



Prediction of Diffusion using the Abraham descriptors

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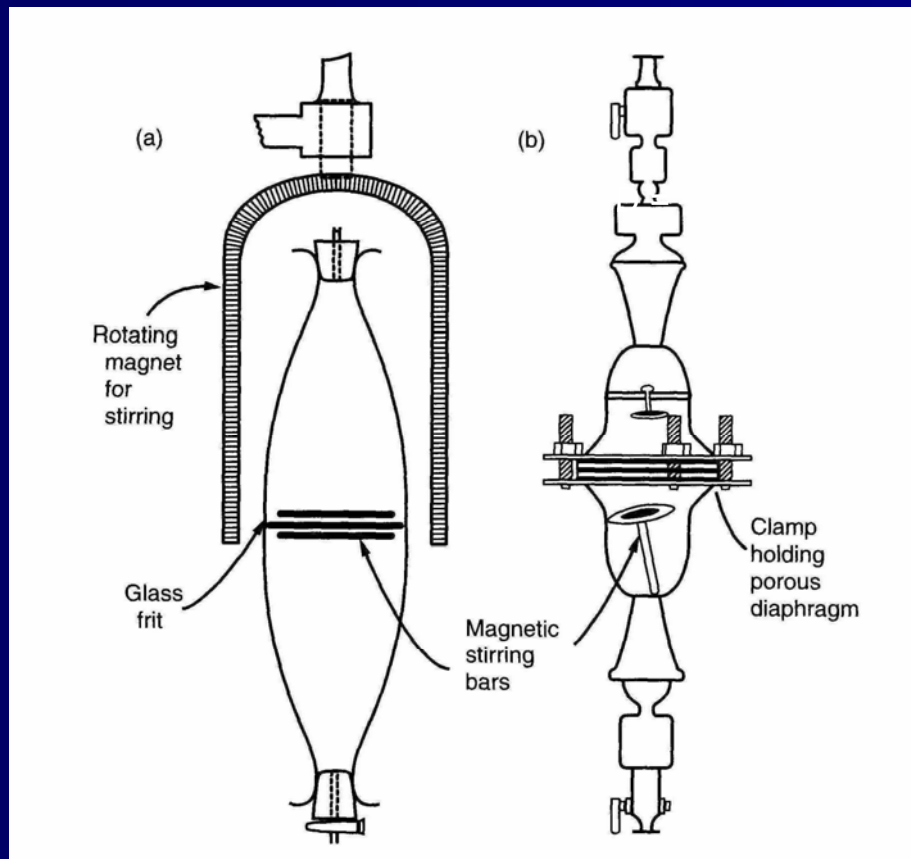
Outline

- Why is diffusion important?
- Experimental methods
- Why predict diffusion?
- Expected factors in the diffusion model
- Diffusion equations
- Comparison of equations with literature
- Summary/conclusions
- Acknowledgements

Diffusion – why?

- Diffusion involved in
 - Blood brain barrier
 - Intestinal absorption
 - Diffusion through skin

Measuring diffusion – standard method



- Two solutions of different concentrations, stirred at 60rpm
- At time t , compartments emptied, concentrations measured

$$D_{12} = \frac{1}{\beta t} \ln \left[\frac{(c_{1,bottom} - c_{1,top})_{initial}}{(c_{1,bottom} - c_{1,top})_{at\ time\ t}} \right]$$

β (in cm^{-2}) is a diaphragm-cell constant, t is the time, and c_1 is the solute concentration

Measuring diffusion – Taylor Aris method

Modified HPLC system

Sample dissolved in solvent, mixed,
filtered into HP vials

- Flow injection system with 10m PEEK tubing instead of column
- Peak widths at half height measured

$$D_{12} = \frac{0.2310r^2tr}{W_{1/2}^2}$$

Why predict diffusion?

- Systems to study drugs currently use permeability coefficients (Caco-2 or permeation through artificial membranes)
- Could use diffusion instead



Prediction of diffusion

- Literature data including drug compounds
- Diffusion in water
- Diffusion in ethanol – less ionisation changes for acids/bases, more compounds soluble in ethanol
- Use Abraham methodology

Abraham Equations

- E is excess molar refraction
- S is dipolarity/polarizability of the solute
- A is the summation hydrogen bond acidity
- B is the summation hydrogen bond basicity
- V is the McGowan's volume

Coefficients e, s, a, b and v derived by MLR

Expect A,B and V

- Equations in the literature depend on V or MW
- Some authors suggest hydrogen bonding also important
- Chan et al looked at hydrogen bond acids and bases with diffusion calc from $1/MW$ –
- Hydrogen bond acids out of line so expect larger term in A

