KP224 Comparative QSAR Analyses of a Series of Benzene Sulfonamide Inhibitors Based on *Ab Initio* MO Calculation of Their Complex Structures with Carbonic Anhydrase

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1. Introduction

Carbonic anhydrase (CA) is a zinc containing metalloprotein (shown in Figure 1), and catalyzes various chemical reactions such as acid-base equilibrium, pH control, and carbon dioxide transportation [1]. Several classical QSAR studies as to CA inhibitors of the sulfonamide type using the Hansch−Fujita approach have been published [2, 3]. In these studies, parameters used in the QSAR equations were derived only from chemical structures of inhibitors, but three-dimensional structural information on inhibitors and their target protein was not considered. In this paper, we discuss detailed interaction mechanisms between CA and a series of benzene sulfonamide derivatives (BSAs) based on results of molecular orbital calculations on their complex structures.

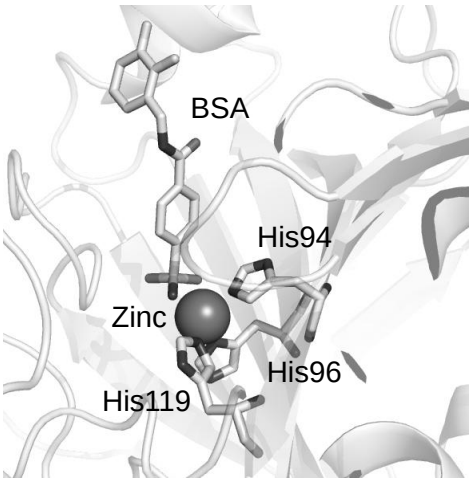

Figure 1. Complex structure of CA with BSA. (PDB; code 1G52)

2. Methods

2-1. Compound Set

Sixteen BSAs were selected from those used in the classical QSAR study reported by Hansch *et al* [2].

2-2. Molecular Modelling of CA−BSA Complexes

The initial geometry of CA−BSA complexes was constructed based on the X-ray crystallographic coordinates (PDB code: 1G52 [4]). As shown in Figure 2, amino acid residues in the active site of CA and BSA were extracted from the total complex structure ("simplified model"), and then geometry optimization was done on the model by means of *ab initio* MO calculations at the HF/3−21G* level.

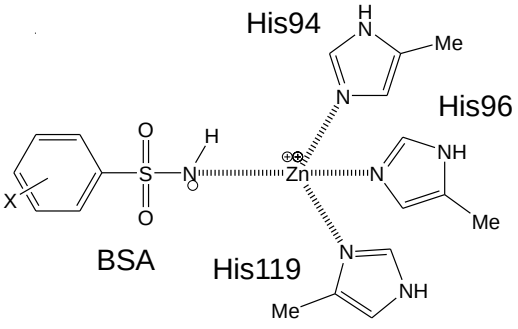

Figure 2. Simplified model of CA−BSA complex.

2-3. QSAR Descriptors

Structure-dependent QSAR descriptors, ΔE_{bind} and Δq(BSA), were defined from each optimized CA−BSA complex structure;

$$\Delta E_{bind} = E(\text{complex}) - [E(\text{protein}) + E(\text{BSA})] \quad (1)$$

$$\Delta q(\text{BSA}) = q(\text{BSA})^{complex} - q(\text{BSA})^{free} \quad (2)$$

ΔE_{bind} and Δq(BSA) were calculated with HF/6−31G(d)//HF/3−21G*and the difference of total charges of BSA between those in complex and in free states is denoted as Δq(BSA).

3. Results and Discussion

Assuming that an ionized form of BSA is the active species that binds with the active site of CA directly, we formulated Eq. 3 for the binding step (K_b) with the Hammett σ constant.

$$pK_b = 1.90\ (\pm 0.179)\sigma - 4.55(\pm 0.109) \quad (3)$$
n =16, r = 0.987, s = 0.184, F = 519

The positive coefficient of σ in Eq. 3 indicates that an electron-donating group increases the binding potency. It should be noted that the coefficient of σ in the QSAR equation originally reported by Hansch *et al* [2] is negative, because they treated the binding and ionization (K_a) steps of BSAs together ($pK_i = pK_a + pK_b$) in their equation.

As expected, σ in Eq. 3 can be successfully replaced by ΔE_{bind}.

$$pK_b = 0.125(\pm 0.0155)\,\Delta E_{bind} + 22.9(\pm 3.34) \quad (4)$$
n = 16, r = 0.977, s = 0.239, F = 300

As can be seen from Eq. 5, the amount of charge transfer between BSA and the active site of CA nicely correlates with ΔE_{bind}.

$$\Delta E_{bind} = 652(\pm 92.8)\,\Delta q(\text{BSA}) - 17.4(\pm 28.3) \quad (5)$$
n = 16, r = 0.971, s = 2.14, F = 229

These results represent that charge transfer and redistribution induced by the complex formation between BSA and CA govern the variations in the binding potency, elucidating a meaning of the Hammett σ constant in Eq. 3. Results for the full complex structures will be presented, as well as those for the simplified model.

References

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