Particuology 7 (2009) 220–224

Contents lists available at ScienceDirect

Particuology

journal homepage: www.elsevier.com/locate/partic

Short communication

Explicit solvent molecular dynamics simulations of chaperonin-assisted rhodanese folding

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ARTICLE INFO

Article history:
Received 23 December 2008
Accepted 13 March 2009

Keywords:
Molecular dynamics simulation
Explicit solvent
Chaperonin-assisted
Protein folding
Molecular chaperonin
Rhodanese

ABSTRACT

Chaperonins are known to facilitate the productive folding of numerous misfolded proteins. Despite their established importance, the mechanism of chaperonin-assisted protein folding remains unknown. In the present article, all-atom explicit solvent molecular dynamics (MD) simulations have been performed for the first time on rhodanese folding in a series of cavity-size and cavity-charge chaperonin mutants. A compromise between stability and flexibility of chaperonin structure during the substrate folding has been observed and the key factors affecting this dynamic process are discussed.

1. Introduction

Extension of particle simulation methods like MD, discrete element method (DEM), pseudo particle modeling (PPM), macro-scale pseudo particle modeling (MaPPM) to different complex systems has paved a way for wider application in practical processes like bio-molecular systems and nano-materials (Ge et al., 2007; Ge & Li, 2001). Among them, protein folding, a fundamental process in living bodies, has attracted more and more attention. *In vivo*, protein folding is assisted by a set of proteins, collectively known as molecular chaperones, which help proteins fold successfully to their native structures in the crowded environment of a cell (Ellis, 2001). One of the most studied chaperonins is the bacterial chaperonin GroEL and its co-chaperonin GroES, that is, the so-called GroEL/ES complex. While its structure is now well characterized as two heptameric rings consisting of seven identical GroEL subunits each, with a dome-shaped heptameric ring consisting of seven identical GroES subunits on top of GroEL, the mechanism of chaperonin-mediated protein folding is still poorly understood. Current experimental techniques are very difficult to unravel the dynamics of the partially folded peptide inside the chaperonin with sufficient temporal and spatial resolutions, making discrete computer simulation a powerful tool to understand the problem at molecular level. However, due to computational limitations, most studies have relied on coarse-grained simulations using a rigid geometry with a homogeneous inner lining to represent the chaperonin and a rough model protein to represent the substrate (Jewett, Baumketner, & Shea, 2004; Klimov, Newfield, & Thirumalai, 2002; Takagi, Koga, & Takada, 2003), thus inevitably ignoring the true chemical characteristics of the cavity and the substrate protein. Implicit solvent models, though having the advantage of reducing computational powers, would incur tremendous errors by approximating the electrostatic properties of the discrete solvent as a dielectric continuum (Lin, Baker, & McCammon, 2002). The all-atom explicit solvent model would be the best choice for a detailed description of such investigations. Recently, with the help of our newly built high-performance computer system with a capacity of 100 T single-precision flops, we have performed the first all-atom explicit solvent MD simulations on this dynamic process for ~150 ns, which is also the longest so far as we know.

Bovine liver rhodanese (Protein Data Bank code 1RHD (Ploegman, Drent, Kalk, & Hol, 1978)), a 293-residue with a molecular weight of ~33 kD, has been widely investigated as a substrate for assisted folding by molecular chaperonin (Horowitz, 1995; Tang et al., 2006). Here, we carry out all-atom, explicit solvent, molecular dynamics simulations of a series of GroEL/ES mutants, and investigate two major physical properties: the size and the charge of the cavity. Only the cis-cavity of GroEL is included in the simulation since the trans-cavity plays no essential role in substrate folding (Tang et al., 2006) but costs tremendous computational time. As shown in Fig. 1, the C-terminus (the end of the amino acid chain terminated by a free carboxyl group) of each GroEL subunit

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1674-2001/$ – see front matter © 2009 Chinese Society of Particuology and Institute of Process Engineering, Chinese Academy of Sciences. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.partic.2009.03.001

