BIOPHYSICAL CHEMISTRY LAB

ANNUAL REPORT 2011

Institute of Biochemistry and Biophysics
Tehran, Iran

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CONTENTS

FOREWORD

The Laboratory of Biophysical Chemistry (LBC) was established in 1986 in the Institute of Biochemistry and Biophysics (IBB) and now functions as the main base and the mother of Biophysical Chemistry in Iran. This laboratory is well-known in the national and international level. It is also famous worldwide in the research area of Thermodynamics of Protein Denaturation and Protein-Ligand Interaction.

This laboratory enjoys from advanced facilities and is equipped with advanced apparatuses for the research on Biothermodynamics and Biomacromolecular Interactions. LBC is equipped with Nano and Micro Differential Scanning Calorimeters (DSC); Nano and Micro Isothermal Titration Calorimeters (ITC); modern Circular Dichroism (CD) Spectropolarometry, Sensitive Densitometer and Tensiometer; Fluorescence and Uv-vis Spectrophotometers, Microviscometers and Biochemical and Biophysical methods as well as and Computational facilities.

LBC is an appropriate place for the promotion of the research and science in the field of Biochemistry, Nanobiophysics, Biotechnology and Biophysical Chemistry. LBC is a suitable laboratory for training PhD students and postdoctorate researchers, associate researchers and sabbatical leaves for faculty members at national and international levels.

Up to the present time, 42 Ph.D and 66 Master students have developed their theses in this laboratory and graduated from the university. Faculty members, postdoctorates and students and foreign research associates using the facilities of this laboratory which have published hundreds of full research articles in international prestigious journals. LBC is an appropriate laboratory for supporting and promoting the research of scientists and researchers at national and international levels.

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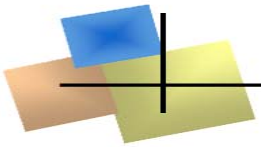

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STUDENTS (Year 2011)

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L. Alaie	Study of thermal inactivation and conformational lock in carbonic anhydrase
M. Goodarzi	Heme degradation during hemoglobin fructation: Emphasizing on reactive oxygen Species (ROS)
E. Kachoie	Study of surface tension changes during conversion of insulin to the amyloid fibrils, and its correlation with toxicity of fibrils.

PUBLICATIONS 2011

1- F. C. Chilaka, C. Okechukwu Nwamba, A. A. Moosavi-Movahedi "Cation Modulation of Hemoglobin Interaction with Sodium n-Dodecyl Sulfate (SDS). I: Calcium Modulation at pH 5" Cell Biochemistry Biophysics 61,573-584 (2011).

2- H. Bahrami, M. Bigdeli, M. D. Davari, M. Zahedi and A. A. Moosavi-Movahedi "Kinetics and mechanism of the autocatalytic dehydration reaction of L-γ-amino-n-butyric acid to 2-pyrrolidone through radical intermediate in moderately concentrated acidic medium" Progress in Reaction Kinetics and Mechanism 36(2) 120-138 (2011).

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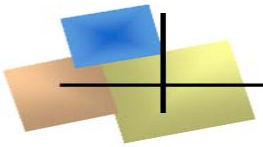

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with Lysozyme" International Journal Biological Macromolecules 49, 616-621 (2011).

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2- R. Nasiri, M. Zahedi,H.Jamet and A.A.Moosavi-Movahedi " Theoretical studies on the thermodynamics and kinetics of the lysine-arginine cross-links derived from alpha-oxoaldehydes: A new mwchanism for glucosepane formation". The abstract published in proceeding of 25th Molecular Modeling Workshop, Erlangen-Nurenberg, Germany. April 4-6, 2011.

