AKB 90 Protein Folding and Molecular Dynamics

Zeit: Mittwoch 14:00–15:30 Raum: TU H2013

AKB 90.1 Mi 14:00 TU H2013

Helical Alanine Polypeptides: DFT versus Force-Field Results — •Marcus John, Joel Ireta und Matthias Scheffler — Fritz-Haber-Institut der Max-Planck-Gesellschaft

Recently it became possible to calculate different conformations of the secondary structure of proteins fully including the hydrogen bond (hb) cooperativity by means of density functional theory (DFT). Although the computational effort restricts this approach to the treatment of only a few conformations it nevertheless provides important insight into the stabilizing function of hbs. DFT in the PBE approximation to the exchange-correlation functional revealed the existence of three different minima on the potential-energy surface of a helix, corresponding to the π-, α-, and 3_{10} conformations [1]. A comparison with some existing force fields (CHARMM27 or AMOEBA) shows that they are not able to reproduce these different basins. We conjecture that this is due to the inability of current force fields to model the effect of cooperative hbs properly. In this contribution we provide an analysis of this phenomenon which may help to develop improved force fields.

[1] J. Ireta, M. Scheffler, J. Neugebauer, A. Rojo, M. Galvan submitted to PRL

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A DFT-GGA based thermodynamic analysis of the secondary structure of proteins — •Lars Ismer[1], Joel Ireta[1], Matthias Scheffler[1], and Jörg Neugebauer[2] — [1]Fritz-Haber-Institut der MPG, Faradayweg 4-6, 14195 Berlin — [2]Theoretische Physik, Universität Paderborn, Warburger Str. 100, 33098 Paderborn

Studies of the thermodynamic stability of the secondary structure of proteins are important for understanding the protein folding process. We have therefore estimated the free energy change to fold a fully extended structure (FES) into the α-helical conformation for isolated infinite polyglycine (Gly) and -alanine (Ala) chains. The calculations have been performed employing DFT-GGA, a plane-wave pseudo-potential approach and the harmonic approximation. Our results reveal [1], that this approach leads to a significantly improved description of thermodynamic data with respect to previous studies based on empirical force fields. Further we find, that the enthalpy to transform an α-helix into an FES strongly reduces with increasing temperature: at room temperature the free energy difference for Gly is close to zero within the numerical error bar (0.5 kcal/mol), whereas for Ala the α-helix is by 1.0 kcal/mol more stable. We conclude, without recoursing to any empirical input parameters, that an isolated Ala-FES will even at room temperature spontaneously fold into an α-helix.

[1] L.Ismer, J. Ireta, S. Boeck and J. Neugebauer, submitted to Phys. Rev. E

AKB 90.3 Mi 14:30 TU H2013

Molecular mechanism of urea-induced protein unfolding — •Martin Stumpe and Helmut Grubmüller — MPI für biophysikalische Chemie, Theoretische und computergestützte Biophysik, Am Fassberg 11, 37077 Göttingen

Chemical denaturation is widely used to analyse protein stability and unfolding. Despite the common use of urea as denaturant, little is known about the molecular mechanism of urea-induced protein unfolding. Both, a direct interaction between urea and the protein as well as an indirect interaction via alteration of the water structure are possible and have been discussed. To shed light on this mechnism, we have carried out molecular dynamics simulations. Our studies of urea-water solutions revealed only minor perturbations of the water structure by the presence of urea. This finding provides new support for the direct interaction of urea with proteins during unfolding. We also achieved a detailled understanding of urea self-aggregation. Unfolding-simulations were performed with the Cold-Shock protein Bc-Csp and the human Prion protein fragment at elevated temperatures in physiological environment and in 8M urea solution. For these proteins, temperature-induced unfolding starts with a loss of secondary structure while the tertiary structure is conserved at the beginning and starts to decay only after the proteins have lost a substantial amount of secondary structure, in line with the hydrophobic-collapse models. Unexpectedly, and in contrast to room temperature results, at high temperatures urea does not seem to accelerate unfolding, which might point towards an entropy-dominated unfolding mechnism.

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How parallel is protein (un)folding? — •Lothar Reich and Thomas R. Weikl — Max Planck Institute of Colloids and Interfaces, Theory Division, 14424 Potsdam

According to the 'old view', proteins fold along well-defined *sequential* pathways, whereas the 'new view' sees protein folding as a highly *parallel* stochastic process on funnel-shaped energy landscapes. We have analyzed parallel and sequential processes on a large number of Molecular Dynamics unfolding trajectories for the protein CI2 at high temperatures. Using rigorous statistical measures, we find that the degree of sequentiality depends on the structural level under consideration. On a coarse substructural level of whole β-sheets and helices, unfolding is predominantly sequential. In contrast, the unfolding process is more parallel on the level of individual contacts between the residues of the protein chain. On an intermediate structural level, the characteristic parallel and sequential events can be understood from simple loop-closure dependencies between the substructural elements.

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All Atom Protein Structure Prediction with Stochastic Optimization Methods — •Wolfgang Wenzel, Thomas Herges, Alexander Schug, and Abhinav Verma — Forschungszentrum Karlsruhe, Institut für Nanotechnologie, Postfach 3640, 76021 Karlsruhe

The prediction of protein tertiary structure remains one of the outstanding problems in biophysical chemistry. According to the thermodynamic hypothesis, the native conformation of a protein can be predicted as the global optimum of its free energy surface with stochastic optimization methods[1] orders of magnitude faster than by direct simulation of the folding process.

We have recently developed an all-atom free energy forcefield (PFF01)[2] which implements a minimal thermodynamic model based on physical interactions. With this forcefield we were able to predictively fold the 20 amino acid trp-cage protein[3], the 40 amino-acid HIV accessory protein[4], the 36 amino-acid villin headpiece and the 60 amino acid bacterial ribosomal protein[5] using various stochastic optimization methods. We will disccuss advantages and limitations of these methods with respect to further improvements of this approach to in-silico all-atom protein strcuture prediction.

[1] W. Wenzel, K. Hamacher, PRL 59, 3003 (1999) [2] T. Herges, W. Wenzel, Biophys. J. 87, 3100 (2004) [3] A. Schug, W. Wenzel, PRL 91, 158102, 2003, EPL 67, 307 (2004) [4] T. Herges, W. Wenzel, PRL (in press) [5] A. Schug, W. Wenzel, JACS (in press)

AKB 90.6 Mi 15:15 TU H2013

Identification of Oxygen Channels in Proteins by Molecular Dynamics — •Jan Saam, Christopher Ozdoba und Hermann-Georg Holzhütter — Institut für Biochemie, Charité, Monbijoustr 2. 10117 Berlin

Cells contain a variety of enzymes that use molecular oxygen in the reactions they catalyze. In most cases the influence of oxygen-protein interaction on the reaction is unknown. We employed molecular dynamics simulations to determine the oxygen pathway from the solvent phase to the active site and to study the oxygen adsorption at the inner surface of two different oxygenases.

Our results show that in each enzyme there exists an oxygen channel different from the substrate entrance leading through the protein matrix to the catalytic site. The channels cannot be seen in the crystal structure but open their different segments temporarily yet allowing oxygen molecules to diffuse to the active center. With its high probability density for oxygen the interior end of the tunnel represents the ideal point for the stereo- and position specific insertion of dioxygen into the substrate. Subsequently these results could be confirmed by mutation experiments.