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Supplementary Material (ESI) for:

QM/MM simulations for methyl transfer in solution and catalysed by COMT: ensemble-averaging of kinetic isotope effects

Natalia Kanaan, J. Javier Ruiz-Pernía and Ian H. Williams*

Details of the Averaged Kinetic Isotope Effect (<KIE>) Method.

Initially we perform molecular dynamics (MD) simulations with umbrella sampling in overlapping windows along a distinguished coordinate for the reaction at the desired temperature and compute a potential of mean force (PMF). The distinguished coordinate is the difference of distances $d_{OC} - d_{CS}$ from the carbon of the transferring methyl group to, respectively, the oxygen of the nucleophile and the sulfur of the nuclefuge. At the free-energy minimum (RC) and maximum (TS) of the PMF, we then optimize to well characterized stationary points in the condensed system by means of the GRACE algorithm as implemented locally within the DYNAMO molecular dynamics library (M. J. Field *et al. J.Comput. Chem*., 2000, **21**, 1088).

Next, from these localized structures several QM/MM molecular dynamics simulations are run (one from the RC and another from the TS) in order to let the system explore a representative number of configurations (Figure 1). The simulations are carried out under NVT conditions (corresponding to the canonical ensemble) using a time step of 1.0 fs for the duration of 1.0 ns. The reactant-state trajectory is completely unconstrained, but the transition-state trajectory is subject to an umbrella constraint to prevent the system collapsing into either the reactant or product valleys.

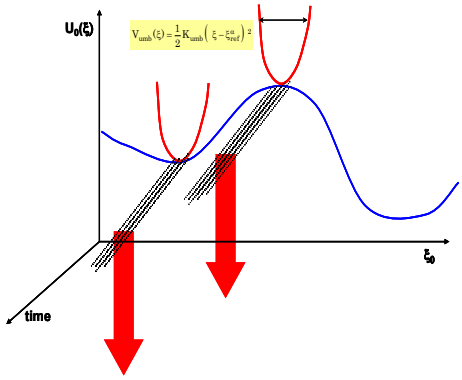

Fig 1. Molecular Dynamics simulations from the localized structures and collection of the structures.

From each of the trajectories (RC and TS) a 100 "snapshot" structures are collected at intervals of 10 ps. This interval is more than sufficient to ensure that the structures are independent from a statistical point of view. Then, for each RC and TS snapshot structure, the geometrical positions of all atoms are frozen except for those of the substrate and the solvent molecules in the first solvation shell, and a new stationary point is determined by constrained optimization to a local RC or TS. The hessian of the flexible part (solute and first solvation shell) is then used in the <KIE> calculation. The first solvation shell is defined to include for each structure all solvent molecules (between 7 and 12 in number) having any atom within 2.8 Å of any solute atom. Provided that each MD trajectory is thermally equilibrated, the collection of snapshots should

correspond approximately to a Boltzmann distribution of energies. Just as the reactant-state and transition state MD trajectories are completely independent, so the collections of RC and TS snapshot structures are completely independent of each other. We do not consider pathways (*e.g.* intrinsic reaction coordinates) that connect particular RC snapshots with particular TS snapshots.

In principle the average KIE could be evaluated as the ratio of averaged partition functions for the isotopically substituted reactant state and transition state; *i.e.*

$$\langle KIE \rangle = (\langle Q_T^H \rangle / \langle Q_R^H \rangle) / (\langle Q_T^D \rangle / \langle Q_R^D \rangle)$$

However, in practice this approach is not compatible with the method described above because the number of molecules in the first solvation shell is not constant for all individual local RC and TS snapshots.

Instead, <KIE> is evaluated by consideration of every possible combination of RC and TS snapshots (Figure 2). The hessians for snapshot RC_i and TS_j are used to compute an individual KIE_{ij} by means of standard semi-classical harmonic oscillator, rigid-rotor approximations using the CAMISO program (IHW, *Chem. Phys. Lett.* 1982, **88**, 462-466, *J. Mol. Struct. (THEOCHEM)*, 1983, **11**, 275-284).

$$KIE_{ij} = (Q_{TS_j}^H / Q_{RC_i}^H) / (Q_{TS_j}^D / Q_{RC_i}^D)$$

In this expression, differences in the number of first-solvation-shell molecules between RC and TS cancel out. The value of <KIE> is obtained as the simple unweighted arithmetic mean over all values of KIE_{ij}., *i.e.*

$$\langle KIE \rangle = (1 / N_{RC} N_{TS}) \sum KIE_{ij}$$

where N_{RC} and N_{TS} are the numbers of RC and TS snapshots. It is not appropriate to employ, for example, a Boltzmann weighting to the individual KIE_{ij} values because the local optimization of the flexible region within the frozen environment leads to structures whose energies have an unclear meaning: certainly they are no longer related to the original (approximate) Boltzmann distribution. We therefore consider that the simple unweighted arithmetic mean is the best way to evaluate an average KIE from the data we have obtained.

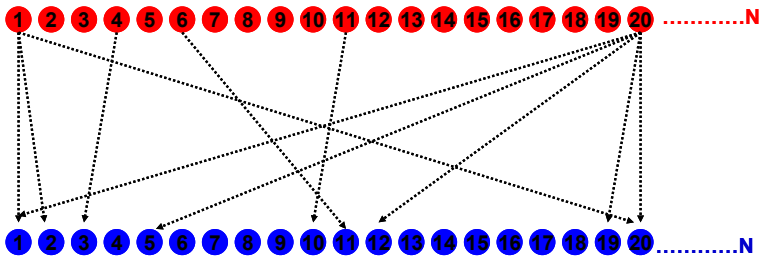

Fig 2. Statistical combination for obtaining the averaged KIE. In red the N (one hundred) characterized Reactant Structures and in blue the N (one hundred) characterized Transition Structures.