MgO – MgO              | -34.2                   | -51.7           | 7.7          | -6.5           |
| Na\(_2\)O – Na\(_2\)O | -6.2                    | -6.4            | -100.4       | -12.8          |
| NaH – NaH              | -8.3                    | -0.6            | -47.1        | -7.0           |
| Na – Na                | -0.5                   | -0.5            | -0.9         | -0.9           |
| Ne – BeH\(_2\)        | -0.2                   | -0.2            | -0.2         | -0.2           |
Table S3: continued from previous page.

| Dimer     | $E_{\text{disp}}^{(2)}$ | $D_{\text{as}}$ | D3(NS) | D3BJ(HF) |
|-----------|-------------------------|-----------------|--------|----------|
| Ne – BeO  | -0.2                    | -0.1            | -0.1   | -0.1     |
| Ne – Li₂O | -0.3                    | -0.6            | -3.0   | -1.2     |
| Ne – LiH  | -0.3                    | -0.5            | -2.4   | -1.2     |
| Ne – MgH₂ | -0.2                    | -0.2            | -0.3   | -0.3     |
| Ne – MgO  | -0.4                    | -0.3            | -0.2   | -0.2     |
| Ne – Na₂O | -0.2                    | -0.3            | -0.6   | -0.5     |
| Ne – NaH  | -0.2                    | -0.1            | -0.5   | -0.6     |

MUE/MURE: 1.1/41.5 18.5/664.9 1.8/107.5

\(^a\) In units of kcal · mol\(^{-1}\).

\(^b\) Benchmark excluded from final $D_{\text{as}}$ parametrization.

\(^c\) D3 correction calculated with no switching.

\(^d\) D3 correction calculated with BJ damping for the HF level of theory.
Table S4: $E_{\text{disp}}^{(2)}$, $D_{\text{as}}^{20}$, and D3 energies$^a$ calculated for each dimer from the S22 database$^b$. Corresponding MUE and MURE values are given.

| Dimer                        | $E_{\text{disp}}^{(2)}$ | $D_{\text{as}}^{20}$ | $D_{\text{3BJ}}(\text{HF})^d$ | $D_{\text{3BJ}}(\text{OLYP})^d$ | $D_{\text{3BJ}}(\text{revPBE38})^d$ | $D_{\text{3J}}(\text{NS})^e$ |
|------------------------------|--------------------------|----------------------|-------------------------------|---------------------------------|---------------------------------|------------------|
| 2-pyridoxine – 2-aminopyridine | -9.7                     | -2.2                 | -2.1                          | -1.9                            | -1.0                            | -0.8             |
| adenine – thymine (stack)    | -10.0                    | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| adenine – thymine (wc)       | -10.3                    | -2.2                 | -2.0                          | -2.0                            | -1.0                            | -0.8             |
| NH$_3$ dimer                 | -9.8                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| C$_6$H$_6$ – NH$_3$          | -10.1                    | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| C$_6$H$_6$ – CH$_3$          | -9.5                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| C$_6$H$_6$ – CH$_2$          | -9.5                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| HCONH$_2$ dimer              | -9.8                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| HCOOH dimer                  | -9.5                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| indole – C$_6$H$_6$ (stack)  | -11.7                    | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| indole – C$_6$H$_6$ (t-shape)| -6.3                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| CH$_4$ dimer                 | -6.3                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| phenol dimer                 | -6.3                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| pyrazine dimer               | -6.3                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| uracil dimer (hb)            | -6.3                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| uracil dimer (stack)         | -6.3                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |
| H$_2$O dimer                 | -6.3                     | -2.2                 | -1.9                          | -2.0                            | -1.0                            | -0.8             |

MUE/MURE: 0.4/7.1 1.0/11.8 2.1/28.8 2.5/34.5 2.8/34.4 3.0/43.2

$^a$In units of kcal · mol$^{-1}$.

$^b$Benchmark reported in Ref. S18.

$^c$D$_{\text{as}}$ revision reported herein.

$^d$D$_3$S$^{19}$ dispersion term calculated with BJ damping for the HF level of theory or given functional.

$^e$D$_3$S$^{19}$ dispersion term calculated without switching.$^{S20}$

$^f$Errors calculated for the S22 dataset restricted to dimers not present in the $D_{\text{as}}$ training set. See Table S2 for the overlapping dimers.
Table S5: $E_{\text{disp}}^{(2)}$, $D_{\text{as}}^{20}$, and D3 energies\(^a\) calculated for each dimer from the NCCE31/05 database\(^b\). Corresponding MUE and MURE values are given.

| Dimer                  | $E_{\text{disp}}^{(2)}$ | $D_{\text{as}}^{20}$\(^c\) | D3BJ(HF)\(^d\) | D3BJ(OLYP)\(^d\) | D3BJ(revPBE38)\(^d\) | D3(NS)\(^e\) |
|------------------------|------------------------|-------------------------------|----------------|--------------------|---------------------|---------------|
| C\(_2\)H\(_2\) dimer  | -1.4                   | -1.3                          | -1.3           | -1.8               | -1.1                | -1.3          |
| C\(_2\)H\(_2\) – ClF  | -5.0                   | -4.9                          | -4.1           | -4.3               | -1.9                | -2.1          |
| C\(_2\)H\(_4\) dimer  | -2.6                   | -2.7                          | -2.9           | -3.8               | -2.1                | -3.1          |
| C\(_2\)H\(_4\) – F\(_2\) | -1.6                  | -1.3                          | -0.9           | -1.2               | -0.6                | -0.9          |
| C\(_6\)H\(_6\) – Ne   | -1.0                   | -0.9                          | -0.8           | -1.1               | -0.7                | -0.6          |
| CH\(_3\)Cl – HCl      | -3.6                   | -3.5                          | -3.4           | -3.9               | -1.9                | -4.8          |
| CH\(_3\)SH – HCl      | -4.6                   | -4.5                          | -4.1           | -4.7               | -2.3                | -6.2          |
| CH\(_4\) dimer        | -1.3                   | -1.2                          | -1.2           | -1.6               | -1.0                | -1.2          |
| CH\(_4\) – Ne         | -0.3                   | -0.3                          | -0.3           | -0.4               | -0.2                | -0.3          |
| H\(_2\)O – ClF        | -4.0                   | -3.8                          | -2.5           | -2.5               | -1.1                | -3.1          |
| H\(_2\)O dimer        | -2.3                   | -2.1                          | -1.6           | -1.7               | -0.7                | -3.6          |
| H\(_2\)S dimer        | -2.1                   | -1.9                          | -1.7           | -2.2               | -1.2                | -2.0          |
| H\(_2\)S – HCl        | -3.0                   | -2.7                          | -2.5           | -2.9               | -1.4                | -3.7          |
| HCN – CH\(_3\)SH      | -2.7                   | -2.8                          | -1.9           | -2.2               | -1.1                | -2.6          |
| HCN – ClF             | -4.2                   | -4.0                          | -2.8           | -3.4               | -1.8                | -3.2          |
| HCOOH dimer           | -8.8                   | -8.7                          | -5.3           | -5.7               | -2.7                | -12.3         |
| HCl dimer             | -2.1                   | -1.9                          | -5.8           | -6.0               | -2.6                | -20.0         |
| HF dimer              | -1.7                   | -1.6                          | -0.1           | -0.1               | -0.1                | -0.1          |
| He – Ar               | -0.1                   | -0.1                          | -0.1           | -0.1               | 0.0                 | -0.1          |
| He – Ne               | -0.1                   | -0.1                          | -1.2           | -1.2               | -0.4                | -3.4          |
| NH\(_3\) – Cl\(_2\)   | -4.7                   | -3.9                          | -0.2           | -0.3               | -0.2                | -0.2          |
| NH\(_3\) – ClF        | -9.2                   | -8.7                          | -0.1           | -0.2               | -0.1                | -0.1          |
| NH\(_3\) – F\(_2\)   | -1.8                   | -1.3                          | -2.7           | -2.9               | -1.4                | -2.2          |
| NH\(_3\) – H\(_2\)O   | -3.0                   | -2.7                          | -4.8           | -4.2               | -1.7                | -7.4          |
| NH\(_3\) dimer        | -2.1                   | -1.8                          | -0.7           | -0.9               | -0.4                | -0.8          |
| Ne – Ar               | -0.3                   | -0.2                          | -2.1           | -2.1               | -0.9                | -4.1          |
| Ne dimer              | -0.2                   | -0.1                          | -1.5           | -1.7               | -0.8                | -2.1          |
| C\(_6\)H\(_6\) dimer (P) | -5.8                 | -5.5                          | -5.1           | -7.2               | -5.0                | -3.9          |
| C\(_6\)H\(_6\) dimer (S) | -4.7                 | -4.4                          | -4.1           | -5.8               | -4.1                | -3.2          |
| C\(_6\)H\(_6\) dimer (T) | -4.1                 | -4.0                          | -4.1           | -5.5               | -3.4                | -3.8          |

