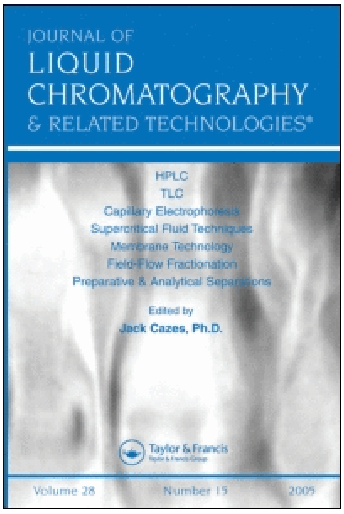

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Hanfa Zou[a]; Yukui Zhang[a]; Minfang Hong[a]; Peichang Lu[a]
[a] National Chromatographic R&A Center Dalian Institute of Chemical Physics Academic Sinica, Dalian, The People's Republic of China

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EFFECT OF HAMMETT'S CONSTANT ON THE QUANTITATIVE CORRELATION OF BENZOIC ACID RETENTION IN RP-IPC WITH n-OCTANOL/WATER PARTITION COEFFICIENTS

HANFA ZOU*, YUKUI ZHANG, MINFANG HONG, AND PEICHANG LU
National Chromatographic R & A Center
Dalian Institute of Chemical Physics
Academia Sinica
Dalian 116011, The People's Republic of China

ABSTRACT

The quantitative correlation of n-octanol/water partition coefficient (logP) vs. extrapolated capacity factor ($\log k^{w}_{ip}$) in RP-IPC and Hammett's constant (σ) with eleven ionic benzoic acids as model compounds is evaluated. There is a high regression coefficient (0.98) with methanol and acetonitrile as organic modifiers, but there is a low regression coefficient (0.80) with tetrahydrofuran as organic modifier. The parameter $\log k^{w}_{ip}$ makes a positive contribution to n-octanol/water partition coefficient whereas the Hammett's constant makes a negative contribution. Methanol and acetonitrile are the solvents of choice for determination of logP value of the ionic solutes. The electronic effect of solutes described by the Hammett's constant plays a quite important role in the retention of ionic compounds in RP-IPC.

INTRODUCTION

The partition coefficient, a medicinal relevant physicochemical property, plays an influential role in many biological processes. Thus, it finds numerous applications in quantitative structure-activity relationship (QSAR) studies[1-5] and estimation of enviromental parameters[6-8]. Partition coefficients have been measured in nearly 100 solvent-water systems, mainly by means of the traditional shake-flask method[5]. n-Octanol/water is widely accepted as the reference system because of its analogy with biomembranes[5]. However, practical disadvantages and the limitation to n-octanol/water partition coefficients (logP values) between -2 and +4 have led researchers to investigate other methods for measuring such partition coefficients[9,10]. Reversed-phase high performance liquid chromatography (RP-HPLC) has become a popular alternative, with capacity factors frequently being used as substitutes for n-octanol/water partition coefficients in QSAR studies.

The measurement of partition coefficients by RP-HPLC is based on the principle of the partition of a solute between a polar eluent and a stationary phase of low polarity[11-13]. It should be noted that many ionic organic compounds such as drugs are only weakly retained or non-retained in RP-HPLC even with pure aqueous buffer or water as the eluent. This makes it difficult to measure the partition coefficient of such ionic species from the capacity factors in RP-HPLC. However, reversed-phase ion-pair liquid chromatography (RP-IPC) has become a well established method for the separation of ionic compounds, in which the retention can be regulated by the nature and concentration of organic modifier and ion-pair reagent as well as by a competing ion with the same charge as that of the analyte [14-18]. Recent studies[19-21] on the retention process of RP-IPC revealed that electrostatic and hydrophobic interactions are important contributors to retention. Quantitative correlations between logP values and retention values in RP-IPC and solute charges has been observed[24]. In this paper, electronic effects described by Hammett's constant on the correlation between the partition coefficient and the retention values in RP-IPC are described.

