Descriptors for Neutral Molecules, Ions, Ionic Species, and Ion Pairs: Application to Partition and Permeation Processes

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Outline

Descriptors for neutral molecules

Descriptors for ions and ionic species

Partition into Solvents

Partition into Liposomes

Permeation into brain

Conclusions

Solute Descriptors

E = Excess Molar Refraction

S = Polarisability / Dipolarity

A = Hydrogen Bond Acidity

B = Hydrogen Bond Basicity

V = McGowan's Volume

General Solvation Equation

SP = Solute property, in a given system

$$SP = c + e.E + s.S + a.A + b.B + v.V$$

Coefficients describe the given system

J. Chromatogr (A), 2004, 1037, 29.

Solute Descriptors

E and V can be calculated

S, A and B need to be obtained.

Three logP values in three systems will yield the three unknowns

Aim to have as many systems as possible

Solvent (wet)	e	s	a	b	v
Octanol	0.6	1.0	0.0	-3.5	3.8
Butyl acetate	1.2	-1.4	-0.1	-3.8	3.7
Chloroform	0.2	-0.4	-3.2	-3.4	4.2
Cyclohexane	0.8	-1.7	-3.7	-4.9	4.6
Toluene	0.5	-0.7	-3.0	-4.8	4.5

Solvent (dry)	e	s	a	b	v
Ethanol	0.4	-1.0	0.2	-3.6	3.9
THF	0.4	-0.4	-0.2	-4.9	4.5
Acetonitrile	0.1	0.3	-1.6	-4.4	3.2

Some values of descriptors

	E	S	A	B	V
Helium	0.00	0.00	0.00	0.00	0.068
Chlorine	0.36	0.32	0.10	0.00	0.353
Dieldrin	2.09	1.69	0.00	0.65	2.007
Fullerene	1.87	1.48	0.00	0.54	3.906
Cortisone	1.96	3.50	0.36	1.87	2.755
Me_2Hg	0.70	0.62	0.00	0.00	0.665

Descriptors for Ions

Same general method as for neutrals

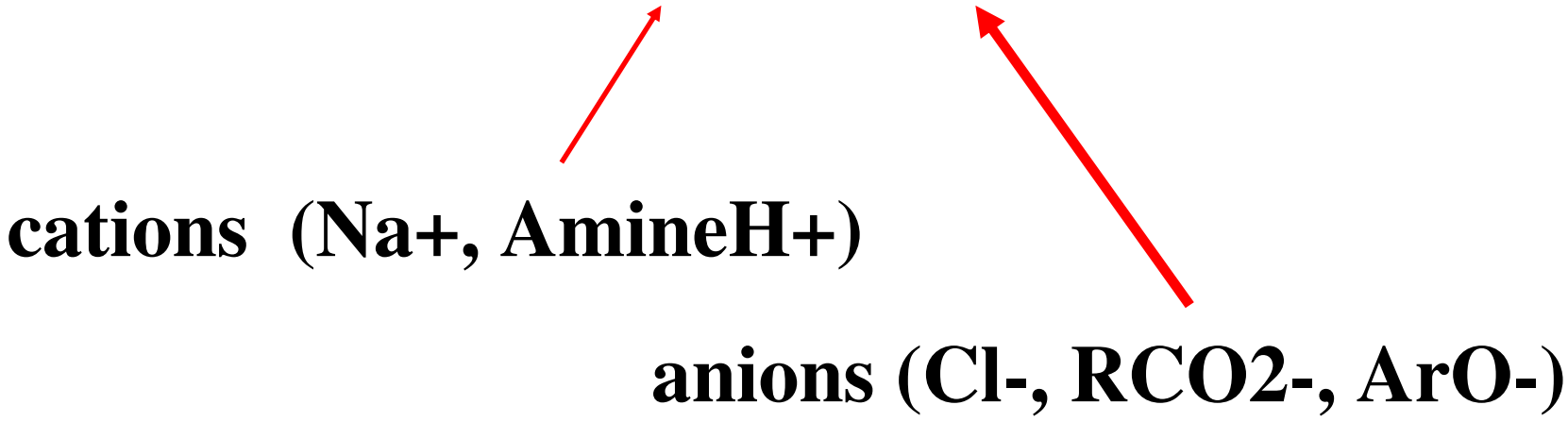
Need log P values for single ions from water to various solvents

