

Supporting Information:

**GFN2-xTB – an Accurate and Broadly
Parametrized Self-Consistent Tight-Binding
Quantum Chemical Method with Multipole
Electrostatics and Density-Dependent Dispersion
Contributions**

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1 Electrostatic and exchange-correlation energy contribution for second order density fluctuations

If no integration ranges are given, the integration goes from $-\infty$ to $+\infty$. In density functional tight-binding, the electrostatic and exchange-correlation contribution to the total energy resulting from second order density fluctuations is given as.^{S1}

$$E_{\text{ES}}^{(2)} + E_{\text{XC}}^{(2)} = \frac{1}{2} \iint \left(\frac{1}{r_{ij}} + \left. \frac{\partial^2 E_{\text{XC}}}{\partial \rho(\mathbf{r}_i) \partial \rho(\mathbf{r}_j)} \right|_{\rho=\rho_0} \right) \delta \rho(\mathbf{r}_i) \delta \rho(\mathbf{r}_j) d\mathbf{r}_i d\mathbf{r}_j \quad (1)$$

The two terms will be approximated individually in the following.

1.1 Anisotropic electrostatics

1.1.1 Multipole expansion in two electronic variables

We will first assume that the Coulomb forces on the same atomic site can be neglected or effectively be absorbed in the XC contribution. Then, we will assume distant atoms and factorize the integral of the Coulomb operator:

$$\lim_{R_{AB} \rightarrow \infty} E_{\text{ES}}^{(2)} \approx \frac{1}{2} \sum_{i \in A, j \in B} \frac{\int \rho_A(\mathbf{r}_i) d\mathbf{r}_i \int \rho_B(\mathbf{r}_j) d\mathbf{r}_j}{r_{ij}}. \quad (2)$$

Here, the particle i is in proximity to the site (atomic center) A with $\mathbf{r}_i = \mathbf{R}_A + \mathbf{r}_{Ai}$ and particle j is close to corresponding center B with $\mathbf{r}_j = \mathbf{R}_B + \mathbf{r}_{Bj}$, The Coulomb operator can

be expanded in a Cartesian multipole expansion to (showing all terms up to second order)

$$\begin{aligned}
\frac{1}{r_{ij}} &\approx \frac{1}{r_{ij}} \Big|_{\mathbf{r}_{A_i}, \mathbf{r}_{B_j}=\mathbf{0}} + \sum_{\alpha=x,y,z} \left[(\alpha_i - \alpha_A) \frac{\partial}{\partial \alpha_i} + (\alpha_j - \alpha_B) \frac{\partial}{\partial \alpha_j} \right] \frac{1}{r_{ij}} \Big|_{\mathbf{r}_{A_i}, \mathbf{r}_{B_j}=\mathbf{0}} \\
&+ \frac{1}{2} \sum_{\alpha,\beta=x,y,z} \left[(\alpha_i - \alpha_A) \frac{\partial}{\partial \alpha_i} + (\alpha_j - \alpha_B) \frac{\partial}{\partial \alpha_j} \right] \left[(\beta_i - \beta_A) \frac{\partial}{\partial \beta_i} + (\beta_j - \beta_B) \frac{\partial}{\partial \beta_j} \right] \frac{1}{r_{ij}} \Big|_{\mathbf{r}_{A_i}, \mathbf{r}_{B_j}=\mathbf{0}} \\
&+ \dots \\
&= \frac{1}{r_{ij}} \Big|_{\mathbf{r}_{A_i}, \mathbf{r}_{B_j}=\mathbf{0}} + \sum_{\alpha=x,y,z} \frac{(\alpha_i - \alpha_A) \alpha_{ij} + (\alpha_j - \alpha_B) \alpha_{ji}}{r_{ij}^3} \Big|_{\mathbf{r}_{A_i}, \mathbf{r}_{B_j}=\mathbf{0}} \\
&+ \frac{1}{2} \sum_{\alpha,\beta=x,y,z} \left[\frac{(\alpha_i - \alpha_A) (\beta_i - \beta_A) (3\alpha_{ij}\beta_{ij} - \delta_{\alpha\beta} r_{ij}^2) + (\alpha_j - \alpha_B) (\beta_i - \beta_A) (3\alpha_{ji}\beta_{ij} + \delta_{\alpha\beta} r_{ij}^2)}{r_{ij}^5} \right. \\
&+ \left. \frac{(\alpha_i - \alpha_A) (\beta_j - \beta_B) (3\alpha_{ij}\beta_{ji} + \delta_{\alpha\beta} r_{ij}^2) + (\alpha_j - \alpha_B) (\beta_j - \beta_B) (3\alpha_{ji}\beta_{ji} - \delta_{\alpha\beta} r_{ij}^2)}{r_{ij}^5} \right] \Big|_{\mathbf{r}_{A_i}, \mathbf{r}_{B_j}=\mathbf{0}} \quad (3) \\
&+ \dots \\
&= \frac{1}{R_{AB}} + \sum_{\alpha=x,y,z} \left[\frac{(\alpha_i - \alpha_A) \alpha_{AB}}{R_{AB}^3} + \frac{(\alpha_j - \alpha_B) \alpha_{BA}}{R_{AB}^3} \right] \\
&+ \frac{1}{2} \sum_{\alpha,\beta=x,y,z} \left[\frac{(\alpha_i - \alpha_A) (\beta_i - \beta_A) (3\alpha_{AB}\beta_{AB} - \delta_{\alpha\beta} R_{AB}^2)}{R_{AB}^5} \right. \\
&+ \frac{(\alpha_j - \alpha_B) (\beta_i - \beta_A) (3\alpha_{BA}\beta_{AB} + \delta_{\alpha\beta} R_{AB}^2)}{R_{AB}^5} \\
&+ \frac{(\alpha_i - \alpha_A) (\beta_j - \beta_B) (3\alpha_{AB}\beta_{BA} + \delta_{\alpha\beta} R_{AB}^2)}{R_{AB}^5} \\
&+ \left. \frac{(\alpha_j - \alpha_B) (\beta_j - \beta_B) (3\alpha_{BA}\beta_{BA} - \delta_{\alpha\beta} R_{AB}^2)}{R_{AB}^5} \right] + \dots .
\end{aligned}$$

Here, $r_{ij} = |\mathbf{r}_j - \mathbf{r}_i|$, $R_{AB} = |\mathbf{R}_B - \mathbf{R}_A|$, and $\alpha_{AB} = -\alpha_{BA} = \alpha_B - \alpha_A$. α and β represent Cartesian components. Energy terms of higher order in \mathbf{r}_{A_i} and \mathbf{r}_{B_j} are not shown in Eq. 3 and will be neglected in our approach. This way, all energy terms up to second order are considered, which ensures that all electrostatic interactions decaying with R_{AB}^{-3} or slower are taken into account. Insertion of Eq. 3 into Eq. 2 and integrating over all positive (clamped

nuclei) and negative (electrons) particles then yields

$$\begin{aligned} \lim_{R_{AB} \rightarrow \infty} E_{\text{ES}}^{(2)} = & \frac{1}{2} \sum_{A \neq B} \left[\frac{q_A q_B}{R_{AB}} + \frac{q_B (\boldsymbol{\mu}_A^T \mathbf{R}_{AB}) + q_A (\boldsymbol{\mu}_B^T \mathbf{R}_{BA})}{R_{AB}^3} \right. \\ & - \frac{3 (\boldsymbol{\mu}_A^T \mathbf{R}_{AB}) (\boldsymbol{\mu}_B^T \mathbf{R}_{AB}) - (\boldsymbol{\mu}_A^T \boldsymbol{\mu}_B) R_{AB}^2}{R_{AB}^5} \\ & \left. + \frac{q_B \mathbf{R}_{AB}^T \boldsymbol{\Theta}_A \mathbf{R}_{AB}}{R_{AB}^5} + \frac{q_A \mathbf{R}_{AB}^T \boldsymbol{\Theta}_B \mathbf{R}_{AB}}{R_{AB}^5} \right] \end{aligned} \quad (4)$$

with

$$\begin{aligned} q_A &= Z_A - \sum_{\kappa \in A} \sum_{\lambda} P_{\kappa\lambda} \underbrace{\langle \phi_\lambda | \phi_\kappa \rangle}_{S_{\lambda\kappa}} \\ \mu_A^\alpha &= \sum_{\kappa \in A} \sum_{\lambda} P_{\kappa\lambda} \left(\alpha_A S_{\lambda\kappa} - \underbrace{\langle \phi_\lambda | \alpha_i | \phi_\kappa \rangle}_{D_{\lambda\kappa}^\alpha} \right) = - \sum_{\kappa \in A} \sum_{\lambda} P_{\kappa\lambda} D_{\lambda\kappa A}^\alpha \\ \theta_A^{\alpha\beta} &= \sum_{\kappa \in A} \sum_{\lambda} P_{\kappa\lambda} \left(\alpha_A D_{\lambda\kappa}^\beta + \beta_A D_{\lambda\kappa}^\alpha - \alpha_A \beta_A S_{\lambda\kappa} - \underbrace{\langle \phi_\lambda | \alpha_i \beta_i | \phi_\kappa \rangle}_{Q_{\lambda\kappa}^{\alpha\beta}} \right) = - \sum_{\kappa \in A} \sum_{\lambda} P_{\kappa\lambda} Q_{\lambda\kappa A}^{\alpha\beta} \end{aligned} \quad (5)$$

and

$$\boldsymbol{\Theta}_A^{\alpha\beta} = \frac{3}{2} \theta_A^{\alpha\beta} - \frac{\delta_{\alpha\beta}}{2} (\theta_A^{xx} + \theta_A^{yy} + \theta_A^{zz}) . \quad (6)$$

Here, q_A , $\boldsymbol{\mu}_A$, and $\boldsymbol{\Theta}_A$ are the cumulative atomic monopole (i.e., charge), dipole, and quadrupole moment, respectively. $S_{\lambda\kappa}$, $D_{\lambda\kappa}^\alpha$, and $Q_{\lambda\kappa}^{\alpha\beta}$ are the overlap, electric dipole, and electric quadrupole moments, respectively. The extra index A in the multipole integrals $D_{\lambda\kappa A}^\alpha$ and $Q_{\lambda\kappa A}^{\alpha\beta}$ indicates that these are evaluated with the origin at the corresponding atomic center, while $D_{\lambda\kappa}^\alpha$ and $Q_{\lambda\kappa}^{\alpha\beta}$ are given with origin $\mathbf{O} = (0 \ 0 \ 0)^T$.

Since the isotropic charge-charge term (first term in Eq. 4) is already captured in a shell-wise manner, the anisotropic terms represent the newly introduced terms in the anisotropic electrostatic (AES) energy. Adding a damping function to damp the AES contributions at short range then leads to the expression given in the manuscript.

1.2 Anisotropic XC kernel contribution

The second order change in the XC energy takes the form of a static XC kernel $f_{\text{XC}}(\mathbf{r}_i, \mathbf{r}_j)$. In accordance with the (semi-)local density functional origin, a local density approximation is applied, which restricts this contribution to same-site terms only:

$$\begin{aligned}
 E_{\text{XC}}^{(2)} &= \frac{1}{2} \iint \frac{\partial^2 E_{\text{XC}}}{\partial \rho(\mathbf{r}_i) \partial \rho(\mathbf{r}_j)} \Big|_{\rho=\rho_0} \delta \rho(\mathbf{r}_i) \delta \rho(\mathbf{r}_j) d\mathbf{r}_i d\mathbf{r}_j \\
 &\approx \frac{1}{2} \iint \delta(\mathbf{r}_i - \mathbf{r}_j) f_{\text{XC}}(\mathbf{r}_i, \mathbf{r}_j) \delta \rho(\mathbf{r}_i) \delta \rho(\mathbf{r}_j) d\mathbf{r}_i d\mathbf{r}_j \\
 &= \frac{1}{2} \int f_{\text{XC}}(\mathbf{r}_i) \delta \rho^2(\mathbf{r}_i) d\mathbf{r}_i
 \end{aligned} \tag{7}$$

In the last line, we have dropped the second redundant index of f_{XC} . For distant atoms with non-overlapping atomic reference densities ρ_{A_0} , the integral can be approximately partitioned in terms of atomic contributions.

$$E_{\text{XC}}^{(2)} \approx \frac{1}{2} \sum_A \int f_{\text{XC}}(\mathbf{r}_i) \delta \rho_A^2(\mathbf{r}_i) d\mathbf{r}_i = \sum_A E_{\text{XC}}^{(2),A} \tag{8}$$

The XC kernel is evaluated on the reference density ρ_0 (see Eq. 7). Hence, in terms of spherically symmetric atomic reference densities, there is no angular dependence (cf. spherical coordinates) of this kernel. So, in terms of spherical coordinates, this integral around the nuclear center A can be written as ($x_{Ai} = r \sin(\vartheta) \cos(\varphi)$, $y_{Ai} = r \sin(\vartheta) \sin(\varphi)$, and $z_{Ai} = r \cos(\vartheta)$):

$$E_{\text{XC}}^{(2),A} = \frac{1}{2} \int_0^{2\pi} \int_0^\pi \int_0^\infty \left(\sqrt{f_{\text{XC}}(r)} \delta \rho(r, \vartheta, \varphi) \right)^2 r^2 \sin(\vartheta) dr d\vartheta d\varphi \tag{9}$$

We will not consider details regarding specific prefactors or the explicit decay of ρ_{A_0} , as the final energy expression relies on fitted parameters anyhow. Nevertheless, for the monotonically decaying reference densities, an LDA-based exchange kernel takes the form $f_{\text{XC}}(r) \sim \rho_{A_0}^{-2/3}(r) \sim e^{cr}$ (c is an atom-specific constant), i.e., a monotonically increasing function with

distance from the nucleus. Due to the faster exponential decay of the density fluctuation, the term in parentheses in Eq. 9 will decay to zero for $r \rightarrow \infty$. Next, we decompose this term into a product of a radial part and an angular part. The angular part will be expressed by a series of spherical harmonic functions.

$$\sqrt{f_{\text{XC}}(r)}\delta\rho(r, \vartheta, \varphi) = R(r) \sum_l \sum_{m=-l}^l a_{l,m} Y_l^m(\vartheta, \varphi) \quad (10)$$

The integral in Eq. 9 then becomes:

$$E_{\text{XC}}^{(2),A} = \frac{1}{2} \int_0^{2\pi} \int_0^\pi \left[\sum_l \sum_{m=-l}^l a_{l,m} Y_l^m(\vartheta, \varphi) \right]^2 \sin(\vartheta) d\vartheta d\varphi \int_0^\infty [R(r)r]^2 dr \quad (11)$$

Next, we exploit the orthogonality properties of spherical harmonics, to expand the squared sum, i.e., we use:

$$\int_0^{2\pi} \int_0^\pi Y_l^m(\vartheta, \varphi) Y_{l'}^{m'}(\vartheta, \varphi) \sin(\vartheta) d\vartheta d\varphi = \delta_{mm'} \delta_{ll'} \quad (12)$$

This way, the integral in Eq. 13 is equivalent to:

$$E_{\text{XC}}^{(2),A} = \sum_l \sum_{m=-l}^l a_{l,m}^2 \frac{1}{2} \int_0^{2\pi} \int_0^\pi [Y_l^m(\vartheta, \varphi)]^2 \sin(\vartheta) d\vartheta d\varphi \int_0^\infty [R(r)r]^2 dr \quad (13)$$

In the derivation of the anisotropic XC contribution in GFN2-xTB, we now make the following approximations: First, we approximate the angular part as:

$$\int_0^{2\pi} \int_0^\pi [Y_l^m(\vartheta, \varphi)]^2 \sin(\vartheta) d\vartheta d\varphi \approx \left[\int_0^{2\pi} \int_0^\pi Y_l^m(\vartheta, \varphi) \sin(\vartheta) d\vartheta d\varphi \right]^2$$

This is a lower bound approximation to the integral, but this way, it becomes possible to use the same CAMM expressions as in the anisotropic electrostatic case. Then we truncate the series at $l = 2$ and express the product of the angular and radial integral as the squared atomic multipole moment (Mulliken approximation) times an l -dependent constant. The XC energy to second order in the density fluctuations is then given as a sum over local CAMM

contributions:

$$E_{\text{XC}}^{(2)} \approx \sum_A \left(f_{\text{XC}}^{q_A} q_A^2 + \underbrace{f_{\text{XC}}^{\mu_A} |\boldsymbol{\mu}_A|^2 + f_{\text{XC}}^{\Theta_A} \|\boldsymbol{\Theta}_A\|^2}_{E_{\text{AXC}}^A} \right) \quad (14)$$

The zeroth order monopole term is already incorporated within the short-ranged damping/on-site contribution in the second order isotropic Coulomb interaction as in DFTB^{S1,S2} and GFN-xTB.^{S3} Here the proportionality constant relates to the chemical hardness of the atom. The same is true (in a shell-wise manner) in GFN2-xTB. The other terms in Eq. 14 describe polarization effects of the atomic density up to second order in the multipole expansion and are included in E_{AXC} in GFN2-xTB.

1.3 Derivation of the potential

A derivation for the tight-binding Fock matrix elements is given below. The final expressions are given in Eqs. 22, 23, 24, and 25, as well as in the manuscript. To derive the potential for the Hamiltonian (or Fock) matrix construction, the total energy including orthonormality constraint needs to be differentiated w.r.t. the molecular orbital coefficients.

$$\frac{\partial}{\partial c_{\nu i}} \left[E_{\text{GFN2-xTB}} - \sum_j n_j \epsilon_j \left(\sum_{A,B} \sum_{\kappa \in A} \sum_{\lambda \in B} c_{\kappa j} c_{\lambda j} S_{\kappa \lambda} - 1 \right) \right] = 0 \quad (15)$$

The derivation for an isotropic second and third order density fluctuation tight-binding model is described extensively in Ref. S2.

1.3.1 Anisotropic electrostatic terms

The potential of the newly included terms can be derived analogously to Ref. S2.

$$\begin{aligned}
\frac{\partial E_{q\mu}}{\partial c_{\nu i}} &= \sum_{A,B} f_3(R_{AB}) \left[\frac{\partial q_B}{\partial c_{\nu i}} (\boldsymbol{\mu}_A^T \mathbf{R}_{AB}) - q_A \left(\frac{\partial \boldsymbol{\mu}_B^T}{\partial c_{\nu i}} \mathbf{R}_{AB} \right) \right] \\
&= \sum_{A,C} \sum_{\lambda \in C} \left[f_3(R_{AD}) (q_A \mathbf{D}_{\nu\lambda D}^T \mathbf{R}_{AD} - S_{\nu\lambda} \boldsymbol{\mu}_A^T \mathbf{R}_{AD}) \right. \\
&\quad \left. + f_3(R_{AC}) (q_A \mathbf{D}_{\nu\lambda C}^T \mathbf{R}_{AC} - S_{\nu\lambda} \boldsymbol{\mu}_A^T \mathbf{R}_{AC}) \right] n_i c_{\lambda i}
\end{aligned} \tag{16}$$

$$\begin{aligned}
\frac{\partial E_{\mu\mu}}{\partial c_{\nu i}} &= - \sum_{A,B} f_5(R_{AB}) R_{AB}^2 \left(\boldsymbol{\mu}_A^T \frac{\partial \boldsymbol{\mu}_B}{\partial c_{\nu i}} \right) - 3f_5(R_{AB}) (\boldsymbol{\mu}_A^T \mathbf{R}_{AB}) \left(\frac{\partial \boldsymbol{\mu}_B^T}{\partial c_{\nu i}} \mathbf{R}_{AB} \right) \\
&= \sum_{A,C} \sum_{\lambda \in C} \left[3f_5(R_{AC}) (\boldsymbol{\mu}_A^T \mathbf{R}_{AC}) (\mathbf{D}_{\nu\lambda C}^T \mathbf{R}_{AC}) - f_5(R_{AC}) R_{AC}^2 (\boldsymbol{\mu}_A^T \mathbf{D}_{\nu\lambda C}) \right. \\
&\quad \left. + 3f_5(R_{AD}) (\boldsymbol{\mu}_A^T \mathbf{R}_{AD}) (\mathbf{D}_{\nu\lambda D}^T \mathbf{R}_{AD}) - f_5(R_{AD}) R_{AD}^2 (\boldsymbol{\mu}_A^T \mathbf{D}_{\nu\lambda D}) \right] n_i c_{\lambda i}
\end{aligned} \tag{17}$$

$$\begin{aligned}
\frac{\partial E_{q\Theta}}{\partial c_{\nu i}} &= \sum_{A,B} f_5(R_{AB}) \left[\frac{\partial q_B}{\partial c_{\nu i}} \mathbf{R}_{AB}^T \boldsymbol{\Theta}_A \mathbf{R}_{AB} + q_A \mathbf{R}_{AB}^T \frac{\partial \boldsymbol{\Theta}_B}{\partial c_{\nu i}} \mathbf{R}_{AB} \right] \\
&= \sum_{A,C} \sum_{\lambda \in C} \left[q_A (f_5(R_{AD}) \text{Tr}(\mathbf{Q}_{\nu\lambda D}) R_{AD}^2 + f_5(R_{AC}) \text{Tr}(\mathbf{Q}_{\nu\lambda C}) R_{AC}^2 \right. \\
&\quad - f_5(R_{AD}) \mathbf{R}_{AD}^T \mathbf{Q}_{\nu\lambda D} \mathbf{R}_{AD} - f_5(R_{AC}) \mathbf{R}_{AC}^T \mathbf{Q}_{\nu\lambda C} \mathbf{R}_{AC}) \\
&\quad \left. - S_{\nu\lambda} (f_5(R_{AD}) \mathbf{R}_{AD}^T \boldsymbol{\Theta}_A \mathbf{R}_{AD} + f_5(R_{AC}) \mathbf{R}_{AC}^T \boldsymbol{\Theta}_A \mathbf{R}_{AC}) \right] n_i c_{\lambda i}
\end{aligned} \tag{18}$$

Here, the terms involving the traces of the Cartesian quadrupole moment integral tensors $\mathbf{Q}_{\nu\lambda D}$ and $\mathbf{Q}_{\nu\lambda C}$ originate from the trace removal term (c.f. Eq. 6).

1.3.2 Anisotropic XC terms

The anisotropic XC (AXC) kernel contributions can be derived analogously:

$$\begin{aligned}
\frac{\partial E_{\mu XC}}{\partial c_{\nu i}} &= \frac{\partial}{\partial c_{\nu i}} \sum_A f_{XC}^{\mu_A} (\boldsymbol{\mu}_A^T \boldsymbol{\mu}_A) \\
&= 2 \sum_A f_{XC}^{\mu_A} \left(\boldsymbol{\mu}_A^T \frac{\partial \boldsymbol{\mu}_A}{\partial c_{\nu i}} \right) \\
&= -2n_i \sum_C \sum_{\lambda \in C} c_{\lambda i} \left(f_{XC}^{\mu_D} \boldsymbol{\mu}_D^T \mathbf{D}_{\nu\lambda D} + f_{XC}^{\mu_C} \boldsymbol{\mu}_C^T \mathbf{D}_{\nu\kappa C} \right)
\end{aligned} \tag{19}$$

$$\begin{aligned}
\frac{\partial E_{\Theta XC}}{\partial c_{\nu i}} &= \frac{\partial}{\partial c_{\nu i}} \sum_A f_{XC}^{\Theta_A} \|\boldsymbol{\Theta}_A\|^2 \\
&= 2 \sum_A f_{XC}^{\Theta_A} \sum_{\alpha, \beta} \Theta_A^{\alpha\beta} \frac{\partial \Theta_A^{\alpha\beta}}{\partial c_{\nu i}} \\
&= \sum_A f_{XC}^{\Theta_A} \sum_{\alpha, \beta} \Theta_A^{\alpha\beta} \left(3 \frac{\partial \Theta_A^{\alpha\beta}}{\partial c_{\nu i}} - \delta_{\alpha\beta} \frac{\partial (\theta_A^{xx} + \theta_A^{yy} + \theta_A^{zz})}{\partial c_{\nu i}} \right) \\
&= -n_i \sum_C \sum_{\lambda \in C} c_{\lambda i} \sum_{\alpha, \beta} \left(3 f_{XC}^{\Theta_D} \Theta_D^{\alpha\beta} Q_{\nu\lambda D}^{\alpha\beta} + 3 f_{XC}^{\Theta_C} \Theta_C^{\alpha\beta} Q_{\nu\kappa C}^{\alpha\beta} \right) \\
&\quad + n_i \sum_C \sum_{\lambda \in C} c_{\lambda i} \sum_{\alpha} \left[f_{XC}^{\Theta_D} \Theta_D^{\alpha\alpha} \text{Tr}(\mathbf{Q}_{\nu\lambda D}) + f_{XC}^{\Theta_C} \Theta_C^{\alpha\alpha} \text{Tr}(\mathbf{Q}_{\nu\kappa C}) \right]
\end{aligned} \tag{20}$$

1.3.3 Fock matrix elements

Dividing all Eqs. 16–20 by $2n_i$, we can now obtain the AES and AXC expressions entering the Fock matrix.

$$\sum_C \sum_{\lambda \in C} c_{\lambda i} \left[\left(H_{\kappa\lambda}^0 + F_{\kappa\lambda}^{\text{IES+IXC}} + \underbrace{F_{\kappa\lambda}^{\text{AES}} + F_{\kappa\lambda}^{\text{AXC}}}_{F_{\kappa\lambda}^{\text{aniso}}} \right) - \varepsilon_i S_{\kappa\lambda} \right] = 0 \tag{21}$$

It is more convenient during the SCF calculations to work with the dipole and quadrupole integrals with the same overall origin (c.f. Eq. 5). By rearrangement of all terms, the respective Fock matrix elements for the anisotropic contributions $F_{\kappa\lambda}^{\text{aniso}} = F_{\kappa\lambda}^{\text{AES}} + F_{\kappa\lambda}^{\text{AXC}}$ to terms, which are proportional to the respective overlap, dipole and quadrupole integrals, yields to

the following expression:

$$F_{\kappa\lambda}^{\text{aniso}} = \frac{1}{2} S_{\kappa\lambda} [V_S(\mathbf{R}_B) + V_S(\mathbf{R}_C)] \quad (22a)$$

$$+ \frac{1}{2} \mathbf{D}_{\kappa\lambda}^T [\mathbf{V}_D(\mathbf{R}_B) + \mathbf{V}_D(\mathbf{R}_C)] \quad (22b)$$

$$+ \frac{1}{2} \sum_{\alpha,\beta} Q_{\kappa\lambda}^{\alpha\beta} [V_Q^{\alpha\beta}(\mathbf{R}_B) + V_Q^{\alpha\beta}(\mathbf{R}_C)], \quad \forall \kappa \in B, \lambda \in C \quad (22c)$$

With the respective integral (overlap, dipole, and quadrupole) proportional potential terms given as:

$$\begin{aligned} V_S(\mathbf{R}_C) = & \sum_A \left\{ \mathbf{R}_C^T \left[f_5(R_{AC}) \boldsymbol{\mu}_A R_{AC}^2 - \mathbf{R}_{AC} 3f_5(R_{AC}) (\boldsymbol{\mu}_A^T \mathbf{R}_{AC}) - f_3(R_{AC}) q_A \mathbf{R}_{AC} \right] \right. \\ & - f_5(R_{AC}) \mathbf{R}_{AC}^T \boldsymbol{\Theta}_A \mathbf{R}_{AC} - f_3(R_{AC}) \boldsymbol{\mu}_A^T \mathbf{R}_{AC} + q_A f_5(R_{AC}) \frac{1}{2} \mathbf{R}_C^2 \mathbf{R}_{AC}^2 \\ & \left. - \frac{3}{2} q_A f_5(R_{AC}) \sum_{\alpha,\beta} \alpha_{AB} \beta_{AB} \alpha_C \beta_C \right\} \\ & + 2f_{XC}^{\mu C} \mathbf{R}_C^T \boldsymbol{\mu}_C - f_{XC}^{\Theta C} \mathbf{R}_C^T [3\boldsymbol{\Theta}_C - \text{Tr}(\boldsymbol{\Theta}_C) \mathbf{I}] \mathbf{R}_C \end{aligned} \quad (23)$$

$$\begin{aligned} \mathbf{V}_D(\mathbf{R}_C) = & \sum_A \left[\mathbf{R}_{AC} 3f_5(R_{AC}) (\boldsymbol{\mu}_A^T \mathbf{R}_{AC}) - f_5(R_{AC}) \boldsymbol{\mu}_A R_{AC}^2 + f_3(R_{AC}) q_A \mathbf{R}_{AC} \right. \\ & \left. - q_A f_5(R_{AC}) \mathbf{R}_C R_{AC}^2 + 3q_A f_5(R_{AC}) \mathbf{R}_{AC} \sum_{\alpha} \alpha_C \alpha_{AC} \right] \\ & - 2f_{XC}^{\mu C} \boldsymbol{\mu}_C + 2f_{XC}^{\Theta C} [3\boldsymbol{\Theta}_C - \text{Tr}(\boldsymbol{\Theta}_C) \mathbf{I}] \mathbf{R}_C \end{aligned} \quad (24)$$

$$\begin{aligned} V_Q^{\alpha\beta}(\mathbf{R}_C) = & - \sum_A q_A f_5(R_{AC}) \left[\frac{3}{2} \alpha_{AC} \beta_{AC} - \frac{1}{2} R_{AB}^2 \right] \\ & - f_{XC}^{\Theta C} \left[3\Theta_C^{\alpha\beta} - \delta_{\alpha\beta} \sum_{\alpha} \Theta_C^{\alpha\alpha} \right] \end{aligned} \quad (25)$$

1.4 Cartesian gradients of E^{AES}

A derivation for the nuclear gradients is given below. For the final expressions, see Section 1.4.5.

