# Effects of ligand binding on the stability of aldo-keto reductases

# 学位論文全文に代わる要約
Extended Summary in Lieu of the Full Text of a Doctoral Thesis

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学位論文要約：
Summary of Thesis

Ligands such as enzyme inhibitors stabilize the native conformation of a protein upon binding to the native state, but some compounds destabilize the native conformation upon binding to the non-native state. The former ligands are termed “stabilizer chaperones” and the latter ones “destabilizer chaperones.” Because the stabilization effects are essential for the medical chaperone hypothesis, here we have formulated a thermodynamic system consisting of a ligand and a protein in its native- and non-native state. Using the differential scanning fluorimetry and the circular dichroism varying the urea concentration and temperature, we found that when the coenzyme NADP+ was absent, inhibitors such as isolithocholic acid stabilized the aldo-keto reductase AKR1A1 upon binding, which showed actually the three state folding, but destabilized AKR1B10. In contrast, in the presence of NADP+ , they destabilized AKR1A1 and stabilized AKR1B10. To explain these phenomena, we decomposed the free energy of stabilization (ΔΔG) into its enthalpy (ΔΔH) and entropy (ΔΔS) components. Then we found that in a relatively unstable protein showing the three state folding, native conformation was stabilized by the negative ΔΔH in association with the negative ΔΔS, suggesting that the stabilizer chaperon decreased the conformational fluctuation of the target protein or increase its hydration. However in other cases, ΔΔG was essentially determined by the delicate balance between ΔΔH and ΔΔS. The proposed thermodynamic formalism is applicable to the system including multiple ligands with allosteric interactions. These findings would promote the development of screening strategies for medical chaperones to regulate the target conformations.