KP208 Kinetic Description and QSAR for the Degradation Reaction of Electrophilic 1-β-*O*-Acyl Glucuronides

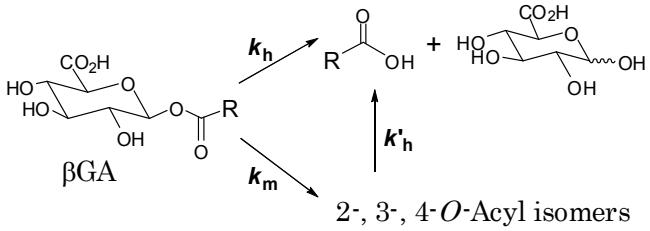
Akiko BABA, Tadao YOSHIOKA

Hokkaido Pharmaceutical University School of Pharmacy, 7-1 Katsuraoka-cho, Otaru, 047-0264
yoshioka@hokuyakudai.ac.jp

1. Introduction

Drug metabolism and pharmacokinetics have played significant roles in the research of adverse drug reactions (ADRs) in the past 20 years, not only in revealing the underlying mechanisms of ADRs, but also in facilitating drug discovery and development. 1-β-*O*-Acyl glucuronides (βGAs), major metabolites of carboxylic acid drugs, are generally labile at physiological pH and have been thought to be causally related to ADRs of some non-steroidal anti-inflammatory drugs (NSAIDs) in that βGAs are capable of irreversible covalent binding to proteins, a process implicated in ADRs such as necrotic and idiosyncratic reactions. Therefore, βGAs have been extensively and increasingly investigated for their metabolic formation, chemical reactivity, and ability to bind covalently to proteins.

βGAs are known to undergo both hydrolysis (rate constant; k_h) and intramolecular acyl migration (rate constant; k_m) of the 1-β-*O*-acyl linkage at physiological pH. Both the electrophilic reactivities, affected by the R group of βGAs, would be associated with the extent of covalent binding to proteins, because a correlation between the ability of some βGAs to bind covalently to HSA and their degradation rate constant (k; $k_h + k_m$) has been reported. However, a QSAR for predicting the k values of structurally diverse βGAs is far from being established.



The aim of this study was to determine the k values of structurally diverse 26 βGAs as well as 3 related compounds under physiological conditions, and to provide a detailed QSAR predicting the electrophilic reactivities of βGAs, which are likely associated with ADRs of parent carboxylic acid drugs, and are also hypothetical metabolites derived from those drug candidates under evaluation for safety.

2. Method

Using our highly β-selective chemo-enzymatic method or applying a reported method to synthesis of βGAs, we obtained 26 βGAs and 3 related compounds from the corresponding carboxylic acids, including 4 kinds of NSAIDs (diclofenac, felbinac, mefenamic acid, and naproxen), shown in Fig. 1. Each compound

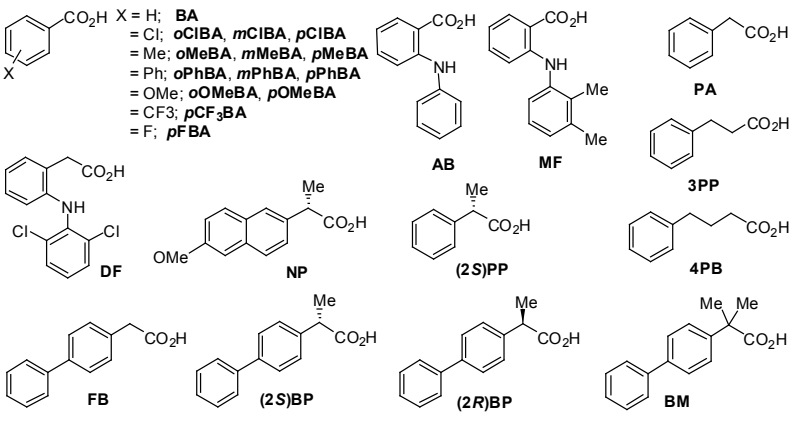
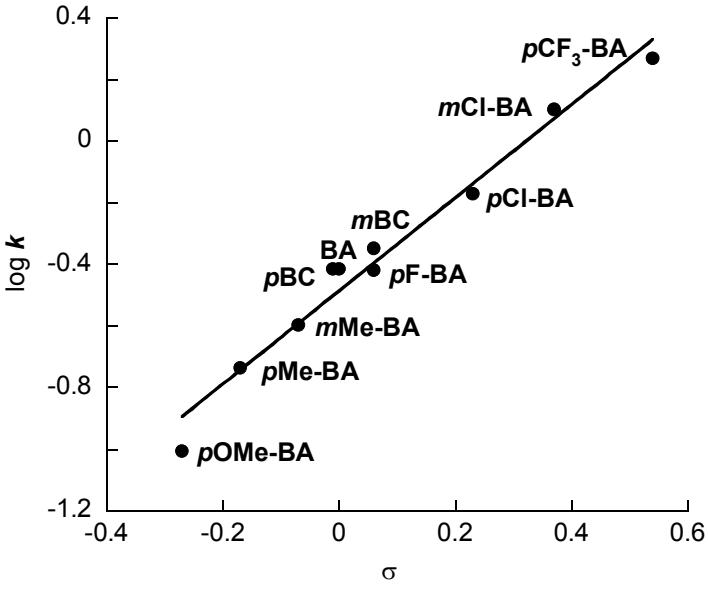