1.4.1 General

$$\frac{\partial R_{AB}}{\partial \alpha_A} = -\frac{\alpha_{AB}}{R_{AB}} = -\frac{\partial R_{BA}}{\partial \alpha_A} = -\frac{\partial R_{AB}}{\partial \alpha_B} \quad (26)$$

The $f_n(R_{AB})$ terms given in the manuscript define the damping and distance dependence of the AES as:

$$f_n(R_{AB}) = R_{AB}^{-n} f_{\text{damp}}(a_n, R_{AB}) \quad (27)$$

with

$$f_{\text{damp}}(a_n, R_{AB}) = \frac{1}{1 + 6 \left(\frac{R_0^{AB}}{R_{AB}} \right)^{a_n}} \cdot \quad (28)$$

$$\begin{aligned} \left. \frac{\partial f_n(R_{AB})}{\partial R_{AB}} \right|_{R_0^{AB}=\text{const.}} &= \frac{\partial R_{AB}^{-n}}{\partial R_{AB}} f_{\text{damp}}(a_n, R_{AB}) + \frac{\partial f_{\text{damp}}(a_n, R_{AB})}{\partial R_{AB}} R_{AB}^{-n} \\ &= -n f_{\text{damp}}(a_n, R_{AB}) R_{AB}^{-n-1} + 6 a_n f_{\text{damp}}^2(a_n, R_{AB}) \left(\frac{R_0^{AB}}{R_{AB}} \right)^{a_n} R_{AB}^{-n-1} \\ &= -\frac{n}{R_{AB}} f_n(R_{AB}) - \frac{a_n}{R_{AB}} [f_{\text{damp}}(a_n, R_{AB}) f_n(R_{AB}) - f_n(R_{AB})] \end{aligned} \quad (29)$$

The above equation would be sufficient if the R_0^{AB} were constants. In GFN2-xTB, however, they are dependent on the coordination numbers of the atoms via:

$$R_0^{AB} = \frac{1}{2} (R_0^{A'} + R_0^{B'}) \quad (30)$$

$$R_0^{A'} = R_0^A + \frac{R_{\text{max}} - R_0^A}{1 + \exp[-\beta(CN_A - N_{\text{val}} - \Delta_{\text{val}})]} \quad (31)$$

Consequently a term, which takes into account the CN-dependence needs to be added, i.e.:

$$\frac{\partial R_0^{A'}}{\partial CN_A} = \beta \frac{R_{\max} - R_0^A}{\{1 + \exp[-\beta(CN_A - N_{\text{val}} - \Delta_{\text{val}})]\}^2} \exp[-\beta(CN_A - N_{\text{val}} - \Delta_{\text{val}})] \quad (32)$$

$$\frac{\partial R_0^{A'}}{\partial \alpha_C} = \frac{\partial R_0^{A'}}{\partial CN_A} \frac{\partial CN_A}{\partial \alpha_C} \quad (33)$$

$$\begin{aligned} \frac{\partial f_n(R_{AB})}{\partial CN_A} &= - \frac{6a_n f_{\text{damp}}^2(a_n, R_{AB})}{R_{AB}^{n+a_n}} (R_0^{AB})^{a_n-1} \left(\frac{\partial R_0^{AB}}{\partial CN_A} \right) \\ &= - \frac{3a_n f_{\text{damp}}^2(a_n, R_{AB})}{R_{AB}^{n+a_n}} (R_0^{AB})^{a_n-1} \left(\frac{\partial R_0^{A'}}{\partial CN_A} \right) \\ &= - \frac{3a_n f_n(R_{AB}) f_{\text{damp}}(a_n, R_{AB})}{R_{AB}^{a_n}} (R_0^{AB})^{a_n-1} \left(\frac{\partial R_0^{A'}}{\partial CN_A} \right) \end{aligned} \quad (34)$$

Hence for nuclear gradients of $f_n(R_{AB})$, this leads to:

$$f_n^{[\alpha_A]}(R_{AB}) = \frac{\partial f_n(R_{AB})}{\partial \alpha_A} = \frac{\partial f_n(R_{AB})}{\partial R_{AB}} \bigg|_{R_0^{AB}=\text{const.}} \frac{\partial R_{AB}}{\partial \alpha_A} + \frac{\partial f_n(R_{AB})}{\partial CN_A} \frac{\partial CN_A}{\partial \alpha_A} + \frac{\partial f_n(R_{AB})}{\partial CN_B} \frac{\partial CN_B}{\partial \alpha_A} \quad (35)$$

It should be noted that due to the CN-dependence, the last terms also survive if an atom different from A or B is moved:

$$f_n^{[\alpha_C]}(R_{AB}) = \frac{\partial f_n(R_{AB})}{\partial CN_A} \frac{\partial CN_A}{\partial \alpha_C} + \frac{\partial f_n(R_{AB})}{\partial CN_B} \frac{\partial CN_B}{\partial \alpha_C} \quad (36)$$

The nuclear derivatives of the CAMM expressions yields:

$$\frac{\partial q_A}{\partial \alpha_C} = (\delta_{AC} - 1) \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \frac{\partial S_{\lambda\kappa}}{\partial \alpha_C} - \delta_{AC} \sum_{\kappa \in C} \sum_{B \neq C} \sum_{\lambda \in B} P_{\kappa\lambda} \frac{\partial S_{\lambda\kappa}}{\partial \alpha_C} \quad (37)$$

$$\begin{aligned}
\frac{\partial \mu_A^\beta}{\partial \alpha_C} &= (1 - \delta_{AC}) \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \left[\beta_A \frac{\partial S_{\lambda\kappa}}{\partial \alpha_C} - \frac{\partial D_{\lambda\kappa}^\beta}{\partial \alpha_C} \right] \\
&\quad + \delta_{AC} \sum_{\kappa \in C} \sum_B \sum_{\lambda \in B} P_{\kappa\lambda} \left[\delta_{\alpha\beta} S_{\lambda\kappa} + \beta_C \frac{\partial S_{\lambda\kappa}}{\partial \alpha_C} - \frac{\partial D_{\lambda\kappa}^\beta}{\partial \alpha_C} \right] \\
&= (\delta_{AC} - 1) \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \frac{\partial D_{\lambda\kappa A}^\beta}{\partial \alpha_C} - \delta_{AC} \sum_{\kappa \in C} \sum_{B \neq C} \sum_{\lambda \in B} P_{\kappa\lambda} \frac{\partial D_{\lambda\kappa C}^\beta}{\partial \alpha_C}
\end{aligned} \tag{38}$$

Here, we have made use of the notation of dipole integrals with origin on the respective atoms, which is more convenient for the evaluation of nuclear gradients.

$$\begin{aligned}
\frac{\partial \theta_A^{\beta\gamma}}{\partial \alpha_C} &= (1 - \delta_{AC}) \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \left[\beta_A \frac{\partial D_{\lambda\kappa}^\gamma}{\partial \alpha_C} + \gamma_A \frac{\partial D_{\lambda\kappa}^\beta}{\partial \alpha_C} - \beta_A \gamma_A \frac{\partial S_{\lambda\kappa}}{\partial \alpha_C} - \frac{\partial Q_{\lambda\kappa}^{\beta\gamma}}{\partial \alpha_C} \right] \\
&\quad + \delta_{AC} \sum_{\kappa \in C} \sum_B \sum_{\lambda \in B} P_{\kappa\lambda} \left[\beta_C \frac{\partial D_{\lambda\kappa}^\gamma}{\partial \alpha_C} + \gamma_C \frac{\partial D_{\lambda\kappa}^\beta}{\partial \alpha_C} - \beta_C \gamma_C \frac{\partial S_{\lambda\kappa}}{\partial \alpha_C} - \frac{\partial Q_{\lambda\kappa}^{\beta\gamma}}{\partial \alpha_C} \right] \\
&\quad + \delta_{\alpha\beta} (D_{\lambda\kappa}^\gamma - \gamma_C S_{\lambda\kappa}) + \delta_{\alpha\gamma} (D_{\lambda\kappa}^\beta - \beta_C S_{\lambda\kappa}) \\
&= (\delta_{AC} - 1) \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \frac{\partial Q_{\lambda\kappa A}^{\beta\gamma}}{\partial \alpha_C} - \delta_{AC} \sum_{\kappa \in C} \sum_{B \neq C} \sum_{\lambda \in B} P_{\kappa\lambda} \frac{\partial Q_{\lambda\kappa C}^{\beta\gamma}}{\partial \alpha_C}
\end{aligned} \tag{39}$$

Again, we made use of the more convenient notation of quadrupole integrals with origin on the respective atoms.

The nuclear gradient for the AXC terms are obtained as $\text{Tr}(\mathbf{P} \frac{\partial}{\partial \alpha_C} \mathbf{F}^{\text{AXC}})$ and are trivial due to their on-site nature. The derivative of the AES energy is given by:

$$\frac{\partial E_{\text{AES}}}{\partial \alpha_C} = \frac{\partial E_{q\mu}}{\partial \alpha_C} + \frac{\partial E_{q\Theta}}{\partial \alpha_C} + \frac{\partial E_{\mu\mu}}{\partial \alpha_C} \tag{40}$$

1.4.2 Nuclear gradients for $E_{q\mu}$

$$\begin{aligned}
\left. \frac{\partial E_{q\mu}}{\partial \alpha_C} \right|_{R_0^{AB}=\text{const.}} &= \frac{\partial}{\partial \alpha_C} \sum_{A,B} f_3(R_{AB}) q_B \boldsymbol{\mu}_A^T \mathbf{R}_{AB} \\
&= \sum_{A,B} \left[\frac{\partial f_3(R_{AB})}{\partial \alpha_C} q_B \boldsymbol{\mu}_A^T \mathbf{R}_{AB} + f_3(R_{AB}) q_B \boldsymbol{\mu}_A^T \frac{\partial \mathbf{R}_{AB}}{\partial \alpha_C} \right. \\
&\quad \left. + f_3(R_{AB}) \left(\frac{\partial q_B}{\partial \alpha_C} \boldsymbol{\mu}_A + q_B \frac{\partial \boldsymbol{\mu}_A}{\partial \alpha_C} \right)^T \mathbf{R}_{AB} \right] \\
&= \sum_B \left[f_3^{[\alpha_C]}(R_{CB}) (q_B \boldsymbol{\mu}_C - q_C \boldsymbol{\mu}_B)^T \mathbf{R}_{CB} \Big|_{R_0^{AB}=\text{const.}} - f_3(R_{CB}) (q_B \mu_C^\alpha - q_C \mu_B^\alpha) \right] \\
&\quad + \sum_{A \neq C} \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \frac{\partial S_{\lambda\kappa}}{\partial \alpha_C} \sum_B \boldsymbol{\mu}_B [f_3(R_{AB}) \mathbf{R}_{AB} + f_3(R_{CB}) \mathbf{R}_{CB}] \\
&\quad - \sum_{A \neq C} \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \sum_B q_B \left[f_3(R_{AB}) \left(\frac{\partial \mathbf{D}_{\lambda\kappa A}}{\partial \alpha_C} \right)^T \mathbf{R}_{AB} + f_3(R_{CB}) \left(\frac{\partial \mathbf{D}_{\lambda\kappa C}}{\partial \alpha_C} \right)^T \mathbf{R}_{CB} \right]
\end{aligned} \tag{41}$$

Here, we exploited the symmetry of $\partial S_{\lambda\kappa}/\partial \alpha_C = \partial S_{\kappa\lambda}/\partial \alpha_C$. Note that $\partial D_{\lambda\kappa A}/\partial \alpha_C \neq \partial D_{\kappa\lambda C}/\partial \alpha_C$, but that $\partial D_{\lambda\kappa A}/\partial \alpha_C = -\partial D_{\kappa\lambda A}/\partial \alpha_A$, which can save a factor of two in the gradient calculation.

1.4.3 Nuclear gradients for $E_{q\Theta}$

Let us first consider the derivative

$$\begin{aligned}
\frac{\partial \left(\mathbf{R}_{AB}^T \boldsymbol{\Theta}_A \mathbf{R}_{AB} \right)}{\partial \alpha_C} &= \delta_{BC} \left(\frac{\partial \mathbf{R}_{AC}^T}{\partial \alpha_C} \boldsymbol{\Theta}_A \mathbf{R}_{AC} + \mathbf{R}_{AC}^T \boldsymbol{\Theta}_A \frac{\partial \mathbf{R}_{AC}}{\partial \alpha_C} \right) \\
&\quad + \delta_{AC} \left(\frac{\partial \mathbf{R}_{CB}^T}{\partial \alpha_C} \boldsymbol{\Theta}_C \mathbf{R}_{CB} + \mathbf{R}_{CB}^T \boldsymbol{\Theta}_C \frac{\partial \mathbf{R}_{CB}}{\partial \alpha_C} \right) + \mathbf{R}_{AB}^T \frac{\partial \boldsymbol{\Theta}_A}{\partial \alpha_C} \mathbf{R}_{AB} \\
&= 2 \sum_{\beta=x,y,z} \left(\delta_{BC} \Theta_A^{\alpha\beta} \beta_{AC} - \delta_{AC} \Theta_C^{\alpha\beta} \beta_{CB} \right) + \mathbf{R}_{AB}^T \frac{\partial \boldsymbol{\Theta}_A}{\partial \alpha_C} \mathbf{R}_{AB} \\
&= 2 \left(\delta_{BC} \mathbf{R}_{AC}^T \boldsymbol{\Theta}_A^\alpha - \delta_{AC} \mathbf{R}_{CB}^T \boldsymbol{\Theta}_C^\beta \right) + \mathbf{R}_{AB}^T \frac{\partial \boldsymbol{\Theta}_A}{\partial \alpha_C} \mathbf{R}_{AB}
\end{aligned} \tag{42}$$

with

$$\frac{\partial \Theta_A}{\partial \alpha_C} = \frac{3}{2} \frac{\partial \theta_A^{\alpha\beta}}{\partial \alpha_C} - \frac{\delta_{\alpha\beta}}{2} \frac{\partial (\theta_A^{xx} + \theta_A^{yy} + \theta_A^{zz})}{\partial \alpha_C}. \quad (43)$$

Then the derivative of the charge-quadrupole interaction is given as:

$$\begin{aligned} \left. \frac{\partial E_{q\Theta}}{\partial \alpha_C} \right|_{R_0^{AB}=\text{const.}} &= \frac{\partial}{\partial \alpha_C} \sum_{AB} f_5(R_{AB}) \left(q_B \mathbf{R}_{AB}^T \Theta_A \mathbf{R}_{AB} \right) \\ &= \sum_B \left[f_5^{[\alpha C]}(R_{CB}) \left(q_C \mathbf{R}_{CB}^T \Theta_B \mathbf{R}_{CB} + q_B \mathbf{R}_{CB}^T \Theta_C \mathbf{R}_{CB} \right) \right]_{R_0^{AB}=\text{const.}} \\ &\quad - 2f_5(R_{CB}) \left(q_C \mathbf{R}_{CB}^T \Theta_B^\alpha + q_B \mathbf{R}_{CB}^T \Theta_C^\beta \right) \\ &\quad + \sum_{AB} f_5(R_{AB}) \left[\frac{\partial q_A}{\partial \alpha_C} \mathbf{R}_{AB}^T \Theta_B \mathbf{R}_{AB} + q_B \mathbf{R}_{AB}^T \frac{\partial \Theta_A}{\partial \alpha_C} \mathbf{R}_{AB} \right] \\ &= \sum_B \left[f_5^{[\alpha C]}(R_{CB}) \left(q_C \mathbf{R}_{CB}^T \Theta_B \mathbf{R}_{CB} + q_B \mathbf{R}_{CB}^T \Theta_C \mathbf{R}_{CB} \right) \right]_{R_0^{AB}=\text{const.}} \\ &\quad - 2f_5(R_{CB}) \left(q_C \mathbf{R}_{CB}^T \Theta_B^\alpha + q_B \mathbf{R}_{CB}^T \Theta_C^\beta \right) \\ &\quad - \sum_{A \neq C} \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \frac{\partial S_{\lambda\kappa}}{\partial \alpha_C} \sum_B \left[f_5(R_{AB}) \mathbf{R}_{AB}^T \Theta_B \mathbf{R}_{AB} + f_5(R_{CB}) \mathbf{R}_{CB}^T \Theta_B \mathbf{R}_{CB} \right] \\ &\quad - \sum_{A \neq C} \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \sum_B \frac{q_B}{2} \left[3f_5(R_{AB}) \mathbf{R}_{AB}^T \frac{\partial \mathbf{Q}_{\lambda\kappa A}}{\partial \alpha_C} \mathbf{R}_{AB} - f_5(R_{AB}) \text{Tr}(\mathbf{Q}_{\lambda\kappa A}) R_{AB}^2 \right. \\ &\quad \left. + 3f_5(R_{CB}) \mathbf{R}_{CB}^T \frac{\partial \mathbf{Q}_{\lambda\kappa C}}{\partial \alpha_C} \mathbf{R}_{CB} - f_5(R_{CB}) \text{Tr}(\mathbf{Q}_{\lambda\kappa C}) R_{CB}^2 \right] \end{aligned} \quad (44)$$

1.4.4 Nuclear gradients for $E_{\mu\mu}$

Let us first consider the derivative of the following terms:

$$\begin{aligned} \frac{\partial \left[\left(\boldsymbol{\mu}_A^T \mathbf{R}_{AB} \right) \left(\boldsymbol{\mu}_B^T \mathbf{R}_{AB} \right) \right]}{\partial \alpha_C} &= \left(\left(\frac{\partial \boldsymbol{\mu}_A}{\partial \alpha_C} \right)^T \mathbf{R}_{AB} \right) \left(\boldsymbol{\mu}_B^T \mathbf{R}_{AB} \right) + \left(\boldsymbol{\mu}_A^T \mathbf{R}_{AB} \right) \left(\left(\frac{\partial \boldsymbol{\mu}_B}{\partial \alpha_C} \right)^T \mathbf{R}_{AB} \right) \\ &\quad + (\delta_{BC} - \delta_{AC}) \mu_A^\alpha \left(\boldsymbol{\mu}_B^T \mathbf{R}_{AB} \right) + (\delta_{BC} - \delta_{AC}) \mu_B^\alpha \left(\boldsymbol{\mu}_A^T \mathbf{R}_{AB} \right) \end{aligned} \quad (45)$$

$$\frac{\partial (\boldsymbol{\mu}_A^T \boldsymbol{\mu}_B R_{AB}^2)}{\partial \alpha_C} = \left(\frac{\partial \boldsymbol{\mu}_A}{\partial \alpha_C} \right)^T \boldsymbol{\mu}_B R_{AB}^2 + \boldsymbol{\mu}_A^T \left(\frac{\partial \boldsymbol{\mu}_B}{\partial \alpha_C} \right) R_{AB}^2 + 2 (\delta_{BC} \boldsymbol{\mu}_A^T \boldsymbol{\mu}_C \alpha_{AC} - \delta_{AC} \boldsymbol{\mu}_C^T \boldsymbol{\mu}_B \alpha_{CB}) \quad (46)$$

$$\begin{aligned} \frac{\partial E_{\mu\mu}}{\partial \alpha_C} \Big|_{R_0^{AB}=\text{const.}} &= \frac{\partial}{2\partial \alpha_C} \sum_{A,B} f_5(R_{AB}) \left[(\boldsymbol{\mu}_A^T \boldsymbol{\mu}_B) R_{AB}^2 - 3 (\boldsymbol{\mu}_A^T \mathbf{R}_{AB}) (\boldsymbol{\mu}_B^T \mathbf{R}_{AB}) \right] \\ &= \sum_B f_5^{[\alpha_C]}(R_{CB}) \left[(\boldsymbol{\mu}_C^T \boldsymbol{\mu}_B) R_{CB}^2 \Big|_{R_0^{AB}=\text{const.}} - 3 (\boldsymbol{\mu}_C^T \mathbf{R}_{CB}) (\boldsymbol{\mu}_B^T \mathbf{R}_{CB}) \right] \\ &\quad - \sum_B f_5(R_{CB}) \left[2 \boldsymbol{\mu}_C^T \boldsymbol{\mu}_B \alpha_{CB} + 3 (\mu_C^\alpha \boldsymbol{\mu}_B^T + \mu_B^\alpha \boldsymbol{\mu}_C^T) \mathbf{R}_{CB} \right] \\ &\quad - \sum_{A \neq C} \sum_{\kappa \in A} \sum_{\lambda \in C} P_{\kappa\lambda} \left\{ \frac{\partial \mathbf{D}_{\lambda\kappa A}}{\partial \alpha_C} \sum_B \left[f_5(R_{AB}) (\boldsymbol{\mu}_B R_{AB}^2 - 3 \mathbf{R}_{AB} (\boldsymbol{\mu}_B^T \mathbf{R}_{AB})) \right] \right. \\ &\quad \left. + \frac{\partial \mathbf{D}_{\lambda\kappa C}}{\partial \alpha_C} \sum_B \left[f_5(R_{CB}) (\boldsymbol{\mu}_B R_{CB}^2 - 3 \mathbf{R}_{CB} (\boldsymbol{\mu}_B^T \mathbf{R}_{CB})) \right] \right\} \end{aligned} \quad (47)$$

1.4.5 Additional terms in AES derivatives due to CN-dependence of R_0^{AB}

The aforementioned formulas for $\partial E_{\text{AES}}/\partial \alpha_C$ have been given for constant values of R_0^{AB} . Due to their CN-dependence, these terms must, however, be included. Therefore, the aforementioned expression have to be augmented with the respective derivatives:

$$\frac{\partial E_{q\mu}}{\partial \alpha_C} = \frac{\partial E_{q\mu}}{\partial \alpha_C} \Big|_{R_0^{AB}=\text{const.}} + \sum_{A,B} \left(\frac{\partial f_3(R_{AB})}{\partial CN_A} \frac{\partial CN_A}{\partial \alpha_C} + \frac{\partial f_3(R_{AB})}{\partial CN_B} \frac{\partial CN_B}{\partial \alpha_C} \right) (q_B \boldsymbol{\mu}_A^T \mathbf{R}_{AB}) \quad (48)$$

$$\frac{\partial E_{q\Theta}}{\partial \alpha_C} = \frac{\partial E_{q\Theta}}{\partial \alpha_C} \Big|_{R_0^{AB}=\text{const.}} + \sum_{A,B} \left(\frac{\partial f_5(R_{AB})}{\partial CN_A} \frac{\partial CN_A}{\partial \alpha_C} + \frac{\partial f_5(R_{AB})}{\partial CN_B} \frac{\partial CN_B}{\partial \alpha_C} \right) (q_B \mathbf{R}_{AB}^T \boldsymbol{\Theta}_A \mathbf{R}_{AB}) \quad (49)$$

$$\begin{aligned} \frac{\partial E_{\mu\mu}}{\partial \alpha_C} = \frac{\partial E_{\mu\mu}}{\partial \alpha_C} \Big|_{R_0^{AB}=\text{const.}} + \frac{1}{2} \sum_{A,B} \left(\frac{\partial f_5(R_{AB})}{\partial CN_A} \frac{\partial CN_A}{\partial \alpha_C} + \frac{\partial f_5(R_{AB})}{\partial CN_B} \frac{\partial CN_B}{\partial \alpha_C} \right) \\ \times \left[(\boldsymbol{\mu}_A^T \boldsymbol{\mu}_B) R_{AB}^2 - 3 (\boldsymbol{\mu}_A^T \mathbf{R}_{AB}) (\boldsymbol{\mu}_B^T \mathbf{R}_{AB}) \right] \end{aligned} \quad (50)$$

The derived formulas and their implementation was tested by comparison of computed analytic and numerical numerical derivatives.

1.5 Dispersion

The two-body London dispersion energy for two distant atoms is given as:

$$E_{\text{disp}} = - \sum_{A<B} \frac{3}{\pi R_{AB}^6} \int \bar{\alpha}_A(i\omega) \bar{\alpha}_B(i\omega) d\omega = - \sum_{A<B} \frac{C_6(\rho_A, \rho_B)}{R_{AB}^6} \quad (51)$$

Here, $\bar{\alpha}_A(i\omega)$ refers to the isotropic dynamic dipole polarizability of atom A . It is a function of the density around the atom, and consequently, the dispersion coefficient is a function of the density on both atoms. Hence, expanding the two-body dispersion energy in terms of density fluctuations leads to:

$$\begin{aligned} E_{\text{disp}} = - \sum_{A<B} \frac{1}{R_{AB}} [C_6(\rho_{A_0}, \rho_{B_0}) + C_6(\delta\rho_A, \rho_{B_0}) + C_6(\rho_{A_0}, \delta\rho_B) + C_6(\delta\rho_A, \delta\rho_B) \\ + C_6((\delta\rho_A)^2, \rho_{B_0}) + C_6(\rho_{A_0}, (\delta\rho_B)^2) + \dots] \end{aligned} \quad (52)$$

Here, all terms up to second order in the density fluctuations are shown. In the D4 dispersion model (see below), all terms in the first line of Eq. 52 will explicitly be taken into account, i.e., all terms of zeroth and first order, as well as the two-center second order terms. This is a result from considering first order effects in the polarizabilities and formation of their products to obtain the dispersion coefficient. Formally, the pairwise dipole-quadrupole dispersion coefficient is handled in the same way.

