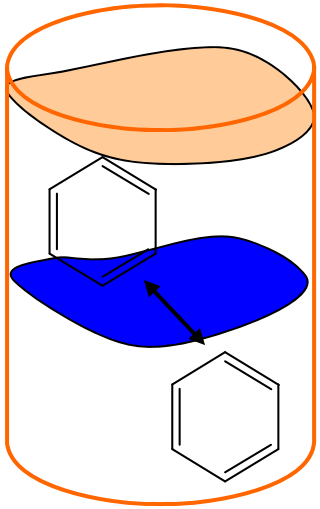
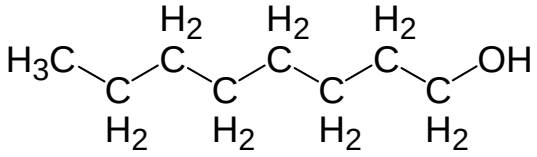
Octanol-Water Partition

- Another phase change

$$A_{water} \leftrightarrow A_{octanol}$$

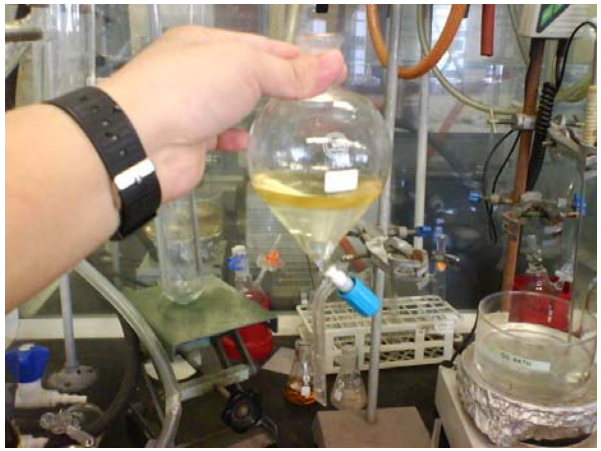
$$K_{ow} = \frac{[A_{octanol}]}{[A_{water}]}$$





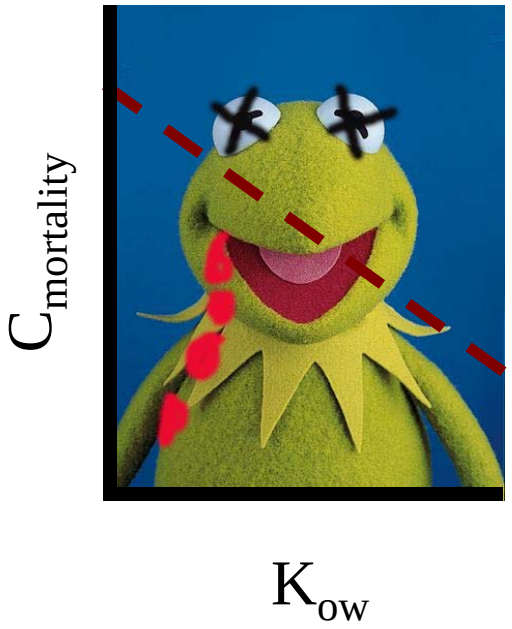
octanol

aqueous solution



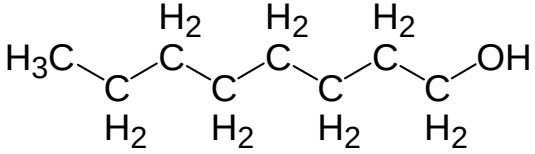
Octanol-Water Partition

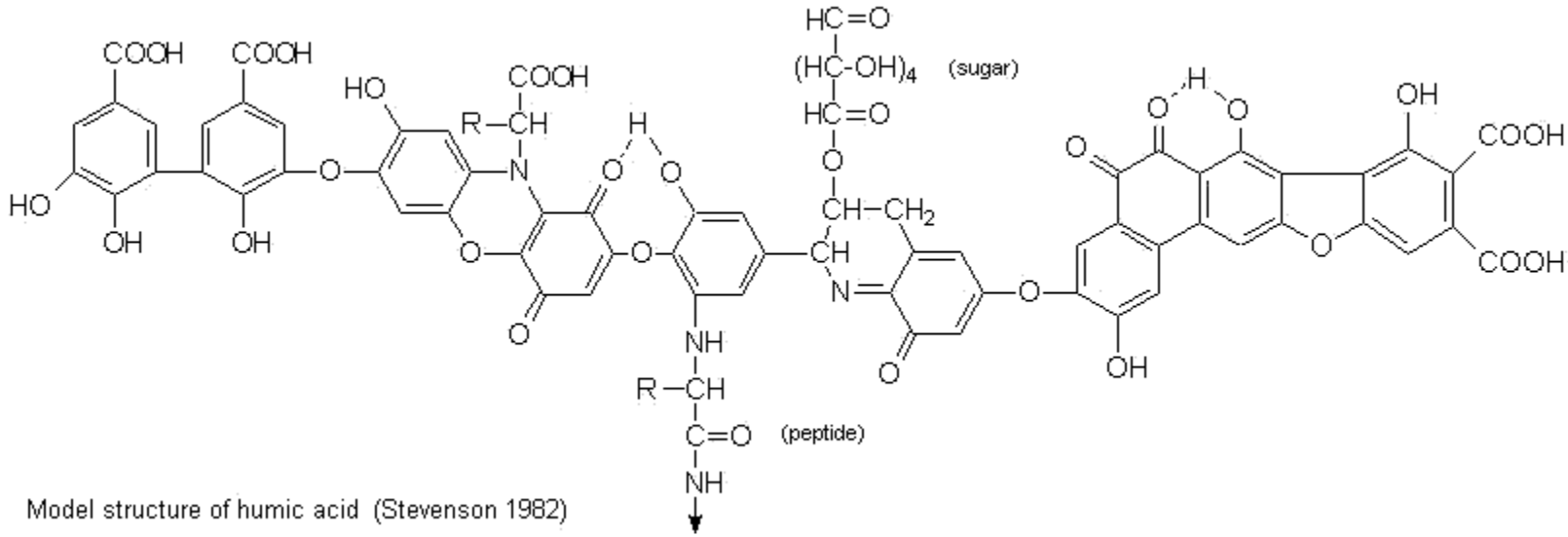
- Why octanol?
  - drug uptake
    - animal testing
    - mortality related to K_{ow}
  - oral absorption (two needs)
    - drug must first pass through lipid bilayers in the intestinal epithelium
    - drug must be hydrophobic enough to partition into the lipid bilayer
    - drug must be hydrophilic enough to avoid retention, non-selective effects



