QSAR study on benzenesulfonamide dissociation constant pKa: physicochemical approach using surface tension

Abhilash Thakur

Department of Chemistry, Rishiraj Institute of technology, Indore, India
E-mail: abhilashthakur@yahoo.com

Abstract

QSAR study on benzenesulfonamide dissociation constant pKa has been made using the physicochemical parameter surface tension (ST). The regression analysis has shown that even in mono-parametric regression this physicochemical parameter gave significant results. Furthermore, using the combination of the surface tension (ST) with the refractive index (η) and indicator parameter, remarkable improvement in the statistics has been observed. The results are discussed critically on the basis of regression data and cross – validation parameters.

Keywords: QSAR, physicochemical properties, regression analysis, dissociation constant pKa, benzenesulfonamide

Introduction

The chemical, physiological and pathological processes in which dissociation constant pKa are involved were thoroughly investigated due to the chemical and pharmacological applications of benzene sulfonamides.[1-3] It has also been shown[2] that some benzene sulfonamide are important clinical agents, mainly they are used in the treatment of gastro-intestinal – duodenal ulcers, neurological disorders, glaucoma, altitude sickness and for some forms of tumor[3-8]

Accordingly, a large number of sulfonamides were synthesized and tested for their biological, physiological and pharmacological potential[9]. In the middle of them benzene derivatives of sulfonamides have attracted much consideration[9,10].

In the earlier part of QSAR studies the study on benzene-sulfonamide were mostly based on the Hansch's[11] approach. In the later QSAR studies, some other related molecular descriptors were used. In our previous study,[12] we have shown that topological indices can be successfully used for this purpose.

Literature shows that no QPAR studies using such physicochemical properties have been reported. In view of this and in persistence to our earlier work,[13-17] the present study deals with

physicochemical investigation on this class of sulfonamide, in which we have used the physicochemical parameter surface tension (ST).

At this stage, it is interesting to record that physicochemical properties are based on the molecular structure and the arrangement of bond in the molecules. Detailed information regarding these physicochemical properties ware reported in the literature[18]. Out of these physicochemical parameters, Molar Refractivity, Refractive Index and electronic parameter (σ) have been used extensively. But there are no examples of quantitative property-activity-relationship (QPAR) studies based on surface tension (ST) available in the literature.[19-23]

The theoretical chemists have been very slow to appreciate the intervening importance of the physicochemical property surface tension (ST) in modifying their biological process.

The dissociation constant pKa depends upon the polarity of molecule and directly or indirectly on the intra and intermolecular forces. It was implicit that for maximum activity, the sulfonamides should have a pKa that gives the proper equilibrium between the inherent activity and penetration, the half-dissociated status appears to present the best compromise between transport and activity.[24,25] The biological activity of the sulfonamides depends upon the way (strength) with which they bind to their receptor/enzyme. This ability to binding depends upon proton-ligand formation/ dissociation constants of the sulfonamides; more commonly expressed by pKa of the sulfonamides.[26,27]

The parameters accounted for the intra and intermolecular forces and steric effect definitely plays a significant role in the modeling of dissociation constant pKa. Surface tension (ST) or Inter facial tension is the cumulative effect of the different intra and intermolecular forces of two different surfaces. 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. Thus, in other words the present study is based on the dominating role of steric effect on the exhibition of pKa.

The relationship between MV, Pc and ST could only be expressed through the expression for parameter. These three forms are expressed by the following equations:

$$\text{Molar Volume} = MV = MW/d$$

$$Pc = (MW/d)\, ST^{1/4}$$

$$\text{Surface Tension} = ST = (Pc/MV)^4$$

Since ST is inversely proportional to MV, therefore, this is inverse steric effect.

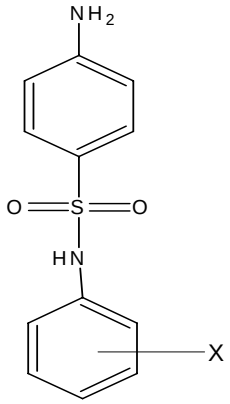

Figure 1. Parent structure of Benzene sulfonamide.

Result and Discussion

In proposing QSAR/QPAR models for modeling the activity, we have used the maximum R^2 method. Initially we have used Pogliani's quality factor Q[28,29] for investigating relative predictive power and finally cross-validation[30] techniques.

