Alkene Hydroboration: Hot Intermediates That React While They Are Cooling

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Abstract: Non-TST behavior has recently attracted a great deal of attention. If such behavior is general, then the standard way in which synthetic chemists rationalize and predict reactivity and selectivity would be at least partially invalid. The work in this article was inspired by recent results which highlighted a departure from the predictions of TST for rationalization of the regiochemical outcome of the hydroboration reaction mechanism, suggesting that the isomeric product ratios arise because of nonstatistical dynamical effects (*J. Am. Chem. Soc.* **2009**, *131*, 3130−3131). We suggest, based on new calculations using a weak collision RRKM-Master Equation (ME) model, an alternative interpretation of the experimental results which preserves a statistical reaction model. While it is a common assumption that all intermediates and transition states along the reaction path are in thermal equilibrium with solvent, our ME results show that hot intermediates may react while they are undergoing stepwise relaxation through weak collisions, even in solution. To our knowledge, this work represents the first application of master equation methodology to a solution phase thermal reaction in organic chemistry that cannot be otherwise explained using conventional TST. Explicit modeling of solvent and solute dynamics is often prohibitively expensive; however, the master equation offers a computationally tractable model with considerable predictive power that may be utilized to investigate whether stepwise collisional relaxation is prevalent in other polyatomic systems.

When discussing reaction mechanisms in solution, it is a common assumption that all intermediates and transition states along the reaction path are in thermal equilibrium with solvent, with statistical energy distributions. Under these conditions, canonical transition state theory (TST) can be invoked, and rates calculated or estimated using free energies of activation, which themselves can be either calculated or estimated based on steric or electronic arguments. Yet in some cases, TST has been shown to fail to reproduce experimental results, and this has been ascribed to a breakdown of energy delocalization in the transition state and to consequent dynamical effects.[1] Oyola and Singleton recently used this explanation when they found that TST does not reproduce their observed anti-Markovnikov product yield in the hydroboration of propene.[1a] We investigate an alternative, statistical model for hydroboration by examining the competition between the reaction of a hot intermediate and its energy relaxation by collision with the solvent, using statistical RRKM theory in conjunction with a weak collision master equation model.

Experimentally, Oyola and Singleton[1a] observed an anti-Markovnikov to Markovnikov product yield ratio of 9:1. The regiochemical preference for "anti-Markovnikov" addition of borane to nonsymmetrical alkenes has classically been argued on the basis of the relative free energies of the transition states,[2] a notion supported qualitatively by theoretical calculations.[3] Oyola and Singleton used high quality electronic structure theory calculations to identify the key stationary points (Figure 1).
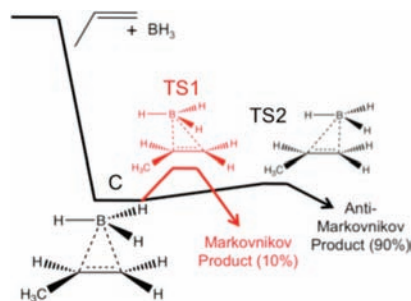

Figure 1. Schematic of kinetically significant stationary points and corresponding experimental selectivity reported by Oyola and Singleton.

Canonical TST calculations based on these stationary points predict a yield ratio of 98−99:1. On-the-fly *ab initio* molecular dynamics simulations provided a yield ratio of 87:13. Oyola and Singleton attributed the selectivity to the combination of a 'direct-trajectory' stage with low selectivity, an RRKM stage with medium selectivity, and a thermally equilibrated stage, developing over several picoseconds. Zheng et al.[4] quantitatively rationalized the Oyola and Singleton results with a model that divides the reaction into 'direct' (66%) and 'indirect' (34%) components. The product ratio for the direct component was calculated by statistical or nonstatistical phase space theory while the product ratio for the indirect component was calculated from TST.

The stochastic energy grained master equation (ME) has been described in detail previously.[5] It has been utilized to understand pressure and temperature dependences for a range of gas phase systems and to model experimental measurements in solution phase organic photochemistry.[6] The important features of the ME model are schematically illustrated in Figure 2 for a simple system wherein reactants A and B, initially in a thermalized Boltzmann distribution, combine to yield an intermediate **C** via **TSa**. From **C**, two respective product channels, **P1** and **P2**, are accessible via **TS1** and **TS2**. The starting point of the ME model is to partition the rovibrational state space of each intermediate and reactant into microcanonical energy bundles, or grains. Using statistical models for describing transition probabilities of (1) conversion between reactants, intermediates, and products and (2) stepwise collisional energy transfer in the presence of a heat bath, such as the solvent, the time dependent populations in each of the energy grains may then be obtained by solving a set of coupled first-order differential equations.

To obtain the results presented herein, we have utilized microcanonical TST (i.e., RRKM theory) to calculate energy resolved rate coefficients, $k(E)$. Collisional energy transfer rate coefficients
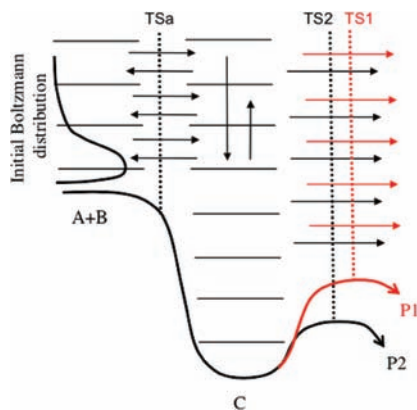
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Figure 2. Schematic of the energy grained ME model.