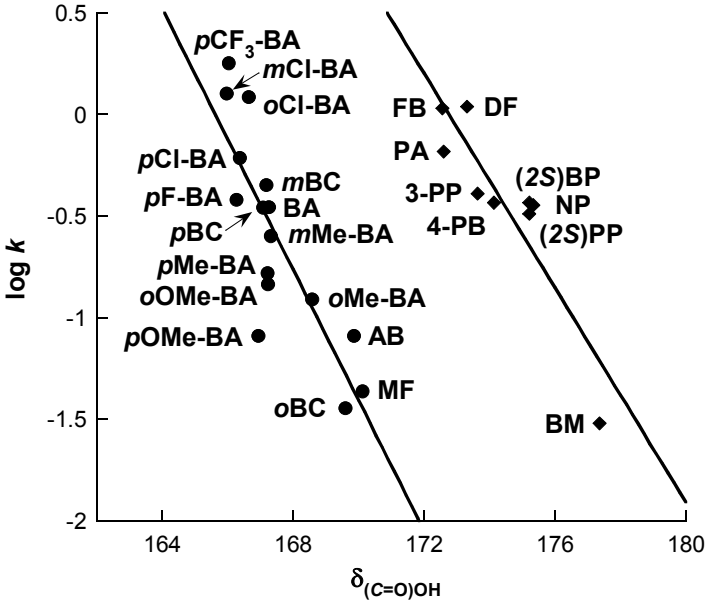
Fig.1 Structures and abbreviations of carboxylic acids used.

was incubated in 100 mM sodium phosphate buffer (pH 7.4) at 37 °C for the time-course analysis with a reversed phase HPLC. For QSAR studies, $\delta_{\boldsymbol{C}=O}$ of 1-β-*O*-acyl linkage of βGAs and $\delta_{COO\boldsymbol{H}}$ and $\delta_{(\boldsymbol{C}=O)OH}$ of the corresponding parent carboxylic acids were measured.

3. Results and Discussion

The degradation reaction of βGAs was shown to obey pseudo first-order reaction kinetics and the k_m was far greater than k_h, indicating that the intramolecular acyl migration is predominant degradation pathway. The k_m of 1-α-*O*-benzoyl glucuronide was greater than that of the β-anomer, probably due to an advantage in the formation of the corresponding 1,2-hemiorthoester intermediates.





1-β-*O*-Benzoyl glucuronide and glucopyranoside gave almost same *k* values. Log *k* of βGAs, derived from *m*- and *p*-substituted benzoic acids, gave a good positive correlation with Hammett's σ constants. Using $\delta_{COO\boldsymbol{H}}$ of the parent carboxylic acids as a descriptor, a similar correlation was observed with βGAs including ones with less sterically bulky *o*-substituents (*o*-Cl, *o*-Me, *o*- OMe). However, the *k* of βGAs with bulkier *o*-substituents deviated downward from the regression line, probably due to a steric effect. The *k* of βGAs derived from *n*-aralkyl acids correlated well with their $\delta_{COO\boldsymbol{H}}$. Of diastereo-isomeric βGAs, the *k* of βGA derived from (2*R*)BP was ca. 2-fold greater than that of βGA derived from (2*S*)BP. Furthermore, the *k* of βGA derived from BM drastically decreased. These results indicate that the intramolecular acyl migration was sterically encumbered by the α-methyl group in βGAs derived from (2*S*)BP and BM. As alternative descriptors, ^{13}C chemical shifts of $\delta_{\boldsymbol{C}=O}$ and $\delta_{(\boldsymbol{C}=O)OH}$ also correlated with log *k*, showing negative correlation coefficients. With each descriptor, two regression lines were obtained with the respective βGAs derived from benzoic acids and aralkyl acids except for (2*R*)BP. The easily measurable $\delta_{(\boldsymbol{C}=O)OH}$ is a better descriptor for predicting *k* of βGAs, because it enables prediction without the synthesis of βGAs. Taken together, the diversity and complexity of *k* values obtained in this study were demonstrated to be mainly dependent on two factors: the electrophilicity of the ester carbonyl carbons and the steric hindrance around them.