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Molecular dynamics simulations of cyclodextrin–cumene hydroperoxide complexes in water

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ABSTRACT

It has well been known that glutathione peroxidase (GPX) mimics based on cyclodextrins (CDs) have great selectivity to hydroperoxide substrates and the preferred hydroperoxide is the aromatic cumene hydroperoxide (CuOOH). The reduction of CuOOH often proceeds much faster than reduction of the more hydrophilic hydroperoxides. The purpose of this study is to provide theoretical evidence of this substrate specificity mechanism. In this contribution, we report our investigation on the intermolecular interaction and modeling calculations on the complexes of three cyclodextrins, viz. α-, β-, and γ-CD, with CuOOH by means of computational molecular dynamics (MD) simulations. The free energy profile along the ordering parameter, association constant, and the corresponding association free energy, as well as the most important interactions which contribute to their stability were studied in detail. The results show that stable inclusion complexes only form when both the host and guest molecules experience a significant decrease in the complexing potential. Among the three CDs, β-CD exhibits the highest propensity to associate with CuOOH. Ranking for binding CuOOH, viz. β-CD > γ-CD > α-CD.

1. Introduction

Native cyclodextrins are cyclic oligosaccharides formed by six or more D-glucopyranose residues attached by α-1,4-linkages in a cyclic array that result from the enzymatic degradation of starch [1]. The most current cyclodextrins contain six, seven, or eight glucose residues and are named α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD), respectively [2]. The steric arrangement of glucose units in the cyclodextrin molecule results in the shape of a hollow truncated cone with a hydrophilic outside surface, which makes them relatively soluble in water, and a hydrophobic internal cavity, which allows them to host hydrophobic molecules in its cavity giving rise to inclusion complexes [3]. Generally, native cyclodextrins bind to a typical substrate in water with binding constants of 10^2–10^4 M^{-1}. In the case of cyclodextrin dimmer, the best substrates can achieve a binding constant exceeding 10^{11} M^{-1}, and is comparable to the binding constants of very strong antibodies [4]. For this reason, cyclodextrins have extensively been exploited as enzyme models and molecular receptors [5].

Glutathione peroxidase (GPX, EC 1.11.1.9), one of the major mammalian selenoenzymes, protects various organisms from oxidative stress by catalyzing the reduction of hydroperoxides by using thiol cofactors [6]. Because many diseases are related to oxidative stress, GPX is an ancient foe of many diseases and regarded as one of the most important antioxidant enzymes in living organisms. Recently, a series of cyclodextrins and their derivatives have been developed as GPx mimics [7–11]. One of the most notable results from these reports is the catalytic specificity for reduction of aryl cumene hydroperoxide (CuOOH) [8–10,12–16]. The reduction of lipophilic CuOOH often proceeds much faster than reduction of the more hydrophilic hydroperoxides. However, this substrate specificity mechanism of these mimics has rarely been investigated substantially [17–19].

Classical molecular-dynamics (MD) simulations are an important computational tool with several applications in the study of the host–guest-type compounds involving CD [20]. Because theory can help rationalize experimental observation, provide information not amenable to experimentation, and even make predictions concerning the outcome of future experiments, it is becoming more widely accepted by experimental scientists as a valuable adjunct to their existing studies [21,22]. In this contribution, we report our investigation on the intermolecular interaction and modeling calculations on the complexes of three cyclodextrins, viz. α-, β-, and γ-CD, with CuOOH by means of computational molecular dynamics (MD) simulations. The free energy profile along the ordering parameter, association constant, and the corresponding association free energy, as well as the most important interactions which contribute to their stability were studied in detail.

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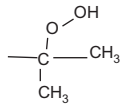
2. Computational method

2.1. Setup of the simulation boxes

The initial coordinates of α-, β-, and γ-CD were taken from three-dimensional crystal structures [23–25]. The initial geometry of CuOOH was constructed, using Chem 3D Ultra, from the crystallographic parameters of Ph groups taken from the Cambridge structural database (CSD). One H-atom of Ph groups was replaced with  groups. The structures of the three CDs and CuOOH were all energy minimized using a conjugate gradient-like algorithm until all eigenvalue of the Hessian matrix were positive. The optimized structures of the three CDs and CuOOH were then used for the molecular docking calculations. Because it is unlikely to observe the spontaneous formation of all possible inclusion complexes in the typical time scales reachable with MD simulations, we decided to start from only two modes which are considered to contribute significantly to the molecular complexing of the cyclodextrins with the bulky aromatic CuOOH molecules (Fig. 1). To identify each of them throughout the text, the inclusion structure which the phenyl ring of CuOOH formed near the wide base (by primary alcohol) of CD is denoted as A mode, while the phenyl ring of CuOOH formed near the narrow base (by secondary alcohol) of CD is denoted as B mode. The initial configurations of these inclusion complexes were constructed by docking CuOOH into CD using the chemical software ArgusLab v4.0.1 [26]. CDs and CuOOH are oriented with their principal axis aligned with the *z* axis. The center of mass of CD is set to the origin of the coordinate system, and the *z* axis points toward the primary side of CD in the A mode, or the *z* axis points toward the secondary side of CD in the B mode. Periodic boundary conditions with a cubic simulation box as the basic unit cell were employed. The box length was ~2.72 nm, containing one host and one guest molecule, and 600 water molecules corresponding to a density of 1 g/cm^3, characteristic of ambient temperature (298 K).

