Structure-Thermodynamic Relationship in Protein-DNA Binding: Heat Capacity Changes

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1 Introduction

Thermodynamic information on protein-nucleic acid interactions is important for understanding the mechanism of molecular recognition and the regulation of gene expression. We have developed an electronically freely accessible thermodynamic database for protein-nucleic acid interactions, ProNIT [5, 6, 8], which contains several experimentally observed thermodynamic data along with experimental conditions, methods, sequence, structure and the other functional details. In order to understand the molecular mechanism of protein-DNA recognition, we are examining the relationship between structure and thermodynamics in protein-DNA interaction. Heat capacity (ΔC_p) is one of the most important thermodynamic quantities to characterize the binding processes. All of the binding processes of proteins to nucleic acids cause the decreases both in ΔC_p and in solvent accessible surface area (ΔASA). In this paper, we will discuss the relationship between experimental ΔC_p and ΔASA upon binding calculated based on the structural information, and the prediction of ΔC_p based on ΔASA.

2 Calculation of ΔASA

In order to calculate polar and nonpolar ΔASA ($\Delta\mathrm{ASA_p}$ and $\Delta\mathrm{ASA_{np}}$) from the three dimensional structure of the complex in Protein Data Bank (PDB), we used GETAREA, which is freely accessible from internet [3]. We also used Analytic Surface Calculation (ASC) for calculation of ΔASA [1].

3 Relationship between ΔASA and experimental values of ΔC_p

The increase in heat capacity (ΔC_p) upon unfolding of proteins is caused by the hydration change of proteins, and the change in hydration is closely related to the change in polar and nonpolar solvent

accessible surface area, $\Delta\mathrm{ASA_p}$ and $\Delta\mathrm{ASA_{np}}$, respectively. Equation (1) has been proposed for estimating heat capacity change upon unfolding from $\Delta\mathrm{ASA_p}$ and $\Delta\mathrm{ASA_{np}}$. Many attempts have been made to determine the coefficients, a and b. The representative coefficients among them are those obtained by Spolar and Record [7], and Murphy and Freire [4].

$$\Delta C_p(\mathrm{calc}) = a \cdot \Delta\mathrm{ASA_{np}} + b \cdot \Delta\mathrm{ASA_p} \tag{1}$$

Spolar *et al.* [7]	$a = 0.32 \pm 0.04$	$b = -0.14 \pm 0.04$	(unit of ΔC_p: cal mol^{-1} K^{-1})
Murphy *et al.* [4]	$a = 0.45 \pm 0.02$	$b = -0.26 \pm 0.03$	(unit of ΔC_p: cal mol^{-1} K^{-1})

As the ΔASA change upon binding of proteins to nucleic acids is also a measure of the hydration change during the binding process, we compared the experimental values of heat capacity change, ΔC_p(exptl), upon binding with ΔC_p(calc). The values of ΔC_p(calc) based on the values of $\Delta\mathrm{ASA_p}$ and $\Delta\mathrm{ASA_{np}}$ estimated by both the relations are smaller in magnitude than the experimental values.

The difference between the calculated and experimental values of ΔC_p may be caused by the conformational and flexibility change of proteins and nucleic acids, and protonation/deprotonation change of proteins and buffers upon binding. These factors may be different among several protein-nucleic acid systems. If hydration change is the major factor which affects ΔC_p upon binding, we may determine the coefficients of equation (1) on the assumption that ΔC_p(calc) should be equal to ΔC_p(exptl). Using the ten samples of complex (PDB codes: 1cjg, 1ihf, 1glu, 6cro, 1ber, 1tro, 1mse, 1lmb, 1cma, and 1ysa), we obtained the following values for coefficients a and b: $a = 1.12 \pm 0.24$ and $b = -0.61 \pm 0.23$ (unit of ΔC_p: cal mol^{-1} K^{-1}), which are much larger in magnitude than the above values indicating stronger dependence of ΔC_p on ΔASA upon binding than upon unfolding. Though the magnitude of the errors for the coefficients are larger than those by Spolar and Murphy, the linear relation between ΔC_p(calc) and ΔC_p(exptl) were kept, showing the validity of the assumption.

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