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Novel use of chemical shift in NMR as molecular descriptor: a first report on modeling carbonic anhydrase inhibitory activity and related parameters

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Abstract—A novel use of NMR chemical shift of the SO_2NH_2 protons (in dioxane as solvent) as a molecular descriptor is described for modeling the inhibition constant for benzene sulfonamides against the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1). The methodology is extended to model diuretic activity and lipophilicity of benzene sulfonamide derivatives. The regression analysis of the data has shown that the NMR chemical shift is incapable of modeling lipophilicity. However, it is quite useful for modeling the diuretic activity of these derivatives. The results are compared with those obtained using distance-based topological indices: Wiener (W)-, Szeged (Sz)-, and PI (Padmakar-Ivan) indices.

1. Introduction

Carbonic anhydrases (CAs, EC 4.2.1.1) are wide spread zinc enzymes present in archaea and bacteria, algae, green plants, and animals. These enzymes are very efficient catalysts for the reversible hydration of CO_2 to bicarbonate and are inhibited by sulfonamides possessing the general formula RSO_2NH_2, where R = aryl; hetaryl; perhaloalkyl. These sulfonamide inhibitors of the zinc enzyme carbonic anhydrase are widely used as pharmacological agents in the treatment of a variety of disorders: treatment of glaucoma, gastro-duodenal ulcers, certain neurological disorders, motion and altitude sickness, and many others.[1] Consequently, a large number of aromatic, heterocyclic, and aliphatic sulfonamides have been synthesized and tested for their CA inhibitory properties and some of them are widely used clinical or investigational drugs. In this regard $-SO_2NH_2$ group plays a dominating role.[1]

In view of the above several quantitative structure–activity relationship (QSAR) studies were carried out[1–10] by others and by us. Such QSAR studies were reported for aromatic as well as heterocyclic sulfamides. The first CA inhibitory QSAR study[5] included substituted benzene sulfonamides of the type $R–C_6H_4–SONH_2$.

Accordingly, the electronic properties of the $-SO_2NH_2$ group are important for the inhibitory effects of a series of 2-, 3-, and 4-substituted benzene sulfonamides.

The parameters used in the earlier QSAR studies were some physicochemical parameters related to molecular structure and also Hansch parameters. In our recent studies we have successfully used distance-based topological indices for modeling inhibitory activity and thus for QSAR studies.[11–16]

One of the authors (PVK) in the recent studies proposed and established that chemical shift in NMR (δ) can be used as a molecular descriptor in developing QSAR and/or QSPR (quantitative structure–property relationship) models.[17,18] Thus, ^{13}C NMR chemical shifts (δ) were used in QSAR studies for modeling toxicity,

Keywords: NMR chemical shift; Carbonic anhydrase inhibitors; Diuretic activity; Lipophilicity; Distance-based topological indices; Regression analysis.
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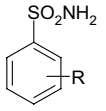
Table 1. Structural details of benzene sulfonamides, their inhibition constant (pK_i), diuretic activity (pC), lipophilicity (log P) and NMR chemical shifts (δ) of the SO_2NH_2 protons



S. No.	R	pK_i	pC	log P	δ (ppm)	IP_1	IP_2	IP_3	IP_4
1	*p*-MeNH	4.82	−0.036	0.31	5.78	0	0	1	0
2	*p*-NH_2	4.64	−0.301	0.025	5.85	0	0	1	0
3	*p*-MeO	5.35	0.188	1.72	6.01	0	0	1	0
4	*p*-Me	5.42	0.182	2.61	6.06	0	0	1	0
5	*m*-Me	5.30	0.176	2.55	6.07	0	1	0	0
6	H	5.22	0.130	0.70	6.12	0	0	0	0
7	*p*-Cl	5.72	0.286	1.69	6.26	0	0	1	0
8	*p*-Br	5.92	0.267	2.98	6.25	0	0	1	0
9	*m*-Cl	5.64	0.292	2.19	6.30	0	1	0	0
10	*p*-Ac	5.96	0.398	0.53	6.34	0	0	1	0
11	*p*-CN	5.96	1.000	0.30	6.42	0	0	1	0
12	*m*-NO_2	5.89	0.678	0.53	6.51	0	1	0	0
13	*p*-NO_2	6.05	0.824	0.31	6.48	0	0	1	0
14	3,4-Cl_2	6.40	0.243	4.07	6.37	0	0	0	1
15	3-NO_2, 4-Cl	6.77	0.322	1.30	6.50	0	0	0	1
16	3-CF_3, 4-NO_2	6.85	0.580	1.90	6.62	0	0	0	1
17	*o*-Me	4.80	0.301	3.53	6.30	1	0	0	0
18	*o*-Cl	5.52	0.301	3.83	6.39	1	0	0	0
19	*o*-NO_2	5.07	0.301	1.69	6.39	0	0	0	0