2.2. Molecular dynamics (MD) simulation

Molecular dynamics (MD) simulations of both A- and B-type complexes were carried out by using the GROMACS package [27,28] (version 3.3.1). This version of the GROMOS force field has specific parameters for saccharides, and hence it is expected to be reliable for the systems studied here. GROMOS96 force field [29] was adopted for the simulation. The equations of motion were integrated using the leapfrog method with a 2 fs time step. The bond lengths and H–O–H angle in water were constrained using the SETTLE algorithm [30], while the LINCS31 [31] algorithm was used to constrain bond lengths in the CuOOH and CD molecules. The cutoff distances for van der Waals was 12.50 Å (precision as fine). Long-range electrostatic forces were taken into account by means of the particle-mesh Ewald approach. To start the simulation, the potential energy of the system was minimized. After that, the system was equilibrated at 298 K by MD simulations. Then the production run was performed by using NVT ensemble for 16 ns, with configurations stored every 10 ps for analysis. Temperature was maintained by the direct velocity scaling method.

2.3. Computational methods [32]

The relative free energies of binding using the adaptive biasing force (ABF) method were calculated as follows:

$$\Delta G_{a\to b} = \int_{\xi_a}^{\xi_b} \left\langle \frac{\partial H(x, p_x, \xi)}{\partial \xi} \right\rangle_{\xi} d\xi \tag{1}$$

where ξ is an appropriate ordering parameter describing host–guest association and $\langle\rangle_{\xi}$ stands for a statistical average computed at a fixed value of ξ. x and p_x are position and momentum variables, respectively. ∂Hx, p_x, $\xi/\partial\xi$ corresponds to the opposite of the force acting on ξ. In this method, the free-energy difference between two states of interest, ξ_a and ξ_b is calculated as an integral of the derivative of the Hamiltonian, $H(x, p_x, \xi)$, with respect to ξ. In the present ABF calculations, the ordering parameter was chosen as the distance separating a reference atom of CuOOH, viz. the C1 atom of its phenyl moiety, from the center of mass of the CD backbone along the *z* direction of Cartesian space (Fig. 1). Convergence was probed by extending the total simulation time and assessing the evolution of the average force as a function of time. The pathway, viz. $-10 < \xi < 10$ Å, was divided into five consecutive windows to further increase the efficiency of the calculations. To improve uniformity of the sampling along ξ and continuity of the average force across adjacent windows, the width of the windows was adapted wherever needed, and convergence of the free energy was probed by extending the simulation time to 2 ns in regions featuring barriers and minima. Instantaneous values of the force were accrued in bins 0.1 Å wide. The standard error of the free energy difference was estimated using the expression given by Rodriguez-Gomez et al. [33]

The association constant may be obtained by integrating the potential of mean force (PMF) along the ordering parameter, ξ, to the limit of association of CuOOH and CD [34]. When CuOOH penetrates within the CD cavity, the trajectory is confined in a small cylinder and the sampled volume of configurational space is restrained to that cylinder, the cross section of which is defined by the possible (x, y)-movement of CuOOH in the cavity. The 1M-standardized association constant may, therefore, the standardized association constant is written as:

$$K_a = \pi N_A \int r_{ave}^2 \exp[-\Delta G(\xi)/RT] d\xi \tag{2}$$

where N_A is Avogadro's number and R is the ideal gas constant. r_{ave} is the average radius of the cross section in each bin, which evidently varies with ξ, and was computed from the trajectories of

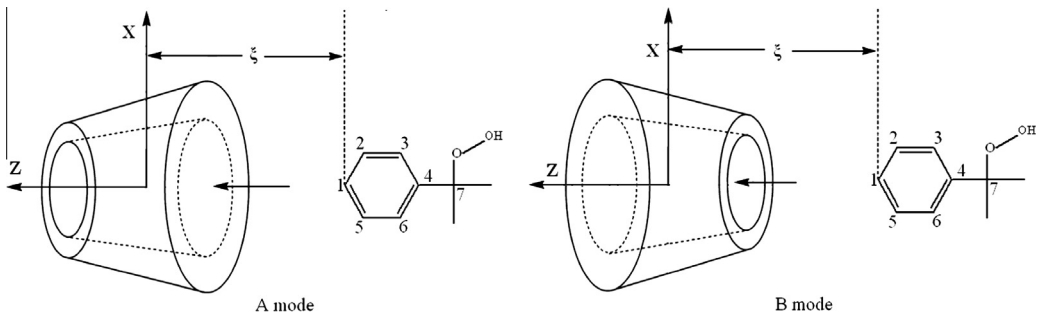


Fig. 1. Two orientations of the cumene hydroperoxide entering the cavity of cyclodextrins.