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Octanol/Water Partition of Ionic Species, Including 544 Cations

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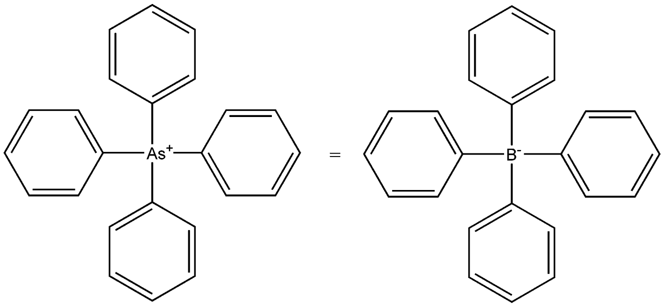

Partition coefficients of single ions in the octanol/water system (log P_{oct}) have been assigned on the (Ph_4As^+, Ph_4P^+) = Ph_4B^- assumption. The log P_{oct} values of Cl^-, Br^-, and I^- ions are then used to obtain the partition coefficients of cations from partition coefficients of the neutral combination of anion and cation. Partition coefficients of 544 cations derived from 585 organic salts from the MedChem database have been studied. The contributions of the aliphatic charge N^+ and aromatic charge n^+ in these cations have been investigated. The results show that the contributions of N^+ and n^+ in different homologous series are affected by the attached functional groups and are not constant, although the effect of the central cation is constant along any given homologous series. The latter can be accounted for qualitatively and semiquantitatively by the electrostatic theory of ionic solvation of Abraham and Liszi. A number of regression equations have been established between partition coefficients of ions and partition coefficients of the corresponding neutral species. These equations can be used to estimate octanol/water partition coefficients for additional cations to about 0.5 log unit.

Introduction

Quantitative structure–activity relationships (QSARs) have proved to be useful tools for the prediction of physicochemical properties.[1–4] These relationships involve the use of a number of descriptors that describe properties of a solute. The partition coefficient in the octanol/water system, defined as the ratio of the concentration of a chemical in octan-1-ol to that in water in a two-phase system at equilibrium, is one of the key descriptors in QSAR studies, as log P_{oct}. This descriptor has been widely used for predicting physicochemical properties and drug activity in environmental sciences and drug industries and has been used in predictions of aqueous solubility, bioconcentration, soil sorption, toxicity, and intestinal absorption.[5–9]

A number of *in silico* methods have been developed for prediction of log P_{oct} from chemical structure. These methods can be classified into two broad categories, namely, group contribution methods and regression methods.[10] Group contribution methods estimate log P_{oct} by identifying important substructures and atom types, either predefined or from some fragmentation scheme, and assigning a contribution to log P_{oct} from each fragment.[11–14] These contributions are found either from

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multiple linear regression or by comparison with measured values for fragments.[15] A number of regression methods based on the relationship between molecular descriptors and log P_{oct} have been published.[16−22] One of them is the linear free energy relationship (LFER) developed by Abraham and co-workers.[3,15−17] A series of solvation properties, SP, are related to five descriptors via the general solvation eq 1.

$$\log \mathrm{SP} = c + eE + sS + aA + bB + vV \qquad (1)$$

The descriptors are defined as follows.[17] E is an excess molar refraction in cm^3 mol^{-1}/10. S is a combined dipolarity/polarizability descriptor. A is the overall solute hydrogen bond acidity, and B is the overall solute hydrogen bond basicity. V is McGowan's characteristic molecular volume in cm^3 mol^{-1}/100. The set of coefficients c, e, s, a, b, and v characterize the system and are determined by multiple linear regression analysis. An example of the application of the LFER to octanol/water partition is given by the following equation.

$$\log P_{\mathrm{oct}} = 0.088 + 0.562E - 1.054S + 0.034A - 3.460B + 3.814V \quad (2)$$

This equation provides valuable information for understanding the distribution of a solute in the octanol/water system. For example, octanol has almost the same hydrogen bond basicity as water (almost zero a-coefficient) but is a weak hydrogen bond acid (negative b-coefficient). The large v-coefficient means that octanol is able to interact with solutes by dispersion forces and/or that the energy required to create a cavity of given size in octanol is relatively low.[17]

Although many methods have been developed to estimate partition coefficients in the octanol/water system, these methods are for neutral compounds. The purpose of the present work is to investigate the partition coefficients of organic salts and to attempt to explain the experimental results to obtain predictive equations for ions, especially cations.

Results and Discussion

1. Partition Coefficients of Ions, as a Dissociated Pair of Ions, between Octanol and Water. The partition of a salt ($M^+ X^-$) can be depicted in the following way in Figure 1. Because salts usually exist in octanol (or water saturated octanol) as an ion pair in equilibrium with a dissociated pair of ions [$M^+ + X^-$], various partition coefficients can be defined:

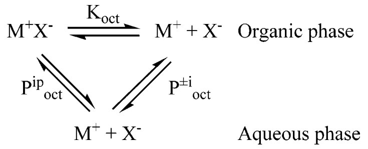

FIGURE 1. Partition of a salt.

$$M^+(\mathrm{aq}) + X^-(\mathrm{aq}) \overset{P^{ip}_{\mathrm{oct}}}{\rightleftharpoons} [M^+X^-]\ (\mathrm{oct}) \qquad (3)$$

$$M^+(\mathrm{aq}) + X^-(\mathrm{aq}) \overset{P^{\pm i}_{\mathrm{oct}}}{\rightleftharpoons} M^+(\mathrm{oct}) + X^-(\mathrm{oct}) \qquad (4)$$

$$M^+(\mathrm{aq}) \overset{P^{+i}_{\mathrm{oct}}}{\rightleftharpoons} M^+(\mathrm{oct}) \qquad (5)$$

$$X^-(\mathrm{aq}) \overset{P^{-i}_{\mathrm{oct}}}{\rightleftharpoons} X^-(\mathrm{oct}) \qquad (6)$$

$$M^+X^-(\mathrm{oct}) \overset{K_{\mathrm{oct}}}{\rightleftharpoons} M^+(\mathrm{oct}) + X^-(\mathrm{oct}) \qquad (7)$$