Expect A,B and V

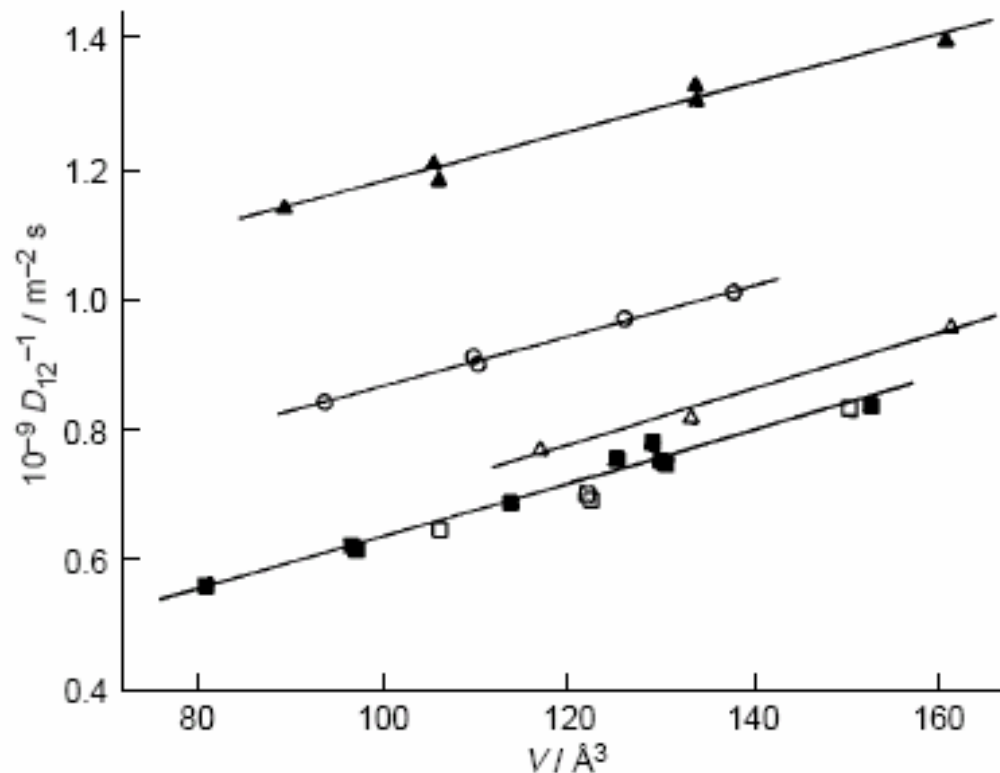


Fig. 1 Variation of $1/D_{12}$ with molecular volume of solutes diffusing in ethanol at 298.2 K: (■) non-associated solutes, (□) aromatic ethers, (△) phenones, (○) aromatic amines and (▲) phenols

