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QSAR study on pK_a vis-à-vis physiological activity of sulfonamides: a dominating role of surface tension (inverse steric parameter)

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Abstract—The paper describes the dominating role of surface tension (ST) on the modeling, monitoring, and estimating pK_a for a large series of 43 substituted sulfonamides. Because of the direct correlation of ST with parachor (Pc) vis-à-vis molecular volume (MV), ST is considered as a steric parameter. Single as well as multi-parametric regressions have indicated that ST has a dominating role in QSAR of the set of sulfonamides used and that excellent results are obtained in multi-parametric regression analysis. The results are discussed critically on the basis of statistical parameters.

1. Introduction

The sulfonamides constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial, anticarbonic anhydrase, diuretic, hypoglycemic, and antithyroid activity among others.[1–3] A large number of structurally novel sulfonamide derivatives have ultimately been reported to show substantial antitumor or antiviral activity in vitro and in vivo.[1–3] Although they have a common chemical motif of aromatic/heterocyclic or amino acid sulfonamide, there are a variety of mechanisms of their biological action, such as carbonic anhydrase inhibition, cell cycle perturbation in the G1 phase, disruption of microtubule assembly, functional suppression of the transcriptional activator NF-Y, and angiogenesis (matrix metalloproteinase, MMP) inhibition among others.[1–4] Some of these compounds selected via elaborate preclinical screenings or obtained through computer-based drug design, are currently being evaluated in clinical trials.[1–4]

The biological activity of the sulfonamides depends upon the way (strength) with which they bind to their receptor/enzyme. This ability of binding depends upon proton-ligand formation constants of the sulfonamides; more commonly expressed by pK_a of the sulfonamides.[5,6] Like many other organic compounds acting as drugs, the physiological activity of the sulfonamide also depends upon their pK_a. Prompted by these results, we have undertaken the present investigation in that we have carried out QSAR (quantitative structure activity relationship) study on a set of sulfonamides (Table 1) with a view to investigate the dominating role of surface tension (ST). This physicochemical parameter is directly related to parachor (Pc), which in turn is related to molar volume (MV). Thus, we can treat ST, as a steric parameter. Consequently the present study is based on the dominating role of steric effect on the exhibition of pK_a, that is for modeling, monitoring, and estimating pK_a of the sulfonamides. Such a study will be helpful to those interested in investigating physiological activity of sulfonamides. We have, therefore, considered a large set of 43 sulfonamides and adopted their pK_a as reported in the literature.[7,8] The results as discussed below

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Table 1. Substituents, observed pK_a and indicator parameters for sulfonamides used in the present study

Compd no.	X	Y	pK_a	I_X	I_Y	I_N
1	H	H	9.10	0	0	0
2	H	4-OMe	9.42	0	1	0
3	H	4-Me	9.35	0	1	0
4	H	4-F	8.90	0	0	0
5	H	4-Cl	8.47	0	0	0
6	H	4-Br	8.50	0	0	0
7	H	3-Br	8.25	0	0	0
8	H	3-NO_2	7.50	0	0	0
9	3-NO_2	H	7.93	0	0	0
10	3-NO_2	4-OMe	8.44	0	1	0
11	3-NO_2	4-Me	8.27	0	1	0
12	3-NO_2	4-F	7.85	0	0	0
13	3-NO_2	4-Cl	7.51	0	0	0
14	3-NO_2	4-Br	7.42	0	0	0
15	4-Cl	H	8.75	0	0	0
16	4-Cl	4-OMe	9.19	0	1	0
17	4-Cl	4-Me	9.02	0	1	0
18	4-Cl	4-F	8.61	0	0	0
19	4-Cl	4-Cl	8.30	0	0	0
20	4-Cl	4-Br	8.24	0	0	0
21	4-Cl	3-NO_2	7.19	0	0	0
22	4-F	H	8.85	0	0	0
23	4-F	4-OMe	9.32	0	1	0
24	4-F	4-Me	9.20	0	1	0
25	4-F	4-F	8.73	0	0	0
26	4-F	4-Cl	8.41	0	0	0
27	4-F	4-Br	8.38	0	0	0
28	4-F	3-NO_2	7.27	0	0	0
29	4-Me	4-OMe	9.80	1	1	0
30	4-Me	4-Me	9.65	1	1	0
31	4-Me	H	9.34	1	0	0
32	4-Me	4-F	9.23	1	0	0
33	4-Me	4-Cl	8.78	1	0	0
34	4-Me	3-NO_2	7.80	1	0	0
35	4-NH_2	H	10.29	0	0	1
36	4-NH_2	4-Me	10.53	0	1	1
37	4-NH_2	3-Me	10.44	0	1	1
38	4-NH_2	4-Cl	9.76	0	0	1
39	H	4-N	6.66	0	0	0
40	3-NO_2	4-NO_2	5.51	0	0	0
41	4-Cl	4-NO_2	6.24	0	0	0
42	4-F	4-NO_2	6.45	0	0	0
43	4-Me	4-NO_2	6.78	1	0	0

