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International Journal of Pharmaceutics 254 (2003) 167–172

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Prediction of Setschenow constants

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Received 5 August 2002; received in revised form 20 December 2002; accepted 20 December 2002

Abstract

The Setschenow (salting out) constant by sodium chloride is related to molar volume, aqueous solubility, and octanol–water partition coefficient, K_{ow}, of the drug solute. This study validates a previously proposed relationship between the salting out constant of a solute and its partition coefficient. It also shows that the partition coefficient is a better descriptor of salting out than either molar volume or solubility.

Keywords: Setschenow constant; Partition coefficient; Intrinsic solubility; Le Bas volume

1. Introduction

The aqueous solubility of a nonelectrolyte has been found generally to be dependent on the concentration and type of salt present in solution. The salt effect is frequently described by the Setschenow equation (Setschenow, 1889).

$$\log S/S_o = -K_{salt}C_{salt} \tag{1}$$

where S and S_o are the solubilities of the organic solute in aqueous salt solution and in water respectively, C_{salt} is the molar concentration of electrolyte, and K_{salt} is the empirical Setschenow constant. Because of its ubiquitous presence in nature, sodium chloride is by far the most studied salt. In this paper, salt will refer only to sodium chloride.

Theoretical treatments to predict the K_{salt} have been developed by Debye and MacAulay (1925), Conway et al. (1964), McDevitt and Long (1952), Masterton and Lee (1970), and by Xie and Yang (1987). However, these theories require several parameters which cannot be unambiguously determined. Also, according to Xie et al. (1997), their predictions are only fairly accurate. They showed that K_{salt} can be simply and more accurately determined by $K_{salt} = 0.0018\,V_{LeBas}$, where V_{LeBas} is the molar volume calculated by the method of Le Bas (Reid et al., 1984). Other workers (Miyazaki et al., 1980; Gould, 1986) have reported that K_{salt} is a function of the intrinsic solubility (S_o) of the solute.

In our previous study (Ni et al., 2000), a simple equation $K_{salt} = 0.039 \log K_{ow} + 0.117$ was proposed to predict the NaCl effect on the solubility of nonelectrolytes. The equation was generated based on 62 compounds and was validated on 15 additional compounds. In this study, all three parameters, K_{ow}, S_o, and V_{LeBas}, were used to predict the Setschenow constants for 101 organic compounds in NaCl solution.

2. Collection of data

All log K_{ow} values were calculated by using ClogP® 4.0 software (Bio Byte Corp., Claremont, CA).

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doi:10.1016/S0378-5173(03)00008-5

Table 1
$\log S_o$, V_{LeBas}, and $\log K_{ow}$ values, experimental K_{salt} values for the 77 compounds

