Hydrophobicity descriptors resulting from bimodal LC behavior (RP and HILIC)

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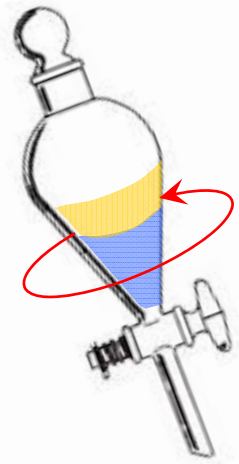
Hydrophobicity: the physical property of a molecule that is seemengly repelled from a mass of water.

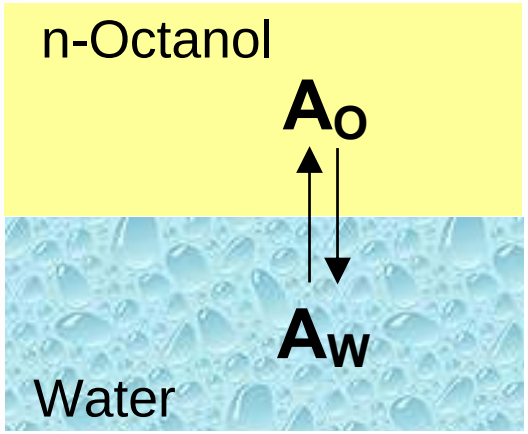
Lipophilicity (as an extension of the hydrophobic character): includes favorable interactions that contribute to the distribution of a chemical entity between water and other solubilizing media, representing a manifestation of the characteristics of the system in which the solute is placed.

log $K_{o/w}$ or simply, log P: a measure of the lipophilic character.

S.K. Poole, S.F. Poole, J. Chromatogr. B, 797 (2003) 3-19.

Experimental determination of log P: the shake flask method





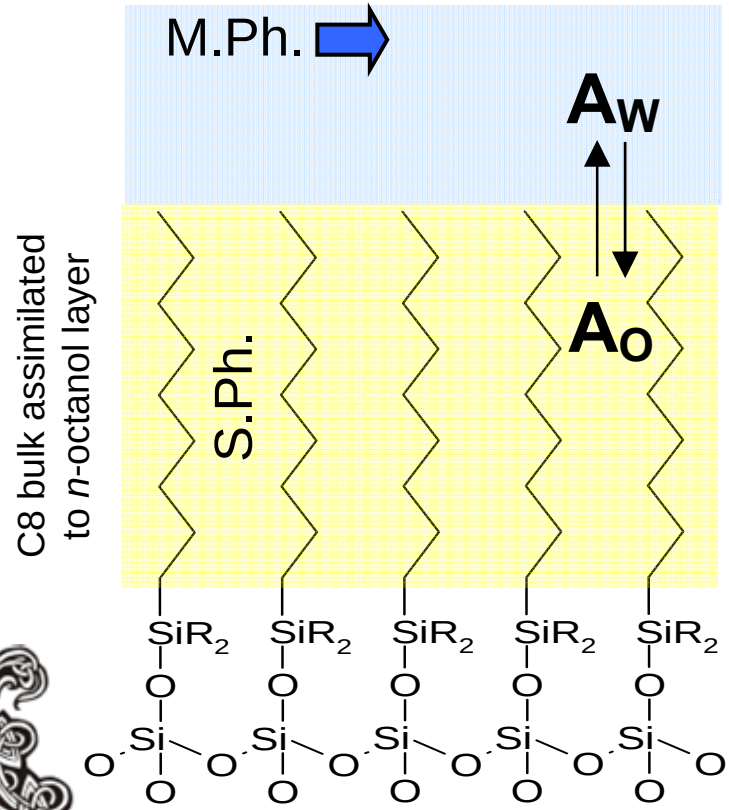
$$K_{O/W} = \frac{[A]_O}{[A]_W}$$

1. If $[A]_o$ or $[A]_W$ are ↘↘, very sensitive methods are necessary for assaying A.

2. Mutual relative solubility of the two media (*n*-octanol in water and water in *n*-octanol, respectively). i.e. - solubility of *n*-octanol in water at 25 ^oC is 0.56 g/L.

log P from chromatographic retention data:

$$K_A = \frac{[A]_{S.Ph.}}{[A]_{M.Ph}} = k \times \frac{V_{M.Ph.}}{V_{S.Ph.}} = k \times \beta$$

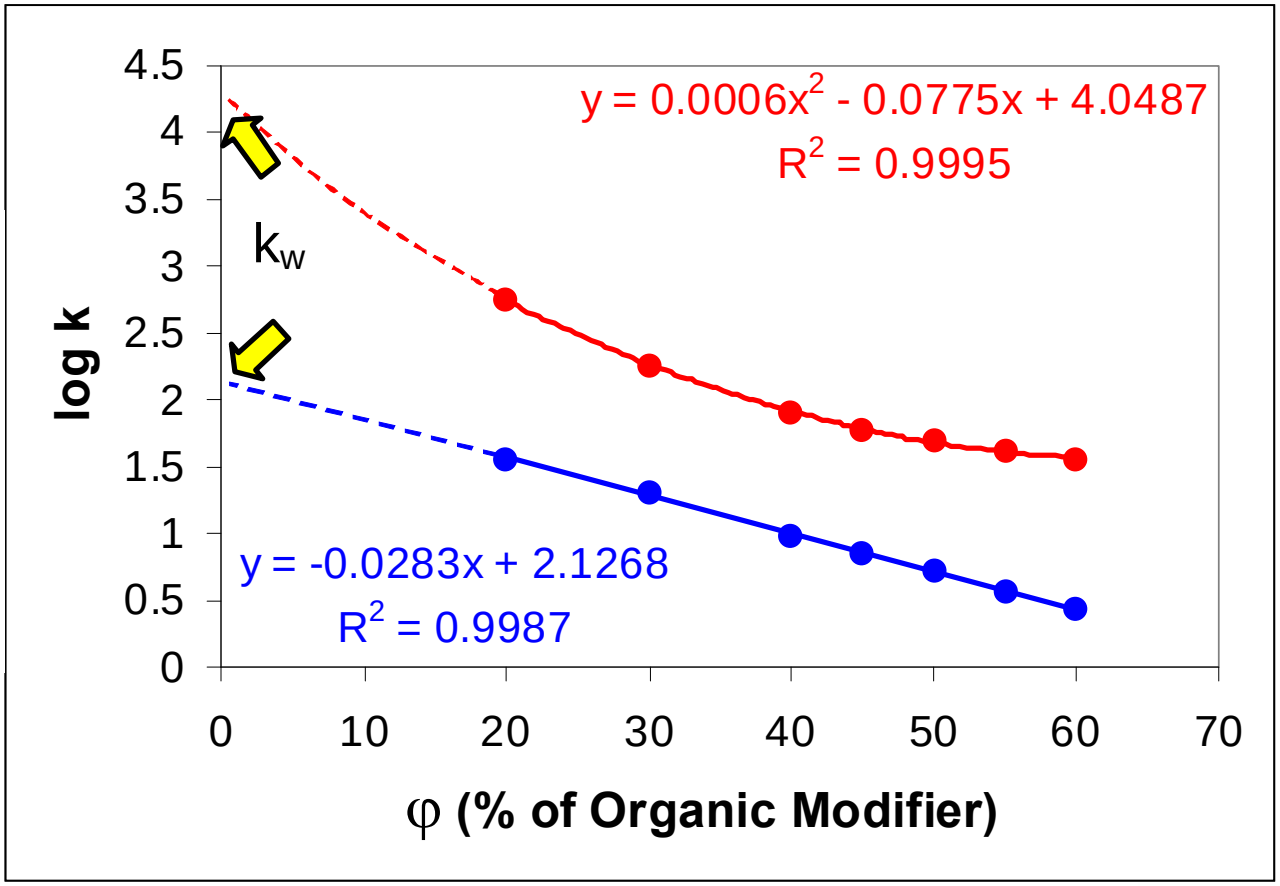


if k_W is the retention factor for a hypothetical M.Ph. composition containing 0% Organic Modifier:

$$K_{O/W}^{A} = k_W \times \beta;$$

$$\log\left(K_{O/W}^{A}\right) = \log P^{A} = \log\left(k_W\right) + Log\left(\beta\right)$$

Some limitations of the model:

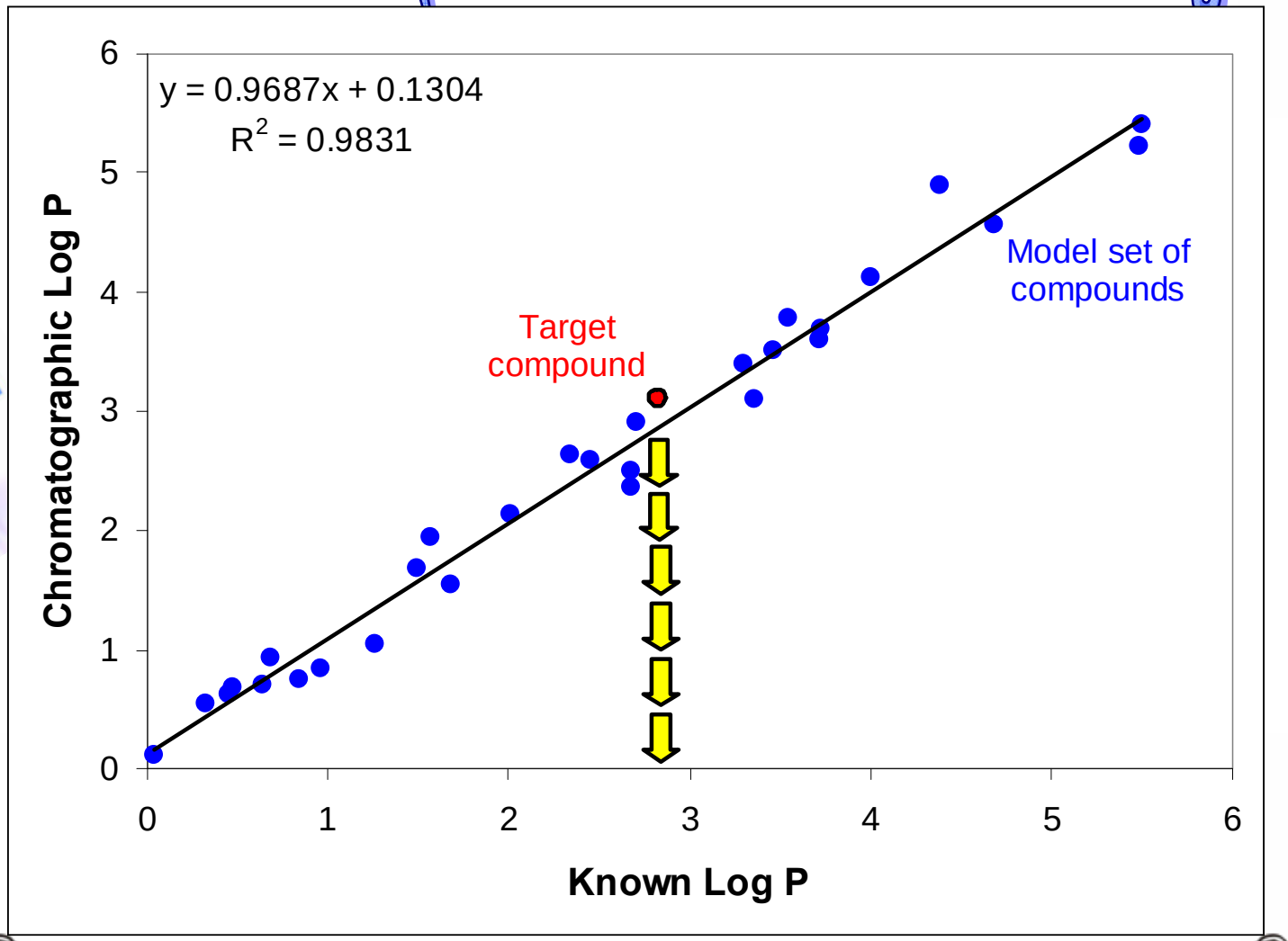


$$\log P = a \log k_W + bS + c$$

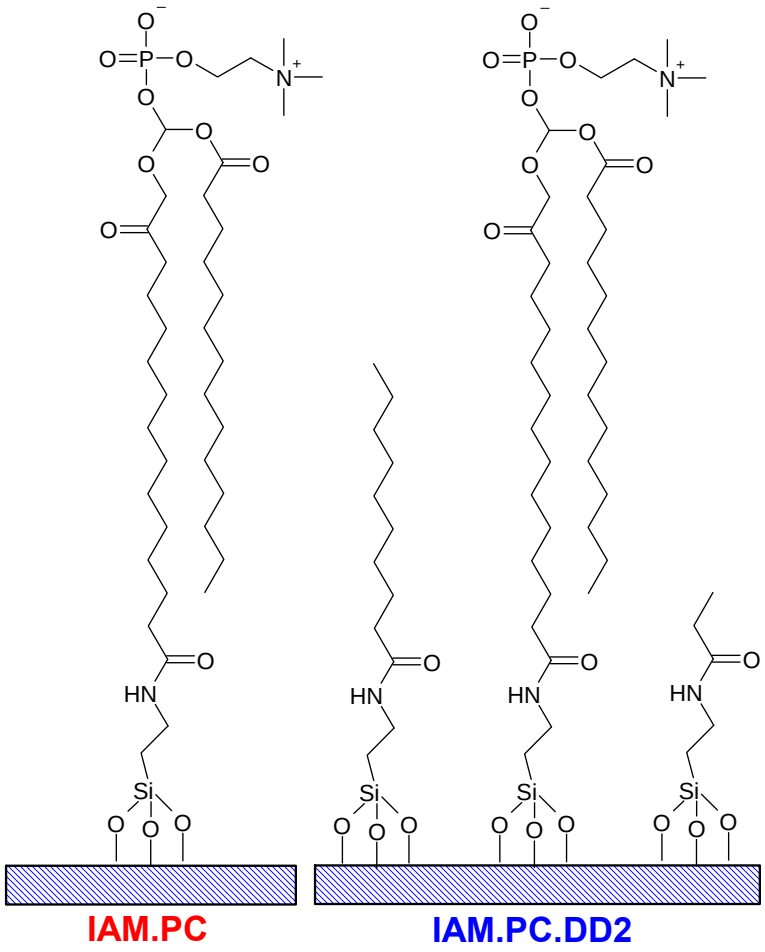
S is the slope of the linear regression,
a, b, c are characteristics of the S.Ph.

K. Valko, V. Slegeli, J. Chromatogr. A, 631 (1993) 49-61.

The best solution (however a time consumming one):



Special Stationary Phases for chromatographiclog P determination: Biomimetic S.Ph. (artificial membranes, liposomes)



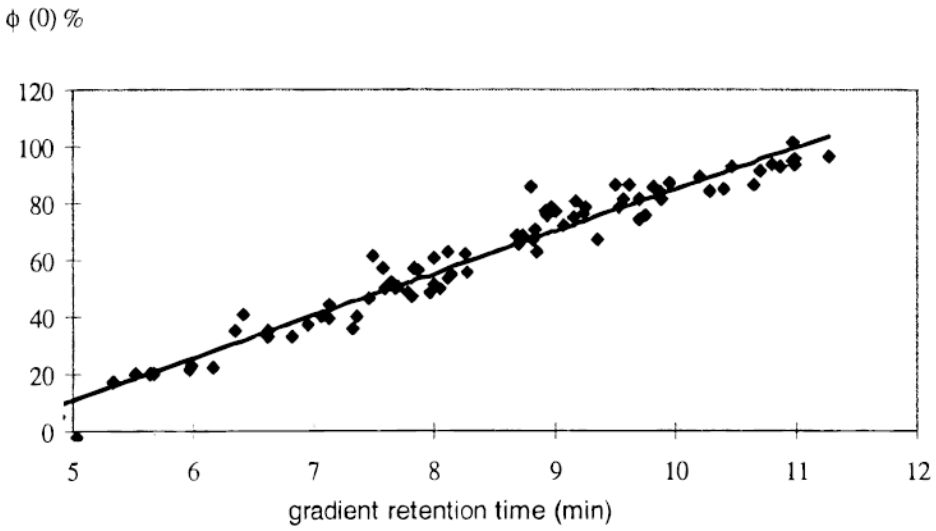
C. Pidgeon, et al., J. Med. Chem., 38 (1995) 590-594.

The CHI lipophilicity scale

The CHI scale: % (v) of ACN required to achieve an equal distribution of the compound between M.Ph. and S. Ph.

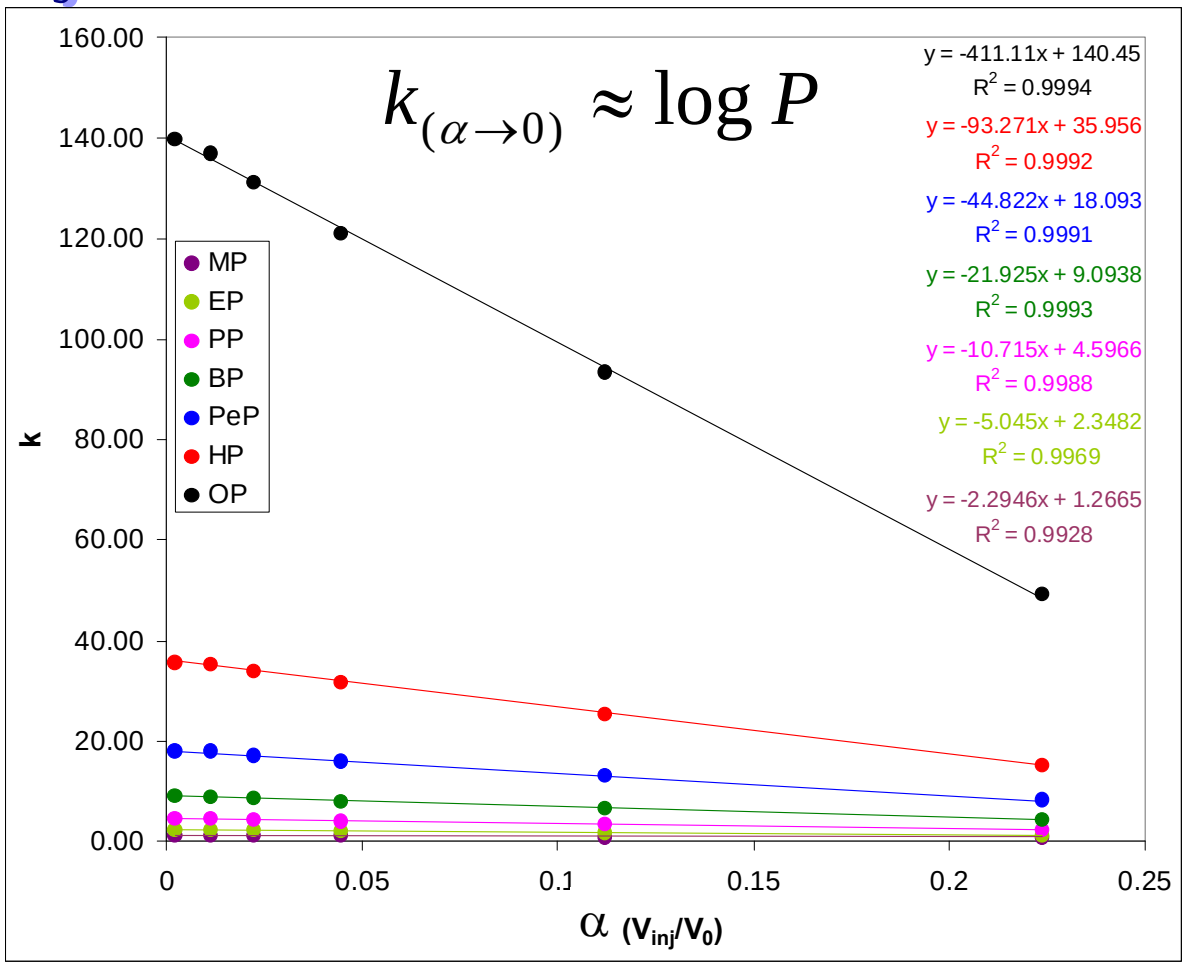
Gradient elution conditions!

$$t_R = f(-\frac{\log k_W}{S})$$



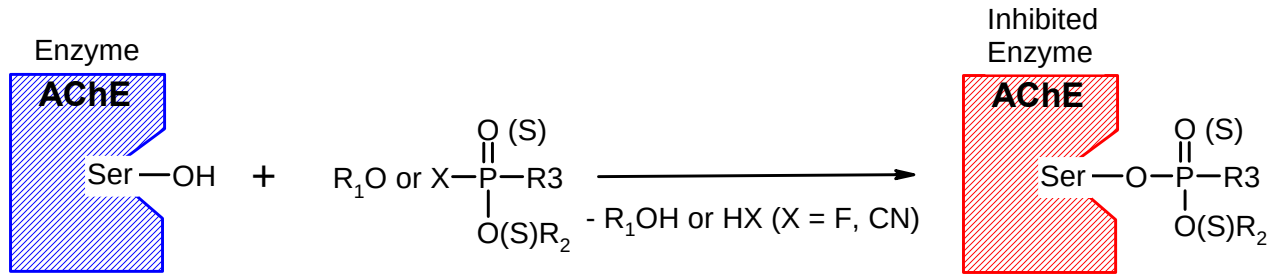
K. Valko, C. Bevan, D. Reynolds, Anal. Chem., 69 (1997) 2022-2029.