1.5.1 The D4 dispersion energy

The total dispersion energy in the context of GFN2-xTB is given by

$$\begin{aligned}
E_{\text{D4}} = & -\frac{1}{2} \sum_A \sum_a^{N_{A,\text{ref}}} \sum_B \sum_b^{N_{B,\text{ref}}} \xi_A^a(q_A, q_{A,a}) \xi_B^b(q_B, q_{B,b}) \\
& \times W_A^a(q_A, q_{A,a}) W_B^b(q_B, q_{B,b}) \sum_{n=6,8} s_n \frac{C_n^{ab}}{R_{AB}^n} f_n^{\text{damp,BJ}}(R_{AB}) \\
& - s_9 \sum_{A>B>C} \frac{(3 \cos(\theta_{ABC}) \cos(\theta_{BCA}) \cos(\theta_{CAB}) + 1) C_9^{ABC} (CN_{\text{cov}}^A, CN_{\text{cov}}^B, CN_{\text{cov}}^C)}{(R_{AB} R_{AC} R_{BC})^3} \\
& \times f_9^{\text{damp,zero}}(R_{AB}, R_{AC}, R_{BC})
\end{aligned} \tag{53}$$

Here, the two-body contribution is augmented with a charge-independent three-body Axilrod-Teller-Muto (ATM) term. The rational damping Becke-Johnson-type damping as in DFT-D3 is used for the two-body contribution

$$f_n^{\text{damp,BJ}}(R_{AB}) = \frac{R_{AB}^n}{R_{AB}^n + (a_1 \cdot R_{AB}^{\text{crit.}} + a_2)^6} \quad \text{with} \quad R_{AB}^{\text{crit.}} = \sqrt{\frac{C_8^{AB}}{C_6^{AB}}} \tag{54}$$

and the zero damping function used for the ATM dispersion is defined slightly different compared to previous implementations of DFT-D3. Namely, we adjust the cutoff radii in the damping function by dropping the factor 4/3 and using the same cutoff radii as in the two-body damping function for a more consistent description of the dispersion energy.

$$f_9^{\text{damp,zero}}(R_{AB}, R_{AC}, R_{BC}) = \left(1 + 6 \left(\sqrt[3]{\frac{R_{AB}^{\text{crit.}} R_{BC}^{\text{crit.}} R_{CA}^{\text{crit.}}}{R_{AB} R_{BC} R_{CA}}} \right)^{16} \right)^{-1} \tag{55}$$

1.5.2 Derivation of the potential

The potential for the dispersion energy is derived by taking the derivative of the dispersion energy expression with respect to the orbital coefficients. Since the ATM term is not

charge dependent it appears not in the potential. The dependencies on the charge and the coordination number are dropped for brevity.

$$\begin{aligned} \frac{\partial E_{D4}}{\partial c_{vi}} &= -\frac{1}{2} \sum_A^{N_{A,\text{ref}}} \sum_a \sum_B^{N_{B,\text{ref}}} \sum_b \frac{\partial \xi_A^a}{\partial c_{vi}} \xi_B^b W_A^a W_B^b \sum_{n=6,8} s_n \frac{C_n^{ab}}{R_{AB}^n} f_n \\ &\quad - \frac{1}{2} \sum_A^{N_{A,\text{ref}}} \sum_a \sum_B^{N_{B,\text{ref}}} \sum_b \frac{\partial \xi_B^b}{\partial c_{vi}} \xi_A^a W_A^a W_B^b \sum_{n=6,8} s_n \frac{C_n^{ab}}{R_{AB}^n} f_n \end{aligned} \quad (56)$$

By renaming the indices we can easily simplify above expression

$$\frac{\partial E_{D4}}{\partial c_{vi}} = - \sum_A^{N_{A,\text{ref}}} \sum_a \sum_B^{N_{B,\text{ref}}} \sum_b \frac{\partial \xi_A^a}{\partial q_A} \frac{\partial q_A}{\partial c_{vi}} \xi_B^b W_A^a W_B^b \sum_{n=6,8} s_n \frac{C_n^{ab}}{R_{AB}^n} f_n \quad (57)$$

$$= - \sum_A^{N_{A,\text{ref}}} \sum_a \sum_B^{N_{B,\text{ref}}} \sum_b \frac{\partial \xi_A^a}{\partial q_A} \left(\delta_{AD} \sum_C \sum_{\kappa \in C} n_i c_{\kappa i} S_{\nu \kappa} + \sum_{\mu \in A} n_i c_{\mu i} S_{\nu \mu} \right) \xi_B^b W_A^a W_B^b \sum_{n=6,8} s_n \frac{C_n^{ab}}{R_{AB}^n} f_n \quad (58)$$

$$= - \sum_d^{N_{D,\text{ref}}} \frac{\partial \xi_D^d}{\partial q_D} \sum_B^{N_{B,\text{ref}}} \sum_b \xi_B^b W_D^d W_B^b \sum_{n=6,8} s_n \frac{C_n^{DB}}{R_{DB}^n} f_n \sum_C \sum_{\kappa \in C} n_i c_{\kappa i} S_{\nu \kappa} \quad (59)$$

We rename and reorder the terms

$$\frac{\partial E_{D4}}{\partial c_{vi}} = - \underbrace{\sum_a^{N_{A,\text{ref}}} \frac{\partial \xi_A^a}{\partial q_A} \sum_B^{N_{B,\text{ref}}} \sum_b \xi_B^b W_A^a W_B^b \sum_{n=6,8} s_n \frac{C_n^{ab}}{R_{AB}^n} f_n}_{d_A} \sum_C \sum_{\kappa \in C} n_i c_{\kappa i} S_{\nu \kappa} \quad (60)$$

Which leads to the compact expression

$$F_{\kappa\lambda}^{D4} = \frac{1}{2} S_{\kappa\lambda} (d_A + d_B), \quad \forall \kappa \in A, \lambda \in B \quad (61)$$

2 Detailed results

2.1 Structures

Table S1: Comparison of computed rotational constants of twelve medium sized molecules to experimentally derived ones (ROT34)^a for different semiempirical methods. The individual values are given in MHz.

	GFN2-xTB	ref.
1 A	4299.3	4293.9
B	1411.8	1395.9
C	1143.5	1130.2
2 A	2630.8 ^b	3322.5
B	912.7 ^b	719.8
C	868.4 ^b	698.0
3 A	3072.3	3071.1
B	1302.1	1285.0
C	1246.2	1248.7
4 A	2789.4	2755.9
B	2699.8	2675.6
C	2682.4	2653.3
5 A	2336.8	2336.9
6 A	1459.6	1464.2
B	772.8	768.2
C	587.5	580.6
7 A	1175.1	1165.7
B	658.6	661.2
C	456.3	454.0
8 A	1236.0	1166.3
B	759.8	767.6
C	525.9	513.0
9 A	876.0	862.5
B	748.5	754.2
C	513.6	513.7
10 A	3100.8	3086.2
B	730.8	723.7
C	687.2	685.0
11 A	1451.9	1432.1
B	819.0	820.5
C	687.1	679.4
12 A	1523.5	1523.2
B	1086.4	1070.5
C	728.2	719.9

^a Rotational constants B_e (excluding vibrational effects) from Ref. S4 with an estimated reference error of 0.2%.

^b A conformer other than the experimental one is obtained. This value is neglected in the statistical analysis of the data set presented in the manuscript.

1: ethynyl-cyclohexane, **2**: isoamyl-acetate,
3: diisopropyl-ketone, **4**: bicyclo[2.2.2]octadiene,
5: triethylamine, **6**: vitamin C, **7**: serotonin, **8**: aspirin,
9: cassyrane, **10**: proline, **11**: lupinene, and **12**: limonene.

Table S2: Untypically long intramolecular bonds (LB12)^a obtained by geometry optimizations with the GFN-xTB and GFN2-xTB methods in comparison to experimental values. The values are given in pm.

system	bond	GFN2-xTB	GFN-xTB	ref.
DIAD	C-C	167.5	167.3	171.0
FLP	P-B	205.4	210.2	212.0
DTFS	Si-N	272.8	207.3	227.0
MESITRAN	Si-N	239.7	226.7	245.0
S ₈ ²⁺	S-S	385.6	230.2	286.0
HAPPOD	Rh-Cr	306.2	298.6 ^b	308.0
KAMDOR	Os-Cr	306.6	297.6 ^b	310.0
PP	C-C	313.8	312.6	312.0
BRCLNA	Br-Cl	302.8	305.8	313.0
C ₂ Br ₆	Br-Br	337.0	340.3	342.0
RESVAN	S-S	374.9	382.6	419.0
BHS	Si-Si	454.1	452.7	443.0
	MD:	6.5 (-1.9) ^c	-13.0	-
	MAD:	19.9 (12.6) ^c	14.7	-
	SD:	35.4 (20.9) ^c	17.9	-
	MAX:	99.6 (45.8) ^c	55.8	-

^a Reference bond lengths of long bonds as used in Ref. S5.

^b Bonds are different w.r.t. Ref. S3 due to the modified GFN-xTB Hamiltonian with CN-dependence for Cr.

^c Statistics without system S₈²⁺ is given in parentheses.

Table S3: Covalent bonds of heavy main group elements (HMGB11)^a from experiment and computed with GFN2-xTB. The values are given in pm.

system	bond	GFN2-xTB	ref.
Cl ₂	Cl-Cl	201.7	198.8
S ₂ H ₂	S-S	204.5	205.5
P ₂ Me ₄	P-P	220.1	221.2
Br ₂	Br-Br	228.2	228.1
Se ₂ H ₂	Se-Se	227.7	234.6
Ge ₂ H ₆	Ge-Ge	236.3	241.0
As ₂ Me ₄	As-As	244.3	242.9
Te ₂ Me ₂	Te-Te	269.5	268.6
Sn ₂ Me ₆	Sn-Sn	281.2	277.6
Sb ₂ Me ₄	Sb-Sb	281.9	281.8
Pb ₂ Me ₆	Pb-Pb	293.9	288.0
	MD:	0.1	-
	MAD:	2.6	-
	RMSD:	3.5	-
	SD:	3.6	-
	MAX:	7.0	-

^a Reference bond lengths are the same as used in Ref. S5.

Table S4: Covalent bonds in transition metal complexes (TMC32)^a from experiment and computed with different semiempirical methods. The values are given in pm.

	GFN2-xTB	GFN-xTB ^b	ref.
1	201.4	201.4	207.6
2	211.1	213.1	216.9
3	204.7	205.5	204.7
4	212.6	213.1	218.5
5	205.5	205.1	205.8
6	214.8	213.7	219.6
7	228.6	229.3	217.5
8	185.7	178.1	198.4
9	151.7	154.5	157.0
10	162.0	163.7	172.9
11	164.3	169.0	173.4
12	165.1	167.9	170.8
13	151.9	153.3	157.3
14	200.4	210.8	213.8
15	178.5	180.9	187.9
16	180.7	182.3	196.3
17	154.8	152.5	157.4
18	167.1	159.8	171.9
19	155.1	153.1	157.7
20	203.4	203.5	212.2
21	154.6	153.0	158.4
22	191.0	180.7	195.4
23	220.3	214.3	215.0
24	226.8	220.3	220.8
25	182.3	182.9	186.3
26	169.9	168.3	175.0
27	147.0	155.0	158.6
28	159.6	163.9	172.4
29	216.8	217.0	214.7
30	178.5	180.6	180.6
31	179.6	178.4	182.9
32	177.1	178.1	181.0
33	200.9	193.4	193.8
34	217.6	210.7	212.3
35	180.2	182.4	187.2
36	166.9	160.8	167.4
37	215.8	206.5	206.4
38	217.2	214.0	211.7
39	176.6	177.5	181.5
40	177.9	178.5	180.6
41	232.1	239.6	237.7
42	179.8	179.3	181.8
43	160.4	160.0	165.8
44	181.1	181.3	183.0
45	181.6	179.7	182.5
46	185.4	185.8	187.6
47	214.8	211.1	209.9
48	194.6	198.9	188.4
49	186.9	190.5	183.2
50	195.9	199.0	191.4
MD:	-2.8	-3.2	-
MAD:	5.7	5.0	-
SD:	6.1	5.7	-
MAX:	15.6	20.3	-

^a Reference bond lengths are from Ref. S6.

^b GFN-xTB values differ from Ref. S3, due to the use of a revised GFN-xTB Hamiltonian, in which 3d-level shifting is activated for the early 3d-transition metals (Sc-Cr).

Table S5: Center of mass (CMA) distances of 22 non-covalently interacting systems (S22)^{S7} computed with GFN2-xTB. The values are given in pm. See Ref. S3 and its supporting information for the results obtained with other semiempirical methods.

	GFN2-xTB	ref.
1	336.4	324.6
2	282.6	291.1
3	300.9	301.1
4	316.7	325.8
5	599.7	606.0
6	501.8	517.7
7	586.0	602.6
8	372.8	371.7
9	390.5	371.8
10	378.6	371.6
11	349.3	376.4
12	328.8	347.9
13	323.0	317.6
14	331.5	349.8
15	306.4	316.7
16	423.5	442.2
17	311.7	333.7
18	321.7	353.9
19	401.5	389.2
20	501.6	490.8
21	480.8	488.7
22	524.0	494.0

1: ammonia dimer, 2: water dimer, 3: formic acid dimer,
4: formamide dimer, 5: uracil dimer,
6: 2-pyridoxine · 2-aminopyridine, 7: adenine · thymine,
8: methane dimer, 9: ethene dimer, 10: benzene · methane,
11: benzene dimer, 12: pyracine dimer, 13: uracil dimer,
14: indole · benzene, 15: adenine · thymine (stack),
16: ethene · ethine, 17: benzene · water,
18: benzene · ammonia, 19: benzene · cyanide, 20: benzene
dimer, 21: indole · benzene (T-shape), 22: phenol dimer.

Table S6: Equilibrium center-of-mass distances between non-covalently bound systems of the S66x8 set^a. The values are given in pm and obtained by a cubic spline interpolation. For the interpolation, interaction energies and center-of-mass distances computed on the 8 structures along the potential energy curve of each complex are used. See Ref. S3 and its supporting information for the results obtained with other semiempirical methods.

#	system	GFN2-xTB	ref.
1	H ₂ O · H ₂ O	286.6	293.9
2	H ₂ O · MeOH	309.0	309.6
3	H ₂ O · MeNH ₂	325.5	334.4
4	H ₂ O · peptide	383.4	384.9
5	MeOH · MeOH	351.3	350.0
6	MeOH · MeNH ₂	330.2	335.8
7	MeOH · peptide	419.5	420.7
8	MeOH · H ₂ O	324.5	328.6
9	MeNH ₂ · MeOH	349.8	354.4
10	MeNH ₂ · MeNH ₂	349.8	348.0
11	MeNH ₂ · peptide	363.1	366.9
12	MeNH ₂ · H ₂ O	301.2	303.4
13	peptide · MeOH	391.0	388.3
14	peptide · MeNH ₂	376.6	388.7
15	peptide · peptide	463.8	468.1
16	peptide · H ₂ O	378.9	382.3
17	uracil · uracil (BP)	569.7	574.6
18	H ₂ O · pyridine	420.2	426.9
19	MeOH · pyridine	445.1	449.9
20	AcOH · AcOH	407.5	407.9
21	AcNH ₂ · AcNH ₂	423.9	432.5
22	AcOH · uracil	503.9	506.0
23	AcNH ₂ · uracil	505.7	512.0
24	benzene · benzene (π - π)	360.8	387.6
25	pyridine · pyridine (π - π)	344.7	369.9
26	uracil · uracil (π - π)	306.3	314.8
27	benzene · pyridine (π - π)	353.5	379.2
28	benzene · uracil (π - π)	326.4	338.9
29	pyridine · uracil (π - π)	320.3	333.7
30	benzene · ethene	329.7	353.2
31	uracil · ethene	325.1	331.2
32	uracil · ethyne	317.2	326.2
33	pyridine · ethene	326.3	345.5
34	pentane · pentane	403.3	382.5
35	neopentane · pentane	467.2	452.8
36	neopentane · neopentane	522.8	525.6
37	cyclopentane · neopentane	477.5	465.7
38	cyclopentane · cyclopentane	440.2	421.7
39	benzene · cyclopentane	396.7	394.3
40	benzene · neopentane	445.3	448.5
41	uracil · pentane	355.6	353.3
42	uracil · cyclopentane	378.7	375.8
43	uracil · neopentane	432.5	434.5
44	ethene · pentane	394.9	375.6
45	ethyne · pentane	361.3	362.9
46	peptide · pentane	376.0	362.2
47	benzene · benzene (TS)	493.9	490.4
48	pyridine · pyridine (TS)	487.7	481.9
49	benzene · pyridine (TS)	491.0	487.1
50	benzene · ethyne (CH- π)	419.7	410.1
51	ethyne · ethyne (TS)	421.2	435.6
52	benzene · AcOH (OH- π)	404.7	417.3
53	benzene · AcNH ₂ (NH- π)	469.7	476.1
54	benzene · H ₂ O (OH- π)	319.4	329.2
55	benzene · MeOH (OH- π)	337.8	342.1
56	benzene · MeNH ₂ (N H- π)	358.8	358.2
57	benzene · peptide (N H- π)	401.5	404.0
58	pyridine · pyridine (N H- π)	581.2	585.7
59	ethyne · H ₂ O (CH-O)	404.2	399.2
60	ethyne · AcOH (OH- π)	385.7	396.4
61	pentane · AcOH	377.8	373.1
62	pentane · AcNH ₂	362.1	358.6
63	benzene · AcOH	375.6	375.3
64	peptide · ethene	364.6	360.0
65	pyridine · ethyne	519.3	533.0
66	MeNH ₂ · pyridine	374.7	372.5

^a Reference structures taken from Ref. S8.

Table S7: Equilibrium center-of-mass distances between non-covalently bound systems of the S22x5 set^a. The values are given in pm and obtained by a cubic spline interpolation. For the interpolation, interaction energies and center-of-mass distances computed on the 5 structures along the potential energy curve of each complex are used.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB-D3(BJ)	ref.
1	586.9	595.6	610.4	608.4	602.6
2	312.6	309.9	331.7	310.5	324.2
3	334.1	326.5	340.6	337.2	329.9
4	287.1	293.8	294.0	289.1	293.8
5	390.6	386.7	359.7	334.6	374.7
6	395.5	407.3	393.8	372.3	381.4
7	419.9	431.7	431.1	414.6	446.3
8	303.9	301.3	310.8	302.9	304.0
9	318.4	329.7	329.0	326.9	328.5
10	319.7	309.3	324.2	309.3	331.3
11	351.4	349.2	338.9	332.9	354.6
12	381.5	380.6	367.7	355.3	378.7
13	503.7	504.2	497.5	491.8	497.5
14	371.5	379.0	384.8	362.5	395.7
15	494.3	493.7	496.7	489.4	493.6
16	350.2	357.2	361.7	345.9	364.2
17	337.1	347.6	358.6	336.1	361.9
18	502.7	514.2	527.7	523.8	519.3
19	498.4	497.4	502.0	493.7	494.7
20	313.5	304.6	329.8	310.8	323.2
21	602.5	609.1	611.4	610.6	607.0
22	402.5	414.3	403.0	390.2	391.3

1: ammonia dimer, 2: water dimer, 3: formic acid dimer, 4: formamide dimer, 5: uracil dimer, 6: 2-pyridoxine · 2-aminopyridine, 7: adenine · thymine, 8: methane dimer, 9: ethene dimer, 10: benzene · methane, 11: benzene dimer, 12: pyracine dimer, 13: uracil dimer, 14: indole · benzene, 15: adenine · thymine (stack), 16: ethene · ethine, 17: benzene · water, 18: benzene · ammonia, 19: benzene · cyanide, 20: benzene dimer, 21: indole · benzene (T-shape), 22: phenol dimer.

Table S8: Equilibrium center-of-mass distances between non-covalently bound systems of the X40 set^{S9}. The values are given in pm and obtained by a cubic spline interpolation of the X40x10 set. For the interpolation, interaction energies and center-of-mass distances computed on the 10 structures along the potential energy curve of each complex are used.

#	system	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB-D3(BJ)	ref.
1	CH ₄ · F ₂	422.1	363.3	427.8	386.4	391.5
2	CH ₄ · Cl ₂	437.2	425.7	388.6	452.0	431.5
3	CH ₄ · Br ₂	462.4	473.1	415.2	482.7	452.6
4	CH ₄ · I ₂	500.7	491.7	425.2	510.5	491.0
5	CH ₃ F · CH ₄	367.7	367.9	351.1	338.6	348.2
6	CH ₃ Cl · CH ₄	382.5	381.0	363.1	356.9	366.4
7	CHF ₃ · CH ₄	337.5	319.5	338.2	318.2	345.8
8	CHCl ₃ · CH ₄	345.1	328.1	319.5	342.9	360.0
9	CH ₃ F dimer	452.1	415.3	466.0	430.1	434.5
10	CH ₃ Cl dimer	520.6	503.7	477.1	525.0	516.2
11	C ₆ H ₃ F ₃ · C ₆ H ₆	353.5	363.9	366.6	347.8	367.9
12	C ₆ F ₆ · C ₆ H ₆	334.2	350.8	350.4	331.3	350.4
13	CH ₃ Cl · CH ₂ O	424.2	393.0	367.9	349.5	395.0
14	CH ₃ Br · CH ₂ O	372.0	351.9	366.1	343.7	371.4
15	CH ₃ I · CH ₂ O	367.3	358.8	372.6	337.2	373.5
16	CF ₃ Cl · CH ₂ O	447.7	435.3	450.9	426.2	452.8
17	CF ₃ Br · CH ₂ O	407.9	417.5	434.3	420.1	430.7
18	CF ₃ I · CH ₂ O	413.0	420.7	417.2	409.0	426.7
19	C ₆ H ₅ Cl · C(CH ₃) ₂ O	611.9	596.9	598.5	572.9	612.8
20	C ₆ H ₅ Br · C(CH ₃) ₂ O	553.3	550.6	565.5	544.4	567.4
21	C ₆ H ₅ I · C(CH ₃) ₂ O	544.2	544.0	551.0	524.0	554.8
22	C ₆ H ₅ Cl · N(CH ₃) ₃	566.3	545.9	560.4	539.1	570.4
23	C ₆ H ₅ Br · N(CH ₃) ₃	506.2	506.1	514.1	504.2	515.8
24	C ₆ H ₅ I · N(CH ₃) ₃	488.9	489.2	481.8	476.4	491.0
25	C ₆ H ₅ Br · CH ₃ SH	539.2	511.6	568.7	516.5	520.0
26	C ₆ H ₅ I · CH ₃ SH	507.2	497.0	500.1	491.6	505.6
27	CH ₃ Br · C ₆ H ₆	403.0	386.0	341.6	388.1	395.8
28	CH ₃ I · C ₆ H ₆	402.3	378.2	344.6	381.4	398.8
29	CF ₃ Br · C ₆ H ₆	441.6	429.3	395.2	449.7	449.2
30	CF ₃ I · C ₆ H ₆	434.5	415.7	385.1	440.9	446.7
31	CF ₃ OH · H ₂ O	333.6	338.0	345.5	340.3	339.6
32	CCl ₃ OH · H ₂ O	349.2	355.3	357.4	358.0	353.7
33	HF · CH ₃ OH	299.4	303.2	324.0	306.8	303.1
34	HCl · CH ₃ OH	346.0	364.9	346.3	345.3	352.1
35	HBr · CH ₃ OH	360.5	400.6	363.6	370.1	370.5
36	HI · CH ₃ OH	384.0	430.6	386.8	381.0	397.6
37	HF · N(CH ₃)H ₂	280.0	270.9	326.1	302.7	288.2
38	HCl · N(CH ₃)H ₂	317.6	304.8	329.0	337.8	324.0
39	CH ₃ OH · CH ₃ F	377.6	358.2	431.7	362.3	359.5
40	CH ₃ OH · CH ₃ Cl	378.6	360.8	394.3	375.5	375.1

2.2 Non-covalent interactions

Table S9: Association energies computed with semiempirical methods for six alkane dimers (ADIM6). Structures and reference energies are taken from Ref. S10. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	0.92	0.69	1.42	1.50	1.34
2	1.29	1.27	1.77	2.32	1.99
3	1.97	2.09	2.79	3.44	2.89
4	2.57	2.75	3.59	4.47	3.78
5	3.08	3.53	4.35	5.61	4.60
6	3.45	3.78	4.77	6.52	5.55
MD:	-1.15	-1.01	-0.24	0.62	-
MAD:	1.15	1.01	0.27	0.62	-
SD:	0.60	0.41	0.29	0.34	-
MAX:	2.10	1.77	0.78	1.01	-

Table S10: Association energies of the HAL59 set^{S9-S11} computed with different semiempirical methods. Numbering and reference values taken from Ref. S10. The values are given in kcal/mol.

#	system	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	PCH-C ₆ H ₅ Br	0.53	2.32	-2.05	2.66	0.85
2	NCH-C ₆ H ₅ Br	-0.90	1.46	0.67	3.58	1.15
3	NH ₃ -C ₆ H ₅ Br	-0.37	2.38	2.23	5.73	2.02
4	MeI-PCH	0.98	2.34	4.19	3.17	0.85
5	MeI-NCH	0.18	1.88	0.81	5.02	1.42
6	MeI-NH ₃	1.85	3.45	2.86	7.64	2.73
7	PCH-C ₆ H ₅ I	0.96	2.36	4.28	3.14	0.92
8	NCH-C ₆ H ₅ I	0.32	2.04	0.86	4.99	1.87
9	NH ₃ -C ₆ H ₅ I	2.07	3.78	3.06	7.60	3.33
10	PCH-F ₃ CI	2.65	2.33	5.36	3.59	0.89
11	NCH-F ₃ CI	3.63	3.27	3.37	6.76	3.61
12	NH ₃ -F ₃ CI	8.22	6.88	7.97	10.03	5.88
13	Br ₂ -PCH	1.58	2.36	-3.07	3.53	1.18
14	Br ₂ -NCH	1.66	2.25	2.52	6.00	3.61
15	Br ₂ -NH ₃	6.89	5.97	7.65	9.78	7.29
16	PCH-C ₄ H ₄ BrNO ₂	1.87	2.71	-0.25	4.63	1.19
17	NCH-C ₄ H ₄ BrNO ₂	1.79	3.84	14.21	8.66	4.32
18	NH ₃ -C ₄ H ₄ BrNO ₂	7.24	10.23	36.83	13.40	8.02
19	PCH-FCl	2.43	3.25	-6.54	4.84	1.16
20	NCH-FCl	3.07	3.03	-3.94	7.99	4.81
21	NH ₃ -FCl	9.65	11.85	-69.17	11.15	10.54
22	PCH-C ₄ H ₄ INO ₂	3.82	3.38	29.22	5.81	1.53
23	NCH-C ₄ H ₄ INO ₂	5.59	5.56	83.24	12.29	5.91
24	NH ₃ -C ₄ H ₄ INO ₂	12.13	13.61	182.55	18.43	10.99
25	PCH-FBr	4.22	3.55	-6.58	5.49	2.07
26	NCH-FBr	5.91	5.05	-2.51	9.55	7.53
27	NH ₃ -FBr	14.89	13.63	-2.23	10.41	15.30
28	FI-PCH	5.29	5.58	16.83	7.28	2.74
29	FI-NCH	8.35	7.67	4.34	13.42	9.33
30	FI-NH ₃	15.09	17.10	4.92	17.11	17.11
31	MeI-FCCH	0.46	0.34	0.18	1.53	0.50
32	Br ₂ -FCCH	0.74	0.33	-0.23	1.33	0.74
33	FI-FCCH	-0.21	-0.40	-0.01	-0.08	0.29
34	MeI-FMe	0.30	1.09	1.38	3.06	1.70
35	Br ₂ -FMe	1.18	0.87	-0.19	3.16	2.87
36	FI-FMe	3.86	7.14	4.20	7.35	5.97
37	MeI-OCH ₂	1.46	2.84	2.13	5.51	2.39
38	Br ₂ -OCH ₂	3.70	3.27	3.25	7.28	4.41
39	FI-OCH ₂	9.71	9.48	4.39	14.30	9.94
40	MeI-OPH ₃	1.32	2.70	8.33	4.65	3.34
41	Br ₂ -OPH ₃	1.92	1.15	3.90	5.64	5.95
42	FI-OPH ₃	6.92	1.93	17.55	11.79	13.36
43	MeI-C ₅ H ₅ N	2.76	3.92	2.92	10.84	3.61
44	Br ₂ -C ₅ H ₅ N	9.31	5.12	4.49	14.94	9.07
45	FI-C ₅ H ₅ N	20.07	18.52	-9.50	25.48	20.34
46	C ₆ H ₃ F ₃ -C ₆ H ₆	4.99	3.50	3.98	5.09	4.40
47	C ₆ H ₆ F ₆ -C ₆ H ₆	6.70	3.96	4.97	6.91	6.12
48	C ₆ H ₅ Cl-CH ₂ O	0.65	0.47	1.27	4.65	1.49
49	C ₆ H ₅ Br-CH ₂ O	0.60	2.40	2.54	5.47	2.43
50	C ₆ H ₅ I-CH ₂ O	2.92	3.89	3.38	7.35	3.46
51	C ₆ H ₅ Cl-N(CH ₃) ₃	0.94	0.92	1.62	7.71	2.11
52	C ₆ H ₅ Br-N(CH ₃) ₃	1.21	3.76	3.92	9.27	3.78
53	C ₆ H ₅ I-N(CH ₃) ₃	4.07	5.28	5.74	12.24	5.81
54	C ₆ H ₅ Br-CH ₃ SH	1.04	2.50	0.69	3.33	2.32
55	C ₆ H ₅ I-CH ₃ SH	1.84	3.24	3.10	4.81	3.08
56	CH ₃ Br-C ₆ H ₆	0.89	1.21	2.63	3.27	1.81
57	CH ₃ I-C ₆ H ₆	1.69	1.60	3.50	3.83	2.48
58	CF ₃ Br-C ₆ H ₆	1.82	1.57	3.65	4.28	3.11
59	CF ₃ I-C ₆ H ₆	3.54	2.13	5.03	4.85	3.91
	MD:	-0.73	-0.36	2.36	2.76	-
	MAD:	1.28	1.34	9.71	3.00	-
	SD:	1.51	2.09	27.92	2.22	-
	MAX:	6.44	11.43	171.56	7.44	-

Table S11: Association energies of the PNICO23 set^{S10,S12} computed with different semiempirical methods. Numering and reference values taken from Ref. S10. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	2.19	1.86	0.39	1.67	1.43
2	5.96	18.56	-10.70	-1.86	8.02
3	3.92	1.87	-0.90	-0.61	0.64
4	4.37	9.41	-7.50	4.63	4.26
5	4.96	3.10	-0.55	3.66	2.86
6	1.18	1.29	1.52	1.38	1.32
7	3.37	7.62	-7.87	4.36	4.29
8	2.62	4.12	-2.37	3.08	2.63
9	6.24	7.34	-6.22	4.05	4.91
10	2.89	2.99	-0.55	2.23	2.21
11	2.44	2.56	-0.17	1.57	1.40
12	4.22	6.03	-4.01	2.88	2.62
13	1.78	1.27	2.25	0.44	3.98
14	4.18	6.80	-4.46	4.02	4.10
15	2.91	2.99	3.54	2.25	4.34
16	2.16	1.97	1.49	1.41	1.78
17	7.22	10.94	5.51	5.43	7.10
18	2.24	1.50	1.24	1.27	2.35
19	5.12	7.70	5.28	3.92	5.95
20	11.47	14.70	9.64	6.16	8.18
21	5.53	6.02	3.83	4.02	4.92
22	8.88	9.02	5.87	6.04	8.03
23	12.41	12.37	8.34	7.88	10.97
MD:	0.43	1.90	-4.12	-1.23	-
MAD:	1.10	2.33	4.26	1.45	-
SD:	1.42	2.79	5.05	2.23	-
MAX:	3.29	10.54	18.72	9.88	-

Table S12: Association energies of 22 non-covalently interacting systems (S22)^a computed with GFN2-xTB. The values are given in kcal/mol. Reference energies taken from Ref. S13. Structures taken from Ref. S7. Running number as in Ref. S14.

system #	GFN2-xTB	ref.
1	2.05	3.13
2	4.90	4.99
3	17.20	18.75
4	16.64	16.06
5	19.63	20.64
6	16.72	16.93
7	15.89	16.66
8	0.38	0.53
9	1.07	1.47
10	1.29	1.45
11	3.83	2.65
12	5.43	4.25
13	9.81	9.80
14	5.40	4.52
15	12.20	11.73
16	1.37	1.50
17	2.26	3.27
18	1.88	2.31
19	2.60	4.54
20	2.31	2.72
21	4.00	5.63
22	5.79	7.10
MD:	-0.36	-
MAD:	0.75	-
SD:	0.88	-
MAX:	1.94	-

1: ammonia dimer, 2: water dimer, 3: formic acid dimer,
4: formamide dimer, 5: uracil dimer,
6: 2-pyridoxine · 2-aminopyridine, 7: adenine · thymine,
8: methane dimer, 9: ethene dimer, 10: benzene · methane,
11: benzene dimer, 12: pyracine dimer, 13: uracil dimer,
14: indole · benzene, 15: adenine · thymine (stack),
16: ethene · ethine, 17: benzene · water,
18: benzene · ammonia, 19: benzene · cyanide, 20: benzene
dimer, 21: indole · benzene (T-shape), 22: phenol dimer.