Name	$\log S_o$	V_{LeBas}	$\log K_{ow}$	K_{salt}	Reference
Benzene	−1.64	96.0	2.14	0.195	Xie et al. (1990)
Toluene	−2.24	118.2	2.64	0.228	Xie et al. (1990)
Ethylbenzene	−2.80	140.4	3.17	0.234	Xie et al. (1997)
o-Xylene	−2.77	140.4	3.09	0.227	Xie et al. (1990)
m-Xylene	−2.82	140.4	3.14	0.248	Xie et al. (1990)
p-Xylene	−2.81	140.4	3.14	0.251	Xie et al. (1990)
iso-Propylbenzene	−3.29	170.0	3.57	0.316	Xie et al. (1997)
1,2,4-Trimethylbenzene	−3.32	162.6	3.59	0.293	Xie et al. (1997)
1,2,3-Trimethylbenzene	−3.20	162.6	3.54	0.321	Xie et al. (1997)
1,3,5-Trimethylbenzene	−3.40	162.6	3.64	0.318	Xie et al. (1997)
sec-Butylbenzene	−3.88	184.8	4.10	0.288	Xie et al. (1997)
tert-Butylbenzene	−3.66	184.8	3.97	0.243	Xie et al. (1997)
Naphthalene	−3.62	147.6	3.32	0.220	Xie et al. (1990)
1-Methyl naphthalene	−3.74	169.8	3.81	0.200	Xie et al. (1997)
1-Ethyl naphthalene	−4.16	169.8	4.34	0.273	Xie et al. (1997)
Biphenyl	−4.35	185.0	4.03	0.276	Xie et al. (1997)
Acenaphthene	−4.60	173.0	3.77	0.238	Xie et al. (1997)
Fluorene	−4.94	188.0	4.08	0.267	Xie et al. (1997)
Phenanthrene	−5.19	199.0	4.49	0.272	Xie et al. (1997)
Anthracene	−6.61	197.0	4.49	0.326	Xie et al. (1997)
2-Methyl anthracene	−6.96	218.7	4.99	0.336	Xie et al. (1997)
1-Ethyl anthracene	−6.89	240.9	5.52	0.313	Xie et al. (1997)
Pyrene	−6.17	214.0	4.95	0.320	Xie et al. (1997)
Fluroanthene	−5.89	217.0	4.95	0.339	Xie et al. (1997)
Chrysene	−8.06	251.0	5.66	0.336	Xie et al. (1997)
1,2-Benzanthracene	−7.38	248.0	5.66	0.354	Xie et al. (1997)
Benzo[*a*]-pyrene	−8.19	263.0	6.12	0.328	Xie et al. (1997)
Chlorobenzene	−2.35	117.0	2.86	0.198	Xie et al. (1994)
o-Dichlorobenzene	−2.97	138.0	3.45	0.247	Xie et al. (1997)
m-Dichlorobenzene	−3.07	138.0	3.57	0.226	Xie et al. (1994)
p-Dichlorobenzene	−3.26	138.0	3.57	0.240	Xie et al. (1994)
1,2,4-Trichlorobenzene	−3.57	159.0	4.16	0.250	Xie et al. (1994)
n-Pentane	−3.28	118.4	3.34	0.221	Xie et al. (1997)
n-Hexane	−3.96	140.6	3.87	0.276	Xie et al. (1997)
Cyclopentane	−2.65	99.5	2.79	0.182	Xie et al. (1997)
Cyclohexane	−3.18	118.2	3.35	0.277	Xie et al. (1997)
Cycloheptane	−3.51	140.4	3.91	0.343	Xie et al. (1997)
Methylcyclopentane	−3.30	121.7	3.31	0.273	Xie et al. (1997)
Methylcyclohexane	−3.84	140.4	3.87	0.274	Xie et al. (1997)
Phenol	−1.05	103.4	1.47	0.111	Xie et al. (1997)
2,4-Dichlorophenol	−1.56	145.2	2.96	0.218	Xie et al. (1994)
2,4,6-Trichlorophenol	−2.39	166.1	3.37	0.228	Xie et al. (1994)
o-Nitrophenol	−1.74	131.9	1.85	0.136	Xie et al. (1997)
m-Nitrophenol	−1.01	131.9	1.85	0.147	Xie et al. (1997)
p-Nitrophenol	−1.08	131.9	1.85	0.165	Xie et al. (1997)
p-Nitrotoluene	−2.49	153.0	2.38	0.163	Xie et al. (1997)
p-Toluidine	−1.22	132.4	1.41	0.170	Xie et al. (1997)
Benzoic acid	−1.55	138.4	1.88	0.177	Xie et al. (1997)
o-Chlorobenzoic acid	−1.87	155.7	2.10	0.182	Xie et al. (1997)
m-Chlorobenzoic acid	−2.54	155.7	2.70	0.180	Xie et al. (1997)
o-Hydroxylbenzoic acid	−1.79	146.7	2.19	0.172	Xie et al. (1997)
Phenylacetic acid	−0.91	157.0	1.41	0.190	Xie et al. (1997)
n-Hexanol	−1.24	148.0	1.88	0.232	Xie et al. (1997)

Table 1 (*Continued*)

Name	$\log S_o$	V_{LeBas}	$\log K_{ow}$	K_{salt}	Reference
Cyclohexanone	−0.59	118.0	0.86	0.202	Xie et al. (1997)
Acetone	1.23	74.0	−0.21	0.110	Xie et al. (1997)
Ethylacetate	−0.04	108.6	0.71	0.172	Xie et al. (1997)
Phenylthiourea	−1.79	152.2	0.75	0.184	Xie et al. (1997)
Propionic acid	1.13	90.6	0.33	0.132	Xie et al. (1985)
Butanoic acid	−0.17	112.8	0.86	0.166	Xie et al. (1985)
Hexanoic acid	−1.05	157.2	1.92	0.220	Xie et al. (1985)
Heptanoic acid	−1.66	179.4	2.45	0.242	Xie et al. (1985)
Acetic acid	1.22	68.4	−0.19	0.064	Xie et al. (1985)
Methane	−2.86	29.6	1.10	0.127	Masterton and Lee (1970)
Ethane	−2.70	51.8	1.75	0.162	Masterton and Lee (1970)
Ethylene	−2.33	44.4	1.27	0.127	Masterton and Lee (1970)
Cystine	−3.10	253.4	−4.46	−0.068	Carta (1988)
Tyrosine	−2.58	200.8	−2.22	0.048	Carta (1988)
Leucine	−0.78	171.4	−1.67	0.114	Carta (1988)
Glycine	0.52	82.6	−3.21	0.002	Carta (1988)
Aniline	−0.41	110.2	0.91	0.136	Carta (1988)
Phthalic acid	−1.37	173.6	0.73	0.178	Bergen and Long (1956)
Benzylamine	0.97	132.4	1.09	0.112	Bergen and Long (1956)
Piperidine	1.07	111.7	0.93	0.156	Bergen and Long (1956)
m-Cresol	−0.68	125.6	1.97	0.182	Carter and Hardy (1928)
Phenytoin	−3.90	263.7	2.08	0.191	Ni et al. (2000)
Theophylline	−1.39	169.4	−0.06	0.100	Ni et al. (2000)
Cytosine	−1.14	100.8	−1.65	−0.005	Ni et al. (2000)

