Prediction of hydrogen bond acidity

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Hydrogen bonding: Why bother?

- Interactions between drug and solvent (permeability, solubility, potency)
- Interactions between drug and target (potency, agonism)
- Interactions between drug molecules in crystal lattice (solubility)

A hydrogen bonding scale

- Equilibrium constant for hydrogen bond formation in 1,1,1-trichloroethane
- Donors: $\log K_{\alpha}$
  - Common acceptor: N-Methylpyrrolidone
- Acceptors: $\log K_{\beta}$
  - Common acceptor: 4-Nitrophenol

Hydrogen bonding and pKa

Compound	**pKa**	**logK_β**	**logK_α**
Pyridine	5.22	2.52	
Pyridazine	2.24	2.53	
N-Methylimidazole	7.25	3.68	
4-Dimethylaminopyridine	9.70	3.54	
Phenol	10.0		2.14
Acetic acid	4.76		2.04

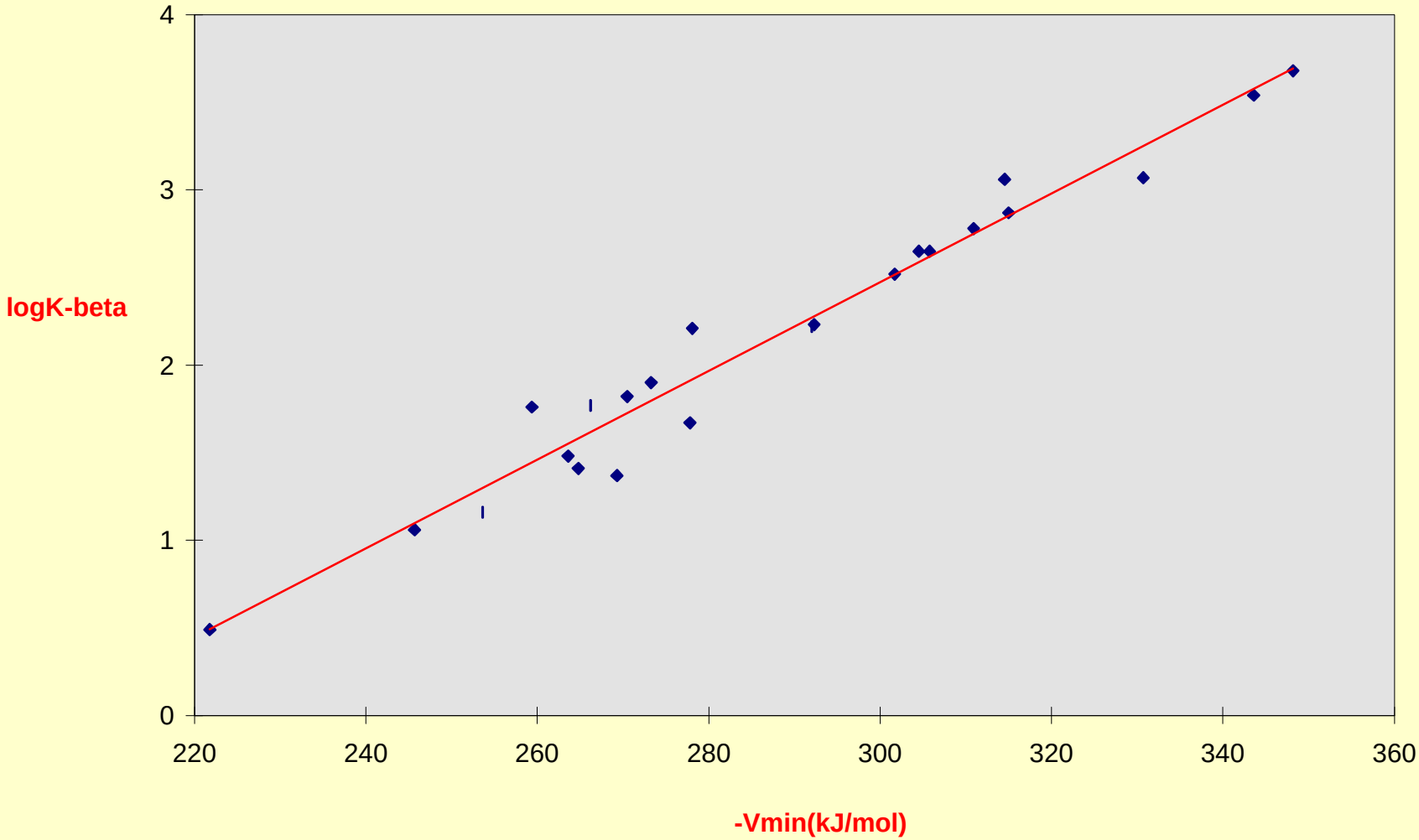
QM calculations and hydrogen bonding

- Supermolecule calculations
  - Appropriate if complexation partner known
  - Need large basis sets to avoid BSSE
  - Multiple minimum problem
- Molecular electrostatic properties
  - No explicit reference to complexation partner
  - More suitable for generic parameterisation