Figure 3. ME calculated anti-Markovnikov 298 and 368 K product yield via **TS1** as a function of collision frequency at different $\langle \Delta E \rangle_d$ values (cm^{-1}).

were calculated using the exponential down model. Despite some shortcomings,[5e,f] this model is used extensively in gas phase reactions, where the average energy loss in a collision, $\langle \Delta E \rangle_d$, for colliders such as He, N$_2$, and O$_2$, ranges from 100 to 500 cm^{-1}; higher values are found for polyatomic colliders. $k(E)$ values for product formation from **C** via **TS1** and **TS2** were calculated using a harmonic oscillator asymmetric rotor approximation in conjunction with the Beyer–Swinehart state counting algorithm. Frequencies and rotational constants were obtained by reoptimizing the B3LYP/6-31G* geometries of Oyola and Singleton. For stationary point energies, we used the results of their CCSD(T)/avqz calculations.[1a] The reactants were represented using a Boltzmann distribution at 298 K, in which the combined density of states (DOS) for BH$_3$ and propene were obtained through convolution of the individual molecular DOS. All of the calculations were carried out using our freely available, open source software package MESMER.[7]

The left-hand panel of Figure 3 shows a plot of the selectivity via **TS2** (leading to the anti-Markovnikov product) at 298 K as a function of collision frequency and $\langle \Delta E \rangle_d$. In the limit of very high collision frequencies, intermediate **C** is fully relaxed to a Boltzmann distribution before reacting via **TS1** or **TS2**, and the 98.8% selectivity of the anti-Markovnikov product is identical to that obtained using canonical TST. In the limit of very low collision frequencies, reaction is much faster than collisional relaxation of **C**, resulting in 87% anti-Markovnikov product, matching the value obtained in zero pressure gas phase direct dynamics simulations.[1a] The observed proportion of 90% anti-Markovnikov product at 298 K lies in between these two limits, suggesting some level of intermediate collisional relaxation captured in neither the zero pressure nor canonical TST approach.

The only adjustable parameters within the ME model are $\langle \Delta E \rangle_d$ and the collision frequency. While applying isolated binary collision models to the solution phase remains controversial, recent work has shown them to be accurate on short time scales.[8] Experimental studies of solution phase intermolecular vibrational relaxation[9] show fast intermolecular energy transfer to the solvent, consistent with binary 'collision frequencies' of 3–10 ps^{-1}. Over this range of collision frequencies, along with values of E_d (900−1100 cm^{-1}) which are broadly consistent with gas phase studies, the left-hand panel of Figure 3 shows that the ME results are in good agreement with the 298 K experimental yield of 0.90.

Oyola and Singleton also experimentally probed the effect of temperature upon regioselectivity. The right-hand panel of Figure 3 shows the yield of anti-Markovnikov product at 368 K over the same $\langle \Delta E \rangle_d$ range, and the same range of solution phase 'collision frequencies' are highlighted. Within the specified window of collision frequencies, the 368 K selectivity at corresponding values
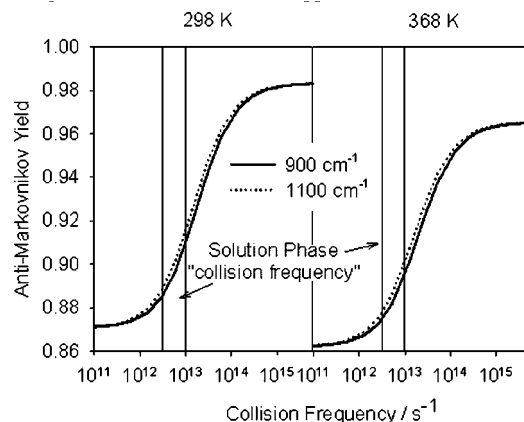
of $\langle \Delta E \rangle_d$ are 1.1−1.5% lower than the 298 K selectivity, in good agreement with the 1.2% decrease in selectivity at 368 K reported by Oyola and Singleton.

This work presents (to our knowledge) the first application of master equation methodology to a thermal solution phase reaction in organic chemistry, though similar 'energy diffusion' effects have previously been invoked to explain reactivity.[10] The relaxation of hot intermediates is a nonequilibrium process where temperature is ill-defined; however, the ME approach that we have utilized herein is fundamentally statistical insofar as it relies on RRKM theory. Oyola and Singleton's experimental measurements are clearly incompatible with canonical TST, suggesting a role for nonstatistical dynamics. While such effects are important in some reactions,[1] the exact extent of their contribution in hydroboration remains unknown. The present ME approach also accounts very well for experiment and, for the first time, the temperature dependence of the product ratio. Oyola and Singleton inferred their non-RRKM 'direct trajectory stage' from the observation that some trajectories afforded product quickly with low selectivity, but this is a small proportion of the overall reaction. Standard models used to account for reactivity and selectivity may therefore remain quite broadly applicable with the caveat that the stepwise collisional relaxation of hot intermediates must not be treated as taking place instantaneously, even in solution.

Given the present interest in extending detailed gas phase models of chemical reactivity to solution phase systems, it will be of interest to examine whether other reactions within solution phase organic chemistry exhibit a similar dependence on stepwise collisional relaxation. Prime targets for further investigation should probably also involve formation of a 'hot' intermediate that may react via competing channels over low barriers.

Supporting Information Available: Includes further details of the calculations regarding (a) software, (b) the EGME model, and (c) geometries, energies, and frequencies used in the ME. This material is available free of charge via the Internet at http://pubs.acs.org.

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