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1 Highlights

2
3
4 Log k for ions and neutral molecules on IAM phases can be used in the same equation

5
6 Predictions of log k for ionized and partially ionized species can be made.

7
8 Ionization of acids reduce log k by 1.08 units; protonation of bases has no effect

9
10 Effects are due to cancellation of large stabilization of ions in water and IAM

**Analysis of immobilized artificial membrane retention factors for both neutral
and ionic species**

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Abstract

Retention data on an immobilised artificial membrane have been taken from the work of Li et al. and from Liu et al., and have been correlated with a set of descriptors that includes descriptors for ionized species, that is anions from deprotonated acids and cations from protonated bases. Log $k(\text{IAM})$ values can be predicted for acids or bases that are partially ionized at the experimental pH and log $k(\text{IAM})$ values for acids and bases can be predicted as a function of the fraction present as the ionized species, equivalent to prediction as a function of pH. It is shown that anions reduce the value of log $k(\text{IAM})$ by about 1.1 log units but that cations have almost no effect by comparison to the neutral species. By comparison to non-polar solvents, carboxylate anions and protonated base cations are considerably stabilized by both water and the IAM phase to about 6-8 log units and so the rather small influence of anions (-1.1 log unit) and cations (-0.1 log unit) on log $k(\text{IAM})$ is due to substantial cancellation of these stabilization effects. Indeed, the effect of change of phase from water to IAM on the neutral species is at least as large as the effect of change of phase on the ionic species.

Keywords

Immobilized artificial membrane

Retention factors

Linear solvation energy relationship

Ionic species

Abraham descriptors

Effect of ionic species on retention

1. Introduction

Although the water-octanol partition coefficient (as $\log P_{\text{oct}}$) is widely used as a model for partitions of chemicals into biological membranes, it is now recognized that biological membranes vary so much in character that it is impossible for any given water-solvent system to be a useful model for all membranes, especially when ionic species are considered [1-5]. Consequently, other phases such as immobilized artificial membrane (IAM) systems where the lipid membrane is a phospholipid monolayer bound to silica gel beads and water-liposome partitioning system have been developed as possible models for biological partition processes. The use of IAM systems as models is particularly attractive because retention factors, $k(\text{IAM})$, can be obtained by relatively straightforward chromatographic procedures. Several workers [6-10] have compared $\log k(\text{IAM})$ values with biological data.

In a recent paper, Li et al. [11] have analyzed $\log k(\text{IAM})$ values obtained on an IAM.PC.DD2 column filled with phosphatylcholine residues using the method that Abraham and Acree later used to correlate $\log k(\text{IAM})$ capacity values of neutral species [12]. Li et al. [11] introduced a δ -value calculated from Eq. (1) and Eq. (2) to include ionic species. Although quite reasonable correlation equations were obtained, they yield no real mechanistic information.

$$\delta = \frac{1}{1 + 10^{(pK_a - \text{pH})}} \quad (1)$$

$$\delta = \frac{10^{(pK_a - \text{pH})}}{1 + 10^{(pK_a - \text{pH})}} \quad (2)$$

Subsequently, Li et al. [13] correlated another selection of $\log k(\text{IAM})$ values with various solute descriptors and obtained Eq. (3) where ClogP is the calculated logarithm of an octanol-water partition coefficient, RotB is the number of rotatable bonds, MW is the solute molecular weight, TSA is the total surface area and Rings is the number of rings in the solute. No account was taken of any ionization of the solute, and the mechanistic implications of Eq. (3) are not at all evident.

$$\text{Log } k(\text{IAM}) = -1.177 + 0.308 \text{ ClogP} - 0.011 \text{ RotB} + 0.002 \text{ MW} + 0.003 \text{ TSA} + 0.213 \text{ Rings} \quad (3)$$

The two sets of $\log k(\text{IAM})$ values determined by Li et al. [11,13] include not only neutral species, but anionic species from the deprotonation of acids and cationic species from the protonation of bases. We have recently determined solute descriptors for a large number of anions and cations and have used these descriptors to analyze water-solvent partitions and a number of biological systems in order to elucidate the factors that influence the behavior of neutral and ionic species [14-22]. No such analysis of IAM systems has ever been reported and so we have taken advantage of the data obtained by Li et al. [11, 13] to obtain this information.

2. Methods

We use the linear free energy relationship, LFER, Eq. (4) to correlate SP values for neutral solutes; SP can be $\log P$ where P is a set of water-solvent partitions in a given system, or it can be a biological end-point, or it can be as in the present case $\log k(\text{IAM})$ for a series of solutes in a given system. The extension of Eq. (4) to include ionic solutes leads to Eq. (5).

$$SP = c + e E + s S + a A + b B + v V \quad (4)$$

$$SP = c + e E + s S + a A + b B + v V + j^+ J^+ + j^- J^- \quad (5)$$

The independent variables, or descriptors, in Eq. (4) and Eq. (5) are properties of solutes as follows [12, 14, 23-26]: E is an excess molar refraction in $\text{cm}^3 \text{ mol}^{-1}/10$, S is a combined dipolarity/polarizability descriptor, A is the overall solute hydrogen bond acidity, B is the overall solute hydrogen bond basicity, V is McGowan's [27] characteristic molecular volume in $\text{cm}^3 \text{ mol}^{-1}/100$, J^+ is a specific descriptor for cations and J^- is a specific descriptor for anions. Cations have $J^- = 0$, anions have $J^+ = 0$ and neutral solutes have $J^+ = J^- = 0$, so that Eq. (5) then reverts to Eq. (4). For some solutes in certain particular systems, a modified hydrogen bond basicity, Bo , has to be used instead of B [28]. These solutes so far identified are aniline, the toluidines, pyridine and alkyl pyridines, and sulfoxides (but not sulfones), and the systems are invariably

two-phase systems in which water is in contact with an organic phase that itself contains a substantial amount of water. Such systems include water-wet octanol and water –wet ether [28].