Computed electrostatic potential as predictor of hydrogen bonding

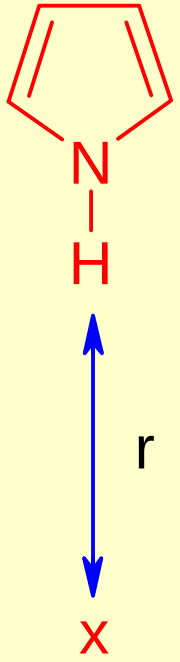
- Minimised electrostatic potential (V_{min}) in lone pair region has been shown to be useful predictor for acceptors
- Analogous stationary points not available for donors; point on van der Waals surface that maximises electrostatic potential ($V_{S,max}$) has been used

logK-beta as function of Vmin



Electrostatic descriptors for donors

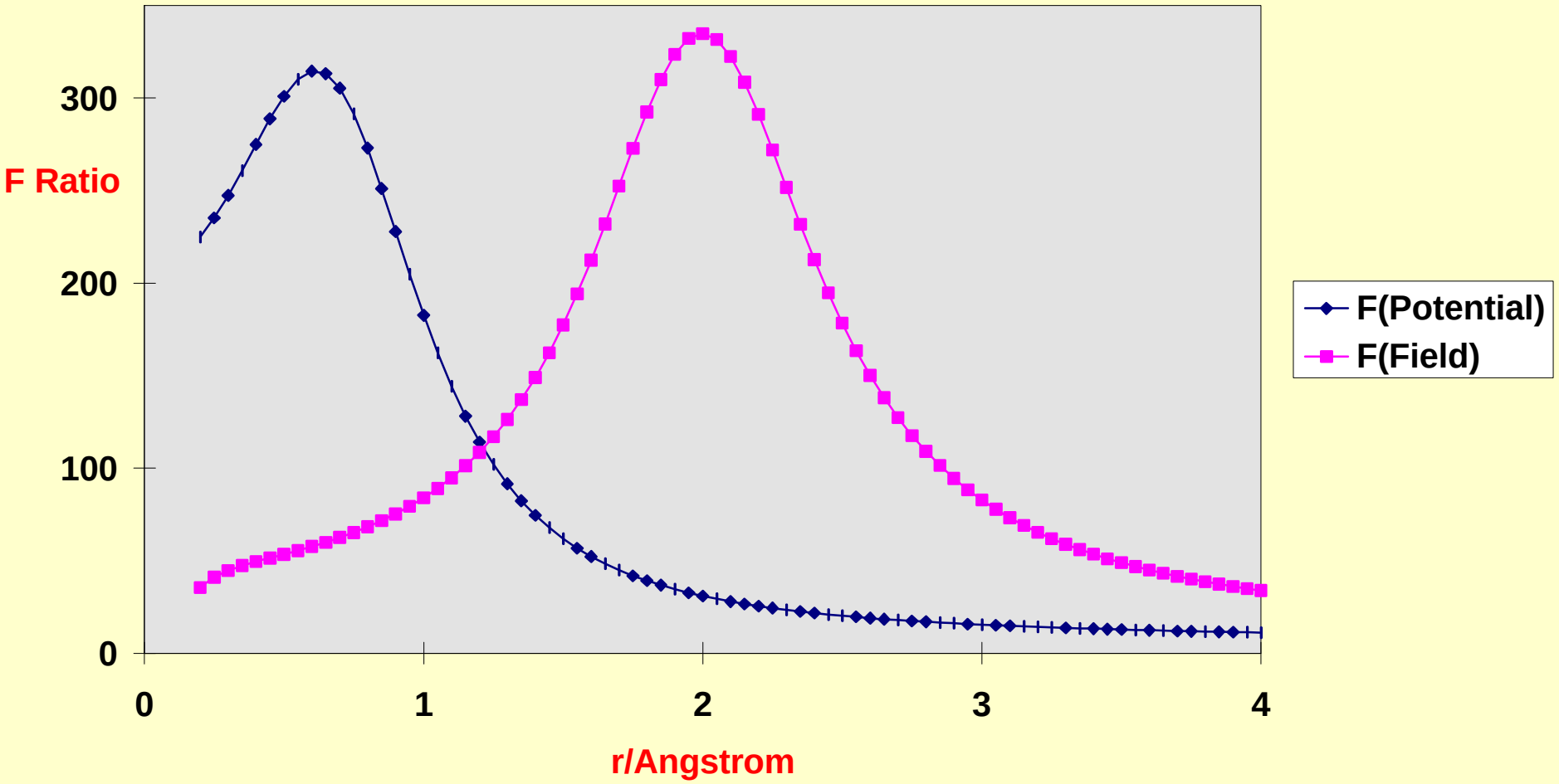
- Computed at distance, r, from hydrogen on N-H axis
- $V_\alpha(r)$: Electrostatic potential
- $|\mathbf{F}_\alpha(r)|$: Magnitude of electric field strength ($\mathbf{F}_\alpha = -\oplus V_\alpha$)