Log P(Ph_4As+) = log P(Ph_4P-)

The coefficients e, s, a, b, v are the same as those in equations for neutrals

Require two additional terms: J+ for cations and J- for anions

$$\text{Log P} = c + e.E + s.S + a.A + b.B + v.V + j+ . J+ + j- . J-$$



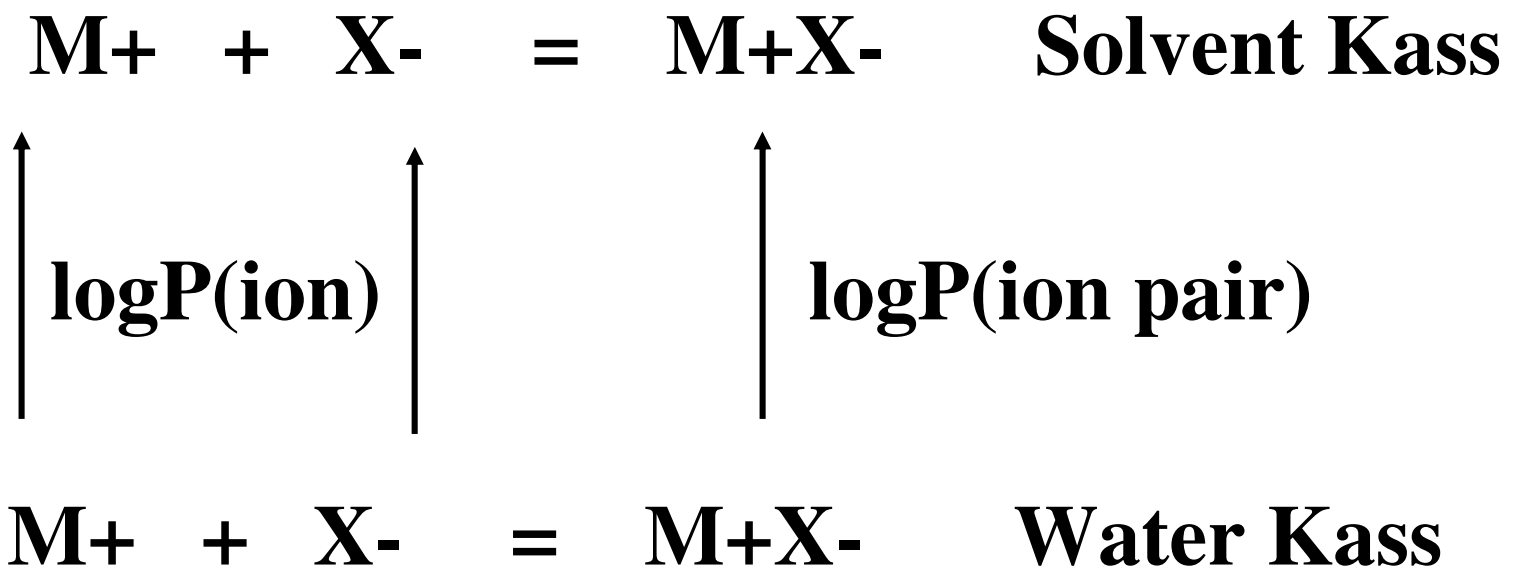
Solute	S	A	B	J+	J-
Me3N	0.2	0.0	0.7	0.0	0.0
Me3NH+	2.2	0.6	0.0	1.1	0.0
Pyridine	0.8	0.0	0.5	0.0	0.0
PyridineH+	2.2	1.2	0.0	1.0	0.0
Acetic acid	0.6	0.6	0.4	0.0	0.0
Acetate-	2.2	0.0	2.9	0.0	2.1

