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Comparative QSAR of the sulfonamide function

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Abstract

The aromatic SO_2NH_2 function has been characterized in biological reactions and in physical organic chemical reactions using the Hammett constant σ, the Swain–Lupton parameter F and steric constants. The results allow comparable support for the biological processes from the much better understood mechanistic organic reactions. The approach is applied to the enzyme carbonic anhydrase and the rate of excretion of Na^+ by rats. From the study of QSAR on the ionization of the amide function, it is clearly apparent that it is the ionized form of SO_2NH_2 that promotes the biological processes. It is clear from Fujita–Nishioka proposal that, in dealing with *ortho* substituents, one should routinely test σ, F and a steric parameter to account for substituent effects.

Keywords: QSAR; Carbonic anhydrase

1. Introduction

We have been interested in formulating QSAR for chemical–biological interactions since 1962 [1]. Gradually it occurred to us that it might be worthwhile to also add LFER equations from studies in physical organic chemistry. At that time, we had no idea that chemical LFER equations could be used to support the biological studies. Slowly, it dawned on us that they could supply important support. Now we have a database of 17,980 equations of which 9000 are from biosystems and the rest are from physical organic chemistry [2]. Of course, the biological QSAR are far more difficult to evaluate and we now realize that a new bio QSAR, standing alone, cannot be taken very seriously. Good statistics alone are not enough. As Mark Twain said, there are "lies, damn lies, and statistics". We have recently published reviews of such comparisons for a variety of substituents where radical reactions are involved [3,4].

The best lateral support for a new biological QSAR comes from another QSAR, especially one from physical organic chemistry where more precise data are readily obtained. Of course, the main connection between the two systems is the Hammett parameters. At present we have 1997 bio QSAR that contain one or more Hammett terms. We now compare results from the two systems for studies with X-$C_6H_4SO_2NH_2$.

2. QSAR from biological systems

The study leading to QSAR 1 was that of Kakeya et al. [5].

2.1. Inhibition of carbonic anhydrase (CA) by X-$C_6H_4SO_2NH_2$ at 0.2 °C

$$\log\frac{1}{K_i} = 0.84(\pm0.17)\sigma + 0.32(\pm0.16)C\log P - 0.61(\pm0.19)B5_2 + 5.90(\pm0.27), \quad (1)$$

$n = 18$, $r^2 = 0.950$, $s = 0.159$, $q^2 = 0.914$,
outlier: 3-Cl

2.2. Inhibition of CA at 15 °C [5]

$$\log\frac{1}{K_i} = 0.87(\pm0.16)\sigma + 0.29(\pm0.15)C\log P - 0.44(\pm0.18)B5_2 + 5.78(\pm0.25), \quad (2)$$

$n = 19$, $r^2 = 0.948$, $s = 0.151$,
$q^2 = 0.924$

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The results from the studies at two different temperatures are essentially identical except for the poor fit of the 3-Cl derivatives in QSAR 1. We believe that an experimental error is the cause of this misfit. A third study on the inhibition of CA is that of Lien et al. [6].

$$\log\frac{1}{C} = 0.88(\pm0.20)\sigma + 0.33(\pm0.15)C\log P - 0.65(\pm0.35)B1_2 + 5.96(\pm0.41), \quad (3)$$
$$n = 19, \quad r^2 = 0.930, \quad s = 0.175, \quad q^2 = 0.853$$

Lien et al. state that their data was selected from several sources including Kakeya et al. [5]. In none of the above three QSAR did the authors attempt to use steric parameters to account for three *ortho*-substituted congeners. They simply omitted the *ortho* results. The reason for the steric parameter B1 in Eq. (3) performing better than B5 used in Eqs. (1) and (2) is not clear.

The sterimol parameters were invented by Verloop et al. Those parameters have been discussed and applications illustrated by us [7]. We have listed values for over 1000 different substituents [8]. Although they have received essentially no attention by physical organic chemists, we have often found them to be superior to Es for intramolecular steric effects and valuable for intermolar steric effects. Checking our phys database we find 304 equations based on Taft's Es and 395 on B1. Actually, a greater disparity exists, since for the first 3000 QSAR entered, we could not make this comparison. The same holds true for bio QSAR where we find 317 QSAR based on Es and 977 based on B1. B1 is primarily a measure of the volume of the first atom of a substituent, B5 is an attempt to define the width of a substituent and L is its length. It is surprising that $B1_2$ works best in QSAR 3, but $B5_2$ works best in QSAR 1 and 2. From a later study by Carotti et al. [9] using bovine CA we developed QSAR 4.

$$\log\frac{1}{K_i} = 0.93(\pm0.28)\sigma + 0.57(\pm0.09)C\log P - 0.37(\pm0.10)B5_3 + 6.12(\pm0.20), \quad (4)$$
$$n = 31, \quad r^2 = 0.890, \quad s = 0.257, \quad q^2 = 0.854,$$
outliers: 3-SO_2NH_2, 4-SO_2NH_2