Although we can attribute physicochemical meanings to descriptors such as A and B , we have so far failed to relate J^+ and J^- to any physicochemical property. We have a number of generalizations such as J^- for alkylcarboxylate anions (1.9), alkylbenzoate anions (2.2), phenoxide anions (1.7) but no more. Since we are unable to relate J^+ and J^- to any physicochemical property, the corresponding equation coefficients, j^+ and j^- , have to be regarded as empirical factors only.

The set of coefficients, c , e , s , a , b , v , j^+ and j^- characterise the system and are determined by multiple linear regression analysis. These coefficients are not just fitting coefficients, but represent the complementary properties of the system: e gives the contribution in Eq. (4) and Eq. (5) of the solute-system general dispersion interaction, s is the solvent dipolarity (plus some polarizability), a is the system hydrogen bond basicity (the complimentary property to solute hydrogen bond acidity) and b is the system hydrogen bond acidity (the complimentary property to solute hydrogen bond basicity). The coefficient v reflects general dispersion interactions that aid solubility of a solute and the solvent-solvent interactions in the system that oppose solubility.

3. Results

Li et al. [11] list capacity values as $\log k(\text{IAM})$ at pH 7.0 and obtained an LFER equation for 53 compounds. Subsequently [13], they examined another set of $\log k(\text{IAM})$ values for 55 compounds, many of which were the same compounds given before [11]. In order to obtain the most general equation, we have collected together all the compounds listed by Li et al. [11, 13] and have used known pK_a values to calculate the fraction of neutral, F_n , and ionic, F_i , species present at that pH. We give in Table 1 the compounds that are present at pH 7.0 almost exclusively as either the neutral form or as the ionized form, together with the required descriptors for Eq. (5). The descriptors for the ionic species were either those used previously [14-18] or were calculated using the equations given before [14]. For the 68 species listed in Table 1 we find Eq. (6).

$$\text{Log } k(\text{IAM}) = -0.607 + 0.881 E - 0.562 S - 0.348 A - 1.794 B + 2.250 V - 0.245 J^+ + 2.010 J^-$$

$$N = 68, SD = 0.431, R^2 = 0.896, FS = 74.2, PRESS = 15.380, Q^2 = 0.857, PSD = 0.506 \quad (6)$$

Here and elsewhere N is the number of data points, R is the correlation coefficient, FS is the F-statistic, $PRESS$ and Q^2 are the leave-one-out statistics and PSD is the predictive standard deviation [29]. There are a number of compounds that are partially ionized at pH 7.0; we treated these compounds separately and used Eq. (6) to predict values of $\log k(\text{IAM})$ for the neutral and ionized species. We can then predict the overall (observed) $\log k(\text{IAM})$ through Eq. (7). Some representative calculations are in Table 2.

$$k(\text{obs}) = F_n.k_n + F_i.k_i \quad (7)$$

Table 1 here

Table 2 here

Liu et al. [30] have determined values of $\log k(\text{IAM})$ chromatographically under conditions in which compounds were present entirely as the neutral form or entirely as the ionized form. The species, the corresponding values of $\log k(\text{IAM})$ and the necessary descriptors are in Table 3.

Table 3 here

Application of the LFER, Eq. (5), leads to Eq. (8) for all 49 species in Table 3. The coefficients in Eq. (8) are reasonably close to those in Eq. (6) bearing in mind the two different IAM systems, but Eq. (8) seems rather the better equation statistically, with SD only 0.302 log units.

$$\text{Log } k(\text{IAM}) = -0.668 + 0.485 E - 0.411 S - 0.117 A - 2.537 B + 2.707 V - 0.791 J^+ + 2.696 J^-$$

$$N = 49, SD = 0.302, R^2 = 0.912, FS = 90.6, PRESS = 5.571, Q^2 = 0.869, PSD = 0.369 \quad (8)$$

4. Discussion

A number of workers have used Eq. (4) for the correlation of $\log k(\text{IAM})$ capacity values for neutral compounds [11, 20] but Eq. (6) and Eq. (8) represent the first equations in which specific descriptors for ionic species have been used. It is then possible to calculate and to predict $\log k(\text{IAM})$ for partially ionized acids and bases, as shown for some representative compounds in Table 2. This can be done for any fraction of ionized species. As an example we show predicted values of $\log k(\text{IAM})$ for hydrochlorothiazide as a function of the fraction of neutral form present, see Fig. 1. Since this fraction depends on the pH of the medium, this is equivalent to predicting $\log k(\text{IAM})$ for hydrochlorothiazide as a function of pH. Such predictions can be made for any acid or base for which the neutral and ionic descriptors are known. It should be noted that the effects of ionized species do not just relate to the $j^+ J^+$ and $j^- J^-$ terms in Eq. (6) and Eq. (8) but are a function also of the other terms in the equations. Thus cations have very large values of S and A , and anions have very large values of S and B . It is the resultant combination of all the terms in Eq. (6) and Eq. (8) that lead to an overall effect on $\log k(\text{IAM})$.