Table S13: Association energies computed with semiempirical methods for 66 non-covalent complexes consisting of main group elements (S66).^{S8} The values are given in kcal/mol.

#	system	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	H ₂ O · H ₂ O	4.91	4.76	5.03	4.86	4.92
2	H ₂ O · MeOH	4.78	4.46	5.58	5.09	5.59
3	H ₂ O · MeNH ₂	5.38	6.15	7.44	4.42	6.91
4	H ₂ O · peptide	7.40	7.08	7.99	8.41	8.10
5	MeOH · MeOH	4.77	4.62	6.32	4.85	5.76
6	MeOH · MeNH ₂	5.74	6.65	6.98	4.48	7.55
7	MeOH · peptide	7.31	7.28	8.19	7.82	8.23
8	MeOH · H ₂ O	4.61	4.76	5.75	4.43	5.01
9	MeNH ₂ · MeOH	2.71	2.51	4.24	2.54	3.06
10	MeNH ₂ · MeNH ₂	2.70	2.56	4.54	2.36	4.16
11	MeNH ₂ · peptide	4.58	4.22	6.14	4.32	5.42
12	MeNH ₂ · H ₂ O	4.98	5.71	7.30	4.09	7.27
13	peptide · MeOH	5.32	4.85	6.49	5.07	6.19
14	peptide · MeNH ₂	6.39	5.76	7.45	4.72	7.45
15	peptide · peptide	8.05	7.54	8.81	7.92	8.63
16	peptide · H ₂ O	4.76	4.78	5.51	4.47	5.12
17	uracil · uracil (BP)	16.54	14.77	16.44	15.11	17.18
18	H ₂ O · pyridine	5.11	5.44	6.78	4.24	6.86
19	MeOH · pyridine	5.57	5.96	6.14	4.31	7.41
20	AcOH · AcOH	17.56	18.68	18.43	19.15	19.09
21	AcNH ₂ · AcNH ₂	16.43	14.45	16.98	15.49	16.26
22	AcOH · uracil	18.24	17.66	18.42	18.40	19.49
23	AcNH ₂ · uracil	19.07	16.71	18.97	17.48	19.19
24	benzene · benzene (π - π)	3.60	3.12	2.89	3.38	2.82
25	pyridine · pyridine (π - π)	4.60	3.35	4.03	3.96	3.90
26	uracil · uracil (π - π)	9.87	8.62	9.08	9.25	9.83
27	benzene · pyridine (π - π)	4.06	3.15	3.55	3.71	3.44
28	benzene · uracil (π - π)	5.81	3.97	5.37	6.02	5.71
29	pyridine · uracil (π - π)	7.39	5.22	6.88	6.92	6.82
30	benzene · ethene	1.88	1.78	1.59	1.89	1.43
31	uracil · ethene	3.14	1.96	3.00	3.60	3.38
32	uracil · ethyne	3.34	1.84	2.70	3.84	3.74
33	pyridine · ethene	2.18	1.81	2.03	2.08	1.87
34	pentane · pentane	2.38	2.56	3.48	4.73	3.78
35	neopentane · pentane	1.93	2.10	2.73	3.45	2.61
36	neopentane · neopentane	1.62	2.08	2.17	2.65	1.78
37	cyclopentane · neopentane	1.95	2.09	2.52	3.39	2.40
38	cyclopentane · cyclopentane	1.96	2.10	2.33	3.67	3.00

39	benzene · cyclopentane	3.27	3.03	3.40	3.73	3.58
40	benzene · neopentane	2.88	2.73	3.46	3.19	2.90
41	uracil · pentane	4.93	4.09	5.55	5.61	4.85
42	uracil · cyclopentane	4.01	3.59	4.53	4.71	4.14
43	uracil · neopentane	3.81	2.81	3.78	3.79	3.71
44	ethene · pentane	1.34	1.15	1.85	2.46	2.01
45	ethyne · pentane	1.60	1.43	1.73	1.91	1.75
46	peptide · pentane	3.21	3.22	4.11	4.72	4.26
47	benzene · benzene (TS)	2.55	2.05	2.52	2.70	2.88
48	pyridine · pyridine (TS)	2.75	2.44	3.03	3.07	3.54
49	benzene · pyridine (TS)	2.65	1.99	2.92	2.86	3.33
50	benzene · ethyne (CH- π)	2.04	0.93	1.96	2.52	2.87
51	ethyne · ethyne (TS)	1.48	0.63	0.82	1.28	1.52
52	benzene · AcOH (OH- π)	3.65	3.08	4.17	4.60	4.71
53	benzene · AcNH ₂ (NH- π)	3.26	3.43	3.92	3.79	4.36
54	benzene · H ₂ O (OH- π)	2.29	1.71	3.36	3.18	3.28
55	benzene · MeOH (OH- π)	3.17	2.49	3.63	3.80	4.19
56	benzene · MeNH ₂ (N H- π)	2.66	2.00	3.23	2.96	3.23
57	benzene · peptide (N H- π)	4.08	3.14	4.81	4.81	5.28
58	pyridine · pyridine (N H- π)	3.09	2.59	3.25	2.05	4.15
59	ethyne · H ₂ O (CH-O)	1.84	1.11	1.95	2.68	2.85
60	ethyne · AcOH (OH- π)	3.95	3.51	2.38	4.22	4.87
61	pentane · AcOH	2.80	2.46	3.59	3.52	2.91
62	pentane · AcNH ₂	3.08	3.28	3.94	4.15	3.53
63	benzene · AcOH	2.98	2.35	3.73	3.79	3.80
64	peptide · ethene	2.07	2.15	2.74	2.91	3.00
65	pyridine · ethyne	3.35	2.18	1.78	2.85	3.99
66	MeNH ₂ · pyridine	2.94	2.68	4.43	2.77	3.97
	MD:	-0.61	-1.05	-0.15	-0.45	-
	MAD:	0.73	1.08	0.47	0.79	-
	SD:	0.65	0.64	0.64	1.04	-
	MAX:	2.29	2.48	2.49	3.18	-

Table S14: Association energies of water clusters (WATER27 set) computed with different semiempirical methods. The values are given in kcal/mol.

system	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
H ₂ O ₂	4.93	4.79	5.19	4.87	5.01
H ₂ O ₃	14.26	14.63	15.00	14.75	15.80
H ₂ O ₄	26.46	24.29	26.25	25.93	27.40
H ₂ O ₅	34.20	30.99	34.01	33.77	35.90
H ₂ O ₆	44.57	45.33	45.68	44.90	46.00
H ₂ O _{6c}	44.16	43.31	44.98	43.94	45.80
H ₂ O _{6b}	43.44	40.71	43.61	42.92	45.30
H ₂ O _{6c2}	42.09	37.80	41.33	42.10	44.30
H ₂ O _{8d2d}	71.48	68.18	72.06	69.92	72.60
H ₂ O _{8s4}	71.35	68.21	71.85	69.76	72.60
H ₂ O ₂₀	193.19	176.71	195.88	186.12	198.60
H ₂ O _{20fc}	208.95	201.24	207.22	204.39	208.00
H ₂ O _{20fs}	207.71	197.38	206.93	202.69	208.00
H ₂ O _{20es}	208.62	196.93	206.49	203.25	209.70
H ₃ O ⁺ H ₂ O	31.16	33.19	28.46	30.55	33.50
H ₃ O ⁺ H ₂ O ₂	53.46	54.34	49.88	52.42	56.90
H ₃ O ⁺ H ₂ O ₃	73.30	72.59	68.15	71.31	76.50
H ₃ O ⁺ H ₂ O _{63d}	112.67	112.76	110.37	108.52	117.80
H ₃ O ⁺ H ₂ O _{62d}	110.36	109.80	108.86	108.74	114.90
OH ⁻ H ₂ O	35.35	38.90	35.08	30.33	26.60
OH ⁻ H ₂ O ₂	55.32	60.02	54.36	53.04	48.40
OH ⁻ H ₂ O ₃	74.70	79.30	73.91	72.51	67.60
OH ⁻ H ₂ O _{4c4}	89.98	96.28	88.20	91.12	84.80
OH ⁻ H ₂ O _{4cs}	89.72	97.25	90.37	90.85	84.80
OH ⁻ H ₂ O ₅	104.43	114.86	103.27	108.40	100.70
OH ⁻ H ₂ O ₆	120.02	129.04	119.01	122.43	115.70
H ₃ O ⁺ H ₂ O ₆ OH ⁻	32.41	42.88	21.09	30.96	28.50
MD:	0.24	0.00	-0.90	-1.16	-
MAD:	3.15	7.51	3.55	4.31	-
SD:	3.92	9.43	4.45	5.07	-
MAX:	8.75	21.89	8.47	12.47	-

Table S15: Association energies of anion-neutral dimer systems (AHB21).^{S17} The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	-13.45	-16.77	-9.44	-15.41	-17.79
2	-26.50	-33.06	-24.13	-30.73	-32.50
3	-58.43	-67.14	-45.41	-61.41	-65.68
4	-7.16	-5.15	-8.59	-8.62	-8.98
5	-13.08	-11.39	-13.77	-17.17	-15.61
6	-24.78	-20.75	-17.38	-28.73	-25.52
7	-18.15	-5.60	-14.37	-19.45	-14.35
8	-37.75	-35.11	-46.30	-42.37	-41.79
9	-20.48	-21.40	-20.08	-17.63	-17.03
10	-43.90	-48.37	-39.26	-40.72	-37.31
11	-7.60	-8.13	-9.18	-7.13	-7.97
12	-14.09	-16.62	-14.84	-13.67	-14.13
13	-29.96	-34.22	-10.45	-24.79	-26.01
14	-17.61	-10.74	-11.14	-12.90	-11.07
15	-7.62	-14.19	-8.85	-7.83	-8.62
16	-13.98	-26.50	-13.87	-15.26	-15.73
17	-26.51	-45.21	-15.95	-25.70	-26.24
18	-10.46	-11.54	-14.08	-9.95	-12.80
19	-18.19	-20.55	-20.50	-19.37	-20.65
20	-18.93	-22.50	-22.86	-23.65	-21.03
21	-32.41	-33.61	-21.66	-33.11	-31.40
MD:	0.53	-1.73	3.34	-0.16	-
MAD:	2.97	4.68	4.75	1.80	-
SD:	3.72	6.51	6.61	2.28	-
MAX:	7.25	18.97	20.27	5.10	-

Table S16: Association energies of the systems in the CARBHB12.^{S10} The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	ref.
1	3.34	4.65	4.74	5.37
2	4.07	5.27	3.56	6.05
3	2.82	3.43	2.77	2.42
4	7.25	10.21	10.86	9.97
5	1.83	2.08	2.63	2.36
6	2.39	2.48	2.39	3.02
7	1.47	1.75	1.46	1.21
8	3.32	4.89	4.43	4.18
9	7.53	7.48	8.30	7.84
10	9.54	10.54	6.81	10.48
11	5.57	5.36	3.65	3.24
12	16.33	16.98	13.51	16.30
MD:	-0.58	0.23	-0.61	-
MAD:	1.08	0.67	1.09	-
SD:	1.33	0.85	1.52	-
MAX:	2.71	2.12	3.67	-

Table S17: Association energies of cation-neutral dimer systems (CHB6).^{S17} The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	ref.
1	-44.31	-42.80	-20.29	-34.43
2	-30.07	-23.15	-11.59	-23.83
3	-23.84	-19.33	-7.45	-17.83
4	-36.74	-40.77	-12.23	-39.09
5	-28.28	-14.76	-29.04	-25.63
6	-24.61	-20.47	-20.35	-19.90
MD:	-4.52	-0.10	9.96	-
MAD:	5.31	3.95	11.25	-
SD:	4.12	6.23	10.92	-
MAX:	9.88	10.87	26.86	-

Table S18: Association energies of the HEAVY28^{S10,S18} set computed with different semiempirical methods. The values are given in kcal/mol.

#	system	GFN2-xTB	GFN-xTB	PM6-D3H4X	ref.
1	(BiH ₃) ₂	1.99	1.36	0.60	1.16
2	BiH ₃ -H ₂ O	1.85	1.49	-1.73	2.49
3	BiH ₃ -H ₂ S	1.41	1.18	0.60	1.36
4	BiH ₃ -HCl	1.06	0.78	-0.08	0.77
5	BiH ₃ -HBr	1.13	0.94	0.69	0.98
6	BiH ₃ -HI	1.04	1.69	4.50	1.30
7	BiH ₃ -NH ₃	1.69	1.13	-2.14	0.60
8	(PbH ₄) ₂	0.94	0.03	2.62	1.25
9	PbH ₄ -BiH ₃	0.57	0.44	0.32	0.55
10	PbH ₄ -H ₂ O	0.82	0.35	0.87	0.36
11	PbH ₄ -HCl	0.64	0.41	0.68	0.75
12	PbH ₄ -HBr	0.59	0.33	-0.16	0.93
13	PbH ₄ -HI	0.65	0.53	1.34	1.18
14	PbH ₄ -TeH ₂	0.61	0.46	0.60	0.65
15	(SbH ₃) ₂	2.19	4.04	-1.61	1.28
16	SbH ₃ -H ₂ O	0.80	1.97	-2.25	1.57
17	SbH ₃ -H ₂ S	0.83	1.41	-0.55	1.06
18	SbH ₃ -HCl	1.01	2.02	-2.92	2.02
19	SbH ₃ -HBr	0.66	1.61	-1.96	1.89
20	SbH ₃ -HI	0.92	2.00	-0.98	1.49
21	SbH ₃ -NH ₃	5.41	8.45	-29.18	2.84
22	(TeH ₂) ₂	0.64	0.80	1.85	0.52
23	TeH ₂ -H ₂ O	2.46	0.40	-1.45	0.68
24	TeH ₂ -H ₂ S	0.94	0.41	0.03	0.48
25	TeH ₂ -HCl	1.92	0.89	0.64	1.23
26	TeH ₂ -HBr	1.26	0.76	0.11	1.22
27	TeH ₂ -HI	0.40	1.25	1.81	0.80
28	TeH ₂ -NH ₃	4.46	2.33	2.18	3.35
	MD:	0.15	0.17	-2.15	-
	MAD:	0.61	0.65	2.70	-
	SD:	0.83	1.29	6.14	-
	MAX:	2.57	5.61	32.02	-

Table S19: Association energies of the anion-cation dimer set (IL16)^{S17} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	-99.31	-94.08	-95.10	-103.22	-100.41
2	-113.75	-120.68	-115.46	-120.99	-120.80
3	-108.50	-115.22	-109.75	-115.42	-116.91
4	-99.47	-94.89	-97.81	-103.72	-105.01
5	-96.87	-100.54	-99.07	-96.85	-104.44
6	-83.17	-94.93	-80.78	-85.80	-87.42
7	-109.04	-104.27	-102.58	-113.63	-114.00
8	-109.28	-104.49	-103.83	-114.36	-113.51
9	-111.65	-106.41	-106.47	-116.92	-114.91
10	-107.51	-112.63	-112.70	-109.00	-112.75
11	-101.14	-116.68	-95.87	-100.03	-104.47
12	-114.78	-110.39	-109.14	-121.29	-118.19
13	-106.28	-112.91	-110.75	-110.38	-112.02
14	-102.33	-118.59	-99.00	-104.47	-106.53
15	-111.55	-110.93	-113.31	-108.70	-110.98
16	-102.18	-103.41	-95.97	-98.54	-102.37
MD:	4.24	1.48	6.07	1.34	–
MAD:	4.32	5.69	6.36	2.46	–
SD:	2.50	7.25	3.64	2.81	–
MAX:	8.41	12.21	11.43	7.59	–

Table S20: Association energies of rare gas complexes (RG18)^{S10} computed with different semiempirical methods. The values are given in kcal/mol.

#	system	GFN2-xTB	GFN-xTB	PM6-D3H4X	ref.
1	Ne ₂	0.05	0.03	0.06	0.08
2	Ar ₂	0.23	0.17	0.01	0.27
3	Kr ₂	0.40	0.74	-0.52	0.40
4	Ne ₃	0.15	0.09	0.18	0.27
5	Ar ₃	0.66	0.46	0.34	0.77
6	Kr ₃	1.11	1.90	-0.48	1.18
7	Ne ₄	0.30	0.18	0.36	0.54
8	Ar ₄	1.30	0.91	0.71	1.51
9	Ne ₆	0.64	0.40	0.76	1.13
10	HFNe	0.27	0.32	-0.29	0.23
11	HFAr	0.95	1.04	-0.10	0.59
12	HFKr	0.76	1.86	1.70	0.72
13	C ₂ H ₂ -Ne	0.14	0.10	0.16	0.12
14	C ₂ H ₂ -Ar	0.38	0.25	-0.11	0.33
15	C ₂ H ₆ -Ne	0.16	0.17	0.26	0.24
16	C ₂ H ₆ -Ar	0.47	0.47	0.12	0.54
17	Benzene-Ne	0.38	0.27	0.40	0.40
18	Benzene-Ar	1.13	0.73	-1.24	1.12
	MD:	-0.05	-0.02	-0.45	-
	MAD:	0.11	0.32	0.57	-
	SD:	0.17	0.45	0.71	-
	MAX:	0.49	1.14	2.36	-

Table S21: Association energies computed with semiempirical methods for 30 large non-covalent complexes containing only main group elements (S30L)^a. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	-25.93	-21.97	-28.83	-28.62	-29.04
2	-18.02	-14.51	-18.63	-19.88	-20.78
3	-22.50	-18.75	-22.41	-23.93	-23.54
4	-21.72	-16.52	-19.18	-18.80	-20.27
5	-33.88	-27.16	-33.96	-34.07	-28.99
6	-25.57	-18.70	-20.83	-24.61	-25.50
7	-42.20	-34.75	-30.95	-38.78	-35.06
8	-48.70	-39.87	-35.57	-44.03	-36.79
9	-34.83	-33.02	-27.66	-36.37	-28.38
10	-35.86	-34.88	-29.12	-38.03	-29.78
11	-41.74	-41.52	-38.69	-44.49	-32.95
12	-42.21	-41.72	-38.45	-44.33	-33.92
13	-22.30	-25.25	-29.32	-26.75	-30.83
14	-25.64	-26.89	-29.45	-30.64	-31.33
15	-24.10	-22.78	-21.86	-36.63	-17.39
16	-25.85	-29.95	-30.06	-42.40	-25.12
17	-26.78	-25.18	-39.73	-31.14	-33.38
18	-20.38	-20.49	-29.11	-23.09	-23.31
19	-13.05	-17.85	-19.32	-17.15	-17.47
20	-15.23	-22.00	-23.48	-22.62	-19.25
21	-22.14	-28.43	-31.35	-28.23	-24.21
22	-36.57	-33.98	-44.06	-33.76	-42.63
23	-60.72	-47.03	-61.72	-41.70	-61.32
24	-136.59	-167.06	-162.49	-162.06	-135.51
25	-28.08	-24.30	-25.95	-29.39	-25.96
26	-28.21	-24.60	-25.89	-29.49	-25.77
27	-83.16	-94.76	-104.03	-95.17	-82.18
28	-79.49	-90.49	-101.22	-89.88	-80.11
29	-50.95	-54.68	-59.62	-58.39	-53.54
30	-50.52	-51.57	-56.39	-56.78	-49.28
MD:	-0.64	-0.90	-3.86	-4.25	-
MAD:	4.05	6.08	5.15	6.90	-
SD:	5.09	8.50	7.47	8.68	-
MAX:	11.91	31.55	26.98	26.55	-

^a Reference structures and numbering are taken from Ref. S19.

Table S22: Interaction energies of 15 charged H-bonded systems (C15)^a computed with different semiempirical methods. The values are given in kcal/mol.

	GFN-xTB	PM6-D3H4X	MSINDO-D3(BJ)H+	OM2-D3(BJ)	DFTB3-D3(BJ)	HF-3c	ref.
CH ₃ COO ⁻ · CH ₃ NH ₂	-9.715	-12.041	-9.385	-8.384	-8.671	-12.313	-11.455
CH ₃ COO ⁻ · CH ₃ OH	-18.057	-19.051	-22.179	-15.111	-17.993	-23.842	-19.753
CH ₃ COO ⁻ · H ₂ O	-21.157	-21.816	-23.603	-17.939	-22.918	-25.393	-21.062
CH ₆ N ₃ ⁺ · CH ₂ O	-16.507	-18.888	-17.938	-16.579	-14.446	-17.684	-18.090
CH ₆ N ₃ ⁺ · CH ₃ NH ₂	-15.008	-19.077	-16.218	-17.384	-11.978	-23.016	-20.196
CH ₆ N ₃ ⁺ · CH ₃ OH	-16.327	-18.828	-18.756	-17.696	-16.246	-21.428	-19.788
CH ₆ N ₃ ⁺ · H ₂ O	-15.799	-16.849	-19.505	-16.185	-15.148	-20.344	-17.467
C ₃ H ₅ N ₂ ⁺ · CH ₂ O	-14.671	-16.065	-15.020	-15.425	-12.179	-17.065	-16.410
C ₃ H ₅ N ₂ ⁺ · CH ₃ NH ₂	-21.838	-22.672	-22.365	-24.485	-13.445	-32.981	-25.977
C ₃ H ₅ N ₂ ⁺ · CH ₃ OH	-14.997	-15.359	-15.962	-17.593	-14.147	-23.245	-18.914
C ₃ H ₅ N ₂ ⁺ · H ₂ O	-14.382	-13.984	-16.918	-16.206	-13.295	-21.700	-16.485
CH ₆ N ⁺ · CH ₂ O	-18.861	-20.474	-19.596	-18.229	-16.788	-20.370	-19.096
CH ₆ N ⁺ · CH ₃ NH ₂	-26.319	-29.002	-28.885	-26.449	-20.156	-36.823	-28.560
CH ₆ N ⁺ · CH ₃ OH	-19.211	-19.652	-21.564	-19.960	-19.461	-26.679	-21.225
CH ₆ N ⁺ · H ₂ O	-18.206	-18.137	-22.412	-18.353	-17.955	-24.902	-18.514

^a Reference energies from Ref. S20.

Table S23: Association energies computed with the GFN-xTB and GFN2-xTB methods for the C15^{S20} set. The values are given in kcal/mol.

system	#	GFN2-xTB	GFN-xTB	ref.
CH ₃ COO ⁻ · CH ₃ NH ₂	1	-8.71	-9.71	-11.46
CH ₃ COO ⁻ · CH ₃ OH	2	-16.81	-18.06	-19.75
CH ₃ COO ⁻ · H ₂ O	3	-18.83	-21.16	-21.06
CH ₆ N ₃ ⁺ · CH ₂ O	4	-14.87	-16.51	-18.09
CH ₆ N ₃ ⁺ · CH ₃ NH ₂	5	-18.04	-15.01	-20.20
CH ₆ N ₃ ⁺ · CH ₃ OH	6	-16.74	-16.33	-19.79
CH ₆ N ₃ ⁺ · H ₂ O	7	-15.96	-15.80	-17.47
C ₃ H ₅ N ₂ ⁺ · CH ₂ O	8	-13.98	-14.67	-16.41
C ₃ H ₅ N ₂ ⁺ · CH ₃ NH ₂	9	-24.59	-21.84	-25.98
C ₃ H ₅ N ₂ ⁺ · CH ₃ OH	10	-16.30	-15.00	-18.91
C ₃ H ₅ N ₂ ⁺ · H ₂ O	11	-15.77	-14.38	-16.48
CH ₆ N ⁺ · CH ₂ O	12	-17.60	-18.86	-19.10
CH ₆ N ⁺ · CH ₃ NH ₂	13	-28.92	-26.32	-28.56
CH ₆ N ⁺ · CH ₃ OH	14	-20.29	-19.21	-21.23
CH ₆ N ⁺ · H ₂ O	15	-19.66	-18.21	-18.51
MD:		1.73	2.13	–
MAD:		1.93	2.14	–
SD:		1.27	1.49	–
MAX:		3.22	5.19	–

Table S24: Association energies computed with the GFN-xTB and GFN2-xTB methods for the I9^{S21} set. The values are given in kcal/mol.

