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Molecular insights into inclusion complexes of mansonone E and H enantiomers with various β-cyclodextrins

Panupong Mahalapbutr[a], Bodee Nutho[b], Peter Wolschann[a,c,d], Warinthorn Chavasiri[e], Nawee Kungwan[f,g], Thanyada Rungrotmongkol[a,h,*]

[a] Structural and Computational Biology Research Group, Department of Biochemistry, Faculty of Science, Chulalongkorn University, Bangkok, 10330, Thailand
[b] Program in Biotechnology, Faculty of Science, Chulalongkorn University, Bangkok, 10330, Thailand
[c] Department of Pharmaceutical Technology and Biopharmaceutics, University of Vienna, Vienna, 1090, Austria
[d] Institute of Theoretical Chemistry, University of Vienna, Vienna, 1090, Austria
[e] Center of Excellence in Natural Products Chemistry, Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok, 10330, Thailand
[f] Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, 50200, Thailand
[g] Research Center on Chemistry for Development of Health Promoting Products from Northern Resources, Chiang Mai University, Chiang Mai, 50200, Thailand
[h] Program in Bioinformatics and Computational Biology, Faculty of Science, Chulalongkorn University, Bangkok, 10330, Thailand

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ABSTRACT

The structural dynamics and stability of inclusion complexes of mansonone E (ME) and H (MH) including their stereoisomers with various βCDs (methylated- and hydroxypropylated-βCDs) were investigated by classical molecular dynamics (MD) simulations and binding free energy calculations. The simulation results revealed that mansonones are able to form inclusion complexes with βCDs. The guest molecules are not completely inserted into the host cavity, their preferably positions are nearby the secondary rim with the oxane ring dipping into the hydrophobic inner cavity. The encapsulation process leads to a higher rigidity of the βCDs enhancing the intramolecular hydrogen bond formation ability and decreasing the chance of glucopyranose rotation. According to the MM-PBSA binding free energy calculation, all considered inclusion complexes are stable and the binding energies are mainly caused by van der Waals interactions. Moreover, the free energy calculations showed significant differences in the complexation energies for the stereoisomers, which could enable the separation of the isomers by analytical techniques for further pharmaceutical applications.

1. Introduction

Quinones and particularly naphthoquinones are cyclic organic compounds ubiquitous in many plants as well as in numerous microorganisms serving as secondary metabolites. These naturally occurring compounds are of intensive research interest due to their wide spectrum of biological activities including antibacterial, antifungal, antimalarial, anti-inflammatory, and antitumor activities [1–4]. The naphthoquinone-containing compounds (NQC), especially mansonones, exhibit great pharmacological activities and have been used in traditional medicine preparations in Thailand over a period of several hundred years. Mansonone E (ME, Fig. 1A) and its hydroxylated form, mansonone H (MH, Fig. 1B) are in the subclass of 1,2-naphthoquinones (*ortho*-naphthoquinone) isolated from the heartwood of *Mansonia gagei* [5] as well as from other plants [2,6–8]. Their various biological activities were reported including antifungal activity, radical scavenging property, larvicidal activity [5], cholinesterase (ChE) inhibitory activity [9], topoisomerase I and II inhibitors [10], trypanosomatid growth inhibitors [11], NADPH-dependent microsomal lipid peroxidation [12], and cytotoxicity against various cancer cell lines [6–8]. The cytotoxic action of NQC against cancer cells is resulted from the quinone moiety in their chemical structures [1,13]. Although many benefits of mansonones were reported, the pharmaceutical and biomedical applications are limited by their low water solubility.

β-Cyclodextrin (βCD, Fig. 1C) is a cyclic oligosaccharide consisting of seven D-(+)-glucopyranose units linked together by α-(1,4) glycosidic bonds. In particular, βCD is produced by intramolecular transglycosylation reaction using a cyclodextrin glycosyltrans-

* Corresponding author at: Structural and Computational Biology Research Group, Department of Biochemistry, Faculty of Science, Chulalongkorn University, Bangkok, 10330, Thailand.
E-mail addresses: thanyada.r@chula.ac.th, t.rungrotmongkol@gmail.com (T. Rungrotmongkol).

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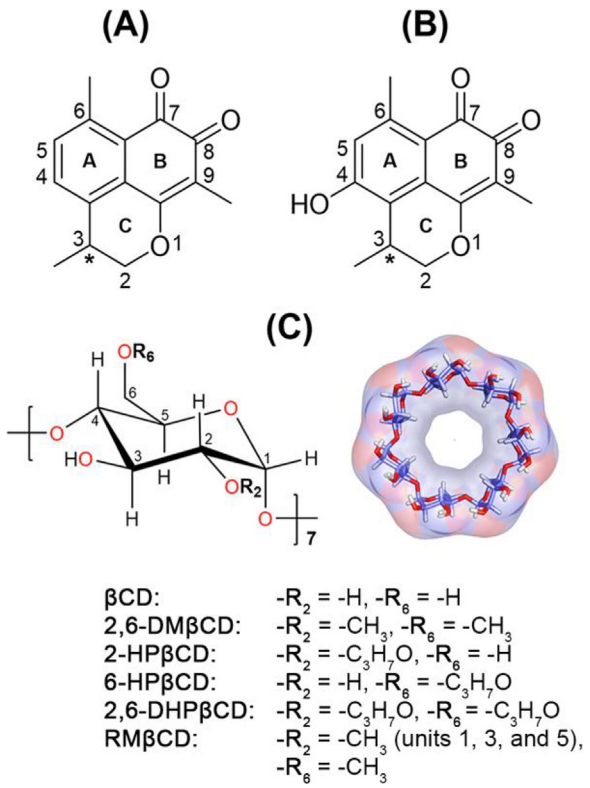