There are a number of relationships between these coefficients.

$$\log P^{\pm i}_{\mathrm{oct}} = \log P^{+i}_{\mathrm{oct}} + \log P^{-i}_{\mathrm{oct}} \qquad (8)$$

$$P^{ip}_{\mathrm{oct}} = P^{\pm i}_{\mathrm{oct}}/K_{\mathrm{oct}} \qquad (9)$$

2. Estimation of Partition Coefficients of Single Ions (log P^{+i}_{oct} or log P^{-i}_{oct}) between Octanol and Water using the (Ph_4As^+, Ph_4P^+) = Ph_4B^- Assumption. A number of assumptions that may be used to obtain free energies of transfer ($\Delta G_t°$) of single ions have been suggested. Several workers have compared assumptions and concluded that the (Ph_4As^+, Ph_4P^+) = Ph_4B^- assumption, TATB, yields realistic single-ion free energies of transfer.[23−25] The rationale behind the TATB assumption is that the four phenyl groups effectively shield the central ionic entity from direct interaction with the solvent. The value of $\Delta G_t°$ for (Ph_4As^+, Ph_4P^+) or for Ph_4B^- is mainly due to a "neutral" part, together with an electrostatic ion−dipole part. Both of these depend on the solute radius, which is very nearly the same for the cations and anion. Table 1 lists partition coefficients (log P) calculated from free energies of transfer ($\Delta G_t° = -RT\ln P$) from water to a number of solvents, based on the TATB assumption.[26−29]

Although single-ion free energies of transfer from water to many different solvents have been obtained using the TATB assumption, the application of the assumption to the octanol/water system has not been

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TABLE 1. Partition Coefficients of Ions between Water and Solvents[a]

	DCM	12DCE	MeOH	EtOH	PrOH	BuOH	DMF	MeCN	DMSO	Me_2CO
Li^+	−5.78	−4.73	−0.88	−1.93	−2.43[b]	−2.93[b]	1.75	−4.38	2.63	−0.88
Na^+	−4.03	−4.38	−1.40	−2.45	−2.95	−3.47	1.75	−2.63	2.28	−1.58
K^+	−3.68	−4.56	−1.75	−2.80	−3.11	−3.47	1.75	−1.40	2.28	−0.70
NMe_4^+	−3.33	−2.63	−1.05	−1.93	−1.86	−2.13	0.88	−0.53	0.35	−0.53
NEt_4^+	−0.70	−0.88	−0.18	−1.05	−0.85	−1.28	1.40	1.23	1.58	1.93
NPr_4^+	1.58	1.58	0.88	1.05	1.12	1.18	2.98	2.28	3.33	3.51
NBu_4^+	3.86	3.15	3.68	1.40	2.96	2.06	5.08	5.43	6.48	6.66
Ph_4P^+	7.54	5.78	4.21	3.68	4.25	3.78	6.84	5.78	6.48	5.78
Ph_4As^+	7.54	5.78	4.21	3.68	4.42	3.53	6.84	5.78	6.48	5.78
F^-	−10.34	−10.52	−2.80	−4.73			−8.94	−8.76	−7.71	−10.52
Cl^-	−8.24	−9.46	−2.28	−3.51	−4.47	−5.12	−8.41	−7.36	−7.01	−9.99
Br^-	−6.84	−6.84	−1.93	−3.15	−3.84	−4.15	−6.31	−5.43	−4.73	−7.36
I^-	−4.73	−4.38	−1.23	−2.28	−3.37	−3.87	−3.51	−2.98	−1.75	−4.38
$Ph4B^-$	7.54	5.78	4.21	3.68	4.42	3.53	6.84	5.61	6.48	5.78

[a] DCM: dichloromethane. 12DCE: 1,2-dichloroethane. MeOH: methanol. EtOH: ethanol. PrOH: propanol. BuOH: butanol. DMF: *N,N′*-dimethylformamide. MeCN: acetonitrile. DMSO: dimethyl sulfoxide. Me_2CO: acetone. Ac^-: acetate. Pic^-: picrate. [b] Estimated values based on the values of sodium ion in alcohol systems.

TABLE 2. Partition Coefficients of Dissociated Pairs of Ions (log $P_{oct}^{\pm i}$) from Water to Alcohols

	N_{eff} [a]	NaCl	KCl	$NaPh_4B$	Me_4NPh_4B	Et_4NPh_4B
MeOH (dry)	1.00	−3.68	−4.03	2.80	3.16	4.03
EtOH (dry)	2.00	−5.96	−6.31	1.23	1.75	2.63
PrOH (dry)	3.00	−7.42	−7.58	1.47	2.56	3.57
BuOH (dry)	4.00	−8.58	−8.59	0.06	1.40	2.25
octanol (wet)	3.21	−7.71	−7.69	1.69	2.62	3.97
octanol/PrOH	1.07[b]	1.04	1.01	1.15	1.02	1.11

[a] Number of carbon atoms in the alcohol. [b] Average value of the octanol/propanol ratio.