Octanol-Water Partition

- Why octanol?
  - environmental transport
    - sorption to organic matter
    - uptake by organisms
    - organic matter and organisms are octanol-like

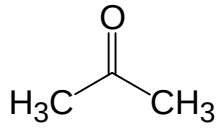




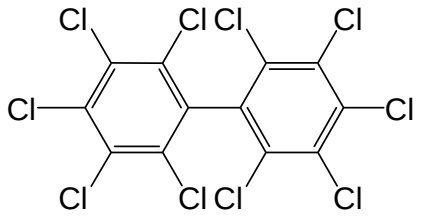
Model structure of humic acid (Stevenson 1982)

Octanol-Water Partition

- Wide range of K_{ow} $10^{-0.24}$



$10^{8.23}$



compound	K_{ow}
benzene	$10^{2.13}$
phenol	$10^{1.45}$
trichloroethene	$10^{2.42}$
phenanthrene	$10^{4.57}$
2,2’,5,5’-tetrachlorobiphenyl	$10^{6.18}$

Octanol-Water Partition

TABLE 5.2 Aqueous Solution Activity Coefficients γ_w^∞ of Some Sparingly Soluble Organic Compounds in Infinitely Dilute Solutions[a]

Compound	γ_w^∞
Benzene	2.4×10^3
Toluene	1.2×10^4
Naphthalene	1.4×10^5
Phenanthrene	7.4×10^6
Benzo(a)pyrene	2.8×10^9
Methylene chloride	4.2×10^2
Chloroform	8.6×10^2
Carbon tetrachloride	1.0×10^4
1,1,1-Trichloroethane	2.4×10^3
Chlorobenzene	1.9×10^4
1,3-Dichlorobenzene	1.7×10^5
1,2,3,5-Tetrachlorobenzene	1.4×10^7
Pentachlorobenzene	1.2×10^8
Hexachlorobenzene	9.8×10^8
2,4′-Dichlorobiphenyl	5.8×10^7
2,2′,5,5′-Tetrachlorobiphenyl	4.2×10^9
2,2′,4,4′,5,5′-Hexachlorobiphenyl	2.9×10^{11}
Methyl ethyl ketone	3.2×10^1
Diethyl ether	1.6×10^2
Ethyl acetate	1.5×10^2
Octanol	3.7×10^3

[a]After Banerjee, 1985.

$$\gamma_{iw} = 3.7 \times 10^3$$

$$1/\gamma_{iw} = x_{iw} = 2.7 \times 10^{-4}$$

1 water for ~4 octanol (Octanol)

8 octanol for ~100000waters (Water)

$$K_{iow} = \frac{C_{io}}{C_{iw}} = \frac{\bar{V}_w}{\bar{V}_o} * \frac{\gamma_{iw}}{\gamma_{io}}$$

pure n-octanol = 0.16L/mol (at 25°C)

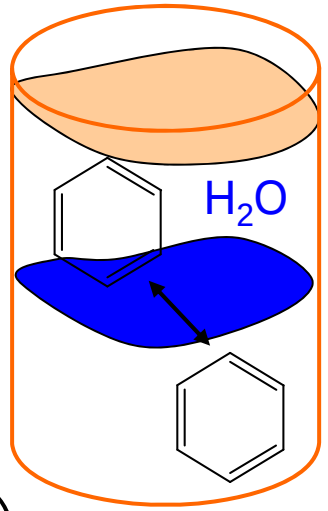
Use approximation or calculate

Vmix =(0.75)(0.16) + (0.25)(0.018) = 0.12 L mol-1

Octanol-Water Partition

- At equilibrium:

$$K_{ow} = \frac{[A_{oct}]}{[A_w]}$$



octanol

aqueous solution

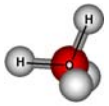
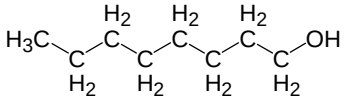
$$K_{ow} = \frac{x_{oct} / \bar{V}_{oct}}{x_w / \bar{V}_w} = \frac{x_{oct}\bar{V}_w}{x_w \bar{V}_{oct}} = \frac{\left(1/\gamma_{oct}\right)\bar{V}_w}{\left(1/\gamma_w\right)\bar{V}_{oct}}$$