The benzene sulfonamide, their adopted dissociation constant (pKa), calculated activity and indicator parameters are reported in the Table 1. The physicochemical properties calculated for the set of 21 benzene sulfonamide derivatives are presented in Table 2.

The correlation of the used parameters and their correlation with the activity are shown in Table 3. The results (Table 3) show that all the three physicochemical parameters (ST, η, D) are mutually correlated. Thus, if any two of them or all the three are present in the regression expression then the model may suffer from the defect due to collinearly. However, their occurrence will be dealt with according to the recommendations made by Randic[31].

The cross validation parameters used for investigating predictive power of the proposed models are recorded in Table 4.

A perusal of Table 3 shows that refractive index(η), surface tension(ST) and density(D) correlates well with the activity. That means that in mono-parametric regressions, these properties are the most appropriate to giving statistically significant results.

Table 1. Substituents, observed and estimated activity (pKa) and indicator parameter used in present study

Comp No	Substituent	pKa(Obsd)	pKa(Estd.)*	Residual	I
1	3,5-di-NO_2	6.19	6.10	0.09	0
2	3-NO_2,5-Cl	6.92	6.90	0.02	1
3	4-NO_2	6.97	7.55	-0.58	0
4	3-NO_2,4-Cl	7.16	6.90	0.26	1
5	4-CN	7.36	7.67	-0.31	0
6	4-SO_2NH_2	7.45	7.52	-0.07	0
7	3,5-di-Cl	7.54	8.13	-0.59	1
8	3-NO_2	7.67	7.55	0.12	0
9	4-COMe [a]	7.61	8.78	-1.17	0
10	3-SO_2NH_2	7.81	7.52	0.29	0
11	3-CN	7.83	7.67	0.16	0
12	3-Cl	8.28	8.26	0.02	1
13	3-COMe	8.34	8.78	-0.44	0
14	4-Cl	8.56	8.26	0.30	1
15	3-OMe	8.72	8.97	-0.25	0
16	H	8.97	8.97	0.00	0
17	3-Me	9.05	9.16	-0.11	0
18	4-Me	9.25	9.16	0.09	0
19	4-OMe	9.34	8.97	0.37	0
20	3-NMe_2	9.01	8.92	0.09	0
21	4-NMe_2	9.46	8.92	0.54	0

a = Data point not included in deriving equation.

I = 1 if Cl substitution present on parent moiety 0 otherwise.

*Calculated from equation (9)

Table 2. Physicochemical parameters used in present study

Comp. No	MR(cm^3)	MV(cm^3)	Pc(cm^3)	η	ST (dynes/cm)	D(g/cm^3)	Pol(cm^3)
1	79.61	204.5	627.4	1.706	88.5	1.654	31.56
2	78.4	204.6	607.5	1.692	77.6	1.601	31.08
3	73.58	192.6	570.3	1.689	76.8	1.522	29.17
4	78.40	204.6	607.5	1.692	77.6	1.601	31.08
5	72.11	190.7	560.9	1.680	74.7	1.430	28.58
6	79.98	209.7	620.9	1.687	76.7	1.560	31.70
7	77.20	204.7	587.5	1.678	67.8	1.549	30.60
8	73.58	192.6	570.3	1.689	76.8	1.522	29.17
9	76.91	212.3	596.8	1.644	62.3	1.367	30.49
10	79.98	209.7	620.9	1.687	76.7	1.560	31.70
11	72.11	190.7	560.9	1.680	74.7	1.43	28.58
12	72.37	192.7	550.4	1.674	66.4	1.466	28.69
13	76.91	212.3	596.8	1.644	62.3	1.367	30.49
14	72.37	192.7	550.4	1.674	66.4	1.466	28.69
15	73.91	204.8	571.9	1.641	60.7	1.358	29.30
16	73.91	204.8	571.9	1.641	60.7	1.358	29.30
17	72.17	197.1	551.5	1.653	61.3	1.330	28.61
18	72.17	197.1	551.5	1.653	61.3	1.330	28.61
19	73.91	204.8	571.9	1.641	60.7	1.358	29.30
20	80.68	218.8	617.9	1.658	63.6	1.331	31.98
21	80.68	218.8	617.9	1.658	63.6	1.331	31.98

* MR = Molar Refractivity, MV = Molar Volume, Pc = Parachor, η = Index of Refraction, ST = Surface Tension, D = Density, Pol = Polarizability.

