

## Thermochemical Aspects of Partition. Quantitative Structure Activity Relationships of Benzyldimethylalkylammonium Chlorides

Yong-Zhong DA, Junko YANAGI, Kyoko TANAKA, and Hideaki FUJIWARA\*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-Oka, Suita, Osaka 565, Japan.

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As an extension of our recent studies on the relationships between thermochemical aspects of partition and biological activities, enthalpies and entropies of partition have been determined for 17 congeners of the titled quaternary ammonium chlorides, and the novel hydrophobic parameters,  $P_H$  and  $P_S$ , have been assigned. The regression equations using these parameters are discussed against the biological activities of pasteurization: a parabolic model is built up with regard to the  $P_H$  and  $P_S$  terms, which gives an improved result compared to a linear model.

**Keywords** partition property; hydrophobicity; enthalpy, entropy; 1-octanol/water; QSAR analysis; benzyldimethylalkylammonium chloride

Studies of the relationships between biological activities and physical parameters within the compounds of variable structures are inevitable for a modern rational design of new drugs. In these studies it is well known that hydrophobic, electronic, and steric factors are three major factors governing drug actions.<sup>1-4</sup> Among these factors hydrophobicity is related to the transportation of drugs across multiple lipophase/water interfaces, and is usually symbolized by the logarithm of partition coefficient,  $\log P$ , in 1-octanol/water system. However, there was no definite reason for selecting this system as a model of biophase, and quite recently micelles and liposomes have become interesting instead of 1-octanol<sup>5-8</sup> because they possess organized structures of long alkyl chains that resemble biophase. From a discussion of thermochemical aspects of partition, we have introduced the novel hydrophobic parameters,  $P_H$ ,  $P_S$ ,  $\pi_H$ , and  $\pi_S$ , which are defined as follows from the enthalpy ( $\Delta H_p^0$ ) and entropy ( $\Delta S_p^0$ ) of partition:

$$\left. \begin{aligned} P_H &= -\Delta H_p^0 / (2.303RT) \\ P_S &= \Delta S_p^0 / (2.303R) \\ \pi_H &= P_H(R:X) - P_H(R:H) \\ \pi_S &= P_S(R:X) - P_S(R:H) \end{aligned} \right\} \quad (1)$$

where  $R$  is the gas constant and  $R$  is a substituent on the phenyl ring. These parameters have given superb quantitative structure activity relationships (QSAR) analyses for fatty alcohol and benzoic acid derivatives, superior to that given using the conventional parameters,  $\log P$  or  $\pi$ .<sup>9,10</sup> In the present work, we put into practice the similar novel QSAR analyses for other kind of compounds, benzyldimethylalkylammonium chlorides (Chart 1).

### Experimental

**Preparation of Quaternary Ammonium Salts** Benzyldimethylalkylammonium chlorides were prepared from the reaction of alkyldimethylamines with substituted benzyl chlorides. Both of these starting materials were obtained commercially. This reaction was carried out in ether or

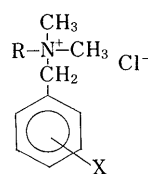


Chart 1

*n*-hexane in an oil bath by refluxing the solution about 10 h. Then the solvent was blown off by an evaporator, and the product was washed several times with ether or *n*-hexane. Finally, the raw product was recrystallized.

**Measurement of Partition Properties,  $\log P$ ,  $P_H$ , and  $P_S$ , for the Quaternary Ammonium Salts** 1–30 mM quaternary ammonium salt was dissolved in 1-octanol. 5 ml of this solution was mixed with 20 ml aqueous solution containing 0.1 M NaCl and then sealed in an ampoule. 1-Octanol and the aqueous solution were presaturated with each other before use. The ampoule was shaken in a constant temperature bath for 24 h. The partition coefficient was calculated from the concentration change of quaternary ammonium salts in the aqueous phase that was measured with a Hitachi U2000 spectrophotometer. A 10 cm cell was used to measure low concentrations in the aqueous phase. The enthalpy and entropy of the partition were determined from the van't Hoff plot<sup>11</sup> after the variable temperature measurements of  $\log P$  at nearly 25, 33, 40, 50, and 60 °C. This plot showed that in some cases there was a decrease from the linear plot at 25 °C. Micellization in the aqueous phase<sup>12</sup> may be a cause of such a decrease. In such a case the measurements were made at slightly higher temperatures. All the experiments were repeated several times to give averages and standard deviations of the measurement.

