

Supplementary Materials for

DNA Phosphates: Effective Catalysts for Asymmetric Ion-Pairing Catalysis in Water

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Computational Methods

Geometries of DNA-catalyst systems were optimized at GFN2-xTB^{4,5} level of theory with *crude* optimization settings. We note that geometry optimizations did not always converge (i.e., converged for some systems but not others) for optimization settings of *vtight*, *tight*, *normal*, *lax*, *loose* and *sloppy*. Only *crude* optimization settings manage to have geometry optimization convergence for all systems.

The xTB-optimized structures were subject to single-point energy calculations using density function theory (DFT), which were performed using the *Gaussian 16* rev. B.01 program.⁶ Single point (SP) corrections were performed using BP86 functional^{7,8} with Grimme's D3 dispersion correction⁹ with Becke-Johnson damping¹⁰⁻¹³ (hereafter denoted BP86-D3BJ) with 6-311+G(d) basis set¹⁴ for all atoms. Dispersion correction (D3BJ) has been added to correctly capture non-covalent interactions.¹⁵⁻¹⁸ The implicit SMD continuum solvation model¹⁹ was used to account for the solvent effect of water that was used in the experimental reactions. The single point energies, calculated at SMD (water)-BP86-D3BJ/6-311+G(d) level of theory, are given in kcal mol⁻¹ and used for discussion throughout. All molecular structures and molecular orbitals were visualized using *PyMOL* software.²⁰

Naming conventions

Structures are named according to the figure below. Structures where the imidazole group and the 4-methylpyridine are in *cis* relationship will be either **A** or **B**, depending on which DNA groove it faces: if the bpy ligand N atoms face major groove, this will be **A** and if minor groove, **B**. Similarly, structures where the imidazole group and the 4-methylpyridine are in *trans* relationship will be either **C** or **D**, where in **C**, the bpy ligand N atoms face major groove and in **D**, the bpy ligand N atoms face minor groove. For fluorination reaction, unprimed labels (**A** to **D**) are used and for Mannich reaction, primed labels are used (**A'** to **D'**).