MUE/MURE:  0.2/8.1  0.8/22.7  0.8/22.4  1.7/48.3  1.3/33.7
MUE/MURE\(_{12}\): 0.2/8.2  0.6/19.9  0.7/21.6  1.5/49.8  1.1/36.4

\(^a\)In units of kcal · mol\(^-1\).
\(^b\)Benchmark reported in Ref. S21.
\(^c\)\(D_{\text{as}}\) revision reported herein.
\(^d\)D3\(^{S19}\) dispersion term calculated with BJ damping for the HF level of theory or given functional.
\(^e\)D3\(^{S19}\) dispersion term calculated without switching.\(^{S20}\)
\(^f\)Errors calculated for the NCCE31/05 dataset restricted to dimers not present in the \(D_{\text{as}}\) training set.

See Table S2 for the overlapping dimers.
Table S6: $E^{(2)}_{\text{disp}}$, $D_{20}^{\text{as}}$, D3, and DD3S energies\textsuperscript{a} calculated for each dimer from the XB51 database\textsuperscript{b}. Corresponding MUE and MURE values are given.

| Dimer         | $E^{(2)}_{\text{disp}}$ | $D_{20}^{\text{as}}$ | D3BJ(HF)\textsuperscript{d} | D3BJ(OLYP)\textsuperscript{d} | D3BJ(revPBE38)\textsuperscript{d} | D3(NS)\textsuperscript{e} | DD3S\textsuperscript{f} |
|---------------|--------------------------|-----------------------|-----------------------------|--------------------------------|---------------------------------|------------------|------------------|
| Br\textsubscript{2} – FCCH | -1.1                     | -1.2                  | -0.9                        | -1.2                           | -0.7                            | -0.9             | -1.2             |
| Br\textsubscript{2} – CH\textsubscript{3}F | -3.0                     | -3.2                  | -2.5                        | -2.9                           | -1.5                            | -3.0             | -3.4             |
| Br\textsubscript{2} – NCH | -3.2                     | -3.0                  | -2.6                        | -2.7                           | -1.3                            | -2.0             | -3.3             |
| Br\textsubscript{2} – NH\textsubscript{3} | -5.5                     | -5.1                  | -3.9                        | -3.8                           | -1.8                            | -2.9             | -4.7             |
| Br\textsubscript{2} – OCH\textsubscript{2} | -4.0                     | -4.1                  | -3.5                        | -3.7                           | -1.8                            | -3.0             | -4.5             |
| Br\textsubscript{2} – PCH | -2.5                     | -2.0                  | -2.7                        | -2.9                           | -1.6                            | -3.3             | -3.4             |
| Br\textsubscript{2} – pyridine | -7.6                     | -7.5                  | -5.2                        | -5.6                           | -2.9                            | 16.5             | -6.4             |
| CH\textsubscript{3}I – FCCH | -0.5                     | -0.5                  | -0.3                        | -0.4                           | -0.3                            | -0.3             | -1.3             |
| CH\textsubscript{3}I – CH\textsubscript{3} | -4.4                     | -5.2                  | -3.8                        | -3.7                           | -1.8                            | -5.3             | -3.1             |
| CH\textsubscript{3}I – NCH | -6.3                     | -7.0                  | -4.9                        | -3.9                           | -1.8                            | 35.2             | -2.5             |
| CH\textsubscript{3}I – NH\textsubscript{3} | -8.8                     | -9.7                  | -6.7                        | -5.5                           | -2.4                            | -10.5            | -3.0             |
| CH\textsubscript{3}I – OCH\textsubscript{2} | -6.3                     | -7.2                  | -5.1                        | -4.5                           | 2.1                             | 21.8             | -4.0             |
| CH\textsubscript{3}I – PCH | -4.8                     | -4.5                  | -5.7                        | -4.2                           | -2.2                            | -5.7             | -3.1             |
| CH\textsubscript{3}I – pyridine | -11.9                    | -13.9                 | -7.9                        | -7.3                           | -3.8                            | 54.2             | -4.8             |
| FI – FCCH | -1.1                     | -1.1                  | -0.9                        | -1.3                           | -0.7                            | -0.9             | -0.4             |
| FI – CH\textsubscript{3}F | -2.6                     | -2.6                  | -2.3                        | -2.9                           | -1.6                            | -2.2             | -4.6             |
| FI – NCH | -2.2                     | -1.9                  | -1.9                        | -2.3                           | -1.2                            | -1.3             | -5.1             |
| FI – NH\textsubscript{3} | -3.0                     | -2.6                  | -2.3                        | -2.8                           | -1.5                            | -1.0             | -7.4             |
| FI – OCH\textsubscript{2} | -3.1                     | -3.0                  | -3.0                        | -3.6                           | -1.9                            | -2.1             | -5.7             |
| FI – PCH | -2.1                     | -1.6                  | -2.4                        | -2.8                           | -1.6                            | -2.8             | -5.4             |
| FI – pyridine | -4.4                     | -4.0                  | -3.7                        | -4.6                           | -2.6                            | 0.7              | -8.7             |
| NCH – F\textsubscript{3}Cl | -2.9                     | -2.7                  | -2.6                        | -2.8                           | -1.4                            | -1.2             | -3.2             |
| NCH – FBr | -5.5                     | -5.9                  | -4.1                        | -3.4                           | -1.5                            | 10.2             | -4.6             |
| NCH – FC\textsubscript{l} | -3.7                     | -4.0                  | -2.8                        | -2.7                           | -1.2                            | -2.7             | -3.5             |
| NCH – PhBr | -1.9                     | -1.6                  | -1.5                        | -1.9                           | -1.0                            | -1.4             | -2.1             |
| NCH – PhI | -2.4                     | -2.1                  | -2.0                        | -2.4                           | -1.3                            | -1.4             | -2.7             |
| NH\textsubscript{3} – F\textsubscript{3}Cl | -4.2                     | -3.8                  | -3.3                        | -3.6                           | -1.8                            | -1.4             | -4.2             |
| NH\textsubscript{3} – FBr | -8.9                     | -9.5                  | -5.9                        | -4.8                           | -2.0                            | -10.4            | -6.7             |
| NH\textsubscript{3} – FC\textsubscript{l} | -7.4                     | -7.9                  | -4.6                        | -4.1                           | -1.7                            | -6.0             | -5.6             |
| NH\textsubscript{3} – PhBr | -2.6                     | -2.1                  | -1.8                        | -2.3                           | -1.2                            | -1.3             | -2.4             |
| NH\textsubscript{3} – PhI | -3.3                     | -2.8                  | -2.5                        | -3.0                           | -1.6                            | -1.1             | -3.2             |
| PCH – F\textsubscript{3}Cl | -2.2                     | -1.8                  | -2.6                        | -2.9                           | -1.7                            | -3.0             | -3.2             |
| PCH – FBr | -4.1                     | -3.7                  | -4.5                        | -3.7                           | -1.8                            | -5.7             | -4.7             |
| PCH – FC\textsubscript{l} | -2.8                     | -2.6                  | -2.9                        | -3.0                           | -1.5                            | -3.8             | -3.6             |
| PCH – PhBr | -2.0                     | -1.4                  | -2.0                        | -2.5                           | -1.4                            | -2.4             | -2.7             |
| PCH – PhI | -2.2                     | -1.7                  | -2.5                        | -2.9                           | -1.7                            | -2.9             | -3.1             |
| Br\textsubscript{2} – OPH\textsubscript{3} | -5.1                     | -5.1                  | -4.8                        | -4.8                           | -2.4                            | -6.0             | -5.9             |
| FI – OPH\textsubscript{3} | -8.2                     | -9.3                  | -6.9                        | -5.7                           | -2.9                            | 8.4              | -7.4             |
| MeI – OPH\textsubscript{3} | -3.8                     | -4.0                  | -4.5                        | -5.1                           | -2.7                            | -5.4             | -5.7             |
| NCH – NBS | -3.5                     | -3.4                  | -2.8                        | -2.8                           | -1.4                            | -1.9             | -3.5             |
| NCH – NIS | -4.3                     | -4.3                  | -3.7                        | -3.5                           | -1.7                            | 3.7              | -4.3             |
Table S6: continued from previous page.