Figure 1 here

Li et al. [11] suggest that carboxylate anions lead to lower retention on IAM compared to the corresponding neutral molecules, but that cations had much less effect. We can use Eq. (6) to calculate $\log k(\text{IAM})$ for the neutral form and for the ionic form of any ionizable compound, as shown in Table 2, but it is much more accurate to start with the observed value of $\log k(\text{IAM})$ for a compound present entirely as an ionized form, and to use Eq. (6) to calculate $\log k(\text{IAM})$ just for the neutral form. In this way we have data on $\log k(\text{IAM})_{\text{neutral}} - \log k(\text{IAM})_{\text{cation}}$ for 14 compounds and on $\log k(\text{IAM})_{\text{neutral}} - \log k(\text{IAM})_{\text{anion}}$ for 13 compounds as shown in Table 4 where we give the mean difference and the SD value of the differences. Exactly the same procedure can be used to examine the data of Liu et al. [30] in Table 3; results are in Table 4. Taking the two sets of data together, our quantitative method shows that anions lower $\log$

1 $k(\text{IAM})$ by 1.09 log units but within a statistical uncertainty of about 0.50 log units cations have
2 no effect on $\log k(\text{IAM})$. Li et al. [11] suggested that the effect of cations is quite small, but
3 anions have a large effect, and our results confirm this suggestion.

4
5 Table 4 here
6
7

8 The effects of ionization on $\log k(\text{IAM})$ are not easy to interpret. As discussed by Avdeef et al.
9 [31], in the liposomal membrane/water partitioning of ionized drugs, the charge distribution in
10 the phospholipid membrane is anisotropic; as the ionized species moves in the direction of the
11 aqueous exterior of the membrane, the first charges it experiences are those of the negatively
12 charged phosphates. Further movement would bring the ionized drug substance in the vicinity of
13 the positively charged trimethylammonium groups. Electrostatic pairing of charges would
14 require a greater movement for weak acids, compared to weak bases. Therefore, the negatively
15 charged solutes have lesser affinity for phosphatidylcholine-based membranes than positively
16 charged solutes. The results from our study with the IAM.PC.DD2 stationary phase are
17 consistent with the suggestion of Avdeef et al [31]. Other workers, Li et al. [11], Barbato et al.
18 [6] and Vrakas et al. [32], have discussed IAM partitioning of ionized drugs on the lines of the
19 suggestion of Avdeef et al. [31], that is in terms of interactions in the IAM phase. However, the
20 effects of ionization relate not just to interactions within the IAM phase but also to interactions
21 within the aqueous phase. Thus there will be four sets of interactions that govern the effect of a
22 carboxylate anion as compared to the effect of the neutral carboxylic acid on values of $\log$
23 $k(\text{IAM})$: (i) interactions of the anion with the IAM phase, (ii) interactions of the anion with the
24 aqueous phase, (iii) interactions of the neutral carboxylic acid with the IAM phase and (iv)
25 interactions of the neutral carboxylic acid with the aqueous phase. These various interactions will
26 include van der Waals forces, hydrogen-bond interactions and electrostatic interactions that
27 involve charged species. In order to assess interactions of species with water, it is useful to
28 analyze transfers from a non-polar phase to water. The most non-polar phase for which we have
29 coefficients in Eq. (5) for transfer from water is 1,2-dichloroethane, DCE [33]. In Eq. (9) are
30 given coefficients for $\log P(\text{DCE})$, the partition of solutes between water and DCE.

$$\text{Log } P(\text{DCE}) = 0.183 + 0.249 E - 0.134 S - 2.801 A - 4.291 B + 4.180 V - 3.429 J^+ - 0.024 J^- \quad (9)$$

We can then use Eq. (9) to estimate partition of a typical acid, 4-phenylbutanoic acid, and its corresponding anion from water to DCE (and hence from DCE to water). For transfer from DCE to water $\log P$ for the 4-phenylbutanoate anion is about eight log units (that is the anion is more stable in water than in DCE), so that by comparison to the neutral carboxylic acid the anion is stabilized by water to about nine log units. We can then deduce that for transfer from DCE to the IAM phase, the anion is stabilized by the IAM phase to almost the same extent as compared to the neutral carboxylic acid.