Table 2

$\log S_o$, V_{LeBas}, and $\log K_{ow}$ values, experimental K_{salt} values for the new 24 added compounds

Name	$\log S_o$	V_{LeBas}	$\log K_{ow}$	K_{salt}	Reference
Methyl acetate	0.52	84.8	0.18	0.185	Segatin and Klofutar (2000)
Propyl acetate	−0.73	133.0	1.24	0.201	Segatin and Klofutar (2000)
Butyl acetate	−1.14	155.2	1.77	0.224	Segatin and Klofutar (2000)
iso-Butyl acetate	−1.26	155.2	1.64	0.225	Segatin and Klofutar (2000)
sec-Butyl acetate	−1.27	155.2	1.77	0.241	Segatin and Klofutar (2000)
tert-Butyl acetate	−1.14	155.2	1.64	0.269	Segatin and Klofutar (2000)
Pentyl acetate	−1.88	177.4	2.30	0.283	Segatin and Klofutar (2000)
Hexyl acetate	−2.46	199.6	2.83	0.312	Segatin and Klofutar (2000)
Caffeine	−0.95	195.3	−0.06	0.128	AL_Maaieh and Flanagan (2002)
Theobromine	−2.89	173.1	−0.69	0.056	AL_Maaieh and Flanagan (2002)
Testosterone	−4.09	343.1	3.22	0.326	Bischoff and Pilhorn (1948)
Progesterone	−4.55	380.1	3.77	0.288	Bischoff and Pilhorn (1948)
5-Fluorouracil	−1.07	102.8	−0.58	0.014	Arakawa et al. (1976)
6-Mercaptopurine	−0.35	146.7	0.71	0.048	Arakawa et al. (1976)
Sulfanilamide	−1.36	166.6	−0.57	0.124	Matsuura and Sekiguchi (1960)
Butane	−2.98	96.2	2.81	0.217	Morrison and Billett (1952)
Propane	−2.85	74.0	2.28	0.194	Morrison and Billett (1952)
Bipyridyl	−1.42	178.8	1.56	0.251	Komar and Zaslavskaya (1973)
Lindane	−4.60	243.6	3.75	0.166	Masterton and Lee (1972)
1-Naphthol	−2.22	155.0	2.65	0.207	Korenman et al. (1979)
2-Naphthol	−2.28	155.0	2.65	0.220	Korenman et al. (1979)
o-Dinitrobenzene	−3.10	153.0	1.63	0.124	Leiga and Sarmousakis (1966)
m-Dinitrobenzene	−2.50	153.0	1.63	0.109	Leiga and Sarmousakis (1966)
p-Dinitrobenzene	−3.39	153.0	1.63	0.097	Leiga and Sarmousakis (1966)

Calculated $\log K_{ow}$ values were used because they are easy to determine for virtually all organic compounds, reproducible, and also in good agreement with the measured $\log K_{ow}$ values that are available. The experimental intrinsic solubility was obtained from the AQUASOL dATAbASE (Yalkowsky, 2002) or Chemfinder website (www.chemfinder.com). Molar volumes were calculated based on the method of Le Bas (Reid et al., 1984). The K_{salt} values for 101 compounds were obtained from the literature and are listed in Tables 1 and 2.

3. Results and discussion

The correlations of K_{salt} with $\log K_{ow}$, $\log S_o$, and V_{LeBas} are shown in the Figs. 1–3, respectively. The open circles in all the figures represent the 77 compounds which were used in our previous study (Ni et al., 2000) and which are listed in Table 1. The filled circles represent 24 added compounds that are listed in Table 2.

Fig. 1 shows that there is a linear relationship between $\log K_{ow}$, and K_{salt} as:

$$K_{salt} = 0.040 \log K_{ow} + 0.114 \quad (n = 101,\ r = 0.7717,\ \text{S.E.} = 0.0410). \tag{2}$$

It is worth noting that Eq. (2) is virtually identical to $K_{salt} = 0.039 \log K_{ow} + 0.117$ which was obtained in our previous study (Ni et al., 2000).