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ORIGINAL PAPER

Cation Modulation of Hemoglobin Interaction with Sodium *n*-Dodecyl Sulfate (SDS). II: Calcium Modulation at pH 5.0

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Abstract We investigate the conformational differences between HbA and HbS in the presence and absence of Ca^{2+} concentrations (0–40 μM) akin to those within the erythrocyte cytoplasm and the membrane mimetic and native structure disrupting environments of the *Plasmodium* parasite food vacuole at pH 5.0. The experiments were monitored by UV–Vis spectrophotometery in the range of 250–650 nm. Our results suggest that the HbS, on interacting with both the membrane mimic and 40 μM Ca^{2+}, undergoes an "expansion" akin to the burst phase of proteins accompanied by tyrosine exposure while that of the HbA occurred with tryptophan exposure. Our results suggest conformational flexibility in the HbS unlike in the HbA. Besides, the spectral results also suggest that the HbS complexes with the Ca^{2+} in its immediate environment without strain (due to its inherent conformational flexibility), unlike the HbA, thus appropriating the cation from its vicinity. The implications of these results are discussed in the light of possible mechanisms employed by the HbS to resist protease digestion or at least slow down the kinetics of the protease activities and on how these same factors can predispose the homozygous HbS individuals to sickling and consequent vaso-occlusive crisis.

Keywords Calcium · Conformational flexibility · Denaturation · Hemoglobin · Membrane mimic · Proteases

Introduction

Malaria is the leading cause of death in sub-saharan Africa where the effect is exacerbated by poverty [1], drug resistance [2, 3], insecticide resistance [4, 5] and global warming [6, 7]. Human malaria is caused by intracellular protozoa of the genus *Plasmodium*, of which *Plasmodium falciparum* is by far the most lethal, accounting for more than 95% of all deaths and morbidity [8]. Despite significant advances in understanding the disease and the parasite, malaria still remains one of the leading causes of morbidity and mortality, particularly in the tropics, with a staggering 500 million new infections and 1 million deaths annually [9].

Individuals heterozygous for the HbS gene are reported to be resistant to the disease [10, 11], probably because the HbS molecule might possess some intrinsic ability to resist attack from the *Plasmodium* parasites. The question then is: what property or properties of the HbS would selectively confer resistance on HbS in comparison to the HbA since both proteins differ by a point mutation? Interestingly, individuals homozygous for HbS suffer sickle cell crises

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ORIGINAL PAPER

Conformational and thermodynamic characterization of the premolten globule state occurring during unfolding of the molten globule state of cytochrome *c*

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Abstract It has already been shown that the mutant Leu94Gly of horse cytochrome *c* exists in a molten globule (MG) state. We have carried out studies of reversible folding and unfolding induced by LiCl of this mutant at pH 6.0 and 25 °C by observing changes in the difference molar absorption coefficient at 402 nm, the mean residue ellipticity at 222 nm, and the difference mean residue ellipticity at 409 nm. This process is a three-state process when measured by these probes. The stable folding intermediate state has been characterized by far- and near-UV circular dichroism, tryptophan fluorescence, 8-anilino-1-naphthalenesulfonic acid binding, and dynamic light scattering measurements, which led us to conclude that the intermediate is a premolten globule (PMG). Analysis of the reversible unfolding transition curves for the stability of different states in terms of the Gibbs free energy change at pH 6.0 and 25 °C led us to conclude that the MG state is more stable than the PMG state by 5.4 ± 0.1 kcal mol^{-1}, whereas the PMG state is more stable than the denatured (D) state by only 1.1 ± 0.1 kcal mol^{-1}. A comparison of the conformational and thermodynamic properties of the LiCl-induced PMG state at pH 6.0 with those of the PMG state induced by NaCl at pH 2.0 suggests that a similar PMG state is obtained under both denaturing conditions. Differential scanning calorimetry measurements suggest that heat induces a reversible two-state transition between MG and D states.

Keywords Calorimetry · Cytochrome · Denaturant · Protein folding · Site-directed mutagenesis

Abbreviations

ANS	8-Anilino-1-naphthalenesulfonic acid
CD	Circular dichroism
DLS	Dynamic light scattering
DSC	Differential scanning calorimetry
MG	Molten globule
PMG	Premolten globule
WT	Wild type

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Introduction

The pathway by which a newly synthesized polypeptide chain spontaneously folds into its native functional form is still a central goal of protein chemists. In recent years, great attention has been focused on detecting and characterizing the intermediates that occur during the folding of proteins. The molten globule (MG) is one such intermediate of significance which has been studied extensively [1–3]. We have been interested for some time in the conformational changes induced by weak salt denaturants of MG states and their thermodynamic characterization [4–6]. These weak salt denaturants have been shown to induce a biphasic