Diffusion in water

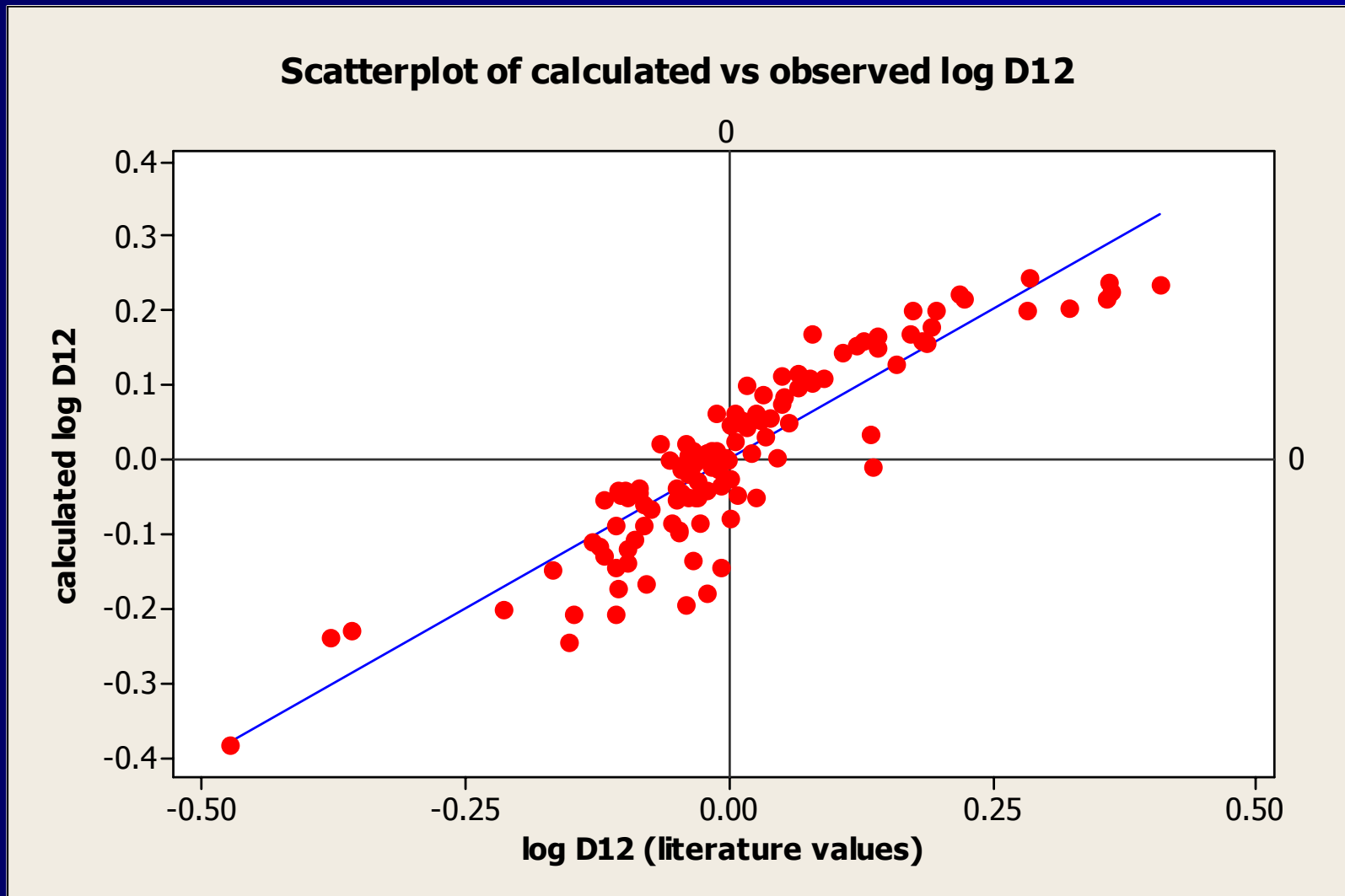
$$\log D_{12} = 0.305 - 0.0730 E + 0.120 S - 0.0940 A - 0.0637 B - 0.358 V$$

$$N = 121 \quad SD = 0.06 \quad r^2 = 0.80 \quad F = 93.01$$

Notation

- We have used D_{12} to represent the diffusion coefficient
- This avoids confusion with $\log D$ – the distribution coefficient

