QSAR Prediction of Henry's Law Constant

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Henry's Law

A textbook definition:

"... the mass of gas dissolved by a given volume of solvent is proportional to the pressure of the gas with which it is in equilibrium..."

Henry's Law

$$w = kp$$

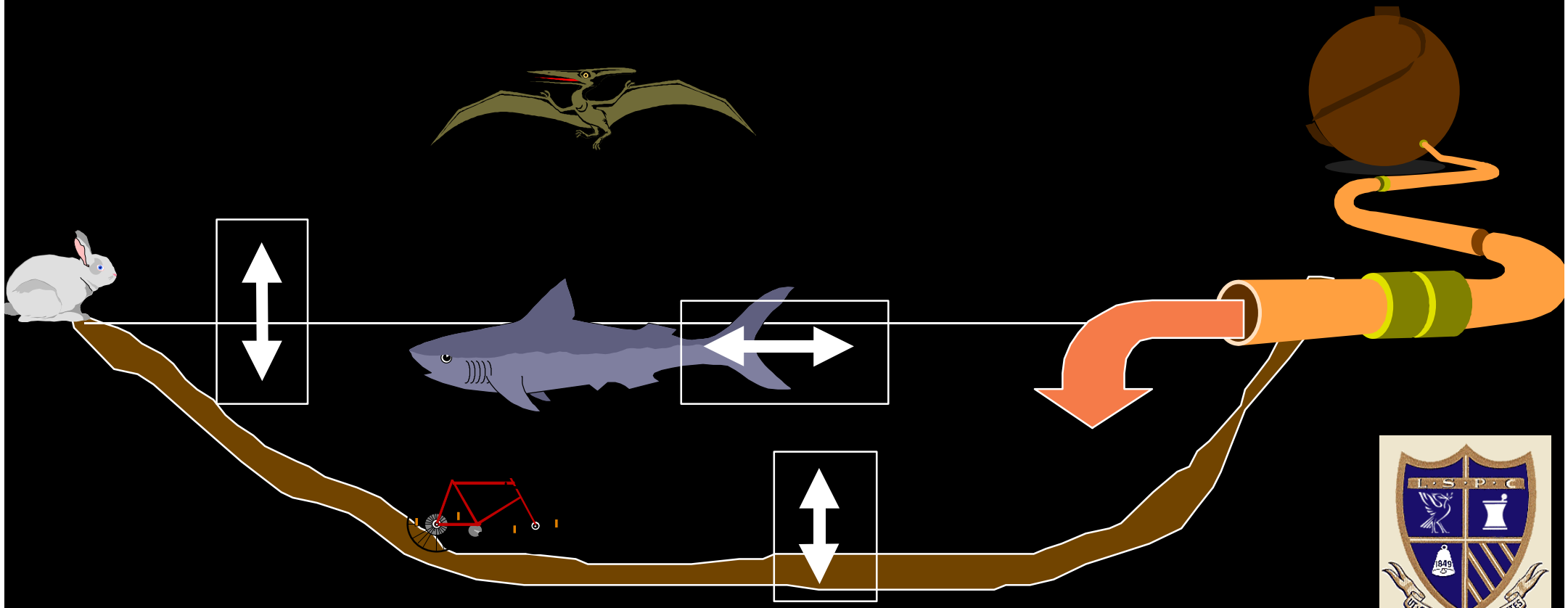
w is the mass of gas dissolved per unit volume of solvent at equilibrium pressure p

k is a constant (the Ostwald coefficient, or inverse of Henry's Law Constant)