#	GFN2-xTB	GFN-xTB	ref.
1	-130.7	-131.3	-134.3
2	-110.9	-130.8	-125.3
3	-165.9	-167.7	-182.0
4	-102.5	-106.6	-120.4
5	-99.4	-119.2	-104.0
6	-112.5	-116.7	-120.4
7	-132.9	-137.5	-145.1
8	-103.1	-124.0	-117.6
9	-122.2	-129.6	-132.4
MD:	11.2	2.0	–
MAD:	11.2	8.0	–
SD:	5.0	9.7	–
MAX:	17.9	15.2	–

2.3 Conformers

Table S25: Relative conformer energies for different alkane conformers (ACONF)^a computed with GFN2-xTB. The results for the other semiempirical methods mentioned in the manuscript can be found in Ref. S3. The values are given in kcal/mol.

	GFN2-xTB	ref.
1	0.604	0.598
2	0.566	0.614
3	1.214	0.961
4	2.483	2.813
5	0.573	0.595
6	0.545	0.604
7	1.176	0.934
8	1.082	1.178
9	1.233	1.302
10	1.741	1.250
11	2.384	2.632
12	2.432	2.740
13	2.862	3.283
14	3.049	3.083
15	4.647	4.925
MD:	-0.061	–
MAD:	0.194	–
SD:	0.246	–
MAX:	0.491	–

^a Reference data taken from Ref. S22.

Table S26: Conformational energies for different amino acid conformers (Amino20x4)^a computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	-0.01	-0.49	-2.15	-0.58	1.17
2	1.47	1.91	0.95	1.60	3.05
3	1.19	1.42	0.56	1.25	3.32
4	5.55	3.90	5.08	4.35	5.04
5	5.18	3.67	6.32	1.81	1.58
6	5.64	3.67	4.66	0.97	2.53
7	7.21	6.02	5.32	3.03	2.80
8	6.28	6.04	5.08	3.79	6.46
9	0.90	1.24	0.99	1.38	0.39
10	4.02	4.42	1.99	4.77	4.11
11	3.79	4.35	3.27	4.57	4.76
12	7.83	8.17	7.72	8.70	6.53
13	-0.03	-0.83	-0.92	1.44	0.16
14	1.64	1.98	0.67	1.68	1.97
15	3.69	2.36	4.54	2.45	2.90
16	1.51	0.11	0.35	3.14	3.11
17	-0.83	-0.63	-3.41	-1.67	0.28
18	0.60	0.17	-0.71	0.31	0.98
19	-0.10	0.04	-1.93	-1.15	0.99
20	2.02	1.84	0.13	0.17	2.37
21	0.28	1.44	-0.72	-0.32	0.42
22	1.93	3.47	0.42	2.56	3.27
23	5.39	6.82	4.84	5.21	4.04
24	4.99	5.78	2.34	5.12	4.15
25	1.78	0.85	2.21	2.02	1.33
26	2.08	1.52	2.42	2.28	1.54
27	3.29	2.57	3.09	3.27	2.94
28	4.63	3.27	4.57	3.58	5.22
29	1.82	2.48	3.88	1.10	1.09
30	3.54	3.24	4.62	3.34	2.63
31	2.14	3.31	4.29	0.88	2.74
32	3.12	3.58	4.44	3.12	4.09
33	2.22	2.18	2.69	2.10	2.77
34	2.29	1.82	2.49	2.02	2.99
35	6.19	5.93	9.22	6.36	7.32
36	7.69	6.45	8.13	7.10	7.37
37	0.02	0.12	-0.16	0.49	0.19
38	0.10	0.06	0.16	0.32	0.59

39	1.07	0.88	2.34	0.96	0.96
40	1.33	1.54	1.62	1.01	0.99
41	-0.71	-0.24	-0.43	-0.42	0.34
42	0.29	0.02	-0.06	-0.16	1.52
43	-0.72	0.08	-0.45	-0.28	1.69
44	1.01	0.94	-0.57	0.55	1.95
45	-0.98	-0.98	-2.20	-0.14	0.06
46	0.29	0.13	0.37	0.12	0.20
47	0.32	0.09	0.17	0.01	0.46
48	-0.12	-0.69	-1.56	0.07	0.54
49	1.02	-0.17	-0.06	0.90	1.81
50	1.96	1.78	0.13	1.48	2.46
51	3.80	2.26	2.54	2.32	2.47
52	2.60	1.78	0.70	1.15	2.90
53	-0.33	-0.91	-0.47	-0.02	0.87
54	0.15	-0.52	-0.77	-0.01	1.72
55	1.90	0.39	2.47	1.81	1.84
56	1.20	0.51	2.29	1.19	1.89
57	1.18	1.59	0.81	1.36	1.40
58	4.05	4.44	3.19	4.69	3.21
59	4.42	5.02	3.24	4.90	4.19
60	6.51	7.67	6.16	7.05	6.01
61	3.40	3.45	3.18	2.68	3.03
62	2.68	2.99	2.99	2.09	3.10
63	3.85	3.77	3.76	3.71	3.51
64	2.17	3.23	3.55	1.98	4.18
65	2.14	0.81	3.44	2.53	1.34
66	0.95	0.27	1.05	1.37	3.08
67	2.18	2.11	3.57	2.89	3.51
68	2.38	1.29	2.12	1.43	4.22
69	-0.86	-0.94	0.46	-0.57	1.29
70	0.42	0.62	0.70	0.52	2.83
71	1.11	0.53	3.22	0.95	3.24
72	1.45	1.28	2.25	1.69	4.06
73	0.26	0.18	0.18	0.23	0.09
74	0.07	-0.64	-0.12	0.24	0.90
75	1.81	0.32	2.47	1.80	1.71
76	0.26	-0.46	-0.68	0.10	1.77
77	0.35	0.07	0.58	-0.29	0.85
78	1.27	0.85	2.70	0.72	0.86
79	1.54	0.65	0.99	0.38	1.35

80	1.26	1.11	-0.42	0.60	1.48
MD:	-0.31	-0.55	-0.53	-0.61	-
MAD:	0.95	1.11	1.37	1.00	-
SD:	1.24	1.28	1.62	1.09	-
MAX:	4.41	3.22	4.74	2.80	-

^a Reference data taken from Ref. S23.

Table S27: Conformational energies of butane-1,4-diol conformers (BUT14DIOL)^{S10,S24} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	-1.07	-0.79	-1.94	-0.41	0.15
2	0.81	0.03	0.75	0.13	0.30
3	0.94	0.08	-0.07	1.02	1.31
4	1.73	0.76	1.19	0.45	1.44
5	0.29	0.16	-1.33	-0.24	1.72
6	-0.05	-0.31	0.53	1.04	2.07
7	3.29	2.65	5.42	2.65	1.77
8	0.34	0.78	1.01	1.85	2.25
9	1.89	1.76	3.29	2.26	2.03
10	2.86	1.84	4.10	2.29	2.10
11	4.72	2.92	6.57	2.98	2.00
12	1.51	1.75	3.20	2.07	2.15
13	0.06	0.64	0.74	1.72	2.22
14	1.49	1.02	1.89	1.91	2.42
15	1.81	2.18	3.30	2.05	2.23
16	2.27	2.20	3.66	2.48	2.25
17	0.55	1.32	1.23	1.77	2.58
18	1.06	1.34	1.60	2.18	2.59
19	1.43	1.70	1.99	2.35	2.63
20	2.05	2.58	3.49	2.08	2.48
21	0.60	1.46	1.44	1.82	2.74
22	2.24	2.53	3.84	2.29	2.55
23	4.01	3.56	6.64	3.25	2.53
24	0.68	1.70	1.17	1.66	2.72
25	1.17	1.70	1.58	2.02	2.69
26	3.27	3.61	5.25	2.13	2.49
27	2.45	2.62	4.28	2.66	2.72
28	1.21	1.75	1.93	2.23	2.83

29	1.19	1.49	1.85	2.21	2.85
30	1.19	1.49	1.85	2.21	2.85
31	3.60	3.55	5.88	2.65	2.52
32	2.05	2.69	3.22	1.91	2.63
33	1.87	1.74	2.21	2.24	3.10
34	1.10	1.74	1.62	1.98	2.72
35	3.48	2.73	4.62	2.61	2.83
36	0.81	1.78	1.28	1.71	2.79
37	2.18	2.62	3.71	2.26	2.79
38	1.08	1.54	1.50	1.81	3.06
39	3.74	2.81	4.97	2.56	3.10
40	2.26	2.05	2.94	2.32	3.30
41	4.39	3.16	6.05	3.60	3.15
42	2.63	1.96	3.44	2.18	3.29
43	1.04	1.20	1.20	2.22	3.59
44	2.66	2.87	3.88	2.36	3.18
45	2.66	2.87	3.88	2.36	3.18
46	1.37	2.11	1.71	1.86	3.37
47	2.26	2.43	2.49	2.31	3.45
48	2.71	3.14	3.67	2.12	3.33
49	2.71	3.14	3.67	2.12	3.33
50	1.60	2.06	2.23	2.20	3.37
51	1.31	1.36	1.62	2.11	3.61
52	2.83	2.11	3.46	2.52	3.42
53	4.60	4.12	6.63	3.08	3.15
54	2.37	3.03	3.25	2.04	3.31
55	1.22	2.11	1.40	1.81	3.45
56	3.83	4.14	5.31	2.50	3.32
57	1.27	2.19	1.42	1.90	3.57
58	3.34	2.56	4.55	3.38	3.52
59	2.57	3.20	3.35	2.23	3.50
60	1.23	2.21	1.34	1.98	3.65
61	1.98	2.39	1.91	2.25	3.78
62	3.30	3.15	3.77	3.01	4.15
63	2.13	2.22	2.01	2.69	4.31
64	2.41	2.57	2.40	2.96	4.70
MD:	-0.82	-0.74	-0.03	-0.69	-
MAD:	1.25	0.95	1.48	0.81	-
SD:	1.19	0.87	1.79	0.65	-
MAX:	2.72	2.39	4.57	1.96	-

Table S28: Conformational energies of small inorganic molecules (ICONF)^{S10} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	0.67	1.09	-1.04	0.85	0.90
2	5.94	5.32	9.41	3.49	5.29
3	1.65	-2.14	-1.77	1.45	0.13
4	4.26	0.61	3.37	3.52	2.33
5	10.41	10.25	4.34	7.78	12.16
6	-0.10	-0.55	0.13	0.00	0.10
7	0.15	0.37	0.72	0.00	1.03
8	0.56	-0.24	2.89	0.00	3.51
9	1.39	2.23	1.16	0.00	1.69
10	-2.88	-2.67	6.83	0.45	1.40
11	2.63	2.11	4.33	1.17	4.39
12	7.50	7.55	9.79	4.01	9.16
13	1.24	0.59	0.73	0.15	0.55
14	6.53	2.92	2.81	0.86	3.55
15	-1.49	-2.33	-3.12	1.52	1.33
16	1.72	-5.35	-7.94	-1.52	3.66
17	3.19	-7.29	-7.42	-2.35	4.35
MD:	-0.72	-2.53	-1.78	-2.01	-
MAD:	1.63	2.63	3.13	2.33	-
SD:	1.89	3.29	4.72	2.37	-
MAX:	4.28	11.64	11.78	6.70	-

Table S29: Conformational energies of melatonin conformers (MCONF)^{S10,S25} computed with different semiempirical methods. The values are given in kcal/mol. Though the results for all semiempirical methods apart from GFN2-xTB are also found in Ref. S3 and its supporting information, they are listed here along with the statistical data, since the reference values have been revised in Ref. S10.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	1.06	0.65	1.37	1.46	0.39
2	1.30	1.53	2.11	1.56	1.74
3	1.60	1.27	2.52	2.01	1.16
4	-0.28	0.29	1.91	0.27	2.20

5	-0.29	-0.05	0.56	-0.63	2.20
6	-0.20	0.52	0.44	-0.17	2.68
7	-0.29	0.48	2.46	0.64	2.92
8	2.15	1.79	3.48	2.62	2.23
9	0.22	1.38	1.42	0.13	2.84
10	2.60	2.40	3.11	4.68	4.24
11	2.90	2.47	3.41	4.68	4.45
12	5.21	3.77	4.17	6.76	3.60
13	2.57	2.11	3.05	2.96	2.25
14	5.44	3.93	4.34	6.92	3.74
15	3.38	2.53	2.23	3.97	5.00
16	3.42	2.78	1.89	4.61	5.11
17	3.53	3.18	4.56	3.94	3.18
18	0.52	1.70	2.14	0.60	3.83
19	1.48	2.06	2.82	1.63	3.80
20	2.82	2.41	3.71	3.38	3.11
21	3.67	3.77	2.98	4.80	5.27
22	3.80	3.80	3.13	4.81	5.31
23	5.92	4.42	4.44	7.51	4.50
24	3.68	4.01	4.90	3.04	3.85
25	5.96	4.44	4.53	7.49	4.55
26	1.83	2.40	3.54	2.12	4.76
27	2.16	2.62	2.94	1.82	4.37
28	6.81	6.07	5.62	7.26	5.27
29	2.24	3.12	3.80	2.35	5.67
30	2.44	3.03	3.33	2.47	4.86
31	5.00	4.50	4.40	6.32	6.24
32	5.08	4.51	4.42	6.34	6.26
33	2.95	3.61	4.54	2.81	5.85
34	3.02	3.97	4.87	2.12	5.37
35	2.60	3.17	3.75	2.56	5.53
36	6.19	5.85	5.21	7.21	7.53
37	2.85	3.50	4.22	3.04	5.88
38	3.41	4.09	4.57	2.84	5.58
39	5.83	5.24	4.59	6.77	6.98
40	5.97	5.34	4.74	6.86	7.07
41	3.51	4.41	5.69	2.67	6.39
42	6.04	5.58	5.02	7.24	7.32
43	6.15	5.65	5.13	7.30	7.39
44	3.89	4.83	5.92	2.98	6.18
45	6.70	6.46	6.42	6.91	7.82

46	6.74	6.57	6.56	6.94	7.89
47	4.03	4.70	5.58	3.53	6.74
48	7.24	6.79	6.34	7.82	8.19
49	7.24	6.81	6.32	7.82	8.20
50	4.47	5.36	6.89	3.59	7.28
51	7.69	7.48	7.68	7.87	8.75
MD:	-1.36	-1.38	-0.98	-0.91	-
MAD:	1.73	1.44	1.34	1.66	-
SD:	1.42	0.89	1.19	1.89	-
MAX:	3.43	2.55	3.22	3.72	-

Table S30: Conformational energies of tri- and tetrapeptide conformers (PCONF21)^{S10,S26,S27} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	3.05	3.45	2.36	0.50	0.02
2	5.19	5.69	5.09	2.21	1.01
3	2.81	3.71	4.68	3.93	0.70
4	3.16	3.02	3.10	0.13	0.85
5	1.70	1.62	1.79	2.85	0.78
6	6.16	7.78	7.84	2.47	1.92
7	2.65	2.75	1.86	1.83	2.18
8	3.56	3.16	4.56	4.09	1.61
9	4.43	3.57	3.85	2.54	1.89
10	3.80	5.42	4.81	0.32	2.07
11	0.64	0.41	-2.03	-2.13	1.07
12	-0.58	0.25	2.49	-0.53	1.23
13	2.88	-1.06	1.20	-1.29	2.44
14	0.14	0.77	-0.19	0.64	2.14
15	0.82	1.59	-2.18	-1.45	1.47
16	1.23	2.67	4.16	1.91	2.80
17	2.32	-2.10	0.41	-1.86	2.27
18	1.58	1.97	0.78	2.14	2.74
MD:	0.91	0.86	0.85	-0.60	-
MAD:	1.76	2.17	2.46	1.79	-
SD:	1.97	2.67	2.73	2.12	-
MAX:	4.24	5.86	5.92	4.13	-

Table S31: Conformational energies of sugar conformers (SCONF)^{S10,S28} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	0.72	0.31	0.62	0.29	0.86
2	4.27	3.54	5.97	2.30	2.28
3	4.84	3.75	6.45	2.51	3.08
4	4.46	4.72	7.54	3.13	4.60
5	4.41	4.32	6.48	3.71	4.87
6	5.28	5.69	8.82	4.16	4.16
7	5.70	6.15	9.02	4.60	4.38
8	5.83	6.22	8.84	4.87	6.19
9	5.85	7.37	8.90	4.98	6.18
10	7.01	8.09	10.64	6.03	5.65
11	6.77	7.88	10.62	5.71	5.59
12	4.83	5.64	6.22	3.04	5.93
13	5.65	6.92	8.54	4.67	6.31
14	5.56	7.83	7.97	4.58	6.22
15	-1.36	-1.47	-2.19	-1.73	0.20
16	-0.40	-7.21	-15.21	-1.25	6.16
17	-1.71	-7.06	-14.26	-0.65	5.54
MD:	-0.62	-0.91	-0.19	-1.60	-
MAD:	1.64	2.50	4.96	1.69	-
SD:	2.59	4.68	7.93	2.16	-
MAX:	7.25	13.37	21.37	7.41	-

Table S32: Conformational energies of RNA-backbone conformers (UPU23)^{S10,S29} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	9.84	6.46	10.06	7.09	4.87
2	6.16	3.69	4.78	4.35	2.97
3	13.56	11.88	13.33	10.46	8.90
4	6.54	3.05	6.68	2.25	2.22
5	4.32	2.68	2.20	3.32	2.02
6	5.24	2.22	5.29	2.63	3.14
7	4.51	0.92	0.97	-1.86	0.57

8	3.63	2.36	5.16	2.67	3.32
9	12.20	6.96	10.64	6.50	7.26
10	8.30	5.00	5.31	4.24	3.96
11	14.56	11.98	13.45	11.61	11.13
12	7.77	5.60	9.07	5.17	4.82
13	17.15	13.85	17.73	13.23	14.41
14	8.56	3.38	7.82	4.15	5.15
15	4.86	4.15	4.98	2.78	5.48
16	10.23	7.83	10.24	5.82	6.84
17	4.46	2.21	4.01	1.29	3.90
18	8.57	4.72	6.82	4.78	6.43
19	9.81	4.89	8.83	4.11	5.42
20	5.43	3.53	5.32	3.60	6.70
21	8.05	7.50	10.77	6.97	5.60
22	13.48	12.31	14.87	11.42	10.42
23	7.50	5.10	7.79	4.17	6.09
MD:	2.74	0.03	2.37	-0.47	–
MAD:	2.91	1.24	2.53	1.34	–
SD:	1.72	1.48	1.89	1.53	–
MAX:	4.97	3.17	5.20	3.10	–

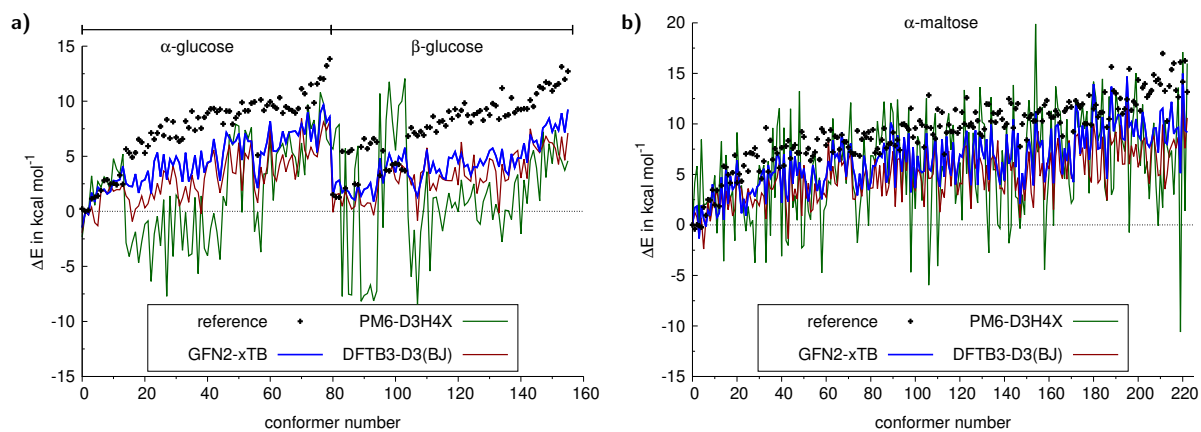


Figure S1: Conformational energies **a)** of 80 α -glucose and 76 β -glucose conformers and **b)** of 205 α -maltose conformers. The energies are given in kcal mol^{-1} and are computed with GFN2-xTB, DFTB3-D3(BJ), and PM6-D3H4X. The structures and reference conformational energies are taken from Ref. S30.

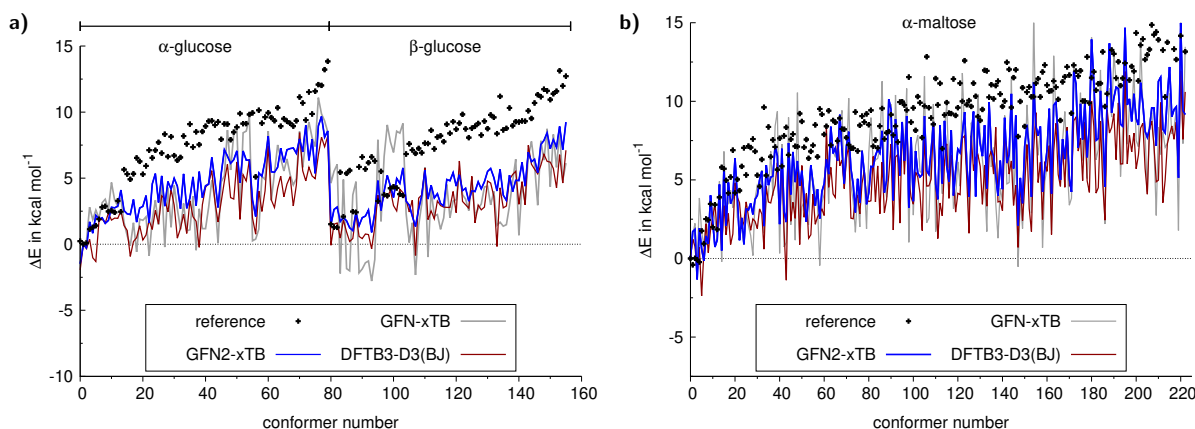


Figure S2: Conformational energies **a)** of 80 α -glucose and 76 β -glucose conformers and **b)** of 205 α -maltose conformers. The energies are given in kcal mol^{-1} and are computed with GFN-xTB, DFTB3-D3(BJ), and PM6-D3H4X. The structures and reference conformational energies are taken from Ref. S30.

Table S33: Conformational energies for different glucose conformers^{S30} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
α -glucose					
1	-1.47	-1.14	-2.34	-1.95	0.23
2	0.00	0.00	0.00	0.00	0.00
3	-0.28	0.20	-0.16	-0.34	0.10
4	1.69	2.80	3.22	0.38	1.14
5	0.84	1.87	0.55	-1.02	1.28
6	2.19	2.58	2.70	-1.31	1.41
7	1.90	1.97	2.20	1.79	1.90
8	2.00	3.14	3.14	1.91	2.80
9	1.58	3.40	2.81	1.60	2.87
10	1.80	2.63	1.79	2.36	2.48
11	2.79	4.68	4.78	1.82	2.54
12	2.75	3.34	3.83	1.98	2.41
13	2.88	2.87	3.40	1.96	3.28
14	4.11	3.51	5.20	2.53	2.46
15	2.54	1.63	-2.86	1.41	5.65
16	2.29	0.64	-4.11	1.04	5.31
17	2.25	-0.12	-2.84	-0.92	4.91
18	3.39	1.63	-1.86	0.20	5.33
19	1.67	-0.58	-4.67	0.49	6.53
20	2.73	1.89	-2.77	1.40	6.27

21	2.87	1.80	-1.17	0.32	5.30
22	3.68	2.08	-0.86	0.70	5.93
23	1.62	-0.89	-6.37	1.82	7.12
24	4.57	1.85	-2.05	1.12	6.54
25	5.34	3.33	-0.44	2.56	7.11
26	3.15	1.49	-3.14	1.54	7.71
27	5.17	4.66	1.06	3.67	6.89
28	2.88	-0.22	-7.72	3.43	8.33
29	4.74	4.28	1.40	2.45	6.63
30	4.17	1.29	-4.10	4.12	8.14
31	4.99	4.45	1.47	2.97	6.71
32	4.40	2.69	0.99	0.46	6.35
33	2.68	1.13	-3.54	1.20	6.57
34	5.32	3.09	-0.09	2.27	8.19
35	2.72	1.01	-4.06	0.82	7.59
36	3.48	1.10	-3.86	3.29	9.09
37	5.09	3.63	1.26	2.09	7.35
38	2.92	-0.46	-5.67	1.73	8.51
39	5.49	2.68	1.40	-0.23	7.54
40	3.52	1.19	-3.37	3.00	8.53
41	4.43	1.18	-4.04	4.31	8.93
42	4.54	2.79	-1.57	4.62	9.31
43	6.57	4.83	-0.19	5.57	9.34
44	4.79	3.32	-1.88	3.22	9.02
45	2.79	0.08	-4.38	1.68	9.26
46	5.34	4.72	1.36	3.21	7.94
47	7.15	5.17	0.50	4.77	9.11
48	6.67	8.64	7.01	6.05	9.09
49	6.12	5.62	6.00	3.53	7.91
50	6.40	8.38	7.90	3.42	8.48
51	7.07	8.82	7.74	6.23	8.86
52	4.66	2.15	-0.09	1.88	9.89
53	7.06	8.44	7.39	5.26	9.13
54	6.36	8.56	6.64	4.79	9.13
55	6.36	9.64	7.62	6.43	9.82
56	3.35	0.26	-1.86	1.98	9.94
57	2.11	0.39	-0.07	0.76	5.10
58	5.39	1.14	-3.71	4.03	10.14
59	5.14	5.14	3.40	2.48	9.16
60	6.32	4.90	3.44	4.04	9.62
61	8.18	8.56	6.63	7.45	9.95

62	5.48	3.32	0.99	3.35	9.59
63	5.45	5.41	5.18	2.78	9.35
64	5.82	7.51	5.70	4.25	10.33
65	7.27	6.50	6.14	5.15	8.93
66	6.21	5.54	4.92	3.59	9.50
67	7.15	6.46	7.26	4.55	9.31
68	7.24	5.26	5.36	5.12	9.15
69	7.29	4.49	4.90	2.90	8.94
70	6.88	4.97	3.13	4.48	9.34
71	7.97	8.54	6.21	8.44	11.14
72	6.99	5.82	3.29	5.56	10.69
73	9.01	7.87	9.70	4.79	9.40
74	6.35	9.25	7.50	5.82	11.52
75	7.94	8.06	8.29	5.17	9.86
76	5.36	7.40	5.27	4.96	11.58
77	8.95	11.09	10.80	6.76	12.08
78	9.67	9.86	9.79	8.10	12.02
79	8.10	9.34	6.57	7.38	13.22
80	8.57	8.49	6.04	8.17	13.84

β -glucose

81	1.46	4.62	5.65	-0.08	1.52
82	2.62	5.52	7.53	1.52	1.29
83	2.82	6.04	7.88	1.61	1.27
84	1.71	-2.21	-7.73	0.46	5.44
85	2.02	4.90	5.72	1.82	2.09
86	1.77	-1.84	-7.53	0.93	5.36
87	1.24	-2.01	-7.59	0.20	5.58
88	1.03	3.74	3.84	0.44	2.47
89	2.42	4.74	5.94	2.30	2.42
90	1.40	-2.17	-8.17	0.59	5.85
91	2.00	-1.88	-7.64	0.43	6.60
92	2.13	-1.41	-7.46	0.77	5.69
93	2.58	-1.26	-6.69	0.73	6.17
94	0.90	-2.79	-8.13	-0.35	6.61
95	2.37	-1.16	-7.25	1.32	6.30
96	4.81	7.91	10.70	3.72	3.26
97	2.55	1.73	-1.48	2.70	5.51
98	4.00	6.63	8.30	3.87	3.75
99	5.21	9.03	11.77	3.52	3.68
100	4.39	7.74	8.15	4.10	4.24
101	3.54	6.95	5.54	2.92	4.35