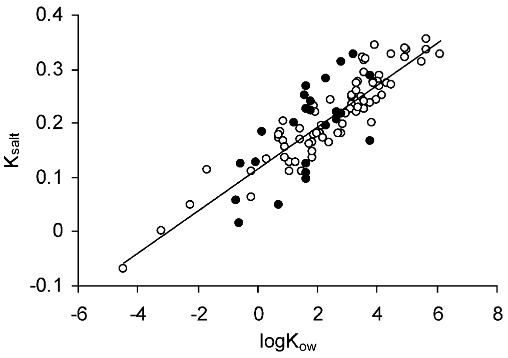

Fig. 1. The K_{salt} values of different compounds in NaCl solution vs. their $\log K_{ow}$ values as calculated by ClogP®.

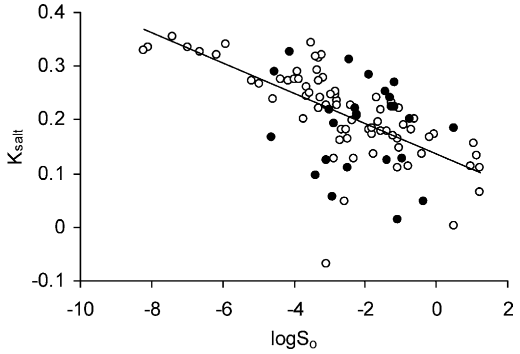

Fig. 2. The K_{salt} values of different compounds in NaCl solution vs. their $\log S_o$ values.

The relationship between $\log S_o$ and K_{salt} for the data shown in Fig. 2 is described by:

$$K_{salt} = -0.027 \log S_o + 0.135 \quad (n = 101,\ r = 0.3908,\ \text{S.E.} = 0.0672). \tag{3}$$

Finally, the relationship between V_{LeBas} and K_{salt} shown in Fig. 3, is:

$$K_{salt} = 0.0012\, V_{LeBas} \quad (n = 101,\ r = 0.0067,\ \text{S.E.} = 0.0781). \tag{4}$$

It is clear that there is a stronger correlation between the Setschenow constants with $\log K_{ow}$ than to either $\log S_o$ or V_{LeBas}. While molar volume correlates well with the salting out of hydrocarbons, it does not account for the differences in polarity of similarly

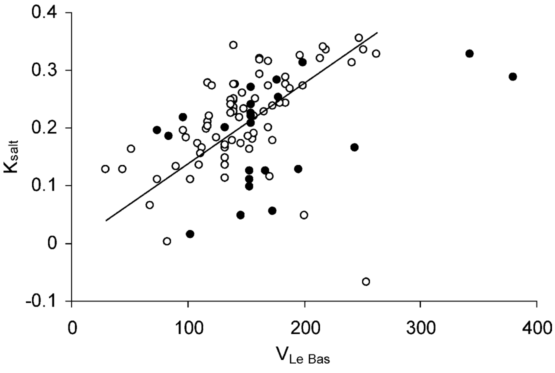

Fig. 3. The K_{salt} values of different compounds in NaCl solution vs. their V_{LeBas} values.

sized groups. Solubility is dependent upon the crystallinity of the solute as well as on its polarity. Since crystallinity can have no effect upon solvent polarity, solubility cannot be expected to correlate with salting out.

The high correlation between $\log K_{\mathrm{ow}}$ and K_{salt} is due to the fact that the octanol–water partition coefficient is a descriptor of the overall polarity of the solute and is independent of crystal structure. The effect of salt on solvent polarity is analogous to the effect of cosolvents. Yalkowsky (1999) has shown that the solubility of nonpolar compounds in mixed solvents is related to cosolvent composition by:

$$\log S/S_{\mathrm{o}} = \sigma_{\mathrm{cosolvent}} C_{\mathrm{cosolvent}} \tag{5}$$

The similarity of the equations for “salting out” and “solventing in” of nonpolar solutes is the result of the fact that both salts and cosolvents mix with water to form a continuum. Polar salts produce a continuum that is more polar than pure water while nonpolar cosolvents produce a continuum that is less polar than water. In both cases, the more nonpolar the solute, the more it is influenced by the polarity of the solvent.

4. Conclusions

Three empirical methods based on three simple parameters, V_{LeBas}, $\log S_{\mathrm{o}}$, and $\log K_{\mathrm{ow}}$ were used to predict the Setschenow constant, K_{salt} of 101 compounds. The most effective correlation is based on $\log K_{\mathrm{ow}}$ as calculated by ClogP$^{®}$ software.

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