TABLE 3. Partition Coefficients of Ions in the Octanol/Water System

		log P_{oct}^{i}		
	log $P_{oct}^{\pm i}$ observed	regression	taken	log P_{oct}^{i} ClogP
Li^+	NA	−2.51	−2.51	−1.32
Na^+	NA	−3.04	−3.04	−1.32
K^+	NA	−3.17	−3.17	−1.32
Cl^-	NA	−4.51	−4.51	−1.32
Br^-	NA	−3.79	−3.79	−1.32
I^-	NA	−3.33	−3.33	−1.32
Me_4N^+	NA	−1.97	−1.97	−4.86
Et_4N^+	NA	−1.06	−0.86	−3.14
Pr_4N^+	NA	1.12	0.60	−1.02
Bu_4N^+	NA	2.29	2.29	1.09
Ph_4P^+	NA	3.93	4.42	7.57
Ph_4B^-	NA	3.87	4.42	7.57
LiCl	−7.36	−7.02	−7.02	−2.64
NaCl	−7.71	−7.55	−7.55	−2.64
KCl	−7.69	−7.68	−7.68	−2.64
$NaPh_4B$	1.69	0.83	1.38	6.25
Me_4NPh_4B	2.62	1.90	2.45	2.71
Et_4NPh_4B	3.97	2.81	3.56	4.43
Pr_4NPh_4B	4.89	4.99	5.02	6.55
Bu_4NPh_4B	5.82	6.16	6.71	8.66

reported. To obtain a single-ion division experimentally, values of log P are required for the dissociated pairs of ions $Ph_4As^+\ Cl^-$ (or $Ph_4P^+\ Cl^-$), $Na^+\ Ph_4B^-$, and $Na^+\ Cl^-$. Unfortunately, we could not determine partition coefficients for $Ph_4As^+\ Cl^-$ or $Ph_4P^+\ Cl^-$. The other possibility, that of using $Ph_4As^+\ Ph_4B^-$, was precluded because of its very high partition coefficient (that we estimated to be some 8 log units). On examining partition coefficients of ions (log $P_{oct}^{\pm i}$) in various alcohol/water systems (Table 2), we find that the log $P_{oct}^{\pm i}$ values in the wet octanol system are close to the values in the dry propanol system. The average value of the ratio is 1.07, and the corresponding effective carbon number, N_{eff}, for wet octanol is 3.21 ($3.21 = 1.07 \times 3$). We can obtain linear correlations between partition coefficients of the ions listed in Table 1 and N_{eff} for the four alcohol systems and can then deduce those in wet octanol using $N_{eff} = 3.21$ for the latter system. Results are in Table 3 as calculated by the "regression method".

The final eight rows in Table 3 compare the observed values for the pairs of dissociated ions with those obtained by summation of the individual ion values as obtained by the regression method. We have suggested that for ions such as those listed in Tables 1−3, mostly obtained by careful experimentation, the error in the individual ionic values must be around 0.5 log unit,[29] so there is reasonable agreement in Table 3. However, inspection of Table 1 suggests that there are systematic errors in some values. For example, there is no consistent change from methanol to butanol for the Ph_4B^- ion, and the values for Bu_4N^+ in the methanol and ethanol systems cannot be correct. Note that Marcus[28] has previously listed experimental values for transfer of Ph_4B^- from water to alcohols and has shown that there are very considerable discrepancies. In addition, Marcus has reviewed the transfer of Bu_4N^+ from water to methanol and ethanol and has suggested that the datum for transfer to ethanol cannot be correct. We therefore smoothed the "regression" values for the R_4N^+ ions, and we chose log P in propanol (4.42) for the Ph_4B^- ion in the octanol system. The final "taken" values in Table 3 lead to good agreement with values for the pairs of ions and are more reasonable than the initial regression values.

Table 3 also lists the calculated log P_{oct}^{i} values from the ClogP program (BioByte V4.0).[30] Whatever the basis for division into single ions, the neutral combination of pairs of dissociated ions should lead to the experimental value. This is not at all the case and confirms our assertion that there is no program available for the calculation of octanol/water partition coefficients for ions.

3. Effects in Homologous Series of Cations on P^{+i}_{oct}. There are over 1000 partition coefficients of salts that are derived from quaternary ammonium ions, as log

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[30] Leo, A. J. *ClogP for Windows*, version 4.0; BioByte Corp.; Claremont, CA, 2001.

$P_{\text{oct}}^{\text{salt}}$, in the octanol/water system, as found in the MedChem database.[31] These salts can be classified into two types: aliphatic (N^+) and aromatic (n^+) salts; most of them are salts of chloride, bromide, and iodide anions. This paper will focus on the investigation of these salts, because we can deduce partition coefficients of chloride, bromide, and iodide anions and hence obtain partition coefficients for a very large number of cations.

We note that many partition coefficients listed in the MedChem database have been defined as the concentration ratio of single species (that is either the cation or the anion) between the octanol and water phases.[31–33] However, in principle, this ratio refers to single ions plus ion pairs. Only if the concentration ratio is found to be independent of solute concentration or is obtained at a very low concentration will it refer only to single ions (see eq 8). On this assumption, the partition coefficients of positive ions can be estimated from the following equation, since we have already established the required single-ion values for the corresponding anions, log P_{oct}^{-i}.

$$\log P_{\text{oct}}^{+i} = 2 \log P_{\text{oct}}(\text{ratio}) - \log P_{\text{oct}}^{-i} \qquad (10)$$

Octanol/water concentration ratios, log P_{oct}(ratio) and the calculated partition coefficient of cationic species (log P_{oct}^{+i}) are listed in Supporting Information for 544 cations. These values are derived from the partition coefficients of 586 halide salts (360 chlorides, 100 bromides and 125 iodides). Although we have suggested that ionic transfers will be subject to an error of around 0.5 log unit [29] when carefully assembled and analyzed, as in Table 1, the error when obtained from concentration ratios is likely to be much larger. Furthermore, when log P_{oct}^{+i} is calculated from eq 10, the cation value will include the entire error on both cation and anion, because log P_{oct}^{-i} is assigned a unique, error free value. Hence, the cation values, log P_{oct}^{+i}, as obtained from by the concentration ratio method, could well be in error by an amount much larger than that for single ions (0.5 log unit).