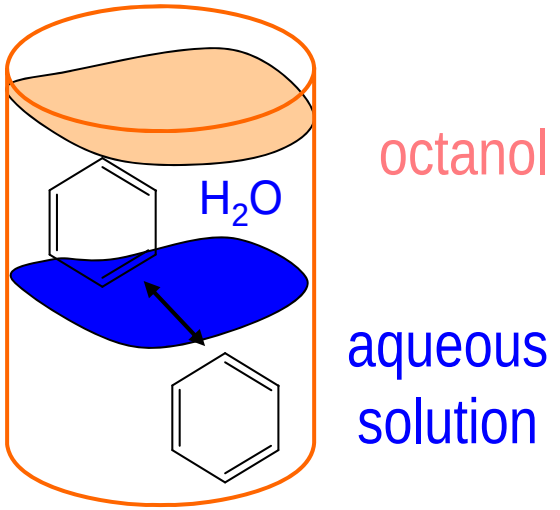
$$K_{ow} = \frac{\gamma_w \bar{V}_w}{\gamma_{oct}\bar{V}_{oct}}$$

Octanol-Water Partition

- At equilibrium:

$$K_{ow} = \frac{[A_{oct}]}{[A_w]} = \frac{\gamma_w \overline{V}_w}{\gamma_{oct} \overline{V}_{oct}}$$

- molar volume of octanol
  - pure octanol, V_{oct} = 0.16 L mol^{-1}
  - water in octanol: 1  :4 
  - V_{oct} = <u>0.12</u> L mol^{-1}
- molar volume of water
  - 1 octanol per 12,500 H_2Os
  - V_w ~= 0.018 L mol^{-1}



Octanol-Water Partition

- Assumptions
  - $\gamma_w^{sat} \approx \gamma_w^{\infty}$
    - even at saturation, solute molecules will not be near each other
  - octanol present in water does not affect γ_w
  - $\gamma_{oct} \approx 1$ to 10 for most compounds

$$K_{ow} = \frac{[A_{oct}]}{[A_w]} = \frac{\gamma_w \overline{V}_w}{\gamma_{oct} \overline{V}_{oct}}$$

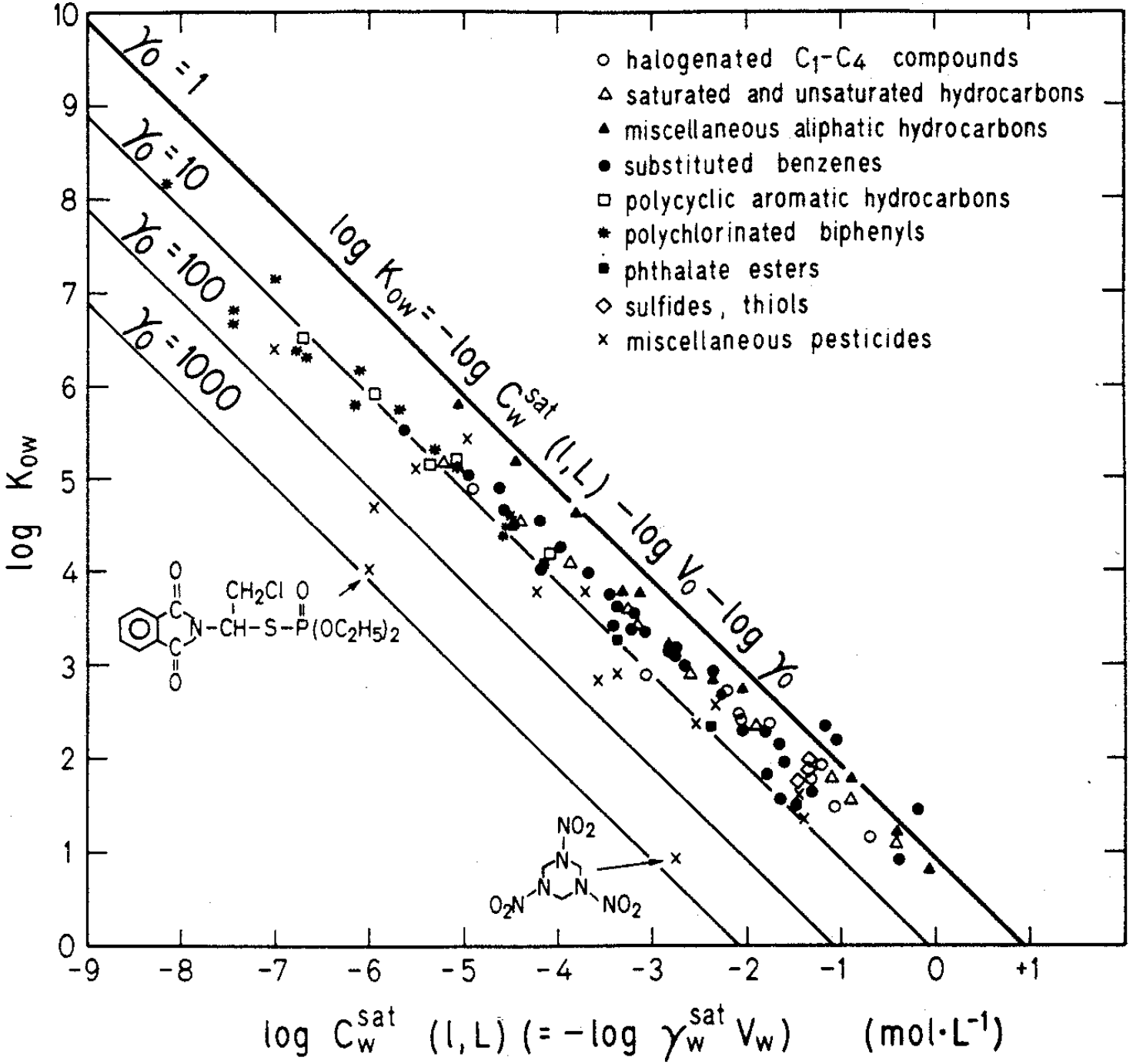
Octanol-Water Partition

- Is K_{ow} related to aqueous solubility?
  - log K_{ow} vs. log C_w^{sat}(L)

$$K_{ow} = \frac{[A_{oct}]}{[A_w]}$$

$$K_{ow} = \frac{C_{oct}^{sat}(L)}{C_w^{sat}(L)} = \frac{1}{C_w^{sat}(L)} \frac{1}{\gamma_{oct} \overline{V}_{oct}}$$

