Alkane/water partition coefficients and hydrogen bonding

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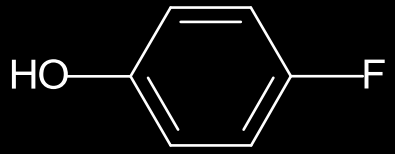
Neglect of hydrogen bond strength: A recurring theme in medicinal chemistry

- Rule of 5
- Rule of 3
- Scoring functions for virtual screening
- Polar surface area (PSA)
- Relationships between thermodynamic properties and buried polar & non-polar surface area

Measuring hydrogen bond strength

Acceptors

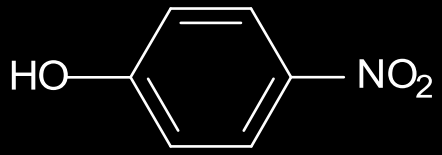
pK_{HB}



(CCl_4)

Taft et al , *JACS* **1969**, 91, 4801-4808
Laurence & Berthelot, *Perspect. Drug. Discov. Des.* **2000**, *18*, 39-60.

$logK_{\beta}$



(CH_3CCl_3)

Abraham *et al*, *JCS Perkin Trans 2* **1989**, 1355-1375

Donors

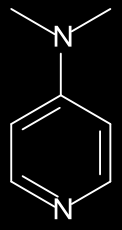
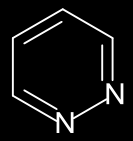
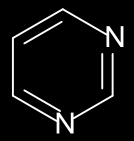
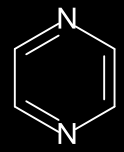
$logK_{\alpha}$

(CH_3CCl_3)

Abraham *et al*, *JCS Perkin Trans 2* **1989**, 1355-1375

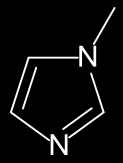
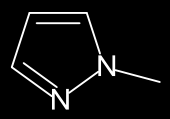
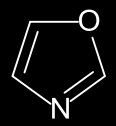
$\log K_\beta$: Heteroaromatic nitrogen

Azines

pKa	**5.22**	**9.70**	**2.24**	**1.23**	**0.65**
$\log K_\beta$	**2.52**	**3.54**	**2.53**	**1.67**	**1.46**

Azoles


pKa	**7.25**	**2.09**	**0.80**	**-2.03**
$\log K_\beta$	**3.68**	**2.22**	**1.67**	**1.06**

Abraham *et al*, *JCS Perkin Trans 2* **1989**, 1355-1375

Modelling Hydrogen Bonding

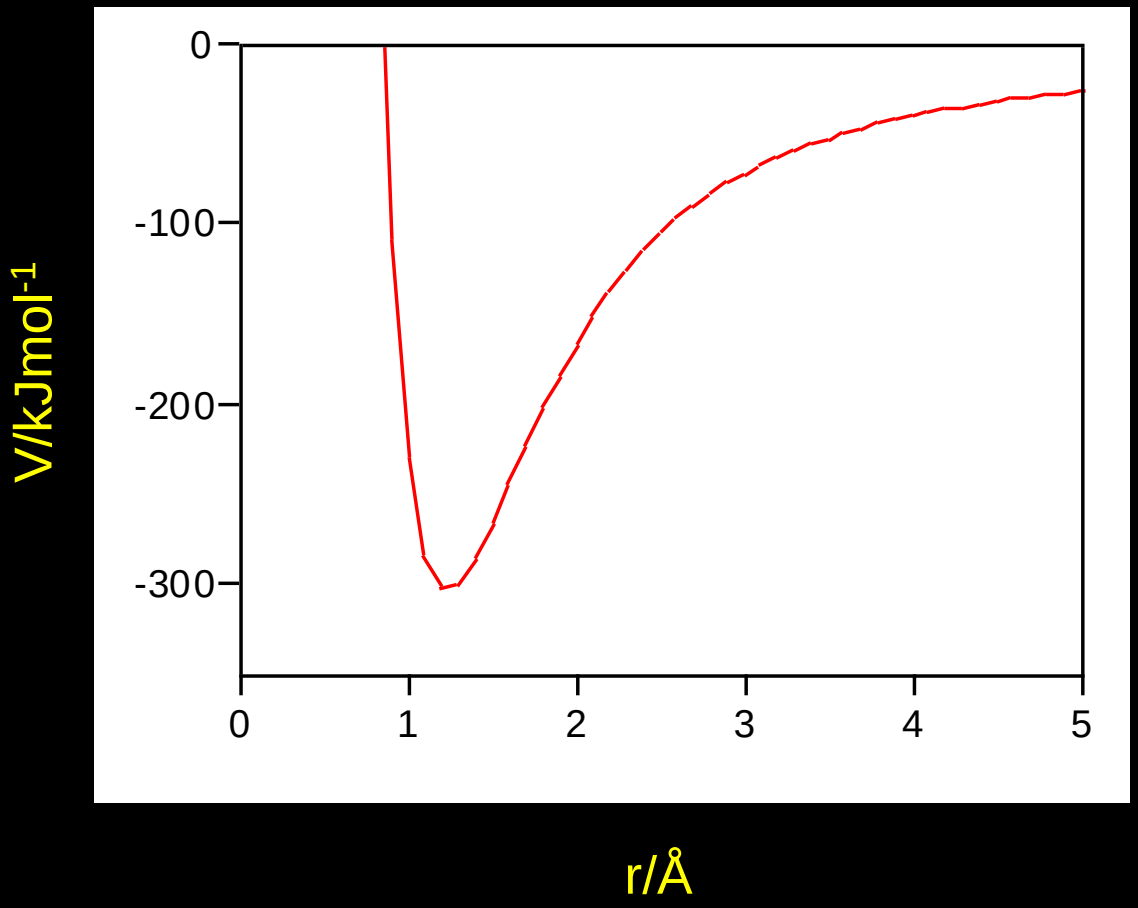
Calculate energy of complex

- Need to know complexation partner
- Need to generate multiple 3D models of complex
- BSSE
- Relevance to physiological media?