The effects of 4-phenylbutanoic acid and its anion on $\log k(\text{IAM})$ can be obtained easily from Eq. (8) and from the descriptors for the two species, as shown also in Table 5. The contributions of interactions of the anion with water and with the IAM phase almost entirely cancel out, leading to an effect of only -0.25 log unit on $\log k(\text{IAM})$. The interactions of the neutral carboxylic acid with water and with the IAM phase actually lead to a greater effect of + 0.90 log units on $\log k(\text{IAM})$, the resultant overall effect being that anions affect $\log k(\text{IAM})$ by - 1.15 log units. Eq. (10) expresses this mathematically; where Int refers to an interaction, and N to the neutral carboxylic acid.

$$\Delta \log k(\text{IAM}) = [\text{Int, Anion (IAM)} - \text{Int, Anion (Water)}] - [\text{Int, N (IAM)} - \text{Int, N (water)}] \quad (10)$$

$$-1.15 = -0.25 - + 0.90$$

Exactly the same calculations can be made for a typical base, pindolol, and its corresponding cation, see Table 5. In the case of a base such as pindolol, $\log k(\text{IAM})$ for the neutral compound and the corresponding cation is almost the same. Again there is a large cancellation of stabilizing effects of water and of IAM on the cation. The mathematical formulation follows Eq. (10), as shown in Eq. (11).

$$\Delta \log k(\text{IAM}) = [\text{Int, Cation (IAM)} - \text{Int, Cation (Water)}] - [\text{Int, N (IAM)} - \text{Int, N (water)}] \quad (11)$$

$$-0.04 = + 1.31 - + 1.35$$

Our analysis thus suggests that both carboxylate anions and protonated base cations are considerably stabilized by IAM and by water by comparison to stabilization in a non-polar solvent. However, the interaction effects between a charged species and water and between a charged species and the IAM phase largely cancel out. The resulting effect of transfer from water to an IAM phase of a charged species may be no more than the effect of transfer of a neutral species from water to an IAM phase. Thus the observed effect of carboxylate anions and protonated base cations on $\log k(\text{IAM})$ by comparison to the neutral species may depend on apparently quite minor effects involving interactions of the neutral compounds with the aqueous phase and with the IAM phase. This is possibly the reason why there is so much difference between effects due to different carboxylic acids / carboxylate anions and between effects due to different bases / protonated bases, see the quite large SD values in Table 4.

Table 5 here

It would be useful if the solute properties that lead to $\log k(\text{IAM})$ for ionized solutes could be deduced from Eq.(5) in the same way that Eq. (4) can be used to provide a term-by-term analysis for neutral compounds. Such an analysis cannot be carried out using Eq. (5) because the terms $j^+ J^+$ and $j^- J^-$ do not relate to any specific properties of cations and anions. The coefficients j^+ and j^- do not, in themselves, yield information as to the effect of charge because the latter depends also on differences in E , S , A , B and V between a neutral species and the corresponding ion. Only for a particular system in which either J^+ or $J^- = 0$ can the descriptors in Eq. (4) and Eq. (5) be used to determine the exact influence of neutral/ionic properties on the dependent variable.

As it happens, j^+ in Eq. (6) is very nearly zero, so for the specific case of neutral bases and their protonated cations we can carry out a term-by-term analysis of the solute factors that influence $\log k(\text{IAM})$. We take nicardipine as an example and give in Table 6 a breakdown of these factors. The discrepancy between the total value of 3.30 for the cation and the value of 3.14 in Table 4 is due to the $j^+ J^+$ term, neglected in Table 5. The cation is much more dipolar than the neutral base, S is much larger and hence the $s S$ term is much more negative. The neutral

species is a weak hydrogen bond acid, the cation is a very strong hydrogen bond acid and hence the $a A$ term is much more negative for the cation. On the other hand, the neutral molecule is a strong hydrogen bond base, the cation has no hydrogen bond basicity properties at all, and so the $b B$ term is much more negative for the neutral molecule. There are smaller effects from the $e E$ and the $v V$ terms (and also the $j^+ J^+$ term) but the overall small change in $\log k(\text{IAM})$ is due to large cancellations of effects on the $s S$, $a A$ and $b B$ terms. Although we cannot carry out such a straightforward analysis of neutral/anion effects, it is clear from the descriptors listed in Table 1 and Table 3 that there will also be large effects due to the $s S$, $a A$ and $b B$ terms.

Table 6 Here

5. Conclusions

It is now possible to construct simple linear equations for the correlation and prediction of values of $\log k(\text{IAM})$ for neutral molecules, carboxylate anions and protonated base cations in a given system. For ionizable compounds, the variation of $\log k(\text{IAM})$ with the fraction of the ionizable species (equivalent to pH) can be predicted. For the IAM systems studied by Li et al. [11, 13] and by Liu et al. [30] anions decrease $\log k(\text{IAM})$ capacity factors by 1.1 log units by comparison to the corresponding neutral compounds but cations have almost no effect. These relatively small effects of anions and cations are due to the cancellation of very large factors for the stabilization of anions and cations in water and in the IAM phase. The constructed equations for the correlation of $\log k(\text{IAM})$ values enables the solute factors that influence $\log k(\text{IAM})$ to be deduced.

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Figure 1.

1 **Legend to Figures**

- 2 Figure. 1. Prediction of $\log k(\text{IAM})$ for hydrochlorothiazide as a function of fraction of the
3 neutral form. Predicted value $\circ$; observed value $\bullet$.

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Table 1

Values of $\log k(\text{IAM})$ at pH 7.0 from Li et al. [11, 13], the fraction of neutral and ionic species present at pH 7.0, and descriptors for the various species.

