

Metadynamics of polyalcohol dehydration in water

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Introduction. The best selection of the solvent is an important challenge in the design of “Green Chemistry” synthesis [1]. Since water is non-toxic, easily tractable due to its non-volatility, and a chemically abundant substance, the stereoselective organic reactions in aqueous solutions is an appropriate choice in terms of green chemistry. In this direction, the dehydration of polyalcohols are one of the prototypical organic reactions taking place in water. This reaction is sensitive to thermodynamic environments, such as the temperature and the pressure, as well as the acidity [2-4]. A particular example of dehydration of polyalcohols is 2,5-hexanediol. Usually, this dehydration takes place with strong acids, but the stereoselectivity can be lost in function of the acid used [3]. Recently, high-temperature and high-pressure conditions with a mild acid have been reported to be highly stereoselective [4]. These experimental findings suggest different reaction mechanisms, i.e. the stereoselective SN₂ reaction via the concerted process between the creation of OC bond and the breaking of CO bond, or the nonselective SN₁ reaction via the carbocation intermediate on breaking the CO bond first (Figure 1). The aim of the present work is to clarify the complete mechanism of the 2,5-hexanediol in acidic water from the theoretical view point and to understand the role of the water. For this purpose, the free energy landscape of the reaction in water was obtained with *ab initio* Car-Parrinello metadynamics simulation [6]. Here, *ab initio* string method [5] and metadynamics simulation of a cluster model was used to select and test the appropriate reaction coordinates for this reaction.

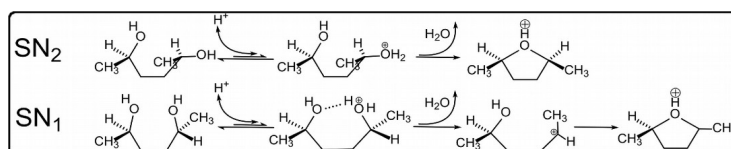


Figure 1. Reaction mechanisms of 2,5-hexanediol

Method. Metadynamics[6] is a general method to obtain the free energy landscape of complex many-body systems along a set of reaction coordinates, called collective variables (CV). Based on the Lagrangian expressed as

$$L = L_{\text{sys}} + \sum_{\alpha=1}^{N_s} \frac{1}{2} \mu_{\alpha} \dot{s}_{\alpha}(t)^2 - \sum_{\alpha=1}^{N_s} \frac{1}{2} k_{\alpha} [S_{\alpha}(R(t)) - s_{\alpha}(t)]^2 + V(t, [s]) \quad (1)$$

one solves the coupled equations of motion between the system of interest and a dynamic variable that travel within the space of CV's. The first term of the equation gives the Lagrangian of the system (L_{sys}). The second term is the kinetic energy of the CV's. By setting large CV masses, the stiff harmonic potential in the second term is able to drag the reaction coordinates of the system adiabatically in accordance with the CV's. A unique feature of metadynamics is the third term, $V(t, [s])$. This makes the CV's move on the bias potential, i.e. the sum of Gaussian hills whose centers are added along the history of its own trajectory. In this way, the metadynamics efficiently explores the space of reaction coordinates until the bias potential completely fill the reactant well. The bias potential thus obtained is approximately the negative sign of the free energy surface.

String method [5] is an efficient algorithm to find the minimum energy path (MEP, or intrinsic reaction coordinate) that interconnects the reactant and the product. The path is described in terms of discrete “images” along the path. From an initial guess, the images are optimized by iterating the two-step procedure: A steepest descent optimization for all images (step 1) and the rearrangement to make all neighboring images equidistant in mass weighted coordinates (step 2).

Results. Before running metadynamics simulations, the string method was used to obtain the MEP's of the SN₁ and SN₂ mechanisms. There, we used a model system with 2,5-hexanediol, six water molecules and an extra proton. The MEP was calculated with two different *ab initio* methods, MP2/def2-SV(P) and PBE/def2-SV(P), using TURBOMOLE [7]. The results for the SN₂ are in Figure 2 and 3. The activation energies of the two mechanisms have a large difference, being the SN₂ more favorable (SN₂=39 kcal/mol, SN₁=62 kcal/mol at PBE/def2-SV(P) level). However, the deprotonation