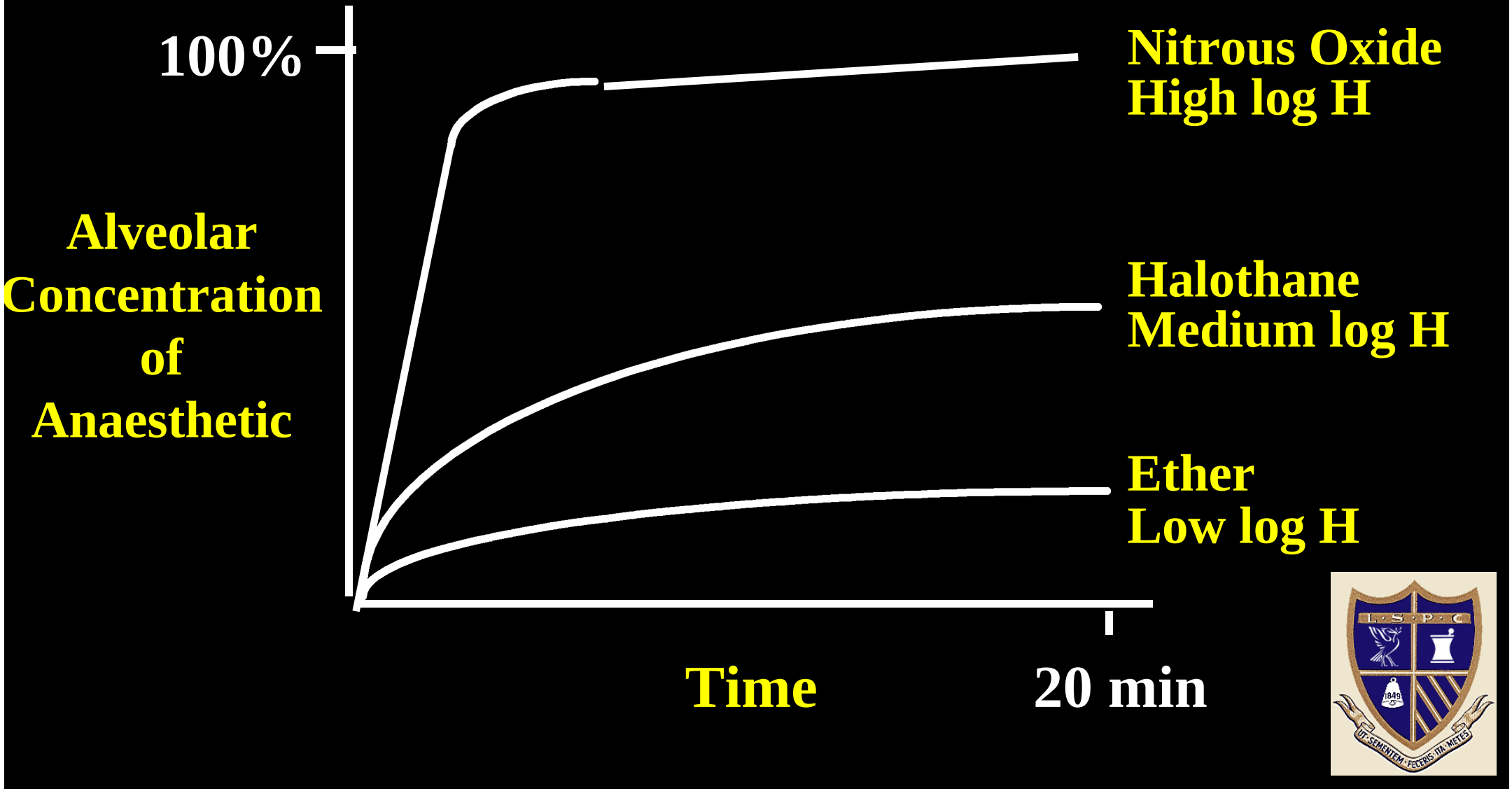
Henry's Law Constant

$$H = \frac{\text{concentration of solute in air}}{\text{concentration of solute in water}}$$

Importance of Henry's Law Constant: Modelling Distribution and Fate of Environmental Pollutants