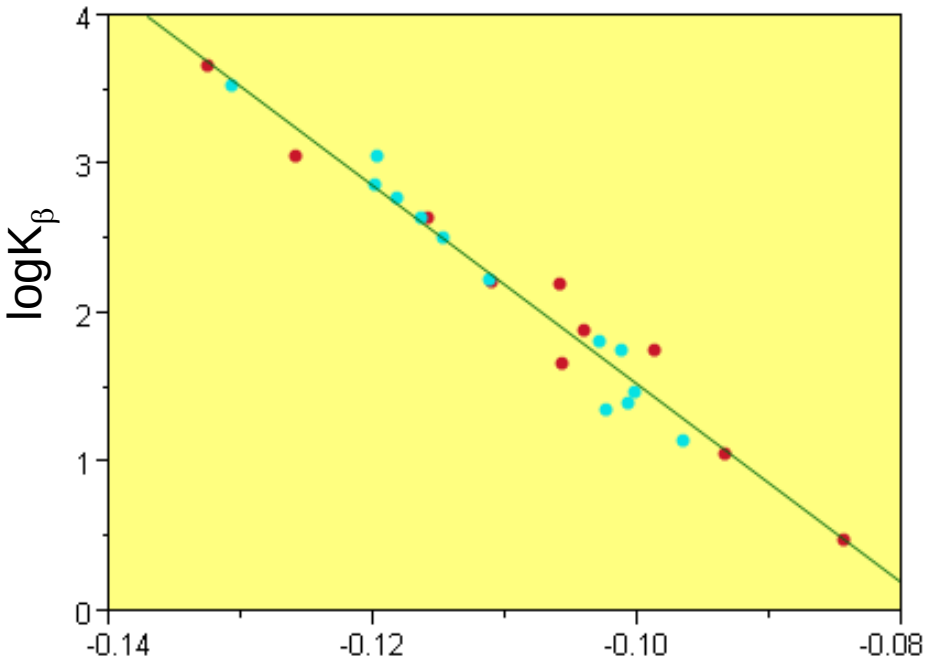
Calculate molecular electrostatic properties

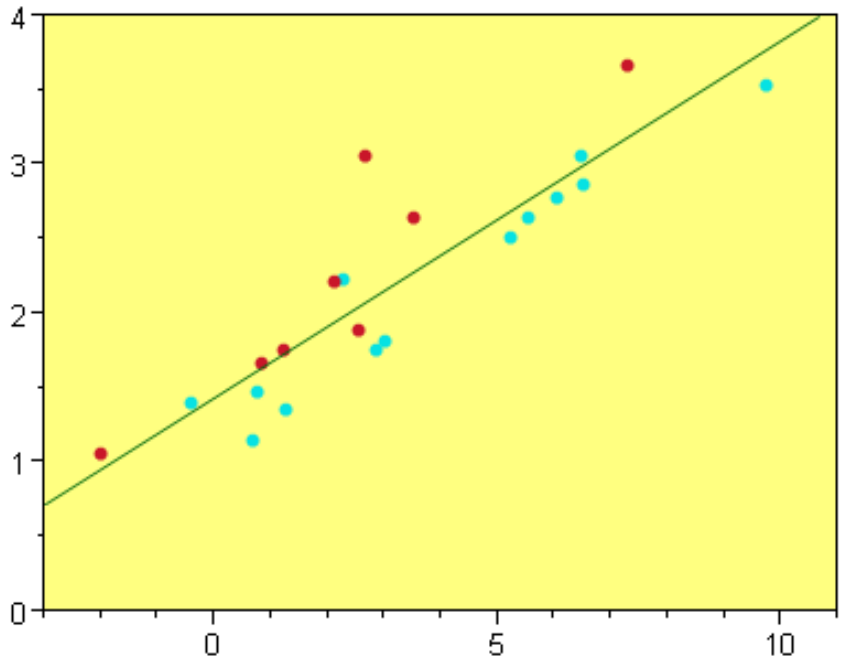
- No explicit reference to complexation partner
- More appropriate to general parameterisation

Electrostatic potential as function of position for acceptor



Comparison of V_{min} and pK_a as predictors of $logK_\beta$

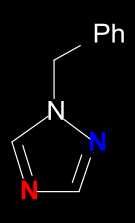
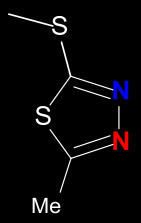
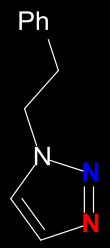
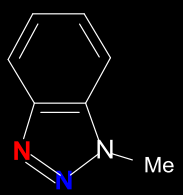
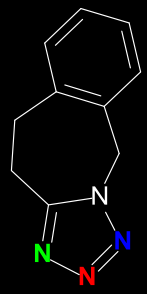




Heteroaromatic nitrogen in five and six-membered rings

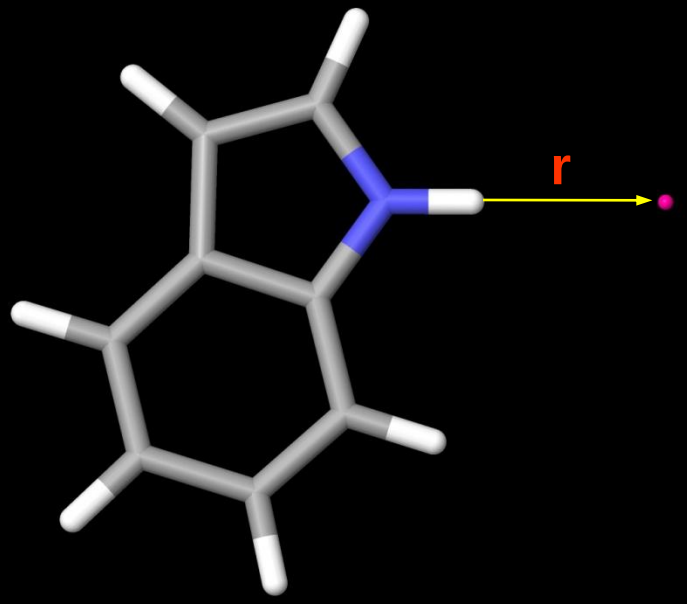
Kenny *JCS Perkin Trans 2* **1994**, 199-202