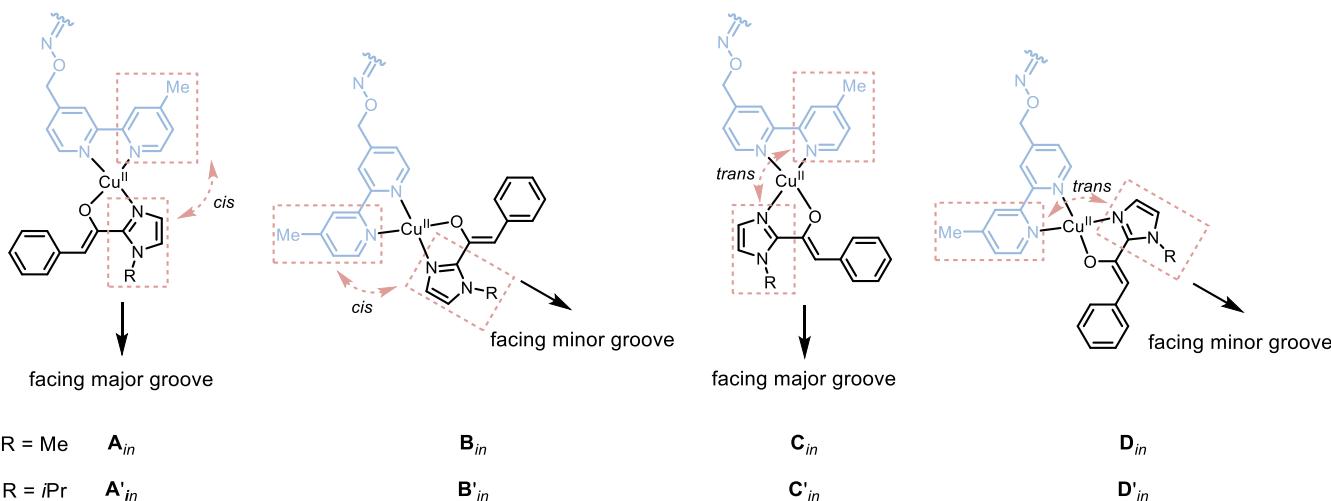
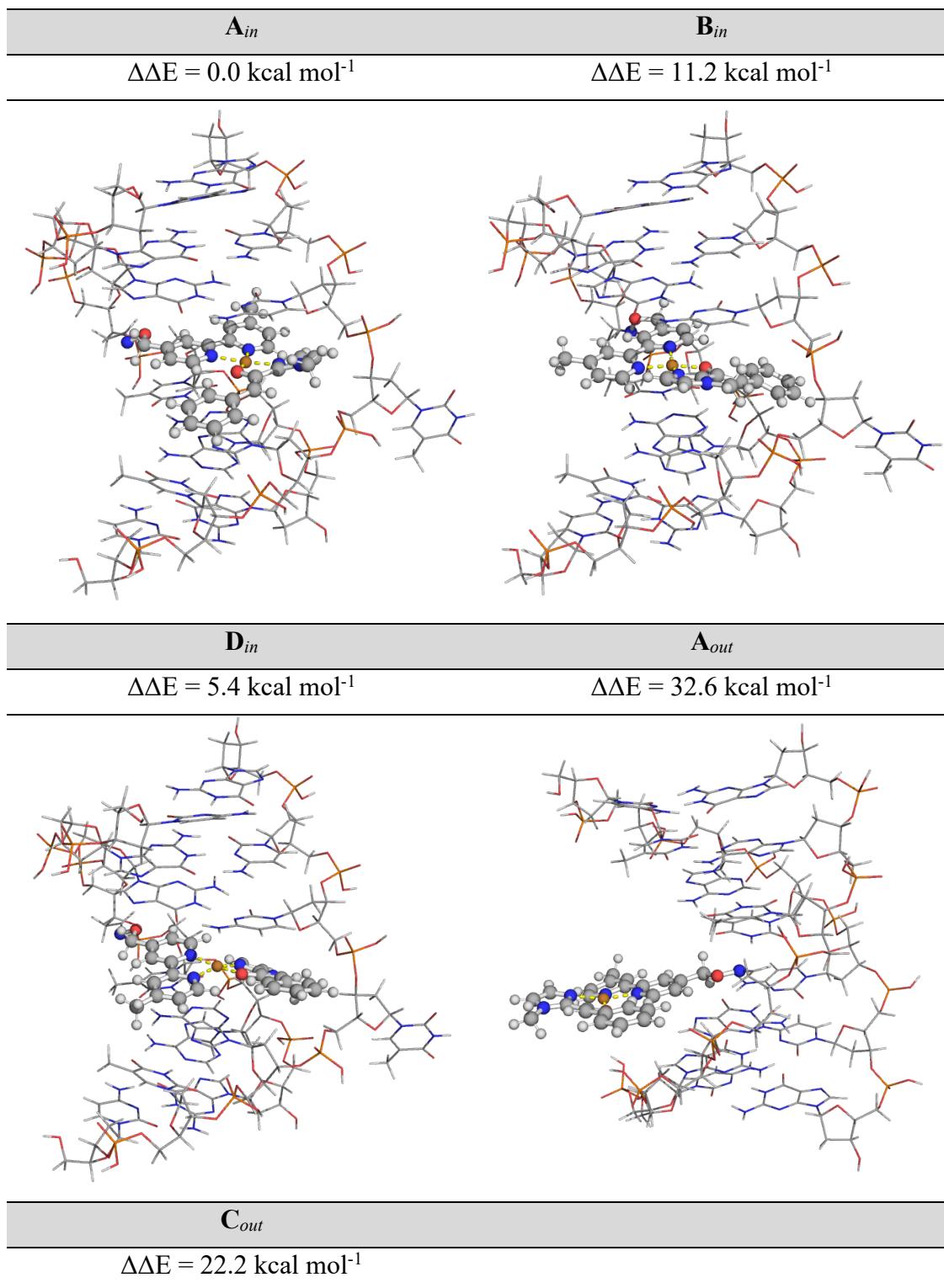


Figure S2. Naming conventions for computational model structures.

Fluorination reaction

Unbound states

The GFN2-xTB-optimized structures of the DNA model system used for fluorination reaction are shown in **Figure S3**. The energies of the structures with the catalyst system in the “out states”, where the opposite base remain inside the duplex, and in the “in states”, where the catalyst system tucks in between DNA base pairs and the opposite base is flipped out, were compared. It was found that the “in states” are lower in energy than the “out states”, thus more thermodynamically stable. This may be due to the more favorable π - π stacking interactions in the “in states”. In particular, structure \mathbf{A}_{in} is the most stable and is taken as the zero-energy reference.



