



Research paper

Proton transfer pathways in an aspartate-water cluster sampled by a network of discrete states



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ABSTRACT

Proton transfer reactions are complex transitions due to the size and flexibility of the hydrogen-bonded networks along which the protons may “hop”. The combination of molecular dynamics based sampling of water positions and orientations with direct sampling of proton positions is an efficient way to capture the interplay of these degrees of freedom in a transition network. The energetically most favourable pathway in the proton transfer network computed for an aspartate-water cluster shows the pre-orientation of water molecules and aspartate side chains to be a pre-requisite for the subsequent concerted proton transfer to the product state.

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1. Introduction

Proton transfer reactions are ubiquitous processes in chemistry such as acid-base reactions, and in biology, e.g. the light activated proton pumping of bacteriorhodopsin [1], the oxidative phosphorylation to produce adenosine triphosphate (ATP) in the respiratory chain [2,3], or the photosynthetic water oxidation [4,5]. Proton transfer is also crucial for bacterial motions [6], the human immune response [7], and antibiotics as gramicidin [8]. Insights into the mechanisms of these reactions could be beneficial to the design of fuel cells [9] or bioprotonic devices [10].

In 1806, Grotthuss proposed a mechanism for the electrical decomposition of water, stating that in an electromotive apparatus only water molecules at the tip of the conducting wires are decomposed, while all intermediate water molecules, although collectively changing their composing principles, still remain to be water [11]. Subsequently, conceptual models to understand the properties of water and its ions were developed in the early 20th century [12,13]. Detailed insight into the proton transfer mechanism, however, was only gained about 50 years later, when *ab initio* molecular dynamics (aiMD) simulations [14–17] as well as the force-field based empirical valence bond approach [18–20] were applied. The essence of all these investigations is today known as the Grotthuss mechanism, proclaiming that protons “hop” stepwise between neighbouring water molecules by exchanging covalent and hydrogen bonds connecting the proton to the donor or

acceptor oxygen respectively [21,22]. Each of these “hops” has to be followed by a reorganisation of the water molecules surrounding the proton-receiving water molecule, resulting in a 1–2 ps time scale for a single proton transfer step. Furthermore, according to Onsager the proton donor or acceptor does not have to be a water molecule, but could in principle be a polar (titratable) amino acid residue (e.g. aspartate) of a protein [23].

An alternative, rather coherent proton transfer mechanism, was suggested by Eigen in 1964 [24]. Here, protons could de-localise over extended water chains, subsequently called proton wires by Nagle and Morowitz [25], involving several simultaneous proton “hops”. Such mechanisms were indeed observed in linear water chains inside channels of proton conducting proteins [26] or carbon nanotubes [27,28]. Furthermore, spectroscopic experiments concerning acid-base reactions in water and ice seem to indicate the formation of transient proton wires, which allow fast proton transfer reactions [29,30]. Rearrangement of a second solvation shell facilitating proton transfer has also been observed in network analyses of proton transfer simulations by multi-state empirical valence bond molecular dynamics simulations [31]. Using aiMD Parrinello and coworkers [32] recently investigated the neutralisation of hydronium and hydroxide ions in water, revealing a collective compression and concerted motion of the proton wire connecting both ions. Furthermore, they suggested that proton transfer in water is a combination of active periods, during which the charge is translocated by concerted motions along proton wires, thereby covering 6–8 Å on a sub-picosecond timescale, and resting periods, in which the protons only “hop” Grotthuss-like to the next water molecule [33].

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The current investigations of proton transfer reactions in solution or in proteins often struggle with the sheer complexity of the problem, i.e. spatially, due to the highly connected hydrogen bond networks in water, as well as temporal, due to different time scales necessary for proton transfer events along proton wires or single Grotthus-like hops. To circumvent the need for a full quantum mechanically (QM) treatment of the whole system, methods have been developed that estimate the probability for a proton transfer between a donor and acceptor pair during an otherwise classical molecular dynamics simulation and either switch to the new protonation state [34], use multi-state valence-bond approaches [18,35,36] or the adjustment of the QM subsystem “on-the-fly” to enable computation of the proton transfer step [37]. Enhancing simulations by “driving” an excess proton can overcome the time scale problem but introduces a bias in the proton transfer pathway. For an unbiased understanding of proton transfer events, sampling of as many pathways as possible with as little pre-selection of pathways (or reaction coordinates) is, however, desirable.

This can be realised by sampling discrete proton transfer pathways between a given pair of end states on a potential energy surface. The discrete path sampling technique was introduced by Wales and coworkers [38,39] and generates a large number of local minima and transition states between them, resulting in a network of connected pathways. A similar method is the Transition Network approach proposed by Noe et al. [40]. The minima used to construct a network can be generated by direct sampling of points on a high-dimensional grid, spanned by either the Cartesian atomic coordinates or internal degrees of freedom of the polyatomic molecular system under investigation. That way, the sampling does not suffer from barriers that are unlikely to be overcome in e.g. a molecular dynamics simulation or the too low acceptance ratio of energetically not favourable structures in Monte-Carlo methods. The difficulty with direct sampling is, however, the large number of minima and transitions that exist on a complex energy surface.