Carotti et al. used π constants instead of $C\log P$ and obtained a poorer result: $r^2 = 0.835$. π values for substituents can be significantly influenced by substituent interaction with strongly polar functional groups. When possible it is preferable to use $C\log P$ [10] that takes such interactions into account. Of course, the outliers are expected since they introduce a second functional group. Note that the coefficient with σ is essentially the same in QSAR 1–4. It is not clear why B5 is needed for *meta* substituents instead of B1 for *ortho* substituents. From data on the inhibition of human CA by X-$C_6H_4SO_2NH_2$ from King and Burgen [11] we have derived QSAR 5.

$$\log k = 1.55(\pm0.36)\sigma + 0.65(\pm0.08)\log P - 5.13\ B1_2 - 3.34(\pm0.32)B1_3 + 15.4(\pm0.56), \quad (5)$$
$$n = 29, \quad r^2 = 0.984, \quad s = 0.192, \quad q^2 = 0.977$$

Eq. (5) is an extremely sharp correlation with no outliers. Earlier we had derived a somewhat different equation based on molecular refractivity (MR) [12]. In QSAR 5, the coefficient with σ is positive, but much larger than in QSAR 1–4. Whether this is due to the human enzyme and/or expressing the results in terms of $\log k$ is not clear. Kakeya et al. did not indicate what kind of CA was employed. The substituents studied by King and Burger are much larger, e.g. $-CO_2R$ and CONR where R ranges from C1 to C7, hence the much larger coefficients with B1. QSAR 5 contains an additional B1 term for *meta* substituents that is quite significant. This may be due to the use of human enzyme.

Moving from enzymes to an in vivo study with rats [13], in which the concentration that increased the urinary excretion of Na^+ by a factor of 3 for X-$C_6H_4SO_2NH_2$ was analyzed, we derived QSAR 6.

$$\log\frac{1}{C} = 0.57(\pm0.15)\sigma + 0.12(\pm0.23)C\log P - 0.16(\pm0.12)C\log P^2 + 3.24(\pm0.11), \quad (6)$$
$$n = 14, \quad r^2 = 0.912, \quad s = 0.104, \quad q^2 = 0.692,$$
outliers: 4-CN, 3-NO_2, 4-Cl,
optimum $C\log P$: 0.39 (−1.2 to 0.79)

Kakeya et al. did not obtain a QSAR for this data set. It is of interest that no steric effect is observed in QSAR 6 and the electronic effect is smaller than that in QSAR 1–5. In a subsequent study on a large set of compounds, Kakeya et al. [14] obtained data from which we have derived QSAR 7.

$$\log\frac{1}{C} = 0.59(\pm0.18)\sigma - 0.67(\pm0.20)B5_2 + 0.12(\pm0.31)C\log P - 0.18(\pm0.17)C\log P^2 - 0.18(\pm0.17), \quad (7)$$
$$n = 18, \quad r^2 = 0.885, \quad s = 0.156, \quad q^2 = 0.744,$$
outlier: 3-NO_2, 4-Cl,
optimum $C\log P$: 0.33 (−11.3 to 0.77)

Although the confidence intervals are not good on the optimum $C\log P$ the agreement between the two studies is good. In both instances the same σ term is present, and the 3-NO_2 and 4-Cl compounds are misfits.

We believe that the 4-Cl is highly activated by the electron-withdrawing SO_2NH_2 and 3-NO_2 groups, so that it undergoes side reactions with nucleophilic functions. It is considerably less active than predicted.

3. Physical organic QSAR

The above results can now be compared with results from physical organic chemistry. Data from Dauphin and Kergomard [15] have lead to the formulation of Eq. (8).

3.1. Ionization of X-$C_6H_4SO_2NH_2$ in aqueous solution at 20 °C

$$\log k = 0.87(\pm 0.07)\sigma + 10.02(\pm 0.04), \quad n = 13, \quad r^2 = 0.985, \quad s = 0.058, \quad q^2 = 0.977 \tag{8}$$

3.2. Ionization of X-$C_6H_4SO_2NH_2$ in aqueous solution at 20 °C [5]

$$\log k = 0.63(\pm 0.09)\sigma - 0.76(\pm 0.32)\mathrm{F2} - 9.9(\pm 0.07), \quad n = 18, \quad r^2 = 0.954, \quad s = 0.105, \quad q^2 = 0.930 \tag{9}$$

Kakeya et al. could not include three examples where *ortho* substituents were present. Using the inductive parameter F for *ortho* substituents we were able to do so. Fujita and Nishioka [16] demonstrated that the role of *ortho* substituents in QSAR could be clarified by testing $\sigma + F +$ Es. We have found that B1 normally is better than Es. Sometimes only F is required as in the case of QSAR 9. At the moment we have 169 examples in the phys database where $S + F$ are required. Of these, 40 also contain B1. There are 17 examples where Es works better than F. We have also found a number of instances in bio QSAR where this approach extends ones reach. The discovery of the value of F as well as a steric parameter for *ortho* substituent is quite important and has largely been neglected by physical organic chemists.