Importance of Henry's Law Constant: Anaesthetic Gases



Importance of Henry's Law Constant: Food Science

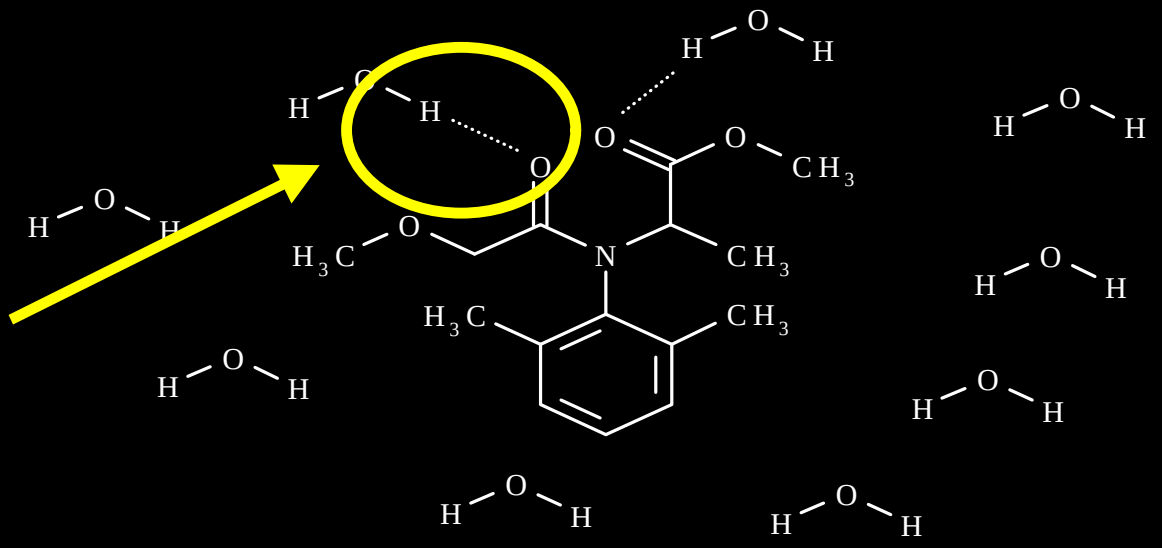
- **Release of volatile compounds following chewing of food influences flavour**
- **Pressurised carbonated drinks**
- **Pressurised gases as propellants**

Factors Affecting Distribution Between Air and Water

Volatisation: Size, Entropy

AIR

WATER



Hydrogen Bonding

Intrinsic Hydrophobicity
Enthalpy of Solvation

Methods to Calculate log H: Group Contribution Methods

Hine and Mookerjee (1975)

Cramer (1980)

Cabani et al (1981)

Meylan and Howard (1991) - HENRYWIN

Methods to Calculate log H: Quantitative Structure-Property Relationships (QSPRs)

Nirmalakhandan and Speece (1988)

Russell et al (1992)

Abraham et al (1994)

Katritzky et al (1996)

Dearden et al (1997, 1999)

Prediction using Solvatochromic Parameters

$$\log 1/H = 0.58\,\Delta MR + 2.55\,\pi + 3.81\,\Sigma\alpha + 4.84\,\Sigma\beta - 0.87\,V_x + 0.99$$

$n = 408$ $r^2 = 0.99$ $s = 0.15$ $F = 16810$

Abraham et al (1994) *J. Chem. Soc. Perkin Trans 2*: 1777-1791

QSPR Prediction from Fundamental Physico-Chemcial Properties

$$\log H = 2.31\ {}^{4}\chi^{v} - 1.14\ MR - 1.00\ HB_{\Sigma ind} + 0.30\ E_{LUMO} - 1.76\ \alpha + 0.14\ B_{R} + 1.09 \log P - 0.44$$

$n = 294$ $r^2_{adj} = 0.91$ $s = 0.67$ $F = 400$

Dearden et al (1999) in Proceedings of 14th European Symposium on QSAR *in press*

Aims of this study

- To investigate the role of the enthalpy of solvation in modelling Henry’s Law Constant
- To refine the QSPR for the prediction of Henry's Law Constant

Henry's Law Constants

- **Training set:**

  log H for 294 compounds largely compiled from Meylan and Howard (1991)