### Results

The thermochemical properties of quaternary ammonium salts are summarized in Table I. The  $\log P$  value is listed at 33 °C: at this temperature the effect of micellization mentioned above was not observed throughout any of the compounds. The value of  $\log P$  is the average of experiments repeated 3–5 times. The  $P_H$  and  $P_S$  calculated from  $\Delta H_p^0$  and  $\Delta S_p^0$  (at 33 °C) are also included in Table I. The  $\log P$  values calculated from an additive rule<sup>13</sup> are also listed in the column of  $\log P_{ref}$ . The biological activities are cited from a reference that reports the concentration of compounds required to kill *Salmonella typhosa* HOPKINS and *Micrococcus pyogenes* var. *aureus* 209 in 10 min.<sup>12</sup> Table I shows that the value of  $\log P$  is always larger than that of  $\log P_{ref}$ . This comes from a common ion effect: 0.1 M  $Cl^-$  ion is always included in the aqueous phase for the constancy of the ionic strength and this ion acts to suppress the dissociation of salt solutes in the aqueous phase enhancing the partition coefficient. According to this additive rule, the  $C_{12}$  alkyl chain contributes to  $\log P_{ref}$  larger by 2.0 units than the  $C_8$  alkyl chain does (Table I). But the experimental data show that the difference between  $C_{12}$  and  $C_8$  congeners varies from 1.1 to 2.5. Also, the difference between the  $C_{14}$  and  $C_8$  congeners amounts to 3.0 units from the additive rule, but the difference from experimental data varies from 0.9 to 2.0. Furthermore, as

TABLE I. Partition Properties and Biological Activities of Quaternary Ammonium Salts

No.	R <sup>a)</sup>	X <sup>a)</sup>	log P	log P <sub>ref</sub> <sup>b)</sup>	$\Delta H_p^0$	$\Delta S_p^0$	P <sub>H</sub>	P <sub>S</sub>	-log C <sub>1</sub> <sup>c)</sup>	-log C <sub>2</sub> <sup>c)</sup>	Analysis (%)	
					(kJ/mol)	(J/K mol)					Calcd N	Found N
1	C8	2-Cl	1.17±0.04	-0.32	-0.60	-0.74	1.99	-0.80	1.92	2.03	4.40	4.36
2	C8	4-Cl	1.74±0.01	-0.38	-0.94	-1.24	2.95	-1.20	2.89	2.60	4.40	4.31
3	C8	4-NO <sub>2</sub>	0.92±0.01	-0.84	-10.18	-14.63	2.74	-1.80	1.92	2.12	8.52	8.34
4	C8	2,4-Cl <sub>2</sub>	1.98±0.01	0.38	-12.26	-1.14	1.84	0.15	2.51	2.64	3.97	3.77
5	C8	3,4-Cl <sub>2</sub>	2.04±0.01	0.38	18.19	-18.68	2.90	-0.86	2.92	2.92	3.97	3.80
6	C8	3,4-(OCH <sub>2</sub> O)	0.97±0.01	-1.13	-14.15	-26.91	2.30	-1.33	2.06	2.06	3.76	3.58
7	C12	H	3.05±0.04	0.92	-25.61	-25.23	4.27	-1.32	3.80	3.75	4.12	3.82
8	C12	2-Cl	3.72±0.01	1.68	-16.49	11.19	2.75	0.08	3.85	4.16	3.72	3.62
9	C12	4-Cl	2.80±0.02	1.62	-12.34	18.71	2.06	0.69	4.24	4.05	3.72	3.58
10	C12	4-NO <sub>2</sub>	2.25±0.06	1.16	-13.62	8.45	2.27	-0.02	3.66	4.22	7.28	7.16
11	C12	3,4-(OCH <sub>3</sub> ) <sub>2</sub>	2.66±0.00	1.00	-12.53	10.01	2.09	0.52	3.68	3.72	3.15	2.80
12	C12	3,4-(OCH <sub>2</sub> O)	3.14±0.02	0.87	-13.83	13.45	2.31	0.70	3.85	4.00	3.27	3.30
13	C12	2-OH,5-NO <sub>2</sub>	2.11±0.04	0.49	-55.71	-143.04	9.29	-7.47	2.59	2.70	6.99	6.23
14	C14	H	2.96±0.13	1.92	-2.32	47.84	0.39	2.50	4.07	4.20	3.81	3.65
15	C14	2-Cl	3.15±0.00	2.68	-12.16	19.37	2.60	0.48	4.17	4.16	3.48	3.24
16	C14	4-NO <sub>2</sub>	2.62±0.00	2.16	-12.53	3.45	2.09	0.18	4.27	4.24	6.78	7.27
17	C14	2,4-Cl <sub>2</sub>	3.20±0.01	3.38	-21.10	-5.46	3.52	-0.29	4.14	4.29	3.21	3.00