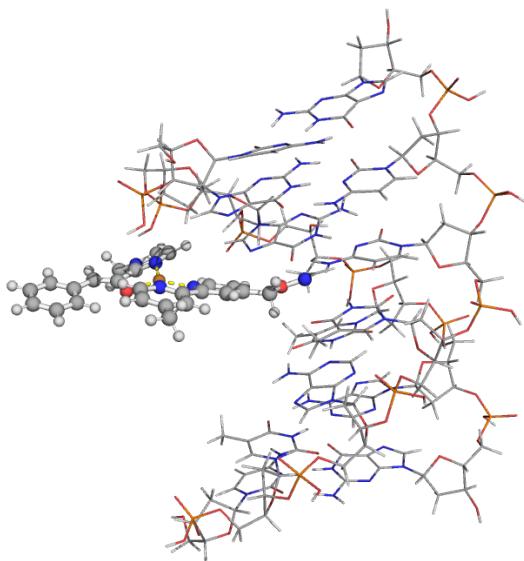
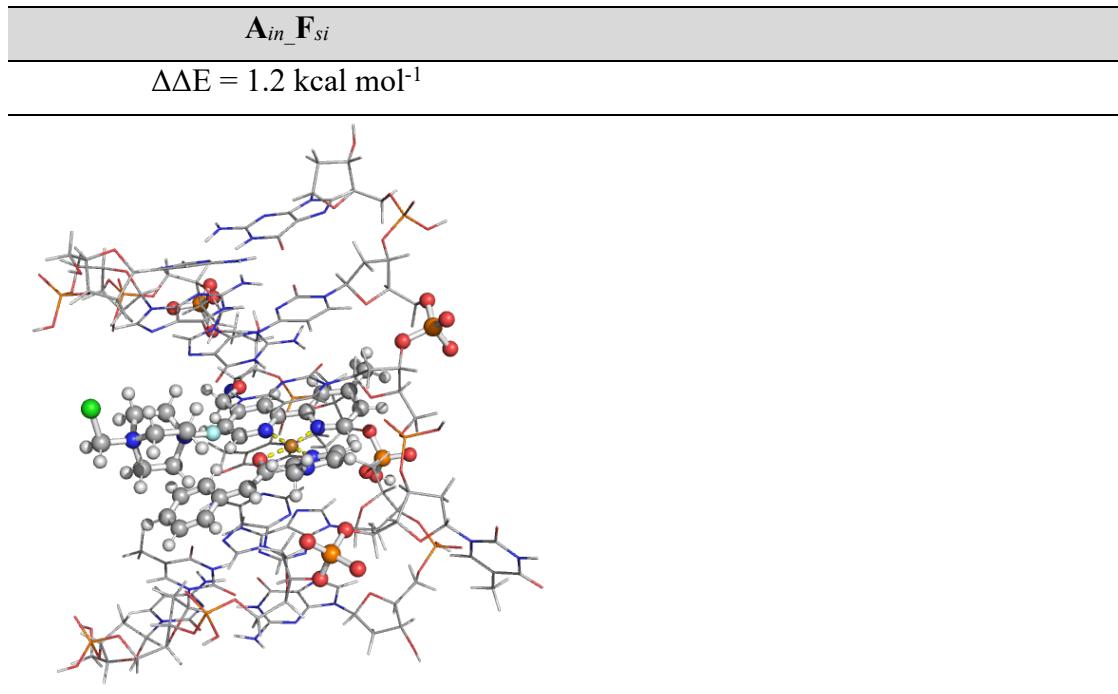


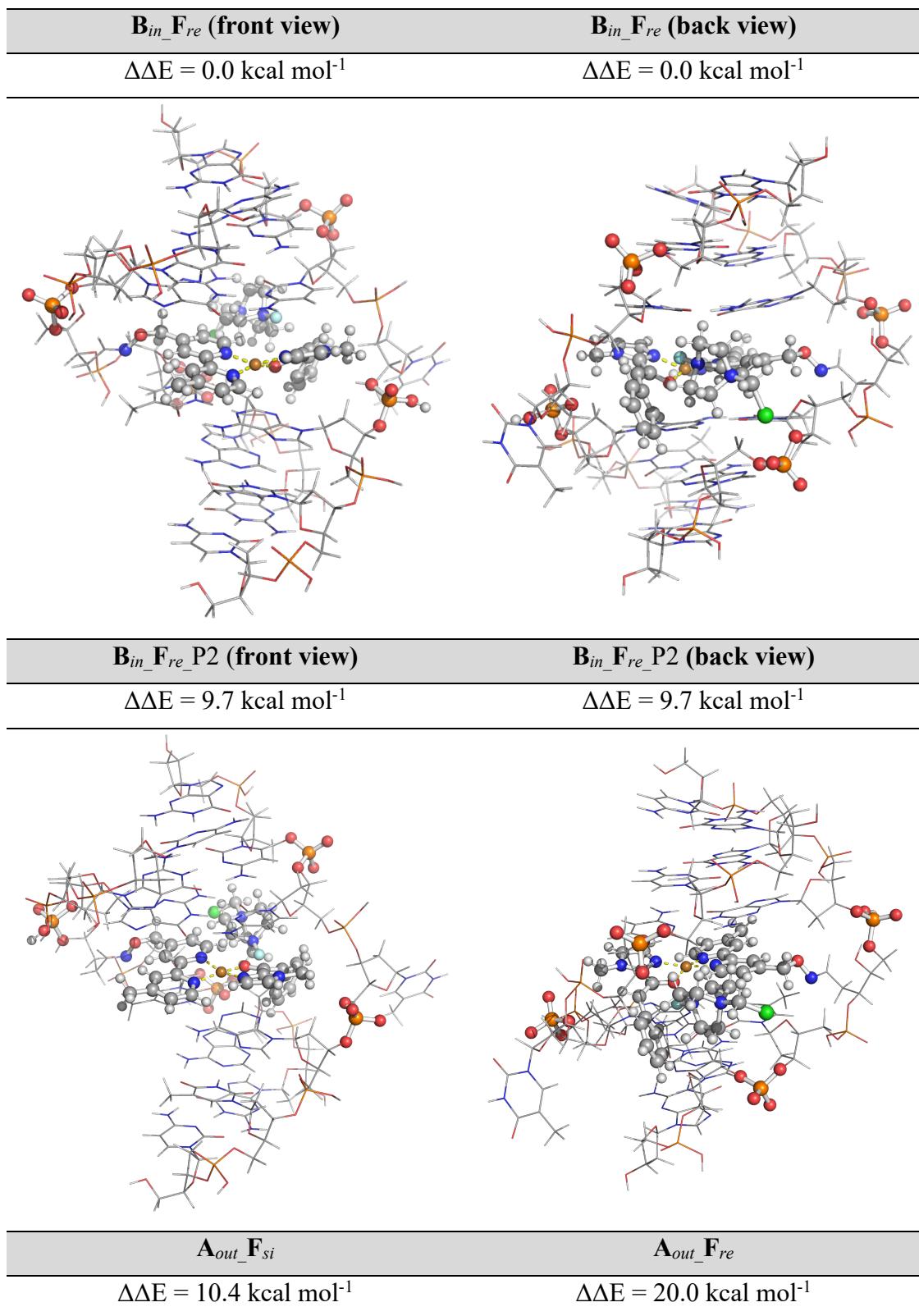
Figure S3. GFN2-xTB-optimized structures of the DNA model system used for fluorination reaction. Energy values are given in kcal mol⁻¹ and taken relative to the most stable complex.