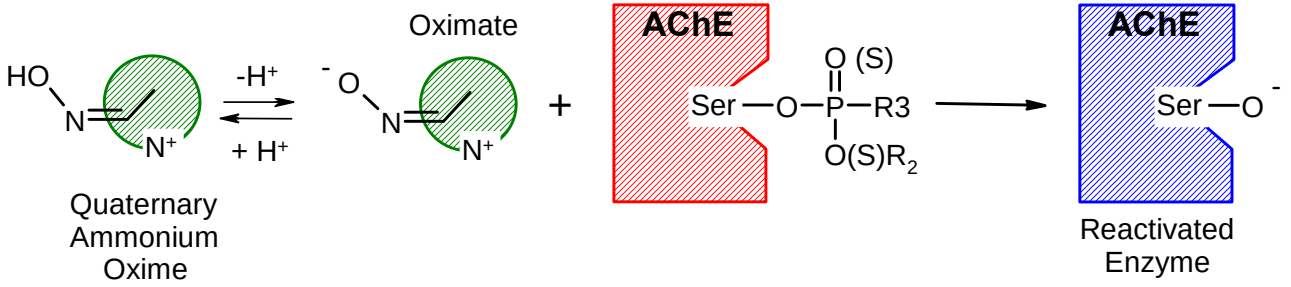
Lipophilicity scale from LVI studies in M.Ph. non-miscible diluents



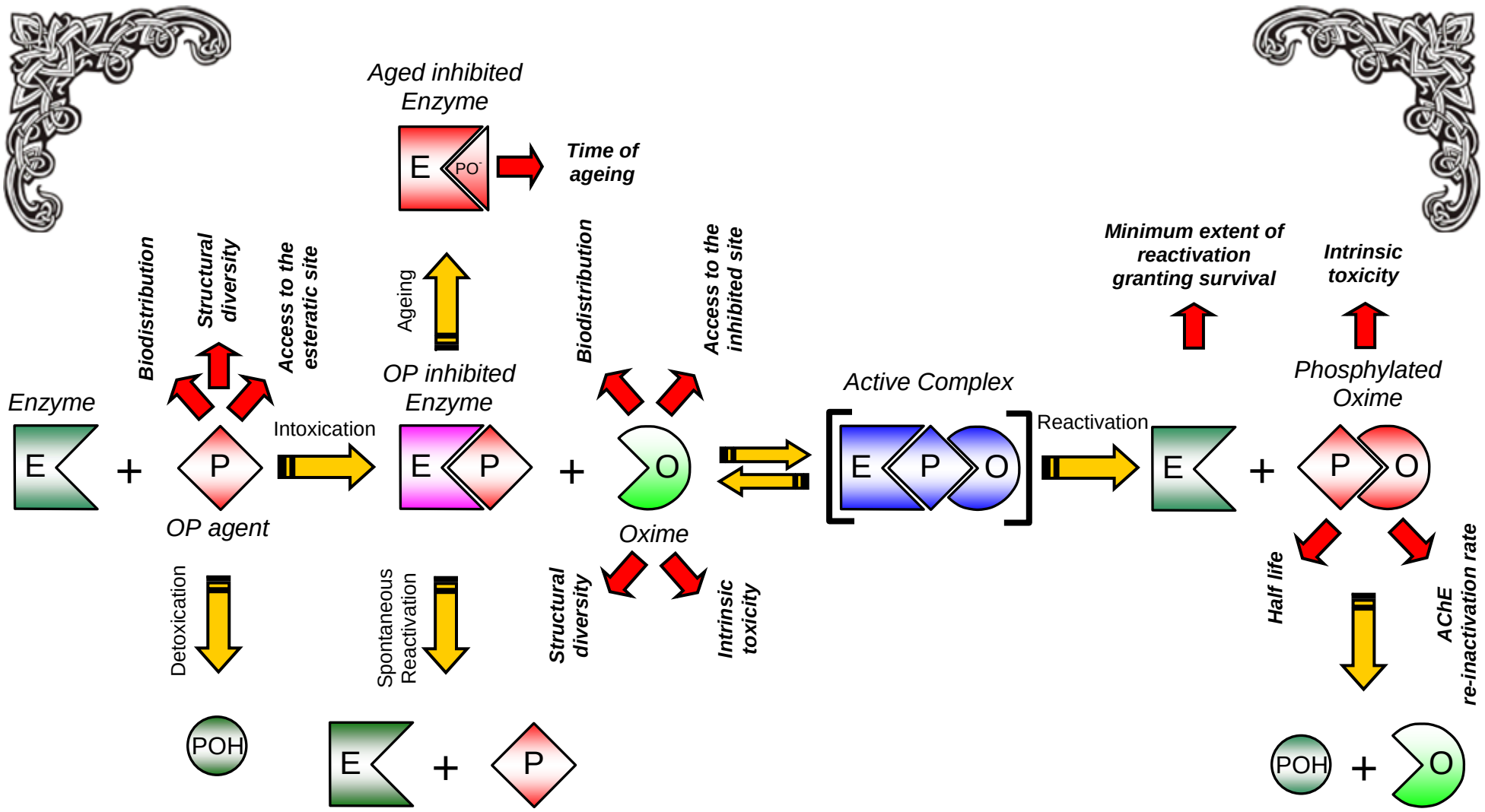
C. Sarbu, R.D. Nascu-Briciu, D. Casoni, A. Kot-Wasik, J. Namiesnik, J. Chromatogr. A, 1266 (2012) 536-544.

Quaternary Oximes: reactivators of phosphylated AChE





V. Voicu, F.S. Radulescu, D., A. Medvedovici, EOMT, 9 (2013) 31-50.



Complex scenarion of OP intoxication / AChE reactivation by oximes

Poor penetrability of oximes through biological barriers!

$$Log\,(BB) = \left[\frac{[A]_{Brain}}{[A]_{Blood}}\right]_{SS}$$

Log(BB) ∈ [-2 ÷ 1] [1]

Favorable distribution: Log(BB) > 0.3;
Poor Distribution: Log(BB) < -1;

Log(BB) = f (*molecular mass – Mw; hydrophobic character – log P; polar surface area – PSA; n°. of rotatable bonds; n°. of H-bond donors; n°. of H-bond acceptors; 3D-molecular field descriptors; electropological state indices; critical micelle concentration – CMC_D; cross sectional area – A_D; permeability coefficient – PC; polarizability – CMR … and others*)

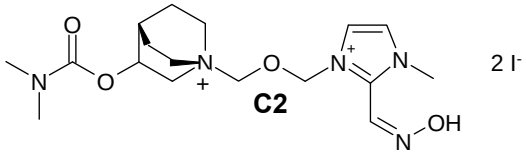
Successful CNS Drug [2]

Descriptor	*Condition*	*Descriptor*	*Condition*
Molecular weight	Mw < 450	Water solubility	S > 60 μg/mL
Hydrophobic character	Log P < 5	Metabolic stability	> 80% after 1 h
No. of H-bond donor	≤ 3	P450 enzyme CIP inhibition	< 50% at 30 μM
No. of H-bond acceptor	< 7	Metabolization by CYP2D6	Not significant
No. of rotatable bonds	< 8	CYP3A4 inducer	No potent
Polar surface area	PSA < 60÷70 $Å^2$	P-glycoprotein substrate	No
H-bonds	<8	Affinity to serum albumin	K_D < 10 μM
Acid character	pK_a ∈ [7.5÷10.5]	Effective permeability	> 1×10^{-6} cm/sec

(1) *M.H. Abraham et al., J. Pharm.Sci., 86 (1992) 310-315.*
(2) *H. Pajouhesh, G.R. Lenz, NeuroRx®, 2 (2005) 541-553.*

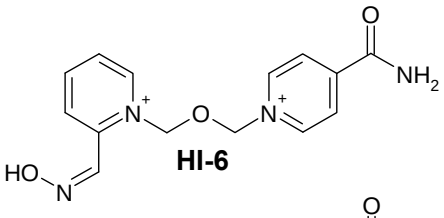
Attempts to determine log P of QO from chromatographic retention data

PAM
(Pralidoxime)

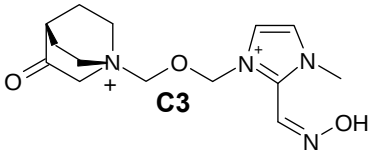


C2

2 I⁻

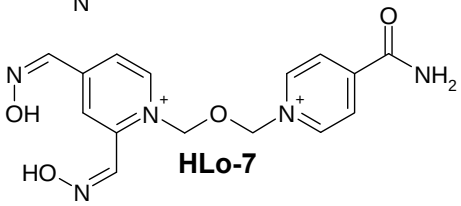


HI-6

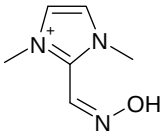


C3

2 I⁻

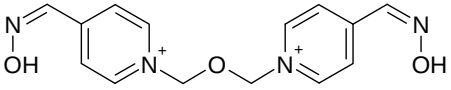


HLo-7



C4

I⁻



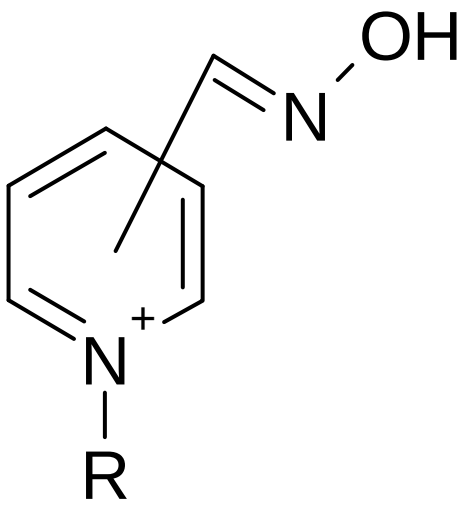
LuH-6
(Obidoxime)

RP (C8); IP (C8); RP (PFP); HILIC; ZIC-HILIC; AGP

Elution at 37 °C, with 0.9% NaCl in the aqueous component of the M.Ph.