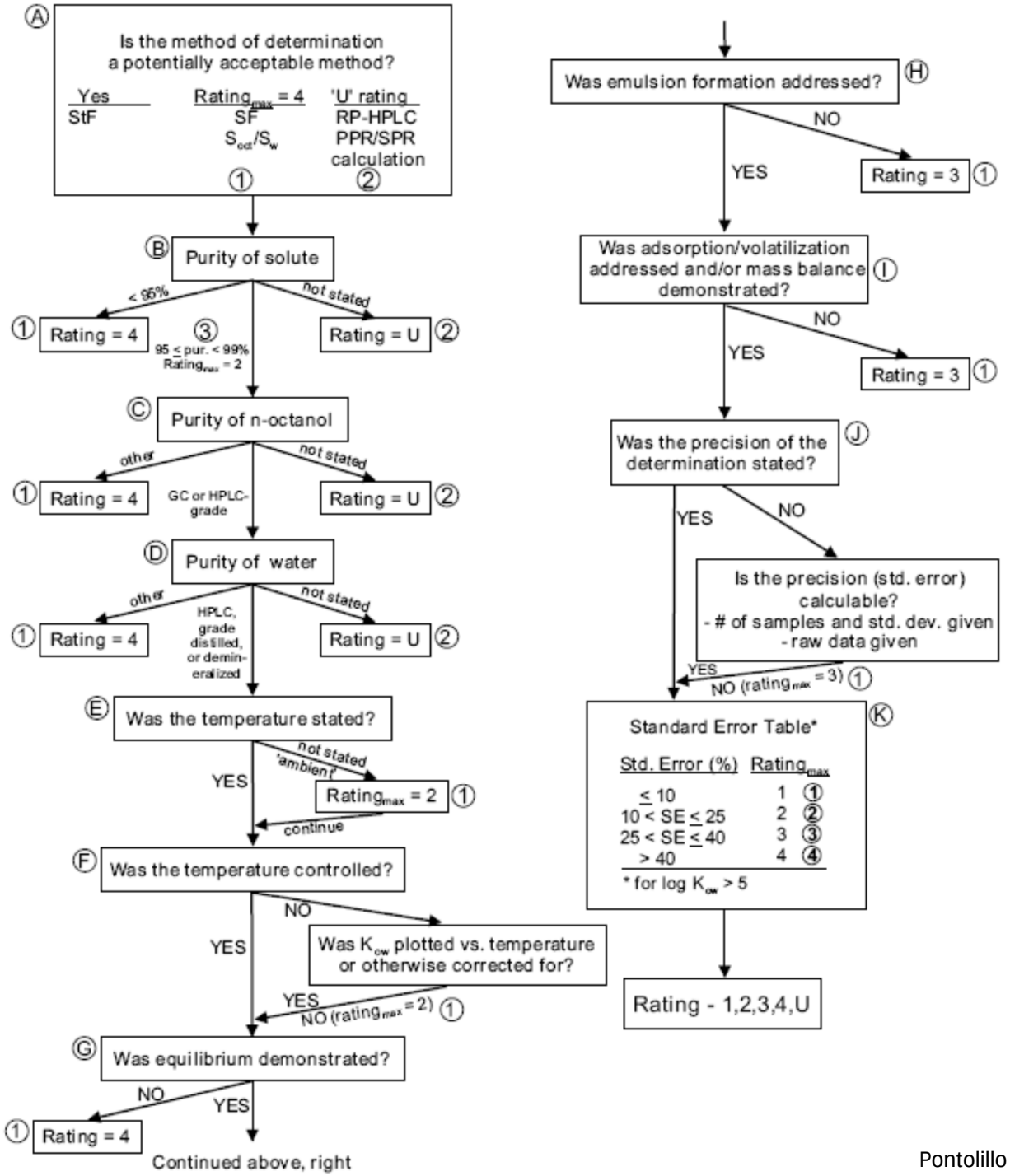
$$\log K_{ow} = -\log C_w^{sat}(L) - \log \gamma_{oct} - \log \overline{V}_{oct}$$


log K_{ow}
log C_w^{sat} (l,L) (= −log $\gamma_w^{sat} V_w$) (mol·L^{-1})
γ_o = 1
γ_o = 10
γ_o = 100
γ_o = 1000
log K_{ow} = −log C_w^{sat} (l,L) − log V_o − log γ_o
halogenated C_1–C_4 compounds
saturated and unsaturated hydrocarbons
miscellaneous aliphatic hydrocarbons
substituted benzenes
polycyclic aromatic hydrocarbons
polychlorinated biphenyls
phthalate esters
sulfides, thiols
miscellaneous pesticides
CH_2Cl O
N–CH–S–P$(OC_2H_5)_2$
NO_2
O_2N
NO_2