Bound states

The GFN2-xTB-optimized structures of the structures where the Selectfluor cation binds are shown in **Figure S4**. The most stably bound species is **B_{in}_F_{re}**, which gives the right enantioselectivity outcome in the fluorination products. We observed that the Selectfluor cation can approach the substrate in the minor groove and interact with the phosphate groups 5 and 15 through ionic interactions. Different protonation states of the phosphates were considered (**B_{in}_F_{re}** where phosphates 3, 5, 15 are deprotonated, and **B_{in}_F_{re}_P2** where phosphates 5, 13, 15 are deprotonated) and the most stable one was located. Note, that we have deprotonated both phosphates 5 and 15 in both cases, as these two are important to form ionic interactions with the positively charged Selectfluor cation.

The complexes where the catalyst is in the “out states” where the Selectfluor cation binds were also considered. These species **A_{out}_F_{si/re}** and **C_{out}_F_{si/re}** have higher energies than the complexes where the catalyst is in the “in states” (Figure S2), similar to the scenario observed for the unbound states (**Figure S3**).





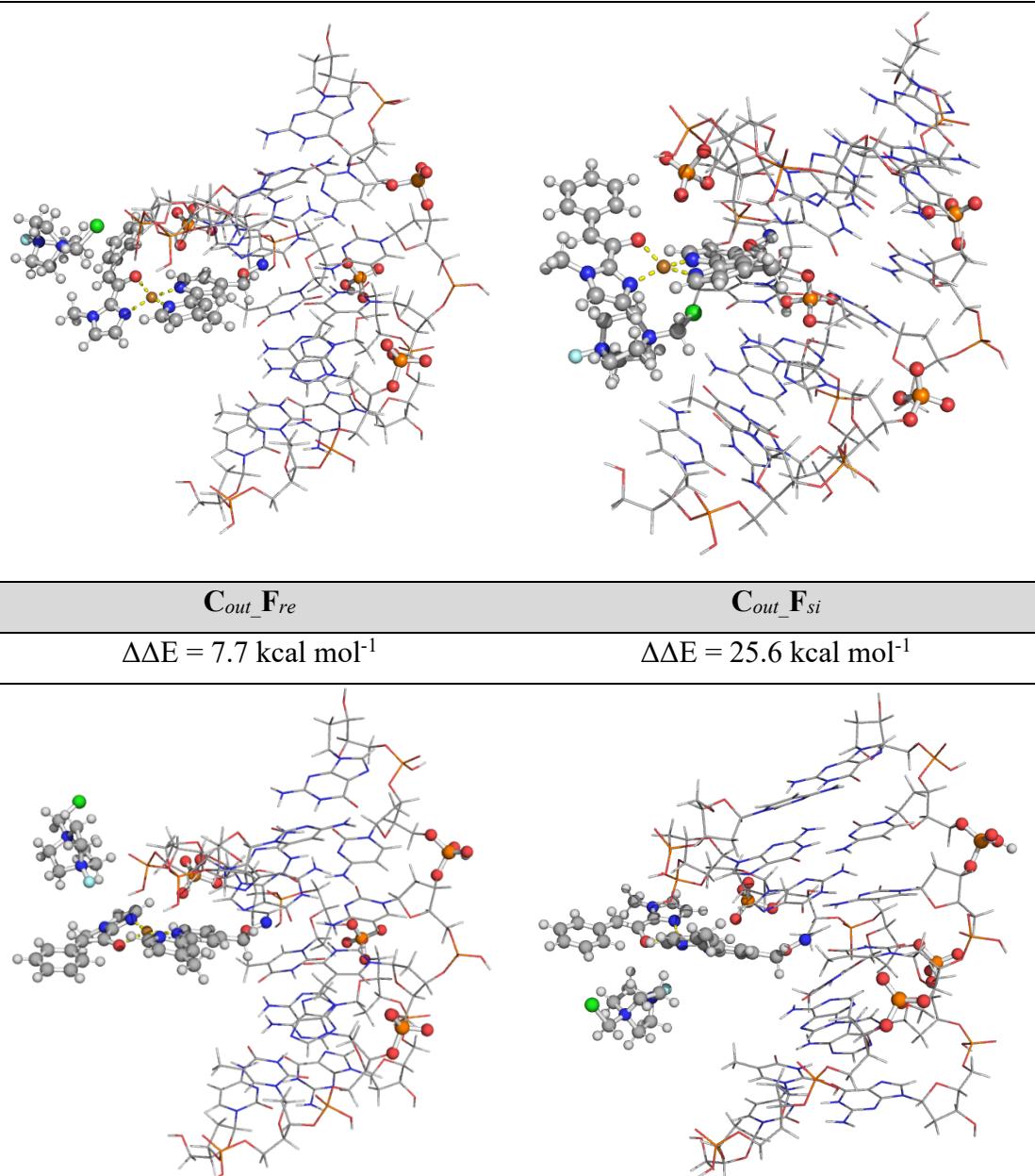


Figure S4. GFN2-xTB-optimized fluorination reaction with Selectfluor binding. Energy values are given in kcal mol^{-1} and taken relative to the most stable complex.

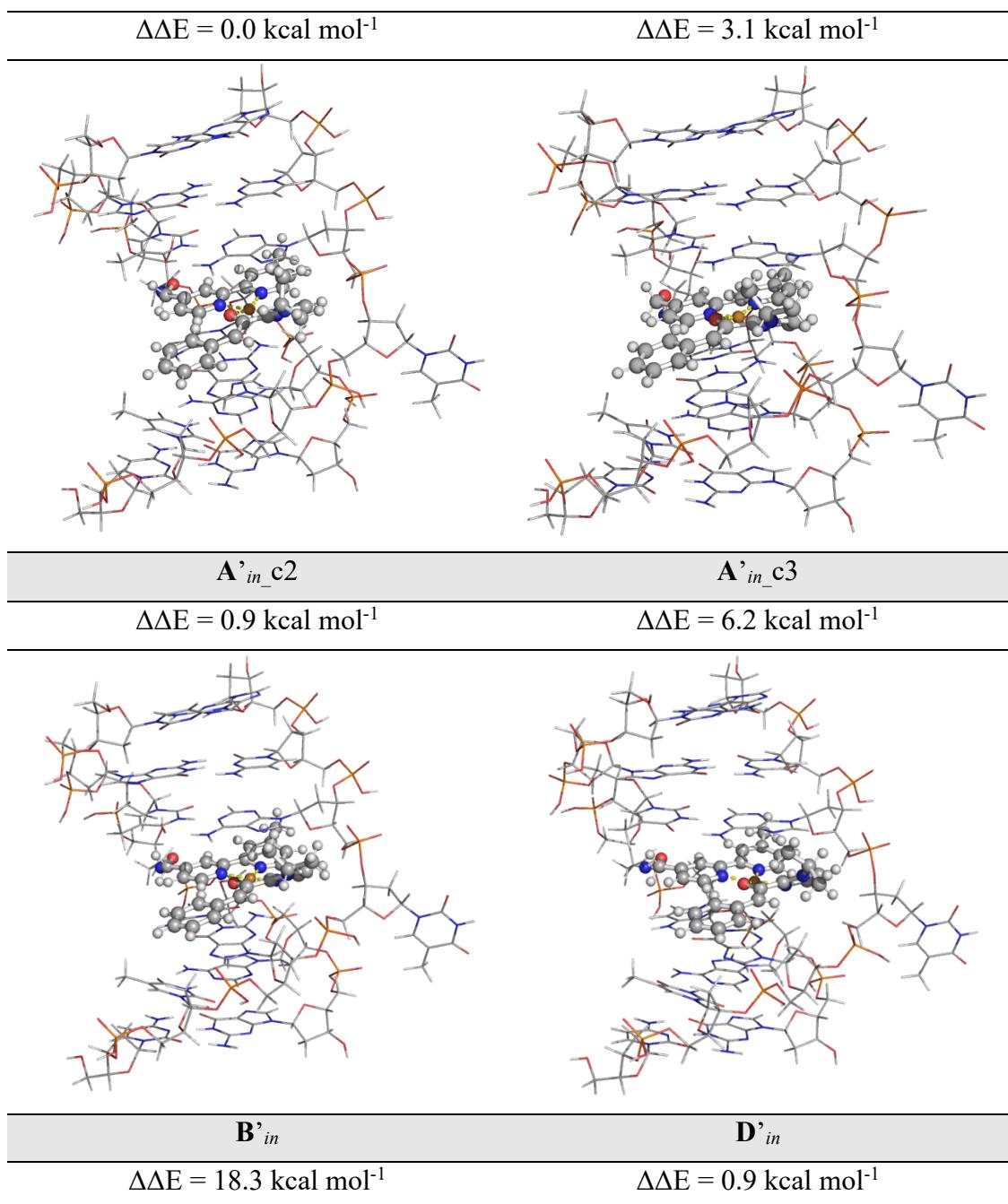
Mannich reaction

Unbound states

The mechanistic basis for these sequence-dependent effects on reactivity and selectivity in the Mannich reaction was studied computationally. The GFN2-xTB-optimized structures of the DNA model used for Mannich reaction were shown in Figure S5.