THEORETICAL

1. Relationship Between the logP Values and the Parameters $\log k^{w}_{ip}$, c_{ip} and Hammett's Constant

It has been reported that the logarithm of capacity factors ($\log k^{w}_{ip}$) decrease linearly with increasing organic modifier concentration (C_b) in RP-IPC[20-24]:

$$\log k'_{ip} = \log k^{w}_{ip} + c_{ip}C_b \qquad (1)$$

where $\log k^{w}_{ip}$ is the logarithm of capacity factor in RP-IPC in the absence of organic modifier and c_{ip} a constant for the chromatographic system. The parameters, $\log k^{w}_{ip}$ and c_{ip}, are dependent upon the electrostatic and molecular interactions. The quantitative relationship between $\log k^{w}_{ip}$ and c_{ip} with retention values in RP-HPLC and solute charge has been reported[23]. One would expect a linear relationship between logP and the paramters, $\log k^{w}_{ip}$ and c_{ip}, if the ionic solutes have the same charges:

$$\log P = c_1 + d_1 \log k^{w}_{ip} \qquad (2)$$

$$\log P = c_2 + d_2 c_{ip} \qquad (3)$$

where c_1, c_2 and d_1, d_2 are constants for the system. It is known that the position of substituents on phenyl ring will affect retention in RP-IPC and that this effect may be taken into account by the use of Hammett's contants(σ)[25,26]:

$$\log P = c_3 + d_3 \log k^{w}_{ip} + e_3\sigma \qquad (4)$$

$$\log P = c_4 + d_4 c_{ip} + e_4\sigma \qquad (5)$$

In this work, we examined the validity of eqns.(2)-(5) by experimentally determined RP-IPC data.

Table 1

The Fragmental logP Values

Fragmental group	Fragmental logP Constant[a)]
$f_{C_6H_5}$	1.90
f^{ϕ}_{Cl}	0.94
$f^{\phi}_{CH_3}$	0.89
f^{ϕ}_{OH}	-0.44
$f^{\phi}_{NH_2}$	-1.00
$f^{\phi}_{NO_2}$	-0.03
$f^{\phi}_{COO^-}$	-4.13
f_H	0.23

a) Values taken from Ref.8 and 29.

2. Calculation of n-Octanol/Water Partition Coefficient

According to Hansch and Leo[27,28], the n-octanol/water partition coefficient logP can be expressed

$$\log P = a_i f_n + b_j F_m \qquad (6)$$

where f_n is the hydrophobic fragmental constant, the lipophilicity contribution of a constituent part of a structure to the total lipophilicity; F_m other factors affecting the partition coefficient; and a_i and b_j, numerical factors indicating the incidence of the given fragmental and other factors in the structure of a complex substance. Table 1 lists the fragmental constants used to calculate the partition coefficient of eleven substituted benzoic acids. Below are given two examples of the use of such constants for the calculation of logP values for benzoic acid or its derivatives:

Benzoic acid

$$\log P = f_{C_6H_5} + f^{\phi}_{COO^-} = 1.90 - 4.35 = -2.23$$

p-Methylbenzoic acid

$$\log P = f_{C_6H_5} + f^{\phi}_{COO^-} - f_H + f^{\phi}_{CH_3} = 1.90-4.13-0.23+0.89 = -1.57$$

EXPERIMENTAL

The data of $\log k^{w}_{ip}$ and c_{ip} utilized in this work were taken from a chapter by Tomlinaon and Riley[30], which gives an exact description of the analytical conditions employed. In this work, the capacity factors of eleven substituted benzoic acids were measured in a chromatographic system with Hypersil-ODS as the stationary phase and three kinds of binary mobile phases mixed from individually measured volumes of methanol, acetonitrile, tetrahydrofuran and water. The ion-pair reagent, 0.5 mmol/l tetradecylbenzyldimethylammonium chloride, 25 mmol/l K_2HPO_4 and pH 7.5 were kept constant in each binary eluent. The column temperature was kept 30 ℃ in each experiment. The $\log k^{w}_{ip}$ and c_{ip} values for those eleven benzoic acids in the above chromatographic systems were calculated and taken, respectively, from a chapter by Tomlinson and Riley[30].