| Dimer     | \(E_{\text{disp}}^{(2)}\) | \(D_{\text{as}}^{20}\) | D3BJ(HF)  | D3BJ(OLYP) | D3BJ(revPBE38) | D3(NS) | DD3S |
|-----------|----------------|----------------|-----------|------------|----------------|--------|------|
| NH3 – NBS | -5.5           | -5.2           | -3.9      | -3.9       | -1.8           | -3.0   | -4.8 |
| NH3 – NIS | -6.8           | -6.8           | -5.3      | -4.8       | -2.3           | -5.1   | -6.1 |
| PCH – NBS | -2.6           | -2.1           | -2.9      | -3.1       | -1.7           | -3.5   | -3.5 |
| PCH – NIS | -3.1           | -2.6           | -3.7      | -3.6       | -2.0           | -4.5   | -4.2 |

MUE/MURE: 0.4/10.3  0.9/18.8  1.0/20.0  2.4/51.9  5.5/89.1  0.7/17.5

*In units of kcal \(\cdot\) mol\(^{-1}\).

Benchmark reported in Ref. S8.

\(D_{\text{as}}\) revision reported herein.

\(D_3^{\text{S19}}\) dispersion term calculated with BJ damping for the HF level of theory or given functional.

\(D_3^{\text{S19}}\) dispersion term calculated without switching.\(^{S20}\)

Method reported in Ref. S21.

Table S7: \(E_{\text{disp}}^{(2)}\), \(D_{\text{as}}^{20}\), \(D_{\text{as}}^{10}\), D3, and DD3S energies\(^a\) calculated for each dimer from the NBC10ext database\(^b\). Corresponding MUE and MURE values are given.