- **Testing set:**

  log H for 48 compounds compiled from a variety of sources

93 Physico-Chemical Descriptors

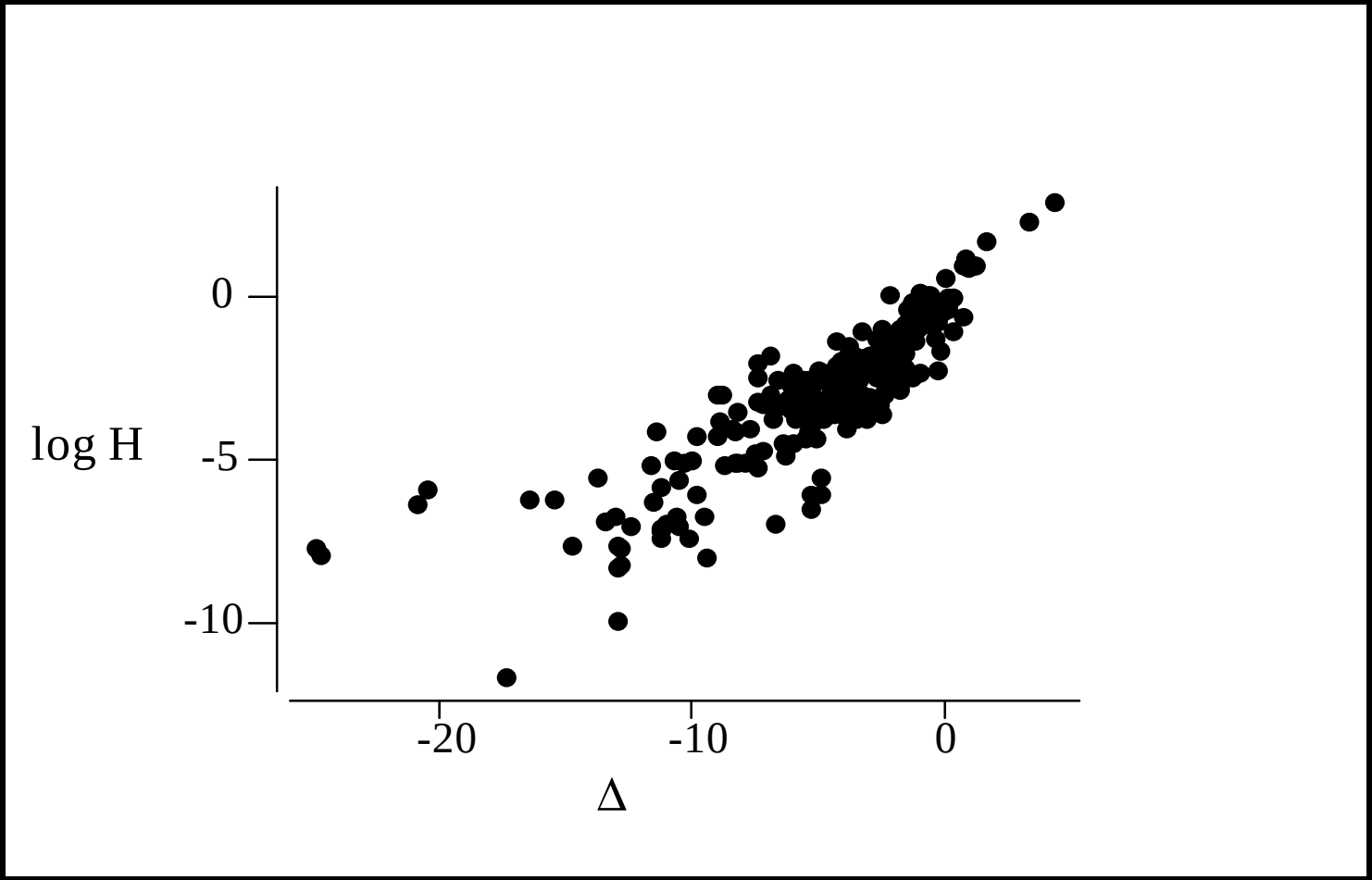
- **Hydrophobicity**
  - **log P**
- **Hydrogen bonding**
  - **counts of acceptors and donors**
  - **HYBOT values**
- **Size, Shape, Topology**
  - **molecular connectivities, topological indices**
  - **molar refractivity**
  - **flexibility, numbers of rotatable bonds**
- **Electronic**
  - **HOMO, LUMO, Dipole Moment**

AMSOL

- Free energy of solvation
- Phosphorous containing compounds produced erroneous values