Table 3. Correlation matrix demonstrating correlation of the physicochemical parameters, indicator parameter used and their correlation with the activity (pKa)

	pKa	MR	MV	Pc	η	ST	D	Pol	I
pKa	1.0000								
MR	-0.2418	1.0000							
MV	0.2110	0.8401	1.000						
Pc	-0.3484	0.9807	0.7942	1.0000					
η	-0.8096	0.2454	-0.3192	0.2959	1.0000				
ST	-0.8754	0.2994	-0.2348	0.4033	0.9467	1.0000			
D	-0.8640	0.3420	-0.1724	0.4013	0.9070	0.8907	1.0000		
Pol	-0.2419	1.0000	0.8409	0.9807	0.2450	0.2991	0.3420	1.0000	
I	-0.2359	-0.0019	-0.1948	-0.0900	0.3433	0.1248	0.4530	0.0015	1.0000

Table 4. Cross-validation parameters for the proposed models

(eq)	Comp.	Parameters	PRESS	SSY	PRESS/SSY	R^2_A
1	21	η	5.8324	11.0998	0.52	----------
2	21	D	4.2910	12.6411	0.33	----------
3	21	ST	3.9554	12.9768	0.30	----------
4	21	D, I	3.7758	13.1564	0.29	0.7522
5	21	ST, I	3.6796	13.2526	0.28	0.7585
6	21	ST, D	3.3739	13.5583	0.25	0.7786
7	21	η, ST, D	2.9625	13.9697	0.21	0.7942
8	21	η, ST, I	2.9260	14.0062	0.21	0.7967
9	20	η, ST, I	1.8055	14.9031	0.12	0.8717

The mono-parametric regression resulted into the following statistically significant models, using the refractive index(η) and density(D)

$$pKa = -35.9319 \times \eta\ (\pm\ 5.9754) + 68.0618 \quad (1)$$

N = 21, r = -0.8094, Se = 0.5540, F = 36.159, Q = 1.46

$$pKa = -7.428 \times D\ (\pm\ 0.9928) + 18.856 \quad (2)$$

N = 21, r = -0.8640, Se = 0.4752, F = 55.973, Q = 1.81

But, the best mono-parametric model obtained with the most significant statistics by the surface tension as-

pKa = -0.0992 x ST (± 0.0126) +14.955 (3)

N = 21, r = -0.8754, Se = 0.4563, F = 62.335, Q = 1.91

Here and thereafter N is the number of data point, Se is the standard error of estimation, r is the regression coefficient, F is the F-ratio and Q is the quality factor.

The aforementioned equations (1),(2) and (3) shows that the physicochemical properties as refractive index, density and surface tension are negatively correlated with the pKa. The Dissociation constant pKa increases with the decrease of magnitude of these properties.

Comparison of the equation (1),(2) and (3) exhibits the significance of surface tension and density. Among the bi-parametric correlation attempted, good correlation shown by the combination of the surface tension and indicator parameter I and density and indicator parameter I.

pKa = -8.1901xD(±1.0733) + 0.4125xI(±0.2632) + 19.8643 (4)

N = 21, r = 0.8815, Se = 0.4580, F = 31.360, Q = 1.92

pKa = -0.0974 x ST(±0.0125) – 0.2712 x I(±0.2335) + 14.8932 (5)

N = 21, r = 0.8847, Se = 0.4521, F = 32.415, Q = 1.95

But the best statistics resulted with the combination of ST and D and the model obtained is as-

pKa = -0.058 x ST(±0.0262) – 3.5058 x D(±1.9905) + 17.1886 (6)

N = 21, r = 0.8948, Se = 0.4329, F = 36.167, Q = 2.06

These all bi-parametric model established the fact that the physicochemical properties ST and D have inverse relationship with activity dissociation constant pKa. It also expresses the significant role of the indicator parameter I in the activity, which is account for the presence of the chlorine substituents on parent moiety.

Addition, of refractive index η to the equation (6) resulted into tri-parametric model with still better statistics.

pKa = -0.099xST(±0.0368) – 4.9325xD(±2.1321) + 23.8724xη(±15.5372) – 17.7542

N = 21 , r = 0.9083, Se = 0.4175, F = 26.721, Q = 2.18 (7)

Successive variation in the combination resulted into several tri-parametric models, the one containing ST, η and indicator parameter I was found to be best.

pKa = -0.1935xST(±0.0474) + 41.0129xη(±19.6012) – 0.7169xI(±0.3021) – 46.8020

N = 21, r = 0.9095, Se = 0.4149, F = 27.125, Q = 2.19 (8)

The equation (7) and (8) expressed that the surface tension, density and indicator parameter I have negative correlation with the activity, while the refractive index η showing positive correlation with the activity dissociation constant pKa.