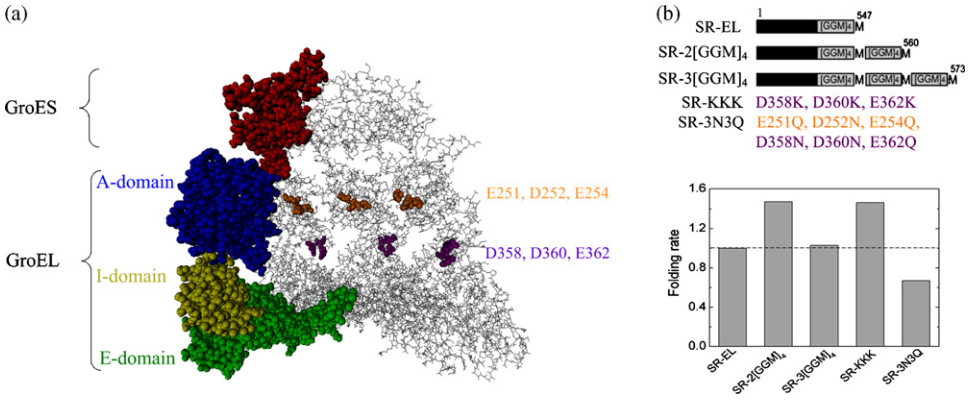

Fig. 1. (a) Architecture of GroEL/ES complex (PDB code 1AON (Xu, Horwich, & Sigler, 1997)) offering a view into the cis-cavity shown with four subunits of GroEL and GroES (only the cis-cavity is shown for clarity). Clusters of negatively charged residues exposed toward the cis-cavity are highlighted in orange (E251, D252, E254) and purple (D358, D360, E362). GroES, the A-domain, I-domain and E-domain of GroEL are shown in red, blue, yellow and green, respectively. (b, top), schematic representation of a series of GroEL; (b, bottom), corresponding experimental results of rhodanese folding rate (Tang et al., 2006), the dashed line representing the folding rate obtained with SR-EL set to 1.0. Nomenclature for the mutants is taken from the experimental work of Tang et al. (2006). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1
Details of all simulations performed.

System	GroEL construct	Cavity volume change (%)	Cavity net charge	No. of atoms
1	SR-EL	0	−42	350,618
2	SR-2[GGM]$_4$	−4.4	−42	350,157
3	SR-3[GGM]$_4$	−8.7	−42	350,146
4	SR-KKK	0	0	350,725
5	SR-3N3Q	0	0	350,741

Note: Nomenclature for mutants according to experimental work of Tang et al. (2006).

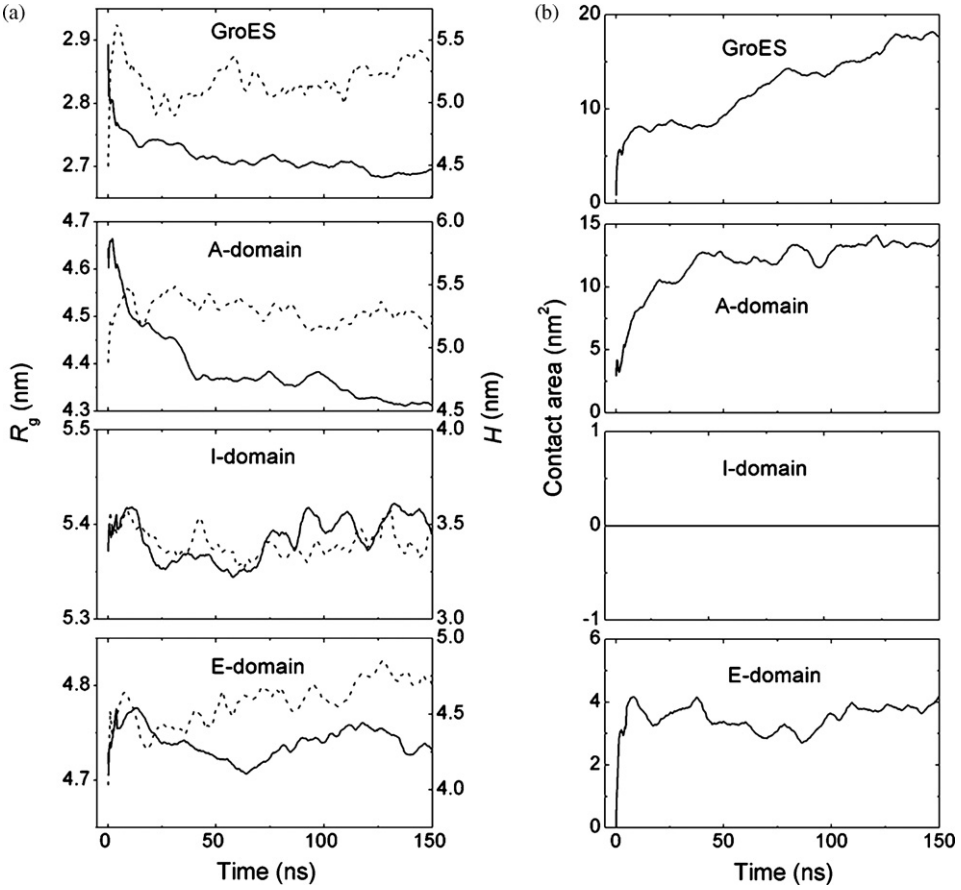

Fig. 2. Plotted as functions of time: (a) R_g (solid line) and H (dash line) of GroES, A-domain, I-domain and E-domain of SR-EL; (b) contact area between the respective domains and rhodanese.