$$\log H = 0.44\ \Delta G_{AM} - 0.79$$

$$n = 280 \quad r^2adj = 0.75 \quad s = 1.08 \quad F = 829$$

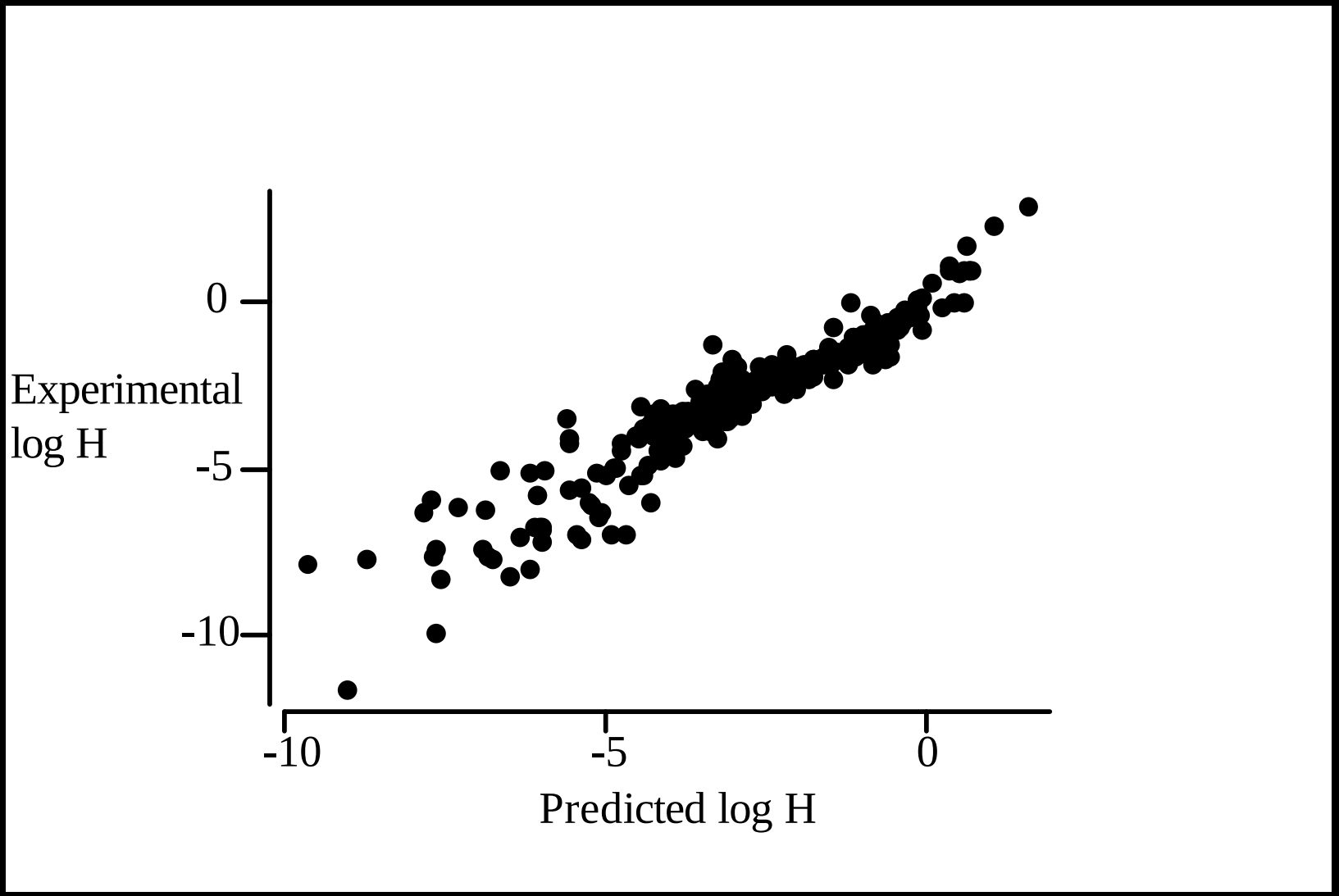


QSPR for Henry's Law Constant

$$\log H = -0.89\,MR - 1.10\,HB_{\Sigma ind} + 0.16\,B_R + 0.71 \log P + 0.19\,\Delta G_{AM} + 0.28$$

$$n = 280 \quad r^2_{adj} = 0.90 \quad s = 0.68 \quad F = 510$$

Predicted vs Experimental log H



Validation - 44 Compound Test Set

$$\log H_{exp} = 0.91 \log H_{pred} - 0.097$$

$$n = 44 \quad r^2_{adj} = 0.95 \quad s = 0.57 \quad F = 799$$

Comparison to SRC HENRYWIN

$$\log H_{exp} = 0.82 \log H_{bond} - 0.35$$

$n = 48 \quad r^2_{adj} = 0.90 \quad s = 0.84 \quad F = 295$

$$\log H_{exp} = 0.91 \log H_{group} - 0.15$$

$n = 34 \quad r^2_{adj} = 0.87 \quad s = 0.79 \quad F = 229$

Conclusions

- **Enthalpy of solvation is an important feature in the description of Henry's Law Constant**
- **A five parameter QSPR, based on fundamental mechanistic understanding, models Henry's Law Constant accurately**

Thank you

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www.staff.livjm.ac.uk/phamcron/qsar/qsar1.htm