No.	<sup>1</sup> H-NMR δ value (CDCl <sub>3</sub> , 250 MHz) <sup>d)</sup>						
	CH <sub>3</sub> (R)	CH <sub>2</sub> (R)	<sup>+</sup> NCCH <sub>2</sub>	<sup>+</sup> NCH <sub>3</sub>	<sup>+</sup> NCH <sub>2</sub> (R)	<sup>+</sup> NCH <sub>2</sub> Ph	Aromatics
1	0.88 (t, J=6.25)	1.26	1.86	3.35	3.68	5.17	7.41—7.51, 8.12 (dd, J=6.75, 2.50)
2	0.87 (t, J=6.25)	1.29	1.78	3.30	3.56	5.18	7.39 (d, J=8.00), 7.69 (d, J=8.00)
3	0.86 (t, J=6.75)	1.24	1.83	3.36	3.62	5.47	8.10 (d, J=8.50), 8.24 (d, J=8.50)
4	0.87 (t, J=6.12)	1.26	1.86	3.35	3.71	5.21	7.39 (dd, J=6.50, 2.50), 7.51 (d, J=2.50), 8.19 (d, J=6.50)
5	0.87 (t, J=6.12)	1.24	1.80	3.31	3.57	5.24	7.50 (d, J=8.00), 7.73 (d, J=8.00), 7.91
6	0.88 (t, J=6.38)	1.26	1.79	3.27	3.52	5.02	6.84 (d, J=7.25), 7.18 (d, J=7.25), 7.28
7	0.88 (t, J=6.50)	1.25	1.80	3.28	3.50	5.00	7.38—7.43, 7.66—7.70
8	0.88 (t, J=6.38)	1.26	1.85	3.36	3.68	5.18	7.41—7.51, 8.13 (dd, J=6.00, 3.00)
9	0.88 (t, J=6.50)	1.25	1.77	3.29	3.51	5.20	7.38 (d, J=8.00), 7.69 (d, J=8.00)
10	0.88 (t, J=6.75)	1.24	1.83	3.36	3.59	5.46	8.09 (d, J=8.50), 8.22 (d, J=8.50)
11	0.88 (t, J=6.38)	1.25	1.81	3.26	3.54	4.97	6.87 (d, J=7.75), 7.19 (dd, J=7.75, 1.25), 7.42 (d, J=1.25)
12	0.88 (t, J=6.75)	1.25	1.78	3.27	3.53	5.01	6.83 (d, J=8.00), 7.18 (dd, J=8.00, 1.75), 7.30 (d, J=1.75)
13	0.87 (t, J=6.62)	1.25	1.85	3.21	3.55	4.87	7.75 (d, J=9.25), 8.04 (d, J=9.25), 8.46
14	0.88 (t, J=6.50)	1.26	1.80	3.31	3.54	5.08	7.39—7.46, 7.67—7.71
15	0.88 (t, J=6.38)	1.25	1.85	3.36	3.70	5.18	7.42—7.50, 8.12 (dd, J=6.75, 1.75)
16	0.88 (t, J=6.12)	1.25	1.83	3.36	3.58	5.46	8.06 (d, J=7.75), 8.23 (d, J=7.75)
17	0.88 (t, J=6.50)	1.26	1.86	3.35	3.69	5.20	7.39 (d, J=8.50), 7.39, 8.18 (d, J=8.50)

a) See Chart 1 for the substituents R and X. C8: *n*-C<sub>8</sub>H<sub>17</sub>, C12: *n*-C<sub>12</sub>H<sub>25</sub>, C14: *n*-C<sub>14</sub>H<sub>29</sub>. b) See ref. 13. c) See ref. 12. d) <sup>+</sup>NCCH<sub>2</sub> and <sup>+</sup>NCH<sub>2</sub>(R) are triplet-like broad signals, whereas <sup>+</sup>NCH<sub>3</sub> and <sup>+</sup>NCH<sub>2</sub>Ph are all singlets.

for the groups on the phenyl ring, the experimental values of group contribution differ from those predicted by the additive rule. These facts show that the additive rule does not work well for the organic salts treated here. In spite of these discrepancies in numerical values, log P and log P<sub>ref</sub> interrelated rather well with each other when collinearity was tested (Fig. 1, *r*=0.86).