3.3. Ionization of X-$C_6H_4SO_2NH_2$ in aqueous solution [17]

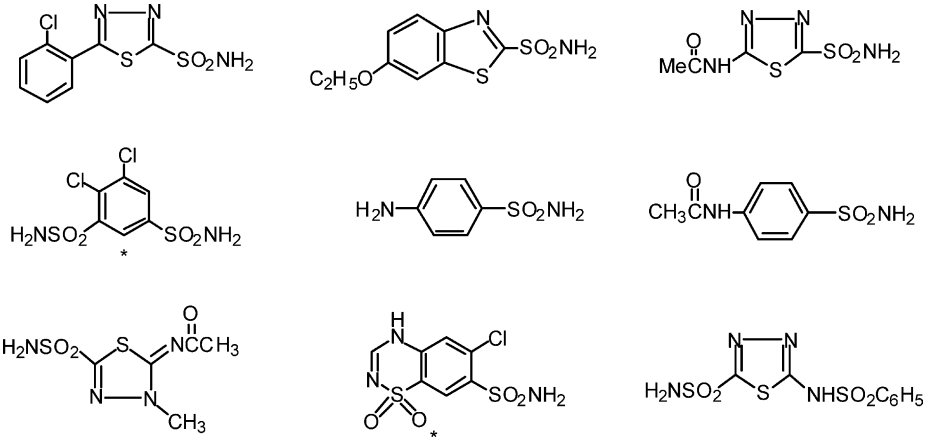
$$\log k = 1.02(\pm 0.07)\sigma + 9.97(\pm 0.04), \quad n = 8, \quad r^2 = 0.992, \quad s = 0.047, \quad q^2 = 0.984 \tag{10}$$

QSAR 8–10 show that the electronic terms in QSAR 1–7 are firmly associated with the ionization of the NH_2 moiety.

It has long been known [18] that CA promotes the reaction $H^+ + HCO_3^- \rightleftharpoons CO_2 + H_2O$. Without this possibility NCO_3^- could not deliver carbon dioxide from the tissues or through the lungs. X-$C_6H_4SO_2NH_2$ that inhibits CA played an important role in this research. A miscellaneous set of compounds containing SO_2NH_2 and acting on dog red cell enzyme yields the following QSAR [19]

$$\log \frac{1}{C} = 0.35(\pm 0.28)\log P - 0.61(\pm 0.19)\ \mathrm{p}K_a + 12.2(\pm 1.5), \quad n = 7, \quad r^2 = 0.953, \quad s = 0.365, \quad q^2 = 0.503, \quad \text{outliers: ethoxyzolamide, chlorothiazide} \tag{11}$$

Compounds covered by QSAR 10:



These data points (*) were omitted in the derivation of QSAR 10. Unfortunately, with such a miscellaneous set

of chemicals, steric effects cannot be assessed; however, pK_a accounts for the electronic effects. To convert pK_a to degree of ionization, multiply by -1. This provides a rough comparison with the other QSAR. Almost all organisms utilize CA to eliminate CO_2 [20]. The acidity of the SO_2NH_2 function is as we have seen important in the inhibition of CA. Thus, it is not surprising that the toxicity of SO_2NH_2 to microorganisms shows a similar dependence on σ. This is illustrated by QSAR 12 developed from the data of Silipo and Vittoria [21].

3.4. MIC of Escherichia coli

$$\log\frac{1}{C} = 1.01(\pm0.16)\sigma + 0.21(\pm0.10)\text{Es-2} + 4.86(\pm0.09),$$
$$n = 36, \quad r^2 = 0.838, \quad s = 0.198, \quad q^2 = 0.802 \quad (12)$$
outliers: 2-OMe, 4-Cl; 2-Cl; 2-I; 2-Cl, 4-SO_2NH_2

There are four significant outliers. The example with the 4-SO_2NH_2 is much more active than predicted, as one would expect from the presence of two SO_2NH_2 groups. Silipo and Vittoria did not consider steric effects as our studies with the isolated enzyme lead us to do. Adding a term in F did not improve the results; however, Es is important.

4. Discussion

We have been able to extend our project to establish the relationship of biological reaction mechanisms with those of physical organic chemistry via electronic and steric parameters. It is of interest that use of the Swain and Lupton [22] field/inductive parameter F enabled us to include *ortho* substituents that other researcher have had to omit from these correlations. The value of the Fujita and Nishioka hypothesis [16], that one should test the combination of σ, F and a steric parameter for *ortho* substituents, has been confirmed. Thus, we could include compounds in our QSAR that others had to omit.

A serious problem for those doing QSAR is that of understanding when a given moiety is acting as a substituent or as a functional group [23]. This is illustrated by examples where two SO_2NH_2 functions have been included in the same compound. This is an obvious problem with SO_2NH_2 but it can be obfuscating in instances such as OH and NH_2 [23].

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