Diffusion in water



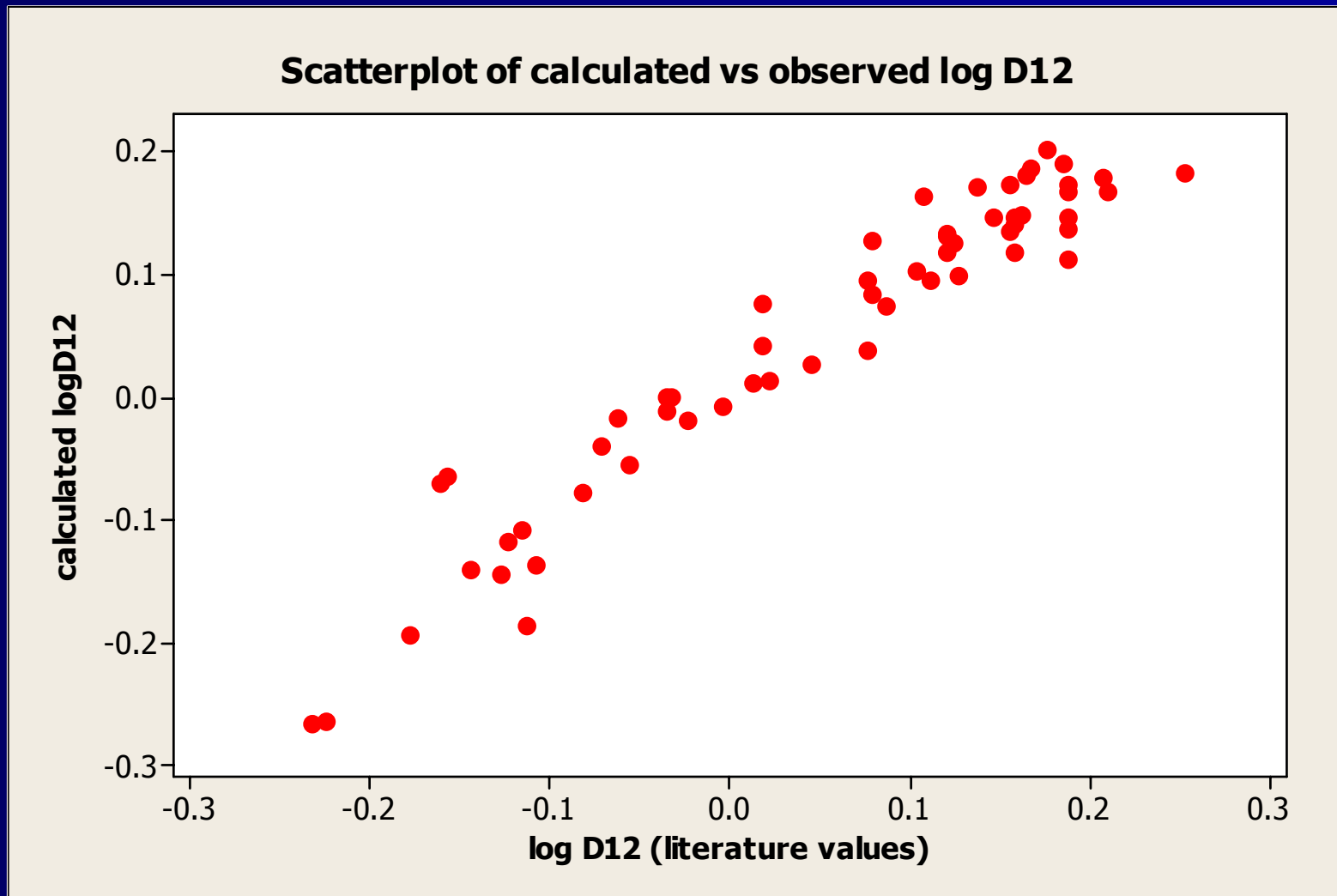
Diffusion in EtOH

$$\log D_{12} = 0.287 - 0.344 A - 0.158 B - 0.114 V$$

$$N = 59 \quad SD = 0.04 \quad r^2 = 0.93 \quad F = 229.25$$

S and E not statistically significant

Diffusion in EtOH



Comparison with literature work (water data)

Method [Ref.]	Formula	Inputs (excluding water parameters)	Absolute Average Error (%)
Hayduk and Laudie [58]	$D_{12} = \frac{13.26 * 10^{-5}}{\eta_W^{1.14} V_B^{0.589}}$	V_B	5.8 (87 solutes)
Wilke-Chang [79]	$D_{12} = \frac{7.4 * 10^{-8} (\phi_W M_W)^{1/2} T}{\eta_W V_B^{0.6}}$	V_B	8.8 (87 solutes)
Scheibel [80]	$D_{12} = \frac{8.2 * 10^{-8} T}{\eta_W V_B^{1/3}} \left[1 + \left(\frac{3V_W}{V_B} \right)^{2/3} \right]$	V_B	6.7 (87 solutes)
Othmer and Thakar ^a [58]	$D_{12} = \frac{1.4 * 10^{-5}}{\eta_W^{1.1} V_B^{0.6}}$	V_B	5.9 (87 solutes)
Reddy and Doraiswamy [81]	$D_{12} = \frac{M_W^{1/2} T K'}{\eta_W (V_W V_B)^{1/3}}$	V_B	<20 (96 solutes)
Venezian [82]	$D_{12} = \frac{6 * 10^{-10} T}{\eta_W (R_M - 0.855)}$ where $R_M = \left(\frac{n_D^2 - 1}{n_D^2 + 2} \right) \left(\frac{M_B}{\rho_B} \right)^{1/3}$	n_D, ρ_B, M_B	

My equation,
AAE = 11.6%

Max error – calc
from
transforming
log D_{12} values
to D_{12}

n = 121

Comparison with literature work (water data)

Avdeef et al (96 compounds)

$$\log D_{12} = -4.113 - 0.4609 \log MW$$

With our data

$$\log D_{12} = -4.13 - 0.448 \log MW$$

N = 121 SD = 0.08 $r^2 = 0.74$ F = 331.30

Eur. J. Pharm. Sci., **2004**, 22 (5), 365-374

Summary/conclusions

- Diffusion in water and ethanol both depend on A , B , V – as expected
- In water E and S are also significant
- Models better than one-descriptor V or MW model
- Performs as well as literature and larger dataset
- Models of bioavailability could include diffusion as bioavailability depends on absorption – currently working on this