V. Voicu, I. Sora, C. Sarbu, V. David, A. Medvedovici, J. Pharm. Biomed. Anal., 52 (2010) 508-516.

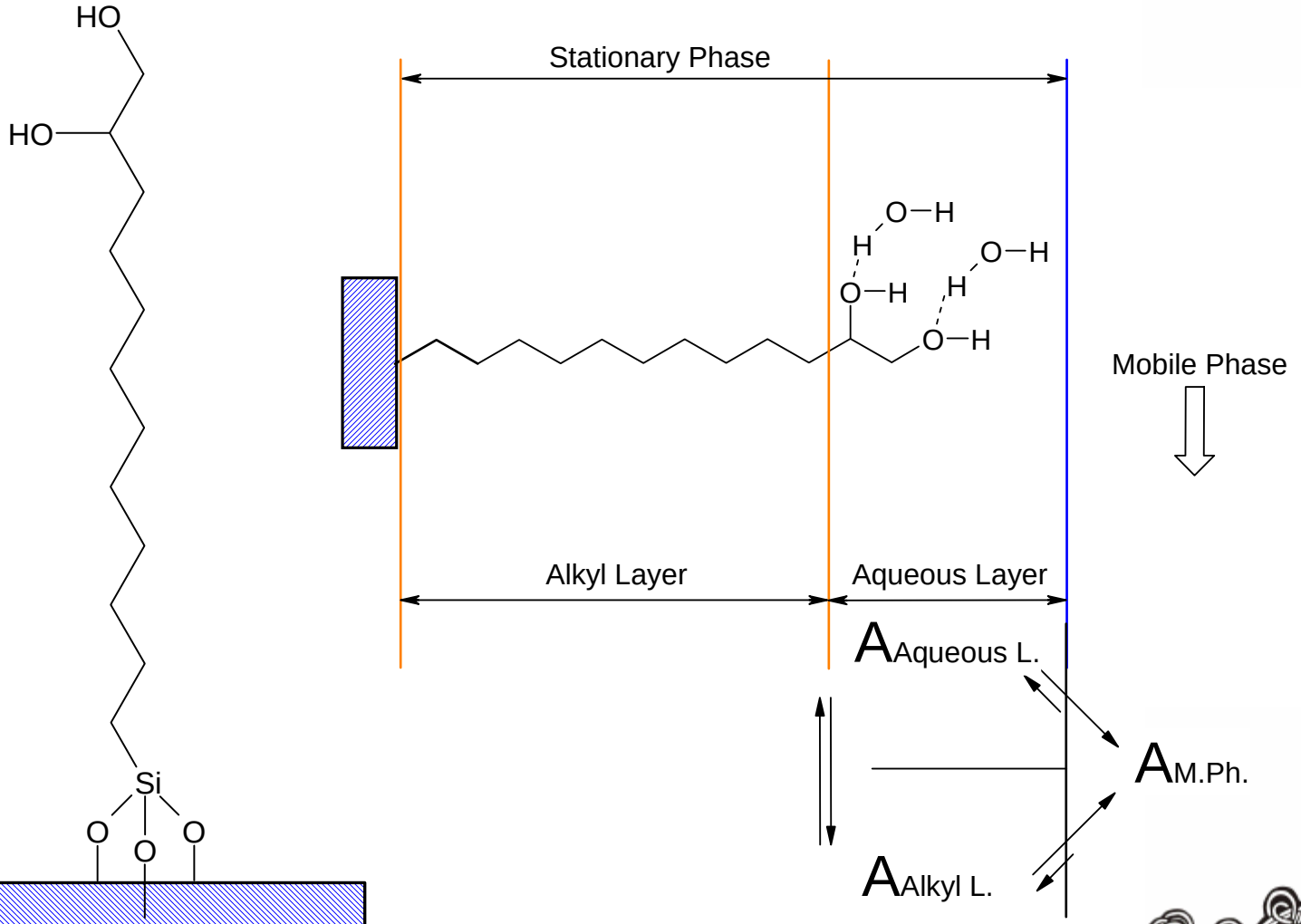
Newly synthesized oximes:
Target: increasing log P to increase log BB



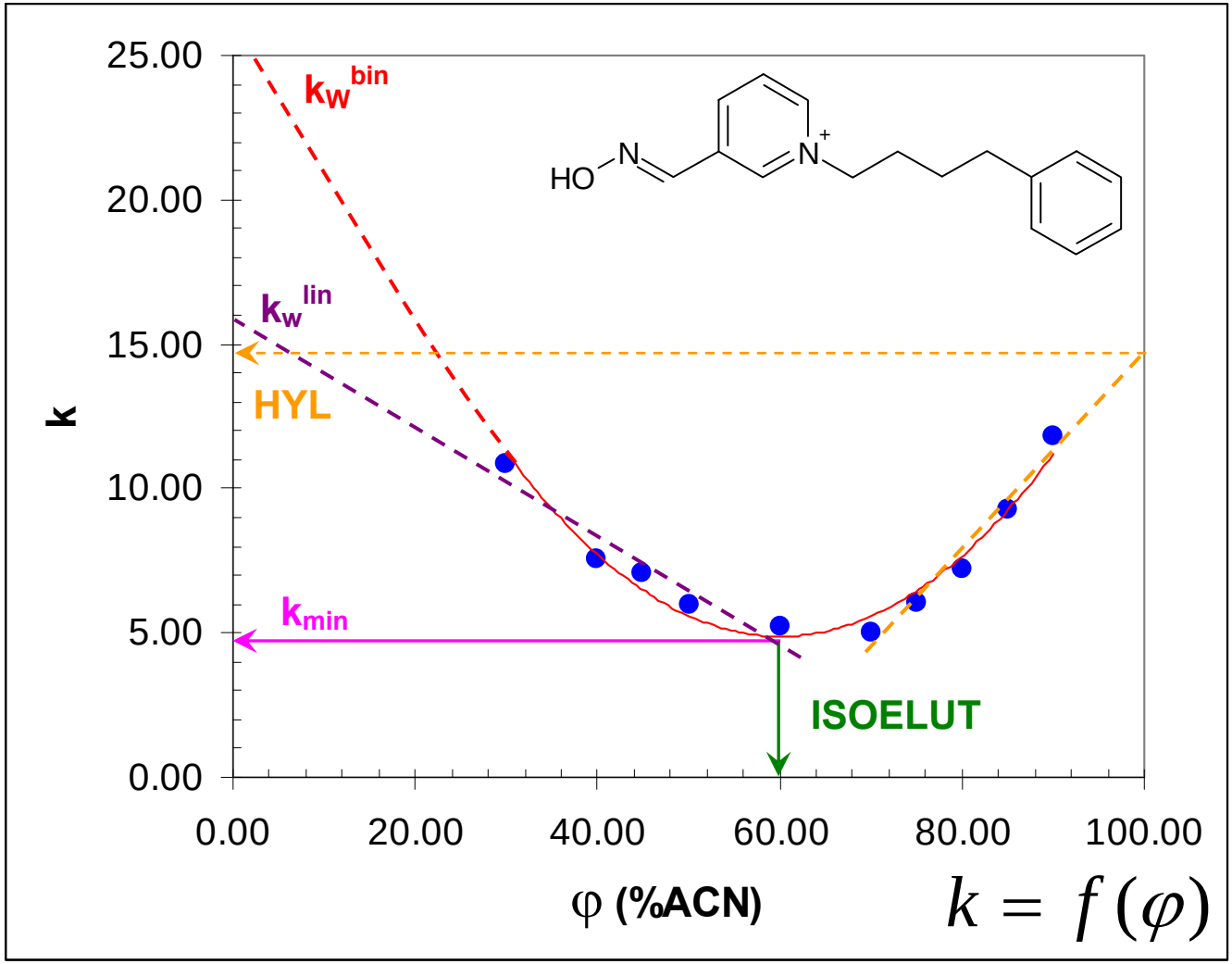
#	Substituent (R) Name	Substituent (R) Formula	Position of the oxime moiety	Acronym(s)
1	Ethyl	$-C_2H_5$	2, 3, 4	2-PAE, 3-PAE, 4-PAE
2	Butyl	$-C_4H_9$	2, 3	2-PAB, 3-PAB
3	Hexyl	$-C_6H_{13}$	2, 3, 4	2-PAH, 3-PAH, 4-PAH
4	Octyl	$-C_8H_{17}$	2, 3, 4	2-PAO, 3-PAO, 4-PAO
5	Decyl	$-C_{10}H_{21}$	2, 3	2-PAD, 3-PAD
6	Dodecyl (Lauryl)	$-C_{12}H_{25}$	2, 3, 4	2-PAL, 3-PAL, 4-PAL
7	Benzyl	$-CH_2-C_6H_5$	2, 3, 4	2-PABn, 3-PABn, 4-PABn
8	Ethyl-phenyl	$-(CH_2)_2-C_6H_5$	2, 3, 4	2-PAPE, 3-PAPE, 4-PAPE
9	Propyl-phenyl	$-(CH_2)_3-C_6H_5$	3	3-PAPP
10	Butyl-phenyl	$-(CH_2)_4-C_6H_5$	3, 4	3-PAPB, 4-PAPB
11	4-Methylbenzyl	$-CH_2-C_6H_4-CH_3$	2, 3, 4	2-PAMB, 3-PAMB, 4-PAMB
12	4-*t*-Butylbenzyl	$-CH_2-C_6H_4-C(CH_3)_3$	3, 4	3-PATB, 4-PATB