Non-equivalent acceptors provide validation set

					
	1.01	1.16	0.94	0.40	0.06
	2.63	1.53	2.50	1.89	1.82
					2.39
Predicted logK_β	2.64	1.68	2.51	1.90	2.50
Measured logK_β	2.38	1.98	2.36	2.17	1.99

Kenny *JCS Perkin Trans 2* **1994**, 199-202

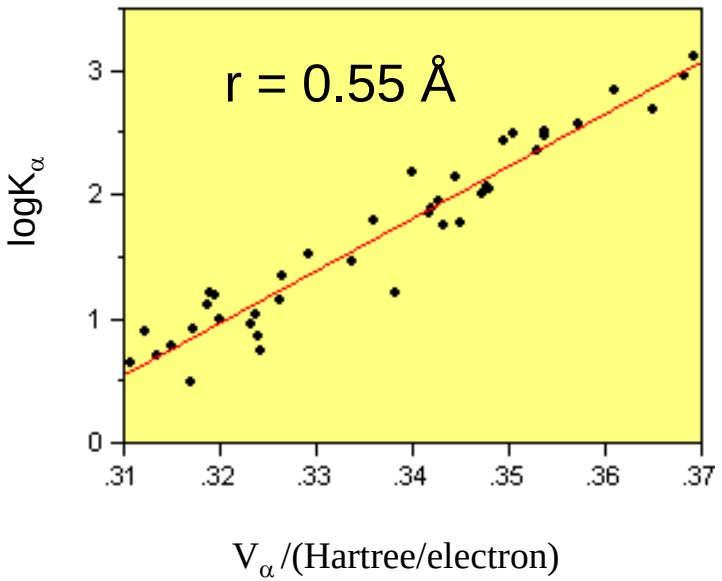
Donors: The $V_{\alpha}(r)$ descriptor

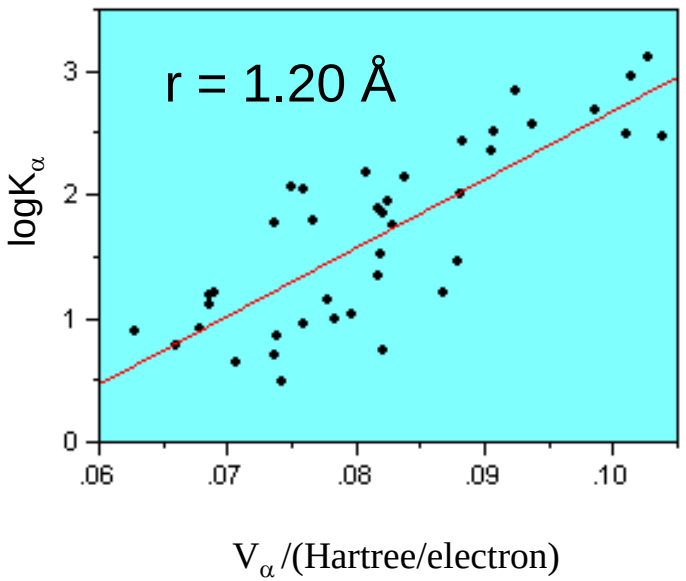


Calculate electrostatic potential (V) at this point

$V_\alpha(r)$ as predictor of $\log K_\alpha$