Acknowledgements

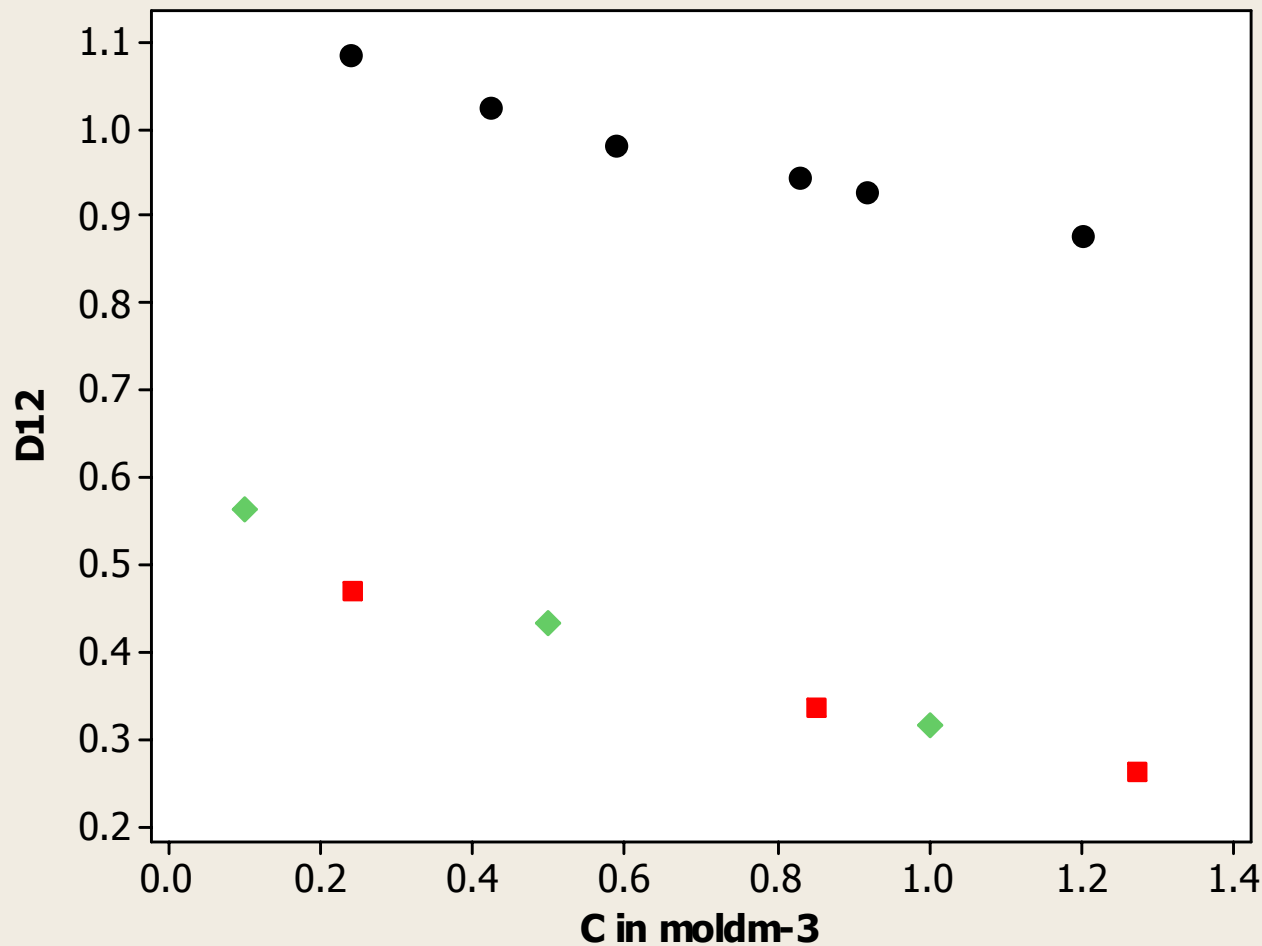
- Thanks to Prof Michael Abraham
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Acids/Bases

Scatterplot of D12 vs C in moldm⁻³



black is
chloroacetic
acid
red is sucrose
green is
nicotine

Acids/Bases

- Diffusion generally measured at high concentrations so no problems with acids and bases as not ionised
- Slopes are the same for chloroacetic acid, nicotine and sucrose
- Extrapolating back to zero should give neutral form for acids and bases

Difference between diffusion and permeability

$$P = \frac{D_{12}}{h}$$

Where h is UWL (Avdeef et al, *Eur. J. Pharm. Sci.*, **2004**, 22 (5), 365-374)

D_{12} units cm^2s^{-1}

P units cms^{-1}