The data

- 42 hydrogen bond donors
- Range in $\log K_{\alpha}$: 0.60 (tetrahydroquinoline) to 3.55 (phenyltetrazole)
- 29 Oxygen donors (alcohols, phenols, carboxylic acids)
- 13 Nitrogen donors (amides, heterocycles, anilines)

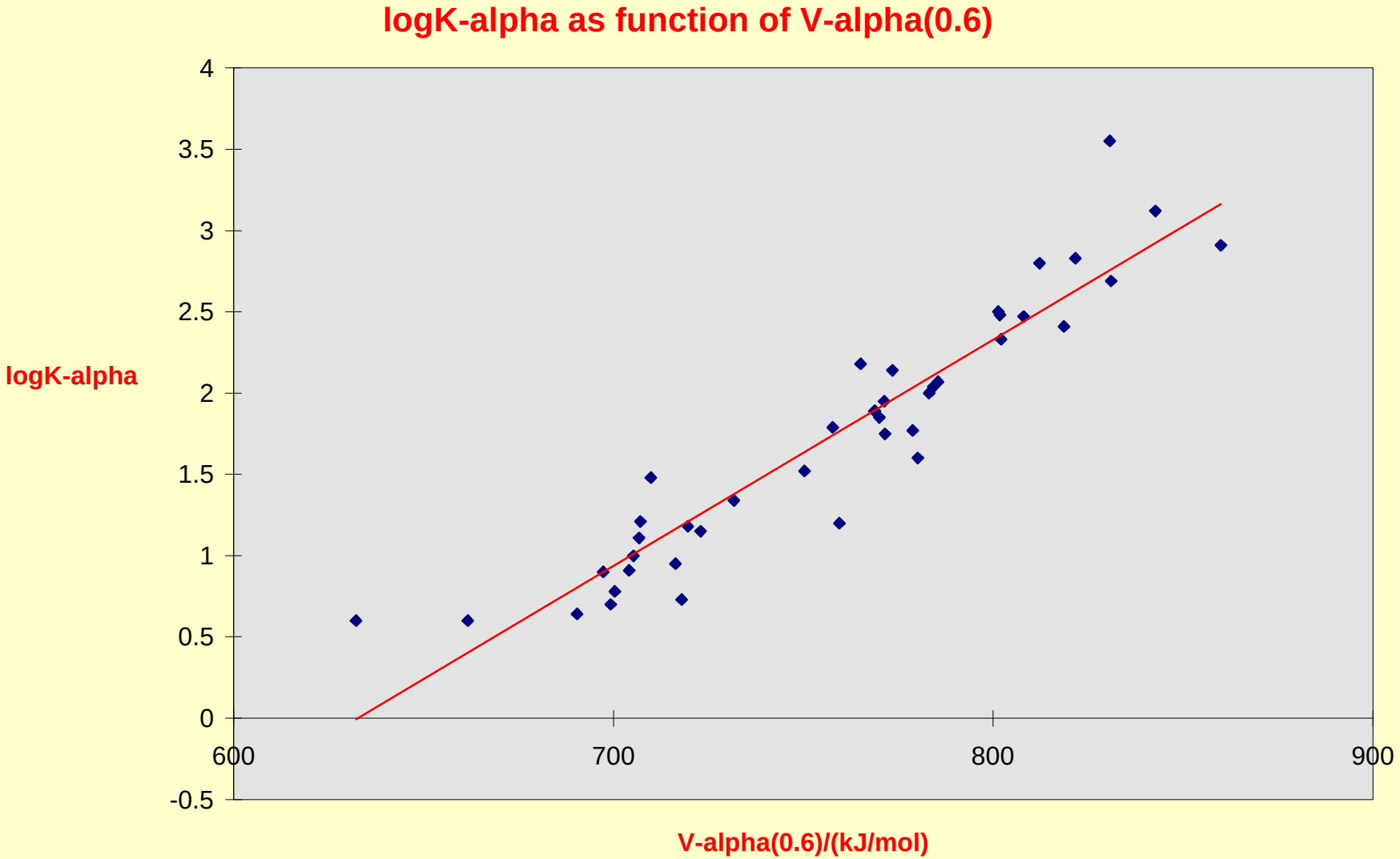
F Ratio as function of distance



Fit as function of calculation level

$$\log K_{\alpha} = A(r) + v(r)V_{\alpha}(r)$$

Level	r/Å	R-square	F ratio
RHF/6-31G*//6-31G*	0.60	0.887	312
RHF/6-31G**//6-31G*	0.60	0.887	314
B3LYP/6-31G**//6-31G*	0.55	0.883	301


logK-alpha as function of V-alpha(0.6)
logK-alpha
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
600
700
800
900
V-alpha(0.6)/(kJ/mol)

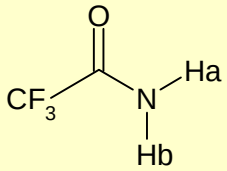
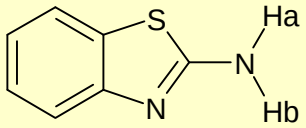
The health warning...

- $\log K_{\alpha}$ measures free energy differences; gas phase electrostatics not expected to deal with entropic effects
- No account taken of steric effects
- Planarity of nitrogen is basis set dependent
- How relevant is hydrogen bonding in 1:1 complex to molecule in solvent bath?

Predicting hydrogen bond acidity

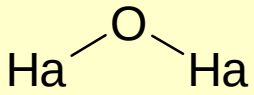
- Use $\log K_\alpha = A(r) + v(r).V_\alpha(r)$
  - r/Å = 0.60
  - A= -8.80 (SE = 0.60)
  - v.(kJmol^{-1}) = 1.39 x 10^{-2} (SE = 7.8 x 10^{-4})
- Prefer $V_\alpha(r)$ to $|\mathbf{F}_\alpha(r)|$ as $\log K_\alpha$ predictor
  - Predicts more effectively closer to donor hydrogen (safer?)

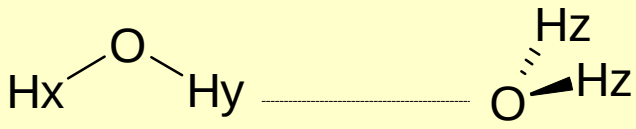