Descriptors for Ion Pairs

- **Need log P values for ion pairs**
- **Obtained from log P for single ions plus the association constant in water and the solvent:**

$$M^+ + A^- = M^+A^- \quad K_{ass}$$

- **Then need both J+ and J- for any ion pair**


M+ + X- = M+X- Solvent Kass
logP(ion)
logP(ion pair)
M+ + X- = M+X- Water Kass

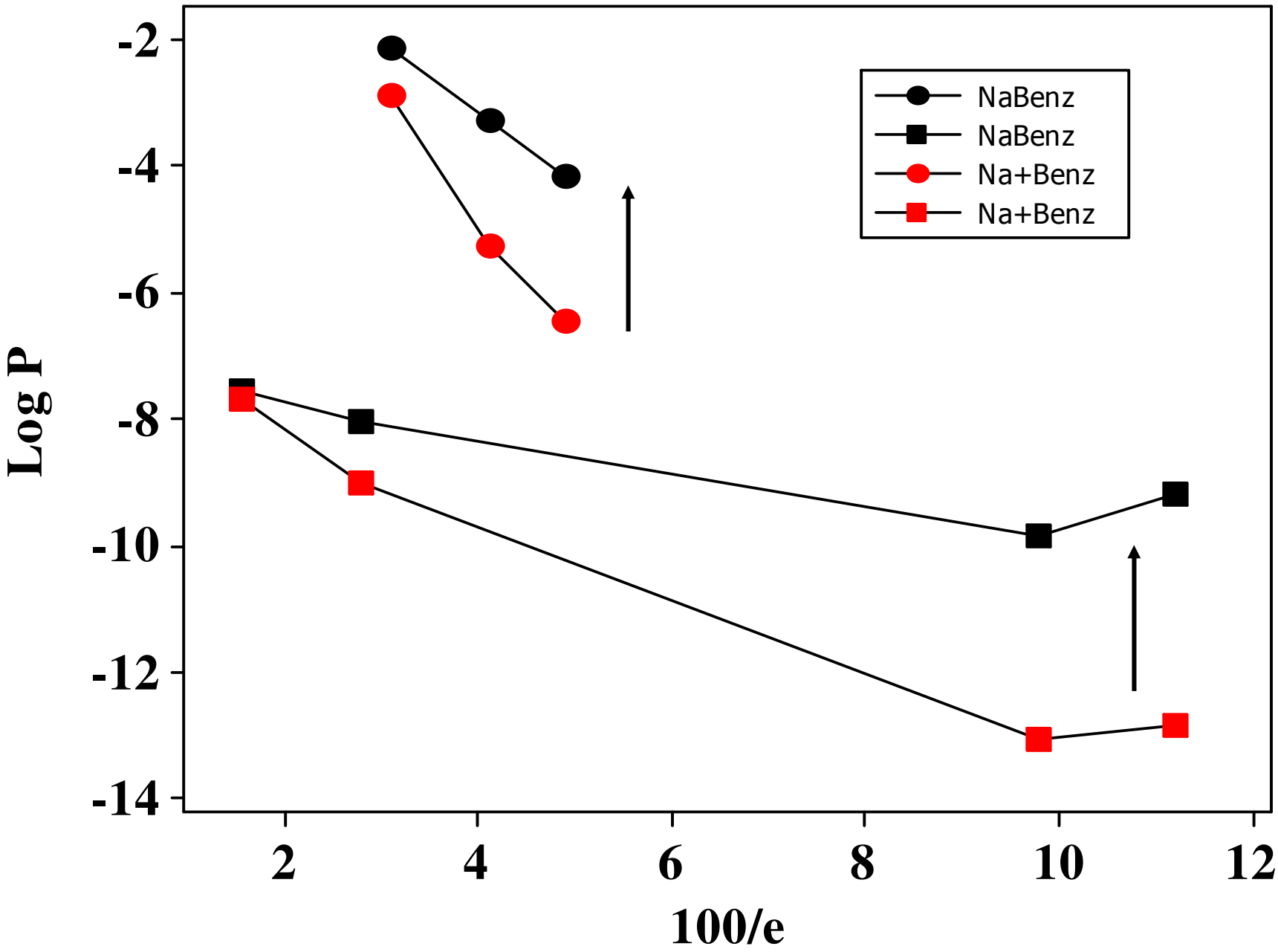
Descriptors for some ion pairs

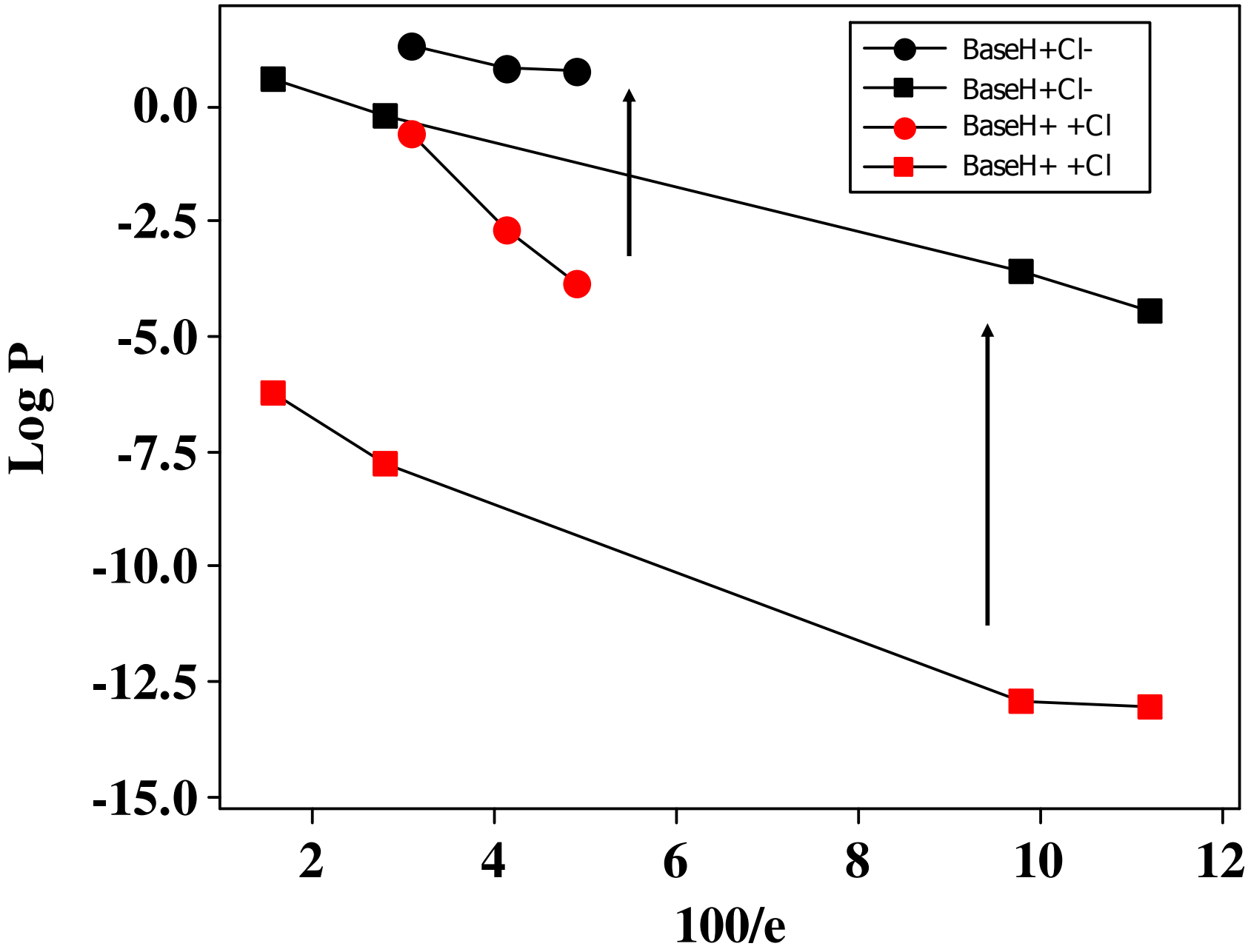
	E	S	A	B	V	J+	J-
Na+Cl-	0.08	3.85	1.29	2.52	0.26	-1.05	1.30
Et4N+I-	0.78	2.73	0.89	1.31	1.76	0.21	-0.19
Na+Acetate-	0.40	2.61	1.18	3.01	0.48	-0.62	1.33
PyridineH+Cl-	0.58	3.47	2.55	2.44	0.92	-0.28	1.13

