Indian Journal of Chemistry
Vol. 28A, July 1989, pp. 606-608

Notes

Application of the Fujita-Ban model in the prediction of dissociation constants of benzoic acids

B K Mishra, S C Dash & G B Behera*
Department of Chemistry, Sambalpur University, Jyotivihar 768 019

Received 25 April 1988; accepted 12 July 1988

The Fujita-Ban model has been used to predict the dissociation constants of substituted benzoic acids; for this purpose the position dependent group contribution constants have been evaluated. The predictability of this model has been compared with the models of Williams and Norrington.

For the quantitative description of structure-activity relations (QSAR), different *de novo* mathematical models have been proposed of which the Free-Wilson model[1] is one. It is based on the assumption that each substituent makes an additive and constant contribution to the activity regardless of the structural variation in the rest of the molecule. Purcell[2] used this model in correlating butyryl-cholinesterase inhibitory potencies of twelve alkyl substituted 3-carbamoylpiperidines and the activities of twenty six other congeners were predicted. Later on one of these predicted derivatives was synthesised. Its biological activity[3] supported the applicability of Free-Wilson model. Since then, few other successful applications of this model have been reported[4-8]. Subsequently two different modifications of the Free-Wilson model based on its additivity concept were developed by Cammarata[9,10] (Eq. 1) and Fujita and Ban[8] (Eq. 2). In Eqs (1) and (2) a_{ij} is the activity contribution of the substituent X_i in position j: $X_{ij} = 1$ if the substituent X_i is in position j; otherwise $X_{ij} = 0$. In Eq. (1) μ_H is the observed biological activity value of the unsubstituted compound whereas in Eq. (2) μ_0 is the predicted activity value of the unsubstituted compound ($X_i = H$).

$$\text{Biological activity} = \sum_{ij} a_{ij}X_{ij} + \mu_H \qquad \ldots (1)$$

$$= \sum_{ij} a_{ij}X_{ij} + \mu_0 \qquad \ldots (2)$$

A comparison of different Free-Wilson models alongwith their applications in QSAR studies was undertaken by Kubinyi[11]. He concluded that the Fujita-Ban model is the most simple and suitable approach.

Herein we report for the first time the use of Fujita-Ban model to predict the dissociation constants of substituted benzoic acids.

Results and discussion

The observed pK_a values[12] of twenty two disubstituted benzoic acids represented in the form of a structural matrix (Table 1) have been subjected to Fujita-Ban analysis[8] (Eq. 2). The a_i values for nine different substituents (Table 2) and μ_0 were obtained by multiple regression analysis of the input equations obtained from Table 1 at 98% confidence level ($r = 0.976$, $s = 0.295$ and $F = 29.50$) the μ_0 value being 4.279.

As the a_i values for different substituents are expected to depend on the field, resonance and steric effects, an additive model[13,14] is proposed to account for the contribution of these various individual effects. The a_i values of nine substituents have been fitted to Eq. (3), where F_k and R_k refer to the field and resonance parameters[15] of substituent k, f_j and r_j are the substituent independent positional weightage factors[16] for position j and SD_k is the steric density parameter[13,14]. The values of the regression coefficients, b_1, b_2 and b_3 have been determined and the corresponding equation (Eq. 4) is obtained.

$$a_i = b_1 f_j F_k + b_2 r_j R_k + b_3 SD_k \qquad \ldots (3)$$

$$a_i = -0.708(\pm 0.156) f_j F_k - 0.661(\pm 0.385) r_j R_k - 0.272(\pm 0.070) SD_k \qquad \ldots (4)$$

$(n = 9, r = 0.973, s = 0.180, F = 30.04)$

From the student's t-test, it is noted that the resonance term ($t = 0.16$) is not significant. To this effect, Williams and Norrington[16] have explained that the *ortho*-substituents render the dissociation of benzoic acids independent of resonance effect because the *ortho*-substituents perturb the co-planarity of the phenyl and carboxyl groups and thereby inhibit the conjugation between their respective *pi*-electrons. Therefore, the resonance term is neglected and the regression of a_i values with field and steric parameters has been made which gives rise to Eq. (5)

$$a_i = -0.723(\pm 0.114) f_j F_k - 0.264(\pm 0.053) SD_k \qquad \ldots (5)$$

$(n = 9, r = 0.973, s = 0.165, F = 53.79)$

Table 1—Structural matrix of disubstituted benzoic acids with their observed and calculated *pK*a values

Substituents	Obs *pK*a	*o*-Me	*o*-OH	*o*-NO_2	*o*-Cl	*m*-Me	*m*-OH	*m*-NO_2	*p*-Me	*p*-NO_2	Calculated *pK*a (Eq. 6)
3,4-Me_2	4.41					1			1		4.47
3,5-Me_2	4.30					2					4.29
3,5-$(OH)_2$	4.02						2				4.01
3,4-$(NO_2)_2$	2.82							1		1	2.50
3,5-$(NO_2)_2$	2.82							2			2.69
2,4-Me_2	4.18	1							1		3.79
2,5-Me_2	3.98	1				1					3.93
2,5-$(OH)_2$	2.95		1				1				2.99
2-OH, 4-NO_2	2.23		1							1	2.33
2-OH, 5-NO_2	2.12		1					1			2.14
2,4-$(NO_2)_2$	1.42			1						1	1.72
2,5-$(NO_2)_2$	1.62			1				1			1.91
2-Cl, 4-NO_2	1.96				1					1	2.06
2-Cl, 5-NO_2	2.17				1			1			2.25
2,6-Cl_2	1.59				2						1.80
2,6-Me_2	3.25	2									3.57
2,6-$(NO_2)_2$	1.15			2							1.12
2-Cl, 6-NO_2	1.34			1	1						1.46
2,6-$(OH)_2$	1.08		2								1.97
2-OH, 6-NO_2	2.24		1	1							1.55
2-OH, 6-Cl	2.63		1		1						1.89
2-OH, 6-Me	3.32	1	1								2.78