| Dimer  | R/\(R_{eq}\) | \(E_{\text{disp}}^{(2)}\) | \(D_{\text{as}}^{20}\) | \(D_{\text{as}}^{10}\) | D3BJ(HF)  | D3BJ(OLYP) | D3BJ(revPBE38) | D3(NS) | DD3S |
|--------|-------------|----------------|----------------|----------------|------------|------------|----------------|--------|------|
| 1 (C\(_6\)H\(_6\) dimer) | | | | | | | | | |
| 0.82   | -12.5       | -12.7          | -13.4          | -11.4          | -15.8      | -9.5       | -8.1           | -15.4 |
| 0.85   | -10.8       | -10.8          | -11.4          | -9.7           | -13.7      | -8.5       | -7.1           | -13.2 |
| 0.87   | -9.3        | -9.3           | -9.7           | -8.4           | -11.9      | -7.6       | -6.2           | -11.2 |
| 0.90   | -8.0        | -7.9           | -8.3           | -7.2           | -10.3      | -6.7       | -5.4           | -9.6  |
| 0.92   | -7.0        | -6.8           | -7.1           | -6.2           | -8.9       | -6.0       | -4.7           | -8.3  |
| 0.95   | -6.0        | -5.9           | -6.1           | -5.4           | -7.7       | -5.3       | -4.1           | -7.1  |
| 0.97   | -5.2        | -5.1           | -5.3           | -4.7           | -6.7       | -4.7       | -3.6           | -6.1  |
| 1.00   | -4.6        | -4.4           | -4.5           | -4.1           | -5.8       | -4.1       | -3.2           | -5.3  |
| 1.03   | -4.0        | -3.8           | -3.9           | -3.6           | -5.0       | -3.7       | -2.8           | -4.6  |
| 1.05   | -3.5        | -3.3           | -3.4           | -3.1           | -4.4       | -3.2       | -2.4           | -4.0  |
| 1.08   | -3.0        | -2.9           | -3.0           | -2.7           | -3.8       | -2.9       | -2.1           | -3.5  |
| 1.15   | -2.0        | -1.9           | -2.0           | -1.9           | -2.6       | -2.0       | -1.5           | -2.3  |
| 1.28   | -1.1        | -1.0           | -1.1           | -1.1           | -1.4       | -1.1       | -0.8           | -1.3  |
| 1.41   | -0.6        | -0.6           | -0.6           | -0.6           | -0.8       | -0.7       | -0.5           | -0.7  |
| 1.54   | -0.4        | -0.4           | -0.4           | -0.4           | -0.5       | -0.4       | -0.3           | -0.4  |
| 1.67   | -0.2        | -0.2           | -0.2           | -0.2           | -0.3       | -0.2       | -0.2           | -0.3  |
| 2.56   | 0.0         | 0.0            | 0.0            | 0.0            | 0.0        | 0.0        | 0.0            | 0.0   |
| 2 (C\(_6\)H\(_6\) dimer) | | | | | | | | |
| 0.86   | -11.0       | -11.4          | -12.3          | -11.2          | -13.0      | -6.7       | -13.1          | -15.2 |
| 0.87   | -10.2       | -10.6          | -11.4          | -10.4          | -12.3      | -6.4       | -11.9          | -14.2 |
| 0.88   | -9.5        | -9.8           | -10.5          | -9.7           | -11.6      | -6.1       | -10.8          | -13.2 |
| 0.90   | -8.2        | -8.4           | -9.0           | -8.4           | -10.3      | -5.6       | -9.0           | -11.5 |
| 0.92   | -7.0        | -7.2           | -7.7           | -7.3           | -9.2       | -5.1       | -7.5           | -9.9  |
| 0.94   | -6.1        | -6.2           | -6.6           | -6.3           | -8.1       | -4.6       | -6.3           | -8.5  |
| 0.96   | -5.2        | -5.3           | -5.6           | -5.4           | -7.1       | -4.1       | -5.2           | -7.3  |
| 0.98   | -4.5        | -4.6           | -4.8           | -4.7           | -6.2       | -3.7       | -4.4           | -6.2  |
| 1.00   | -3.9        | -3.9           | -4.1           | -4.0           | -5.4       | -3.3       | -3.7           | -5.3  |
| Dimer | $R/R_{eq}$ | $E_{\text{disp}}^{(2)}$ | $D_{\text{as}}^{20}$ | $D_{\text{as}}^{10}$ | D3BJ(HF) | D3BJ(OLYP) | D3BJ(revPBE38) | D3(NS) | DD3S |
|-------|------------|-----------------|-----------------|-----------------|---------|-----------|--------------|--------|------|
|       | 1.02       | -3.4            | -3.4            | -3.5            | -4.7    | -3.0      | -3.2         | -4.6   |
|       | 1.04       | -3.0            | -2.9            | -3.0            | -4.1    | -2.7      | -2.7         | -3.9   |
|       | 1.06       | -2.6            | -2.5            | -2.6            | -3.6    | -2.4      | -2.3         | -3.4   |
|       | 1.08       | -2.2            | -2.2            | -2.2            | -3.1    | -2.1      | -2.0         | -2.9   |
|       | 1.10       | -2.0            | -1.9            | -2.0            | -2.7    | -1.9      | -1.7         | -2.5   |
|       | 1.12       | -1.7            | -1.7            | -1.7            | -2.3    | -1.7      | -2.2         | -2.2   |
|       | 1.20       | -1.0            | -1.0            | -1.0            | -1.4    | -0.8      | -0.8         | -1.2   |
|       | 1.30       | -0.6            | -0.5            | -0.6            | -0.7    | -0.6      | -0.4         | -0.7   |
|       | 1.40       | -0.3            | -0.3            | -0.3            | -0.4    | -0.3      | -0.2         | -0.4   |
|       | 1.50       | -0.2            | -0.2            | -0.2            | -0.2    | -0.2      | -0.1         | -0.2   |
|       | 1.60       | -0.1            | -0.1            | -0.1            | -0.2    | -0.1      | -0.1         | -0.1   |
|       | 0.75       | -9.3            | -9.2            | -8.3            | -11.8   | -7.6      | -6.2         | -11.2  |
|       | 0.78       | -9.2            | -9.1            | -9.5            | -11.7   | -7.5      | -6.1         | -11.1  |
|       | 0.81       | -9.0            | -9.0            | -9.4            | -11.5   | -7.4      | -6.1         | -10.9  |
|       | 0.84       | -8.8            | -8.7            | -9.1            | -11.3   | -7.2      | -5.9         | -10.6  |
|       | 0.88       | -8.5            | -8.5            | -8.8            | -10.9   | -7.1      | -5.8         | -10.3  |
|       | 0.91       | -8.2            | -8.1            | -8.5            | -10.5   | -6.8      | -5.6         | -9.9   |
|       | 0.94       | -7.8            | -7.8            | -8.1            | -10.1   | -6.6      | -5.4         | -9.5   |
|       | 0.95       | -7.6            | -7.6            | -7.9            | -9.9    | -6.4      | -5.3         | -9.3   |
|       | 0.97       | -7.4            | -7.4            | -7.7            | -9.7    | -6.3      | -5.2         | -9.1   |
|       | 0.98       | -7.2            | -7.2            | -7.5            | -9.4    | -6.1      | -5.1         | -8.8   |
|       | 1.00       | -7.0            | -7.0            | -7.3            | -9.1    | -6.0      | -4.9         | -8.6   |
|       | 1.06       | -6.8            | -6.8            | -7.1            | -8.9    | -5.8      | -4.8         | -8.3   |
|       | 1.11       | -6.6            | -6.6            | -6.9            | -8.6    | -5.7      | -4.7         | -8.1   |
|       | 1.22       | -6.2            | -6.1            | -6.4            | -5.7    | -5.3      | -4.4         | -7.6   |
|       | 1.33       | -5.8            | -5.7            | -5.9            | -7.5    | -5.0      | -4.1         | -7.0   |
|       | 1.44       | -5.3            | -5.2            | -5.5            | -4.9    | -4.6      | -3.8         | -6.5   |
|       | 1.56       | -4.9            | -4.8            | -5.0            | -4.5    | -4.3      | -3.6         | -6.0   |
|       | 1.67       | -4.5            | -4.4            | -4.5            | -4.1    | -5.8      | -3.9         | -5.4   |
|       | 0.83       | -10.3           | -11.4           | -13.1           | -10.3   | -12.4     | -6.1         | -11.0  |
|       | 0.84       | -9.5            | -10.5           | -12.0           | -9.5    | -11.7     | -5.8         | -10.0  |
|       | 0.87       | -8.1            | -8.9            | -10.2           | -8.2    | -10.4     | -5.3         | -8.3   |
|       | 0.89       | -7.0            | -7.6            | -8.7            | -7.0    | -9.2      | -4.9         | -6.9   |
|       | 0.92       | -6.0            | -6.5            | -7.4            | -6.0    | -8.0      | -4.4         | -5.8   |
|       | 0.95       | -5.1            | -5.6            | -6.3            | -5.1    | -7.0      | -4.0         | -4.9   |
|       | 0.97       | -4.4            | -4.8            | -5.3            | -4.3    | -6.1      | -3.6         | -4.1   |
|       | 1.00       | -3.8            | -4.1            | -4.6            | -3.7    | -5.2      | -3.2         | -3.5   |
|       | 1.03       | -3.2            | -3.5            | -3.9            | -3.2    | -4.5      | -2.8         | -3.0   |
|       | 1.05       | -2.8            | -3.0            | -3.3            | -2.7    | -3.9      | -2.5         | -2.5   |
|       | 1.08       | -2.4            | -2.6            | -2.9            | -2.3    | -3.4      | -2.2         | -2.2   |
|       | 1.11       | -2.1            | -2.3            | -2.5            | -2.0    | -2.9      | -2.0         | -1.9   |
|       | 1.18       | -1.3            | -1.5            | -1.6            | -1.3    | -1.9      | -1.4         | -1.2   |
Table S7: continued from previous page.