	Acetone	50%EtOH	D(aq)
Benzoic acid	1.85	1.21	9.1
Benzoate-	-9.58	-0.04	9.4
Na+Benzoate-	-9.15	-0.64	6.8
Na+ + Benz	-10.86	-0.88	10.3
4-MeAniline	1.82	1.98	9.1
4-MeAnilineH+	0.83	1.44	9.3
4-MeAnH+Cl-	-6.49	0.70	5.6
4-MeAnH+ +Cl-	-9.21	0.54	12.8

Partition from water to solvents

	c	e	s	a	b	v	j+	j-
MeOH	0.28	0.33	-0.71	0.24	-3.32	3.55	-2.61	3.03
Oct/w	0.09	0.56	-1.05	0.03	-3.46	3.81	-3.02	2.58
MeCN	0.41	0.08	0.33	-1.57	-4.39	3.36	-2.34	0.10
Acetone	0.31	0.31	-0.12	-0.61	-4.75	3.94	-2.29	0.08
DMSO	-0.19	0.33	0.79	1.26	-4.54	3.36	-3.29	0.13
12DCE	0.18	0.29	-0.13	-2.80	-4.29	4.18	-3.43	0.01
CH2C2	0.32	0.10	- 0.19	-3.06	-4.09	4.32	-3.99	0.09


-2
-4
-6
-8
-10
-12
-14
Log P
2
4
6
8
10
12
100/e
NaBenz
NaBenz
Na+Benz
Na+Benz


BaseH+Cl-
BaseH+Cl-
BaseH+ +Cl
BaseH+ +Cl
0.0
-2.5
-5.0
-7.5
-10.0
-12.5
-15.0
Log P
2
4
6
8
10
12
100/e

Water-liposome distribution

Esher et al Env.Sci.Technol. 1996, 30, 260

Dipalmitoylphosphatidylcholine

LogK for neutral phenols, phenoxides

anilines and anilineH+

Only neutrals and ions partition – no ion pairs

22 Neutral species, 20 phenoxides, 2 amineH+

LogK = -0.41 + 1.00 E – 0.60 S + 1.01 A
- 2.07 B + 3.06 V – 3.00 J+ + 2.39 J-

N = 44, SD = 0.36, R^2 = 0.896, F = 44.1

Anilines/AnilinesH+ = 1.6
Phenols/Phenoxides 1.2 to 74, av = 15

Xiangli Liu and co-workers

J.Pharm.Sci, in press

Cerasome liposome - hydrogenated lecithin, cholesterol, ceramides and fatty acids. Model for skin.

LogK measured for 38 neutral compounds, 17 anions and 16 cations.