Sensitivity to distance from donor hydrogen



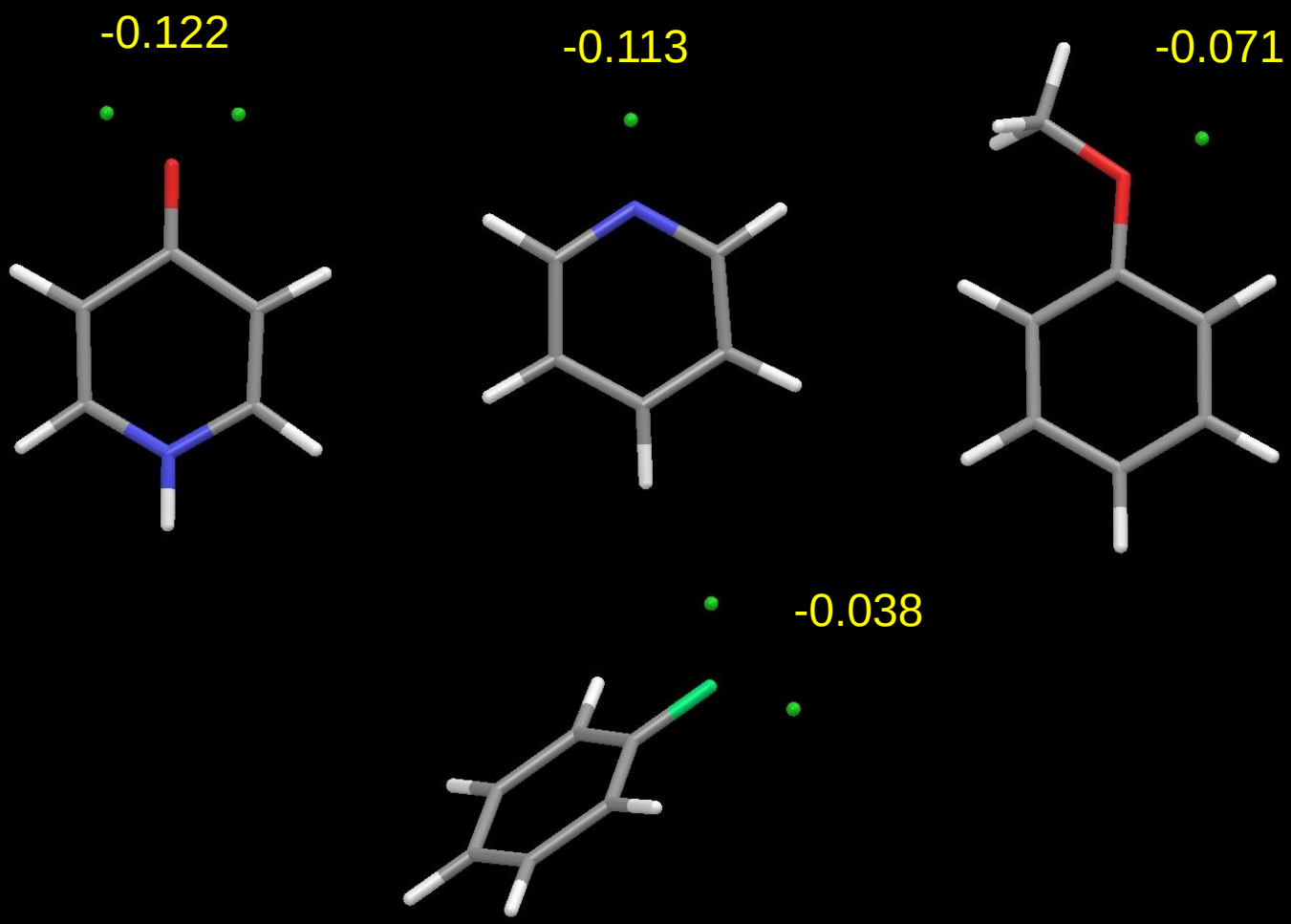


R^2 = 0.93
RMSE = 0.20

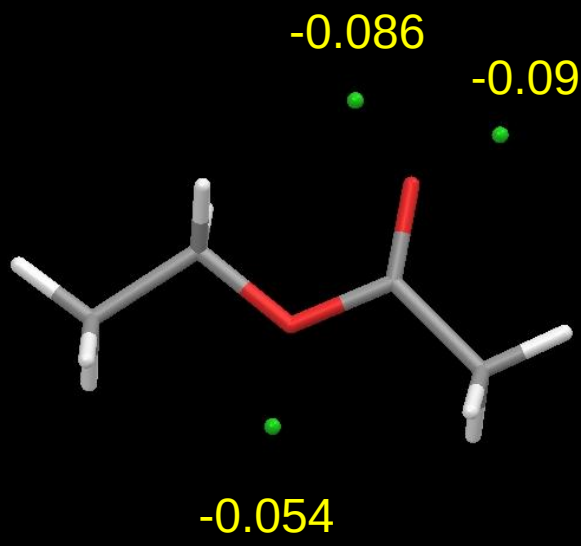
R^2 = 0.65
RMSE = 0.43

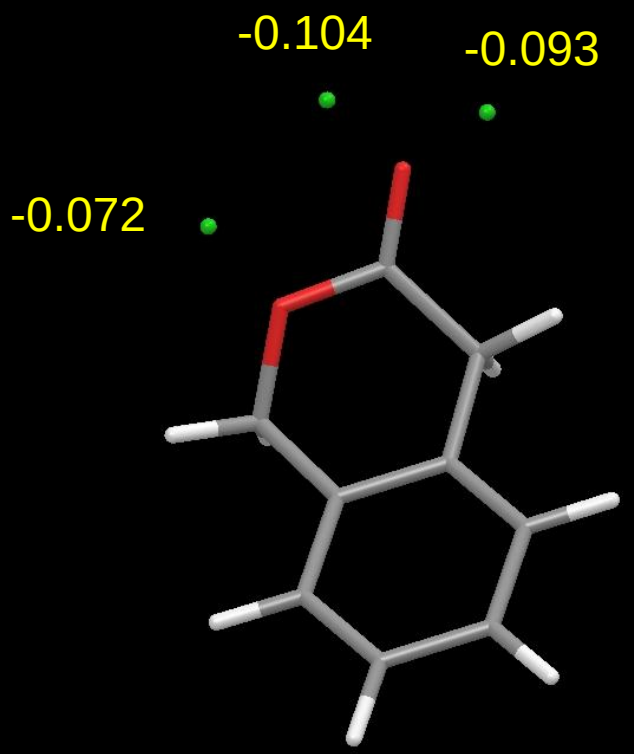
Kenny, *JCIM*, **2009**, *49*, 1234-1244

Fluorine: A weak hydrogen bond acceptor



Hydrogen bonding of esters





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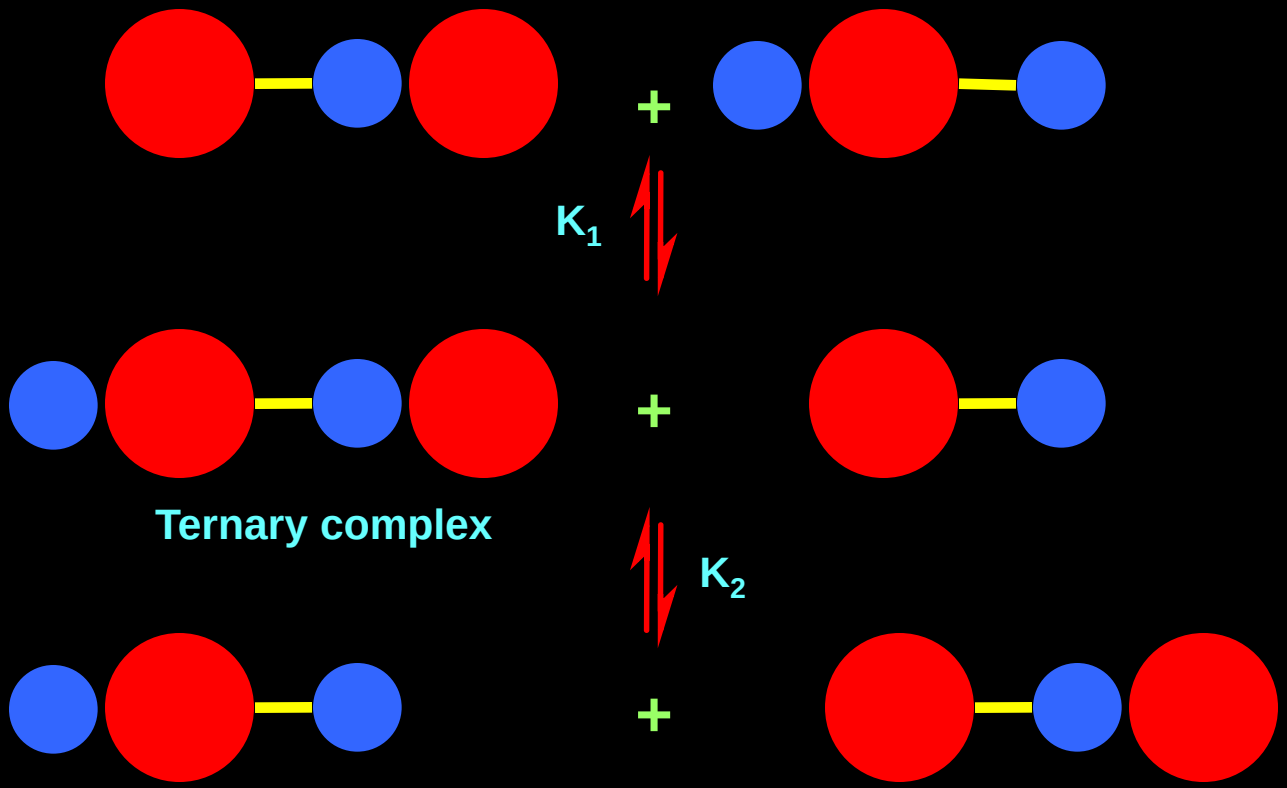
Quantifying the effect of complex formation