Me—methyl, Ac—acetyl, *o*—ortho, *m*—meta, *p*—para, IP_1—indicator parameter for *ortho*-substitution, IP_2—indicator parameter for *meta*-substitution, IP_3—indicator parameter for *para*-substitution, IP_4—indicator parameter for di-substitution.

organic reactivity, H-acidity, s-character, steric energy, ultrasonic sound velocity etc.[19–22] This has prompted us to use NMR chemical shift (δ) for modeling carbonic anhydrase inhibition constant and other related parameters of benzene sulfonamides. Since, –SO_2NH_2 group dominates the inhibition, we have used NMR chemical shift (δ) of the –SO_2NH_2 protons (in dioxan as solvent) for this purpose. Fortunately such chemical shifts for the series of sulfonamides used (Table 1) in the present study are available in the literature.[21] We have, therefore, used the reported NMR chemical shifts in the present study. The results, as discussed below, show that the NMR chemical shifts (δ) of the –SO_2NH_2 protons can be used very successfully for modeling, monitoring, and estimating inhibition activity (pK_i) as well as diuretic activity (pC) of the series of sulfonamides used in the present study. However, the methodology is not that useful for modeling lipophilicity (log P) of the sulfonamides used. In addition, we have also investigated and compared the relative power of the –SO_2NH_2 NMR shifts for modeling pK_i and pC and compared them with the important distance-based topological indices: Wiener (W)-,[23] Szeged (Sz)-,[24,25] and PI (Padmakar-Ivan) indices[26–28] used by us earlier.

2. Results and discussion

The set of 19 benzene sulfonamides used in the present investigation is given in Table 1. The corresponding values of the inhibition constant K; and diuretic activities ($1/c$) are expressed as pK_i and pC, along with pK_i (log P), are presented in Table 1. The NMR chemical shift (δ) of the –SO_2NH_2 protons in dioxane as solvent, are also summarized in Table 1. The calculated values of Wiener (W)-, Szeged (Sz)-, and PI (Padmakar-Ivan) indices are shown in Table 2.

(i) Modeling inhibition activity pK_i ($-\log K_i$): The simple regression analysis considering all the 19 sulfon-

Table 2. Calculated values of distance-based topological indices (W, Sz, PI), Hammett σ parameters and Hansch hydrophobic parameter (π) for the benzene sulfonamides used in the present study (Ref. Table 1)

S. No.	W	Sz	PI	σ	π
1	201	306	126	−0.840	−0.231
2	152	236	104	−0.660	−1.137
3	201	306	126	−0.268	0.163
4	162	236	104	−0.170	0.505
5	148	228	104	−0.069	0.540
6	114	177	84	0.000	0.000
7	152	236	104	0.227	0.531
8	152	236	104	0.232	1.053
9	148	228	104	0.373	0.981
10	325	472	176	0.502	−0.105
11	201	306	126	0.660	−0.083
12	240	354	150	0.710	0.242
13	252	378	126	0.778	0.328
14	189	291	126	0.600	1.134
15	289	427	176	0.937	1.603
16	484	694	266	1.208	1.420
17	144	220	104	—	0.526
18	144	220	104	—	0.427
19	228	330	150	—	0.033

Table 3. Regression parameters and quality of correlation for modeling pK_i, pC, log P, and pKa of benzene sulfonamides using δ