Most of the 544 ions fall into various homologous series. For many of them, the methylene increment is constant along the series, and the relationship between the number of carbon atoms (CH_2) and log P_{oct}^{+i} values can be described by a linear equation. The slope of the equation is the contribution of the methylene group, and the intercept is log P_{oct}^{+i} of the parent ion in the series. In Table 4 are listed the linear equations for a number of representative homologous series. In Figure 2 is an example of a plot of log P_{oct}^{+i} against the number of CH_2 groups for a particular homologous series. If the positive charge always makes the same contribution to log P_{oct}^{+i}, then the slopes for different homologous series should be the same or similar. Examination of the slopes for different homologous series shows that some series have similar slopes, i.e., series 4–12 in Table 4. However, there are some series whose slopes are considerably different; for example, series 3, 15, and 20 in Table 4. The average slope of all the series is 0.78, which is quite high by comparison to the contribution of CH_2 for neutral compounds (0.53) as used in the ClogP program. In eq 2, the CH_2 contribution is 3.814 × 0.1409 (the volume of the CH_2 group), which is 0.537, very close to the ClogP increment.

TABLE 4. Regression Results between log P_{oct}^{+i} and the Number of CH_2 Groups in Some Homologous Series[a]

series	No[b]	slope	intercept	N	R	SD
1	1–8	0.56	−2.49	8	0.96	0.81
2	84–87	0.58	−4.23	4	0.99	0.32
3	88–90	1.03	−7.74	3	1.00	0.23
4	95–108	0.80	−1.76	14	0.95	1.48
5	120–128	0.75	−3.69	9	1.00	0.40
6	129–135	0.72	−2.93	7	0.96	1.02
7	136–142	0.79	−2.33	7	0.97	0.99
8	143–149	0.84	−3.10	7	0.98	1.04
9	150–155	0.93	−4.02	6	0.98	0.80
10	165–167	0.76	−2.27	3	0.99	0.18
11	178–182	0.68	2.10	5	0.95	0.80
12	195–200	0.71	4.73	6	1.00	0.06
13	206–211	0.55	1.82	6	1.00	0.21
14	223–227	0.84	−1.61	5	0.96	1.16
15	228–230	1.04	0.33	3	0.99	0.21
16	231–235	0.88	−2.11	5	1.00	0.24
17	236–238	0.63	−2.02	3	0.96	0.27
18	401–403	0.82	0.08	3	1.00	0.05
19	468–480	0.41	0.64	13	0.90	1.11
20	520–525	1.07	3.17	6	1.00	0.34
21	526–536	0.99	4.81	11	0.99	0.38

[a] *N*: number of ions. *R*: regression coefficient. SD: standard deviation. [b] These series are listed in Supporting Information.

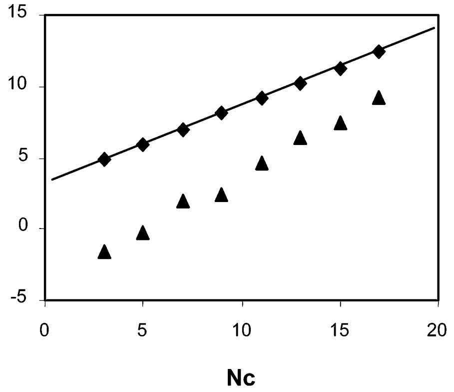

FIGURE 2. Plot of log P_{oct}^{+i} against the number of CH_2 groups, N_c, for the ions No 120–128 (the full line is the corresponding plot of log P^N against N_c).

We shall later separate log P_{oct}^{+i} into an electrostatic part, log P^E, and a neutral part, log P^N. The latter can be estimated, by taking E, S, A, and B as zero in eq 2, so that log $P^N = 0.088 + 3.814V$. In Figure 2 are shown plots of log P_{oct}^{+i} for the homologous series of compounds 120–128, and the corresponding log P^N values against the number of methylene groups, N_c. Because the slopes of the lines are different, 0.53 and 0.78, the difference between the cation and its neutral part becomes smaller as N_c becomes larger. The constancy of the slope for the series shown in Figure 2, and for most other series, indicates that the influence of the positive charge on log P_{oct}^{+i} is the same, or very nearly the same, along the entire homologous series. This is a very surprising result, because we would expect the effect of the positive charge to diminish along the series.

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4. Mechanism of Charge Contribution Effect in Homologous Series. To attempt to explain the situation shown in Figure 2, we used the method of Abraham and Liszi[34] for the calculation of the electrostatic contribution to the solvation Gibbs energy of a gaseous ion. The equations derived by Abraham et al.[35] and implemented by Abraham and Liszi[36] are given as eqs 11 and 12. Here, ΔG_w and ΔG_o are the electrostatic contribution to the Gibbs energies of solvation of a gaseous ion in water and octanol, respectively, a is the radius of the ion in Å, x and g are parameters of the solvents water and octanol, respectively, ϵ_w and ϵ_o are the dielectric constants of water and octanol, respectively, and the factors 83.0 and 166.0 give the Gibbs energies in kcal mol^{-1}. From eqs 11 and 12, eq 13 simply gives the electrostatic contribution to the Gibbs energy of transfer of an ion from water to octanol. If we collect terms and relate the Gibbs energy of transfer to the partition coefficient, we obtain the final eq 14 for the electrostatic contribution to the partition coefficient. Here, we have used for water $\epsilon_w = 78.36$ and $x = 1.553$ Å and for octanol $\epsilon_o = 10.30$ and $g = 3.204$ Å, the latter from the molar volume of octanol of 158.5 cm^3 mol^{-1} as explained before.[34]

$$\Delta G_w = -83.0\left(\frac{1}{a} - \frac{1}{a+x}\right) + 166\left(\frac{1}{\epsilon_w} - 1\right)\left(\frac{1}{a+x}\right) \quad (11)$$

$$\Delta G_o = -83.0\left(\frac{1}{a} - \frac{1}{a+g}\right) + 166\left(\frac{1}{\epsilon_o} - 1\right)\left(\frac{1}{a+g}\right) \quad (12)$$

$$\Delta G_o - \Delta G_w = \frac{83.0}{a+g} - \frac{83.0}{a+x} + 166\left(\frac{1}{\epsilon_o} - 1\right)\left(\frac{1}{a+g}\right) - 166\left(\frac{1}{\epsilon_w} - 1\right)\left(\frac{1}{a+x}\right) \quad (13)$$

$$\log P^E = 49.02\left(\frac{1}{a+3.204}\right) - 61.48\left(\frac{1}{a+1.553}\right) \quad (14)$$