Comparison of the both equations exhibits that the magnitude of indicator parameter I is higher than the density D in combination with ST and η.

For the further improvement in the statistics and QPAR analysis outlier concept is introduced and from the series of 21 benzene sulfonamide derivatives compound no. 9 was outlier, which resulted into excellent improvement in the statistics.

Model obtained after the deletion of compound no. 9 is as-

$$pKa = -0.1604xST(\pm0.0398) + 24.3608x\eta(\pm16.72760) - 0.5955xI(\pm0.2476) - 21.2724 \quad (9)$$
$$N = 20,\ r = 0.9444,\ Se = 0.3359,\ F = 44.025,\ Q = 2.81$$

When earlier work[1] was repeated using an entirely new set of parameters, the new results should show either better statistics or be of an equivalent quality. If some descriptors give the excellent correlation coefficient (>0.99) the further QSAR studies can't be stop and we cant deny the significance of other parameters or descriptors in the modeling of the particular activity. In the present study the models (Eq 1 to 9) exhibiting significant statistics with totally different parameters then the model proposed by Hansch and co-workers[1] in their review study on positive hydrophobic parameters.

These equations exhibit the inverse relationship between surface tension and activity pKa, i.e, benzene sulfonamide derivatives with higher interfacial tension having low dissociation affinity. The equations also show that the refractive index plays positive role in dissociation constant pKa of benzene sulfonamides. Equations express the inverse relationship between activity pKa and indicator parameter I. i.e. Cl substitution on benzene sulfonamide inhibits the dissociation constant pKa.

Equation (9) also shows that the compound 9 has an exceptional behavior then the parent series. The higher predictive power of equation (9) also justifies the outlier of compound 9.

In order to confirm our results we have calculate predictive correlation coefficient (R_{pre}^2) by correlated estimated dissociation constant pKa with the experimental pKa.
The obtained predictive correlation coefficients $R_{pre}^2 = 0.9045$ confirm our findings.

We have undergone a cross-validation[28] methodology for deciding predictive power of the proposed models. This is needed because a model with good statistics may not have good predictive potential. The various cross-validation parameters, calculated for the proposed models, are presented in Table 4 and are discussed below.

PRESS (predicted residual sum of squares) appears to be the most important cross-validation parameter accounting for a good estimate of the real predictive error of the models. Its value less than SSY (sum of the squares of response value) indicate that the model predicts better than chance and can be considered statistically significant. In our case (Table 4) PRESS << SSY indicating that all the models obtained are statistically significant and are better than chance.

To be a reasonable QSAR model, PRESS/SSY should be smaller than 0.4 and the data presented in Table 4 indicates that all the models proposed by us are significant except equation (1) and there is an increase in predictive power from Eq. (1) to (9).

Conclusions

From the aforementioned results and discussion we conclude that the Surface Tension (ST) can be used successfully for modeling dissociation constant pKa of the sulfonamides studied here. The physicochemical parameter surface tension (ST) is found better than the widely used physicochemical parameters as Molar Refractivity (MR) for modeling the pKa. The predictive

power of surface tension increased by the combination with refractive index (η) and an indicator parameter I.

Experimental Section

Activity. The dissociation constant (pKa) of the benzene sulfonamide derivatives were adopted from the litrature[1].

Physicochemical parameters. The Molar volume(MV), Parachor(Pc), Molar Refractivity (MR), Refractive Index (η), Surface Tension (ST), Density (D) and Polarizability (α), for the set of benzene sulfonamide were calculated from ACD Lab software[32].

Indicator parameters. These are the dummy parameters sometimes used for accounting those structural feature not covered in any molecular descriptor used. They assumed only two values 1 or 0. If the assumed structural feature is present; then the indicator parameters are 1 otherwise it is 0. The details of such parameters, used in the present study are already given in the Result and Discussion section.(ref. Table-1)

Statistical analysis. Maximum R^2 method together with stepwise regression[30] was carried for arriving at statistically significant models. In present study linear mathematical models are developed to study Quantitative structure/Property- Activity Relationship (QSAR). Multiple linear regressions are used to develop these models.

The predictive potential of these models are discussed on the basis of quality factor (Q)[28,29].

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