RESULTS AND DISCUSSION

The values of logP calculated by Hansch's method and the Hammett's constant taken from Jing et al[26] for eleven m- and p-substituted benzoic acides are listed in Table 2. Table 3 gives the parameters $\log k^{w}_{ip}$ and c_{ip} in retention equation of RP-IPC with the methanol, acetonitrile and tetrahydrofuran as the organic modifiers. The results of quantitative correlation of the partition coefficient logP versus the parameters $\log k^{w}_{ip}$ and c_{ip} according to eqns.(2) and (3) as well as the quantitative

Table 2

The Calculated logP Values by Hansch's Method for Eleven Benzoic Acids and Their Hammett's Constant

Solute	logP	Hammett's Constant[a)]
Benzoic acid	-2.23	0.00
n-Aminobenzoic acid	-3.46	-0.66
m-Aminobenzoic acid	-3.46	-0.16
p-Hydroxybenzoic acid	-2.90	-0.37
m-Hydroxybenxoic acid	-2.90	0.12
p-Nitrobenzoic acid	-2.49	0.78
m-Nitrobenzoic acid	-2.49	0.71
p-Methylbenzoic acid	-1.57	-0.17
m-Methylbenzoic acid	-1.57	-0.07
p-Chlorobenzoic acid	-1.52	0.23
m-Chlorobenzoic acid	-1.52	0.37

a) Values taken from Ref.26.

Table 3

The Parameters $\log k^{w}_{ip}$ and c_{ip} in RP-IPC with Methanol, Acetonitrile and Tetrahydrofuran as Organic Modifiers

Solute	MeOH/Water		ACN/Water		THF/Water	
	$\log k^{w}_{ip}$	c_{ip}	$\log k^{w}_{ip}$	c_{ip}	$\log k^{w}_{ip}$	c_{ip}
Benzoic acid	2.94	-4.74	2.80	-7.94	2.96	-9.29
n-Aminobenzoic acid	1.43	-3.21	1.24	-4.54	1.44	-6.46
m-Aminobenzoic acid	1.84	-3.84	1.67	-5.55	1.92	-7.36
p-Hydroxybenzoic acid	2.20	-4.22	1.58	-5.27	2.12	-7.39
m-Hydroxybenzoic acid	2.82	-5.03	2.34	-7.18	2.93	-7.71
p-Nitrobenzoic acid	3.44	-5.38	3.36	-8.62	5.19	-15.3
m-Nitrobenzoic acid	3.53	-5.51	3.48	-9.07	5.73	-17.4
p-Methylbenzoic acid	3.53	-5.35	3.49	-8.38	4.74	-14.9
m-Methylbenzoic acid	3.63	-5.48	3.66	-9.93	4.67	-14.7
p-Chlorobenzoic acid	4.14	-6.11	4.10	-10.6	4.54	-13.0
m-Chlorobenzoic acid	4.10	-6.00	4.08	-10.4	4.55	-13.1

a) Chromatographic system and parameters as mentioned in experimental section. The $\log k^{w}_{ip}$ and c_{ip} values were taken from Ref.30.

correlation according to eqns.(4) and (5) taking into account Hammett's constants are shown below for three organic modifiers:

Methanol as organic modifier

$\log P = -5.573 + 1.069 \log k_{ip}^{w} - 0.912\sigma$, $n=11$, $r=0.9872$

$\log P = -4.709 + 0.765 \log k_{ip}^{w}$, $n=11$, $r=0.9113$

$\log P = -7.631 - 1.068\, c_{ip} - 0.996\sigma$, $n=11$, $r=0.9512$

$\log P = -5.973 - 0.722\, c_{ip}$, $n=11$, $r=0.8651$

Acetonirtrile as organic modifier

$\log P = -4.953 + 0.913 \log k_{ip}^{w} - 0.854\sigma$, $n=11$, $r=0.9872$

$\log P = -4.306 + 0.668 \log k_{ip}^{w}$, $n=11$, $r=0.9122$

$\log P = -5.768 - 0.434\, c_{ip} - 0.793\sigma$, $n=11$, $r=0.9577$

$\log P = -4.942 - 0.323\, c_{ip}$, $n=11$, $r=0.8963$

Tetrahydrofuran as organic mofifier

$\log P = -4.670 + 0.641 \log k_{ip}^{w} - 1.118\sigma$, $n=11$, $r=0.8289$

$\log P = -3.769 + 0.722 \log k_{ip}^{w}$, $n=11$, $r=0.8289$

$\log P = -4.357 - 0.176\, c_{ip} - 0.527\sigma$, $n=11$, $r=0.7256$

$\log P = -3.911 - 0.134\, c_{ip}$, $n=11$, $r=0.6946$

Figure 1 shows the comparison of $\log P_H$ calculated by Hansch's method with $\log P_R$ calculated by eqns.(2) and (4) with methanol as the organic modifier. It can be seen that: (1) The coefficient d_3 (or d_1) is always positive and the coefficient d_4 (or d_2) is negative with methanol, acetonitrile and tetrahydrofuran as organic modifiers. This indicates that the $\log k_{ip}^{w}$ term makes a positive whereas the c_{ip} term, a negative, contribution to the n-octanol/water partition coefficient. (2) The intercept values c_1 and c_3 (or c_2 and c_4) for different mobile phases increase in the order methanol/water < acetonitrile/water < tetrahydrofuran/ water, which is the same as the order of their hydrophobicity as an organic modifier. (3) The coefficient e_3 (or e_4) is always negative, which means that the Hammett's constant always makes

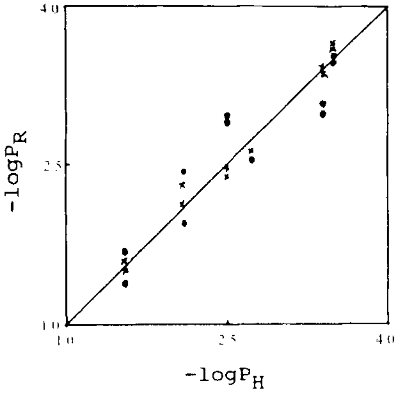

Figure 1 Comparison of $\log P_H$ values calculated by Hansch's method with $\log P_R$ calculated by eqns.(2) and (4).
Data point for $\log P_H$ vs. $\log P_R$ by eqn.(2):
$\log P_R = -0.396 + 0.833 \log P_H$, n=11, r=0.9113.
Data point for $\log P_H$ vs. $\log P_R$ by eqn.(4),
$\log P_R = -0.069 + 0.976 \log P_H$, n=11, r=0.9855

a negative contribution to the n-octanol/water partition coefficient, and the quantitative correlation of logP vs. $\log k_{ip}^{w}$ or logP vs. c_{ip} is greatly improved by taking into account the Hammett constant. For example, the regression coefficient is 0.987 and 0.980 for the logP vs. $\log k_{ip}^{w}$ correlation in coperating the Hammett constant with methanol or acetonitrile as organic modifier. However, it is only 0.911 and 0.912 for relationship of logP vs. $\log k_{ip}^{w}$ without such Hammett correction, which means that the electronic effect described by Hammett's constant plays quite an important role in the retention of benzoic acids in RP-IPC. (4) As far as the organic modifier is concerned, methanol and acetonitrile appear to be the solvents of choice for the determination of n-octanol/water partition coefficient of ionic compounds by RP-IPC. For example, the regression coefficient for the quantitative correlation of logP vs. $\log k_{ip}^{w}$ is 0.987 and

0.981 with methanol and acetonitrile as organic modifiers respectively, as opposed to only 0.829 with tetrahydrofuran as the modifier. It can be concluded that it is possible to measure the n-octanol/water partition coefficient of ionic solutes by RP-IPC, if appropriate organic modifiers are employed and Hammett constants are used to correct for electronic effects of substituents.

CONCLUSION

It can be concluded that (1) RP-IPC can be used in quantitative correlation between retention values and n-octanol/water partition coefficient, (2) Hammett constants can significantly improve the fit of such correlations due to their correction for electronic effects.

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