Model	Activity/property	A	B	Se	r	Q
(1) For entire set of 19 sulfonamides using chemical shift δ						
1	pK_i	−5.5140	1.7788	0.6227	0.6813	1.0941
2	pC	−5.9342	0.9988	0.2921	0.7797	2.6692
3	log P	−3.5278	0.8359	1.2541	0.1520	0.1212
(2) For 16 sulfonamides (deleting 3 ortho-substituted sulfonamide) using chemical shift δ						
1	pK_i	−8.6805	2.3091	0.6198	0.9142	1.4749
2	pC	−6.2251	1.0490	0.3196	0.8029	2.5122
3	log P	−1.4763	0.4736	1.1791	0.0983	0.0833
(3) For 16 sulfonamides using σ						
1	pK_i	5.5137	0.9770	0.2530	0.9190	3.6324
2	pC	−0.2279	−0.4200	0.2129	0.7657	3.5965
3	LogP	−0.1120	0.2780	0.5576	0.2881	0.5166
(4) For 16 sulfonamides using π						
1	pK_i	5.4393	0.7013	0.3933	0.7901	2.0088
2	pC	−0.2708	−0.1290	0.3176	0.2817	0.8869
3	log P	−0.3301	0.6553	0.3388	0.8134	2.4008

A, B—regression parameters (A—intersect, B—slope), Se—standard error of estimation, r—correlation coefficient, F—F statistics, Q—quality factor (r/Se).

amides gave the following regression expression for modeling pK_i ($-\log K_i$) using chemical shifts of $-SO_2NH_2$ protons δ.

$$pK_i = -5.5140 + 1.7788\delta$$
$$n = 19,\ \mathrm{Se} = 0.6227,\ r = 0.6813,\ F = 14.7223, \quad (1)$$
$$Q = 1.0941$$

This low order statistics of (Eq. 1) may be attributed to be due to differential behavior of compounds **17**–**19** due to *ortho*-effect. In view of this we have deleted these compounds from the regression procedure and repeated simple regression with remaining 16 compounds, which gave excellent results:

$$pK_i = -0.6805 + 2.3091\delta$$
$$n = 16,\ \mathrm{Se} = 0.6198,\ r = 0.9420,\ F = 110.2236, \quad (2)$$
$$Q = 1.5198$$

In the aforementioned equations, n is the number of data set, Se is standard error of estimation, r is correlation coefficient, F is F-statistics, and Q is quality factor defined[28–30] as the ratio of correlation coefficient to the standard error of estimation ($Q = R$/Se).

When δ is used for modeling diuretic activity (pC) and log P of the entire set of 19 sulfonamides again poor statistics are resulted. The regression parameters and quality of correlations for such analysis are given in Table 3. The data presented in Table 3 show that δ is not a suitable parameter to be used in modeling log P, however, it is a good parameter for modeling pC. Once again the poor statistical results using all the 19 compounds may be attributed to the *ortho*-effect exhibited by the compounds **17**–**19**. The deletion of these three compounds for the regression procedure yielded better results.

Modeling diuretic activity (pC):

$$pC = -6.2251 + 1.04090\delta$$
$$n = 16,\ \mathrm{Se} = 0.3196,\ r = 0.8029,\ F = 25.3922, \quad (3)$$
$$Q = 2.5122$$

The above results show that the NMR chemical shift of $-SO_2NH_2$ protons can be successfully used for modeling, monitoring, and estimating inhibition constants (pK_i) of the CA inhibitors as well as their diuretic activity (pC). Our further study will, therefore, be centered on the estimation of these parameters only.

It will be interesting to investigate potential of the use of NMR chemical shift (δ) by comparing the results obtained when Hammett's substitution constants (σ) and Hansch's parameters (π) are independently used for modeling inhibition constant (pK_i) and pC, respectively. The values of σ and π used for this purpose are given in Table 2. Here, $\pi = \log P_X - \log P_H$, where, $P_{X,H}$ represent the partition coefficient of the X-substituted and un-substituted (H) benzene sulfonamides used. Also, σ is the sum of σ values of the substitutents on the sulfonamide used. Use of σ for modeling pK_i and pC independently give the following regression expressions:

$$pK_i = 5.5137 + 0.9771\sigma$$
$$n = 16,\ \mathrm{Se} = 0.2530,\ r = 0.9190,\ F = 14.0000, \quad (4)$$
$$Q = 3.6324$$

$$pC = -0.2279 - 0.4200\sigma$$
$$n = 16,\ \mathrm{Se} = 0.2129,\ r = 0.7657,\ F = 19.8327, \quad (5)$$
$$Q = 3.5985$$