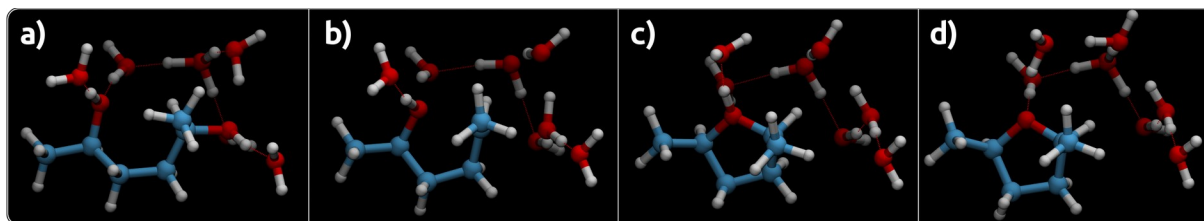


Figure 2. Structures obtained with string method for SN₂ mechanism: reactive (a), TS (b), intermediate (c) and product (d).

mechanisms are similar: the protonated product is meta-stable intermediate (point 50 in Figure 3). From the reactant to TS the protonated intermediate is not observed within this resolution. On the other hand, the MEP gives an important information on the necessary CV's for the reaction. First, the main difference between SN₁ and SN₂ is the dihedral angle of the outgoing alcohol. While in SN₁ the reaction proceeds at $\sim 90^\circ$, in SN₂ it takes place at $\sim 175^\circ$. Later, the protonation and the change in the distance of the alcohols and the reactive carbon are the principal changes for the reaction (Figure 2). For this reason, three CV's were selected in the metadynamics: the difference in the OC and CO distances, the proton coordination number of the oxygen atom of the outgoing alcohol and the dihedral angle. These were checked with the model system in *ab initio* metadynamics, using TURBOMOLE for the potential energy (PBE/def2-SV(P)), which resulted in a free energy barrier of 35 kcal/mol similar to the result of string method.

Next, *ab initio* metadynamics has been carried out with CPMD[6] at 523 K for a system composed of a hexandiol molecule, 70 water molecules and a proton in a cubic box with the side length of 14.93 Å, to mimic the experiments performed in mild acidic solution at 523 K and 20 MPa [4]. The calculation is based on PBE functional and the ultrasoft pseudopotential with the plane wave cutoff of 25.0 Ryd. The results show that the meta-stable protonated alcohol is formed before the main reaction occurs at around 20 kcal/mol. Later the concerted process occurs, forming the meta-stable protonated cyclic ether, in a similar way as in the string method and the previous metadynamics with the model system. The water environment is fundamental in the bond breaking.

References.

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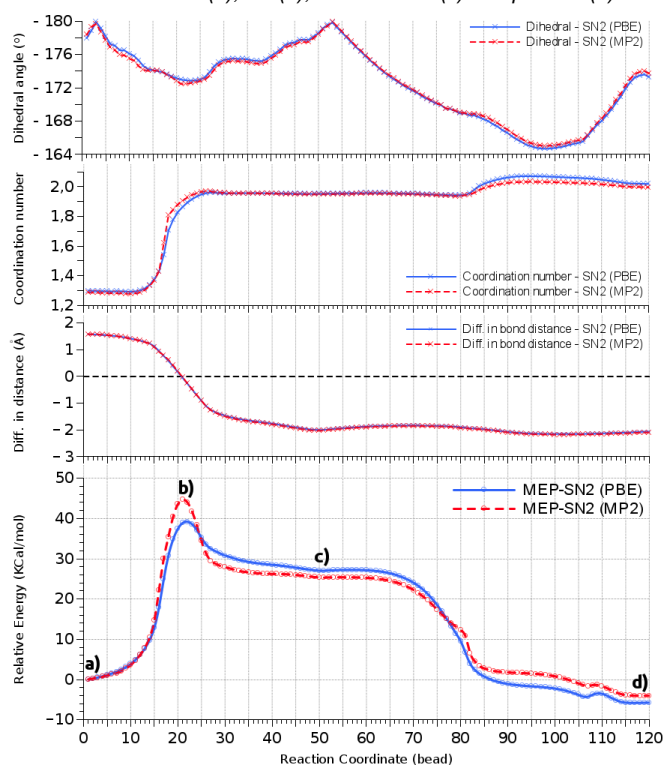


Figure 3. The evolution of the energy and the 3 CV's for the SN₂ mechanism obtained by the string method with two different *ab initio* methods. The structures of Figure 2 are marked in the energy profile.

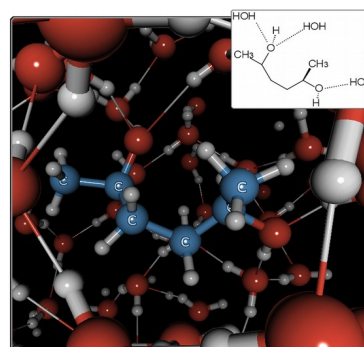


Figure 4. Snapshot and scheme of metadynamics of dehydration.

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