Table 2—Group contribution values of Substituents

Substituent	a_i	Substituent	a_i
Evaluated from Training Set		Evaluated from Eq. (5)	
o-Me	−0.352	*o*-Br	−1.974
o-OH	−1.152	*m*-OMe	−0.293
o-NO_2	−1.577	*m*-Cl	−0.489
o-Cl	−1.237	*m*-Br	−0.515
m-Me	0.005	*p*-OMe	−0.299
m-OH	−0.132	*p*-OH	−0.352
m-NO_2	−0.796	*p*-Cl	−0.499
p-Me	0.189	*p*-*t*.Bu	−0.075
p-No_2	−0.983		

The group contribution (a_i) values of other substituents have been calculated using Eq. (5) and are listed in Table 2. All a_i values, thus obtained, can be utilised to predict the *pK*a of polysubstituted benzoic acids using Eq. (6) where 4.279 is the evaluated

$$pKa = 4.279 + \sum_i X_i a_i \quad \ldots (6)$$

*pK*a value of unsubstituted benzoic acid (observed value = 4.203). Using this model the pentanitroben-

Table 3—Prediction of *pK*a of polysubstituted benzoic acids using Eq. (6) and a_i values from Table 2.

Substituent	*pK*a		Difference		
	Obs.	Calc.	Present	Ref. 13	Ref. 16
3,4-$(OH)_2$	4.13	3.79	0.34	0.78	0.24
2,3-$(OH)_2$	2.91	2.99	0.08	0.00	1.20
2,4-$(OH)_2$	3.22	2.77	0.45	0.23	1.23
2-Cl, 3-NO_2	2.02	2.25	0.23	0.12	1.02
2,4-Cl_2	2.68	2.54	0.14	0.27	0.77
2,5-Cl_2	2.47	2.55	0.08	0.07	0.91
2-OH, 5-Cl	2.63	2.64	0.01	0.13	1.23
2-OH, 5-Br	2.61	2.61	0.00	0.13	1.24
2,3-Me_2	3.74	3.93	0.19	0.21	0.62
2,3-$(NO_2)_2$	1.85	1.91	0.06	0.10	0.66
2-Br, 6-NO_2	1.37	0.73	0.64	0.01	1.41
3,4,5-$(OMe)_2$	4.13	3.67	0.46	0.57	0.05
2-OH, 3-NO_2	1.87	2.33	0.74	0.62	1.66
3,6-Me_2, 4-CMe_3	3.44	3.65	0.21	0.36	1.16
2-OH, 3,5-$(NO_2)_2$	0.70	1.54	0.84	1.15	2.12
2,4,6-Me_3	3.44	3.76	0.32	0.33	1.32
4-Me, 3,5-$(NO_2)_2$	2.97	2.88	0.09	0.10	0.08
2,4,6-$(NO_2)_3$	0.65	0.14	0.51	0.45	0.81

zoic acid is found to have the maximum acidity in polysubstituted benzoic acids (pKa = − 1.45). Some more predicted pKa values of polysubstituted benzoic acids are given in Table 3.

References

1 Free S M & Wilson J W, *J med Chem*, 7 (1964) 395.
2 Purcell W P, *Biochim Biophys Acta*, 105 (1965) 201.
3 Beasly J G & Purcell W P, *Biochim Biophys Acta*, 178 (1969) 175.
4 Smithfield & Purcell W P, *J pharm Sci*, 56 (1967) 577.
5 Purcell W P & Clayton J M, *J med Chem*, 11 (1968) 199.
6 Ban T & Fujita T, *J med Chem*, 12 (1969) 353.
7 Hudson D R, Bass G E & Purcell W P, *J med Chem*, 13 (1970) 1184.
8 Fujita T & Ban T, *J med Chem*, 14 (1971) 148.
9 Cammarata A & Yau S J, *J med Chem*, 13 (1970) 93.
10 Cammarata A, *J med Chem*, 15 (1972) 573.
11 Kubinyi H & Kehrhahn O H, *J med Chem*, 19 (1976) 578.
12 Barlin G & Perrin D D, *Quart Rev chem Soc*, 20 (1966) 75.
13 Dash S C & Behera G B, *Indian J Chem*, 19A (1980) 541.
14 Dash S C & Behera G B, *J Indian chem Soc*, 57 (1980) 542.
15 Swain C G & Lupton E C, *J Am chem Soc*, 90 (1968) 4328.
16 Williams S G & Norrington F E, *J Am chem Soc*, 98 (1976) 508.