The corresponding expressions based on π parameter yielded following expressions:

$$pK_i = 5.439 + 0.7013\pi$$
$$n = 16,\ \mathrm{Se} = 0.3933,\ r = 0.7901,\ F = 23.2538,\quad (6)$$
$$Q = 2.0089$$

$$pC = -0.2709 - 0.1290\pi$$
$$n = 16,\ \mathrm{Se} = 0.3176,\ r = 0.2817,\ F = 1.2058,\quad (7)$$
$$Q = 0.8869$$

The above results and the data presented in Table 3 indicate the following:

(1) Relative correlation potential of the NMR chemical shift (δ) is more or less similar to that of Hammett's substitution constant (σ) in modeling the inhibition constant (pK_i). However, Hansch parameter (π) is quite inferior for this purpose.
(2) In the modeling diuretic activity (pC), the NMR chemical shift (δ) is far superior that the Hammett's parameter (σ), while the Hansch parameter (π) is useless for this purpose.
(3) For modeling lipophilicity ($\log P$), both chemical shift (δ) as well as Hammett's parameters (σ) are useless. On the other hand the Hansch parameter (π) is the only parameter useful for this purpose.

2.1. Relative potential of the NMR chemical shift (δ) and distance-based topological indices (W, Sz, PI) in modeling inhibition constant (pK_i) and diuretic activity (pC)

It will now be very interesting to investigate relative potential of δ, W, Sz, and PI in modeling pK_i and pC. This is important as in our earlier publications we found these topological indices quite useful for this purpose. Instead of making a detailed statistical analysis we will investigate their potential based on correlation coefficient (r) and the standard error of estimation (Se). These data are summarized below:

(1) For modeling inhibition constant (pK_i) ($n = 16$)

Parameters used	r	Se	Q
δ	0.9142	0.2446	3.7375
W	0.6767	0.4724	1.4324
Sz	0.6797	0.4707	1.4440
PI	0.7029	0.4564	1.5400

(2) For modeling diuretic activity (pC) ($n = 16$)

Parameters used	R	Se	Q
δ	0.8029	0.2446	3.2825
W	0.4281	0.2991	1.4312
Sz	0.4302	0.2988	1.4397
PI	0.4254	0.2496	1.7043

The data presented above indicate that compared to the distance-based topological indices used (W, Sz, PI), the chemical shift δ is far superior in modeling both pK_i and pC. Furthermore, all the three topological indices are worse for modeling diuretic activity (pC). This is consistent with our earlier results in that we have shown that such topological indices are incapable of giving statistically significant models in monoparametric regressions.

In order to confirm our results we have estimated both pK_i and pC from the respective models and compared them with the observed values of pK_i and pC. Such comparisons are shown in Tables 4 and 5. The residue that is difference between the observed and calculated values of pK_i and pC, respectively, are in accordance with the results discussed above. Furthermore, the quality factors (Q) recorded in Table 3 are also consistent with the results discussed above.

Table 4. Observed and calculated inhibition constant (pK_i) for the sulfonamides used

S. No.	pK_i (obs)	pK_i calculated using					
		δ		σ		π	
		Cal.	Res.	Cal.	Res.	Cal.	Res.
1	4.82	4.666	0.1540	5.3766	0.5566	5.2773	0.4573
2	4.64	4.8277	0.1877	4.8689	−0.2289	4.6420	0.0020
3	5.35	5.1971	0.1529	5.2519	0.0981	5.5536	−0.2036
4	5.42	5.3126	0.1074	5.3476	0.0724	5.7934	−0.3734
5	5.30	5.3357	−0.0357	5.4463	−0.1463	5.8180	−0.5180
6	5.22	5.4511	0.2311	5.5137	−0.2937	5.4393	−0.2193
7	5.52	5.7744	−0.2544	5.2919	0.2281	5.8116	−0.2916
8	5.92	5.7513	0.1687	5.2871	0.6329	6.1777	−0.2577
9	5.64	5.8668	−0.2268	5.1493	0.4907	6.1272	−0.4872
10	5.96	5.9591	0.0009	5.0225	0.9375	5.3657	0.5943
11	5.96	6.1439	−0.1839	4.8669	1.0911	5.3811	0.5789
12	5.89	4.5413	0.5487	4.8200	0.2700	5.6090	−0.5190
13	6.05	−6.2824	0.2324	4.7536	1.2964	5.6693	0.3807
14	6.40	6.0284	0.3716	4.9275	1.4725	6.2345	0.1655
15	6.72	6.3282	0.3914	4.5982	2.1218	6.5634	0.1566
16	6.85	6.6057	0.2443	4.3334	2.2723	6.4351	0.4149