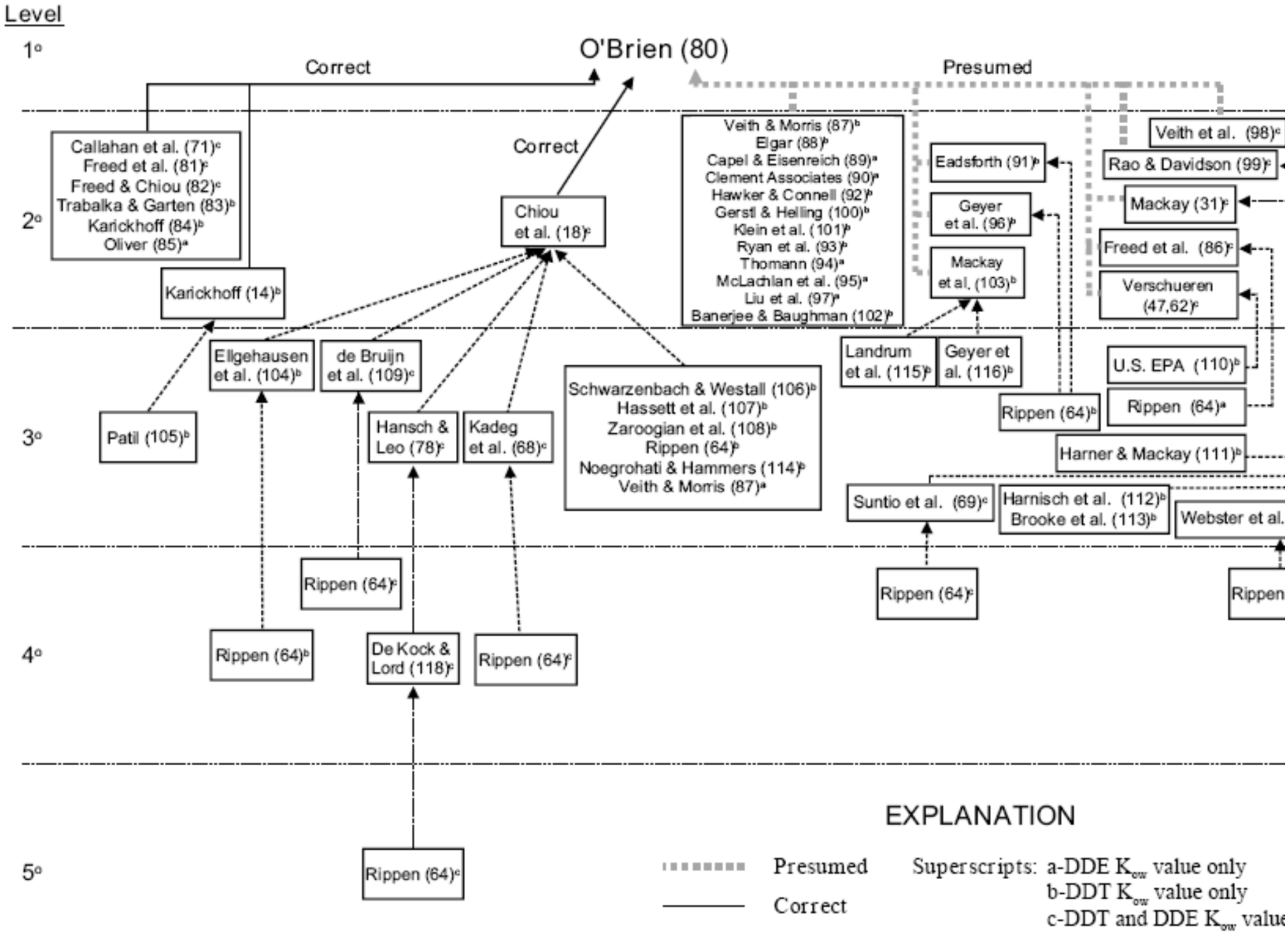
Octanol-Water Partition

- Experimental determination of K_{ow}
  - "shake flask"
  - measure solute distribution in octanol and water phases
  - (should be) limited to $K_{ow} < 10^5$
  - poor reproducibility among researchers
    - e.g., DDT, log K_{ow} range of 4.89 to 6.91; over 60 different papers (Pontolillo and Eganhouse, 2001)
    - need for reliable estimation method