I_X = accounting for alkyl substitution at X, I_Y = accounting for alkyl substitution at Y, I_N = accounting for amide substitution.

establishes the dominating role of ST and that excellent results are obtained for multi-parametric model for that some distance-based topological indices together with some indicator parameters are needed.

2. Results and discussion

In our earlier results we have shown that we can use distance-based topological indices for modeling inhibition activities of benzenesulfonamides.[9–13] In addition, some physicochemical parameters were also used successfully for modeling the inhibitory activity.[14,15] Our earlier studies[16–18] related to other type of organic compounds acting as drugs, indicated that one can use topological indices for modeling their pK_a. Consequently, our results herein relates to the use of surfaces tension (ST), distance based topological indices (W, $^1\chi$, J, Sz) along with indicator parameters (I_X, I_Y, I_I) for modeling, monitoring and estimating pK_a of the sulfonamides used. The details of these molecular descriptors are given in the experimental section. The set of 43 sulfonamides and their pK_a are same as reported in the literature[7,8] (Table 1). In doing QSAR study we have used maximum R^2 method and followed step-wise regression analysis[19] and used the correlation matrix (Table 3). This matrix shows that W, Sz, and $^1\chi$ are highly linearly correlated and that these topological indices along with ST can be used to yield a multi-parametric model for modeling pK_a of the sulfonamides used (Fig. 1).

The simple regression analysis has shown that among the molecular descriptors used (Table 2), surface tension (ST) gives better results. This, therefore, indicates the dominating role of ST in modeling pK_a of the sulfonamides used. The mono-parametric model is found as below:

$$\begin{aligned} \mathrm{p}K_a &= 15.0504 - 0.1120(\pm 0.0207)\mathrm{ST}, \\ n &= 43,\ \ \mathrm{Se} = 0.8739,\ \ R = -0.6450, \\ F &= 29.231,\ \ Q = -0.7400 \end{aligned} \tag{1}$$

Here and there after, n—number of compounds, Se—standard error of estimation, R—simple correlation coefficient, and R^2_A-adjustable R-square. Eq. 1 indicates that pK_a is inversely proportional to ST, that is, pK_a goes on increasing with decrease in the magnitude of ST. Since ST is related to parachor (Pc), which in turn is related to molar volume (MV) it (ST) accounts for steric effect. We can, therefore, say the decrease in pK_a is due to increase in the steric effect.

In successive regression analysis we have carried out several bi-parametric regression analyses in three ways:

(i) combination of ST with one of the indicator parameters,
(ii) combination ST with one of the nontopological parameters, and
(iii) combination ST with one of the topological indices.

In all such bi-parametric regression analysis better results than the mono-parametric model discussed above (Eq. 1) are obtained. However, the bi-parametric regression containing ST and I_N yielded excellent model according to the following equation:

$$\begin{aligned} \mathrm{p}K_a &= 16.4519 - 0.1401(\pm 0.0097)\mathrm{ST} \\ &\quad + 2.6977(\pm 0.2145)I_N, \\ n &= 43,\ \ \mathrm{Se} = 0.3971,\ \ R = 0.9394, \\ R^2_A &= 0.8765,\ \ F = 150,\ \ Q = 2.36 \end{aligned} \tag{2}$$

Looking to the sample size, this is an excellent model. Only a single physicochemical property viz ST is capable of modeling pK_a excellently. This model once again establishes the dominating role of ST in modeling, monitoring, and estimating pK_a of the benzene sulfonamides used. Like earlier case here also the coefficient ST term