As mentioned above, the neutral contribution to the partition coefficient is obtained through eq 2 by setting E, S, A, and B as zero and calculating the ionic volume as McGowan's volume.[37] Finally, the electrostatic and neutral contributions can be summed as in eq 15.

$$\log P^{+i} = \log P^E + \log P^N \quad (15)$$

In Figure 3, we give plots of $\log P^{+i}$ and $\log P^E$ against N_c, for the same series of compounds, 120−128, shown in Figure 2. The full line is for $\log P^N$, which is exactly the same as that in Figure 2. It can be seen that the plot of the calculated $\log P^{+i}$ values against N_c is essentially the same as that of the observed values for the series of ions No 120−128 in Figure 2. The slope of the calculated $\log P^{+i}$ values against N_c is 0.62, and the observed slopes for $\log P_{oct}^{+i}$ vary from 0.55 to 1.07 (the average is 0.78 in Table 5), with that for the series of compounds 120−128 being 0.75. The general agreement of the calculated and observed slopes is remarkable. First of all, the electrostatic component is derived as a small difference between two very large quantities, those for the electrostatic contribution to solvation of the gaseous ions in water and in octanol. Second, we have used solvent parameters for dry octanol, and not wet octanol. However, our objective is not to try to predict $\log P_{oct}^{+i}$ values but to explain their dependence on N_c.

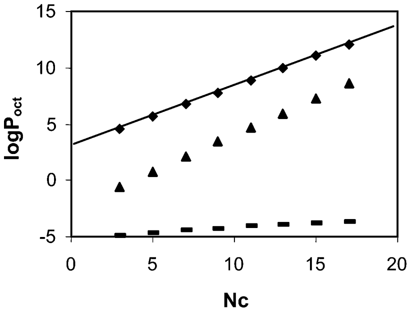

FIGURE 3. Plot of $\log P_{oct}$ against number of CH_2 groups for ions No 120−128. ◆, $\log P_{oct}^N$; — —, $\log P_{oct}^E$; ▲, $\log P_{oct}^{+i} = \log P_{oct}^N + \log P_{oct}^E$.

TABLE 5. Regression Results between $\log P_{oct}^{+i}$ and $\log P_{oct}$(neutral)

group[a]	No	slope	intercept	N	R	SD	AE	AAE
group 0	120−155	1.45	−8.08	36	0.98	0.83	0.00	0.63
group 1	1−205	1.34	−6.92	182	0.97	0.93	0.00	0.76
group 2	206−211	1.03	−5.09	6	1.00	0.21	0.00	0.13
group 3	212−219	1.07	−3.50	8	0.89	0.40	0.00	0.32
group 4	220−407	1.66	−1.64	186	0.94	0.75	0.00	0.57
group 5	408−467	1.43	−0.66	59	0.96	0.58	0.00	0.43
group 6	468−480	1.23	−1.44	8	0.97	0.56	0.00	0.42
group 7	481−511	1.03	1.77	31	0.88	0.58	0.00	0.46
group 8	512−519	1.59	0.95	8	0.97	0.35	0.00	0.26
group 9	520−544	1.66	−4.95	25	0.99	0.73	0.00	0.58
total	1−544	0.75	−0.78	544	0.69	2.66	0.00	2.12

[a] General structures for 544 positive ions are shown in Scheme 1. Details of each individual structure can be found from the SMILES given in Supporting Information. SD: standard deviation of regression for ions. AE: average error between observed and predicted $\log P_{oct}^{+i}$. AAE: absolute average error between observed and predicted $\log P_{oct}^{+i}$.

As is well-known, the electrostatic contribution to the Gibbs energy of solvation of an ion, or to the partition coefficient for transfer from the gas phase to a solvent, depends markedly on the radius of the ion. For transfer from water to another solvent, there will be considerable cancellation of effects, so that the dependency decreases. In the present case, as the ion becomes larger going along a homologous series, the change in ionic radius is actually very small. Note that even for $N_c = 0$, the ionic radius is still large; for the series 120−128, it is 2.82 Å. Thus, in the typical series of compounds 120−128, on going from ion 122 to 123 the ionic radius increases from 3.50 to 3.61, and on going from 127 to 128 it increases from 4.38 to 4.45. These very small increases in ionic radius, combined with the cancellation of effects in transfer from water to octanol, result in the electrostatic contribution to $\log P_{oct}^{+i}$ values being almost the same for all members of the homologous series, as shown in Figure 3. This is why the effect of the positive charge on $\log P_{oct}^{+i}$ appears to be the same for all members of the homologous series.

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(34) Abraham, M. H.; Liszi, J. *J. Chem. Soc., Faraday Trans. 1* **1978**, *74*, 1604−1614.

(35) Abraham, M. H.; Liszi, J.; Meszaros, L. *J. Chem. Phys.* **1979**, *70*, 2491−2496.

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(37) Zhao, Y. H.; Abraham, M. H.; Zissimos, A. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1848−1854.

Our calculation of the electrostatic effect on the partition of members of a homologous series is a relative calculation of log P^{+i}_{oct}. All we are predicting is the slope of the plot of log P^{+i}_{oct} against the carbon number. To predict the actual equation for a homologous series, it would be necessary to predict the absolute values of log P^{+i}_{oct}. This is not possible to do with sufficient precision with present calculational methods. Hence, each homologous series has to be taken separately, and it is not possible to obtain a general model that covers all homologous series.