The correlation coefficients between log P, P<sub>H</sub> and P<sub>S</sub> are quite small except between P<sub>H</sub> and P<sub>S</sub>: P<sub>H</sub> and P<sub>S</sub> are inversely correlated rather well with each other (*r*=-0.92). This inverse correlation indicates that P<sub>H</sub> and P<sub>S</sub> compensate each other in contributing to log P.<sup>14)</sup> Therefore, it will be expected that a separate observation of P<sub>H</sub> and P<sub>S</sub> will disclose a new trend in the partition properties which might be masked when observed in the overall parameter log P.

When log P, P<sub>H</sub> and P<sub>S</sub> are correlated with other physical parameters, significant contributions are found for the incremental volume of the alkyl chain ( $\Delta V_{W_{CH_2}}$ ) and of the

substituent on the aromatic ring ( $\Delta V_{W_X}$ )<sup>15)</sup> as well as for the resonance effect parameter *R*<sup>16)</sup> by Swain and Lupton (*R<sub>m</sub>* and *R<sub>p</sub>* for the *meta* and *para* positions):

$$\left. \begin{aligned} \log P &= 0.36(0.14)\Delta V_{W_{CH_2}} - 0.04(0.45)\Delta V_{W_X} + 1.49(1.89)R_m \\ &\quad - 1.27(1.64)R_p + 1.48(0.72) \quad r=0.867, F=9.06, S.D.=0.47 \\ P_H &= -0.07(0.45)\Delta V_{W_{CH_2}} - 1.00(1.44)\Delta V_{W_X} - 6.48(6.08)R_m \\ &\quad - 1.54(5.26)R_p + 3.47(2.31) \quad r=0.730, F=3.42, S.D.=1.50 \\ P_S &= 0.43(0.48)\Delta V_{W_{CH_2}} + 0.95(1.56)\Delta V_{W_X} + 7.91(6.60)R_m \\ &\quad + 1.81(5.71)R_p - 1.98(2.51) \quad r=0.742, F=3.68, S.D.=1.62 \end{aligned} \right\} (2)$$

In these eqs. the number of data treated equals 17, and 95% confidence intervals are depicted in parentheses. Although these intervals are rather large in most cases, some trends can be deduced as follows. The length of the alkyl chain, which is reflected in  $\Delta V_{W_{CH_2}}$ , is seen to be significant to P<sub>S</sub> and log P (but not to P<sub>H</sub>), whereas the bulkiness of substituents on the phenyl ring,  $\Delta V_{W_X}$  is significant to P<sub>H</sub>

and  $P_S$  (but cancelled in contributing to  $\log P$ ).

**QSAR Analyses and Discussion**

The QSAR analyses of quaternary ammonium salts are shown in Table II. Hitherto, QSAR analyses according to the partition coefficients estimated by an additive rule have given a quadratic equation with regard to the pasteurization concentration ( $\log C_1$ ) to *Salmonella typhosa* ( $r=0.902$ ). Likewise, QSAR analyses using  $\log P$  values obtained experimentally in the present work give a little better correlation ( $r=0.925$ ). As for the pasteurization concentrations ( $\log C_2$ ) to *Micrococcus pyogenes*, a quite similar situation is observed (Table II).

Recently, we have been reexamining the QSAR analyses from the standpoint of thermochemical aspects after separating  $\log P$  into  $P_H$  and  $P_S$ . That is, for several cases where biological data  $\log C$  are tested as a linear function of  $\log P$  (Eq. 3),

$$-\log C = a \log P + c \tag{3}$$

the following equation has given better fittings for the biological data.

$$-\log C = aP_H + bP_S + c \tag{4}$$

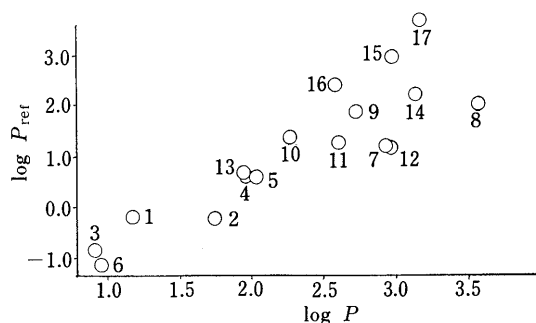


Fig. 1. Interrelation of  $\log P_{ref}$  and  $\log P$  Measured in the Present Study. The numbering corresponds to that in Table I.

