Seminar on Lipophilicity including a method for estimating the logP of organic compounds

Lecture notes follow circa 1989

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LIPOPHILICITY

Backgroud

Crum-Brown and Fraser (1865)

$\Phi = F(c)$ F : physiological activity
c : chemical constitution

Meyer Overton hypothesis.

Hansch Equations.

$\log 1/C = a \log P + b$

$\log 1/C = a(\log P)^2 + b\log P + c$

logP : Lipophilicity, P: partition coefficient

PARTITION COEFFICIENT or LIPOPHILICITY

1. Direct mearsurement
   a. solvent system: octanol-water
   b. Temperature
   c. Purity

2. AKUFVE System

3. Reverse Phase TLC system

   $R_m = \log(1/R_f - 1)$
   $\log P = \log K + R_m$ K: constant from $P = K(1/R_f - 1)$

4. HPLC

   $k' = (t_R - t_o)/t_o$
   $\log P = \log K + \log k'$

CALCULATION of LIPOPHILICITY (partition coefficient)

1. π - method

$$\pi_i = \log P_i - \log P_o$$

$$\log P = \log P_o + \sum \pi_i$$

2. Hydrophobic Fragmental Constant f

$$\log P = \sum a_i f_i$$

a_i : incidence of a given fragment
f_i : hydrophobic fragmental constant

$$\log P = \sum a_i f_i + c$$

3. Molecular Connectivity

$$\chi \propto \sum f_i$$

$${}^n\chi = \sum (\delta_i \cdots\cdots \delta_k)^{1/2}, \qquad k - i = n$$

$$\delta^v = Z^v - h$$

Z^v : number of valence electron
h : number of hydrogen atom attached

$$\sum {}^n\chi \propto \sum f_i$$

REFERENCES

QSAR, HANSCH EQUATIONS

1. S.K.S. Non Research Seminar abstract and references therein
2. *Acc.Chem. Res.* **19**, 392 (1986)

LIPOPHILICITY

3. Progress in Drug Research **23**, 97 (1979)

Π - SYSTEM

4. " Substituent Constants for Correlation Analysis in Chemistry and Biology" by C. Hansch and A. Leo (1979)

f

5. "The Hydrophobic Fragmental Constant" by R. F. Rekker (1977)

MOLECULAR CONNECTIVITY

6. "Molecular Connectivity in Chemistry and Drug Research" by L.B. Kier and L.H. Hall

HPLC : *J. Med. Chem.* **19**, 615 (1976)
TLC : *J. Med. Chem.* **13**, 511 (1970)
AKUFVE : *Chem. and Ind.* 488 (1970)

Early experiments.

TABLE 5.1: *Narcosis of Mice.*

	P	N	C_{oil}	p_s	Activity
Nitrous oxide	1.4	100	0.06	59300	0.01
Acetylene	1.8	65.0	0.05	51700	0.01
Dimethylether	11.6	12.0	0.06	6100	0.02
Methylchloride	14.0	6.5	0.07	5900	0.01
Ethylene oxide	31.0	5.8	0.07	1900	0.02
Ethyl chloride	40.5	5.0	0.08	1780	0.02
Diethyl ether	50.0	3.4	0.07	830	0.03
Methylal	75.0	2.8	0.08	630	0.03
Ethyl bromide	95.0	1.9	0.07	725	0.02
Dimethyl acetal	100	1.9	0.06	288	0.05
Diethyl formal	120	1.0	0.05	110	0.07
CHCl=CHCl	130	0.95	0.05	450	0.02
Carbon disulphide	160	1.1	0.07	560	0.02
Chloroform	265	0.5	0.05	324	0.01

P = partition coefficient (oil:vapour); N = narcotic concentration (volume %); C_{oil} = concentration (molar) of the substance in olive oil which would be in equilibrium with the narcotic concentration; p_s = saturated vapour pressure (mm Hg) at 37°C; Activity = p_t/p_s where p_t, the partial pressure in the anaesthetic mixture is calculated by multiplying the narcotic concentration by atmospheric pressure, e.g. for diethyl formal $p_t = \frac{1}{100} \times 760$ mm Hg.

(From results of Meyer and Hemini, *Biochim. Z.* (1935), no. 277, p. 54.)

Beginning of Modern QSAR

TABLE 5.2: *Activity of phenoxyacetic acids: C is the concentration producing 10% growth of the* Avena *(grass) samples in the standard time; P is the partition coefficient; π is the effect of the substituent on* log *P, taking phenoxyacetic acid as standard, and σ is the effect of the substituent on the* pK$_a$ *of benzoic acid.*

Substituent	σ	P	π	log 1/C (calc.)	log 1/C (obs.)
3-CF_3	0.55	320	1.09	6.8	6.5
4-Cl	0.37	168	0.80	6.3	6.4
3-I	0.28	325	1.08	6.1	6.3
4-F	0.34	43	0.20	5.0	6.3
3-Br	0.23	254	0.97	5.9	6.0
3-SF_5	0.68	1190	1.64	6.2	6.0
3-Cl	0.23	178	0.82	5.9	5.7
3-NO_2	0.78	29	0.04	5.7	5.3
3-SCH_3	−0.05	105	0.59	4.9	5.3
3-C_2H_5	−0.15	200	0.87	4.9	5.3
3-n-C_3H_7	−0.15	890	1.52	4.2	4.7
3-OCH_3	−0.27	36	0.13	3.1	4.7
3-CN	0.63	16	−0.23	4.1	4.5
3-CH_3	−0.17	75	0.44	4.3	4.3
3-CH_3CO	0.52	22	−0.08	4.5	4.0
3-F	0.06	41	0.18	4.2	3.5
H	0.00	27	0.00	3.4	3.5
3-OH	−0.36	5	−0.73	−1.8	3.7
3-COOH	0.27	21	−0.13	3.5	3.0
3-n-C_4H_9	−0.15	3100	2.03	2.4	0.0

(From results of Hansch, Maloney, Fujita and Muir, *Nature* (1962), no. 194, p. 178.)

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