For the \mathbf{A}' “in states”, the conformers of the iPr -group on the Cu-bound substrate were considered (\mathbf{A}'_{in} , \mathbf{A}'_{in_c2} and \mathbf{A}'_{in_c3}) and the lowest one (\mathbf{A}'_{in}) is used as the zero- energy reference. We also found that the structure with the oxime in Z configuration (\mathbf{A}'_{in_Z}) is higher in energy, by $3.1 \text{ kcal mol}^{-1}$, than the structure with oxime in E configuration (\mathbf{A}'_{in}), as expected. The “out states” are again higher in energies than the “in states”.





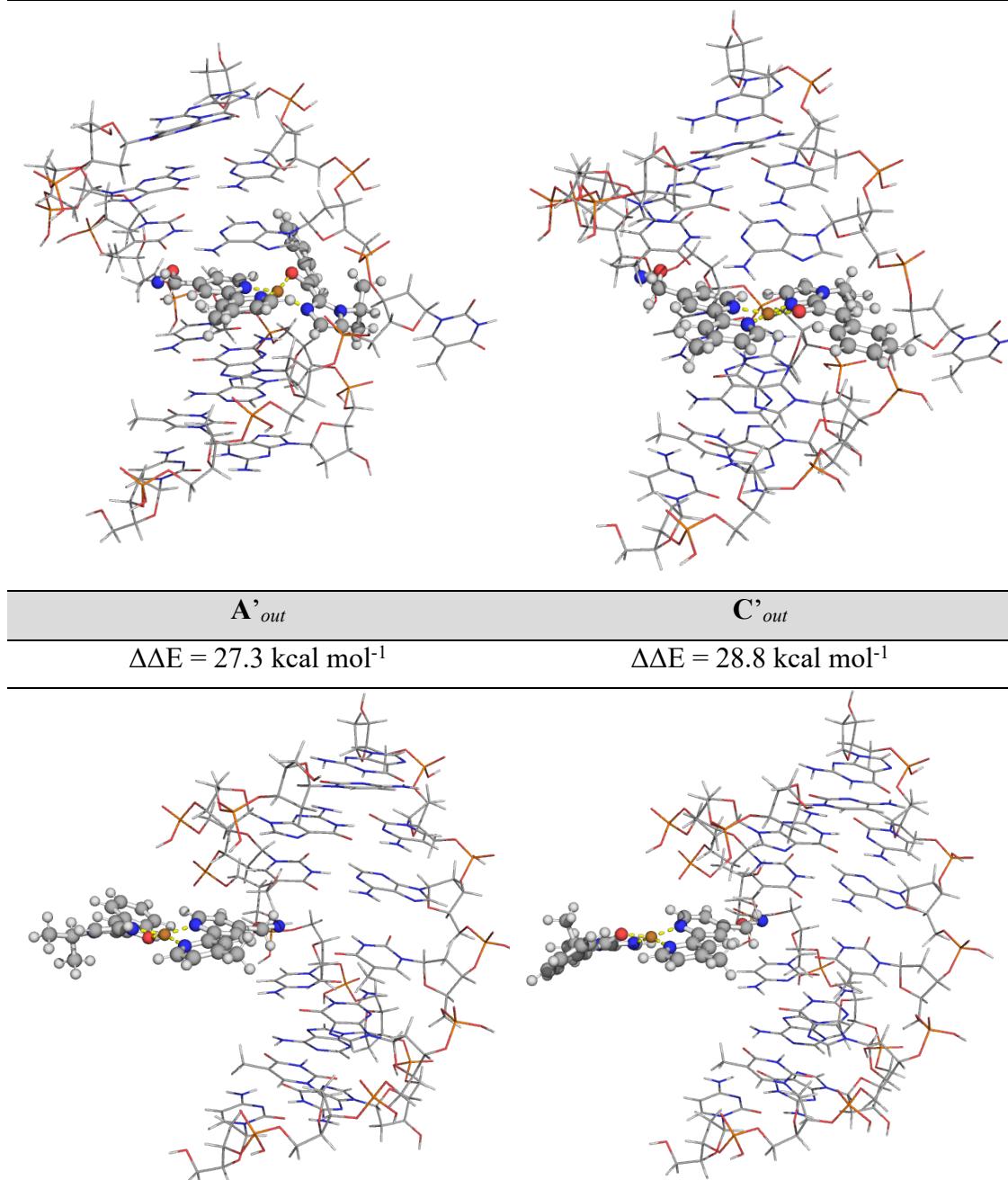


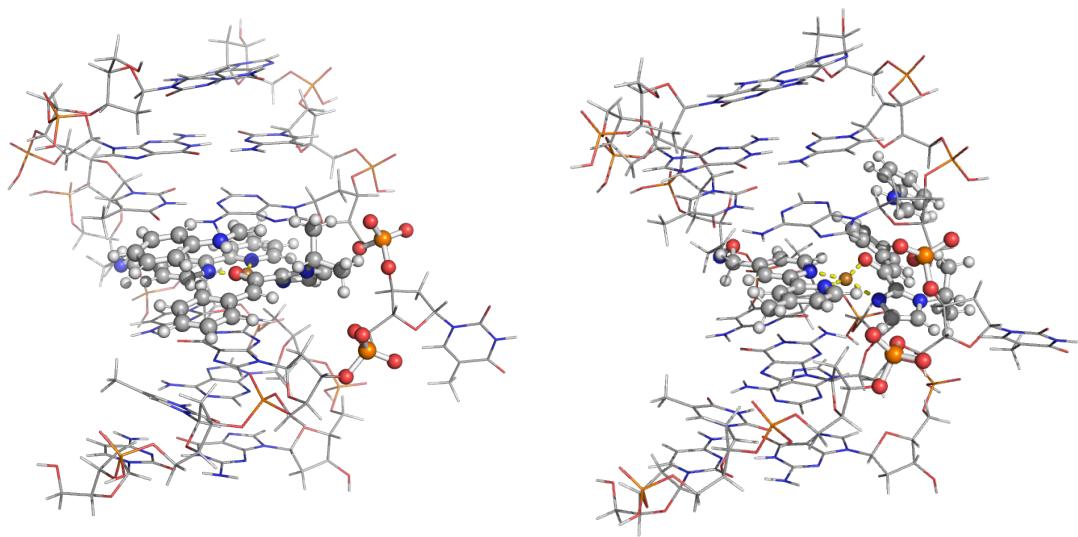
Figure S5. GFN2-xTB-optimized structures of the DNA model system used for the Mannich reaction. Energy values are given in kcal mol⁻¹ and taken relative to the most stable complex.

Bound states