H. Ohta, T. Ohmori, S. Suzuki, H. Ykegaya, K. Sakurada, T. Takatori, Pharm. Res., 23 (2006) 2827-2833.

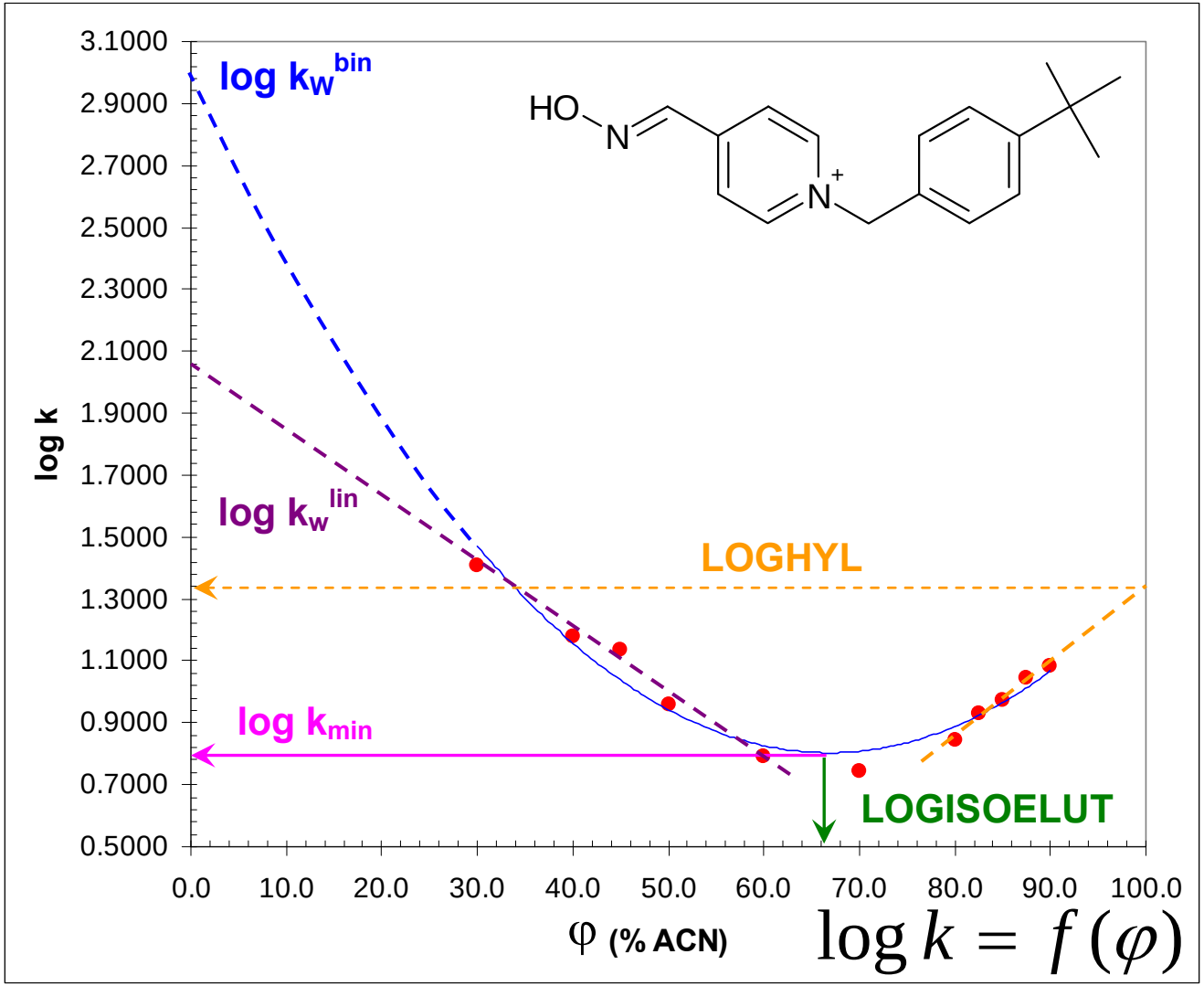
The stationary phase: A bimodal action (RP + HILIC)!



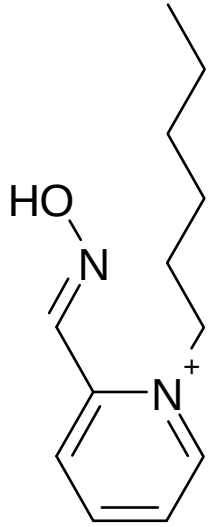
Results: "U" shaped retention profiles (I)

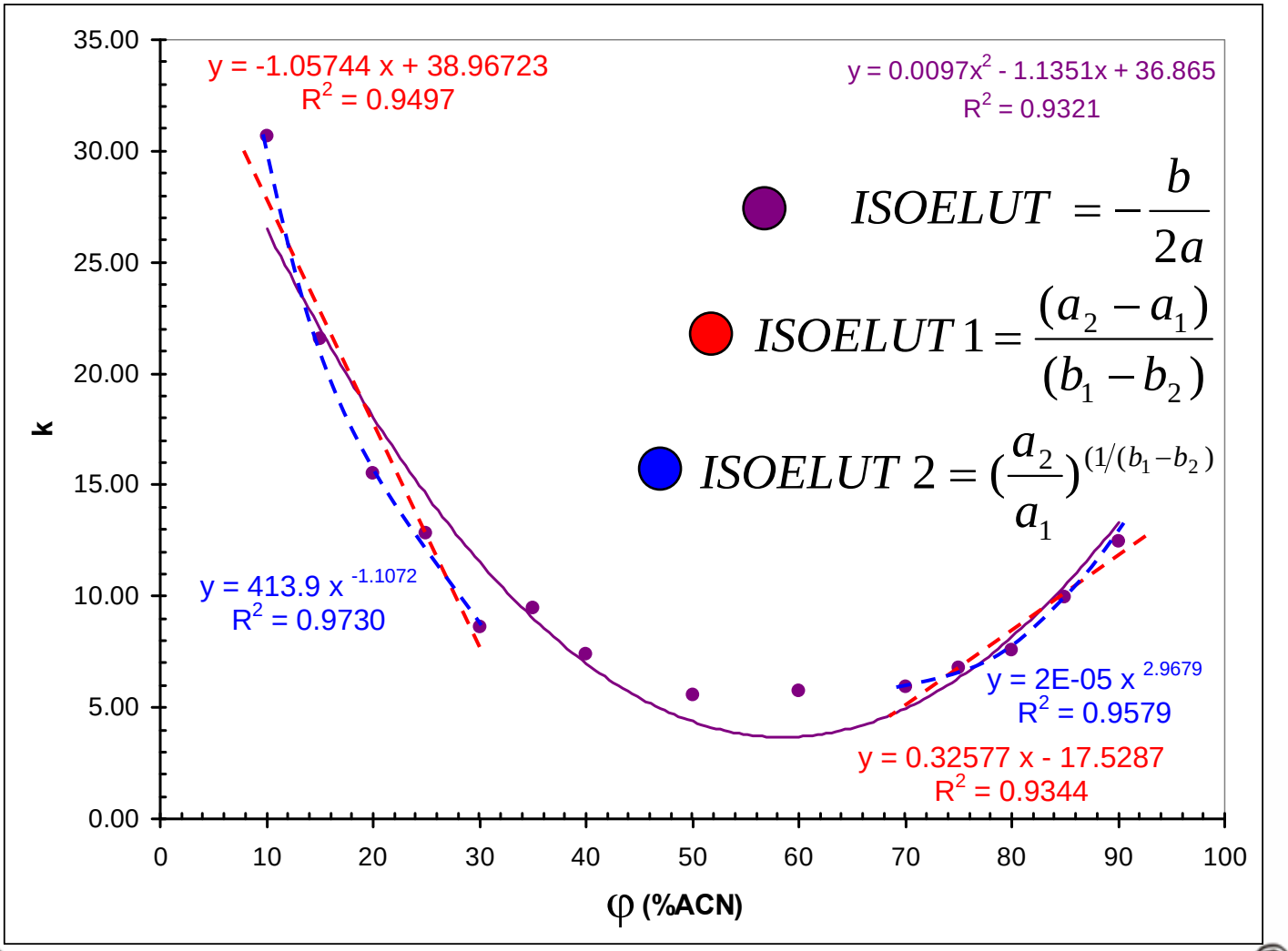


Results: "U" shaped retention profiles (II)