K_{ow}

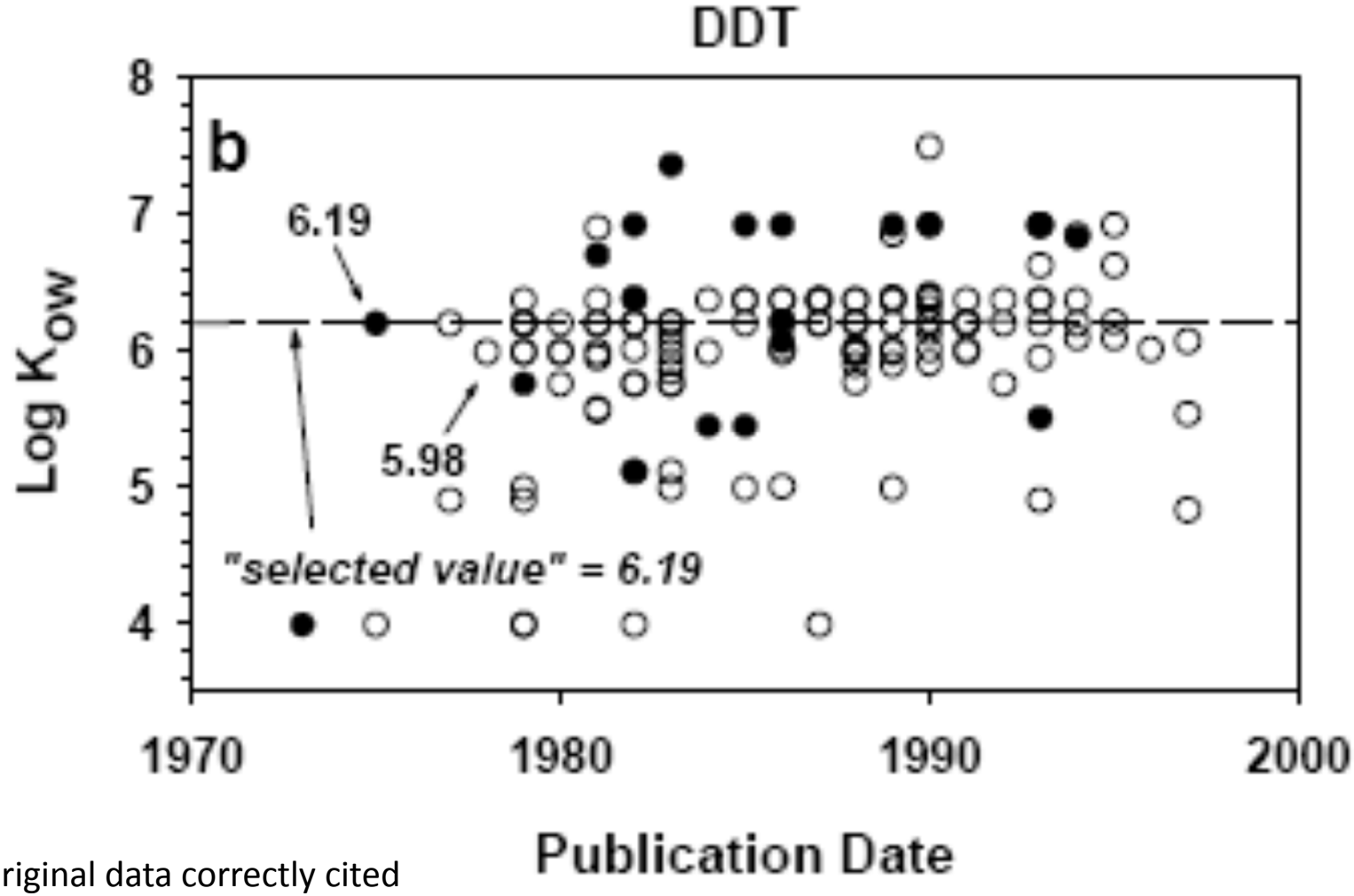


Pontolillo and Eganhouse (2001)



Pontolillo and Eganhouse (2001)

Octanol-Water Partition



● original data correctly cited

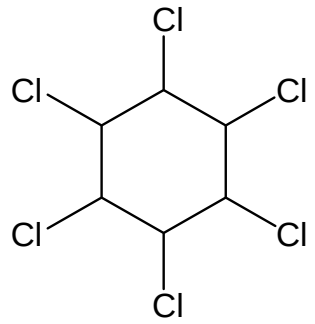
○ "erroneous data" (incorrectly cited)

Pontolillo and Eganhouse (2001)

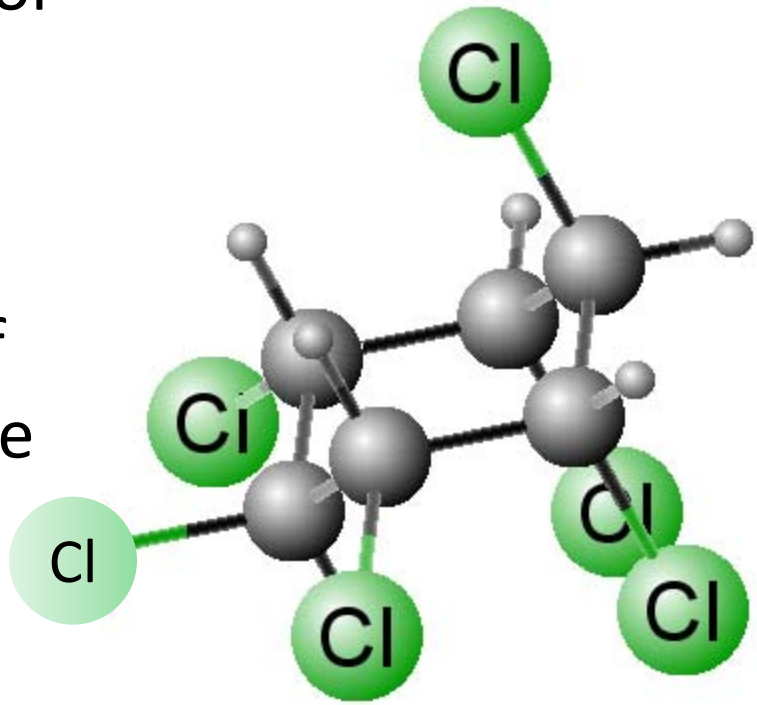
Octanol-Water Partition

- Example: lindane
  - 10^{-6} mole of lindane is added to 100 mL separatory funnel containing 10 mL of octanol and 90 mL of water.

    At equilibrium and 25°C, what concentration (M) of lindane will be found in the water?