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Dioxane enhanced immobilization of urease on alkyl modified nano-porous silica using reversible denaturation approach

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ABSTRACT

Efficient immobilization of urease was achieved upon dioxane-induced unfolding/refolding strategy on alkyl modified porous silica with an average pore size of 66 nm. Structural exploration of the urease was carried out to find the optimum condition of solvent polarity which provides efficient adsorptive immobilization through emphasizing on dual approaches: creation of hydrophobic intermediates as molten globule like states and improved accessibility of substituted alkyl chains. The optimum percent volume of dioxane in phosphate buffer to fulfill such aim was achieved at 30% (v/v). Restoring of native-like secondary structure was observed using circular dichroism; moreover, improved exposure of hydrophobic surfaces of urease was confirmed using a set of UV-analysis, intrinsic fluorescence, and differential 8-anilino-1-naphthalene-sulfonate fluorescence spectroscopy, at 30% as an optimum concentration of dioxane. The yield of immobilization was doubled using reversible denaturation approach and storage stability of the immobilization product of urease was noticeably improved (half live of the multi-used immobilized urease was resulted to be 6.5 folds higher than the half live of the free enzyme). Moreover, 7–13.5 folds activation of the enzyme was resulted upon immobilization. Improved immobilization ensures the efficiency of this strategy, for applied approaches, along with providing further evidences for enhanced surface hydrophobicity of the multimeric urease at defined concentration of dioxane.

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Beta casein-micelle as a nano vehicle for solubility enhancement of curcumin; food industry application

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ABSTRACT

Curcumin is a potent anticancer and antioxidant natural polyphenol poorly soluble in aqueous solutions. Beta-casein (B-CN), an amphiphilic self-assembling protein that can form micellar nanostructures, could be used as a carrier system for hydrophobic therapeutic agents such as curcumin. In this study, camel B-CN was used for curcumin encapsulation. Critical micelle concentration of camel B-CN was determined at 25, 30 and 37 °C using pyrene fluorescence and the solubility of curcumin was evaluated according to the solvent-evaporation technique. Presence of camel B-CN increased the solubility of curcumin at least 2500 fold. Analysis of fluorescence emission of curcumin showed that hydrophobic interactions are predominant in its formulation with B-CN. Additionally, the cytotoxicity of curcumin to human leukemia cell line K-562 was enhanced in the presence of B-CN micelles giving inhibitory concentration (IC_{50}) values of 26.5 and 17.7 μmol/L for free and encapsulated curcumin, respectively. Antioxidant activity of curcumin encapsulated in B-CN was higher than that of both free B-CN and curcumin.

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International Journal of Nanomedicine

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ORIGINAL RESEARCH

Targeted delivery of doxorubicin-utilizing chitosan nanoparticles surface-functionalized with anti-Her2 trastuzumab

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Background: Targeting drugs to their sites of action to overcome the systemic side effects associated with most antineoplastic agents is still a major challenge in pharmaceutical research. In this study, the monoclonal antibody, trastuzumab, was used as a targeting agent in nanoparticles carrying the antitumor drug, doxorubicin, specifically to its site of action.

Methods: Chitosan-doxorubicin conjugation was carried out using succinic anhydride as a crosslinker. Trastuzumab was conjugated to self-assembled chitosan-doxorubin conjugate (CS-DOX) nanoparticles (particle size, 200 nm) via thiolation of lysine residues and subsequent linking of the resulted thiols to chitosan. Conjugation was confirmed by gel permeation chromatography, differential scanning calorimetry, Fourier transform infrared spectroscopy, and ^{1}H nuclear magnetic resonance spectroscopy studies. Dynamic light scattering, transmission electron microscopy, and zeta potential determination were used to characterize the nanoparticles.