| Dimer     | R/Req | $E^{(2)}_{\text{disp}}$ | $D^{20}_{\text{as}}$ | $D^{10}_{\text{as}}$ | D3BJ(HF) | D3BJ(OLYP) | D3BJ(revPBE38) | D3(NS) | DD3S |
|-----------|-------|-------------------------|----------------------|----------------------|----------|------------|----------------|--------|------|
| 4 (C$_6$H$_6$ − SH$_2$) | 1.25   | -1.0                    | -1.1                 | -1.1                 | -0.9     | -1.3       | -1.0           | -0.9   | -1.2 |
|           | 1.32   | -0.7                    | -0.8                 | -0.8                 | -0.7     | -1.0       | -0.7           | -0.6   | -0.9 |
|           | 1.38   | -0.5                    | -0.6                 | -0.6                 | -0.5     | -0.7       | -0.5           | -0.5   | -0.6 |
|           | 1.45   | -0.4                    | -0.4                 | -0.4                 | -0.4     | -0.5       | -0.4           | -0.3   | -0.5 |
|           | 1.58   | -0.2                    | -0.2                 | -0.2                 | -0.2     | -0.3       | -0.2           | -0.2   | -0.3 |
|           | 1.71   | -0.1                    | -0.1                 | -0.1                 | -0.1     | -0.2       | -0.1           | -0.1   | -0.2 |
|           | 1.84   | -0.1                    | -0.1                 | -0.1                 | -0.1     | -0.2       | -0.1           | -0.2   | -0.2 |
|           | 1.97   | 0.0                     | -0.1                 | -0.1                 | -0.1     | -0.1       | -0.1           | 0.0    | -0.1 |
|           | 0.83   | -6.7                    | -6.2                 | -6.9                 | -6.4     | -7.7       | -3.8           | -7.7   | -8.8 |
|           | 0.84   | -6.2                    | -5.8                 | -6.4                 | -6.0     | -7.2       | -3.7           | -7.0   | -8.2 |
|           | 0.87   | -5.3                    | -4.9                 | -5.4                 | -5.1     | -6.4       | -3.3           | -5.8   | -7.0 |
|           | 0.89   | -4.6                    | -4.2                 | -4.6                 | -4.4     | -5.6       | -3.0           | -4.8   | -6.0 |
|           | 0.92   | -3.9                    | -3.6                 | -4.0                 | -3.8     | -4.9       | -2.7           | -4.0   | -5.1 |
|           | 0.95   | -3.4                    | -3.1                 | -3.4                 | -3.2     | -4.3       | -2.5           | -3.3   | -4.4 |
|           | 0.97   | -2.9                    | -2.6                 | -2.9                 | -2.8     | -3.7       | -2.2           | -2.8   | -3.7 |
| 5 (C$_6$H$_6$ − CH$_4$) | 1.00   | -2.5                    | -2.3                 | -2.5                 | -2.4     | -3.2       | -2.0           | -2.4   | -3.2 |
|           | 1.03   | -2.2                    | -1.9                 | -2.1                 | -2.0     | -2.8       | -1.8           | -2.0   | -2.7 |
|           | 1.05   | -1.9                    | -1.7                 | -1.8                 | -1.7     | -2.4       | -1.6           | -1.7   | -2.3 |
|           | 1.08   | -1.6                    | -1.5                 | -1.6                 | -1.5     | -2.1       | -1.4           | -1.4   | -2.0 |
|           | 1.11   | -1.4                    | -1.3                 | -1.4                 | -1.3     | -1.8       | -1.2           | -1.2   | -1.7 |
|           | 1.16   | -1.1                    | -0.9                 | -1.0                 | -1.0     | -1.3       | -1.0           | -0.9   | -1.2 |
|           | 1.21   | -0.8                    | -0.7                 | -0.8                 | -0.7     | -1.0       | -0.8           | -0.7   | -0.9 |
|           | 1.26   | -0.6                    | -0.5                 | -0.6                 | -0.6     | -0.8       | -0.6           | -0.5   | -0.7 |
|           | 1.32   | -0.5                    | -0.4                 | -0.4                 | -0.4     | -0.6       | -0.5           | -0.4   | -0.5 |
|           | 1.37   | -0.4                    | -0.3                 | -0.3                 | -0.3     | -0.5       | -0.4           | -0.3   | -0.4 |
|           | 1.42   | -0.3                    | -0.3                 | -0.3                 | -0.3     | -0.4       | -0.3           | -0.2   | -0.3 |
|           | 1.47   | -0.2                    | -0.2                 | -0.2                 | -0.2     | -0.3       | -0.2           | -0.2   | -0.3 |
|           | 1.58   | -0.1                    | -0.1                 | -0.1                 | -0.1     | -0.2       | -0.2           | -0.1   | -0.2 |
| 6 (CH$_4$ dimer) | 0.86   | -3.0                    | -2.8                 | -2.9                 | -3.0     | -3.7       | -1.8           | -3.3   | -4.1 |
|           | 0.88   | -2.7                    | -2.6                 | -2.7                 | -2.7     | -3.5       | -1.7           | -3.0   | -3.7 |
|           | 0.89   | -2.5                    | -2.3                 | -2.4                 | -2.5     | -3.2       | -1.6           | -2.7   | -3.4 |
|           | 0.92   | -2.1                    | -2.0                 | -2.0                 | -2.1     | -2.7       | -1.4           | -2.2   | -2.8 |
|           | 0.94   | -1.8                    | -1.7                 | -1.7                 | -1.7     | -2.3       | -1.3           | -1.8   | -2.3 |
|           | 0.97   | -1.5                    | -1.4                 | -1.5                 | -2.0     | -2.0       | -1.2           | -1.5   | -1.9 |
|           | 1.00   | -1.2                    | -1.2                 | -1.2                 | -1.7     | -1.0       | -1.0           | -1.2   | -1.6 |
|           | 1.03   | -1.1                    | -1.0                 | -1.0                 | -1.0     | -1.4       | -0.9           | -1.0   | -1.3 |
|           | 1.06   | -0.9                    | -0.8                 | -0.9                 | -0.9     | -1.2       | -0.8           | -0.9   | -1.1 |
|           | 1.08   | -0.8                    | -0.7                 | -0.7                 | -0.7     | -1.0       | -0.7           | -0.7   | -1.0 |
|           | 1.11   | -0.6                    | -0.6                 | -0.6                 | -0.6     | -0.9       | -0.6           | -0.6   | -0.8 |
|           | 1.14   | -0.5                    | -0.5                 | -0.5                 | -0.5     | -0.7       | -0.5           | -0.5   | -0.7 |
|           | 1.17   | -0.5                    | -0.5                 | -0.5                 | -0.6     | -0.6       | -0.5           | -0.4   | -0.6 |
|           | 1.19   | -0.4                    | -0.4                 | -0.4                 | -0.5     | -0.5       | -0.4           | -0.4   | -0.5 |
Table S7: continued from previous page.