γ-hexachlorocyclohexane

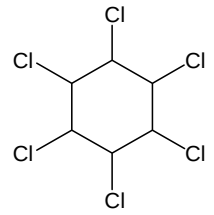


Octanol-Water Partition

by Sean Delonas
New York Post - Jan. 18, 1995

Octanol-Water Partition

- Lindane
  - $K_{ow} = 10^{3.78}$



γ-hexachlorocyclohexane

$$f_w = \frac{\text{total moles in water}}{\text{total moles in octanol and water}}$$

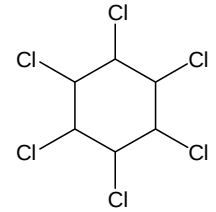
$$f_w = \frac{[lin]_w V_w}{[lin]_o V_o + [lin]_w V_w}$$

$$K_{ow} = \frac{[lin]_o}{[lin]_w} \qquad [lin]_o = K_{ow}[lin]_w$$

$$f_w = \frac{[lin]_w V_w}{K_{ow}[lin]_w V_o + [lin]_w V_w}$$

$$f_w = \frac{V_w}{K_{ow} V_o + V_w}$$

Octanol-Water Partition



γ-hexachlorocyclohexane

- Lindane
  - $K_{ow} = 10^{3.78}$

$$f_w = \frac{V_w}{K_{ow}V_o + V_w}$$

$$f_w = \frac{90\,\text{mL}}{(10^{3.78} \times 10\,\text{mL}) + 90\,\text{mL}}$$

$$f_w = 0.0015$$

$$n_{lin,w} = f_w n_{lin,T} = (0.0015)(10^{-6}\ \text{mol}) = 1.5 \times 10^{-9}\ \text{mol}$$

$$[lin]_w = \frac{n_{lin,w}}{V_w} = \frac{1.5 \times 10^{-9}\ \text{mol}}{0.090\ L} = 1.7 \times 10^{-8}\ M$$

Octanol-Water Partition

- Estimation of K_{ow}
  - related to partitioning in other solvents
    - butanol, hexane
    - not much data
  - related to aqueous solubility and activity coefficients (Table 7.3, book)

$$\log K_{ow} = -a \log C_w^{sat} + b'$$

$$\log K_{ow} = a \log \gamma_w + b$$

  - related to retention time in chromatography (Figure 7.7 next slide)

Octanol-Water Partition

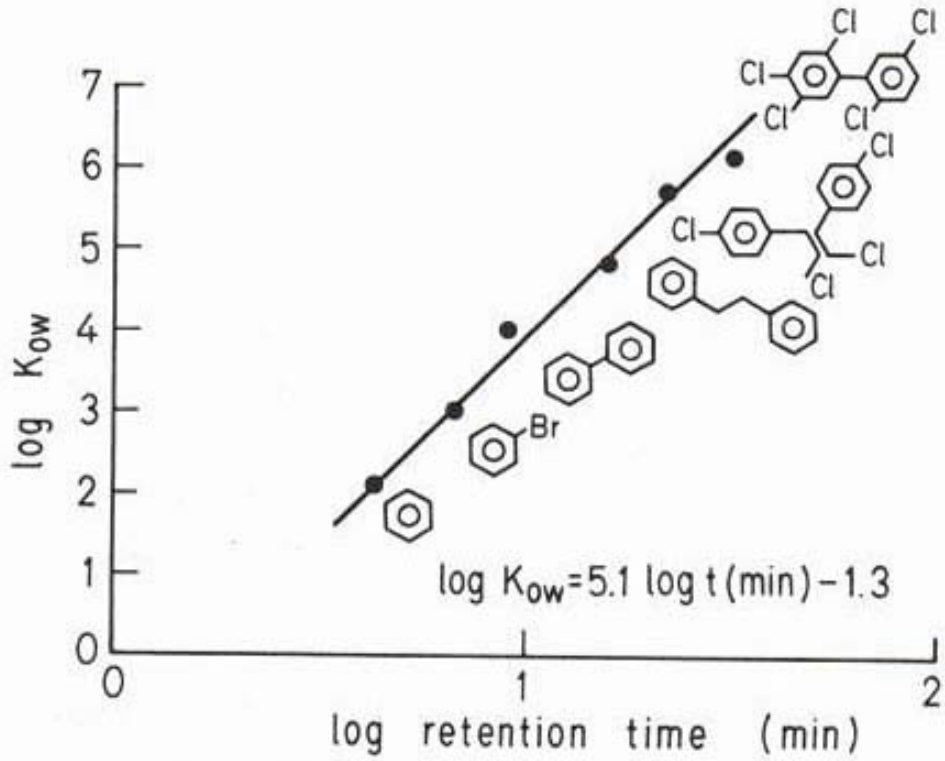
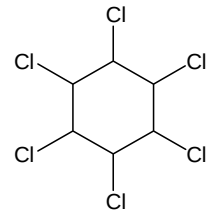


Figure 7.7 Relation between log octanol–water partition constants and log retention times on a reversed-phase liquid chromatography system for a series of nonpolar organic compounds (data from Veith et al., 1979).

C-18 column, MeOH: Water system, use reference compounds

Octanol-Water Partition



γ-hexachlorocyclohexane

- Example
  - estimate the K_{ow} of lindane using its aqueous solubility and T_m = 112 °C

now Table 7.3, SGI (2003)

TABLE 7.2 Linear Free-Energy Relationships Between Octanol–Water Partition Constants and (Liquid) Aqueous Solubilities for Various Sets of Compounds

			$\log K_{ow} = -a \log C_w^{sat}(1, L) + b$	
Set of Compounds	n	R^2	$a(\pm\sigma)$	$b(\pm\sigma)$
Alkanes	16	0.91	0.81	−0.20
Polycyclic aromatic hydrocarbons	8	0.99	0.87(±0.03)	0.68(±0.16)
Substituted benzenes				
Only nonpolar substituents	23	0.98	0.86(±0.03)	0.75(±0.09)
Including polar substituents	32	0.86	0.72(±0.05)	1.18(±0.16)
Phthalates	5	1.00	1.06(±0.03)	−0.22(±0.09)
PCBs	14	0.92	0.85(±0.07)	0.78(±0.47)
Alcohols	41	0.94	0.90	0.83
Miscellaneous pesticides	14	0.81	0.84(±0.12)	0.12(±0.49)