102	4.97	8.55	9.60	2.52	4.26
103	4.61	8.41	9.99	4.17	3.79
104	5.78	9.14	12.06	3.90	3.69
105	3.26	2.34	-0.50	3.39	6.83
106	2.96	0.13	-5.94	2.44	7.60
107	2.11	1.62	-1.69	3.34	7.13
108	1.34	-2.33	-8.45	-0.84	6.87
109	2.67	1.42	-1.88	3.49	7.25
110	3.68	3.06	0.27	3.73	6.92
111	5.60	5.83	3.60	5.77	7.65
112	3.42	-0.97	-5.43	1.87	7.62
113	4.46	4.08	1.21	2.52	8.62
114	3.50	2.14	1.28	1.92	7.21
115	3.83	2.25	-0.10	3.27	8.11
116	3.08	1.13	-1.80	2.93	8.21
117	2.91	1.99	0.02	2.81	7.77
118	4.90	4.52	1.67	2.79	9.08
119	4.81	1.99	0.33	2.78	8.39
120	5.41	3.28	0.80	3.99	9.28
121	4.40	3.37	-0.06	2.38	8.70
122	5.26	5.51	2.85	6.30	9.16
123	4.06	3.75	0.54	3.24	9.83
124	4.23	3.41	0.81	2.98	8.73
125	3.26	2.54	1.36	2.73	8.07
126	4.05	4.89	2.49	5.14	8.78
127	3.99	2.18	-0.80	1.62	8.93
128	4.72	2.68	-1.17	2.97	9.14
129	4.19	3.05	0.88	2.60	8.26
130	4.73	4.34	1.68	2.81	9.31
131	5.51	4.39	2.65	4.78	8.75
132	5.73	2.98	-0.78	4.63	9.79
133	5.05	4.00	0.64	3.63	9.60
134	4.04	1.44	-0.32	-0.17	8.37
135	5.67	1.67	-2.78	4.27	11.19
136	3.71	1.36	0.10	2.75	8.65
137	3.32	1.48	0.05	2.90	8.77
138	5.22	2.92	-0.75	4.92	10.31
139	3.98	4.77	2.57	5.27	8.97
140	4.84	6.44	3.33	5.53	9.28
141	4.82	0.68	-2.06	3.02	9.25
142	6.19	4.60	2.85	4.74	9.33

143	4.40	3.16	0.70	2.98	9.31
144	6.97	6.63	4.61	7.49	10.10
145	6.24	7.78	5.54	6.05	9.52
146	6.43	6.00	3.94	5.68	10.69
147	5.41	2.95	0.94	5.33	11.32
148	7.56	7.83	7.23	5.99	11.16
149	7.85	6.36	3.08	6.80	11.73
150	8.44	8.74	6.14	6.28	11.61
151	7.23	4.36	4.33	6.21	10.94
152	7.92	8.32	7.38	5.73	11.39
153	7.35	5.82	5.19	4.26	11.58
154	8.92	8.49	4.58	6.78	13.13
155	7.16	4.84	3.72	4.63	11.98
156	9.24	6.14	4.58	7.11	12.72
MD:	-3.07	-3.79	-6.01	-4.40	-
MAD:	3.24	4.57	7.05	4.42	-
SD:	1.95	3.55	5.40	2.13	-
MAX:	6.59	9.68	16.05	8.54	-

Table S34: Conformational energies for different maltose conformers^{S30} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	0.00	0.00	0.00	0.00	0.00
2	1.71	1.47	4.18	1.24	-0.40
3	1.86	2.24	5.83	0.76	0.01
4	-1.33	-0.53	-0.01	-0.87	-0.07
5	1.93	3.85	8.45	0.71	-0.23
6	0.63	1.69	2.06	-2.38	1.76
7	-0.15	0.83	2.02	0.41	0.94
8	1.43	2.44	2.45	2.20	2.51
9	0.94	1.39	0.60	0.37	2.45
10	4.02	2.73	2.98	1.83	3.47
11	2.27	3.24	4.90	2.62	1.99
12	0.73	2.44	-0.82	3.46	3.42
13	1.17	1.31	3.57	1.65	1.85
14	4.71	4.91	8.27	3.17	3.89
15	0.50	-0.22	-3.59	0.56	5.80
16	5.75	6.81	6.92	3.36	5.71
17	2.07	3.39	3.74	1.50	4.97
18	4.83	3.49	2.57	2.86	4.16

19	3.50	4.34	3.42	0.89	5.18
20	3.85	3.23	-1.56	1.55	6.89
21	6.39	6.19	9.15	4.81	4.18
22	3.94	2.61	3.71	3.90	5.03
23	1.16	2.30	3.86	3.55	4.32
24	2.58	1.90	1.23	1.90	5.86
25	0.90	0.88	-0.61	2.34	7.04
26	3.15	2.91	1.81	3.60	5.31
27	3.08	2.09	-0.04	2.69	7.15
28	3.51	1.47	0.47	1.80	7.06
29	2.81	0.18	-3.75	2.52	7.60
30	3.77	3.80	3.02	2.36	6.81
31	4.01	4.68	5.91	1.90	5.29
32	4.98	4.48	4.89	3.16	4.58
33	5.57	5.63	5.92	2.83	6.30
34	2.05	1.61	-3.73	0.59	9.62
35	5.94	3.51	6.30	4.58	5.28
36	4.67	4.07	-1.05	3.59	8.37
37	5.17	6.82	9.60	3.53	6.47
38	5.23	3.99	2.70	4.16	7.55
39	7.14	8.42	9.74	4.67	7.10
40	6.52	9.36	11.55	6.09	5.65
41	2.18	0.33	-3.09	2.50	7.65
42	6.99	7.28	9.62	6.30	5.87
43	2.98	0.74	-1.54	1.84	7.80
44	2.31	1.02	-2.03	-1.38	8.34
45	7.35	8.97	11.50	6.61	6.59
46	4.07	2.14	1.70	2.37	7.58
47	6.78	6.31	2.91	3.58	7.91
48	4.86	1.17	0.47	2.56	7.14
49	6.20	10.55	13.23	5.53	7.12
50	4.62	1.20	-2.27	0.89	9.22
51	5.59	3.28	-2.04	5.92	8.72
52	3.91	3.60	4.34	2.62	7.07
53	2.33	2.65	1.35	4.14	7.57
54	3.93	2.14	0.51	1.28	6.37
55	5.93	5.28	5.99	1.51	6.81
56	4.77	4.88	6.87	4.10	7.20
57	3.35	4.29	3.40	2.18	8.50
58	4.41	3.33	4.66	2.64	6.47
59	2.54	-0.45	-4.75	2.89	9.51

60	4.27	3.55	1.43	3.14	9.17
61	4.74	4.09	1.99	2.73	7.89
62	6.32	7.19	4.33	8.31	8.41
63	5.36	3.49	4.05	4.53	9.40
64	8.39	7.97	10.53	5.80	7.21
65	6.69	6.78	5.68	4.11	8.78
66	7.02	6.47	4.11	3.88	8.66
67	6.22	6.78	7.70	7.71	7.48
68	9.14	8.52	6.37	5.90	8.92
69	6.94	9.43	8.22	6.27	8.24
70	4.76	4.91	4.10	4.44	8.22
71	7.18	6.12	7.96	6.42	7.69
72	8.07	10.20	12.11	7.17	7.23
73	5.71	4.70	3.94	2.57	7.01
74	4.74	3.67	2.97	2.52	7.02
75	2.93	1.67	-1.79	3.70	9.32
76	5.07	4.28	1.39	4.04	6.84
77	3.53	2.00	3.51	2.83	8.47
78	6.85	6.90	8.52	4.78	9.06
79	5.44	5.10	4.53	5.63	8.68
80	3.45	1.89	-0.08	3.76	9.20
81	4.20	6.72	6.85	3.62	8.51
82	5.85	8.96	6.84	3.67	9.43
83	5.83	6.01	6.11	6.49	7.14
84	6.55	6.26	10.28	3.59	7.53
85	6.93	6.37	7.96	5.89	7.03
86	6.71	6.97	8.91	2.84	8.42
87	8.12	11.28	12.20	6.13	9.55
88	4.19	5.11	7.88	2.91	7.60
89	4.96	3.89	4.07	3.74	8.00
90	10.12	8.77	12.08	5.30	8.08
91	9.49	9.81	11.10	7.28	9.15
92	3.69	3.75	4.62	1.81	7.85
93	8.87	10.40	12.40	6.46	8.42
94	6.92	6.25	7.58	6.60	7.41
95	5.28	5.73	2.85	2.25	9.95
96	8.69	8.24	8.05	8.62	9.98
97	6.21	6.09	2.97	5.36	9.76
98	9.06	10.82	11.48	8.69	9.44
99	3.23	1.03	-4.68	5.03	11.54
100	7.70	7.59	5.70	3.91	8.67

101	3.64	2.76	1.59	3.45	9.58
102	6.83	7.17	8.78	5.50	8.15
103	5.43	7.85	8.07	5.19	10.30
104	5.19	5.55	2.42	4.14	9.91
105	5.34	5.41	6.95	1.77	7.69
106	9.06	11.59	12.54	7.87	9.70
107	5.58	2.28	-5.96	4.60	12.84
108	5.36	2.57	-0.05	4.62	9.60
109	6.85	6.56	8.90	5.05	8.94
110	8.65	9.83	11.06	8.61	8.54
111	4.73	1.72	-4.07	4.97	11.45
112	3.77	2.85	2.94	1.26	9.77
113	8.48	6.34	5.84	3.53	11.14
114	4.75	4.12	4.94	2.71	6.99
115	8.75	8.35	9.69	6.18	9.13
116	5.90	9.75	11.03	7.29	9.92
117	4.88	5.75	7.44	3.83	9.25
118	8.16	7.96	9.90	6.56	9.22
119	4.00	3.18	2.12	5.29	11.42
120	5.55	3.93	3.71	2.95	9.10
121	6.96	6.15	6.18	4.15	9.60
122	6.72	4.60	0.47	4.06	11.15
123	7.94	11.80	13.36	7.65	10.00
124	9.32	8.04	5.06	7.81	12.59
125	5.99	6.54	9.18	5.09	9.79
126	3.92	2.22	2.86	1.61	10.05
127	7.79	8.64	9.11	7.81	9.67
128	9.35	7.16	3.77	5.60	11.15
129	3.95	5.05	2.17	6.41	10.32
130	8.97	10.45	13.65	6.61	9.03
131	7.32	7.75	10.18	5.87	8.78
132	6.51	6.27	9.96	3.45	9.48
133	8.48	4.93	2.09	5.92	11.97
134	4.46	1.71	-2.77	3.32	11.94
135	9.94	9.39	12.64	6.44	10.26
136	6.93	5.82	5.46	6.86	11.06
137	6.50	7.06	5.49	5.37	10.16
138	5.27	3.50	0.04	8.35	11.00
139	4.00	1.29	-0.33	3.59	11.28
140	6.22	4.47	7.37	3.64	10.46
141	4.41	3.68	4.29	3.04	9.67

142	8.96	9.10	10.02	7.82	10.01
143	6.07	4.75	-1.81	6.98	12.48
144	6.59	4.83	-0.15	5.37	12.03
145	10.48	11.41	13.86	6.21	9.61
146	5.72	3.75	2.80	3.38	11.51
147	9.10	6.95	2.61	4.67	12.01
148	2.10	-0.53	-0.36	0.70	7.76
149	5.13	3.76	2.99	4.95	9.99
150	3.51	1.91	0.99	2.41	10.87
151	7.14	5.12	8.96	4.71	8.40
152	8.51	9.77	12.34	7.25	10.59
153	7.00	7.04	8.93	3.18	10.91
154	3.92	2.89	4.86	1.71	10.29
155	11.21	15.33	19.89	6.92	10.29
156	8.43	8.03	7.20	9.28	11.15
157	7.80	6.57	7.99	4.83	11.44
158	8.40	8.17	11.66	6.12	10.28
159	4.23	0.69	-4.44	2.48	11.87
160	5.64	4.89	1.86	6.16	12.31
161	6.87	5.79	5.18	5.54	11.03
162	9.53	8.83	11.29	7.18	10.64
163	4.12	1.78	-0.06	1.53	10.68
164	9.76	12.90	13.71	6.82	11.29
165	9.94	9.09	11.54	8.60	10.90
166	7.61	8.49	11.24	5.35	10.12
167	5.01	5.61	7.07	4.58	8.78
168	7.59	7.49	4.56	7.34	11.24
169	6.32	9.35	10.47	4.53	11.56
170	8.12	5.96	4.07	8.35	12.19
171	5.07	3.39	2.16	4.63	11.67
172	4.24	3.83	2.57	4.64	9.24
173	11.90	12.46	12.44	8.76	12.30
174	11.10	10.22	9.69	8.99	11.92
175	7.05	7.91	9.72	6.83	11.61
176	9.84	10.55	11.85	7.64	11.95
177	7.57	6.25	9.49	4.95	10.02
178	9.99	10.06	11.26	8.69	10.01
179	6.43	5.09	3.13	4.94	12.83
180	8.33	7.88	11.70	4.21	9.89
181	13.94	14.07	14.19	10.02	11.50
182	11.21	10.28	12.64	8.41	11.88

183	7.52	6.28	8.35	4.16	10.70
184	7.63	6.94	9.24	4.51	11.12
185	10.67	12.00	14.45	8.72	11.14
186	8.51	6.03	3.73	4.80	13.15
187	4.57	2.19	2.40	2.44	9.67
188	10.39	10.14	12.71	9.45	10.48
189	13.69	10.84	2.97	7.98	15.64
190	9.28	9.00	3.62	8.33	13.27
191	10.22	12.94	13.16	9.22	13.02
192	10.90	11.30	11.45	6.28	11.48
193	10.81	11.50	8.64	9.90	12.52
194	8.55	5.21	8.27	6.01	11.00
195	8.41	8.27	7.28	6.02	11.47
196	14.68	13.78	14.67	11.90	12.43
197	9.77	7.28	-0.74	6.02	15.44
198	10.15	9.68	9.08	7.84	11.35
199	8.72	9.16	11.11	6.78	12.22
200	10.48	11.90	15.02	7.98	11.91
201	8.88	7.50	7.75	5.71	14.35
202	8.50	7.11	5.86	6.58	11.30
203	11.19	13.88	11.93	8.29	13.58
204	9.87	9.69	5.09	8.60	13.96
205	8.09	7.85	6.28	5.74	12.66
206	7.71	4.25	2.56	4.09	12.96
207	8.24	8.68	7.05	8.24	13.30
208	9.58	9.29	10.11	8.74	14.86
209	9.58	7.21	3.90	7.16	14.24
210	7.17	2.74	-0.07	4.88	14.41
211	11.27	8.34	5.45	4.98	13.92
212	11.52	6.62	1.71	9.92	16.97
213	8.22	8.06	10.23	3.55	13.26
214	7.99	7.07	7.76	4.99	10.28
215	10.38	7.33	6.68	7.31	13.75
216	12.18	10.49	7.35	7.88	15.38
217	9.01	7.92	3.01	8.43	16.00
218	9.48	8.31	8.14	7.58	13.32
219	9.65	9.47	13.59	8.68	12.66
220	5.13	1.79	-10.60	5.62	16.11
221	14.99	15.32	17.11	11.94	14.17
222	9.39	7.31	1.38	7.58	16.25
223	9.16	13.47	15.98	10.60	13.16

MD:	-2.87	-3.27	-3.64	-4.39	-
MAD:	3.11	3.81	5.07	4.44	-
SD:	2.44	3.47	5.63	2.55	-
MAX:	10.98	14.32	26.71	10.49	-

2.4 Rotational and vibrational free energy computations

Table S35: Rotational and vibrational reaction free energies ΔG_{RRHO} for the AL2X6^{S10} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	-1.04	-1.09	-1.35	-1.25
2	-2.16	-2.20	-2.21	-2.43
3	-2.67	-2.70	-2.66	-2.96
4	-4.15	-1.63	-1.80	-2.57
5	-4.54	-1.70	-2.27	-3.10
6	-4.92	-1.50	-2.45	-2.04
MD		1.44	1.12	0.85
MAD		1.49	1.25	1.11
SD		1.65	1.37	1.32
MAX		3.42	2.47	2.87

Table S36: Rotational and vibrational reaction free energies ΔG_{RRHO} for the DARC^{S10} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	0.39	0.41	0.40	0.35
2	-0.01	0.12	0.13	0.09
3	0.53	0.54	0.57	0.57
4	0.06	0.18	0.22	0.28
5	0.58	0.59	0.48	0.52
6	0.04	0.17	0.14	0.27
7	1.31	1.33	1.32	1.32
8	1.32	1.35	1.31	1.46
9	1.21	1.26	1.25	1.29
10	1.22	1.28	1.29	1.34
11	1.14	1.16	1.15	1.15
12	1.15	1.14	1.15	1.13
13	1.04	1.09	1.09	1.12
14	1.04	1.07	1.12	1.19
MD		0.05	0.04	0.07
MAD		0.05	0.06	0.09
SD		0.05	0.07	0.09

MAX	0.13	0.17	0.22
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Table S37: Rotational and vibrational reaction free energies ΔG_{RRHO} for the HEAVYSB11^{S10} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	-1.37	-1.36	-1.73	-1.59
2	-2.56	-2.68	-2.57	-2.40
3	-5.98	-2.64	-2.71	-2.59
4	-0.39	-0.38	-0.45	-0.48
5	-0.61	-0.59	-0.63	-0.69
6	-2.53	-2.30	-2.67	-2.69
7	-1.80	-1.87	-1.96	-2.01
8	-2.16	-2.23	-2.35	-2.45
9	-2.47	-2.47	-2.62	-2.61
10	-0.14	-0.13	-0.12	-0.14
11	-0.26	-0.25	-0.23	-0.29
MD		0.31	0.20	0.21
MAD		0.35	0.40	0.43
SD		1.01	1.02	1.06
MAX		3.34	3.27	3.40

Table S38: Rotational and vibrational reaction free energies ΔG_{RRHO} for the ISOL24^{S10} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	0.50	0.18	0.35	0.68
2	2.00	2.12	2.40	2.40
3	0.37	0.56	0.57	0.47
4	4.34	4.50	4.74	4.76
5	1.82	1.77	1.98	2.05
6	0.39	0.36	0.53	0.51
7	0.66	0.72	0.73	0.73
8	-1.38	-1.45	-1.67	-1.58
9	0.20	0.29	0.07	0.11

10	0.19	0.04	0.17	0.29
11	-0.55	-0.47	-0.74	-0.18
12	0.07	0.00	-0.06	-0.04
13	-0.27	-0.36	-0.29	-0.13
14	0.35	0.33	0.24	0.35
15	0.67	0.79	1.18	1.14
16	0.35	0.35	0.12	0.26
17	0.70	0.76	0.83	0.80
18	0.06	0.07	0.07	0.09
19	-0.06	-0.07	-0.06	-0.08
20	-0.01	-0.03	0.04	0.01
21	1.30	1.29	1.36	1.38
22	-0.83	-0.95	-1.01	-0.94
23	1.16	1.21	1.12	1.18
24	0.47	0.42	0.37	0.25
MD		-0.00	0.02	0.08
MAD		0.08	0.15	0.15
SD		0.11	0.21	0.19
MAX		0.32	0.51	0.47

Table S39: Rotational and vibrational reaction free energies ΔG_{RRHO} for the TAUT15^{S10} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	0.78	0.18	0.17	0.12
2	0.64	0.53	0.49	0.60
3	0.05	0.52	0.02	0.38
4	0.27	0.36	-0.27	0.15
5	0.17	0.27	-0.33	0.12
6	0.03	0.02	0.01	0.01
7	0.13	0.13	0.09	0.13
8	0.00	-0.17	-0.02	-0.19
9	0.07	0.01	0.01	-0.01
10	0.08	-0.00	0.00	-0.03
11	0.09	0.04	0.02	0.02
12	0.04	0.03	0.02	0.03
13	-0.01	-0.02	-0.03	-0.06
14	-0.19	-0.18	-0.07	-0.14

15	-0.22	-0.25	-0.09	-0.16
MD		-0.03	-0.13	-0.07
MAD		0.12	0.16	0.12
SD		0.21	0.23	0.20
MAX		0.60	0.62	0.67

Table S40: Rotational and vibrational reaction free energies ΔG_{RRHO} for the ALK8^{S10} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	-5.08	-5.42	-4.66	-5.49
2	-6.87	-7.04	-6.55	-6.53
3	-4.41	-4.44	-3.70	-3.75
4	-1.40	-1.97	-1.33	-1.91
5	-0.78	-1.30	-0.77	-0.85
6	-0.93	-1.10	-2.43	-2.33
7	-2.46	-2.45	-2.82	-2.49
8	0.22	0.23	0.15	0.20
MD		-0.22	-0.05	-0.18
MAD		0.23	0.43	0.43
SD		0.23	0.67	0.62
MAX		0.57	1.50	1.41

Table S41: Rotational and vibrational reaction free energies ΔG_{RRHO} for the G2RC^{S10} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	-1.51	-1.42	-1.65	-1.61
2	0.05	0.05	0.03	0.02
3	-0.65	-0.65	-0.71	-0.67
4	-1.10	-1.13	-1.31	-1.17
5	0.16	0.16	0.18	0.20
6	-0.12	0.43	0.47	0.50
7	0.59	1.03	0.16	0.47
8	-0.06	0.06	0.05	-0.00

9	-0.04	-0.06	-0.02	-0.05
10	0.01	0.05	-0.18	-0.14
11	0.15	0.10	0.31	0.27
12	0.28	0.28	0.31	0.25
13	0.10	0.23	0.16	0.11
14	0.15	0.16	0.22	0.25
15	0.04	0.04	0.05	0.03
16	0.20	0.18	0.20	0.23
17	-0.26	-0.13	-0.17	-0.23
18	-0.16	-0.14	-0.14	-0.14
19	0.02	0.03	0.03	0.02
20	-0.21	-0.18	-0.17	-0.18
21	-0.20	-0.18	-0.25	-0.24
22	0.20	0.20	0.17	0.16
23	-0.02	-0.02	-0.02	-0.07
24	-0.17	0.22	0.14	-0.02
25	-0.21	-0.21	-0.11	-0.20
MD		0.08	0.02	0.02
MAD		0.09	0.11	0.07
SD		0.15	0.18	0.14
MAX		0.55	0.60	0.62

Table S42: Rotational and vibrational reaction free energies ΔG_{RRHO} for the ISO34^{S10} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	-0.17	-0.07	0.24	-0.15
2	-0.47	-0.38	-0.45	-0.47
3	-0.46	-0.47	-0.56	-0.53
4	0.05	0.00	0.01	0.05
5	0.10	0.09	0.06	0.06
6	-0.14	-0.13	-0.18	-0.17
7	-0.51	-0.55	-0.62	-0.61
8	0.45	0.46	0.40	0.45
9	-0.07	-0.07	-0.06	-0.06
10	0.16	0.18	0.01	0.00
11	0.46	0.47	0.34	0.41
12	-0.32	-0.89	-0.87	-0.81

13	-0.02	-0.06	0.04	0.02
14	0.14	0.13	0.06	0.06
15	0.00	0.01	0.02	0.02
16	-0.40	-0.41	-0.51	-0.46
17	0.09	0.09	0.11	0.17
18	0.24	0.18	0.18	0.20
19	-0.01	-0.00	-0.00	0.03
20	0.05	0.03	0.03	-0.00
21	-0.54	0.03	0.56	0.56
22	0.16	0.13	-0.31	-0.31
23	0.00	-0.00	0.02	0.03
24	0.03	0.04	0.08	0.06
25	-0.47	-0.47	-0.55	-0.50
26	0.48	-0.06	0.02	0.04
27	0.35	-0.27	-0.22	0.44
28	-0.25	-0.32	-0.50	-0.37
29	0.68	0.67	0.74	0.66
30	-0.31	-0.34	-0.22	-0.18
31	0.59	1.10	1.04	1.19
32	1.29	1.27	1.33	1.27
33	0.22	-0.42	0.37	0.40
34	-0.09	-0.14	-0.13	-0.04
MD		-0.04	-0.02	0.00
MAD		0.12	0.17	0.14
SD		0.24	0.29	0.27
MAX		0.64	1.10	1.10

Table S43: Rotational and vibrational reaction free energies ΔG_{RRHO} for the MOR41^{S31} set computed with different methods. The values are given in kcal/mol and B97-3c served as reference in the manuscript.

reaction #	B97-3c	PBEh-3c	GFN-xTB	GFN2-xTB
1	1.37	1.27	1.48	1.50
2	1.26	1.10	0.98	1.23
3	1.43	1.45	1.48	1.43
4	0.24	0.35	-1.56	-0.37
5	1.62	1.69	1.67	1.59
6	0.56	0.44	0.41	0.34
7	0.02	-0.11	-0.01	0.17

8	0.35	0.35	0.31	0.30
9	0.86	0.78	0.20	0.41
10	1.94	1.89	1.94	1.93
11	2.56	2.42	2.66	3.09
12	1.73	1.61	1.47	1.85
13	1.48	1.51	2.18	1.68
14	2.10	2.13	2.11	2.16
15	1.81	1.85	1.96	1.99
16	1.86	2.74	1.86	1.55
17	1.62	1.66	1.78	1.99
18	2.40	2.36	2.49	2.55
19	2.41	2.47	2.07	2.82
20	2.46	2.38	2.49	2.72
21	2.63	1.61	1.66	1.79
22	2.46	2.51	2.76	3.04
23	2.23	1.59	2.40	2.37
24	2.53	2.61	2.61	2.59
25	2.00	2.11	2.32	2.17
26	2.88	2.85	3.10	3.27
27	0.52	0.54	0.53	0.88
28	0.17	0.09	0.23	0.39
29	-0.32	0.35	0.16	0.53
30	0.23	-0.25	0.24	0.35
31	0.07	0.53	0.47	0.66
32	-1.51	-1.50	-1.71	-1.20
33	1.26	1.31	0.83	1.41
34	0.93	0.93	0.78	1.04
35	0.83	1.48	0.92	1.02
36	0.71	0.13	0.81	-0.31
37	3.99	5.50	5.46	5.63
38	5.02	5.10	5.22	4.95
39	2.57	2.54	2.37	2.44
40	2.08	0.83	3.52	2.01
41	1.00	0.68	0.17	0.69
MD		-0.01	0.01	0.10
MAD		0.25	0.32	0.31
SD		0.45	0.53	0.44
MAX		1.51	1.80	1.65

2.5 Other properties

Table S44: Barrier heights of divers reactions (BHDIV10)^{S10} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	32.76	32.42	20.23	23.91	25.65
2	50.31	50.87	31.70	70.47	56.90
3	32.95	36.65	23.99	26.48	36.53
4	87.32	86.99	91.73	86.29	96.17
5	8.05	8.70	12.68	-19.76	15.94
6	7.99	5.65	-9.91	-1.94	13.64
7	28.05	26.27	15.65	–	27.49
8	40.82	39.35	59.35	36.73	50.24
9	59.52	45.74	48.70	–	65.84
10	90.17	79.45	94.91	71.48	64.93
MD:	-1.54	-4.12	-6.43	-8.29 ^a	–
MAD:	8.12	8.40	14.25	13.32 ^a	–
SD:	10.65	9.70	16.36	15.02 ^a	–
MAX:	25.24	20.10	29.98	35.70 ^a	–

^a Missing values are neglected in statistical analysis.

Table S45: Barrier heights of pericyclic reactions (BHPERI)^{S32} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	44.67	43.43	40.18	41.25	35.30
2	23.45	21.99	35.45	25.01	30.80
3	27.95	28.16	38.95	33.97	28.10
4	29.17	29.73	42.56	34.15	39.70
5	27.86	27.74	43.03	25.03	28.30
6	21.96	22.04	42.66	27.46	35.80
7	8.14	8.85	26.06	10.56	22.30
8	7.21	9.22	29.25	12.65	18.00
9	7.12	9.55	31.21	14.51	14.50
10	35.88	39.46	38.10	31.44	26.40
11	12.60	14.01	26.06	31.70	27.60
12	6.46	8.97	20.52	23.07	20.00
13	5.51	5.04	26.97	11.24	13.80
14	4.14	5.79	24.99	9.94	11.80

15	-1.11	0.24	10.75	8.60	6.50
16	-2.34	-2.60	8.91	4.62	4.70
17	-0.75	-0.22	18.46	8.09	13.10
18	-3.26	-3.46	12.18	3.07	5.90
19	-3.42	-4.50	13.55	-2.62	0.50
20	6.81	8.88	29.99	12.96	18.10
21	5.85	5.96	27.71	–	16.60
22	10.67	11.79	29.19	16.67	22.90
23	12.53	12.35	36.02	23.60	27.80
24	6.27	10.77	36.12	18.25	21.30
25	6.87	10.33	34.54	15.74	21.60
26	14.52	19.36	36.84	23.96	31.30
MD:	-8.77	-7.69	8.37	-2.45 ^a	–
MAD:	10.22	9.32	8.49	4.54 ^a	–
SD:	6.90	6.61	4.84	4.66 ^a	–
MAX:	16.78	15.45	16.71	11.74 ^a	–

^a Missing value is neglected in statistical analysis.

