Supplementary Information

Generation and benchmarking of a diverse reaction database of quantum mechanical liquid-phase activation Gibbs free energies

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S1. CONFORMER SELECTION DETAILS

For several reaction subsets in LiPRED-2026, multiple stable conformers are not expected to play an important role. These include the three S_N2 reactions in DMSO; the S_N2 reactions in acetonitrile for R = Me, Et, iPr, tBu, and neopentyl; the Diels-Alder reactions that do not involve an acyclic diene; and the aromatic nucleophilic substitution reaction.

For reaction subsets in which multiple conformers may be relevant, our conformer selection followed one of two routes.

1. Cases with published optimised geometries available: For reactions sourced from prior computational studies that provide optimised geometries, we use the reported conformer as the starting geometry and re-optimised at our level of theory. This applies to the Diels-Alder reactions involving an acyclic diene, the Menschutkin reaction between phenacyl bromide and pyridine, and the Williamson ether synthesis reactions. To validate these starting conformations, we perform an MMFF94 conformer search and confirm that the literature conformer corresponds to a low-energy structure in nearly all cases. The only discrepancies identified are for 2-isopropyl-1,3-butadiene and 2-neopentyl-1,3-butadiene in the Diels-Alder set, where MMFF94 favours an s-trans conformer while a twisted (gauche-like) conformer is used in the reaction set. We attribute this to the twisted conformer being the reaction-ready geometry and the bulky substituent increasing the interconversion barrier, so the reactive conformer can be kinetically relevant even if not the MMFF94 global minimum. For the Oxyma-DIC adduct cyclisation reactions, systematic conformer searches of the reactants and transition states have been reported in our previous publication,[1] and we refer the reader to that work for full details.

2. Cases without published optimised geometries (flexible SN2 substrates and amino-acid activation): For the SN2 reactions of chloropropane, isobutyl chloride, allyl chloride, benzyl chloride, and for amino-acid activation reactions, we generate conformers using an MMFF94 conformer search and selected the lowest-energy MMFF94 conformer as the initial geometry for subsequent QM optimisation.

REFERENCE

1. L. Gui, C. S. Adjiman, A. Galindo, F. B. Sayyed, S. P. Kolis and A. Armstrong, *Ind. Eng. Chem. Res.*, 2023, **62**, 874–880.