The GFN2-xTB-optimized structures of the iminium bound species are shown in **Figure S6**. The most stable species is **D'_{in_Im_{si}}**, which benefits from favourable hydrogen bonding and electrostatic attraction between the N–H group of the iminium cation and the deprotonated phosphate 14.

The complexes where the catalyst is in the “out states” where the iminium cation binds were also considered. These species **A'_{out_Im_{si/re}}** and **C'_{out_Im_{si/re}}** have higher energies than the complexes where the catalyst is in the “in states” (**Figure S6**), similar to the scenario observed for the unbound states (**Figure S5**).

A'_{in_Im_{si}}	B'_{in_Im_{re}}
$\Delta\Delta E = 24.3 \text{ kcal mol}^{-1}$	$\Delta\Delta E = 70.8 \text{ kcal mol}^{-1}$

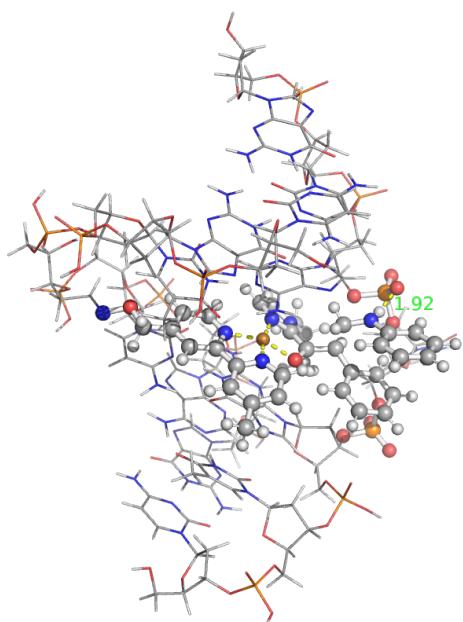


$D'_{in_Im_{si}}$ (front view)

$D'_{in_Im_{si}}$ (back view)

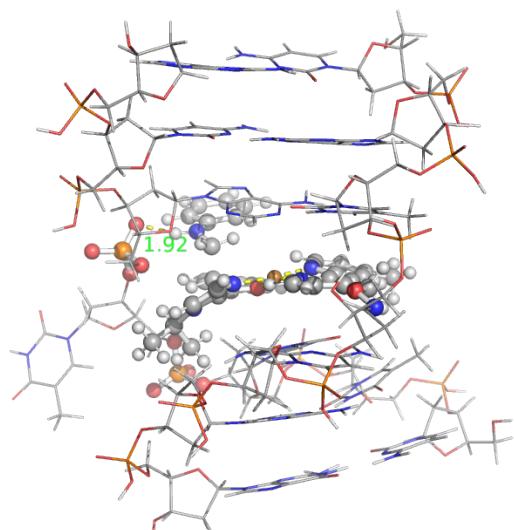
$\Delta\Delta E = 0.0 \text{ kcal mol}^{-1}$