Compound	Log $k(\text{IAM})$	pKa	State	F_n	F_i	E	S	A	B	V	J^+	J^-
Acetophenone	0.81		Neutral	1.000	0.000	0.818	1.01	0.00	0.48	1.0139	0.000	0.000
Acetaminophen	0.34	9.5	Neutral	1.000	0.000	1.120	1.63	1.01	0.91	1.1724	0.000	0.000
Acyclovir	-0.33	9.04	Neutral	1.000	0.000	1.900	2.27	0.82	2.19	1.5217	0.000	0.000
Benzene	0.93		Neutral	1.000	0.000	0.610	0.52	0.00	0.14	0.7164	0.000	0.000
Benzyl alcohol	0.35		Neutral	1.000	0.000	0.803	0.87	0.39	0.56	0.9160	0.000	0.000
Biphenyl	2.88		Neutral	1.000	0.000	1.360	0.99	0.00	0.26	1.3242	0.000	0.000
Butanone	-0.38		Neutral	1.000	0.000	0.166	0.70	0.00	0.51	0.6879	0.000	0.000
Butyl acetate	0.63		Neutral	1.000	0.000	0.071	0.60	0.00	0.45	1.0284	0.000	0.000
Caffeine	0.31	0.60	Neutral	1.000	0.000	1.500	1.82	0.08	1.25	1.3632	0.000	0.000
Carbamazepine	1.53	2.3	Neutral	1.000	0.000	2.154	1.90	0.50	1.15	1.8106	0.000	0.000
Cilnidipine	3.3	~2	Neutral	1.000	0.000	2.320	2.33	0.25	2.20	3.6816	0.000	0.000
Chloroform	0.56		Neutral	1.000	0.000	0.425	0.49	0.15	0.02	0.6167	0.000	0.000
Dichloromethane	0.22		Neutral	1.000	0.000	0.387	0.57	0.10	0.05	0.4943	0.000	0.000
Dexamethasone acetate	2.37		Neutral	1.000	0.000	1.950	3.16	0.56	2.09	3.2107	0.000	0.000
Ethyl acetate	-0.29		Neutral	1.000	0.000	0.106	0.62	0.00	0.45	0.7466	0.000	0.000
Estradiol	3.51		Neutral	1.000	0.000	1.800	1.77	0.86	1.10	2.1988	0.000	0.000
n-Heptane	1.97		Neutral	1.000	0.000	0.000	0.00	0.00	0.00	1.0949	0.000	0.000
n-Hexane	1.69		Neutral	1.000	0.000	0.000	0.00	0.00	0.00	0.9540	0.000	0.000
Hydrocortisone	1.49		Neutral	1.000	0.000	2.030	3.49	0.71	1.90	2.7976	0.000	0.000
Lovastatin	3.71		Neutral	1.000	0.000	1.290	2.73	0.31	1.76	3.2859	0.000	0.000
Mannitol	-1.32		Neutral	1.000	0.000	0.836	2.33	0.87	1.77	1.3062	0.000	0.000

Medroxyprogesterone	3.13		Neutral	1.000	0.000	1.640	3.35	0.25	1.31	2.8211	0.000	0.000
Methyl acetate	-0.94		Neutral	1.000	0.000	0.142	0.64	0.00	0.45	0.6057	0.000	0.000
Naphthalene	2.24		Neutral	1.000	0.000	1.340	0.92	0.00	0.20	1.0854	0.000	0.000
Nifedipine	2.39	~2	Neutral	1.000	0.000	1.503	2.45	0.23	1.45	2.4945	0.000	0.000
Nimodipine	2.94	2.0	Neutral	1.000	0.000	1.600	2.40	0.23	1.79	3.1168	0.000	0.000
Nitrendipine	3.08	2.0	Neutral	1.000	0.000	1.720	2.47	0.32	1.53	2.6400	0.000	0.000
Omeprazole	1.76	4.4,8.7	Neutral	0.980	0.020	2.670	2.94	0.35	1.70	2.5161	0.000	0.000
Phenol	0.77	9.86	Neutral	1.000	0.000	0.805	0.89	0.60	0.30	0.7751	0.000	0.000
Propiophenone	1.18		Neutral	1.000	0.000	0.804	0.95	0.00	0.51	1.1548	0.000	0.000
Progesterone	2.98		Neutral	1.000	0.000	1.450	3.29	0.00	1.14	2.6215	0.000	0.000
Pyridine ^a	0.10	5.17	Neutral	1.000	0.000	0.631	0.84	0.00	0.47	0.6753	0.000	0.000
Pyramide	-0.36	0.50	Neutral	1.000	0.000	0.629	0.95	0.00	0.61	0.6340	0.000	0.000
Sucrose	-0.68		Neutral	1.000	0.000	2.320	2.60	2.19	2.81	2.2279	0.000	0.000
Tetrachloromethane	1.61		Neutral	1.000	0.000	0.458	0.38	0.00	0.00	0.7391	0.000	0.000
Thiourea	-0.77	1.44	Neutral	1.000	0.000	0.840	0.79	0.82	0.90	0.5696	0.000	0.000
Tinidazole	0.26	2.30	Neutral	1.000	0.000	1.400	2.77	0.00	1.36	1.7000	0.000	0.000
Theophylline	0.15	8.54	Neutral	0.972	0.028	1.500	1.60	0.54	1.34	1.2223	0.000	0.000
Tinidazole	0.26	2.3	Neutral	1.000	0.000	1.400	2.77	0.00	1.36	1.7000	0.000	0.000
Triamcinolone	1.97		Neutral	1.000	0.000	2.270	3.10	1.03	2.25	2.8310	0.000	0.000
m-Xylene	2.23		Neutral	1.000	0.000	0.663	0.56	0.00	0.16	0.9982	0.000	0.000
Atenolol	0.65	9.17	Cation	0.007	0.993	1.300	6.27	2.91	0.00	2.1978	2.480	0.000
Albuterol	0.48	9.3	Cation	0.005	0.995	1.226	5.87	3.02	0.00	2.0001	2.155	0.000
Amlodipine	3.11	9.1	Cation	0.008	0.992	1.450	6.48	2.91	0.00	3.0454	2.718	0.000
Bupivacaine	1.88	8.10	Cation	0.074	0.926	1.170	4.67	2.92	0.00	2.5354	1.592	0.000
Esmolol	1.18	9.5	Cation	0.003	0.997	0.920	5.66	2.49	0.00	2.4385	2.190	0.000
Nefopam	2.03	8.98	Cation	0.010	0.990	1.450	4.16	2.35	0.00	2.1001	1.958	0.000
Prilocaine	0.99	8.03	Cation	0.085	0.915	0.870	4.28	2.35	0.00	1.9395	1.607	0.000