LogK = -1.92 + 0.20 E – 0.63 S - 0.11 A
- 1.45 B + 1.76 V + 0.34 J+ + 1.96 J-

N = 71, SD = 0.29, R^2 = 0.814, F = 39.5

Acid/acid anion = 4.00 av of 17

Base/BaseH+ cation = 0.36 av of 16

Diffusion in water

E. Hills et al., Fluid Phase Eq., 2011, 303, 45-55

Diffusion coefficient in 10^5 cm^2/sec

Log Diff = 0.31 – 0.027 A – 0.36 V + 0.096 J+

-0.004 J-

133 Neutrals, SD = 0.080

29 Cations, 28 Anions, SD = 0.091

Some values of Diff in 10^6 D

Benzoic acid	9.1	Picric acid	6.8
Benzoate-	9.4	Picrate	6.9
Na+Benzoate-	6.8	Na+Picrate-	6.2
Na+ + Benz	10.3	Na+ + Picrate-	9.5
4-MeAniline	9.1	PyridineH+	13.4
4-MeAnilineH+	9.3	Et4N+	8.9
4-MeAnH+Cl-	5.6	ImidazoleH+	14.7
4-MeAnH+ +Cl-	12.8	CodeineH+	5.2

Vascular Perfusion (Saline pH 7.4)

Rate of transfer from perfusate (saline, blood) to brain after intravenous injection. Passive transfer

$Pm*S$ in $cm^3\ s^{-1}\ g^{-1}$

Pm in $cm\ s^{-1}$ Permeability

$Pm*l$ in $cm^2\ s^{-1}$ Diffusion coefficient

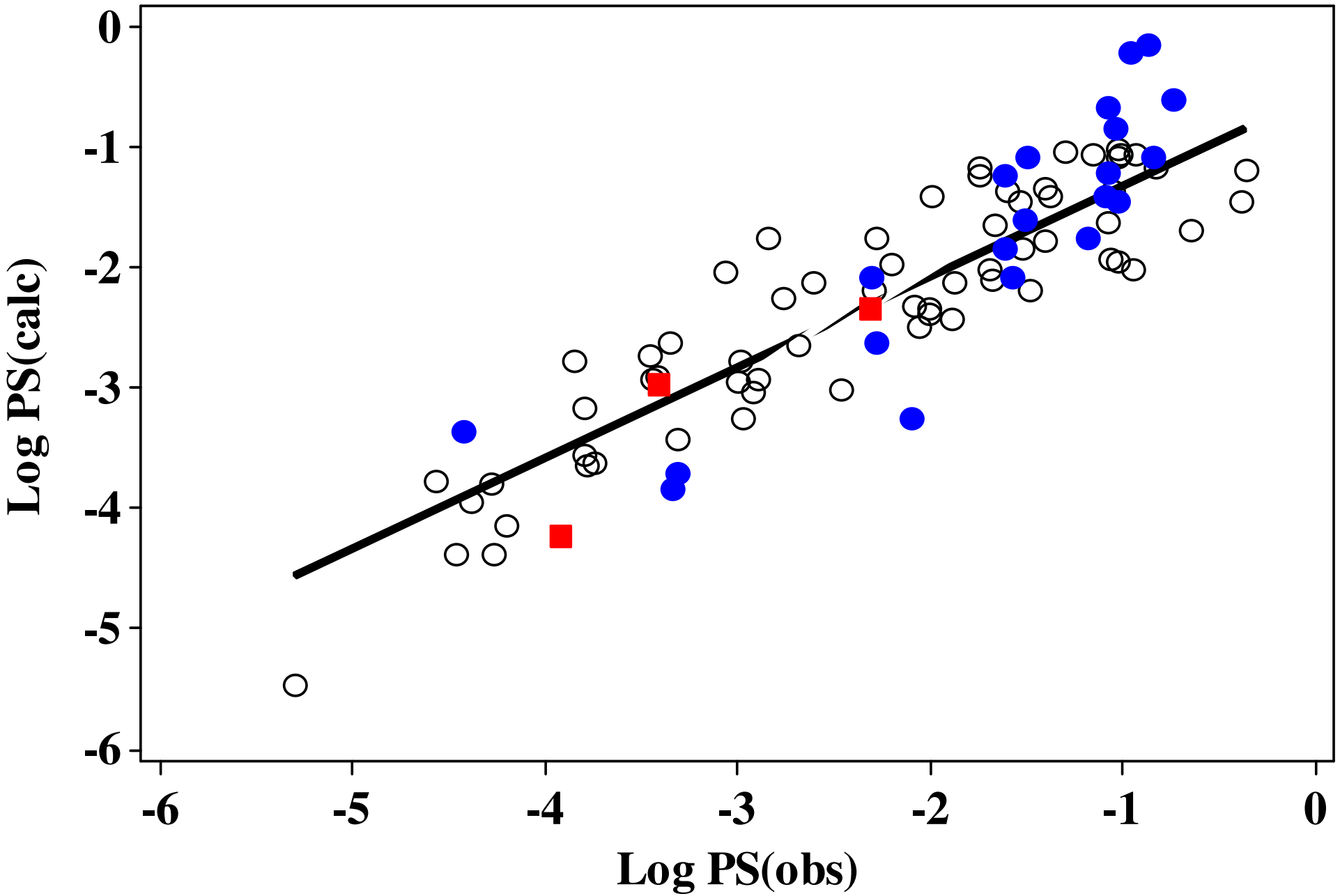
J. Pharm. Sci., 2011, 100, 1690-1701.