Results: CS-DOX conjugated nanoparticles had a spherical shape and smooth surface with a narrow size distribution and core-shell structure. Increasing the ratio of doxorubicin to chitosan in the conjugation reaction gave rise to a higher doxorubicin content but lower conjugation efficiency. Trastuzumab-decorated nanoparticles (CS-DOX-mAb) contained 47 μg/mg doxorubicin and 33.5 μg/mg trastuzumab. Binding of trastuzumab to the nanoparticles was further probed thermodynamically by isothermal titration calorimetry. Fluorescence microscopy demonstrated enhanced and selective uptake of CS-DOX-mAb by Her2$^+$ cancer cells compared with nontargeted CS-DOX nanoparticles and free drug.

Conclusion: Antibody-conjugated nanoparticles were shown to discriminate between Her2$^+$ and Her2$^-$ cells, and thus have the potential to be used in active targeted drug delivery, with reduction of drug side effects in Her2$^+$ breast and ovarian cancers.

Keywords: chitosan, doxorubicin, self-assembled nanoparticles, active targeting, trastuzumab

Introduction

The main objective in anticancer drug development is to deliver therapeutic agents in a targeted and selective fashion to their site of action, and to decrease adverse effects

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PLoS one

Intracellular ROS Protection Efficiency and Free Radical-Scavenging Activity of Curcumin

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Abstract

Curcumin has many pharmaceutical applications, many of which arise from its potent antioxidant properties. The present research examined the antioxidant activities of curcumin in polar solvents by a comparative study using ESR, reduction of ferric iron in aqueous medium and intracellular ROS/toxicity assays. ESR data indicated that the steric hindrance among adjacent big size groups within a galvinoxyl molecule limited the curcumin to scavenge galvinoxyl radicals effectively, while curcumin showed a powerful capacity for scavenging intracellular smaller oxidative molecules such as H_2O_2, $HO^{\bullet}$, $ROO^{\bullet}$. Cell viability and ROS assays demonstrated that curcumin was able to penetrate into the polar medium inside the cells and to protect them against the highly toxic and lethal effects of cumene hydroperoxide. Curcumin also showed good electron-transfer capability, with greater activity than trolox in aqueous solution. Curcumin can readily transfer electron or easily donate H-atom from two phenolic sites to scavenge free radicals. The excellent electron transfer capability of curcumin is because of its unique structure and different functional groups, including a β-diketone and several π electrons that have the capacity to conjugate between two phenyl rings. Therfore, since curcumin is inherently a lipophilic compound, because of its superb intracellular ROS scavenging activity, it can be used as an effective antioxidant for ROS protection within the polar cytoplasm.

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THE JOURNAL OF PHYSICAL CHEMISTRY A

ARTICLE

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Cross-Linking Mechanisms of Arginine and Lysine with α,β-Dicarbonyl Compounds in Aqueous Solution

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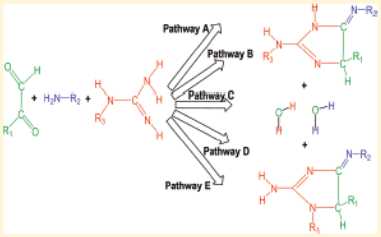
Supporting Information

ABSTRACT: Cross-linking in proteins by α,β-dicarbonyl compounds is one of the most damaging consequences of reactive carbonyl species in vivo and in foodstuffs. In this article we investigate computationally the cross-linking of glyoxal and methylglyoxal with lysine and arginine residues using density functional theory and the wB97XD dispersion-corrected functional. Five pathways, A−E, have been characterized. In pathways A and B, the reaction proceeds via formation of the Schiff base, aldimine, followed by addition of arginine. In contrast, in pathways C−E, direct addition of arginine to the dicarbonyl compounds occurs first, leading to a dihydroxyimidazolidine intermediate, which then reacts with lysine after dehydration and proton transfer reactions. The results reveal that pathways A, C, and E are competitive whereas reactions via pathways B and D are much less favorable. Inclusion of up to five explicit water molecules in the proton transfer and dehydration steps is found to lower the energy barriers in the feasible pathways by about 5−20 kcal/mol. Comparison of the mechanisms of methylglyoxal-derived imidazolium cross-linking (MODIC) and glyoxal-derived imidazolium cross-linking (GODIC) shows that the activation barriers are lower for GODIC than MODIC, in agreement with experimental observations.