Table 5. Observed and calculated diuretic activity (pC) for the sulfonamides used

S. No.	pC (Obs)	pC calculated using					
		δ		σ		π	
		Cal	Res	Cal	Res	Cal	Res
1	−0.036	−0.2087	0.2447	0.1249	0.0889	−0.2411	−0.2051
2	−0.301	−0.1359	0.4369	0.0493	0.2517	−0.1242	−0.1768
3	0.188	0.0307	0.1573	0.1154	0.3034	−0.2918	0.4798
4	0.182	0.0827	0.0993	0.1565	0.3385	−0.3359	0.5179
5	0.176	0.0931	0.0829	0.1990	−0.3750	−0.3404	0.5164
6	0.130	0.1452	−0.0152	−0.2279	0.3579	−0.2708	0.4008
7	0.286	0.2909	−0.0049	−0.3232	0.6092	−0.3392	0.6282
8	0.267	0.2805	0.0135	−0.3253	0.5923	−0.4066	0.6736
9	0.292	0.3325	0.0405	−0.3845	0.6765	−0.1265	0.4185
10	0.398	0.3742	0.0238	−0.4387	0.8367	−0.2573	0.6553
11	1.000	0.4574	0.5426	−0.5044	1.5044	−0.2601	0.5202
12	0.678	0.5511	0.1269	−0.5261	1.2041	−0.3020	0.9800
13	0.824	0.5199	0.3041	−0.5539	1.3779	−0.3131	1.1371
14	0.243	0.4054	−0.1624	−0.4799	0.7229	−0.4170	0.6600
15	0.322	0.5407	−0.2187	−0.6207	0.9427	−0.4775	0.7995
16	0.580	0.6656	−0.0856	−0.7345	1.3145	−0.4539	1.0339

For supporting our results we have also calculated three important statistical parameters namely PE (probable error of coefficient of correlation), LSE (least square error), and LOF (Friedman's act of fit measure) for the best models represented by Eqs. 2, 3, 5–7. These values are recorded in Table 6. The expressions used to calculate these statistical parameters are as follows:

$$\mathrm{PE} = \frac{2}{3}\frac{1-r^2}{\sqrt{n}} \tag{8}$$

where, r is the correlation coefficient and n is the number of compounds used.

$$\mathrm{LSE} = (Y_{\mathrm{obs}} - Y_{\mathrm{cal}})^2 \tag{9}$$

where, Y_{obs} and Y_{cal} are the observed and calculated properties/activities.

$$\mathrm{LOF} = \frac{\mathrm{LSE}}{[1-(c+dp)/n]}^2 \tag{10}$$

where, LSE is the least square error, c is the number of descriptor + 1, p is the independent parameters, n is the number of compound, d is the smoothing parameter which controls the bias in the scoring factor between equations with different number of terms and was kept 1.0.

It is argued that if $r < \mathrm{PE}$, then r is not significant. If $r > \mathrm{PE}$, several times, at least three times greater, then correlation is indicated. On the other hand if $r > 6$ PE

Table 6. Detail calculations for PE, LSE, and LOF for models represented by equations 2, 3, 5–8

