

DFT Calculation Workflow

This workflow integrates semi-empirical rapid conformational sampling with high-precision DFT calculations to systematically investigate reaction mechanisms and thermodynamic barriers, as outlined below:

CREST XTB Conformational Search (Initial Conformation Generation) To comprehensively cover the low-energy conformational space of the reaction system, CREST (Conformer-Rotamer Ensemble Search Tool) combined with XTB (Extended Tight-Binding) semi-empirical method is first employed for conformational search. XTB, a fast electronic structure method based on density functional tight-binding approximation, retains reasonable accuracy (errors typically <5 kcal/mol) while significantly reducing computational cost, making it suitable for large-scale conformational sampling (1-2). **Input Preparation** : The 3D structure of the reaction substrate (e.g., small molecule or ligand) is input (generated via tools like Chem3D or OpenBabel). **Parameter Setup** : CREST uses XTB2 (with dispersion correction by default) and sets convergence thresholds (e.g., energy difference ≤ 0.5 kcal/mol, RMSD ≤ 0.5 Å) and a maximum number of conformations (e.g., 100–200) to avoid redundancy.

Output : CREST generates a set of low-energy conformations (including global minima and several local minima), sorted by energy,

providing an initial structural library for subsequent high-precision optimization in Gaussian.

2. Gaussian 16 Structural Optimization

Five to ten lowest-energy conformations from the CREST library are imported into Gaussian 16 for DFT-level structural optimization to obtain thermodynamically stable geometries (3). The optimization is performed under the SMD (Solvation Model Based on Density) implicit solvation model to simulate aqueous environments (e.g., buffer solutions). Theory and Basis Set : The ω B97X-D functional (with D3 dispersion correction, suitable for weak-interaction systems) combined with the 6-31+G(d,p) basis set (balancing computational cost and accuracy) is employed. Solvent Parameters : The SMD model is configured with water as the solvent

Optimization Convergence : Gradient threshold ≤ 0.0001 Hartree/Bohr, displacement ≤ 0.00001 Å, and energy change $\leq 1 \times 10^{-6}$ Hartree are applied to ensure the structure reaches a local energy minimum.

Output : Optimized structures of reactants, products, and potential intermediates (if multi-step reactions exist) are obtained.

Frequency calculations are performed on optimized reactants, products, intermediates, and TS structures to confirm structural stability

(no imaginary frequencies for minima, one imaginary frequency for TS) and extract thermodynamic parameters (e.g., zero-point vibrational energy (ZPE), enthalpy (H), entropy (S)). Calculation Setup : Computations are conducted at the same theoretical level (ω B97X-D/6-31+G(d,p)) and SMD solvent model to ensure data comparability.

References:

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