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A Minimum Free Energy Reaction Path for the E2 Reaction between Fluoroethane and a Fluoride Ion

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Accurate prediction of the key parameters for chemical reaction, such as the mechanism and the free-energy profile, remains an important challenge not only for enzyme catalysis¹ but also for seemingly simple reactions such as the prototype E2 reaction. Although both the base-induced 1,2-elimination (E2) reaction and the bimolecular nucleophilic substitution (S_N2) reaction are fundamental processes in organic chemistry, the E2 reaction² has been the subject of relatively few theoretical studies. One of the reasons for this apparent lack of attention is its relatively complex mechanism, which involves the making or breaking of three bonds (four if we count the C=C bond) in a not necessarily synchronous manner. This leads to a spectrum of possible transition states schematically shown in Figure 1. On one side is the unimolecular elimination (E1-like) limit leading to a metastable carbocation as the leaving group, L, departs in the first step. On the other side is the E1cb-like limit in which the attacking base, A[−], grabs an acidic β-hydrogen in the first step leading to a metastable anionic “conjugate base” intermediate.

Due to the complexity of the E2 reaction, localizing the transition-state structure and finding the minimal energy path (e.g., the intrinsic reaction coordinate³) are difficult tasks with standard quantum chemistry methods, based e.g. on a saddle point search.⁴ Moreover, computation of the reaction free-energy profile is very cumbersome with constrained molecular dynamics (MD) and umbrella sampling, because a single reaction coordinate is not known a priori.⁵

In the present study, we explicitly consider the three relevant bonds that are broken and formed during the E2 reaction between F[−] and CH₃CH₂F and compute the three dimensional (3D) free-energy surface with the “hills method” described in ref 6 at a temperature of 300 K. Within this 3D free-energy surface we find the lowest free-energy path connecting the reactant minimum to the product minimum. In a second step, we use the free energy along this path, ξ, as the biasing potential to perform a (now one-dimensional) umbrella sampling⁷ to accurately calculate the free-energy profile along ξ. Previously, people have used (zero-Kelvin) minimum energy paths to perform umbrella sampling to access the entropic contributions to the reaction barrier.⁸

Choosing coordination numbers (cn) instead of bond distances (r) for three collective variables avoids predetermining the leaving β-proton. The coordination number is defined as $cn_{ab} = \sum_b (1 - (r_{ab}/r_c)^6) / (1 - (r_{ab}/r_c)^{12})$ and estimates the number of atoms *b* within a cutoff radius *r_c* of atom *a*.⁹ During an MD simulation, these would normally fluctuate around their equilibrium values, $cn(F_L - C) = 1$, $cn(F_A - H) = 0$ and $cn(C_\beta - H) = 3$ in the reactant state (or the values 0, 1, 2 in the product state, HF_A + CH₂=CH₂ + F_L[−]).

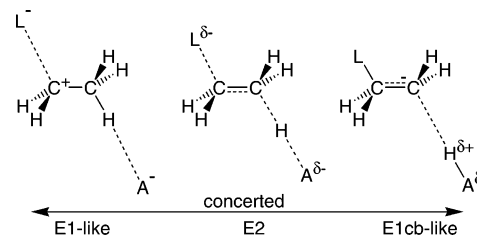


Figure 1. Mechanistic spectrum of possible transition states of the bimolecular elimination reaction (L = leaving group, A = attacking base).

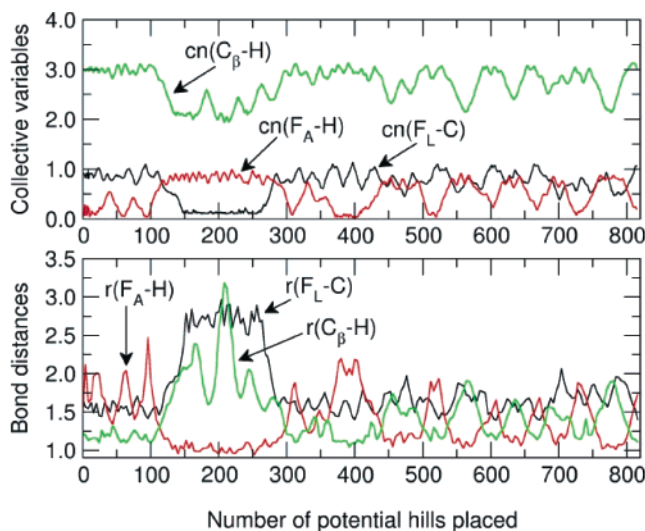


Figure 2. Upper graph: the collective variables, *cn*. Lower graph: selected distances, *r*, as a function of the number of hills that have been added to the system. The stride between subsequent hills is 100 MD steps (= 10 fs).

The transition-state barrier is sufficiently high to prohibit the observation of the spontaneous reaction within a standard Car–Parrinello MD simulation. With the hills method, however, a series of small repulsive Gaussian potentials (hills) centered on the current values of the collective variables are added during the dynamics, discouraging the system from revisiting points in configurational space. In this manner, a history-dependent multidimensional biasing potential is gradually constructed.

Figure 2 shows the evolution of the three *cn* variables while adding Gaussian hills with a height of 0.2 kcal/mol. After roughly 100 hills, the reactant well is apparently filled, and the system escapes into the product well, which is subsequently filled after a total of 300 hills. After that, the system travels barrier-free back and forth, but also spends much of its time in other local minima (configurations with either only the F_L or only the F_AH groups leaving while the other part is still bonded to the alkane).