Fig. 1. Chemical structures of (**A**) ME, (**B**) MH; A, B, and C represent aromatic, quinone, and oxane rings, respectively; C3-position presents the chiral center. (**C**) Survey of the βCD derivatives used in this study and the 3D structure of βCD.

ferase (CGTase) enzyme [14]. From the geometry of βCD, the outer surface is hydrophilic to some extent, whilst the inner cavity is rather hydrophobic. Since the D-(+)-glucopyranose units exist in a chair form, the shape of βCD is that of a truncated cone rather than a perfect cylinder [15]. Consequently, βCD can form inclusion complexes with various lipophilic guest molecules by an encapsulation process into its hydrophobic inner cavity. In the recent years, cyclodextrin complexation technology was successfully used to enhance the solubility, stability against oxidative and light degradation, dissolution rate, masking malodors, and bioavailability of many hydrophobic drugs [14–16]. Moreover, βCDs can be used as the chiral selector of many racemic mixtures [17–20] in both the pharmaceutical and chemical industries [21]. However, the practical applications of βCD in pharmaceutical products are still limited by its low water solubility (18.5 mg/mL at 25 °C) and nephrotoxicity [22]. Therefore, the use of higher water-soluble and lower toxic βCD derivatives are immensely required. For instance, 2,6-dimethyl-βCD (2,6-DMβCD), randomly methylated-βCD (RMβCD), and hydroxypropyl-βCD (HPβCD) exhibit a greater water solubility and lower toxicity [15,22]. Several studies have shown that the water solubility, stability, and biological activities of NQC are increased, while the toxicity of those molecules is reduced by a complexation with βCDs [23–27].

Accordingly, the aims of this work are to predict the encapsulation of ME and MH stereoisomers by suitable βCD derivatives as well as to understand the structural and dynamics properties of the formed inclusion complexes using computational tools.

2. Computational methods

The optimized structures of βCD and its four derivatives (2,6-DMβCD, 2-HPβCD, 6-HPβCD, and 2,6-DHPβCD) were taken from our previous study [28]. Note that the commercially available HPβCD is a partially substituted poly(hydroxypropyl) ether of βCD with various degrees of substitution (DS) [29]. Three models of HPβCD derivatives including 2-HPβCD (DS = 1), 6-HPβCD (DS = 1) and 2,6-DHPβCD (DS = 2) [30] were used as representative structures for studying the encapsulation reaction. For the RMβCD, the structure was constructed by removing some substituents from 2,6-DMβCD according to the strength of nucleophilicity (primary hydroxyl groups > secondary hydroxyl groups). Therefore, the three methyl groups are located on the secondary rim at the D-(+)-glucopyranose units 1, 3 and 5, while the hydroxyl groups on the primary rim were fully substituted by seven methyl groups. The starting structures of two mansonones, ME and MH, including their stereoisomers were built and subsequently optimized by the HF/6-31(d) basis set using Gaussian09 program [31]. The inclusion complexes between each mansonone molecule and all six βCDs were constructed by a docking procedure with 500 independent runs using the CDOCKER module implemented in the Accelrys Discovery Studio 2.5 (Accelrys, Inc.). Subsequently, the best three docked complexes at each binding mode were then studied by the classical MD simulations in aqueous solutions using the AMBER14 software package [32]. According to the standard procedures [33–36], the electrostatic potential (ESP) charges around the optimized mansonone structures were calculated by HF/6-31(d) level of theory using Gaussian09 program. The charge fitting procedure (antechamber module) and parmchk module were used for generating the restrained electrostatic potential (RESP) charges and their parameters of two mansonones, respectively. The Glycam06 force field [37] was applied for βCD and its derivatives, whereas the mansonones were treated by the generalized AMBER force field (GAFF).

To release bad contacts and to relax the structures prior to MD simulations, all hydrogen atoms of βCDs and the mansonone molecules were minimized with 1000 steps of the steepest descents (SD) method and continued by 3000 steps of conjugated gradient (CG) method. Afterwards, the inclusion complexes were solvated using TIP3P water model with the minimum distance of 15 Å from the system surface. As a result, all systems consisted of 2100 ± 42 water molecules in an approximately $50 \times 50 \times 50$ Å^3 truncated octahedron periodic box. The water molecules were then only minimized with the SD (1000 steps) and CG (3000 steps). Finally, the whole system was minimized using the same minimization process. The periodic boundary condition with *NPT* ensemble was applied for all simulated systems using a time step of 2 fs. Pressure and temperature were controlled by the Berendsen weak coupling algorithm [38]. The cutoff distance for long-range electrostatic interactions was set to 12 Å using the Particle Mesh Ewald (PME) summation approach [39]. The SHAKE algorithm [40] was used to constrain all bonds involving hydrogen atoms. The models were heated up to 298 K with the relaxation time of 60 ps, and continuously held at this temperature for another 30 ns. The cpptraj module of AMBER14 program was used to calculate the root-mean-square displacement (RMSD), the potential energy surface (PES), the flipped angle of glucopyranose units, the distance between the centers of gravity of each mansonone ring and βCD(s), and the radial distribution function (RDF). The MM-PBSA binding free energy of all inclusion complexes were estimated by mm_pbsa.pl module [41] using the 100 snapshots extracted from the last 5-ns simulation.

3. Results and discussion

Three independent simulations with different initial structures gave rather similar results. Accordingly, the results from only one system of each stereoisomer are presented here for a simplified