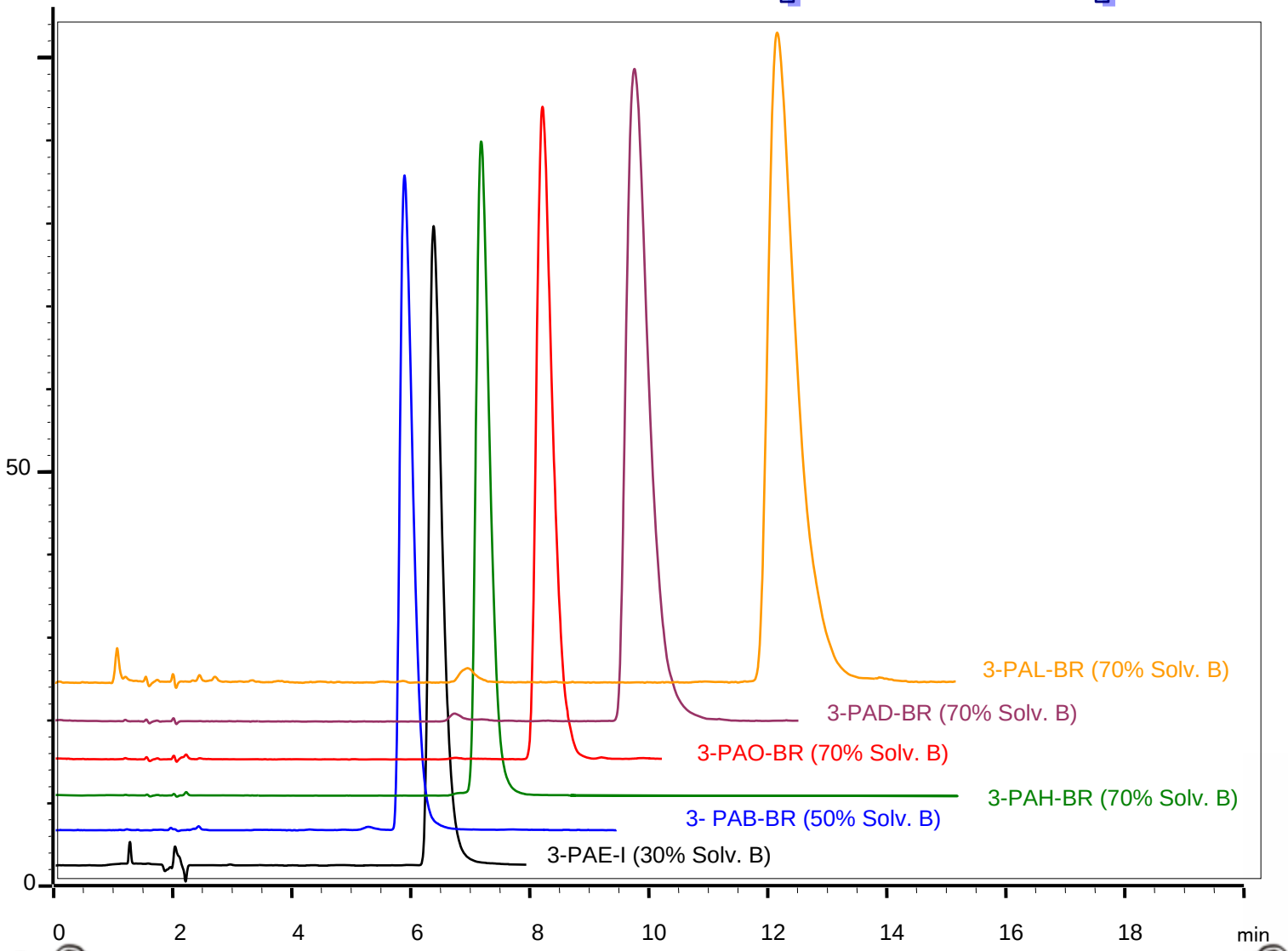


(LOG)ISOLELUT determination alternatives

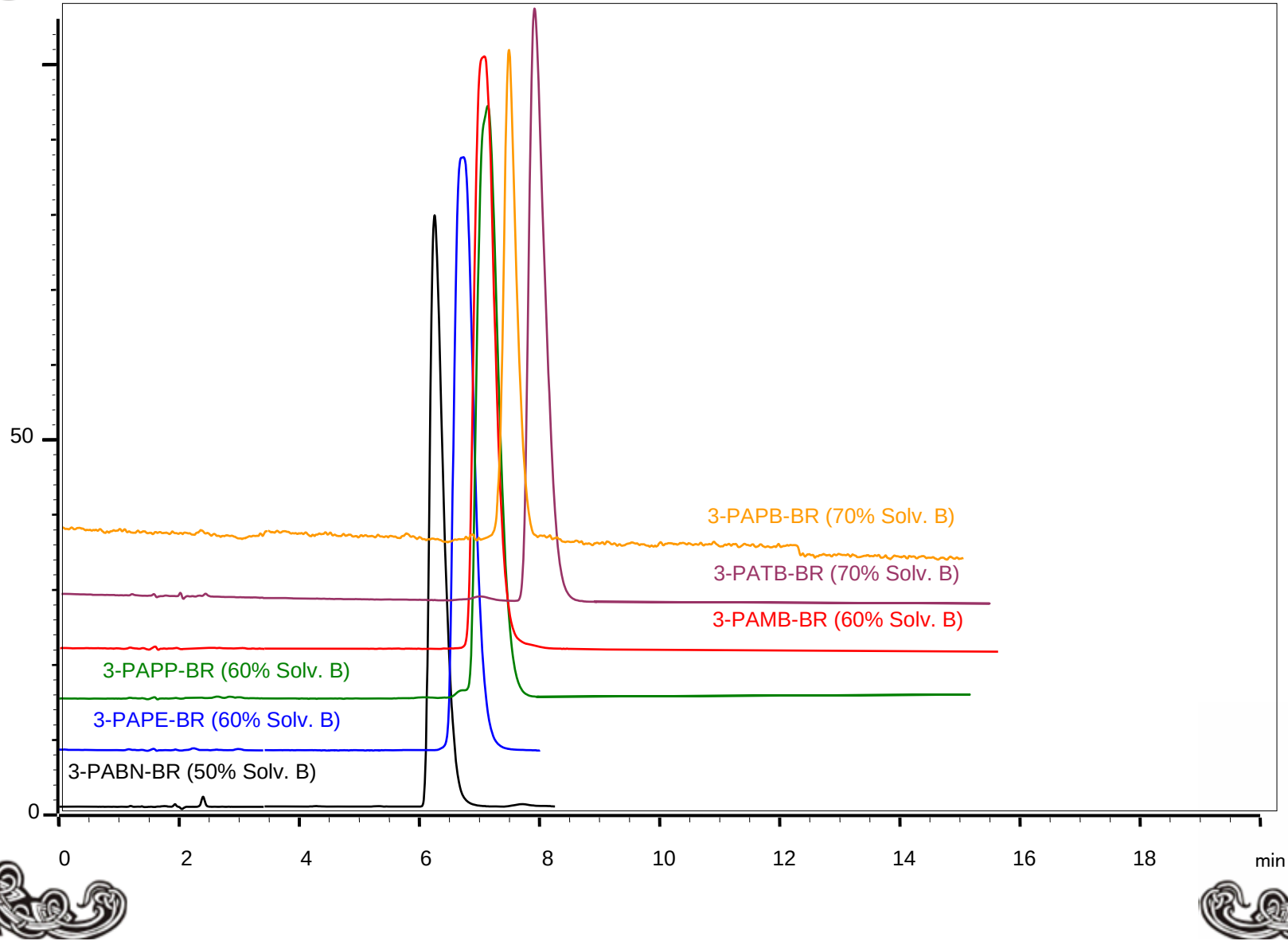




No concerns about peak shapes!



No concerns about peak shapes!



Correlation between determined indices and calculated log P values.

Correlated sets	Correlation Coefficients										
	ALOGPs	AC logP	miLogP	KOWWIN	XLOGP2	XLOGP3	Hy	MLOGP	ALOGP	LogD7	SlogD7.4
k_{min}	0.958	0.977	0.934	0.963	0.977	0.983	-0.758	0.935	0.943	0.884	0.969
log k_{min}	0.938	0.977	0.927	0.973	0.964	0.978	-0.849	0.954	0.944	0.918	0.969
ISOELUT	0.842	0.915	0.835	0.942	0.895	0.899	-0.891	0.914	0.904	0.931	0.902
LOG ISOELUT	0.809	0.881	0.810	0.904	0.865	0.873	-0.874	0.880	0.855	0.894	0.864
ISOELUT 1	0.479	0.512	0.460	0.508	0.484	0.529	-0.518	0.577	0.393	0.537	0.503
LOG ISOELUT 1	0.678	0.740	0.661	0.752	0.700	0.750	-0.817	0.806	0.640	0.788	0.738
ISOELUT 2	0.552	0.598	0.526	0.602	0.558	0.621	-0.730	0.668	0.493	0.642	0.609
LOG ISOELUT2	0.193	0.209	0.117	0.214	0.201	0.226	-0.267	0.240	0.135	0.232	0.227
k_w^{lin}	0.788	0.784	0.767	0.753	0.793	0.787	-0.546	0.803	0.770	0.652	0.770
log k_w^{lin}	0.847	0.862	0.836	0.843	0.862	0.863	-0.672	0.878	0.840	0.766	0.845
k_w^{bin}	0.754	0.812	0.756	0.787	0.817	0.800	-0.570	0.814	0.778	0.714	0.771
log k_w^{bin}	0.139	0.278	0.202	0.304	0.246	0.239	-0.377	0.257	0.259	0.374	0.230
HYL	0.488	0.472	0.479	0.413	0.458	0.502	-0.327	0.520	0.363	0.363	0.464
LOG HYL	0.430	0.405	0.420	0.346	0.400	0.440	-0.245	0.464	0.298	0.291	0.396

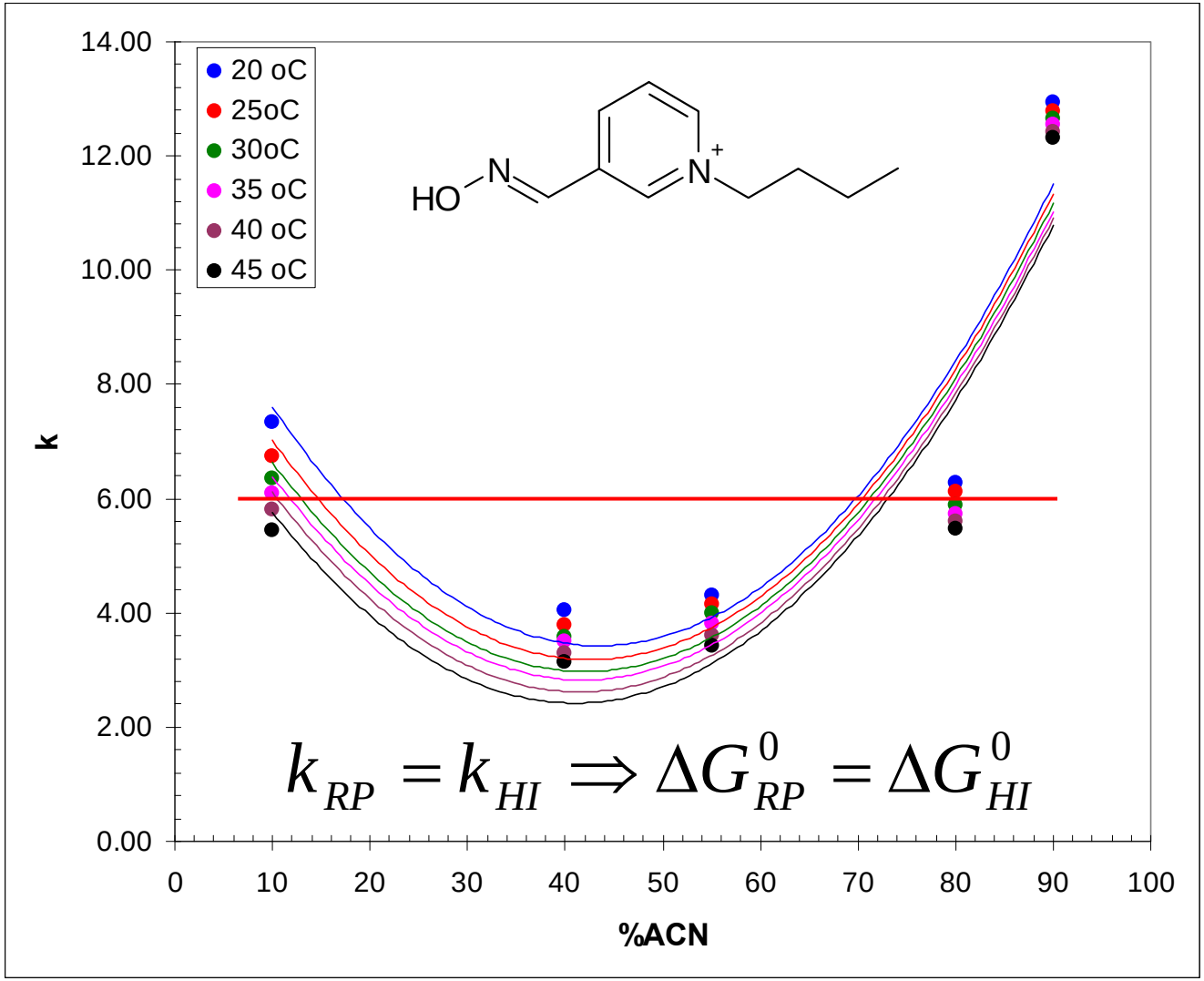
V. Voicu, C. Sarbu, F. Tache, F. Micale, S.F. Radulescu, K. Sakurada, H. Ohta, A. Medvedovici, Talanta, 122 (2014) 172-179.