$$\text{Log PmS} = -1.268 - 0.047\,E - 0.876\,S - 0.719\,A$$

$$- 1.571\,B + 1.767\,V + 0.469\,J^{+} + 1.663\,J^{-}$$

$$N = 88,\ R^2 = 0.810,\ SD = 0.534,\ F = 48.8$$

Acid/acid anion = 120 Base/base cation = 10


0
-1
-2
-3
-4
-5
-6
Log PS(calc)
-6
-5
-4
-3
-2
-1
0
Log PS(obs)

Human Intestinal Absorption %

HIA = 95.6 -2.3 E – 0.4 S -14.3 A -21.4 B +16.5V

Neutrals, N = 257, SD = 15.1%, R^2 = 0.605

HIA = 100.0 +0.7 E – 6.0 S -6.3 A – 25.5 B

+ 20.6 V - 5.9 J^+ + 29.2 J^-

Neutral/Ions, N = 257, SD = 15.5%, R^2 = 0.588

Acid – Anion = 3%, Base-Cation = 1%,

Log k = 0.553 + 0.003 E – 0.105 S – 0.083 A

-0.388 B + 0.310 V + 0.083 J+ + 0.464 J-

N = 257, SD = 0.238, R2 = 0.605, F = 54.5

Acid/Acid anions = 1.39, Base/BaseH+ = 1.25

- **Structural effects are very small**
- **Acid anions and base cations absorbed at almost the same rate as the neutral species.**