Octanol-Water Partition

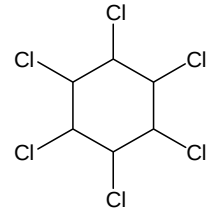
- Lindane
  - alkane? PCB?

$$\log K_{ow} = -0.85 \log C_w^{sat}(L) + 0.78$$

  - $C_w^{sat}(L)$
    - solubility of liquid or subcooled liquid
    - no melting for octanol-water partition

$$C_w^{sat}(L) = C_w^{sat}(s) \frac{p_L^*}{p_s^*}$$

Octanol-Water Partition

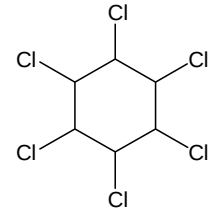


γ-hexachlorocyclohexane

- Lindane
  - $C_w^{sat}(s) = 10^{-4.60}$ M
  - p_s^*/p_L^* ?
    - τ = ?
    - σ = ?

$$\ln \frac{p_s^*}{p_L^*} = -\left(6.8 + 1.1\tau - 2.3\log\sigma\right)\left(\frac{T_m}{T} - 1\right)$$

Octanol-Water Partition



γ-hexachlorocyclohexane

- Lindane
  - What is the torsional bond number τ for lindane?

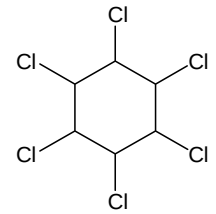
A. 0
B. 5
C. 5.5

$$\tau = \sum \left(SP3 + 0.5SP2 + 0.5RING \right) - 1$$

$$\tau = \sum \left(0 + 0.5\left(0\right) + 0.5\left(1\right) \right) - 1$$

$$\tau = 0$$

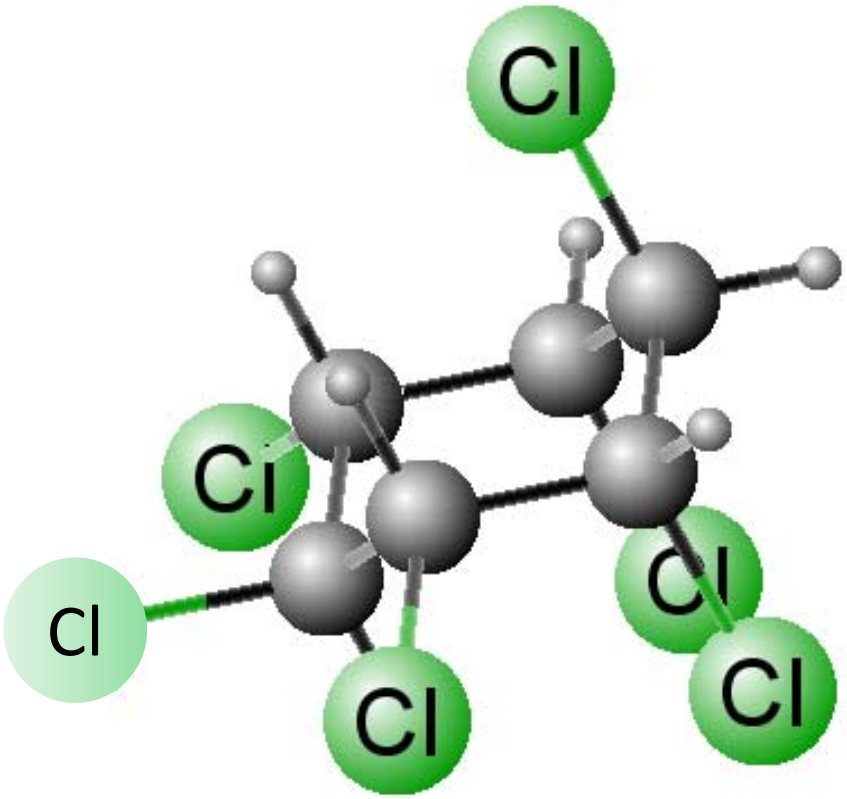
Octanol-Water Partition



γ-hexachlorocyclohexane

- Lindane
  - What is the rotational symmetry number σ for lindane?

A. 1
B. 2
C. 4
D. 12



Octanol-Water Partition

- Lindane
  - C_w^{sat}(s) = $10^{-4.60}$ M
  - p_s^*/p_L^*
    - $\tau = 0;\ \sigma = 1$

$$\ln \frac{p_s^*}{p_L^*} = -\left(6.8 + 1.1(0) - 2.3\log(1)\right)\left(\frac{385.2}{298.2} - 1\right)$$

$$\ln \frac{p_s^*}{p_L^*} = -1.98$$

$$\frac{p_s^*}{p_L^*} = 0.14 \qquad \frac{p_L^*}{p_S^*} = 7.2$$

Octanol-Water Partition

- Lindane

$$C_w^{sat}(L) = C_w^{sat}\frac{p_L^*}{p_s^*} = 10^{-4.60}\,(7.2)$$

$$C_w^{sat}(L) = 10^{-3.74}\ \mathrm{M}$$

$$\log K_{ow} = -0.85 \log C_w^{sat}(L) + 0.78$$

$$\log K_{ow} = -0.85(-3.74) + 0.78$$

$$\log K_{ow} = 3.96$$

measured log K_{ow} = 3.78