Correlations to other descriptor sets:

Descriptors	Mw	Mol.Vol.	Diff. Coef.	P_{eff}	Log (MDCK COS)	P_{cornea}	Log (Sw)	Log (FaSSGF)	Log (FaSSIF)	Log (FeSSIF)	LogBBB	PrUnbnd	Vd
k_{min}	0.861	0.946	-0.887	0.711	-0.764	0.304	-0.899	-0.969	-0.859	-0.894	0.852	-0.416	0.889
log k_{min}	0.909	0.967	-0.953	0.726	-0.728	0.401	-0.939	-0.966	-0.924	-0.932	0.792	-0.539	0.884
ISOELUT	0.929	0.950	-0.971	0.776	-0.707	0.512	-0.941	-0.923	-0.931	-0.949	0.648	-0.629	0.849
LOG ISOELUT	0.894	0.914	-0.947	0.729	-0.633	0.486	-0.900	-0.884	-0.905	-0.905	0.647	-0.622	0.836
k_w^{lin}	0.600	0.720	-0.717	0.438	-0.687	0.105	-0.661	-0.736	-0.673	-0.708	0.754	-0.205	0.629
log k_w^{lin}	0.724	0.820	-0.822	0.544	-0.709	0.217	-0.774	-0.827	-0.777	-0.809	0.768	-0.339	0.732

M_w - molecular mass; **Mol. Vol.** - Molecular Volume: **Diff. Coeff.** – molecular diffusion coefficient in water; **P_{eff}** – human jejunal effective permeability; **log MDCK** – apparent MDCK COS permeability; **P_{cornea}** – permeability through rabbit cornea; **log(FaSSGF)** – solubility in fasted state simulated gastric fluid, **log(FaSSIF)** – solubility in fasted state simulated intestinal fluid, **log(FeSSIF)** – solubility in fed state simulated intestinal fluid; **Log BBB** - the logarithm of the brain/blood barrier; **PrUnbnd** – the percent unbound to blood plasma proteins; **V_d** – the pharmacokinetic volume of distribution in humans; by ADMET Predictor, vers. 5.0.0012, Simulation Plus Inc. (U.S.A)

Extra-analytical aspects of the bimodal behavior



Calculation of the Water layer volume acting as S.Ph. in HILIC

$$\Delta G^0_{RP} = \Delta H^0_{RP} - T \times \Delta S^0_{RP}; \Delta G^0_{RP} = \Delta H^0_{HILIC} - T \times \Delta S^0_{HILIC};$$

$$\ln k_{RP} = -B_{RP} \times \frac{1}{T} + A_{RP}; \ln k_{HILIC} = -B_{HILIC} \times \frac{1}{T} + A_{HILIC}$$

$$\Delta H^0_{RP} = -R \times B_{RP}; \Delta H^0_{HILIC} = -R \times B_{HILIC};$$

$$\frac{\Delta S^0}{R} + \ln \varphi = A; \frac{\Delta S^0}{R} = A - \ln \varphi; \Delta S^0 = R \times (A - \ln \frac{V_{FS}}{V_{FM}})$$

$$\Delta S^0_{RP} = R \times (A_{RP} - \ln \frac{V^{RP}_{FS}}{V_{FM}}); \Delta S^0_{HILIC} = R \times (A_{HILIC} - \ln \frac{V^{HILIC}_{FS}}{V_{FM}})$$

$$\Delta H^0_{RP} - \Delta H^0_{HILIC} = T \times (\Delta S^0_{RP} - \Delta S^0_{HILIC})$$

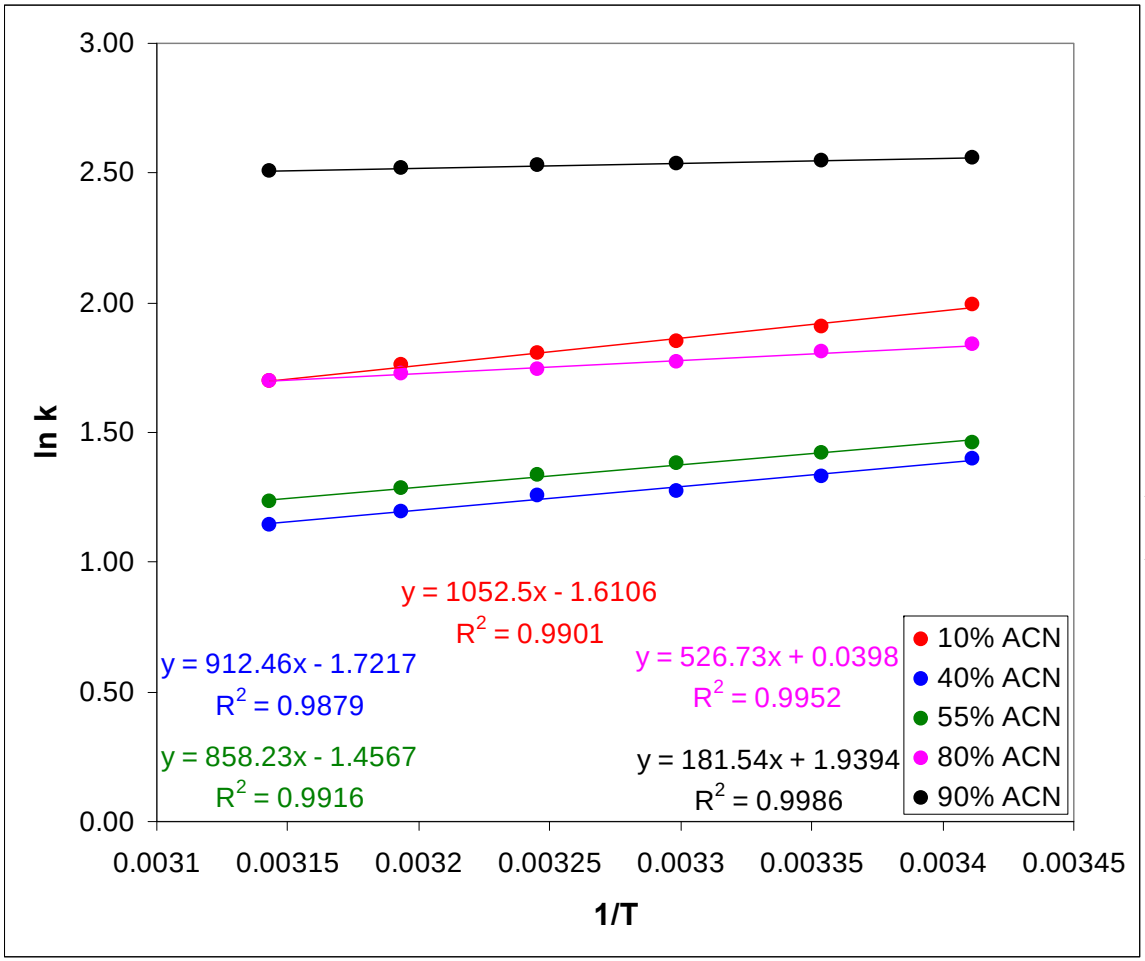
$$\frac{R \times (B_{HILIC} - B_{RP})}{T} = \Delta S^0_{RP} - \Delta S^0_{HILIC}$$

$$V^{HILIC}_{FS} = V^{RP}_{FS} \times 2.71828^{(e^{\frac{\Delta B^{HILIC/RP} + T\Delta A^{HILIC/RP}}{T}})}$$

van't Hoff plots and the final results:

$\Delta H^0_{RP} = -8.75 KJ/mol^0K$

$\Delta H^0_{HILIC} = -4.38 KJ/mol^0K$

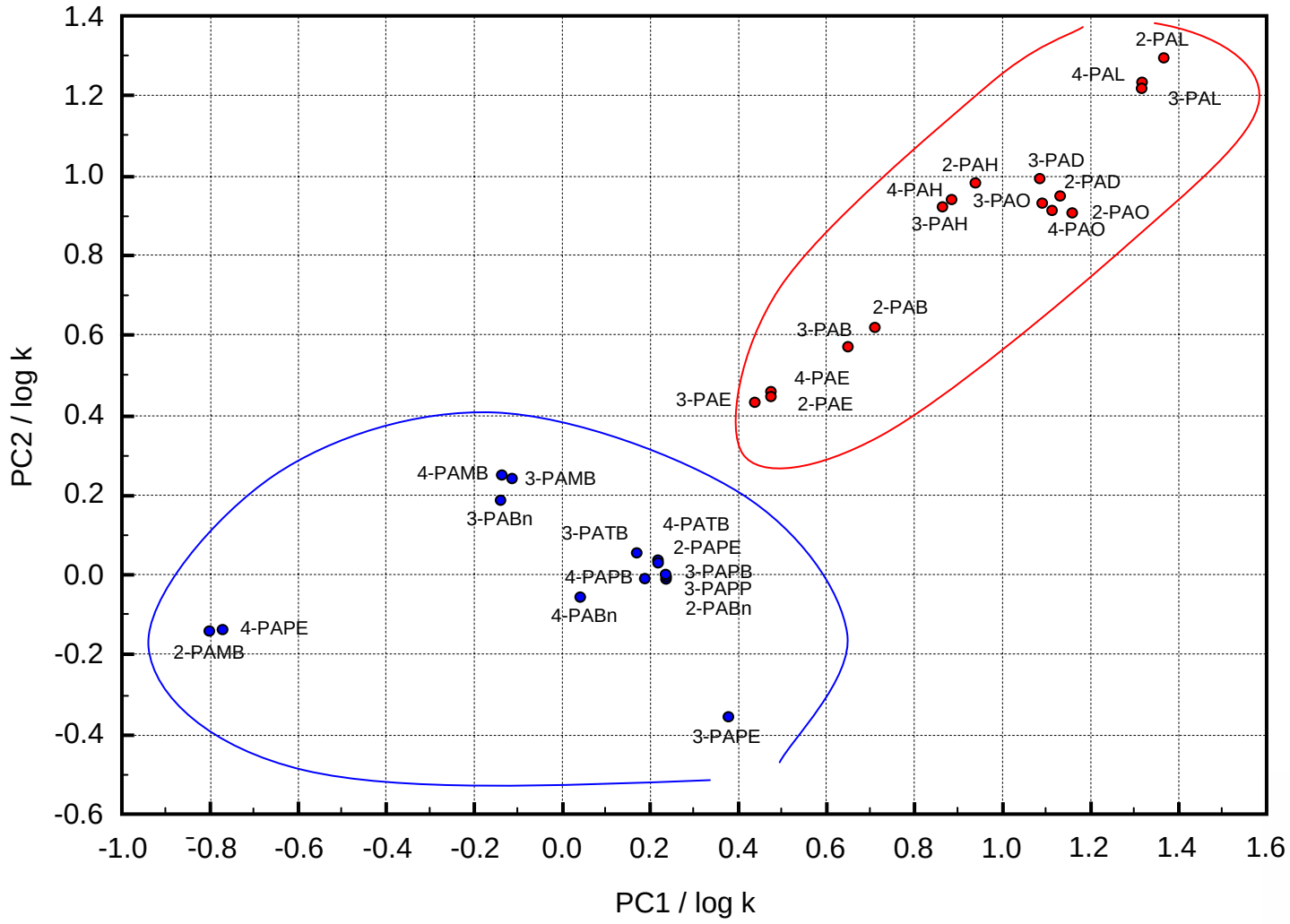


$\Delta S^0_{RP} = 6.38 J/mol^0K$

$\Delta S^0_{HILIC} = 19.93 J/mol^0K$

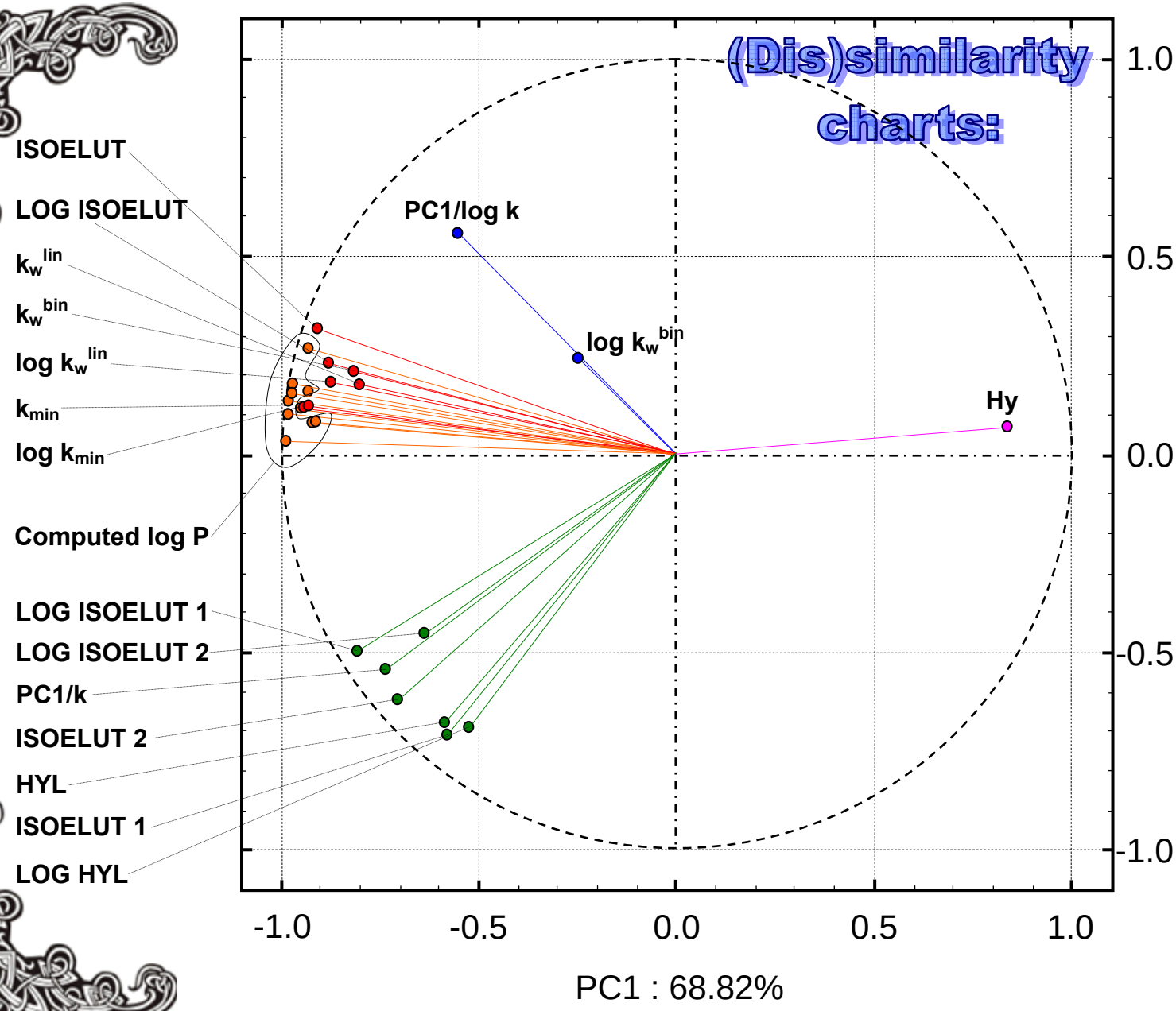
$$V^{RP}_{S.Ph.} \approx V^{HILIC}_{S.Ph.}$$

Some chemometric approaches:



PCA on covariance matrices k/log k and computed descriptors

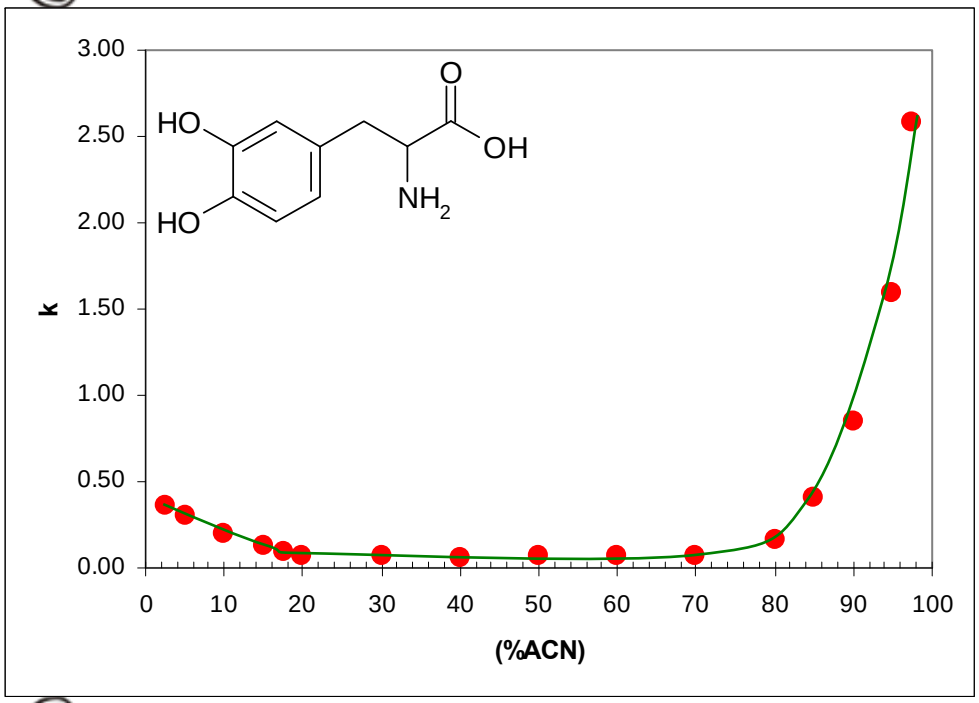
(Dis)similarity charts:



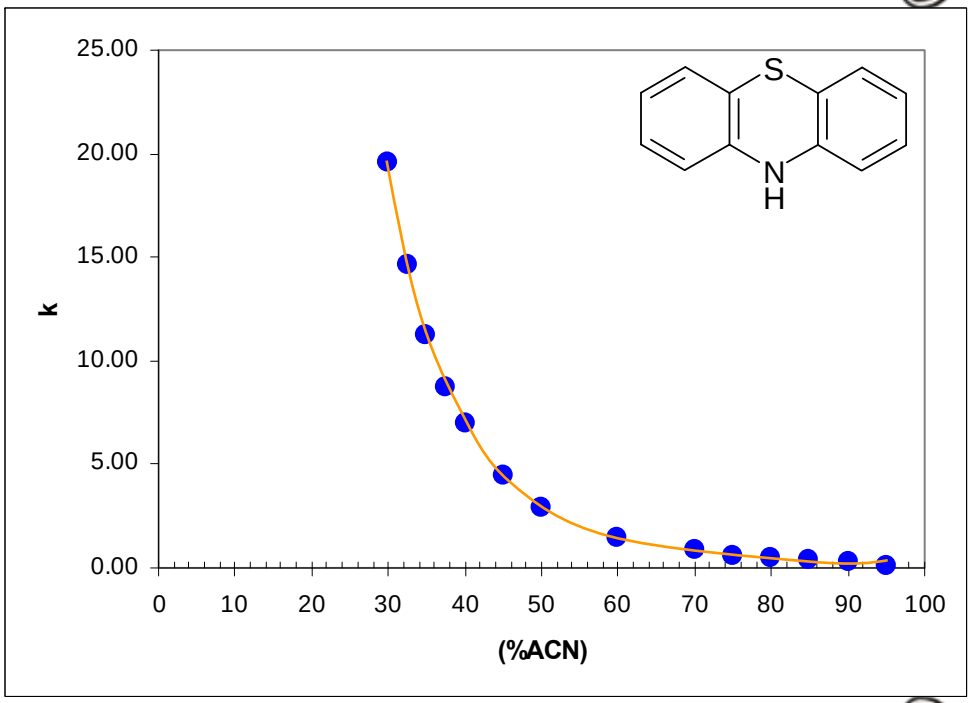
Loadings representation after applying PCA on matrices formed by calculated log P and lipophilicity indices.

Does it allways works?

log P = -2.39



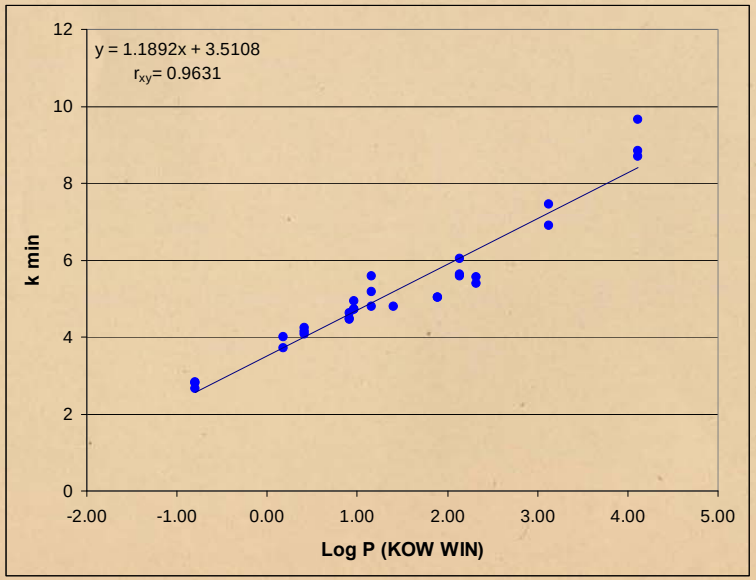
log P = 4.15



Conclusions:

1. Bimodal chromatographic retention behaviour may successfully produces indices for lipophilicity scales.

2. k_{min}, ISOELUT, log k_{min}, LOGISOLEUT closely correlate with log P.



3. Better correlations are obtained within compound classes.

Thank you for your attention and patience!

Things you'll meet, of many a kind,
Sights and sounds, and tales, no end,
But to keep them all in mind,
Who would bother to attend?
Very little doest it matter
If you can yourself fulfil,
That, with idle empty chatter,
Days go past and days come still.

M. Eminescu, Glossa
Translation: Corneliu M. Popescu

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