S. No.	pK_i			pC		
	Eq. 2 (δ) $(Y_{\mathrm{obs}} - Y_{\mathrm{calc}})^2$	Eq. 5 (σ) $(Y_{\mathrm{obs}} - Y_{\mathrm{calc}})^2$	Eq. 7 (π) $(Y_{\mathrm{obs}} - Y_{\mathrm{calc}})^2$	Eq. 3 (δ) $(Y_{\mathrm{obs}} - Y_{\mathrm{calc}})^2$	Eq. (6) (σ) $(Y_{\mathrm{obs}} - Y_{\mathrm{calc}})^2$	Eq. 8 (π) $(Y_{\mathrm{obs}} - Y_{\mathrm{calc}})^2$
1	0.0598	0.0079	0.0420	0.0237	0.3098	0.2091
2	0.1908	0.0633	0.0312	0.0352	0.0523	0.00004
3	0.0247	0.0920	0.2302	0.0233	0.0096	0.0414
4	0.0098	0.1145	0.2682	0.0115	0.0052	0.1394
5	0.0068	0.1406	0.2666	0.0012	0.0214	0.2683
6	0.0002	0.1280	0.1606	0.0534	0.0862	0.0480
7	0.00002401	0.37111	0.3946	0.0647	0.0520	0.0850
8	0.0001	0.3508	0.4537	0.0284	0.4005	0.0664
9	0.0016	0.4576	0.1751	0.0514	0.2407	0.2373
10	0.0005	0.7000	0.4294	0.000081	0.8789	0.3531
11	0.2944	2.2632	0.2706	0.0338	1.1904	0.3351
12	0.0161	1.4498	0.9604	0.3010	0.0729	0.2693
13	0.0924	1.8986	1.2929	0.0540	1.6806	0.1449
14	0.0263	0.5225	0.4356	0.1380	2.1682	0.0273
15	0.0478	0.8886	0.6392	0.1531	4.5020	0.0245
16	0.0073	1.7279	1.0689	0.0596	5.1633	0.1721
	LSE = 0.7786 LOF = 1.1795 PE = 0.0893	LSE = 11.1764 LOF = 16.9313 PE = 0.0187	LSE = 7.1192 LOF = 10.7850 PE = 0.0592	LSE = 1.0323 LOF = 1.5638 PE = 0.0259	LSE = 16.8343 LOF = 25.5026 PE = 0.0620	LSE = 2.4212 LOF = 3.6679 PE = 0.1534

then the correlation is definitely good. In our case each of the model has $r \gg PE$ indicating them to be good correlations. This is found to be the case with all the eight equations discussed above which yield PE = 0.0892, 0.0187, 0.0592, 0.1600, 0.0259, 0.0689, 0.0620, and 0.1534, respectively.

The lowest values of LSE and LOF also indicates that the correlations are good. It is recommended that it is better to use LOF than LSE for investigating goodness of fit. This is because former does not decrease with increased number of descriptors and the lowest value is found for an equation (model) with optimum number of parameters (descriptors). Thus values of PE, LSE, and LOF (Table 6) are also in favor of our findings.

3. Conclusions

The results and discussion made above indicate that we can use NMR chemical shift (δ) for modeling inhibition constant and diuretic activity of the sulfonamides. In fact it (δ) can be used successfully for monitoring, modeling and estimating other physiological properties/activities of sulfonamides. However, it is less effective for modeling lipophilicity/hydrophobicity.

4. Experimental

(i) Inhibition constant (pK_i), diuretic activity (pC) and lipophilicity (log P): These parameters/activities are taken from the literature.[3]

(ii) NMR chemical shift (δ): The NMR chemical shift for $-SO_2NH_2$ protons were obtained from their NMR spectra.[3,4]

(iii) Hammett's (σ) and Hansch (π) parameters: The Hammett's (σ) and Hansch parameters (π) are taken from the literature.

(iv) Topological indices: All the distance based topological indices were calculated from the molecular graphs of the sulfonamides used. These molecular graphs are obtained by deleting all the carbon–hydrogen as well as heteroatom–hydrogen bond from the respective molecular structures of the sulfonamides. The calculations of these indices are well documented.

The regression analysis is made using the method of maxim R^2 method[27] in the literature and, therefore, these calculations are not discussed here. However, it is worthy to mention that their calculations were made using the programme provided by Istvan Luckovits of Hungarian Academy of Sciences, Budapest, Hungary.

(v) Statistical analysis: The regression analysis is made using the method of maxim R^2 method[29–31] and using software of Lukovits.

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