

Quantum Molecular Similarity and QSAR

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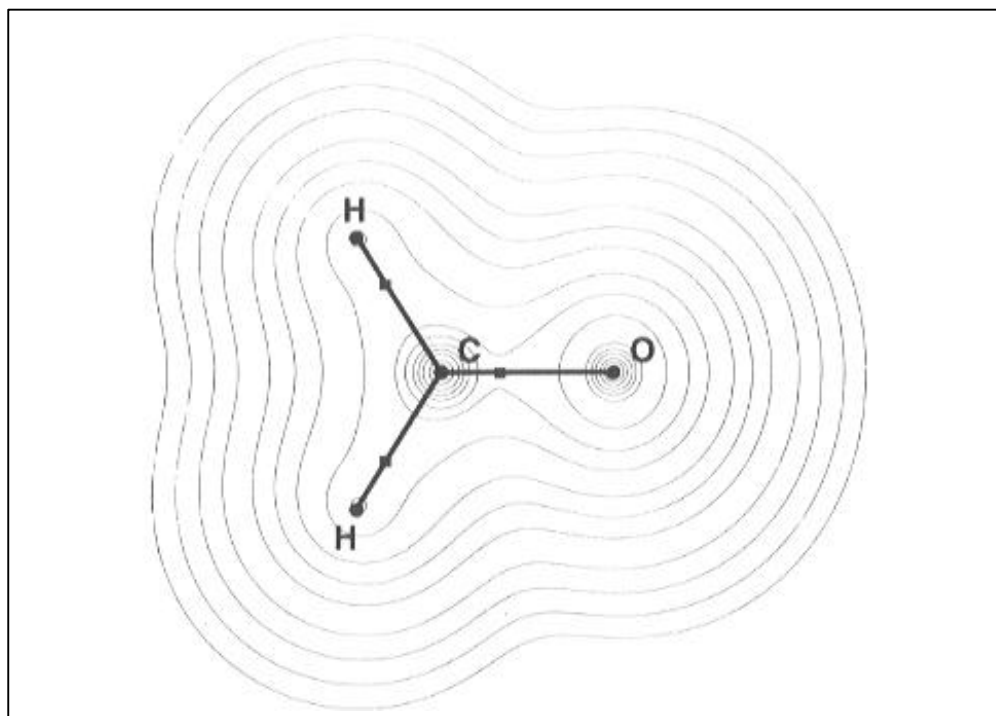
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Chronological Account :

- ◆ Electron density " ρ " is source of information.
- ◆ Compare two densities :
superimpose two molecules A and B and
minimise $e_{AB} = \int_{all\ space} dV |\mathbf{r}_A - \mathbf{r}_B|^2$ or
- ◆ Special points in density ?
Theory of "Atoms in Molecules"
(topological analysis of ρ)
- ◆ Bond Critical Point (BCP) : $\nabla\rho = \mathbf{0}$
- ◆ Example : methanal

[From : "Atoms in Molecules. An Introduction",
P.Popelier, Pearson, Harlow, 1999.]



◆ Properties evaluated at the BCP :

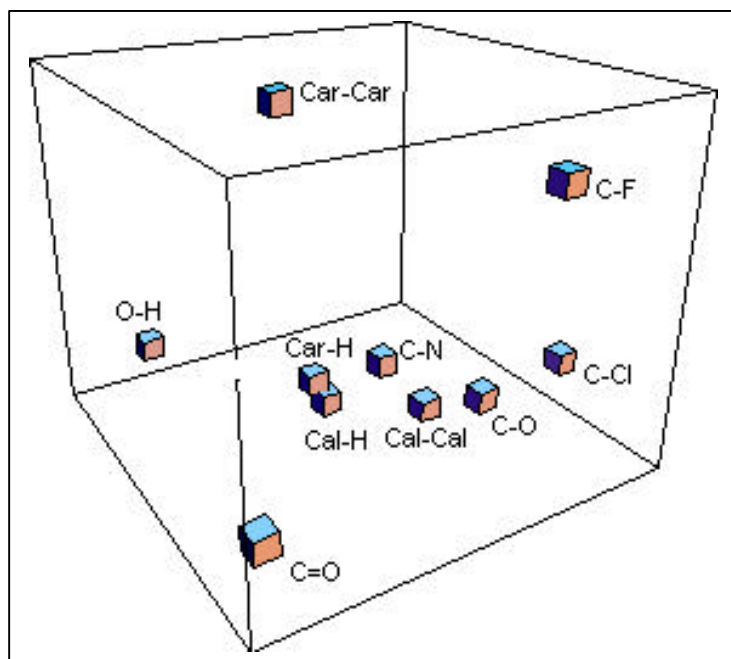
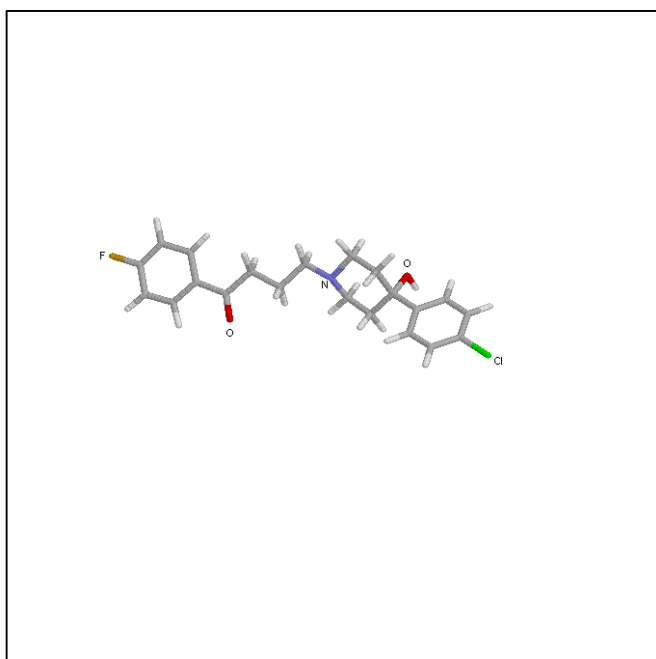
Electron density : ρ_b	(bond order)
Laplacian of ρ : $\nabla^2\rho_b$	(ionicity)
Ellipticity : ε_b	(π -character)