Procaine	0.68	9.04	Cation	0.009	0.991	2.060	6.57	4.09	0.00	2.7761	2.356	0.000
Ropivacaine	1.54	8.16	Cation	0.065	0.935	1.170	4.67	2.92	0.00	2.3945	1.592	0.000
Propranolol	2.2	9.47	Cation	0.003	0.997	1.690	4.31	2.07	0.00	2.1695	2.432	0.000
Pseudoephedrine	0.36	9.59	Cation	0.003	0.997	0.766	3.74	1.38	0.00	1.4600	1.941	0.000
Timolol	0.90	9.21	Cation	0.006	0.994	1.320	5.67	2.83	0.00	2.3974	2.269	0.000
Venlafaxine	1.49	9.4	Cation	0.004	0.996	1.160	4.75	1.74	0.00	2.3964	2.432	0.000
Verapamil	2.84	8.92	Cation	0.012	0.988	1.657	7.70	4.33	0.00	3.8076	2.404	0.000
Aspirin	-1.19	3.50	Anion	0.000	1.000	1.000	4.15	0.00	3.28	1.2664	0.000	2.256
Captopril	-0.79	3.70	Anion	0.001	0.999	1.300	4.39	0.00	3.91	1.5985	0.000	2.339
Diclofenac	2.21	4.5	Anion	0.003	0.997	1.960	5.31	0.03	3.35	2.0035	0.000	2.624
Flurbiprofen	1.54	3.91	Anion	0.001	0.999	1.590	4.56	0.07	3.36	1.8174	0.000	2.538
Furosemide	1.16	3.34	Anion	0.000	1.000	2.456	6.08	0.19	4.19	2.0817	0.000	2.718
Ibuprofen	1.35	4.55	Anion	0.004	0.996	0.880	3.50	0.08	3.31	1.7556	0.000	2.419
Indomethacin	2.19	4.5	Anion	0.003	0.997	2.390	5.62	0.10	4.38	2.5084	0.000	2.990
Ketoprofen	0.93	4.6	Anion	0.004	0.996	1.800	5.49	0.01	3.39	1.9564	0.000	2.485
Meloxicam	1.88	4.2	Anion	0.002	0.998	2.750	6.50	0.08	4.18	2.2941	0.000	2.857
Naproxen	0.99	4.20	Anion	0.002	0.998	1.660	5.07	0.02	3.11	1.7606	0.000	2.426
Piroxicam	1.4	5.46	Anion	0.028	0.972	2.710	6.85	0.05	4.18	2.2285	0.000	2.726
Pidotimod	-1.62	3.14	Anion	0.000	1.000	1.810	5.21	0.09	4.06	1.6069	0.000	2.397
Salicylic acid	0.08	2.97	Anion	0.000	1.000	1.050	3.54	0.09	2.21	0.9689	0.000	1.982

^a The value of 0.47 is for the hydrogen bond basicity B^o .

Table 2

Prediction of $\log k(\text{IAM})$ for partially ionized bases and acids through Eq. (7) and Eq. (8).