In this work, we therefore employ a combination of direct sampling for degrees of freedom that generate only a low number of states and are likely separated by substantial energy barriers, and molecular dynamics (MD) simulations based sampling for degrees of freedom that can result in a large number of states which are, however, connected by barriers that can be easily overcome. The combination of all states thus sampled and their connections constitutes the transition network on which the energetically most favourable proton transfer pathways are then determined.

In order to validate this combination approach we focus here on a small system (see Methods section) that can be understood as a model for water-filled protein channels and hydrogen-bonded networks in proteins. Such networks are found in e.g. Photosystem II [41], Cytochrome *c* oxidase [42,43], or gramicidin-like channels [8,44,45]. The highly connected hydrogen bond networks in these systems render direct sampling unfeasible due to the prohibitive large number of states to consider. Many of those states, however, are energetically not favourable and therefore irrelevant for the determination of the most probable proton transfer pathways. To explore a large number of pathways so as to reflect the high diversity of proteins, it is important to sample many energetically accessible routes. The transition networks constructed from combined sampling, as presented in this work, allow an efficient and comprehensive sampling of such proton transfer pathways that can be easily applied to more complex protein environments.

2. Methods

Proton transfer pathways were calculated for a model system consisting of thirteen water molecules embedded in a cylinder, one excess proton, and two aspartate-like molecules at either

end of the cylinder that can be understood as a small model system for water-filled protein channels. The aspartate-like molecules consist of a carboxyl group, representing the side chain of aspartate amino acids, and a bulky *t*-butyl-“backbone”, forming the top and bottom of a cylinder that was kept stationary in all simulations. The walls of the cylinder were modelled by a harmonic potential, setting on at 3.0 Å away from the cylindrical axis with a force constant of 500 kcal/mol/Å².

Two configurations with the excess proton located on either of the two aspartate mimics, were prepared as reactant and product state, i.e. end-states of the overall proton transfer reaction (see Fig. 1).

A transition network has the structure of a weighted, undirected graph. To construct the transition network for sampling proton transfer pathways, nodes were generated from initial structures, different in protonation state, dihedral conformation of the aspartate mimics, and water positions and orientations. To this end, two approaches were combined.

In the first, direct sampling approach, protonation states were sampled by placing the excess proton on either of the water molecules or on the carboxyl groups of the aspartate mimics, resulting in 17 different protonation states. For each of these structures, the side chain dihedral angle of the aspartate mimics was varied with a step size of 45°.

In the second approach, the set of configurations generated by this direct sampling was augmented by samples taken from short (1 ns) classical MD simulations, carried out for the thirteen different water protonation states (for details see supplementary information). Snapshots were saved at 1 ps intervals, thereby generating 1000 configurations per water protonation state.

In an additional control, we applied direct sampling of side chain rotations, proton positions, and the position of the water molecule, carrying the excess proton. For the latter the respective water molecule was displaced by 2 Å forward and backward, respectively, in all three directions of Cartesian space.

All configurations were then subjected to an energy minimisation with a convergence criterion of 0.001 kcal/mol/Å using the semi-empirical OM2 method [46] as energy function for QM optimisations. An evaluation of the OM2 method for computation of proton transfer along water molecules between two aspartate side chains is provided as supplementary information.

After minimisation, the optimised geometries were assigned to a network node, i.e. a discrete state. The assignment was based on the dihedral angle of the carboxylic side chains, the protonation state, i.e. the location of the excess proton on either a water molecule or an aspartate mimic, and a “water pattern”, characterised by the displacement and rotation of water molecules with the reactant state as reference. Note that also proton holes can be identified in the assignment but do not occur in the nodes of the present transition networks.

Assigned nodes are labelled as SC0.SC1.Wi.P. Here SC0 and SC1 correspond to the number of dihedral steps of the side chain of molecule 0 and molecule 1, Asp1 and Asp2, respectively. Due to their symmetry, a torsion of the side chains by 180° (four steps) results in the initial state and is hence treated as zero rotation. For the same reason, a (backward) rotation of three steps corresponds to a (forward) rotation by one step.

Wi is the *i*th water pattern of all thirteen water molecules. Different water patterns, that is different orientations of the water molecules, can be achieved by translation or rotation of a single or several water molecules, discretised in displacement steps of 2 Å for translation and 22.5° for rotation, respectively. The complete labelling of a water pattern consists of 78 digits in total. These are three digits for the number of translation steps in *x*, *y*, and *z*-direction, respectively, and three digits for the rotation steps around the three principal axes, respectively, for each water

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