| Dimer       | R/Req | \(E_{\text{disp}}^{(2)}\) | \(D_{\text{as}}^{0}\) | \(D_{\text{as}}^{10}\) | D3BJ(HF)  | D3BJ(OLYP) | D3BJ(revPBE38) | D3(NS)  | DD3S  |
|-------------|-------|-----------------|-----------------|-----------------|----------|------------|----------------|--------|-------|
| CH₄ dimer   | 1.22  | -0.3            | -0.3            | -0.3            | -0.3     | -0.5       | -0.3           | -0.3   | -0.4  |
|             | 1.28  | -0.3            | -0.3            | -0.3            | -0.3     | -0.3       | -0.2           | -0.3   | -0.3  |
|             | 1.33  | -0.2            | -0.2            | -0.2            | -0.3     | -0.2       | -0.2           | -0.2   | -0.2  |
|             | 1.39  | -0.1            | -0.1            | -0.1            | -0.2     | -0.1       | -0.1           | -0.1   | -0.1  |
|             | 1.50  | -0.1            | -0.1            | -0.1            | -0.1     | -0.1       | -0.1           | -0.1   | -0.1  |
|             | 1.61  | -0.1            | -0.1            | -0.1            | -0.1     | -0.1       | -0.1           | -0.1   | -0.1  |
| pyridine    | 0.84  | -13.1           | -14.8           | -12.1           | -16.6    | -9.6       | -7.8           | -16.5  |       |
| dimer       | 0.86  | -11.2           | -12.5           | -10.3           | -14.4    | -8.7       | -7.0           | -14.0  |       |
|             | 0.89  | -9.6            | -10.6           | -8.9            | -12.5    | -7.7       | -6.2           | -12.0  |       |
|             | 0.92  | -8.3            | -9.0            | -7.6            | -10.8    | -6.9       | -5.4           | -10.2  |       |
|             | 0.95  | -7.1            | -7.7            | -6.5            | -9.3     | -6.1       | -4.7           | -8.7   |       |
|             | 0.97  | -6.2            | -6.6            | -5.6            | -8.1     | -5.4       | -4.1           | -7.5   |       |
|             | 1.00  | -5.3            | -5.6            | -4.9            | -7.0     | -4.8       | -3.6           | -6.4   |       |
|             | 1.03  | -4.6            | -4.9            | -4.2            | -6.0     | -4.3       | -3.2           | -5.5   |       |
|             | 1.05  | -4.0            | -4.2            | -3.7            | -5.2     | -3.8       | -2.8           | -4.8   |       |
|             | 1.08  | -3.5            | -3.6            | -3.2            | -4.5     | -3.3       | -2.4           | -4.2   |       |
|             | 1.11  | -3.0            | -3.2            | -2.8            | -4.0     | -2.9       | -2.1           | -3.6   |       |
|             | 1.14  | -2.7            | -2.8            | -2.5            | -3.5     | -2.6       | -1.9           | -3.1   |       |
|             | 1.16  | -2.3            | -2.4            | -2.2            | -3.0     | -2.3       | -1.6           | -2.7   |       |
|             | 1.19  | -2.0            | -2.1            | -1.9            | -2.6     | -2.0       | -1.5           | -2.4   |       |
|             | 1.22  | -1.8            | -1.9            | -1.7            | -2.3     | -1.8       | -1.3           | -2.1   |       |
|             | 1.27  | -1.4            | -1.4            | -1.3            | -1.8     | -1.4       | -1.0           | -1.6   |       |
|             | 1.35  | -1.0            | -1.0            | -0.9            | -1.3     | -1.0       | -0.7           | -1.2   |       |
|             | 1.49  | -0.5            | -0.6            | -0.6            | -0.7     | -0.6       | -0.4           | -0.7   |       |
|             | 1.62  | -0.3            | -0.3            | -0.3            | -0.4     | -0.4       | -0.2           | -0.4   |       |
|             | 1.76  | -0.2            | -0.2            | -0.2            | -0.3     | -0.2       | -0.1           | -0.2   |       |
|             | 1.89  | -0.1            | -0.1            | -0.1            | -0.1     | -0.2       | -0.1           | -0.2   |       |
| pyridine    | 0.84  | -13.7           | -15.5           | -13.0           | -15.0    | -7.4       | -16.4          | -17.8  |       |
| dimer       | 0.87  | -10.4           | -11.1           | -10.3           | -12.4    | -6.4       | -11.4          | -14.0  |       |
|             | 0.88  | -9.9            | -10.5           | -11.0           | -9.8     | -11.9      | -6.2           | -10.7  | -13.4 |
|             | 0.89  | -9.0            | -9.5            | -9.9            | -9.0     | -11.1      | -5.9           | -9.4   | -12.3 |
|             | 0.91  | -7.9            | -8.3            | -8.7            | -7.9     | -10.0      | -5.4           | -8.0   | -10.9 |
|             | 0.92  | -7.2            | -7.6            | -7.9            | -7.2     | -5.1       | -7.2           | -9.9   |       |
|             | 0.94  | -6.2            | -6.4            | -6.7            | -6.2     | -4.6       | -5.9           | -8.4   |       |
|             | 0.96  | -5.3            | -5.5            | -5.7            | -5.3     | -4.2       | -4.9           | -7.2   |       |
|             | 0.98  | -4.5            | -4.7            | -4.8            | -4.5     | -3.8       | -4.1           | -6.1   |       |
|             | 1.00  | -3.9            | -4.0            | -4.1            | -3.9     | -3.4       | -3.5           | -5.2   |       |
|             | 1.02  | -3.4            | -3.5            | -3.4            | -4.6     | -3.0       | -2.9           | -4.4   |       |
|             | 1.04  | -2.9            | -3.0            | -2.9            | -4.0     | -2.7       | -2.5           | -3.8   |       |
|             | 1.06  | -2.5            | -2.6            | -2.5            | -3.5     | -2.4       | -2.1           | -3.2   |       |
|             | 1.08  | -2.2            | -2.3            | -2.2            | -3.0     | -2.1       | -1.8           | -2.8   |       |
|             | 1.10  | -1.9            | -2.0            | -1.9            | -2.6     | -1.9       | -1.6           | -2.4   |       |
Table S7: continued from previous page.