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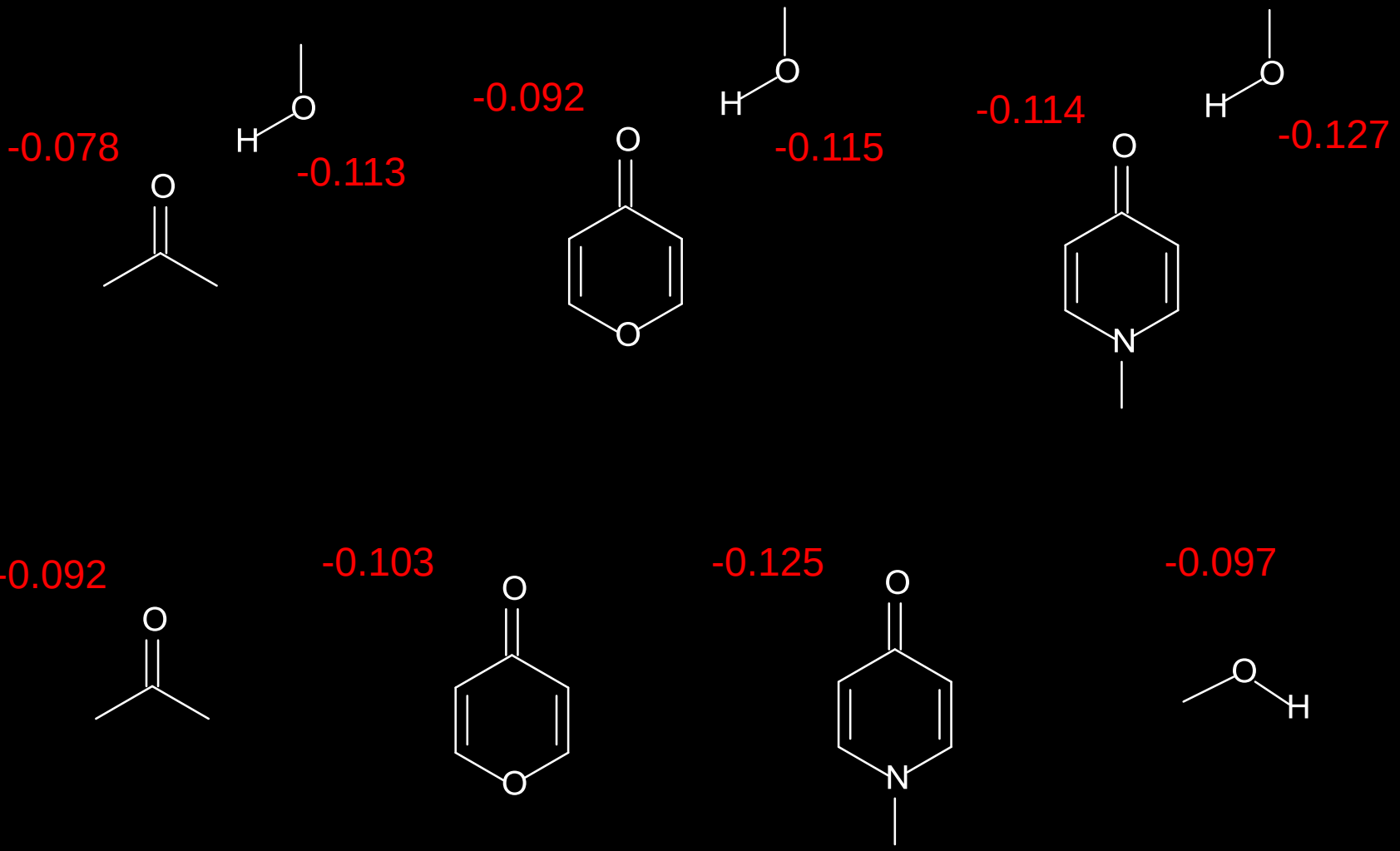
Effect of complex formation on V_{min}



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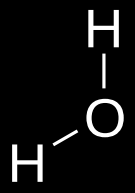
Effect of complex formation on predicted logK_α

1.2

(~ Alcohol)

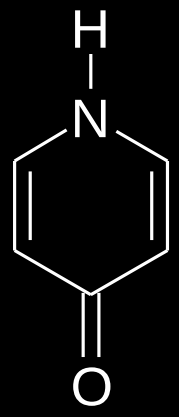
2.0

(~ Phenol)