Analysis of Permeation

Observed quantity, Pm*S

$$Pm = P*Diff/L$$

$$\text{Log } Pm*S = \log P + \log Diff + \text{constant}$$

$$\text{Log } Pm*S \approx \log P + \text{constant}$$

Log P for water - membrane perfusion

Log k for human intestinal absorption

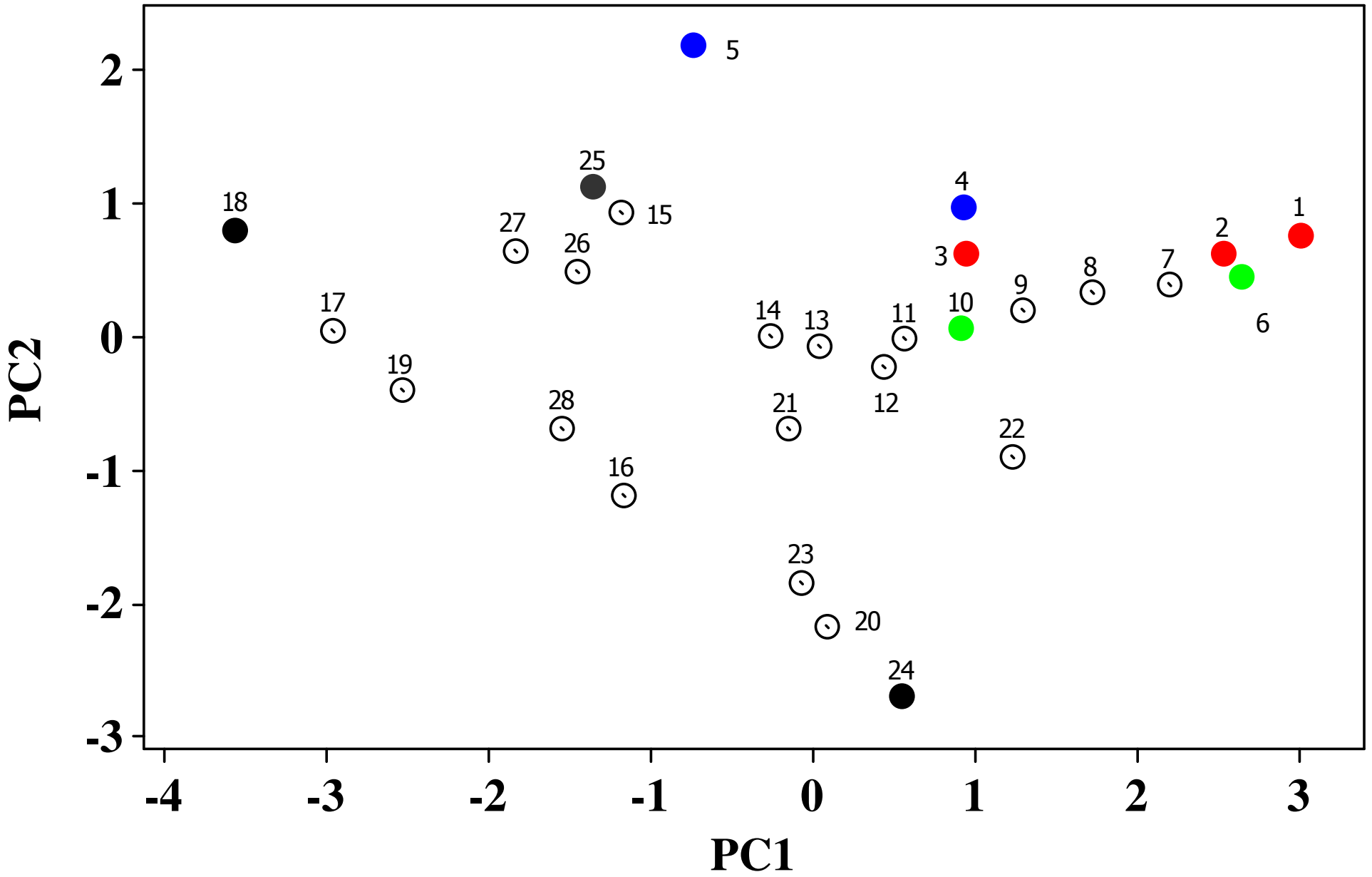
Log P for water - solvents

Log K for water- liposome (Esher)

Log K for water- cerasome

Log Diff for diffusion in water

Compare coefficients by PCA


PC2
PC1
2
1
0
-1
-2
-3
-4
-3
-2
-1
0
1
2
3
5
25
18
15
27
26
4
3
1
2
6
17
14
13
11
10
9
8
7
19
28
21
12
22
16
23
20
24

1	Log Diff	6	10 % Ethanol
2	Log k(HIA)	10	50 % Ethanol
3	Log PS	18	Hexadecane
4	Log K(Cerasome)	24	Nitromethane
5	Log K(Esher)	25	Wet octanol

Conclusions

HIA very close to simple diffusion.

Neutral species and ions diffuse at almost the same rate.

Hence strong bases and strong acids are absorbed no matter if ionized or not.

Base/cation = 1.25 Acid/ anion = 1.39

Permeation from saline

1. **Partition from water into a very polar part of the membrane, that is close to 50% ethanol- 50% water in properties. Structural effects on this partition lead to obs PS values.**

2. **Structural effects in the subsequent diffusion across the nonpolar part of the membrane are relatively small**

3. **Neutral species permeate faster than ions.**

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