Table S46: Barrier heights of bond rotations around single bonds (BHROT27)^{S10} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	2.58	1.95	1.26	2.18	2.73
2	6.12	4.87	5.49	4.91	7.01
3	2.62	2.50	2.13	3.02	3.46
4	2.55	2.12	2.16	2.64	3.72
5	1.62	1.02	1.05	0.99	1.01
6	2.74	1.53	1.80	1.75	2.28
7	-1.01	-0.79	-0.57	-0.91	1.01
8	7.24	6.31	8.11	3.91	7.17
9	2.06	2.07	3.49	2.05	5.79
10	5.97	4.62	4.81	3.69	8.03
11	1.05	0.17	-1.57	1.84	1.62
12	6.07	3.69	9.64	4.46	8.41
13	6.07	5.02	8.49	3.02	6.91
14	1.49	0.76	0.39	2.73	2.68
15	17.88	15.29	18.30	13.19	17.24
16	14.12	11.75	14.43	11.71	14.52
17	2.64	1.84	3.47	0.66	2.10

18	5.12	6.67	0.52	6.89	3.89
19	4.36	4.50	-0.73	6.72	2.09
20	3.88	3.52	0.59	4.42	1.78
21	3.01	3.51	-0.60	4.68	1.39
22	5.47	4.85	0.63	5.47	6.30
23	3.16	3.16	-0.03	3.47	3.35
24	10.71	6.54	5.64	14.84	10.36
25	10.50	5.21	5.02	15.01	10.24
26	15.15	10.96	12.17	18.02	17.20
27	14.95	9.63	11.54	18.20	17.08
MD:	-0.42	-1.71	-1.92	-0.36	-
MAD:	1.17	2.38	2.38	2.22	-
SD:	1.43	2.49	2.19	2.78	-
MAX:	3.73	7.45	5.67	4.77	-

Table S47: Barrier heights for inversions and racemizations (INV24)^{S33} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	31.39	21.45	15.03	16.50	31.70
2	70.15	79.34	66.09	36.13	69.30
3	62.58	69.50	5.59	122.64	60.60
4	42.84	29.21	35.42	31.54	37.00
5	78.08	85.22	71.57	57.43	74.20
6	7.80	10.05	10.48	5.48	9.70
7	14.68	14.29	0.00	10.66	18.90
8	54.13	65.53	34.27	36.74	43.20
9	72.17	60.78	59.94	- ^a	79.70
10	35.88	44.35	18.40	22.34	31.20
11	27.20	31.69	18.09	18.85	29.30
12	9.88	8.95	10.84	8.54	10.30
13	6.30	4.98	7.45	4.57	4.50
14	24.22	22.25	24.94	24.30	24.70
15	32.88	31.00	31.80	35.17	37.60
16	5.44	4.06	8.29	3.86	4.10
17	10.60	10.66	14.55	10.19	13.10
18	11.70	11.37	11.57	13.80	11.20
19	4.07	5.23	8.49	6.52	6.20
20	24.94	24.55	29.02	26.34	21.30

21	49.07	45.63	46.86	46.20	42.30
22	22.36	26.80	34.19	25.32	27.20
23	10.21	10.43	11.00	12.43	8.40
24	76.28	74.64	83.64	80.81	68.60
MD:	0.86	1.15	-4.45	-1.23 ^a	–
MAD:	3.45	5.80	8.59	9.07 ^a	–
SD:	4.39	8.37	13.82	16.52 ^a	–
MAX:	10.93	22.33	55.01	62.04 ^a	–

^a Abnormally high repulsion energy in transition state geometry of PCL₃. Hence, this value is neglected in statistical analysis.

Table S48: Barrier heights for proton exchange reactions (PX13)^{S10,S34} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	67.02	71.22	60.14	69.08	59.30
2	40.36	43.69	37.03	52.38	46.90
3	46.16	54.41	33.18	56.37	48.40
4	51.94	47.30	46.39	49.94	48.60
5	26.94	24.94	18.06	26.96	29.80
6	22.60	23.88	12.18	22.94	26.60
7	27.76	29.23	10.56	26.17	30.10
8	34.96	35.86	14.83	30.07	35.10
9	39.42	29.90	59.91	46.46	42.30
10	18.74	5.51	43.13	31.96	20.70
11	14.16	0.34	36.79	30.41	14.70
12	14.95	-1.20	38.41	33.70	14.60
13	17.26	-1.91	44.24	38.92	16.60
MD:	-0.88	-5.43	1.63	6.28	–
MAD:	2.74	8.30	15.98	8.66	–
SD:	3.55	9.23	18.42	9.10	–
MAX:	7.72	18.51	27.64	22.32	–

Table S49: Barrier heights for proton transfer reactions (WCPT18)^{S10,S35} computed with different semiempirical methods. The values are given in kcal/mol.

system #	GFN2-xTB	GFN-xTB	PM6-D3H4X	DFTB3-D3(BJ)	ref.
1	35.39	36.90	42.20	33.97	36.76
2	30.09	31.33	35.27	37.22	36.21
3	62.98	64.45	61.14	61.42	60.95
4	36.65	46.46	47.61	53.16	47.52
5	61.07	73.25	65.97	72.62	65.68
6	79.41	77.77	87.58	84.77	81.24
7	30.39	40.97	36.53	37.22	32.00
8	21.44	35.81	31.36	35.76	28.97
9	51.32	65.56	61.34	62.72	58.80
10	2.89	-0.83	0.57	3.90	5.40
11	1.54	-4.66	-1.05	4.95	2.68
12	27.57	23.68	23.93	25.81	28.78
13	9.92	9.78	6.61	11.71	8.68
14	28.72	33.73	31.03	26.27	33.89
15	51.74	49.35	44.90	51.98	59.63
16	3.84	12.18	4.28	9.73	5.83
17	0.86	6.91	0.14	7.83	3.54
18	31.38	45.51	34.90	37.03	33.22
MD:	-3.48	1.02	-0.86	1.57	-
MAD:	3.84	5.30	3.47	4.08	-
SD:	3.41	6.37	4.83	4.45	-
MAX:	10.87	12.29	14.73	7.65	-

Table S50: Molecular dipole moments computed with GFN2-xTB, GFN-xTB, and PM6. The reference is a CCSD(T)/CBS estimate and taken from Ref. S36. All quantities are given in Debye.

system	$N_\alpha - N_\beta$	GFN2-xTB	GFN-xTB	PM6	ref.
AlF	0	1.7690	3.3490	1.9660	1.4729
AlH ₂	1	1.3360	1.6550	0.2020	0.4011
BeH	1	1.3590	1.2270	0.5000	0.2319
BF	0	1.4760	0.5170	0.2550	0.8194
BH	0	1.5380	0.9280	0.5070	1.4103
BH ₂	1	0.0570	0.3170	0.5040	0.5004
BH ₂ Cl	0	1.0480	0.8410	1.0030	0.6838

BH ₂ F	0	0.8240	0.9630	1.1990	0.8269
BHCl ₂	0	1.0090	1.0440	1.0360	0.6684
BHF ₂	0	1.0320	1.1160	1.3590	0.9578
BN	2	2.1650	2.0600	2.5140	2.0366
BO	1	2.1910	2.8970	2.2260	2.3171
BS	1	2.3410	1.1380	1.7720	0.7834
C ₂ H	1	1.0190	0.5960	0.3090	0.7601
C ₂ H ₃	1	0.8190	0.8290	0.7930	0.6867
C ₂ H ₅	1	0.5610	0.5240	0.4780	0.3140
CF	1	1.0930	0.6960	0.0080	0.6793
CF ₂	0	0.3990	0.0910	0.3440	0.5402
CH	1	1.6430	1.6120	1.3570	1.4328
CH ₂ BH	0	0.2670	0.5200	1.4510	0.6238
CH ₂ BOH	0	2.5010	2.8340	2.5990	2.2558
CH ₂ F	1	1.5450	1.5540	1.3770	1.3796
CH ₂ NH	0	1.9890	2.3310	2.4070	2.0673
CH ₂ PH	0	1.1980	0.5680	1.2460	0.8748
CH ₂ -singlet	0	1.7970	1.9180	1.9270	1.4942
CH ₂ -triplet	2	0.6790	0.5910	0.7780	0.5862
CH ₃ BH ₂	0	0.8140	0.8650	0.6100	0.5751
CH ₃ BO	0	3.2660	4.0640	3.3970	3.6779
CH ₃ Cl	0	1.9770	1.8720	1.9800	1.8981
CH ₃ F	0	2.2740	2.1760	1.6350	1.8083
CH ₃ Li	0	4.6150	4.2520	5.2400	5.8304
CH ₃ NH ₂	0	1.5380	1.8970	2.0520	1.3876
CH ₃ O	1	3.3450	4.0510	2.3290	2.0368
CH ₃ OH	0	1.9690	2.4940	2.1250	1.7091
CH ₃ SH	0	2.3830	1.4790	1.7700	1.5906
ClCN	0	3.2960	3.0390	2.5610	2.8496
ClF	0	1.5800	1.5770	0.0830	0.8802
ClO ₂	1	2.1230	3.2720	5.1490	1.8627
CN	1	0.6100	1.5010	1.3500	1.4318
CO	0	0.6140	0.5040	0.0960	0.1172

CS	0	1.5060	1.6040	0.9750	1.9692
CSO	0	0.2610	1.6170	0.4800	0.7327
FCN	0	1.7630	2.0650	1.9950	2.1756
FCO	1	0.8190	1.6440	0.5290	0.7678
FH-BH ₂	1	3.0470	3.4460	2.0560	2.9730
FH-NH ₂	1	4.5960	5.7790	4.4340	4.6265
FH-OH	1	2.7590	2.8860	2.6710	3.3808
FNO	0	1.6060	1.4040	1.8310	1.6971
H ₂ CN	1	2.9730	3.0610	2.8030	2.4939
H ₂ O	0	2.2710	2.8400	2.1170	1.8601
H ₂ O-Al	1	4.0710	1.2550	3.4880	4.3573
H ₂ O-Cl	1	2.7640	3.2920	2.3630	2.2383
H ₂ O-F	1	3.3960	3.6030	2.1940	2.1875
H ₂ O-H ₂ O	0	2.9470	3.6130	2.6880	2.7303
H ₂ O-Li	1	6.0590	4.2560	0.9300	3.6184
H ₂ O-NH ₃	0	3.7330	4.5840	4.0230	3.5004
H ₂ S-H ₂ S	0	1.2410	1.1010	0.9520	0.9181
H ₂ S-HCl	0	2.3110	3.0090	2.3880	2.1328
HBH ₂ BH	0	1.5500	1.3870	2.0880	0.8429
HBO	0	2.1720	3.0380	2.6370	2.7322
HBS	0	2.4970	1.4420	1.7920	1.3753
HCCCl	0	0.2030	0.2530	0.3550	0.5009
HCCF	0	1.4140	0.9450	0.5750	0.7452
HCHO	0	2.3870	3.3280	2.8020	2.3927
HCHS	0	2.2010	1.5610	1.4730	1.7588
HCl	0	1.0580	1.8390	1.4580	1.1055
HCl-HCl	0	1.7160	2.5480	1.9740	1.7766
HCN	0	2.6600	2.9140	2.6740	3.0065
HCNO	0	3.0650	3.5010	1.9790	2.9560
HCO	1	1.6680	2.5050	1.8220	1.6912
HCOF	0	2.0880	2.8230	2.3230	2.1169
HCONH ₂	0	4.3700	5.1600	4.1830	3.9152
HCOOH	0	1.7630	1.8870	1.5510	1.3835

HCP	0	0.9730	0.9600	0.5610	0.3542
HF	0	2.5140	2.3850	1.3600	1.8059
HF-HF	0	4.3790	4.1870	2.3840	3.3991
HN ₃	0	2.0470	2.3340	2.1060	1.6603
HNC	0	2.7090	3.1300	2.4480	3.0818
HNCO	0	2.2530	2.9820	2.2570	2.0639
HNO	0	1.7270	2.8660	1.8610	1.6536
HNO ₂	0	2.5880	3.6690	1.5300	1.9345
HNS	0	1.4520	1.9980	1.8370	1.4062
HO ₂	1	2.9370	3.3380	2.0910	2.1659
HOCl	0	1.5840	2.4420	1.6260	1.5216
HOCN	0	4.0520	4.2440	3.4310	3.7998
HO ₂ F	0	2.3570	2.4980	1.6050	1.9168
HO ₂ OH	0	2.0350	2.4110	1.5760	1.5732
HPO	0	2.4570	4.0430	3.1330	2.6291
LiBH ₄	0	5.7880	5.2390	7.4990	6.1281
LiCl	0	6.4350	6.6300	7.8990	7.0960
LiCN	0	6.9370	6.5560	7.4270	6.9851
LiF	0	6.2180	5.6960	6.4710	6.2879
LiH	0	6.2200	6.3000	3.8400	5.8286
LiN	2	6.2690	5.8470	7.0160	7.0558
LiOH	0	3.8580	3.0640	4.3200	4.5664
N ₂ H ₂	0	2.8770	3.7340	3.4080	2.8771
N ₂ H ₄	0	3.0760	3.7680	3.7040	2.7179
NaCl	0	7.3410	9.8670	9.8760	9.0066
NaCN	0	8.0880	9.1610	9.0750	8.8903
NaF	0	7.5970	8.0630	8.3250	8.1339
NaH	0	7.0670	7.9210	5.8930	6.3966
NaLi	0	1.9860	3.2990	6.2780	0.4837
NaOH	0	5.7750	5.6160	6.1820	6.7690
NCl	2	2.4670	2.5910	1.8780	1.1279
NCO	1	0.9960	0.2820	1.4860	0.7935
NF	2	0.5030	0.4910	0.6230	0.0671

NF ₂	1	0.2140	0.1440	0.6670	0.1904
NH	2	1.7030	2.2410	1.8270	1.5433
NH ₂	1	1.9950	2.5490	2.3290	1.7853
NH ₂ Cl	0	1.7410	2.4130	2.4130	1.9468
NH ₂ F	0	2.6380	2.9490	2.3520	2.2688
NH ₂ OH	0	0.8060	1.3610	0.9420	0.7044
NH ₃	0	1.8390	2.1680	2.3150	1.5289
NH ₃ -BH ₃	0	6.1630	6.2280	5.8760	5.2810
NH ₃ -NH ₃	0	2.2460	2.6630	2.7650	2.1345
NH ₃ O	0	6.4900	7.2100	6.3200	5.3942
NO	1	0.1730	0.6150	0.7770	0.1271
NO ₂	1	0.9040	1.4740	0.5770	0.3350
NOCl	0	0.2430	0.7030	3.1080	2.0773
NP	0	1.9520	4.0770	2.6680	2.8713
NS	1	2.0260	1.9780	1.8140	1.8237
O ₃	0	1.1780	1.3300	2.0050	0.5666
OCl	1	2.3060	3.5640	2.0680	1.2790
OCl ₂	0	0.8550	1.8340	0.8530	0.5625
OF	1	0.5810	1.1200	0.4650	0.0205
OF ₂	0	0.4580	0.1690	0.5870	0.3252
OH	1	2.0750	2.5100	1.4920	1.6550
P ₂ H ₄	0	1.6320	1.4440	2.7680	0.9979
PCl	2	0.6730	1.0530	0.3530	0.5657
PF	2	0.8810	1.1920	0.8570	0.8104
PH	2	1.1180	0.6230	1.4470	0.4375
PH ₂	1	1.2320	0.8210	1.8020	0.5472
PH ₂ OH	0	0.5050	1.2450	0.7790	0.6836
PH ₃	0	1.1930	1.0330	1.9480	0.6069
PH ₃ O	0	3.2420	4.4790	5.5290	3.7704
PO	1	1.7150	3.4710	1.9100	1.9617
PO ₂	1	1.1350	2.1950	2.1090	1.4426
PPO	0	2.0310	3.2430	0.9870	1.8812
PS	1	0.8040	1.8950	0.5970	0.6825

S ₂ H ₂	0	1.8460	1.5780	1.3300	1.1425
SCl	1	1.3440	0.4260	0.0500	0.0690
SCl ₂	0	0.5170	0.6470	0.7220	0.3891
SF	1	0.8180	1.1010	0.9750	0.8139
SF ₂	0	1.3920	1.5520	1.5240	1.0555
SH	1	1.4420	1.2010	0.7880	0.7727
SH ₂	0	1.9480	1.5860	1.3710	0.9939
SiH	1	0.2730	0.6130	0.6440	0.1138
SiH ₃ Cl	0	1.7150	1.0290	1.4490	1.3645
SiH ₃ F	0	1.3580	0.9240	1.3790	1.3123
SiO	0	3.0560	5.1760	5.3940	3.1123
SO ₂	0	2.9590	2.3450	3.3750	1.6286
SO-triplet	2	1.9100	2.4540	2.1480	1.5606

3 Element-specific parameters in GFN2-xTB

Table S51: Element-specific atomic parameters employed in GFN2-xTB: atomic Hubbard parameter (η_A), its charge derivative (Γ_A), the exponential scaling parameter α_A and Y_A^{eff} (both entering the repulsion potential), the anisotropic XC scaling parameters $f_{\text{XC}}^{\mu A}$ and $f_{\text{XC}}^{\Theta A}$, and the offset radius R_0^A for the damping in the AES energy. The parameter N_{val} is only used if $R_0^A \neq 5$. All quantities are given in atomic units.

element	η_A	Γ_A	α_A	Y_A^{eff}	$f_{\text{XC}}^{\mu A}$	$f_{\text{XC}}^{\Theta A}$	R_0^A	N_{val}
H	0.405771	0.08	2.213717	1.105388	0.0556389	0.00027431	1.4	1.0
He	0.642029	0.2	3.604670	1.094283	-0.01	-0.00337528	3.0	1.0
Li	0.245006	0.130382	0.475307	1.289367	-0.005	0.0002	5.0	
Be	0.684789	0.0574239	0.939696	4.221216	-0.00613341	-0.00058586	5.0	
B	0.513556	0.0946104	1.373856	7.192431	-0.00481186	-0.00058228	5.0	
C	0.538015	0.15	1.247655	4.231078	-0.00411674	0.00213583	3.0	3.0
N	0.461493	-0.063978	1.682689	5.242592	0.0352127	0.0202679	1.9	3.0
O	0.451896	-0.0517134	2.165712	5.784415	-0.0493567	-0.00310828	1.8	2.0
F	0.531518	0.142621	2.421394	7.021486	-0.0833918	-0.00245955	2.4	1.0
Ne	0.850000	0.05	3.318479	11.041068	0.1	-0.005	5.0	
Na	0.271056	0.179873	0.572728	5.244917	0	0.0002	5.0	
Mg	0.344822	0.234916	0.917975	18.083164	-0.00082005	-0.00005516	5.0	
Al	0.364801	0.14	0.876623	17.867328	0.0263334	-0.00021887	5.0	
Si	0.720000	0.193629	1.187323	40.001111	-0.0002575	-0.0008	3.9	3.0
P	0.297739	0.0711291	1.143343	19.683502	0.0211022	0.00028679	2.1	3.0
S	0.339971	-0.0501722	1.214553	14.995090	-0.00151117	0.00442859	3.1	3.0
Cl	0.248514	0.149548	1.577144	17.353134	-0.0253696	0.00122783	2.5	1.0
Ar	0.502376	-0.0315455	0.896198	7.266606	-0.0207733	-0.010834	5.0	
K	0.247602	0.203309	0.482206	10.439482	-0.00103383	0.00025	5.0	
Ca	0.320378	0.20069	0.683051	14.786701	-0.00236675	0.0001	5.0	
Sc	0.472633	0.05	0.574299	8.004267	-0.00515177	-0.00042004	5.0	
Ti	0.513586	0.176727	0.723104	12.036336	-0.00434506	0.0005966	5.0	
V	0.589187	0.09	0.928532	15.677873	-0.0035	0.00009764	5.0	
Cr	0.396299	0.03	0.966993	19.517914	0.00149669	0.00137744	5.0	
Mn	0.346651	0.06	1.071100	18.760605	-0.00759168	0.00229903	5.0	

Fe	0.271594	-0.05	1.113422	20.360089	0.00412929	0.00267734	5.0	
Co	0.477760	0.03	1.241717	27.127744	-0.00247938	0.00048237	5.0	
Ni	0.344970	-0.02	1.077516	10.533269	-0.0126189	-0.0008	5.0	
Cu	0.202969	0.05	0.998768	9.913846	-0.007	-0.00345631	5.0	
Zn	0.564152	0.23129	1.160262	22.099503	-0.001	0.00007658	5.0	
Ga	0.432236	0.233427	1.122923	31.146750	0.00267219	-0.00003616	5.0	
Ge	0.802051	-0.0064775	1.222349	42.100144	0.0010846	-0.00003589	5.0	
As	0.571748	0.110604	1.249372	39.147587	-0.00201294	0.00014149	5.0	
Se	0.235052	0.0913725	1.230284	27.426779	-0.00288648	0.00085728	3.9	3.0
Br	0.261253	0.13	1.296174	32.845361	-0.0108859	0.00216935	4.0	1.0
Kr	0.424373	0.0239815	0.908074	17.363803	-0.00889357	-0.00415024	5.0	
Rb	0.210481	0.29162	0.574054	44.338211	-0.00093328	0.00015	5.0	
Sr	0.340000	0.18	0.697345	34.365525	-0.00459925	0.00015	5.0	
Y	0.711958	0.01	0.706172	17.326237	-0.00637291	0.0001046	5.0	
Zr	0.461440	0.07	0.681106	24.263093	-0.00599615	-0.00012944	5.0	
Nb	0.952957	0.05	0.865552	30.562732	-0.00288729	0.00041491	5.0	
Mo	0.586134	0.0919928	1.034519	48.312796	0.00346327	0.00312549	5.0	
Tc	0.368054	0.06	1.019565	44.779882	-0.00458416	0.00155242	5.0	
Ru	0.711205	-0.05	1.031669	28.070247	-0.00081922	0.00359228	5.0	
Rh	0.509183	0.03	1.094599	38.035941	0.00007016	0.0000857	5.0	
Pd	0.273310	0.08	1.092745	28.674700	-0.00310361	-0.00040485	5.0	
Ag	0.263740	0.02	0.678344	6.493286	-0.00800314	-0.0002081	5.0	
Cd	0.392012	0.207322	0.936236	26.226628	-0.00105364	0.0001225	5.0	
In	0.461812	0.19	1.024007	63.854240	0.00951079	-0.00002031	5.0	
Sn	0.900000	-0.0178396	1.139959	80.053438	0.00085029	-0.00008243	5.0	
Sb	0.942294	0.11	1.122937	77.057560	-0.00015519	-0.0002063	5.0	
Te	0.750000	0.0953683	1.000712	48.614745	-0.00263414	-0.00026864	5.0	
I	0.383124	0.12	1.017946	63.319176	-0.00603648	0.0006966	5.0	
Xe	0.424164	-0.0118925	1.012036	51.188398	-0.00214447	-0.001562	5.0	
Cs	0.236569	0.240419	0.585257	67.249039	-0.0008	0.00008	5.0	
Ba	0.245937	0.20691	0.716259	46.984607	-0.0026	0.00015	5.0	
La	0.597716	0.0012793	0.737643	50.927529	-0.00395198	-0.0003	5.0	
Ce	0.662889	-0.01	0.729950	48.676714	-0.00723806	-0.00025	5.0	

Pr	0.660710	-0.0100002	0.734624	47.669448	-0.00704819	-0.00024615	5.0
Nd	0.658531	-0.0100004	0.739299	46.662183	-0.00685832	-0.00024231	5.0
Pm	0.656352	-0.0100006	0.743973	45.654917	-0.00666845	-0.00023846	5.0
Sm	0.654173	-0.0100008	0.748648	44.647651	-0.00647858	-0.00023462	5.0
Eu	0.651994	-0.010001	0.753322	43.640385	-0.00628871	-0.00023077	5.0
Gd	0.649815	-0.0100012	0.757996	42.633120	-0.00609884	-0.00022692	5.0
Tb	0.647635	-0.0100013	0.762671	41.625854	-0.00590897	-0.00022308	5.0
Dy	0.645456	-0.0100015	0.767345	40.618588	-0.0057191	-0.00021923	5.0
Ho	0.643277	-0.0100017	0.772020	39.611322	-0.00552923	-0.00021538	5.0
Er	0.641098	-0.0100019	0.776694	38.604057	-0.00533936	-0.00021154	5.0
Tm	0.638919	-0.0100021	0.781368	37.596791	-0.00514949	-0.00020769	5.0
Yb	0.636740	-0.0100023	0.786043	36.589525	-0.00495961	-0.00020385	5.0
Lu	0.634561	-0.0100025	0.790717	35.582259	-0.00476974	-0.0002	5.0
Hf	0.662597	-0.01	0.852852	40.186772	-0.00537685	-0.00016478	5.0
Ta	0.449812	0.02	0.990234	54.666156	-0.00200343	0.00039599	5.0
W	0.685426	-0.02	1.018805	55.899801	0.00065886	0.0106331	5.0
Re	0.224623	0.08	1.170412	80.410086	-0.00587636	0.0030687	5.0
Os	0.364388	0.08	1.221937	62.809871	-0.0051009	0.00759049	5.0
Ir	0.548507	-0.01	1.197148	56.045639	-0.00673822	0.00322935	5.0
Pt	0.353574	0.06	1.204081	53.881425	-0.00423684	0.00098019	5.0
Au	0.438997	0.085	0.919210	14.711475	0.00393418	-0.0002032	5.0
Hg	0.457611	-0.0116312	1.137360	51.577544	-0.0025	-0.00032901	5.0
Tl	0.418841	-0.0533933	1.399312	58.801614	0.00374018	-0.00008506	5.0
Pb	0.168152	0.02	1.179922	102.368258	0.0100702	-0.0000167	5.0
Bi	0.900000	-0.0337508	1.130860	132.896832	-0.00737252	0.00162529	5.0
Po	1.023267	0.187798	0.957939	52.301232	-0.0134485	0.00013818	5.0
At	0.288848	0.184648	0.963878	81.771063	-0.00348123	0.00021624	5.0
Rn	0.303400	0.0097834	0.965577	128.133580	-0.00167597	-0.00111556	5.0

^(a) It is noted that R_0^A is a fitted parameter only for 12 elements and set to a value of 5.0 for the rest of the periodic table.