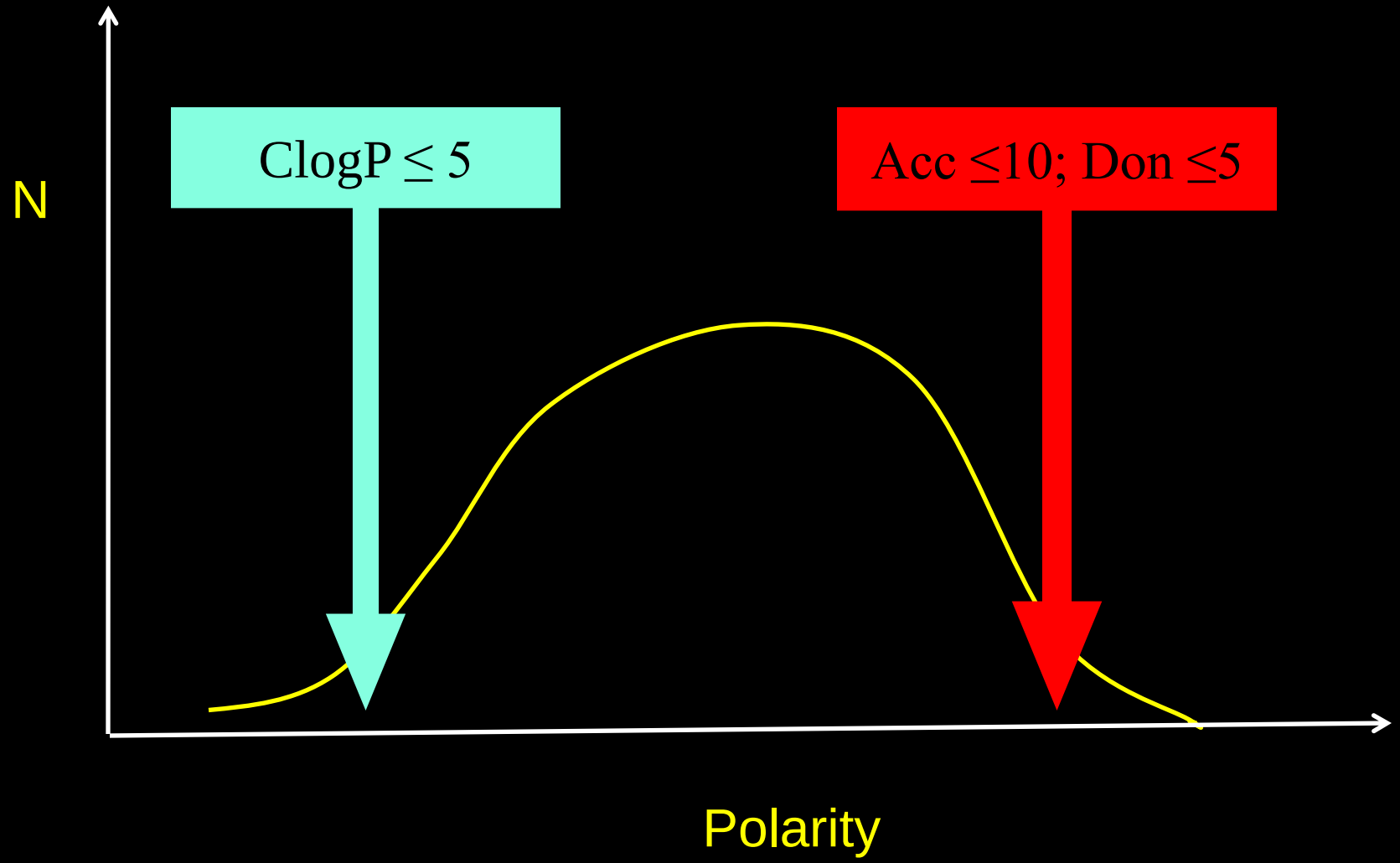
2.8

(~ 4-CF_3Phenol)