Predicting $\log K_{\alpha}$ for non-equivalent donors

Structure		Predicted	Measured
	Ha	1.63	
	Hb	1.87	
	Tot:	2.07	1.52
	Ha	1.17	
	Hb	0.71	
	Tot:	1.30	~1.1

Water dimer: Polarisation effects

- Predicted logK_α
  - Ha 1.11
  - Hx 0.28
  - Hz 1.81





Conclusions

- Electrostatic potential and its gradient, the electric field strength, are equivalent and effective descriptors for hydrogen bond acidity.
- Effects of structural changes can be compared across series and substituent effects can be obtained in context.
- V_α most predictive of $\log K_\alpha$ within van der Waals radius of hydrogen. This has implications for CoMFA and fitting charges to electrostatic potentials.
- Including both V_α and $\mathbf{F}_\alpha$ in CoMFA is equivalent to using finer grid.

References

- MH Abraham, *Chem. Soc. Rev.* **1993**, *22*, 73: Review on hydrogen bonding scales.
- MH Abraham, PP Duce, DV Prior, DG Barratt, JJ Morris & PJ Taylor, *J. Chem Soc. Perkin Transactions 2* **1989**, 1355: $\log K_\alpha / \log K_\beta$ hydrogen bonding scales.
- JS Murray & P Politzer, *J. Chem. Res (S)* **1992**, 110: V_{min} and $V_{S,max}$ descriptors; these authors have been very active in this area.
- PW Kenny, *J. Chem Soc. Perkin Transactions 2* **1994**, 199: $V_\beta(r)$ & $\mathbf{F}_\beta(r)$ descriptors defined and compared with V_{min}.
- www.gaussian.com: Website for Gaussian Inc; the calculations described in this talk can be carried out with unmodified commercially available software.