Octanol/Water Partition Coefficient of Substituted Benzene Derivatives Containing Halogens and Carboxyls: Determination Using the Shake-Flask Method and Estimation Using the Fragment Method

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Octanol/water partition coefficients K_{ow} of 10 kinds of selected halogen benzoic acids were determined for the first time using the shake-flask method. Then, a set of group values and factors used to estimate the K_{ow} of halogen benzoic acids were obtained. For estimation of the K_{ow} of the selected compounds, the average absolute error of log K_{ow} is 0.15, and the average relative error of K_{ow} is 39 %.

Introduction

Benzoic acids are important materials or intermediates for antiseptics, spiceries, dyes, medications, etc. They are widely used in the industry. So, it is necessary to study the octanol/water partition coefficient (K_{ow}) of these benzoic acids. Current K_{ow} data compilations[1,2] show gaps among the cited K_{ow} values for a number of benzoic acids.

There are many methods to determine the K_{ow} values, such as the shake-flask method, the slow-stirring method, the generator-column method, the chromatographic method, and so on.

The K_{ow} values of the selected halogen benzoic acids were measured using the shake-flask method.[3] The shake-flask method is a traditional method used to determine K_{ow} values. It is easy to achieve and has good repeatability and good accuracy when the log K_{ow} of the determined compounds is between 0 and 4.

It is also very necessary to find a good method to estimate the K_{ow} of these compounds. Among the many methods used to estimate K_{ow}, the most used methods are the fragmental method and the group contribution method. Many group contribution methods have been reported, such as the AFC group contribution method by Meylan,[4] the three-level group contribution method by Marrero,[5] the GC-K1 group contribution method by Chen Hongping,[6] and so on. Compared with the group contribution method, the fragmental method is more consummate, and there have been corresponding software (like CLOGP, KowWin, and XLOGP[7]) to estimate K_{ow}. Derawi[8] compared these two methods, and the results indicate that the fragmental method is better than the group contribution method.

The existing estimation methods are suitable for almost all compounds, so the error is larger when they are used to estimate the K_{ow} of compounds with a complicated structure such as the substituted benzene derivatives, the halogen benzoic acids, and so on. It is necessary to build a new model for these special structures.

Fifty-seven K_{ow} data points were used to regress for the parameters of the fragmental model which is suitable to estimate the K_{ow} of halogen benzoic acids. Then, the fragmental method was used to estimate the K_{ow} of the compounds that participate in the regression.

Table 1. Purities of Chemicals Used in the Experiment

chemicals	purities	chemicals	purities
hydrochloric acid	(36 to 38) %	*n*-octanol	99.8 %
2-chloro-3-fluorobenzoic acid	99.7 %	2-fluoro-5-chlorobenzoic acid	99.6 %
4-chloro-2-fluorobenzoic acid	99.8 %	2-chloro-4-fluorobenzoic acid	99.7 %
2-bromo-5-fluorobenzoic acid	99.5 %	2-chloro-5-fluorobenzoic acid	99.0 %
3-bromo-4-fluorobenzoic acid	99.6 %	2-chloro-5-bromobenzoic acid	99.7 %
2-fluoro-4-bromobenzoic acid	99.8 %	2-fluoro-5-bromobenzoic acid	99.1 %

Experimental Section

Chemicals and Standards. The halogen benzoic acids were purchased from the Xinyi chemical plant (Suzhou, China). The hydrochloric acid was purchased from the Potou chemistry reagent factory (Hebei province, China), and the *n*-octanol was purchased from Kewei Co. (Tianjin University, China). The purities of these chemicals are shown in Table 1.

Equipment and Procedure. The halogen benzoic acids could be dissociated in water, so we used dilute HCl (0.2 $\text{mol}\cdot\text{L}^{-1}$) to take the place of water to inhibit the dissociation. The dilute HCl was gained by diluting the purchased HCl. The shake-flask experiments were carried out at 25 ± 0.1 °C, always in duplicate for each concentration level of the individual test substance. In a 50 mL cone bottle, 20 mL of octanol-saturated dilute HCl was overlaid by 10 mL of dilute HCl-saturated octanol, which contains the chemical to be equilibrated (in concentrations of (0.0040 to 0.0080) $\text{mol}\cdot\text{L}^{-1}$ or (0.0005 to 0.0010) $\text{mol}\cdot\text{L}^{-1}$). After being sealed, the cone bottle was shaken in a constant temperature shaker (WE-1, Tianjin Honor Instrument Co., Tianjin, China) for 48 h. Then the phases were allowed to separate for 48 h, and afterward, samples of the water phase were taken to be analyzed. The quantification was done using an ultraviolet spectrophotometer (U-3010, Hitachi, Ltd., Tokyo Japan).