5. Estimation of Partition Coefficients of Ions. Although the equations in Table 4 can be used to predict partition coefficients in the water to octanol system, it is limited to ions in homologous series. Also, the equations can only be derived if there are enough ions in the training set to establish linear models and if the data are consistent. Examination of the partition coefficients of salts in the various homologous series, see Supporting Information, shows that in several series, the data are not self-consistent. Partition coefficients along a homologous series should increase with increase in N_c. This is not the case for the ions from No 1 to 4, 95 to 99, and 133 to 135. The partition coefficients for some of the series actually decrease with an increase in N_c. In homologous series of ions with the same parent ion, the intercept in the plots against N_c should be the same. However, the intercept of series 3 in Table 4 is far away from that of series 4 because there seems to be a very large error for ion 88 (log $P^{\text{salt}}_{\text{oct}}$ of ion 88 should be higher than that of ion 97) in series 3 and there is only limited data in series 3 ($N = 3$). In our view, these inconsistencies are probably due to experimental errors in the determination of partition coefficients by the concentration ratio method and indicate that great care has to be taken in developing any general model for partition of ionic species.

To examine whether there is a relationship between the partition coefficient of a charged species and an equivalent neutral species, we substitute carbon for N^+ or n^+ in aliphatic and aromatic cations to convert an ion into the equivalent neutral species. We refer to log P_{oct} for such a species as log P_{oct}(neutral). Note that this is not the same as log P^{N}. We calculate log P_{oct}(neutral) for the equivalent neutral species by estimating the Abraham descriptors and then introducing these into eq 2. For example, ion No 121 (*N*-butylpyridinium) is first converted to its neutral species by substituting carbon for n^+ (to give butylbenzene), descriptors for the latter are estimated by the method of Platts et al.[38] ($E = 0.77$, $S = 0.56$, $A = 0$, $B = 0.14$, $V = 1.28$) and are substituted into eq 2 to obtain log P_{oct}(neutral) = 4.33. The reason for calculating log P_{oct}(neutral) in this way is that the structures of all 544 ions, as SMILES strings, can be entered into a computer program and the descriptors calculated en block. We also checked in a few instances that the ClogP program gave very similar values for log P_{oct}(neutral). For example, the calculated log P_{oct}(neutral) for butylbenzene from ClogP program is 4.23, and that from the Abraham eq 2 is 4.33. The observed log P_{oct}(neutral) for butylbenzene is 4.38.

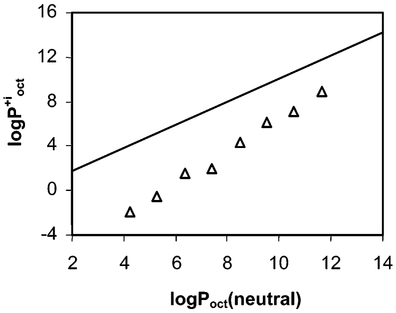

FIGURE 4. Plot of log P^{+i}_{oct} of ions No 120−128 against log P_{oct}(neutral) (the full line is that of unit slope, through the origin).

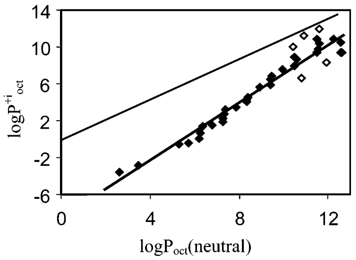

FIGURE 5. Plot of log P^{+i}_{oct} against log P_{oct}(neutral) for ions No 120−155 (the higher line is that of a slope of unity and the zero intercept for the neutral species).

There is clearly a good linear relationship between log P^{+i}_{oct} and log P_{oct}(neutral) for homologous series (see Figure 4), with a slope appreciably larger than unity, as expected. The homologous series of ions 120−128 has a simple hydrocarbon chain with no functional groups. If a homologous series is considered that has a particular functional group in the chain, we would expect a very similar linear relationship to that found with the simple homologous series of ions 120−128 if the central charge does not interact with the functional group. However, if the central positive charge interacts with the functional group, then any relationship between log P^{+i}_{oct} and log P_{oct}(neutral) will not be the same as for the simple, unsubstituted series. In Figure 5 is shown a plot of log P^{+i}_{oct} against log P_{oct}(neutral) for five homologous series of ions No 120−155 (see Supporting Information and structures in Scheme 1) with one or two methyl groups attached at different positions on a pyridinium (aromatic) ring. The resulting straight line indicates that the effect of the central charge is not influenced by the additional methyl groups. We can then obtain a combined model for all ions No 120−155 in order to predict partition coefficients of ions from the corresponding values of log P_{oct}(neutral). Details are given in Table 5, including the regression standard deviation, SD, the average error, AE, and the average absolute error, AAE. As mentioned above, there are a number of outliers (marked with ◇ in Figure 5) in these series due, we suggest, to rather obvious experimental errors.