Table S52: Element-specific shell parameters employed in GFN2-xTB: the polynomial scaling parameters $k_{A,l}^{poly}$, the shell-specific scaling parameters of the Hubbard parameter κ_A^l , the CN'_A dependent enhancement factors for the energy levels, the constant part of the energy levels (H_A^l), and the corresponding Slater exponents ζ_l . The energy levels and their CN'_A dependent enhancement factors are given in eV, ζ_l is given in atomic units, whereas $k_{A,l}^{poly}$ and κ_A^l are dimensionless.

element	level	$k_{A,l}^{poly}$	κ_A^l ^(a)	$H_{CN'_A}^l$ / eV	H^l / eV	ζ_l
H	1s	-0.00953618	0.0	-0.05	-10.707211	1.230000
He	1s	-0.0438682	0.0	0.207428	-23.716445	1.669667
	2p	0.00710647	0.0	0.0	-1.822307	1.500000
Li	2s	-0.047504	0.0	0.162084	-4.900000	0.750060
	2p	0.204249	0.197261	-0.0623876	-2.217789	0.557848
Be	2s	-0.0791039	0.0	0.118776	-7.743081	1.034720
	2p	-0.00476438	0.965847	0.0550528	-3.133433	0.949332
B	2s	-0.0518315	0.0	0.0120462	-9.224376	1.479444
	2p	-0.0245332	0.399408	-0.0141086	-7.419002	1.479805
C	2s	-0.0229432	0.0	-0.0102144	-13.970922	2.096432
	2p	-0.00271102	0.105636	0.0161657	-10.063292	1.800000
N	2s	-0.08506	0.0	-0.195534	-16.686243	2.339881
	2p	-0.025042	0.116489	0.0561076	-12.523956	2.014332
O	2s	-0.149553	0.0	0.0117826	-20.229985	2.439742
	2p	-0.0335082	0.149702	-0.0145102	-15.503117	2.137023
F	2s	-0.130119	0.0	0.0394362	-23.458179	2.416361
	2p	-0.123008	0.167738	-0.0538373	-15.746583	2.308399
Ne	2s	-0.163778	0.0	-0.0014933	-24.500000	3.084104
	2p	-0.0486055	0.119058	0.0232093	-18.737298	2.312051
	3d	-0.169223	-0.32	0.109671	-5.517827	2.815609
Na	3s	-0.040335	0.0	-0.0042211	-4.546934	0.763787
	3p	0.208739	0.101889	-0.0144323	-1.332719	0.573553
Mg	3s	-0.111674	0.0	0.116444	-6.339908	1.184203
	3p	0.39077	1.4	-0.0079924	-0.697688	0.717769
	3d	0.126911	-0.05	0.119241	-1.458197	1.300000
Al	3s	-0.106781	0.0	0.0715422	-9.329017	1.352531

	3p	-0.124428	-0.0603699	-0.0244485	-5.927846	1.391201
	3d	0.163111	0.2	0.0406173	-3.042325	1.000000
Si	3s	0.0235852	0.0	0.185848	-14.360932	1.773917
	3p	-0.0790041	-0.558004	-0.138307	-6.915131	1.718996
	3d	0.113662	-0.23	-0.193549	-1.825036	1.250000
P	3s	-0.198318	0.0	0.054761	-17.518756	1.816945
	3p	-0.0551558	-0.155806	-0.048993	-9.842286	1.903247
	3d	0.263975	-0.35	0.242951	-0.444893	1.167533
S	3s	-0.258555	0.0	-0.0256951	-20.029654	1.981333
	3p	-0.0804806	-0.108587	-0.0098465	-11.377694	2.025643
	3d	0.259939	-0.25	0.200769	-0.420282	1.702555
Cl	3s	-0.16562	0.0	0.0617972	-29.278781	2.485265
	3p	-0.0698643	0.49894	-0.0181618	-12.673758	2.199650
	3d	0.380456	0.5	0.167277	-0.240338	2.476089
Ar	3s	-0.238939	0.0	0.0000554	-16.487730	2.329679
	3p	-0.0372732	-0.0461133	0.0065921	-13.910539	2.149419
	3d	0.268129	-0.01	-0.273217	-1.167213	1.950531
K	4s	-0.0607606	0.0	-0.0339245	-4.510348	0.875961
	4p	0.211873	0.348366	0.0174542	-0.934377	0.631694
Ca	4s	-0.0971872	0.0	0.057093	-5.056506	1.267130
	4p	0.319734	1.5	-0.0074926	-1.150304	0.786247
	3d	0.0952865	-0.25	0.101375	-0.776883	1.380000
Sc	3d	-0.345023	-0.08	0.202678	-5.196187	2.440000
	4s	0.00686569	0.0	0.0991293	-8.877940	1.358701
	4p	0.380449	-0.204672	-0.0281241	-2.008206	1.019252
Ti	3d	-0.277244	-0.38	0.102819	-7.234331	1.849994
	4s	0.0456123	0.0	0.100702	-10.900000	1.469983
	4p	0.518016	-0.492111	-0.0237074	-1.928783	0.957410
V	3d	-0.298276	-0.45	0.0164476	-9.015342	1.673577
	4s	0.0970248	0.0	0.0235696	-9.573347	1.383176
	4p	0.511783	-0.0379088	-0.0108232	-0.706647	0.938025
Cr	3d	-0.279716	-0.47	0.0289291	-7.209794	1.568211
	4s	0.133762	0.0	-0.0232087	-9.201304	1.395427

Mn	4p	0.480922	0.740587	-0.0188919	-0.696957	1.080270
	3d	-0.312559	-0.6	-0.0195827	-10.120933	1.839250
	4s	0.285197	0.0	-0.0275	-5.617346	1.222190
Fe	4p	0.263466	0.0545811	-0.0015839	-4.198724	1.240215
	3d	-0.28615	-0.65	-0.0274654	-10.035473	1.911049
	4s	0.115278	0.0	-0.404988	-5.402911	1.022393
Co	4p	0.394599	0.404662	-0.075648	-3.308988	1.294467
	3d	-0.223556	-0.65	0.012198	-10.580430	2.326507
	4s	0.0916846	0.0	-0.0227872	-8.596723	1.464221
Ni	4p	0.254247	-0.241849	0.0076513	-2.585753	1.298678
	3d	-0.253856	-0.6	-0.0066417	-12.712236	2.430756
	4s	0.208395	0.0	0.0310301	-8.524281	1.469945
Cu	4p	0.308864	-0.0611188	0.0226796	-2.878873	1.317046
	3d	-0.265089	0.07	-0.0173684	-9.506548	2.375425
	4s	0.177983	0.0	0.334905	-6.922958	1.550837
Zn	4p	0.149778	1.33331	-0.261945	-2.267723	1.984703
	4s	-0.0924032	0.0	0.201191	-7.177294	1.664847
	4p	0.222718	0.0684343	-0.0055135	-0.991895	1.176434
Ga	4s	-0.190182	0.0	-0.0234627	-12.449656	1.720919
	4p	-0.0113779	-0.541655	0.130583	-4.469873	1.591570
	4d	0.354019	-0.3	0.0165604	-0.582255	1.050000
Ge	4s	-0.213337	0.0	0.0361068	-16.369792	1.990429
	4p	-0.0974904	-0.380909	-0.0014474	-8.207673	1.830340
	4d	0.286347	-0.15	-0.104256	-0.994226	1.100000
As	4s	-0.238207	0.0	-0.012964	-16.421504	2.026128
	4p	-0.106442	-0.410474	-0.023647	-9.311147	1.949257
	4d	0.307111	-0.5	0.233014	-0.276830	1.040181
Se	4s	-0.245064	0.0	-0.0061654	-20.584732	2.230969
	4p	-0.137658	0.119211	-0.0435018	-10.910799	2.150656
	4d	0.296111	-0.25	0.276856	-0.110636	1.317549
Br	4s	-0.250051	0.0	0.000615	-23.583718	2.077587
	4p	-0.145201	0.5203	-0.0058347	-12.588824	2.263120
	4d	0.36614	0.4	0.225018	0.047980	1.845038

Kr	4s	-0.326587	0.0	-0.0070305	-17.221422	2.445680
	4p	-0.136001	-0.250322	0.0076023	-13.633377	2.210494
	4d	0.232047	-0.07	0.0349523	-0.940657	1.884991
Rb	5s	0.043254	0.0	-0.151693	-4.353793	1.017267
	5p	0.232551	0.938649	0.0203437	-1.392938	0.870130
Sr	5s	-0.145068	0.0	0.040902	-6.291692	1.419028
	5p	0.20214	1.5	-0.0418725	-1.872475	0.928932
	4d	0.108162	-0.25	0.0401255	-0.890492	1.500000
Y	4d	-0.395295	-0.45	-0.127034	-8.015206	2.670141
	5s	-0.0212587	0.0	0.193752	-12.194181	1.633876
	5p	0.521619	-0.334929	-0.0641897	-0.966195	1.165412
Zr	4d	-0.283589	-0.11	-0.0566943	-7.409832	2.238668
	5s	0.075389	0.0	0.126655	-10.199105	1.702480
	5p	0.589141	-0.442263	0.0279435	-1.066939	1.129590
Nb	4d	-0.279637	-0.05	-0.135649	-8.440821	1.706832
	5s	-0.0514108	0.0	0.255596	-11.384021	1.666463
	5p	0.556542	-0.356295	-0.0002341	-0.103760	1.132172
Mo	4d	-0.225737	-0.3	0.0620172	-7.995133	1.777658
	5s	-0.00583137	0.0	0.300841	-7.336245	1.639917
	5p	0.291996	-0.430137	-0.104035	-3.686225	1.159781
Tc	4d	-0.273426	-0.6	-0.0066526	-9.587897	1.918066
	5s	0.36096	0.0	-0.0586205	-6.792444	1.918167
	5p	0.250957	0.395682	-0.0087319	-3.325525	1.346082
Ru	4d	-0.275832	-0.65	-0.0263914	-10.285405	2.102697
	5s	0.101063	0.0	0.447116	-5.332608	1.749643
	5p	0.340287	-0.305231	-0.0034723	-3.307153	1.348322
Rh	4d	-0.196561	-0.65	0.0104368	-11.756644	2.458187
	5s	0.154133	0.0	0.0066741	-7.850495	1.811796
	5p	0.310707	-0.188177	-0.0213308	-3.007906	1.398452
Pd	4d	-0.271731	-0.6	0.0060285	-11.963518	2.353691
	5s	0.0620014	0.0	0.026682	-9.714059	1.828354
	5p	0.453413	0.0931707	0.0503075	-2.035281	1.333352
Ag	4d	-0.164907	-0.03	-0.0062719	-9.591083	2.843549

	5s	0.0109149	0.0	-0.0065794	-8.083960	1.798462
	5p	0.115614	0.802485	0.167717	-2.934333	1.266649
Cd	5s	-0.0607687	0.0	0.141815	-7.252341	1.846689
	5p	0.376719	0.238867	-0.0309814	-0.744865	1.141823
In	5s	-0.219385	0.0	-0.0098312	-13.040909	1.963283
	5p	-0.0194965	-0.586746	0.0994688	-4.507143	1.685138
	5d	0.313545	-0.28	0.0168649	-0.805666	1.050000
Sn	5s	-0.175182	0.0	-0.0454629	-19.970428	2.551510
	5p	-0.0780287	-0.509075	-0.0320651	-7.367059	1.893784
	5d	0.126111	-0.06	-0.145941	-2.077548	1.100000
Sb	5s	-0.175435	0.0	-0.0147626	-18.371244	2.307407
	5p	-0.124946	-0.62785	-0.0091175	-7.350148	2.179752
	5d	0.308727	-0.55	0.160287	0.909033	1.256087
Te	5s	-0.248939	0.0	0.0115389	-21.930653	2.434144
	5p	-0.11232	-0.155533	-0.0082051	-9.480374	2.182459
	5d	0.318432	0.06	0.301323	0.978922	1.373076
I	5s	-0.269575	0.0	-0.050615	-20.949407	2.159500
	5p	-0.141833	-0.0338735	0.0084766	-12.180159	2.308379
	5d	0.282119	0.3	0.307713	-0.266596	1.691185
Xe	5s	-0.310965	0.0	-0.0020195	-19.090498	2.715140
	5p	-0.161979	-0.230267	0.0017246	-11.249471	2.312510
	5d	0.19049	-0.23	0.0327039	-0.497097	1.855707
Cs	6s	-0.00713637	0.0	-0.13126	-4.041706	1.225688
	6p	0.20637	0.249431	-0.01	-1.394193	0.823818
Ba	6s	-0.140366	0.0	0.0352001	-5.900000	1.528102
	6p	0.187741	2.22475	-0.0926576	-2.133395	0.991572
	5d	0.113897	-0.23	0.0147995	-1.514900	1.500000
La	5d	-0.378201	-0.3	-0.0777542	-8.958783	2.875048
	6s	-0.0673201	0.0	0.107168	-11.877410	1.731390
	6p	0.541364	-0.469967	-0.0239967	-0.601717	1.303590
Ce	5d	-0.419892	-0.3	-0.0638958	-7.381991	2.870000
	6s	-0.0610774	0.0	0.133515	-8.537781	1.725197
	6p	0.376634	-0.553966	-0.019832	-3.017508	1.309804

Pr	5d	-0.412865	-0.276923	-0.0543909	-7.280875	2.872308
	6s	-0.0604017	0.0	0.134944	-8.504806	1.729767
	6p	0.381948	-0.546278	-0.0198184	-2.873159	1.315495
Nd	5d	-0.405838	-0.253846	-0.0448861	-7.179760	2.874615
	6s	-0.0597259	0.0	0.136373	-8.471830	1.734337
	6p	0.387261	-0.538591	-0.0198048	-2.728809	1.321186
Pm	5d	-0.398811	-0.230769	-0.0353812	-7.078644	2.876923
	6s	-0.0590501	0.0	0.137803	-8.438855	1.738907
	6p	0.392574	-0.530903	-0.0197912	-2.584460	1.326877
Sm	5d	-0.391784	-0.207692	-0.0258764	-6.977529	2.879231
	6s	-0.0583743	0.0	0.139232	-8.405879	1.743478
	6p	0.397888	-0.523216	-0.0197776	-2.440110	1.332567
Eu	5d	-0.384758	-0.184615	-0.0163715	-6.876413	2.881538
	6s	-0.0576986	0.0	0.140661	-8.372904	1.748048
	6p	0.403201	-0.515528	-0.019764	-2.295761	1.338258
Gd	5d	-0.377731	-0.161538	-0.0068667	-6.775298	2.883846
	6s	-0.0570228	0.0	0.142091	-8.339929	1.752618
	6p	0.408514	-0.507841	-0.0197504	-2.151411	1.343949
Tb	5d	-0.370704	-0.138461	0.0026382	-6.674182	2.886154
	6s	-0.056347	0.0	0.14352	-8.306953	1.757188
	6p	0.413827	-0.500153	-0.0197369	-2.007062	1.349640
Dy	5d	-0.363677	-0.115384	0.012143	-6.573067	2.888462
	6s	-0.0556712	0.0	0.144949	-8.273978	1.761758
	6p	0.419141	-0.492466	-0.0197233	-1.862712	1.355331
Ho	5d	-0.35665	-0.0923072	0.0216479	-6.471951	2.890769
	6s	-0.0549955	0.0	0.146379	-8.241003	1.766328
	6p	0.424454	-0.484778	-0.0197097	-1.718363	1.361022
Er	5d	-0.349623	-0.0692302	0.0311527	-6.370836	2.893077
	6s	-0.0543197	0.0	0.147808	-8.208027	1.770899
	6p	0.429767	-0.477091	-0.0196961	-1.574013	1.366713
Tm	5d	-0.342596	-0.0461533	0.0406576	-6.269720	2.895385
	6s	-0.0536439	0.0	0.149237	-8.175052	1.775469
	6p	0.435081	-0.469403	-0.0196825	-1.429664	1.372403

Yb	5d	-0.335569	-0.0230763	0.0501624	-6.168604	2.897692
	6s	-0.0529681	0.0	0.150667	-8.142076	1.780039
	6p	0.440394	-0.461716	-0.0196689	-1.285314	1.378094
Lu	5d	-0.328542	0.0000007	0.0596673	-6.067489	2.900000
	6s	-0.0522924	0.0	0.152096	-8.109101	1.784609
	6p	0.445707	-0.454028	-0.0196553	-1.140965	1.383785
Hf	5d	-0.340957	0.1	0.017655	-7.181755	2.638729
	6s	-0.0273193	0.0	0.22715	-10.626891	2.194333
	6p	0.33515	-0.448616	-0.0069771	-1.603430	1.427467
Ta	5d	-0.303963	0.05	-0.0620136	-8.481353	2.018969
	6s	-0.157077	0.0	0.0988501	-13.073088	1.996498
	6p	0.60186	-0.339438	-0.047254	0.655254	1.407714
W	5d	-0.256771	0.37	-0.0192494	-9.501505	2.155885
	6s	0.0620898	0.0	0.254364	-11.093016	1.892022
	6p	0.492738	-0.34192	0.0236479	-1.420389	1.458186
Re	5d	-0.317231	-0.6	-0.0322139	-11.189119	2.262783
	6s	0.138901	0.0	0.111757	-12.685198	2.187549
	6p	0.339733	0.658686	-0.133516	-3.851981	1.636996
Os	5d	-0.284611	-0.65	-0.0095346	-10.382841	2.509631
	6s	0.213168	0.0	0.0346183	-8.731460	2.173991
	6p	0.280972	0.135022	-0.0208758	-3.546379	1.597888
Ir	5d	-0.246934	-0.65	0.0051977	-11.018475	2.756134
	6s	0.207338	0.0	-0.0123672	-9.349164	2.117548
	6p	0.183032	-0.0977957	-0.0079864	-3.603762	1.680343
Pt	5d	-0.272439	-0.6	-0.0204828	-12.047728	2.704492
	6s	0.0673756	0.0	0.113953	-10.482306	2.329136
	6p	0.192595	-0.0203212	0.140803	-3.778297	1.623286
Au	5d	-0.0641082	-0.6	-0.0154462	-9.578599	3.241287
	6s	0.0469154	0.0	0.147934	-7.688552	2.183171
	6p	0.252503	0.0614126	0.104807	0.883399	2.084484
Hg	6s	-0.0983345	0.0	-0.0352252	-11.538066	2.244504
	6p	0.156289	-0.537512	0.0205401	-2.532581	1.470848
Tl	6s	-0.229422	0.0	-0.0255975	-17.319333	2.294231

	6p	0.131098	-0.71334	0.0901364	-4.460584	1.731592
Pb	6s	-0.229551	0.0	-0.389346	-24.055207	2.960592
	6p	-0.0880527	0.783825	0.343712	-5.893816	1.953130
Bi	6s	-0.217501	0.0	0.0160425	-19.843840	2.788267
	6p	-0.107739	-0.6	0.0248659	-7.297456	2.277039
Po	6s	-0.209233	0.0	-0.0046813	-20.205380	3.314810
	6p	-0.184264	-0.810916	-0.0100437	-8.476927	2.389456
At	6s	-0.3055	0.0	-0.0287369	-17.050229	2.220421
	6p	-0.171085	-0.253207	-0.0007993	-9.499822	2.408112
	5d	0.23825	0.25	0.280581	-0.096063	1.500000
Rn	6s	-0.352454	0.0	-0.0001712	-21.000000	3.109394
	6p	-0.119897	-0.0302388	-0.000528	-10.496406	2.541934
	5d	0.21167	-0.23	-0.320602	-1.415056	1.790000

An STO-3G expansion is used for 1s levels (H and He) and for all d levels .

An STO-4G expansion is used for the ns and np levels with $n = [2, 5]$.

An STO-6G expansion is used for the 6s and 6p levels.

^(a) It is noted that for s-functions, κ_A^l is not a fitted parameter but always set to zero.

References

- (S1) Elstner, M.; Porezag, D.; Jungnickel, G.; Elsner, J.; Haugk, M.; Frauenheim, T.; Suhai, S.; Seifert, G. Self-consistent-charge density-functional tight-binding method for simulations of complex materials properties. *Phys. Rev. B* **1998**, *58*, 7260–7268.
- (S2) Gaus, M.; Cui, Q.; Elstner, M. DFTB3: Extension of the Self-Consistent-Charge Density-Functional Tight-Binding Method (SCC-DFTB). *J. Chem. Theory Comput.* **2011**, *7*, 931–948.
- (S3) Grimme, S.; Bannwarth, C.; Shushkov, P. A Robust and Accurate Tight-Binding Quantum Chemical Method for Structures, Vibrational Frequencies, and Noncovalent

- Interactions of Large Molecular Systems Parametrized for All spd-Block Elements ($Z = 1 - 86$). *J. Chem. Theory Comput.* **2017**, *13*, 1989–2009.
- (S4) Risthaus, T.; Steinmetz, M.; Grimme, S. Implementation of Nuclear Gradients of Range-Separated Hybrid Density Functionals and Benchmarking on Rotational Constants for Organic Molecules. *J. Comput. Chem.* **2014**, *35*, 1509–1516.
- (S5) Grimme, S.; Brandenburg, J. G.; Bannwarth, C.; Hansen, A. Consistent structures and interactions by density functional theory with small atomic orbital basis sets. *J. Chem. Phys.* **2015**, *143*, 054107.
- (S6) Bühl, M.; Kabrede, H. Geometries of Transition-Metal Complexes from Density-Functional Theory. *J. Chem. Theory Comput.* **2006**, *2*, 1282–1290.
- (S7) Jurečka, P.; Šponer, J.; Cerny, J.; Hobza, P. Benchmark database of accurate (MP2 and CCSD(T) complete basis set limit) interaction energies of small model complexes, DNA base pairs, and amino acid pairs. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1985–1993.
- (S8) Řezáč, J.; Riley, K. E.; Hobza, P. S66: A Well-balanced Database of Benchmark Interaction Energies Relevant to Biomolecular Structures. *J. Chem. Theory Comput.* **2011**, *7*, 2427.
- (S9) Řezáč, J.; Riley, K. E.; Hobza, P. Benchmark Calculations of Noncovalent Interactions of Halogenated Molecules. *J. Chem. Theory Comput.* **2012**, *8*, 4285–4292.
- (S10) Goerigk, L.; Hansen, A.; Bauer, C.; Ehrlich, S.; Najibi, A.; Grimme, S. A look at the density functional theory zoo with the advanced GMTKN55 database for general main group thermochemistry, kinetics and noncovalent interactions. *Phys. Chem. Chem. Phys.* **2017**, *19*, 32184–32215.
- (S11) Kozuch, S.; Martin, J. M. L. Halogen Bonds: Benchmarks and Theoretical Analysis. *J. Chem. Theory Comput.* **2013**, *9*, 1918–1931.

- (S12) Setiawan, D.; Kraka, E.; Cremer, D. Strength of the Pnictogen Bond in Complexes Involving Group Va Elements N, P, and As. *J. Phys. Chem. A* **2015**, *119*, 1642–1656.
- (S13) Marshall, M. S.; Burns, L. A.; Sherrill, C. D. Basis set convergence of the coupled-cluster correction, $\delta_{\text{MP2}}^{\text{CCSD(T)}}$: Best practices for benchmarking non-covalent interactions and the attendant revision of the S22, NBC10, HBC6, and HSG databases. *J. Chem. Phys.* **2011**, *135*, 194102.
- (S14) Grimme, S.; Hansen, A.; Brandenburg, J. G.; Bannwarth, C. Dispersion-Corrected Mean-Field Electronic Structure Methods. *Chem. Rev.* **2016**, *116*, 5105–5154.
- (S15) Bryantsev, V. S.; Diallo, M. S.; van Duin, A. C. T.; Goddard, W. A. Evaluation of B3LYP, X3LYP, and M06-Class Density Functionals for Predicting the Binding Energies of Neutral, Protonated, and Deprotonated Water Clusters. *J. Chem. Theory Comput.* **2009**, *5*, 1016–1026.
- (S16) Anacker, T.; Friedrich, J. New accurate benchmark energies for large water clusters: DFT is better than expected. *J. Comput. Chem.* **2014**, *35*, 634–643.
- (S17) Lao, K. U.; Schäffer, R.; Jansen, G.; Herbert, J. M. Accurate description of intermolecular interactions involving ions using symmetry-adapted perturbation theory. *J. Chem. Theory Comput.* **2015**, *11*, 2473–2486.
- (S18) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **2010**, *132*, 154104.
- (S19) Sure, R.; Grimme, S. Comprehensive Benchmark of Association (Free) Energies of Realistic Host–Guest Complexes. *J. Chem. Theory Comput.* **2015**, *11*, 3785–3801.
- (S20) Řezáč, J.; Hobza, P. Advanced Corrections of Hydrogen Bonding and Dispersion for

- Semiempirical Quantum Mechanical Methods. *J. Chem. Theory Comput.* **2012**, *8*, 141–151.
- (S21) Christensen, A. S.; Elstner, M.; Cui, Q. Improving intermolecular interactions in DFTB3 using extended polarization from chemical-potential equalization. *J. Chem. Phys.* **2015**, *143*, 084123.
- (S22) Gruzman, D.; Karton, A.; Martin, J. M. L. Performance of Ab Initio and Density Functional Methods for Conformational Equilibria of C_nH_{2n+2} Alkane Isomers ($n = 4 - 8$). *J. Phys. Chem. A* **2009**, *113*, 11974–11983.
- (S23) Kesharwani, M. K.; Karton, A.; Martin, J. M. L. Benchmark ab Initio Conformational Energies for the Proteinogenic Amino Acids through Explicitly Correlated Methods. Assessment of Density Functional Methods. *J. Chem. Theory Comput.* **2016**, *12*, 444–454.
- (S24) Kozuch, S.; Bachrach, S. M.; Martin, J. M. Conformational Equilibria in Butane-1,4-diol: A Benchmark of a Prototypical System with Strong Intramolecular H-bonds. *J. Phys. Chem. A* **2014**, *118*, 293–303.
- (S25) Kozuch, S.; Martin, J. M. L. Spin-component-scaled double hybrids: An extensive search for the best fifth-rung functionals blending DFT and perturbation theory. *J. Comput. Chem.* **2013**, *34*, 2327–2344.
- (S26) Řeha, D.; Valdés, H.; Vondrášek, J.; Hobza, P.; Abu-Riziq, A.; Crews, B.; de Vries, M. S. Structure and IR Spectrum of Phenylalanyl–Glycyl–Glycine Tripeptide in the Gas-Phase: IR/UV Experiments, Ab Initio Quantum Chemical Calculations, and Molecular Dynamic Simulations. *Chem. Eur. J.* **2005**, *11*, 6803–6817.
- (S27) Goerigk, L.; Karton, A.; Martin, J. M. L.; Radom, L. Accurate quantum chemical energies for tetrapeptide conformations: why MP2 data with an insufficient basis set should be handled with caution. *Phys. Chem. Chem. Phys.* **2013**, *15*, 7028–7031.

- (S28) Csonka, G. I.; French, A. D.; Johnson, G. P.; Stortz, C. A. Evaluation of Density Functionals and Basis Sets for Carbohydrates. *J. Chem. Theory Comput.* **2009**, *5*, 679–692.
- (S29) Kruse, H.; Mladek, A.; Gkionis, K.; Hansen, A.; Grimme, S.; Sponer, J. Quantum Chemical Benchmark Study on 46 RNA Backbone Families Using a Dinucleotide Unit. *J. Chem. Theory Comput.* **2015**, *11*, 4972–4991.
- (S30) Marianski, M.; Supady, A.; Ingram, T.; Schneider, M.; Baldauf, C. Assessing the Accuracy of Across-the-Scale Methods for Predicting Carbohydrate Conformational Energies for the Examples of Glucose and α -Maltose. *J. Chem. Theory Comput.* **2016**, *12*, 6157–6168.
- (S31) Dohm, S.; Hansen, A.; Steinmetz, M.; Grimme, S.; Checinski, M. P. Comprehensive Thermochemical Benchmark Set of Realistic Closed-Shell Metal Organic Reactions. *J. Chem. Theory Comput.* **2018**, *14*, 2596–2608.
- (S32) Karton, A.; Goerigk, L. Accurate reaction barrier heights of pericyclic reactions: Surprisingly large deviations for the CBS-QB3 composite method and their consequences in DFT benchmark studies. *J. Comput. Chem.* *36*, 622–632.
- (S33) Goerigk, L.; Sharma, R. The INV24 test set: how well do quantum-chemical methods describe inversion and racemization barriers? *Can. J. Chem.* **2016**, *94*, 1133–1143.
- (S34) Karton, A.; O’Reilly, R. J.; Chan, B.; Radom, L. Determination of Barrier Heights for Proton Exchange in Small Water, Ammonia, and Hydrogen Fluoride Clusters with G4(MP2)-Type, MPn, and SCS-MPn Procedures—A Caveat. *J. Chem. Theory Comput.* **2012**, *8*, 3128–3136.
- (S35) Karton, A.; O’Reilly, R. J.; Radom, L. Assessment of Theoretical Procedures for Calculating Barrier Heights for a Diverse Set of Water-Catalyzed Proton-Transfer Reactions. *J. Phys. Chem. A* **2012**, *116*, 4211–4221.

- (S36) Hait, D.; Head-Gordon, M. How Accurate Is Density Functional Theory at Predicting Dipole Moments? An Assessment Using a New Database of 200 Benchmark Values. *J. Chem. Theory Comput.* **2018**, *14*, 1969–1981.