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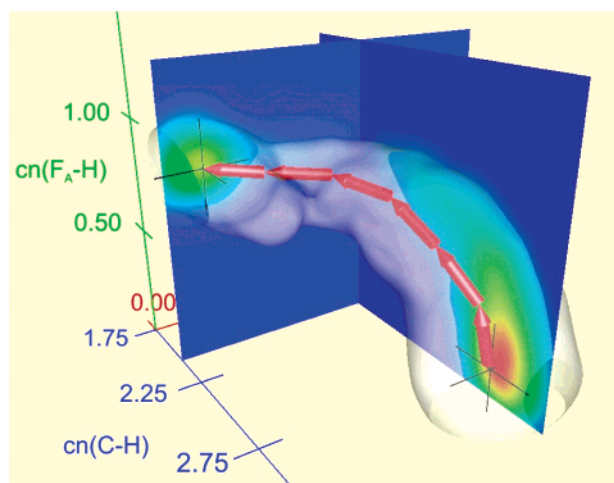


Figure 3. Three dimensional free-energy surface of the E2 reaction with on the bottom-right the reactant well and on the top-left the product well (the minima are located at the black crosses). The red arrows, which depict the lowest free-energy reaction path, ξ , yield the reaction mechanism.

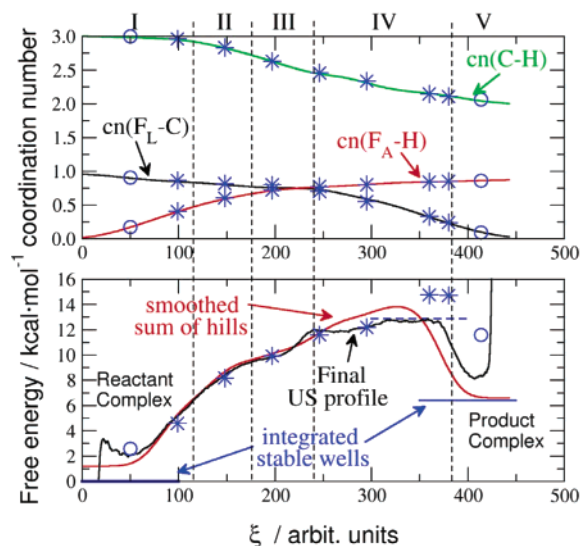


Figure 4. Collective variables (upper graph) and the reaction free-energy profiles (lower graph) obtained with the hills method (red curve) and with umbrella sampling (black curve) as a function of the reaction coordinate, ξ . Circles and crosses denote total and constrained geometry optimization (0 K) energies, respectively.

Figure 3 shows the resulting 3D free-energy surface for the elimination reaction, in which we locate the lowest free-energy path, ξ , from the reactant minimum to the product minimum (red arrows). The free energy along this path, $V_{\text{umbr}}(\xi)$ is shown in Figure 4 by the red curve. $V_{\text{umbr}}(\xi)$ is used as a bias potential to perform the umbrella sampling simulation.⁹ The minor discrepancy between the curves of $V_{\text{umbr}}(\xi)$ and the umbrella sampling result in Figure 4, shows that indeed the hills method already gives a rather good estimate of the free-energy profile after only sampling two barrier crossings (see Figure 2).

The estimate of the free energies of the stable reactant complex and product complex states (horizontal blue lines) is obtained by fitting these well regions by a parabola and integrating over the parabola. Taking the reactant complex free energy as the zero of the free-energy scale, we find a reaction free energy of 6.4 kcal/mol and a free-energy barrier of 12.9 kcal/mol. Comparison with the zero-Kelvin reaction energy (9.0 kcal/mol) and barrier (12.2 kcal/mol; circles and crosses in Figure 4), shows that the entropic effect contributes mostly to the formation of the product complex,

as expected for a system that transforms from two to three weakly bound particles. The upper graph shows the collective variables as a function of the reaction coordinate ξ .

Combining the two graphs in Figure 4, we can identify five regions marked I to V. Region I is the reactant complex well region, with only the attacking base F_A^- approaching. In region II, a β -proton starts to leave, and in region III HF_A is formed which leaves together with the leaving group F_L^- , the latter causing the bump in the profile. Then in region IV, there is a plateau in the profile where F_L^- moves around C_α and finally forms a weak bond with an ethylene hydrogen in the product complex well which marks region V.

Summarizing, we have introduced a novel strategy, combining the multidimensional hills method with umbrella sampling, to compute the free-energy profile and the lowest free-energy reaction path for a prototype binuclear elimination reaction. This should provide a very powerful tool to study intrinsically multidimensional activated processes, such as complex chemical reactions and nucleation. The true strength of our method will become evident in the study of reactions in aqueous solution, which requires additional collective variables that describe the changing solvation of the attacking and leaving groups during these reactions.

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Supporting Information Available: Computational details of the simulations, justification of the coordination number variables, umbrella sampling probability distributions, optimized structures along ξ compared to MP2 calculations and plots of the changing HOMO and LUMO along ξ . This material is available free of charge via the Internet at <http://pubs.acs.org>.

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