We next investigated whether other functional groups behave similarly to methyl groups, that is, do they or do they not interact with the central charge? If all the functional groups behave as the methyl groups, we should obtain a model for all ions that is similar to the model of ions No 120−155. However, as more and more series are

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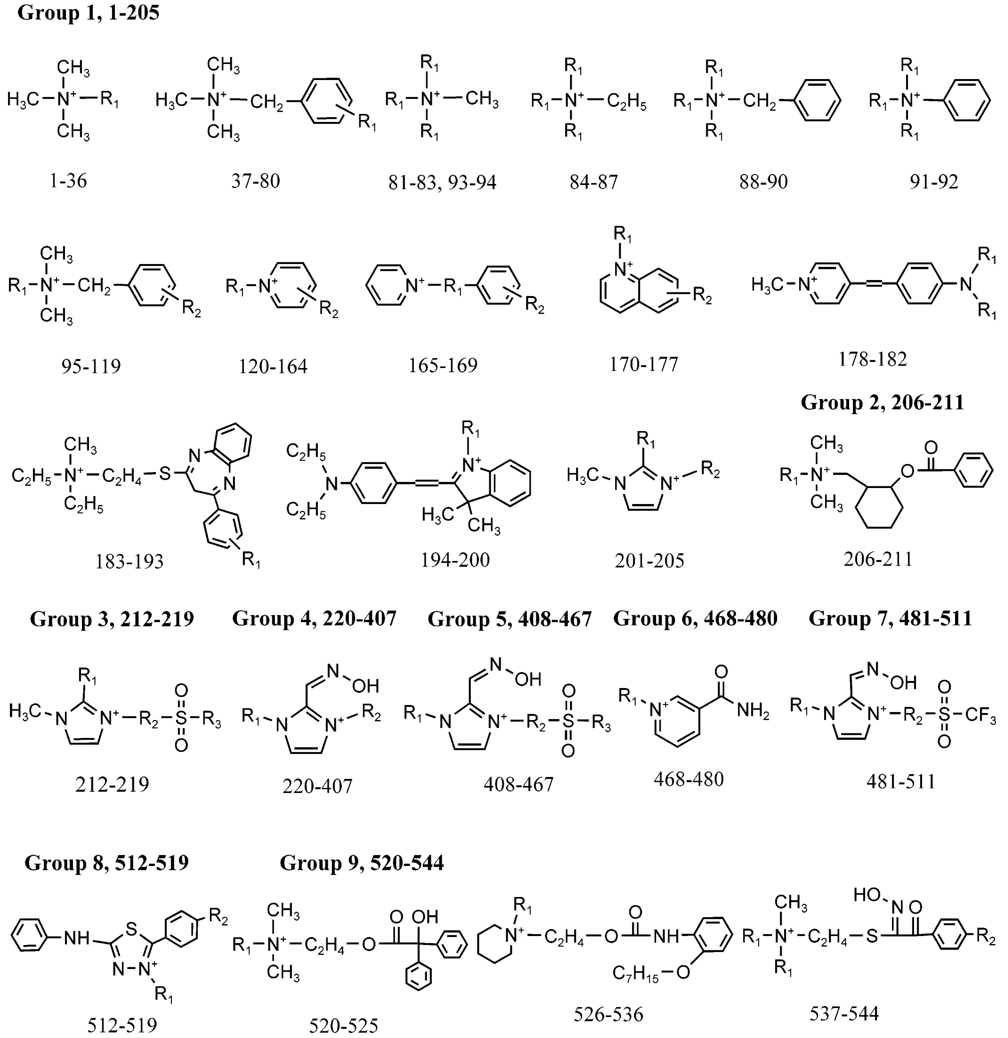
[38] Platts, J. A. Abraham, M. H.; Hersey, A.; Butina, D. *J. Chem. Inf. Comput. Sc.***2000**, *40*, 71−80.

SCHEME 1. Structures of Various Groups of Ions



combined, the AAE value increases considerably. For the total set of cations, a regression involving 544 cations leads to an equation with AAE of 2.12 log units, much too large an error to be of practical use in the prediction of further cation log P_{oct}^{+i} values. It seems clear that functional groups in the ions can affect the charge contribution.

To investigate the effect of functional groups on the charge contribution, we classified ions into different sets on the basis of structure similarity (see structures in Scheme 1). First, we found that the ions with aromatic charge n^+ (see ions No 120−155) and aliphatic charge N^+ (see ions No1−119) can be combined. This shows that the charge contribution does not depend on whether it is an aliphatic or aromatic charge entity. We also found that various other functional groups do not make a large contribution to the charge effect, except for two particular kinds of functional groups. They are the group S(=O)=O and groups containing hydrogen bond acidic atoms. Removing these two kinds of ions leads to a relatively good general model for 211 ions, groups 1 and 2, with $R = 0.94$, SD = 1.35, and AAE = 1.02. It is difficult to say whether the homologous series with the functional group C(=O)O should be left out from the 211 ion set; but in the event, we put these ions into another group (group 2), leaving 205 ions in group 1.

Although the model derived from 205 ions is reasonably good and the estimation errors predicted from the model are in the range of experimental error ($\log P_{\mathrm{oct}}^{+i} = 1.32 \log P_{\mathrm{oct}}(\mathrm{neutral}) - 6.79$, $R = 0.94$, SD = 1.33, AAE = 0.99), the estimation error from the model is rather too high for predictive purposes. On examining 23 outliers from the 205 ions in group 1 plus another three outliers from groups 4 and 5, we found that most of outliers come from some particular homologous series. For example, the standard deviation between log P_{oct}^{+i} and log P_{oct}(neutral) for the homologous series 4 is very high, at 1.48 log units. A similar situation was found for series 6, 8, 14, and 19 (see Table 4). We can be almost sure that these outliers are due to experimental error. To check data on the outliers, we surveyed the original literature. We found that the ions 84−87 were studied at only one concentration; no correction was made for ion-pair formation, and the equilibration time was very short indeed.[39] The log P_{oct}(ratio) for ions 88−90 was concentration dependent;[40] ion 164 was regarded as an outlier by the authors,[41] and the log P_{oct}(ratio) for ions 204, 377, and 439 are uncertain or unreliable.[31] No ion-pair cor-

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[39] Eldefrawi, M. E.; O'Brien, R. D. *J. Exp. Biol.* **1967**, *46*, 1−12.

[40] Bellando, M.; Trotta, A. *Plant Sci. Lett.* **1980**, *17*, 467−472.

[41] Altomare, C.; Carrupt, P.-A.; El Tayar, N.; Testa, B. *Helv. Chim. Acta* **1991**, *74*, 290−296.