$\Delta\Delta E = 0.0 \text{ kcal mol}^{-1}$



$A'_{out_Im_{si}}$

$\Delta\Delta E = 25.7 \text{ kcal mol}^{-1}$



$A'_{out_Im_{re}}$

$\Delta\Delta E = 39.0 \text{ kcal mol}^{-1}$

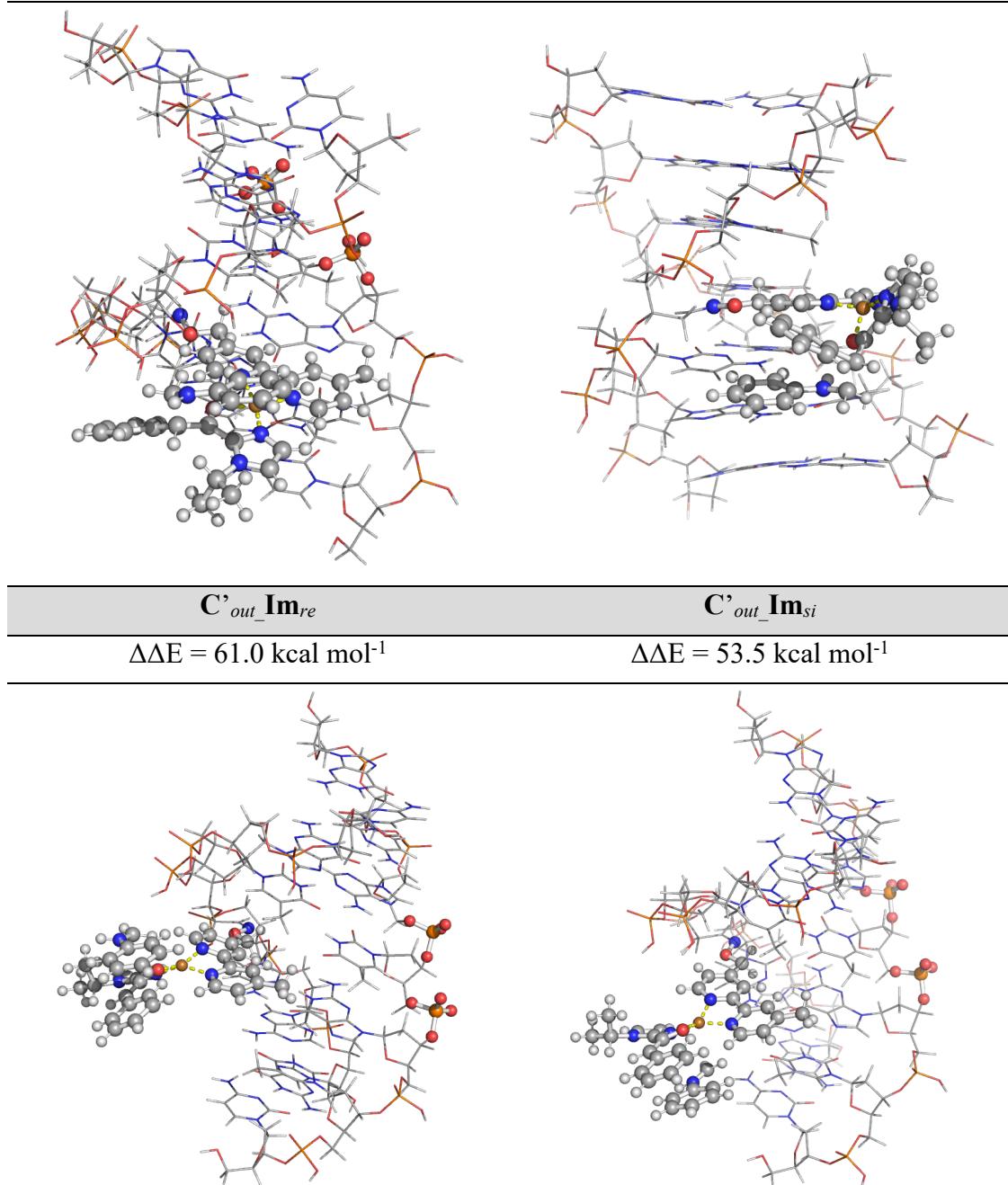


Figure S6. GFN2-xTB-optimized Mannich reaction model system with iminium binding. Energy values are given in kcal mol^{-1} and taken relative to the most stable complex.

xTB-optimized structures

Geometries of all xTB-optimized structures (in .xyz format) are included in a separate folder named *xTB_optimized_structures* with an associated *readme.txt* file. All these data have been uploaded to zenodo.org at <https://zenodo.org/records/14043521>, with DOI: [10.5281/zenodo.14043521](https://doi.org/10.5281/zenodo.14043521).

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