TABLE II. The QSAR Analyses of Quaternary Ammonium Salts<sup>a)</sup>

Equations	$r$	$r'$	$r''$	$F$	S.D.
$-\log C_1 = -0.134(0.126)(\log P_{ref})^2 + 0.893(0.314)\log P_{ref} + 2.824(0.274)$	0.902	0.887	0.874	30.39	0.407
$-\log C_1 = -0.212(0.301)(\log P)^2 + 1.893(1.326)\log P + 0.181(0.318)$	0.925	0.914	0.904	43.54	0.355
$-\log C_1 = 0.953(0.264)\log P + 1.110(0.648)$	0.893	0.885	0.879	59.10	0.399
$-\log C_2 = -0.142(0.120)(\log P_{ref})^2 + 0.927(0.297)\log P_{ref} + 2.882(0.259)$	0.915	0.902	0.891	36.17	0.385
$-\log C_2 = -0.181(0.291)(\log P)^2 + 1.738(1.279)\log P + 0.470(1.278)$	0.931	0.921	0.911	45.72	0.340
$-\log C_2 = 0.995(0.233)\log P + 1.069(0.577)$	0.920	0.914	0.909	82.54	0.354

a) The values in parentheses indicate 95% confidence intervals. The number of data is 17 for all data.  $r$ : multiple correlation coefficient.  $r'$ : multiple correlation coefficient adjusted for the degree of freedom.  $r''$ : multiple correlation coefficient doubly adjusted for the degree of freedom.  $F$ : variance ratio. S.D.: standard deviation between the observed and the recalculated values.

TABLE III. The QSAR Analyses of Quaternary Ammonium Salts: the Parabolic Case Including  $P_H$  and  $P_S$ <sup>a)</sup>

Equations	$\alpha$	$r$	$r'$	$r''$	$F$	S.D.
$-\log C_1 = 0.924(0.270)X + 1.190(0.684)$	1.05	0.921	0.909	0.898	39.29	0.357
$-\log C_1 = -0.241(0.267)X^2 + 1.964(1.167)X + 0.243(1.158)$	1.05 (0.04)	0.938	0.929	0.921	31.95	0.329
$-\log C_2 = 0.863(0.262)X + 1.384(0.673)$	1.09	0.920	0.908	0.897	38.34	0.367
$-\log C_2 = -0.212(0.301)X^2 + 1.893(1.326)X + 0.181(0.318)$	1.04 (0.03)	0.936	0.926	0.918	40.51	0.331

a)  $X = P_H + \alpha P_S$ . The values in parentheses indicate 95% confidence intervals. The confidence intervals of  $\alpha$  is also given when a least squares program SALS is used in the analysis (SALS: Osaka University Computation Center). The number of data used is 17. See footnote in Table II for other symbols.

This equation is converted to Eq. 4a,

$$-\log C = a(P_H + \alpha P_S) + c \tag{4a}$$

which is comparable to the conventional regression equation (Eq. 3),  $\log P$  being replaced with  $X = P_H + \alpha P_S$ .

Then, what type of equation would be suitable for the conventional quadratic (parabolic) equation using  $\log P$  (Eq. 5),