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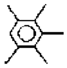
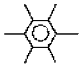
Table 2. Results of Experiment

compounds	max absorption wavelength/nm	log K_{ow}
2-chloro-3-fluorobenzoic acid	225	1.74
4-chloro-2-fluorobenzoic acid	229	2.28
2-bromo-5-fluorobenzoic acid	236	2.21
3-bromo-4-fluorobenzoic acid	229	3.56
2-fluoro-4-bromobenzoic acid	236	2.67
2-fluoro-5-chlorobenzoic acid	222	1.59
2-chloro-4-fluorobenzoic acid	232	2.63
2-chloro-5-fluorobenzoic acid	222	2.39
2-chloro-5-bromobenzoic acid	201	3.16
2-fluoro-5-bromobenzoic acid	202	3.43

Table 3. Group Values n_i and Factors f_i for the Fragmental Method

Groups or factors	values	Groups or factors	values
	1.102	-Br	0.733
	1.095	-F	0.082
	1.190	-I	0.964
	1.109	-COOH	-0.247
	1.050	f_1	0.181
	0.853	f_2	-0.416
-Cl	0.591		

Results and Discussion

Result of Experiment. The maximum absorption wavelength of the 10 compounds and the results of log K_{ow} are shown in Table 2. The K_{ow} value of each compound was obtained from two experiments in which the tested compound's concentrations of the added octanol solution were different. The two results have little difference, and the results shown in the table are the average of the two results.

In the experiment, the error of mass is less than ± 0.0001 g, and when preparing the octanol solution containing the tested compound, the error of volume is less than ± 0.00001 L. The errors of volumes of the water phase or octanol phase are less than ± 0.0001 L. So, the error of the log K_{ow} is less than ± 0.1.

Result of Estimation. By combining the collected K_{ow} data containing 28 halogen benzenes, benzoic acid, and 18 other halogen benzoic acids with the 10 K_{ow} data determined by the experiment, a set of values containing 11 group values and 2 factors were obtained to estimate the log K_{ow} of halogen benzoic acids using the fragmental method.

The model of the fragmental method here is

$$\log K_{ow} = \sum_{i=1}^{11} (n_i \cdot k_i) + \sum_{j=1}^{2} (l_j \cdot f_j) + 1.117 \qquad (1)$$

where n_i is the number of group i; k_i is the value of group i; f_j is the factor; and l_j is the number of the factor.

In this model, the factors are used to modify the effect of the related position of halogens and carboxyl, f_1, for the para position and, f_2, for the ortho position. For example, 2-fluoro-4-bromobenzoic acid contains an f_1 and an f_2, and 2,6-dichlorobenzoic acid contains two f_2's.

To analyze the error of the results, the absolute error of log K_{ow}, AE, is calculated by formula 2, and the related error of K_{ow}, RE, is calculated by formula 3. The results are shown in Table 4.