◆ BCP space :

abstract space in which the molecule can be summarised compactly and reliably

[e.g. 3D \rightarrow ($\rho_b, \nabla^2\rho_b, \varepsilon_b$)]

◆ Example : drug haloperidol (51 BCPs)



Example :

$C_{\text{arom}}-C_{\text{arom}}$ cluster contains bonds adjacent to C-X
 Halogen X is π -donor (F>Cl) \Rightarrow increased ε_b

[From : P.Popelier in "Molecular Similarity in Drug Design", Ed. P.M.Dean, Blackie, p.215, 1994]

◆ Distance measure in BCP space :

$$d(A, B) = \sum_{i \in A} \sum_{j \in B} d_{ij}$$

where d_{ij} is the distance between BCP i and BCP j

- ◆ The distance between BCPs is given in terms of the components of BCP space, i.e. the properties evaluated at the BCPs. Example :

$$d_{ij} = \left[(\mathbf{r}_{b,i} - \mathbf{r}_{b,j})^2 + (\nabla^2 \mathbf{r}_{b,i} - \nabla^2 \mathbf{r}_{b,j})^2 + (\mathbf{e}_{b,i} - \mathbf{e}_{b,j})^2 \right]^{1/2}$$

- ◆ Standardisation of the components : $x \rightarrow (x-\mu)/\sigma$

- ◆ **Application :**

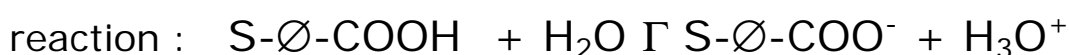
ionisation constants of benzoic acids

(both *para* and *meta*).

- ◆ Hammett equation :

$$\rho = \log \frac{K_S}{K_H} = \rho K_{a,H} - \rho K_{a,S}$$

where σ is Hammett's substituent constant for the general



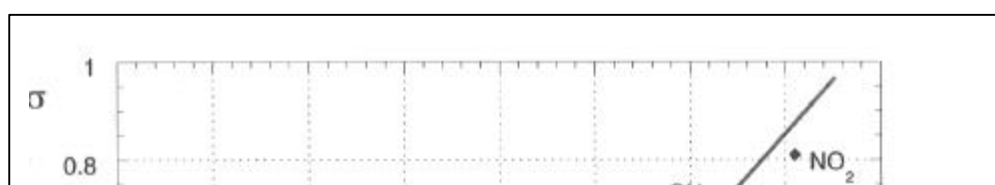
- ◆ Which bonds should be included to obtain the correct experimental acidity ?

