LERE-QSAR Analysis of Binding of γ-Lactum Hydroxamic Acid Derivatives with Tumor Necrosis Factor-Alpha Converting Enzyme

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Tumor necrosis factor-alpha converting enzyme (TACE) is a metal enzyme that contains a zinc atom, and TACE converts TNF-alpha into an activated form by hydrolysis. Rheumatism arthritis and Crohn's disease are caused by overproduction of the activated form TNF-alpha. In this study, we examined the atomic and electronic mechanism underlying binding between TACE and hydroxamic acid derivatives, which have a γ-lactum ring [1] (Figure 1), using the ONIOM calculation and LERE (Linear Expression by Representative Energy terms)-QSAR procedure [2]. We constructed complex structures of TACE with each hydroxamic acid derivative using the MM/MD and ONIOM calculations. In the current study, we assumed that the observed overall free-energy change (ΔG_{obs}) in the complex formation can be expressed as a sum of the intrinsic interaction energy (ΔE_{bind}^{ONIOM}) and polar contribution of the solvation free-energy change (ΔG_{sol}^{pol}), and dispersion interaction energy change (E_{disp}), calculated with the ONIOM(HF/6-31G: Amber) mechanical embedding (ME) method, PB calculation, and MM calculation, respectively. The sum of these three representative energy terms is nicely linear with ΔG_{obs}, resulting in the following LERE-QSAR equation;

$$\Delta G_{obs} = 0.129\,[\Delta E_{bind}(\text{ONIOM/HF/ME}) + E_{disp} + \Delta G_{sol}^{pol}] + 16.1$$
$$n = 11,\ r = 0.912,\ s = 0.844 \text{ kcal/mol}$$

Figure 2 shows that there is a negative correlation between ΔE_{bind}(ONIOM/HF/ME) and ΔG_{sol}^{pol}, and that ΔG_{obs} parallels with E_{disp}. These results suggest that the variation of ΔG_{obs} among the derivatives is governed by E_{disp}. We also discuss a detailed binding mechanism by decomposing the binding energy obtained with the FMO calculation into individual contributions of amino acid residues.

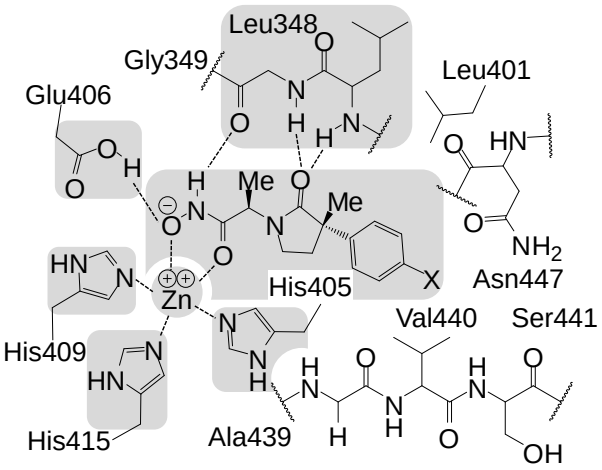

Figure 1. Schematic representation of a γ-lactum hydroxamic acid derivative bound in the TACE active site. Atoms in shadow areas are treated as the quantum region in the ONIOM calculation.

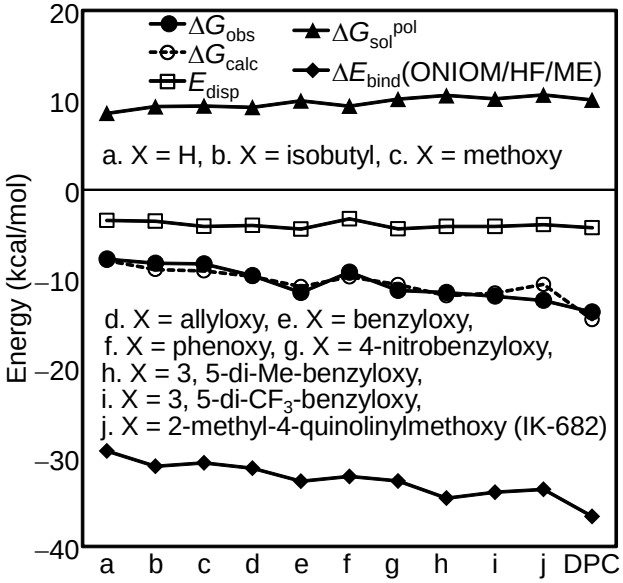

Figure 2. Variation in ΔG_{obs}, ΔG_{calc}, E_{disp}, ΔG_{sol}^{pol}, and ΔE_{bind}(ONIOM/HF/ME).

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[2] T. Yoshida, S. Hitaoka, A. Mashima, T. Sugimoto, H. Matoba, and H. Chuman, *J. Phys. Chem. B*, **2012**, *116*, 10283–10289.