Species	pKa	<i>F</i>	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	<i>J+</i>	Log <i>k</i> (IAM)	
									Obs	Calc
Minoxidil neutral	6.3	0.834	1.800	2.10	0.72	1.45	1.5882	0.0000		0.46
Minoxidil cation		0.166	1.650	4.96	2.75	0.00	1.6097	2.2088		0.12
Total									0.59	0.42
Cimetidine neutral	6.72	0.840	1.700	1.73	0.67	1.93	1.9563	0.0000		0.75
Cimetidine cation		0.160	1.550	5.95	2.24	0.00	1.9778	2.9438		0.66
Total									0.96	0.74
Phentolamine neutral	7.7	0.834	2.150	1.47	0.63	1.30	2.2352	0.0000		2.26
Phentolamine anion		0.166	2.300	5.40	0.10	4.13	2.2137	2.8627		1.60
Total									2.18	2.21
Phenobarbital neutral	7.36	0.696	1.630	1.72	0.71	1.18	1.6999	0.0000		1.08
Phenobarbital anion		0.304	1.780	4.90	0.07	3.77	1.6784	2.4878		0.52
Total									0.80	1.06

Table 3

Compound	log <i>k</i>	p <i>K</i> _a	State	<i>F</i> _n	<i>F</i> _i	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	<i>J</i> ⁺	<i>J</i>
Acridine	2.42	5.58	N	1.000	0.000	2.356	1.32	0.00	0.58	1.4133	0.0000	0.0000
Aniline	0.26	4.60	N	1.000	0.000	0.955	0.96	0.26	0.41	0.8162	0.0000	0.0000
N-Ethylaniline	1.04	5.12	N	1.000	0.000	0.945	0.85	0.17	0.43	1.0980	0.0000	0.0000
2-Chloroaniline	1.14	2.64	N	1.000	0.000	1.033	0.92	0.25	0.31	0.9386	0.0000	0.0000
2-Aminobiphenyl	2.02	3.82	N	1.000	0.000	1.600	1.48	0.26	0.41	1.4240	0.0000	0.0000
Phenylacetonitrile	0.94	N	N	1.000	0.000	0.751	1.03	0.00	0.50	1.0120	0.0000	0.0000
Acetophenone	0.86	N	N	1.000	0.000	0.818	1.01	0.00	0.48	1.0139	0.0000	0.0000
Nitrobenzene	0.99	N	N	1.000	0.000	0.871	1.11	0.00	0.28	0.8906	0.0000	0.0000
2-Chloronitrobenzene	1.58	N	N	1.000	0.000	1.020	1.24	0.00	0.24	1.0130	0.0000	0.0000
Benzyl alcohol	0.58	N	N	1.000	0.000	0.803	0.87	0.39	0.56	0.9160	0.0000	0.0000
4-Chlorobenzylalcohol	1.21	N	N	1.000	0.000	0.911	0.96	0.40	0.50	1.0384	0.0000	0.0000
3-Chlorophenol	1.77	9.11	N	1.000	0.000	0.909	1.06	0.69	0.15	0.8975	0.0000	0.0000
3-Nitrophenol	1.38	8.40	N	1.000	0.000	1.050	1.57	0.79	0.23	0.9493	0.0000	0.0000
Corticosterone	1.67	N	N	1.000	0.000	1.860	3.43	0.40	1.63	2.7389	0.0000	0.0000
Dexamethasone	1.79	N	N	1.000	0.000	2.040	3.51	0.71	1.92	2.9132	0.0000	0.0000
Estradiol	2.65	N	N	1.000	0.000	1.800	1.77	0.86	1.10	2.1988	0.0000	0.0000
Estrone	1.92	N	N	1.000	0.000	1.730	2.05	0.50	1.08	2.1558	0.0000	0.0000
Hydrocortisone	1.35	N	N	1.000	0.000	2.030	3.49	0.71	1.90	2.7976	0.0000	0.0000
Hydrocortisone-21-acetate	1.78	N	N	1.000	0.000	1.890	2.88	0.46	2.16	3.0951	0.0000	0.0000
Progesterone	3.01	N	N	1.000	0.000	1.450	3.29	0.00	1.14	2.6215	0.0000	0.0000
Testosterone	2.51	N	N	1.000	0.000	1.540	2.59	0.32	1.19	2.3827	0.0000	0.0000
C ₆ H ₅ (CH ₂) ₂ COOH	-0.25	4.52	Anion	0.000	1.000	0.900	3.43	0.03	3.02	1.1920	0.0000	2.1879
C ₆ H ₅ (CH ₂) ₃ COOH	0.06	4.72	-	0.000	1.000	0.910	3.59	0.04	3.01	1.3329	0.0000	2.2184
C ₆ H ₅ (CH ₂) ₄ COOH	0.43	4.55	-	0.000	1.000	0.920	3.63	0.04	3.10	1.4718	0.0000	2.2794
C ₆ H ₅ (CH ₂) ₇ COOH	2.02	5.03	-	0.000	1.000	0.940	3.87	0.07	3.26	1.8965	0.0000	2.4256
C ₆ H ₅ COOH	-0.62	4.20	-	0.000	1.000	0.880	3.64	0.00	2.88	0.9102	0.0000	2.3950