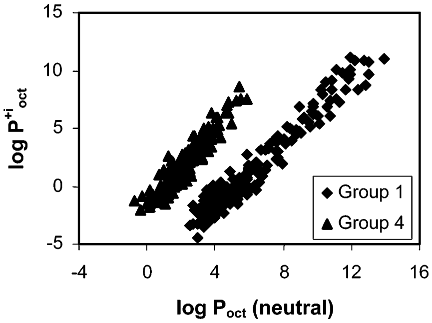

FIGURE 6. Plot of log P_{oct}^{+i} against log P(neutral) for groups 1 and 4.

rection was made for the other outliers. As we have mentioned, experimental errors in values of log P_{oct}^{+i} can be very large, and so it is not surprising that we have encountered a number of outliers that could well be due to experimental error. All these outliers are identified in Supporting Information. Removing these outliers leads to a model for 182 ions (R = 0.97, SD = 0.93, AAE = 0.76), which is quite similar to the model for the ions No 120−155 (see Table 5). Thus, using the regression equation in Table 5 for the 182 ions No 1−205 (less 23 outliers) will enable predictions to be made with an AAE of about 0.76 log unit.

Our classification of groups for ions (see structures in Scheme 1 and Supporting Information) is based on the above findings. Group 1 contains all the ions except those ions with functional groups containing S(=O)=O or hydrogen bond acidic atoms. Other groups contain either hydrogen bond acidic atoms and/or the S(=O)=O group. Details can be seen from the structure in Scheme 1. The linear regression models for each group are listed in Table 5. Figure 6 is an example of the relationship between log P_{oct}^{+i} and log P_{oct}(neutral) for two large groups, groups 1 and 4, containing 182 and 186 ions, respectively. The AAE for the 186 group 4 ions is only 0.57 log unit, and we doubt if any better regression can be achieved over such a range of cations.

From the various groups listed in Table 5, it is possible to estimate octanol/water partition coefficients of ions, even if they do not form part of a homologous series. All that is required is that the ion has a similar structure to ions in a particular group. In this way, partition coefficients of ions can be estimated from the equations for each group. For the nine groups (1−9) in Table 5, the AAE is 0.44 log unit and the SD is 0.57 log unit, which we feel is all that can be achieved, with regard to the experimental error.

The partition coefficients of ions calculated from the equations in Table 5 are shown in Supporting Information.

Conclusion

The partition of ions between octanol and water is a much more complex process than that of neutral species. Although the latter is complicated in the case of ionized or associated compounds, the partition of ionic species involves additional problems. The observed concentration ratio for the cation or anion of a salt is related not only to the partition of the ion but also to the partition of the ion pair (eq 17). Even when partition data are available for the ions, excluding any contribution from the ion pair, it is still not easy to separate the transfer partition coefficients into contributions from the cation and anion. However, we have managed to accomplish this for a number of ions, as shown in Table 3. Using these single-ion values as a basis, it is now possible to obtain single-ion transfer coefficients, and hence log P_{oct}^{+i}, for a very large number of cations.

In any homologous series, there is a constant CH_2 increment that implies that the effect of the positive charge is constant along the series. This seems contrary to any theory of relaying electronic effects along a carbon chain. However, we show that this can be qualitatively and semiquantitatively accounted for by the electrostatic continuum theory of Abraham and Lizsi and is a direct consequence of the very small increase in ionic radius on addition of a CH_2 group to the central cationic moiety.

Our results show that it is possible to predict partition coefficients for additional cations by comparison with log P_{oct} for the corresponding neutral analogue with an AAE of about 0.5 log unit and a SD of 0.6 log unit.

Experimental Section

Salts were all more than 99% pure, and no further purification was carried out before experiments. The partition coefficients of some tetraphenylborates ($P_{oct}^{\pm i}$) were calculated from the observed extraction ratio, P_{oct}^{ext}, eq 16, of salts determined using the shake-flask method. Both octanol and water were presaturated with water or octanol, respectively. A solution of a given salt was made up in octanol-saturated water and its concentration determined by UV spectroscopy. A given volume of water-saturated octanol was allowed to equilibrate with the salt solution, and the equilibrium concentration in the aqueous layer was again determined by UV spectroscopy. The equilibrium concentration in the organic phase was obtained by difference and the extraction ratio obtained from the equilibrium concentrations in the two phases. For any given salt, the entire procedure was carried out six times, over aqueous concentrations, from about 10^{-6} 3 to 10^{-5} mol dm^{-3}. The partition coefficients ($P_{oct}^{\pm i}$) of the dissociated pair of ions were calculated from the observed partition coefficients using an in-house program, Yiew9, on the basis of eq 17, exactly as described by Ling.[42]

$$[M^+ \text{ or } X^-](aq) \overset{P_{oct}^{ext}}{\rightleftharpoons} [M^+ \text{ or } X^- + M^+X^-](oct) \qquad (16)$$

$$P_{oct}^{ext} = [X^-]_{aq}(f_{aq}^{\pm})^2 P_{oct}^{\pm i}/K_{oct} + (P_{oct}^{\pm i})^{1/2} f_{aq}^{\pm}/f_{oct}^{\pm} \qquad (17)$$

In eq 17, $f_{aq}^{\pm}$ and $f_{oct}^{\pm}$ are the mean activity coefficients of the ionic species in the aqueous and octanol phases, respectively. Table 3 shows the values of the obtained partition coefficients for the tetraphenylborates and also includes partition coefficients of the dissociated pairs of ions LiCl, NaCl, and KCl between water and wet octanol.[43]

Supporting Information Available: Observed and calculated values of partition coefficients for 544 positive ions, together with their SMILES. This material is available free of charge via the Internet at http://pubs.acs.org.

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(42) Ling, H. C. Ph.D. Thesis, University of Surrey, Surrey, UK, 1981; pp 17−19.

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