$$-\log C = a(\log P)^2 + b \log P + c \tag{5}$$

when  $\log P$  is separated into  $P_H$  and  $P_S$ ? By analogy with

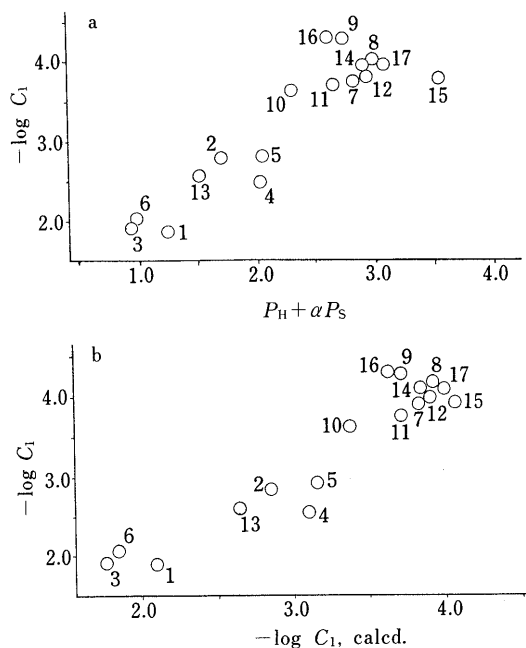


Fig. 2. Plots of the Observed Biological Activity  $-\log C_1$  against  $P_H + \alpha P_S$ ,  $\alpha$  Being Equal to 1.05 (Fig. 2a), and against the  $-\log C_1$  Recalculated According to the Parabolic Equation of  $-\log C_1 = -0.241\{P_H + \alpha P_S\}^2 + 1.964\{P_H + \alpha P_S\} + 0.243$ ,  $\alpha$  Being Equal to 1.05 (Fig. 2b)

Eq. 4a, Eq. 5 would be converted to the following type by substituting  $\log P$  with  $X$ .

$$-\log C = aX^2 + bX + c, \quad X = P_H + \alpha P_S \quad (6)$$

This eq. has four unknowns,  $a$ ,  $b$ ,  $c$ , and  $\alpha$ , to be determined in the simulation of biological data. Whereas, when a parabolic type is assumed separately for  $P_H$  and  $P_S$ , an equation such as  $-\log P = aP_H^2 + bP_H + cP_S^2 + dP_S + e$  follows, which contains five unknowns to be determined. Therefore, a type of Eq. 6 is preferred, which contains a smaller number of unknowns and which is derived from conventional types of equations by substituting  $\log P$  with  $P_H + \alpha P_S$  quite in common with a linear case. The regression analyses using the above types of equations are listed in Table III. Comparison of the results in Tables II and III shows that the correlation coefficients are improved slightly but definitely when a parabolic equation is adopted instead of a linear one. This situation is also seen in Fig. 2a and b. Also a slightly parabolic nature is observed in Fig. 2a in the region of increased  $P_H + \alpha P_S$ .

Although regression analyses are improved by substituting  $\log P$  with  $P_H$  and  $P_S$  in the linear and parabolic equations, the improvement is not so striking as already observed in the case of alcohol toxicities.<sup>9,10</sup> This is typical of a case of  $\alpha = 1$  for which  $\log P$  is equivalent to  $P_H + P_S$ . Since the  $\alpha$  value obtained in the present study is close to unity under the linear as well as parabolic equations, the important process of the quaternary ammonium salts that happens in biophase can be thought to resemble the partition process in the model 1-octanol/water system. That is, the model system works well in simulating the biophase system. This trend is in clear contrast with that reported previously.<sup>10</sup> The salt compounds as treated in the present study are highly polar whereas the alcohols treated in the previous study are not. Therefore, a possible explanation of observing  $\alpha = 1$  in the present study is that highly polar solutes can not discriminate between the model and biophase systems since the two systems are far less polar, whereas less polar alcohols can discriminate between the model and biophase systems which differ from each other in polarity when viewed from the alcohol molecules. The preference of a parabolic Eq. 6 over linear Eq. 4a is suggested (Fig. 2 and Table III). For a rigorous test of this subject the measurement of partition properties with more hydrophobic ammonium salts might be necessary. But, since the partition coefficient becomes larger for these compounds, precise measurement of partition properties

becomes less easy. It may, however, be clear that for more hydrophobic ammonium salts the biological activities decrease and a parabolic nature is inevitable for a full explanation.

In conclusion, the thermochemical study of partition has been extended to a case of parabolic type in QSAR analysis. A parabolic equation is presented on the basis of the enthalpy/entropy duality in the conventional  $\log P$  term. For the biological activities of benzyldimethylalkylammonium salts, which are selected as target compounds of the parabolic case, the enthalpy and entropy terms contribute almost equally different from the previously reported cases.<sup>9</sup>

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The value of  $\Delta V_{WCH_2}$  is calculated to be 0.68 from the van der Waals volumes of 10.23 ml/mol for  $CH_2$  and 3.45 ml/mol for H, multiplied by 0.1 as commonly done in  $\Delta V_W$  to make it more nearly equiscalar with the Hammett type parameters.
- 16) The Hammett  $\sigma$  ( $\sigma_m$  and  $\sigma_p$ ) can be used instead of  $R$  ( $R_m$  and  $R_p$ ) for  $\log P$ , but not for  $P_H$  and  $P_S$ . The parameters  $R$  and  $\sigma$  are cited from:  
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