THE JOURNAL OF PHYSICAL CHEMISTRY B

ARTICLE

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Vesicular Mixed Gemini–SDS–Hemin–Imidazole Complex as a Peroxidase-Like Nano Artificial Enzyme

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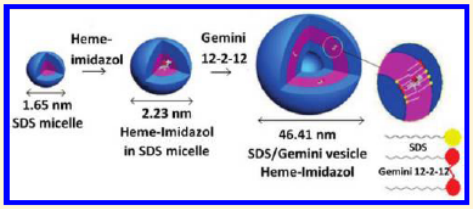
ABSTRACT: A biomimetic was designed for the construction of a new efficient peroxidase-like nano artificial enzyme with a heme–imidazole component complexed with gemini 12-2-12/SDS supramolecules. The presence of a simple surfactant mixture (SDS/gemini 12-2-12 at a particular concentration) provided an apoprotein-like hydrophobic pocket for the heme–imidazole moiety, which produced a peroxidase active site containing positive and negative charges distributed on the colloidal surface. Vesicular structures that stabilized the heme–imidazole complexes formed multienzyme advanced colloids. The enzymatic activation parameters indicated that the catalytic efficiency of the novel nano artificial enzyme was 27% as efficient as the native horseradish peroxidase (HRP). The imidazole moiety, which functionally corresponded to the histidine ligand in the native HRP, increased the reactivity and catalytic efficiency of the artificial enzyme. The nano biocatalyst did not exhibit suicide inactivation until high concentrations of hydrogen peroxide, indicating that the vesicle hydrophobic pocket effectively shielded the active site, thereby controlling the concentration of hydrogen peroxide at the heme moiety and enabling high rates of enzymatic turnover.



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PLoS one

A Folding Pathway-Dependent Score to Recognize Membrane Proteins

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Abstract

While various approaches exist to study protein localization, it is still a challenge to predict where proteins localize. Here, we consider a mechanistic viewpoint for membrane localization. Taking into account the steps for the folding pathway of α-helical membrane proteins and relating biophysical parameters to each of these steps, we create a score capable of predicting the propensity for membrane localization and call it FP_3mem. This score is driven from the principal component analysis (PCA) of the biophysical parameters related to membrane localization. FP_3mem allows us to rationalize the colocalization of a number of channel proteins with the Cav1.2 channel by their fewer propensities for membrane localization.

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Research paper

The mechanism of antioxidant activity of IRFI005 as a synthetic hydrophilic analogue of vitamin E

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ABSTRACT

Developing a rational strategy to control intracellular reactive oxygen species (ROS) requires understanding the mechanism of antioxidant activity. In this investigation the properties of a novel synthetic analog of vitamin E (IRFI005) with potent antioxidant activity are described. A mechanism is proposed for its efficient radical-scavenging effects. Cellular antioxidant and antitoxicity assays showed IRFI005 to freely permeate across cellular membranes, enabling it to be an effective suppressor of intracellular ROS and to protect cells against toxicity induced by free radical generating compounds. The free radical-scavenging activity of IRFI005 examined by UV–Vis and electron spin resonance (ESR) techniques clearly confirmed a "two electrons and/or H-atom" donation mechanism for each molecule of IRFI005. Reducing power assay as well as semi-empirical calculations revealed that under physiological conditions (pH ~ 7) almost all IRFI005 molecules are in the anionic state ($IRFI005^-$). Data indicated that the electron donating ability of $IRFI005^-$ was dominant at physiological pH because of higher stability of quinine-$IRFI005^-$ and less barrier energy of $IRFI005^-$ than neutral IRFI005. Consequently, the efficient cellular protection of IRFI005 against toxic free radicals can be explained by a two electron-transfer process, because of reduced inter-frontier molecular orbital energy gap barrier at physiological pH. Our findings suggest that hydrophilic vitamin E-like antioxidants are good candidates in designing novel therapeutic strategies for inhibition of oxidative stress associated with different human diseases.

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