4-BrC ₆ H ₄ COOH	0.32	3.97	-	0.000	1.000	1.150	3.25	0.00	2.60	1.0852	0.0000	2.1480
3-ClC ₆ H ₄ COOH	0.06	3.83	-	0.000	1.000	0.990	3.13	0.00	2.57	1.0326	0.0000	2.0340
4-IC ₆ H ₄ COOH	0.51	3.96	-	0.000	1.000	1.460	3.29	0.00	2.61	1.1684	0.0000	2.0590
1-Naphthoic acid	0.13	3.69	-	0.000	1.000	1.610	4.13	0.05	2.87	1.4416	0.0000	1.6100
Aspirin	-0.15	3.48	-	0.000	1.000	0.931	3.91	0.04	3.03	1.2664	0.0000	2.1227
Flurbiprofen	1.78	3.91	-	0.000	1.000	1.590	4.56	0.07	3.36	1.8174	0.0000	2.5383
Ketoprofen	1.26	4.29	-	0.000	1.000	1.800	5.49	0.01	3.39	1.9564	0.0000	2.4851
Naproxen	1.35	4.15	-	0.000	1.000	1.660	5.07	0.02	3.11	1.7606	0.0000	2.4260
Indomethacin	2.37	4.50	-	0.000	1.000	2.390	5.62	0.10	4.38	2.5084	0.0000	2.9899
Mefenamic acid	2.35	4.33	-	0.000	1.000	1.800	4.71	0.09	3.14	1.8996	0.0000	2.6427
4-MeC ₆ H ₄ CH ₂ NHMe	0.96	9.93	Cation	0.000	1.000	0.650	2.58	1.42	0.00	1.2604	1.2835	0.0000
4-MeC ₆ H ₄ CH ₂ NHEt	1.02	10.04	+	0.000	1.000	0.640	2.66	1.44	0.00	1.4013	1.2994	0.0000
4-MeC ₆ H ₄ CH ₂ NHPr	1.30	9.98	+	0.000	1.000	0.630	2.63	1.37	0.00	1.5422	1.3290	0.0000
4-MeC ₆ H ₄ CH ₂ NHBu	1.87	9.98	+	0.000	1.000	0.620	2.62	1.34	0.00	1.6831	1.3349	0.0000
4-MeC ₆ H ₄ CH ₂ NH(CH ₂) ₄ Me	2.27	10.08	+	0.000	1.000	0.610	2.60	1.34	0.00	1.8240	1.3136	0.0000
4-MeC ₆ H ₄ CH ₂ NH(CH ₂) ₅ Me	2.77	10.17	+	0.000	1.000	0.600	2.60	1.36	0.00	1.9649	1.2956	0.0000
4-MeC ₆ H ₄ CH ₂ NH(CH ₂) ₆ Me	2.92	10.02	+	0.000	1.000	0.590	2.63	1.36	0.00	2.1058	1.2969	0.0000
Metoprolol	1.45	9.63	+	0.000	1.000	1.020	5.35	2.16	0.00	2.2819	2.3476	0.0000
Metipranolol	1.78	9.54	+	0.000	1.000	1.010	6.97	3.53	0.00	2.5794	2.1598	0.0000
Oxprenolol	1.70	9.57	+	0.000	1.000	1.160	5.09	2.35	0.00	2.2389	2.2029	0.0000
Penbutolol	3.70	9.92	+	0.000	1.000	0.775	4.66	1.98	0.00	2.6195	1.9630	0.0000
Pindolol	1.31	9.54	+	0.000	1.000	1.550	4.60	2.36	0.00	2.0305	2.2661	0.0000
Propranolol	2.48	9.53	+	0.000	1.000	1.690	4.31	2.07	0.00	2.1695	2.4319	0.0000

Table 4

The effect of ionization on values of log $k(\text{IAM})$ capacity values.

	Ref	No of compounds	Diff	SD
Log $k(\text{IAM})_{\text{cation}}$ - log $k(\text{IAM})_{\text{neutral}}$	11, 13	14	- 0.39	0.40
Log $k(\text{IAM})_{\text{anion}}$ - log $k(\text{IAM})_{\text{neutral}}$	11, 13	13	-1.10	0.41
Log $k(\text{IAM})_{\text{cation}}$ - log $k(\text{IAM})_{\text{neutral}}$	30	13	0.23	0.58
Log $k(\text{IAM})_{\text{anion}}$ - log $k(\text{IAM})_{\text{neutral}}$	30	15	- 1.08	0.30

Table 5

Estimation of partition from water (W) to 1,2-dichloroethane (DCE), and the effect on $\log k(\text{IAM})$ for 4-phenylbutanoic acid and pindolol.

4-Phenylbutanoic acid			
Process	Neutral	Anion	Anion-Neutral
W to IAM, $\log k$	0.90	-0.25	-1.15
DCE to W, $\log P$	-1.06	8.12	9.18
DCE to IAM, $\log k$	-0.16	7.87	8.03
Pindolol			
Process	Neutral	Cation	Cation-Neutral
W to IAM, $\log k$	1.35	1.31	-0.04
DCE to W, $\log P$	-2.02	5.87	7.89
DCE to IAM, $\log k$	-0.67	7.18	7.85

Table 6

A term-by term analysis of the effect of properties of neutral nicardipine and its cation on $\log k(\text{IAM})$, through Eq. (8).

Species	<i>c</i>	<i>e E</i>	<i>s S</i>	<i>a A</i>	<i>b B</i>	<i>v V</i>	Total
Neutral	-0.461	0.655	-0.992	-0.101	-2.421	7.130	3.81
Cation	-0.461	0.612	-2.398	-1.627	0.000	7.172	3.30