Table 4. Estimation Results of the 57 Compounds Participating in the Regression

	experimental results[1,2]	results of the fragmental method	
compounds	log K_{ow}	log K_{ow}	AE
chlorobenzene	2.84	2.81	0.03
iodobenzene	3.25	3.18	0.07
bromobenene	2.99	2.95	0.04
fluorobenzene	2.27	2.30	0.03
o-dibromobenzene	3.64	3.68	0.04
m-dibromobenzene	3.75	3.68	0.07
p-dibromobenzene	3.79	3.68	0.11
m-dichlorobenzene	3.53	3.39	0.14
o-dichlorobenzene	3.43	3.39	0.04
p-dichlorobenzene	3.44	3.39	0.05
m-difluorobenzene	2.21	2.38	0.17
o-difluorobenzene	2.37	2.38	0.01
p-difluorobenzene	2.13	2.38	0.25
p-diiodobenzene	4.11	4.14	0.03
1,2,3-trichlorobenzene	4.05	4.08	0.03
1,2,4-trichlorobenzene	4.02	4.08	0.06
1,3,5-trichlorobenzene	4.19	4.08	0.11
1,3,5-tribromobenzene	4.51	4.51	0.00
1,2,4-trifluorobenzene	2.52	2.55	0.03
1,2,4,5-tetrabromobenzene	5.13	5.16	0.03
1,2,3,4-tetrachlorobenzene	4.60	4.59	0.01
1,2,3,5-tetrachlorobenzene	4.56	4.59	0.03
1,2,4,5-tetrachlorobenzene	4.64	4.59	0.05
pentachlorobenzene	5.17	5.12	0.05
pentafluorobenzene	2.53	2.58	0.05
hexachlorobenzene	5.73	5.52	0.21
hexabromobenzene	6.07	6.37	0.30
hexafluorobenzene	2.55	2.46	0.09
benzoic acid	1.87	1.97	0.10
o-chlorobenzoic acid	2.05	2.14	0.09
m-chlorobenzoic acid	2.68	2.56	0.12
p-chlorobenzoic acid	2.65	2.74	0.09
o-bromobenzoic acid	2.20	2.28	0.08
m-bromobenzoic acid	2.87	2.70	0.17
p-bromobenzoic acid	2.86	2.88	0.02
o-fluorobenzoic acid	1.77	1.63	0.14
m-fluorobenzoic acid	2.15	2.05	0.10
p-fluorobenzoic acid	2.07	2.23	0.16
o-iodobenzoic acid	2.40	2.51	0.11
m-iodobenzoic acid	3.13	2.93	0.20
p-iodobenzoic acid	3.02	3.11	0.09
2,5-dichlorobenzoic acid	2.82	2.83	0.01
2,6-dichlorobenzoic acid	2.23	2.41	0.18
3,4-dichlorobenzoic acid	3.25	3.42	0.17
3,5-dichlorobenzoic acid	3.00	3.24	0.24
2,6-difluorobenzoic acid	1.59	1.39	0.20
2-chloro-6-fluorobenzoic acid	2.11	1.90	0.21
2-chloro-3-fluorobenzoic acid	1.74	2.32	0.58
4-chloro-2-fluorobenzoic acid	2.28	2.50	0.22
2-bromo-5-fluorobenzoic acid	2.21	2.45	0.24
3-bromo-4-fluorobenzoic acid	3.56	3.06	0.50
2-fluoro-4-bromobenzoic acid	2.76	2.64	0.12
2-fluoro-5-chlorobenzoic acid	1.59	2.32	0.73
2-chloro-4-fluorobenzoic acid	2.63	2.50	0.13
2-chloro-5-fluorobenzoic acid	2.39	2.32	0.07
2-chloro-5-bromobenzoic acid	3.16	2.97	0.19
2-fluoro-5-bromobenzoic acid	3.43	2.46	0.97

$$\mathrm{AE} = |\log K_{ow,calcd} - \log K_{ow,lit}| \qquad (2)$$

$$\mathrm{RE} = |(K_{ow,calcd} - K_{ow,lit})/K_{ow,lit}| \cdot 100\ \% \qquad (3)$$

The average AE and average RE of the new fragmental method are 0.15 and 39 %, respectively, and the maximum AE of the method is 0.97.

Conclusion

Octanol/water partition coefficients of 10 kinds of selected halogen benzoic acids including 2-chloro-3-fluorobenzoic acid, 4-chloro-2-fluorobenzoic acid, 2-bromo-5-fluorobenzoic acid, 3-bromo-4-fluorobenzoic acid, 2-fluoro-4-bromobenzoic acid, 2-fluoro-5-chlorobenzoic acid, 2-chloro-4-fluorobenzoic acid, 2-chloro-5-fluorobenzoic acid, 2-chloro-5-bromobenzoic acid, and 2-fluoro-5-bromobenzoic acid were first determined using the shake-flask method.

A set of values containing 11 group values and 2 factors used to estimate the K_{ow} of halogen benzoic acids were obtained, and these values were used to estimate the K_{ow} of the selected compounds.

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