| Dimer | R/Req | E_{disp}^{(2)} | D_{20}^{20} | D_{10}^{as} | D3BJ(HF) | D3BJ(OLYP) | D3BJ(revPBE38) | D3(NS) | DD3S |
|-------|-------|----------------|-------------|-------------|----------|------------|----------------|--------|------|
| 8 (pyridine dimer) | | | | | | | | | |
| 1.12  | -1.6  | -1.7           | -1.7        | -1.6        | -2.2     | -1.6       | -1.4           | -2.1   |      |
| 1.16  | -1.3  | -1.3           | -1.3        | -1.7        | -1.7     | -1.3       | -1.0           | -1.6   |      |
| 1.22  | -0.9  | -0.9           | -0.9        | -1.1        | -1.1     | -0.9       | -0.7           | -1.1   |      |
| 1.33  | -0.5  | -0.5           | -0.5        | -0.6        | -0.5     | -0.4       | -0.6           | -0.6   |      |
| 1.43  | -0.3  | -0.3           | -0.3        | -0.4        | -0.4     | -0.3       | -0.2           | -0.3   |      |
| 1.63  | -0.1  | -0.1           | -0.1        | -0.1        | -0.1     | -0.1       | -0.1           | -0.1   |      |
| 1.84  | 0.0   | 0.0            | 0.0         | -0.1        | -0.1     | -0.1       | 0.0            | -0.1   |      |
| 9 (C6H6 dimer) | | | | | | | | | |
| 0.75  | -12.5 | -12.6          | -13.3       | -11.3       | -15.7    | -9.5       | -8.0           | -15.4  |      |
| 0.78  | -12.3 | -12.5          | -13.1       | -11.2       | -15.6    | -9.4       | -8.0           | -15.2  |      |
| 0.81  | -12.1 | -12.2          | -12.9       | -11.0       | -15.3    | -9.3       | -7.9           | -14.9  |      |
| 0.84  | -11.8 | -11.9          | -12.5       | -10.7       | -15.0    | -9.1       | -7.7           | -14.5  |      |
| 0.87  | -11.4 | -11.5          | -12.1       | -10.4       | -14.5    | -8.8       | -7.6           | -14.1  |      |
| 0.90  | -10.9 | -11.1          | -11.6       | -10.0       | -14.0    | -8.6       | -7.3           | -13.6  |      |
| 0.93  | -10.4 | -10.6          | -11.1       | -9.6        | -13.4    | -8.2       | -7.1           | -13.0  |      |
| 0.94  | -10.2 | -10.3          | -10.8       | -9.4        | -13.1    | -8.1       | -6.9           | -12.7  |      |
| 0.96  | -9.9  | -10.0          | -10.6       | -9.1        | -12.8    | -7.9       | -6.8           | -12.3  |      |
| 0.97  | -9.6  | -9.7           | -10.3       | -8.9        | -12.5    | -7.7       | -6.6           | -12.0  |      |
| 0.99  | -9.4  | -9.5           | -10.0       | -8.6        | -12.1    | -7.5       | -6.4           | -11.7  |      |
| 1.00  | -9.1  | -9.2           | -9.6        | -8.4        | -11.7    | -7.3       | -6.3           | -11.3  |      |
| 1.05  | -8.8  | -8.9           | -9.3        | -8.1        | -11.4    | -7.1       | -6.1           | -10.9  |      |
| 1.16  | -8.2  | -8.3           | -8.7        | -7.6        | -10.6    | -6.6       | -5.7           | -10.2  |      |
| 1.26  | -7.7  | -7.6           | -8.0        | -7.1        | -9.9     | -6.2       | -5.4           | -9.5   |      |
| 1.37  | -7.1  | -7.0           | -7.4        | -6.5        | -9.1     | -5.8       | -5.0           | -8.7   |      |
| 1.47  | -6.5  | -6.4           | -6.7        | -6.0        | -8.4     | -5.3       | -4.6           | -8.0   |      |
| 1.58  | -5.9  | -5.8           | -6.1        | -5.5        | -7.6     | -4.9       | -4.3           | -7.3   |      |
| 10 (C6H6 dimer) | | | | | | | | | |
| 0.75  | -6.9  | -6.8           | -7.1        | -6.2        | -8.9     | -6.0       | -4.7           | -8.2   |      |
| 0.78  | -6.9  | -6.7           | -7.0        | -6.1        | -8.8     | -5.9       | -4.7           | -8.1   |      |
| 0.82  | -6.7  | -6.6           | -6.9        | -6.0        | -8.6     | -5.8       | -4.6           | -8.0   |      |
| 0.85  | -6.6  | -6.5           | -6.7        | -5.9        | -8.4     | -5.7       | -4.5           | -7.8   |      |
| 0.88  | -6.4  | -6.3           | -6.5        | -5.7        | -8.2     | -5.6       | -4.4           | -7.6   |      |
| 0.92  | -6.1  | -6.0           | -6.3        | -5.5        | -7.9     | -5.4       | -4.3           | -7.3   |      |
| 0.95  | -5.9  | -5.8           | -6.0        | -5.3        | -7.6     | -5.2       | -4.1           | -7.0   |      |
| 0.97  | -5.7  | -5.6           | -5.9        | -5.2        | -7.4     | -5.1       | -4.0           | -6.9   |      |
| 0.98  | -5.6  | -5.5           | -5.7        | -5.1        | -7.2     | -5.0       | -3.9           | -6.7   |      |
| 1.00  | -5.5  | -5.4           | -5.6        | -5.0        | -7.1     | -4.9       | -3.9           | -6.5   |      |
| 1.06  | -5.3  | -5.2           | -5.4        | -4.8        | -6.9     | -4.7       | -3.8           | -6.4   |      |
| 1.12  | -5.2  | -5.1           | -5.3        | -4.7        | -6.7     | -4.6       | -3.7           | -6.2   |      |
| 1.18  | -5.0  | -4.9           | -5.1        | -4.6        | -6.5     | -4.5       | -3.6           | -6.0   |      |
| 1.29  | -4.7  | -4.6           | -4.8        | -4.3        | -6.1     | -4.2       | -3.4           | -5.6   |      |
| 1.41  | -4.4  | -4.3           | -4.4        | -4.0        | -5.7     | -3.9       | -3.2           | -5.2   |      |
| 1.53  | -4.1  | -3.9           | -4.1        | -3.7        | -5.3     | -3.7       | -2.9           | -4.9   |      |
| 1.65  | -3.7  | -3.6           | -3.8        | -3.4        | -4.8     | -3.4       | -2.7           | -4.5   |      |
Table S7: continued from previous page.

| Dimer    | R/Req | \( E_{\text{dispx}}^{(2)} \) | \( D_{\text{as}}^{20} \) | \( D_{\text{as}}^{10} \) | D3BJ(HF) | D3BJ(OLYP) | D3BJ(revPBE38) | D3(NS) | DD3S |
|----------|-------|-------------------------------|--------------------------|--------------------------|----------|------------|----------------|--------|------|
|          | 1.76  | -3.4                          | -3.3                     | -3.4                     | -3.2     | -4.4       | -3.1           | -2.5   | -4.1 |
| MUE/MURE |       | 0.1/4.1                       | 0.3/6.0                  | 0.3/5.3                  | 1.3/30.0 | 0.9/15.3   | 1.1/20.3       | 1.2/25.0 |      |

- \( a \) In units of kcal \( \cdot \) mol\(^{-1} \).
- \( b \) Benchmark reported in Ref. S7.
- \( c \) \( D_{\text{as}} \) revision reported herein.
- \( d \) \( D_{\text{as}} \) revision reported in Ref. S22.
- \( e \) D3\(^{19} \) dispersion term calculated with BJ damping for the HF level of theory or given functional.
- \( f \) D3\(^{19} \) dispersion term calculated without switching.
- \( g \) Method reported in Ref. S21.

Table S8: MP2 and MED interaction energy with its \( E_{EL,MTP}^{(10)} \) and \( D_{\text{as}}^{20} \) contributions\(^a\), computed for uPA inhibitors.

| Inhibitor | \( pIC_{50}^{b} \) | \( E_{EL,MTP}^{(10)} \) | \( D_{\text{as}}^{20} \) | MED | MP2\(^c\) |
|-----------|-------------------|------------------------|---------------------|-----|----------|
| 1         | 8.19              | -157.6                 | -69.1               | -226.7 | -135.8 |
| 2         | 6.27              | -129.8                 | -55.6               | -185.4 | -122.6 |
| 3         | 6.12              | -149.9                 | -56.4               | -206.3 | -133.2 |
| 4         | 6.11              | -130.3                 | -50.8               | -181.1 | -124.0 |
| 5         | 3.80              | -102.1                 | -37.2               | -139.3 | -119.6 |

- \( a \) In units of kcal \( \cdot \) mol\(^{-1} \).
- \( b \) Numbering of the inhibitors is consistent with Ref. S23, from which the \( pIC_{50} \) values were taken.
- \( c \) Values were provided by Grzywa et al.\(^{S23} \).

Table S9: MP2 and MED interaction energy with its \( E_{EL,MTP}^{(10)} \) and \( D_{\text{as}}^{20} \) contributions\(^a\), computed for HB alcohol dimers.

| Dimer \(^b\) | SAPT\(^b\) | MP2 | \( E_{EL,MTP}^{(10)} \) | \( D_{\text{as}}^{20} \) | MED |
|--------------|-----------|-----|------------------------|---------------------|-----|
| H\(_2\)O     | -4.6      | -3.2 | -4.9                   | -2.3                | -7.1 |
| MeOH         | -5.4      | -5.5 | -7.1                   | -4.8                | -11.8 |
| EtOH         | -5.6      | -5.7 | -6.8                   | -5.3                | -12.0 |
| nPrOH        | -5.9      | -5.9 | -6.3                   | -5.4                | -11.7 |
| nBuOH        | -6.0      | -5.9 | -5.8                   | -5.5                | -11.4 |
| iPrOH        | -6.5      | -6.5 | -5.9                   | -6.9                | -12.7 |
| tBuOH        | -7.2      | -7.3 | -7.7                   | -7.6                | -15.4 |

- \( a \) In units of kcal \( \cdot \) mol\(^{-1} \).
- \( b \) Naming of dimers is consistent with Ref. S24, from which the reference SAPT energy values were taken.
Table S10: Performance of the selected empirical scoring functions\(^a\) for the ranking of uPA inhibitors.