We need to determine "i \in A" and "j \in B" in d(A,B)

→ determination of "active center"

- ◆ Only the bonds in COOH are able to reproduce the experimental sequence

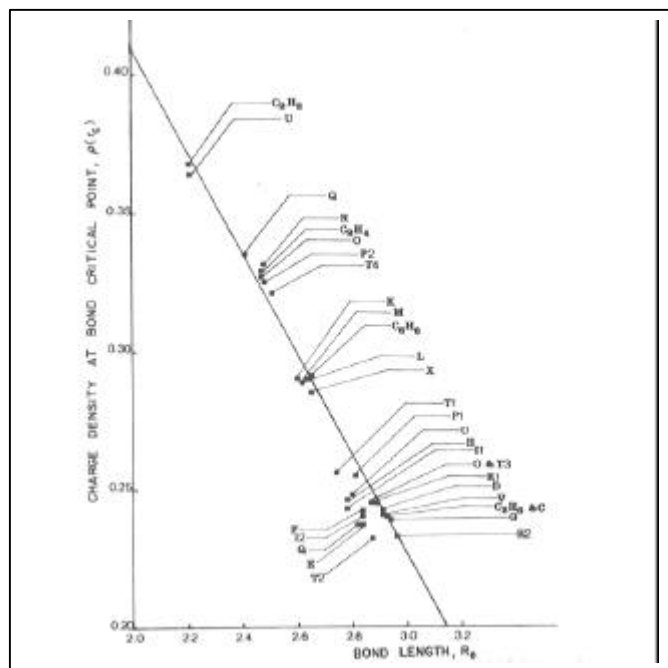
[P.Popelier, J.Phys.Chem. A, **103**, 2883 (1999)]



$d(\text{NH}_2, \text{S})$

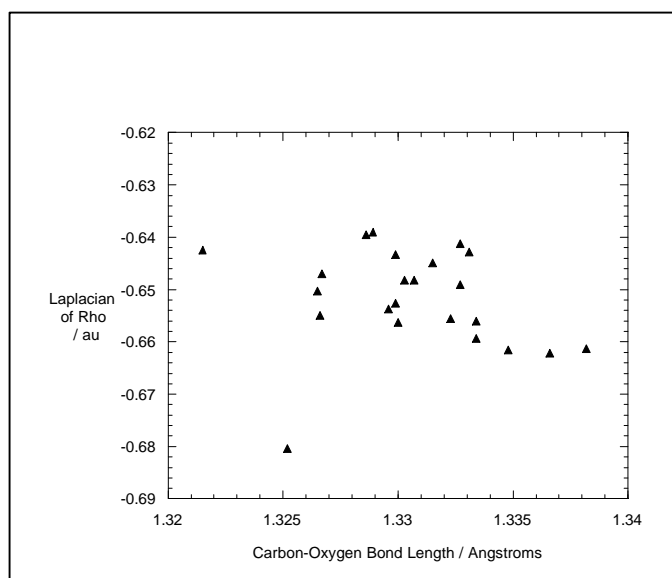
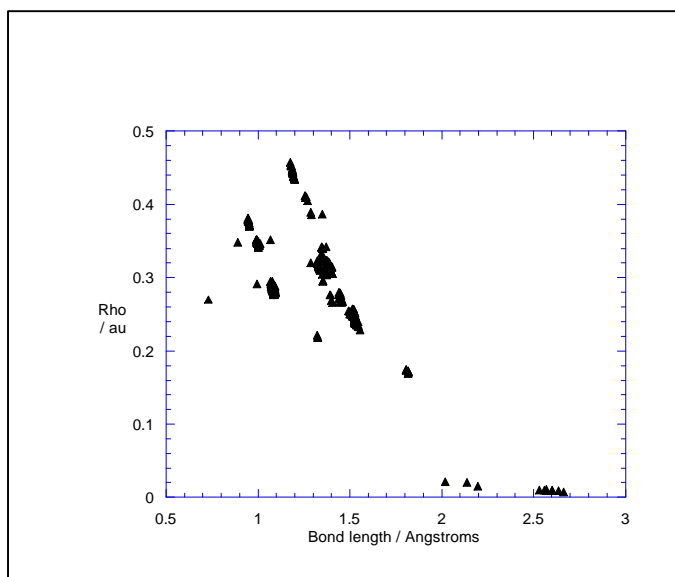
- ◆ $d(\text{NH}_2, \text{S})$ is proposed similarity distance from the least active *p*-benzoic acid.
- ◆ Extra substituents COCH_3 , CHO and phenyl correctly predicted.
- ◆ Works also for *meta*
(different ranking of substituents)
- ◆ Extrapolation : O^- indeed left of NH_2 .

- ◆ Highly linear correlation between ρ_b and R_e in C-C bonds for 30 hydrocarbons (Bader *et al.*, 1983)



- ◆ Local linear relationships exist provided the bonds vary little in their chemical surroundings.

[S.E.O'Brien, P.Popelier, *Can.J.Chem.*, **77**, 28 (1999)]
 57 molecules drawn from 20 amino acids, 731 BCPs



731 BCPS : ρ_b vs R_e
 R_e

C-OH BCPS : $\nabla^2 \rho_b$ vs