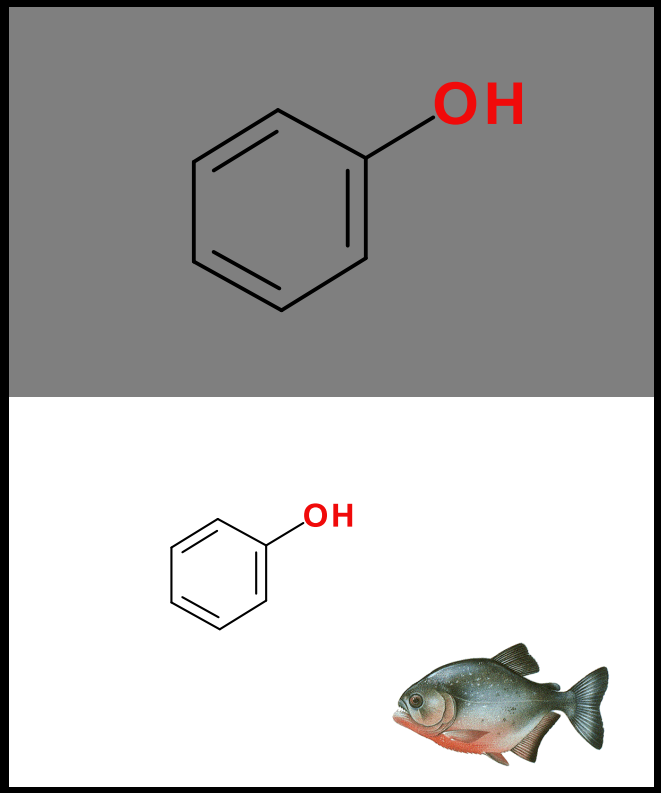


Kenny, *JCIM*, **2009**, *49*, 1234-1244

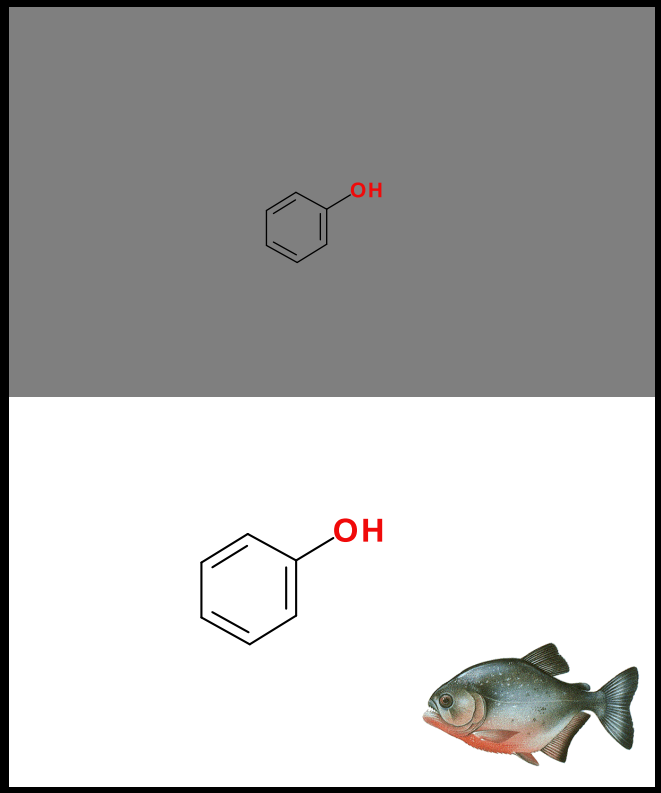
An alternative view of the Rule of 5



Octanol/water is not the only partitioning system



Octanol/Water

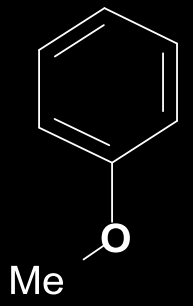


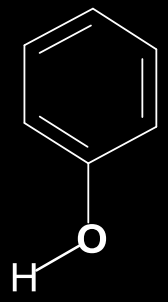
Alkane/Water

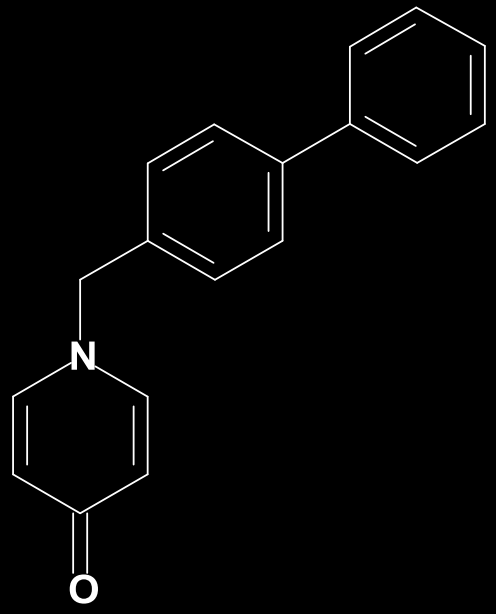
$logP_{alk}$: Experimental challenges

- Many polar solutes are poorly soluble in alkane solvents
- Self-association
  - Masks polarity
  - Limits concentration at which measurements can be made.
  - Need to vary concentration to demonstrate that it is not an issue

Differences in octanol/water and alkane/water logP values reflect hydrogen bonding between solute and octanol







$logP_{oct}$ = 2.1	$logP_{oct}$ = 1.5	$logP_{oct}$ = 2.5
$logP_{alk}$ = 1.9	$logP_{alk}$ = -0.8	$logP_{alk}$ = -1.8
$\Delta logP$ = 0.2	$\Delta logP$ = 2.3	$\Delta logP$ = 4.3

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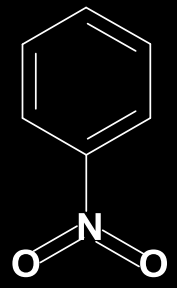
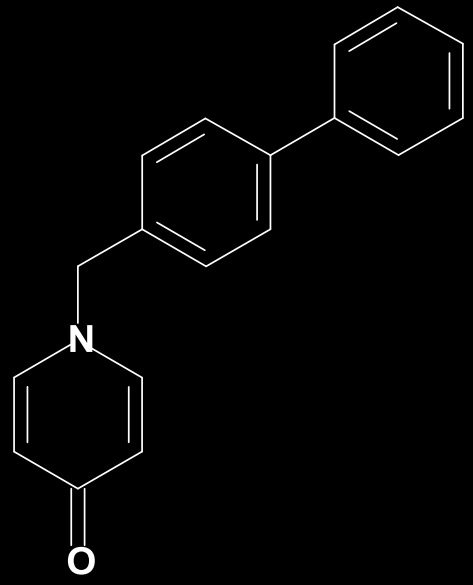
PSA is not predictive of hydrogen bond strength



ΔlogP = 0.5

PSA = 48 Å^2



ΔlogP = 4.3

PSA = 22 Å^2

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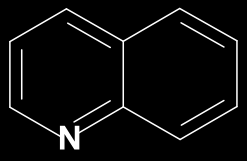
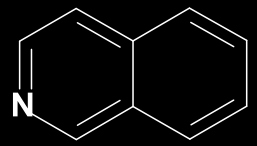
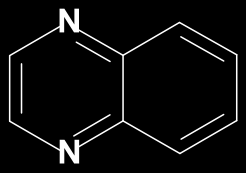
Measured values of ΔlogP



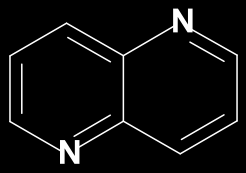
1.0



1.1



0.8



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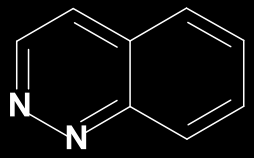

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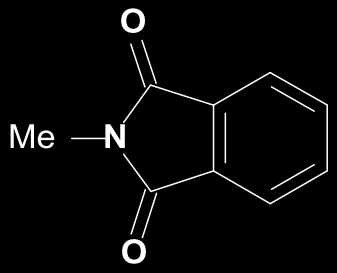
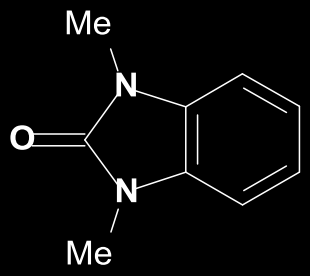