| Inhibitor | PLANTS\(^b\) | PLANTS\(^c\) | PLANTS\(^d\) | PLANTS\(^e\) | PLANTS\(^f\) | ChemScore | CHEMPLP | Vina | DSX | GoldScore | AutoDock | RankScore | \(R^2\) | \(N_{\text{pred}}\) | \(X_{\text{pred}}\) |
|-----------|-------------|-------------|-------------|-------------|-------------|------------|---------|------|-----|-----------|----------|-----------|------|-----------|-----------|
| 1         | 45.5        | 0.0         | 53.9        | 1.5         | -38.8       | 9.4        | 25.3    | 15.4 | 35.4 | 30.5       | 42.4     | 2.1       | 0.86 | 0.81       | 0.74      | 0.00      |
| 2         | 47.2        | -17.4       | 56.1        | -1.9        | -44.9       | 14.1       | 29.2    | 24.9 | 44.5 | 31.5       | 37.0     | 1.7       | 0.81 | 0.63       | 0.66      | 0.00      |
| 3         | 44.8        | -12.6       | 54.4        | -0.5        | -32.0       | 13.0       | 25.0    | 9.8  | 35.1 | 29.5       | 32.0     | 3.1       | 0.81 | 0.40       | 0.40      | 0.00      |
| 4         | 48.1        | 2.2         | 46.1        | 0.2         | -25.2       | 1.6        | 5.7     | 11.1 | 6.0  | 26.1       | 30.0     | 1.6       | 0.81 | 0.37       | 0.37      | 0.00      |
| 5         | 58.0        | -31.8       | 66.2        | -4.5        | -60.1       | 18.2       | 41.4    | 21.6 | 37.2 | 30.0       | 40.0     | 4.6       | 0.81 | 0.86       | 0.74      | 0.00      |

\(^a\)The scores obtained with particular scoring functions are given in units of kcal \(\cdot\) mol\(^{-1}\) (PLANTS\(^{PLP}\), PLANTS\(^{CHEMPLP}\), Vina, AutoDock) or in arbitrary units (GoldScore, ChemScore, ChemPLP, ASP, DSX, RankScore).

\(^b\)Numbering of the inhibitors is consistent with Ref. S23.

\(^c\)Correlation coefficient between the energy obtained at a given level of theory and the experimental inhibitory activity (expressed as \(pIC_{50}\) values) taken from Ref. S23. In the case of GoldScore, ChemScore, ChemPLP and ASP functions, for which higher score indicates greater inhibitory activity, the opposite of the correlation coefficient value is given to facilitate direct comparison with the results of the remaining empirical scoring functions (or the MED model), wherein the more potent inhibitor is associated with a lower score (or the binding energy) value.

\(^d\)Percentage of successful predictions \([\%]\).
Table S11: Differential intermediate state stabilization\textsuperscript{a} in ketosteroid isomerase-catalyzed reaction.\textsuperscript{b}

| Residue | $E_{EL,MTP}^{(10)}$ | $D_{as}^{20}$ | MED |
|---------|---------------------|---------------|-----|
| TYR14  | -7.7                | -0.7          | -8.5|
| LEU18  | -0.2                | -0.1          | -0.3|
| PRO39  | 0.3                 | 0.0           | 0.3 |
| PHE54  | 0.4                 | 0.4           | 0.8 |
| TYR55  | -1.6                | 0.0           | -1.7|
| SER58  | 0.8                 | 0.1           | 0.9 |
| LEU59  | 0.0                 | 0.0           | 0.0 |
| LEU61  | 0.2                 | 0.0           | 0.2 |
| LEU63  | 0.0                 | 0.0           | 0.0 |
| VAL65  | -0.2                | 0.0           | -0.2|
| PHE80  | 0.1                 | 0.0           | 0.1 |
| PHE82  | -1.0                | -0.1          | -1.1|
| VAL84  | -0.1                | -0.1          | -0.2|
| PHE86  | -0.2                | 0.2           | 0.1 |
| THR93  | 0.2                 | 0.0           | 0.2 |
| VAL95  | 0.5                 | 0.0           | 0.5 |
| PRO97  | -0.3                | -0.1          | -0.4|
| ASP99  | -6.4                | -0.5          | -7.0|
| MET112 | -2.1                | -0.4          | -2.5|
| ALA114 | -1.0                | -0.5          | -1.5|
| PHE116 | 1.2                 | -0.2          | 1.0 |
| ILE121 | -0.1                | 0.0           | -0.1|
| total  | -17.3               | -2.1          | -19.4|

\textsuperscript{a}In units of kcal · mol\textsuperscript{-1}.

\textsuperscript{b}The structures of enzyme-intermediate and enzyme-substrate complexes of\textit{C. testosteroni} ketosteroid isomerase were derived from the QM/MM simulation reported in Ref. S25.
Table S12: Differential intermediate state stabilization\textsuperscript{a} in ketosteroid isomerase-catalyzed reaction — amino acid residue rotamers optimized with respect to DISS lowering. For comparison with the total DISS value characterizing the KSI structures reported in Ref. S25, the respective DISS contributions of Pro39, Pro97, and Ala114 residues are included without rotamer modification.

| Residue  | $E_{EL,MT}^{(10)}$ | $D_{as}^{20}$ | MED  |
|----------|-------------------|--------------|------|
| TYR14    | -5.7              | -0.5         | -6.2 |
| LEU18    | -0.4              | 0.0          | -0.4 |
| PRO39\textsuperscript{b} | 0.3              | -0.0         | 0.3  |
| PHE54    | 0.0               | 0.0          | 0.0  |
| TYR55    | -0.9              | 0.0          | -0.9 |
| SER58    | -0.3              | 0.1          | -0.2 |
| LEU59    | 0.0               | 0.0          | 0.0  |
| LEU61    | 0.0               | 0.0          | 0.0  |
| LEU63    | -0.1              | 0.0          | 0.0  |
| VAL65    | -0.2              | 0.0          | -0.2 |
| PHE80    | -0.4              | 0.0          | -0.4 |
| PHE82    | -1.5              | -0.2         | -1.8 |
| VAL84    | -0.8              | -0.1         | -0.8 |
| PHE86    | -0.3              | 0.2          | -0.1 |
| THR93    | 0.0               | 0.0          | 0.0  |
| VAL95    | -0.4              | 0.0          | -0.4 |
| PRO97\textsuperscript{b} | -0.3              | -0.1         | -0.4 |
| ASH99    | -6.5              | -0.4         | -6.9 |
| MET112   | -2.0              | -0.2         | -2.2 |
| ALA114\textsuperscript{b} | -1.0              | -0.5         | -1.5 |
| PHE116   | 1.2               | -0.1         | 1.1  |
| ILE121   | 0.1               | 0.0          | 0.1  |
| total    | -19.0             | -1.8         | -20.8 |

\textsuperscript{a}In units of kcal \cdot mol\textsuperscript{-1}.

\textsuperscript{b}The structures of enzyme-intermediate and enzyme-substrate complexes of \textit{C. testosteroni} ketosteroid isomerase were derived from the QM/MM simulation reported in Ref. S25.
Figure S1: Signed relative errors (in percent) of the new $D_{\text{as}}^{(2)}$ function with respect to the benchmark $E_{\text{disp}}^{(2)}$ for all dimers from the training set.
Figure S1: continued from previous page.
Figure S1: continued from previous page.
Figure S1: continued from previous page.
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