0.8



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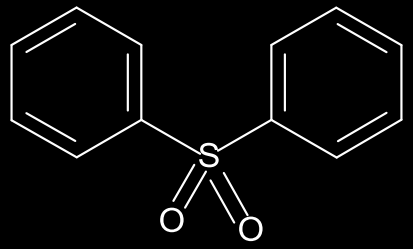

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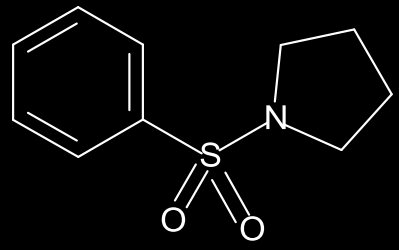

1.1

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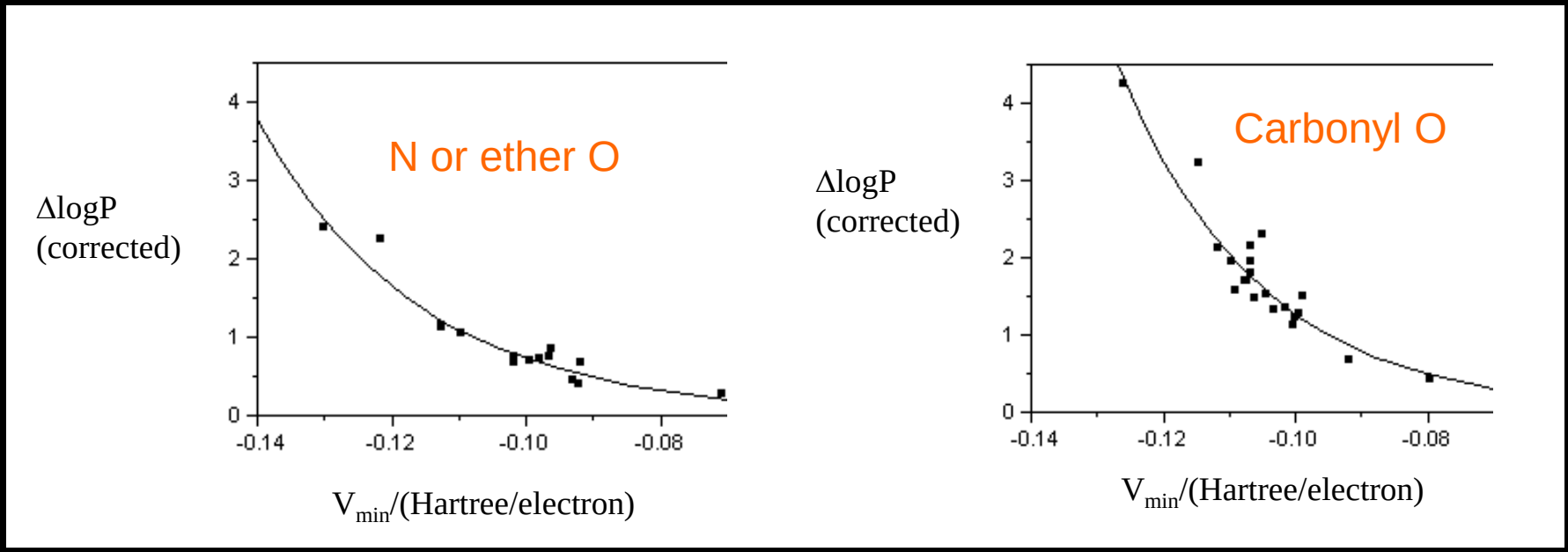
Prediction of contribution of acceptors to ΔlogP



$$\Delta logP = \Delta logP_0 \times \exp(-kV_{min})$$

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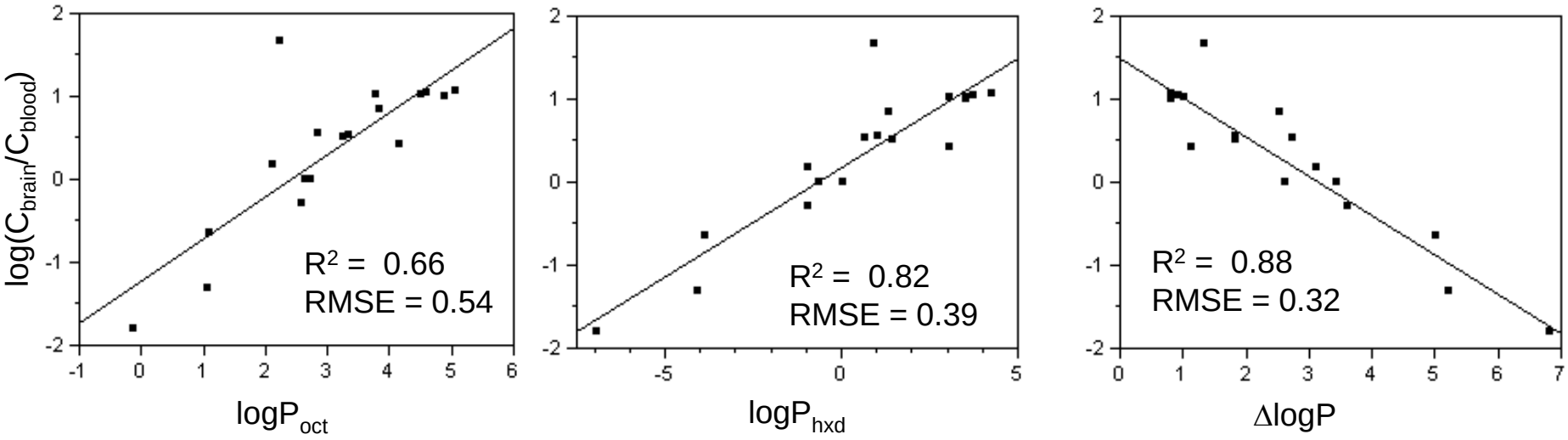
Prediction of blood/brain partitioning



Toulmin et al, *J. Med. Chem*. **2008**, *51*, 3720-3730

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