

Six Lectures on the Nature of the Hydrogen Bond
Lecture 4

*The Dual H-Bond as a Chemical Reaction:
A Basis for a Comprehensive H-bond Theory*

Edited by

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and

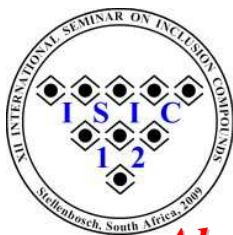
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The topics of the present lecture have been previously presented to other meetings and, in particular, to:



ISIC-12
XII International Seminar on Inclusion
Compounds

Stellenbosch, South Africa, 4-9 April 2009

Ab Initio Prediction of H-Bond Energies and/or Geometries

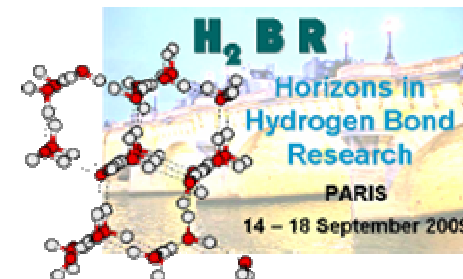
Paola Gilli



H₂ BR
XVIII International Conference on
"Horizons in Hydrogen Bond Research"
Paris, 14-18 September 2009

The Nature of the Hydrogen Bond:
Models and Theories

Paola Gilli



CUSO Summer School 20-24 August 2012
2012 Villars sur Ollon,
on Hydrogen Bonding Switzerland

Six Lectures on the Nature of the Hydrogen Bond

Gastone Gilli

H-Bond: Classical Definitions

Three-Center-Four-Electron Interaction



where **D** is the **Proton Donor** {an electronegative atom such as F, O, N, C, S, Cl, Br, I} and **:A** the **Proton Acceptor** or **Electron-Pair Carrier** {a second electronegative atom or the π -bond of a multiple bond}

Otherwise:

A proton sharing two electron pairs coming from two adjacent electronegative atoms

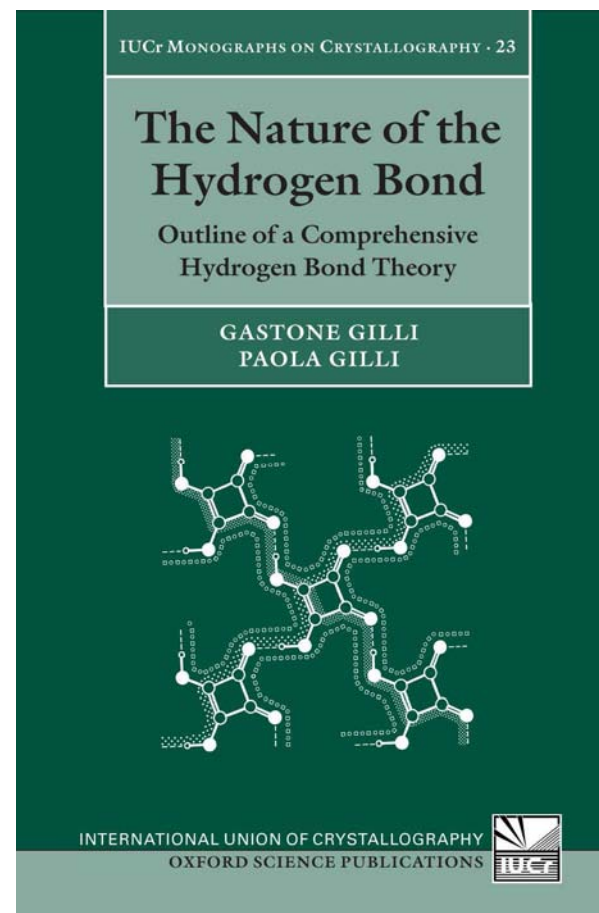


This second formulation makes clear that:

- Both donor and acceptor **electronegativities**, $\chi(\text{D})$ and $\chi(\text{A})$, must be greater than that of the central hydrogen, $\chi(\text{H})$;
- Any H-bond will be the stronger, the greater both donor/acceptor **electronegativities** are (i.e., the greater both **proton affinities** are);
- Both $\text{D}^-:$ and $:\text{A}$ must be bases, so introducing the use of **acid-base quantities** {gas-phase proton affinities [PA(D^-) and PA(A)] or water acid-base dissociation constants [p*K*_{AH}($\text{D}-\text{H}$) and p*K*_{BH⁺}($\text{A}-\text{H}^+$)]} in any H-bond treatment.

Some Basic References

1. W.M. Latimer, W.H. Rodebush, *J. Am. Chem. Soc.* **42**: 1419-1433 (1920).
2. L. Pauling, *The Nature of the Chemical Bond* (Cornell University Press, Ithaca, NY, 1960)
3. G.C. Pimentel, A.L. McClellan, *The Hydrogen Bond* (Freeman: San Francisco, 1960).
4. S.N. Vinogradov, R.H. Linnel, *Hydrogen Bonding* (Van Nostrand Reinhold: New York, 1971).
5. G.A. Jeffrey, *An Introduction to Hydrogen Bonding* (Oxford University Press: Oxford, 1997).
6. G. Gilli, P. Gilli, *The Nature of the Hydrogen Bond. Outline of a Comprehensive Hydrogen Bond Theory* (Oxford University Press: Oxford, 2009).
7. P. Gilli, L. Pretto, V. Bertolasi, G. Gilli, *Predicting H-bond strengths from acid-base molecular properties. Acc. Chem. Res.* **42**: 33-44 (2009).
8. P. Gilli, G. Gilli, *H-bond models and theories: The dual H-bond model and its properties. J. Mol. Struct.* **972**: 2-10 (2010).



The H-Bond Strength

The outstanding H-bond property is the **H-bond strength**, quantified as

- H-bond-dissociation energy, E_{HB} , or
- H-bond-dissociation enthalpy, ΔH_{DIS} ,

but often monitored by

- the D...A contact distance, $d_{\text{D}\cdots\text{A}}$, or
- the sum $d'_{\text{D}\cdots\text{A}} = d_{\text{D-H}} + d_{\text{H}\cdots\text{A}}$, a quantity naturally accounting for D-H-A angle changes.

Empirically, energies and geometries are found to be **interrelated** and **encompassed between two extremes**:

- (i) **weak, long, dissymmetric, proton-off-centered, and mostly bent** D–H...:A bonds of **electrostatic nature**; and
- (ii) **strong, short, symmetric, proton-centered, and linear** D...H...A bonds reducible to three-centre-four-electron interactions of **covalent nature**.

The H-Bond Puzzle and the Prediction of the H-Bond Strength

Unlike normal chemical bonds, H-bonds feature properties that **do not simply depend on the donor/acceptor nature but undergo large variations even for a same donor-acceptor couple.**

For example, weak HO–H···OH₂ bonds in neutral water [$E_{\text{HB}} \approx 5 \text{ kcal mol}^{-1}$; $d_{\text{O}\cdots\text{O}} \approx 2.70\text{-}2.75 \text{ \AA}$] change, in acidic and basic medium, to the very strong [H₂O···H···OH₂]⁺ or [HO···H···OH]⁻ bonds having $E_{\text{HB}} \approx 26\text{-}31 \text{ kcal mol}^{-1}$ and $d_{\text{O}\cdots\text{O}} \approx 2.38\text{-}2.42 \text{ \AA}$.

This surprising behavior, that we have called *the H-bond puzzle*, practically **prevents the prediction of H-bond strengths** from molecular properties.

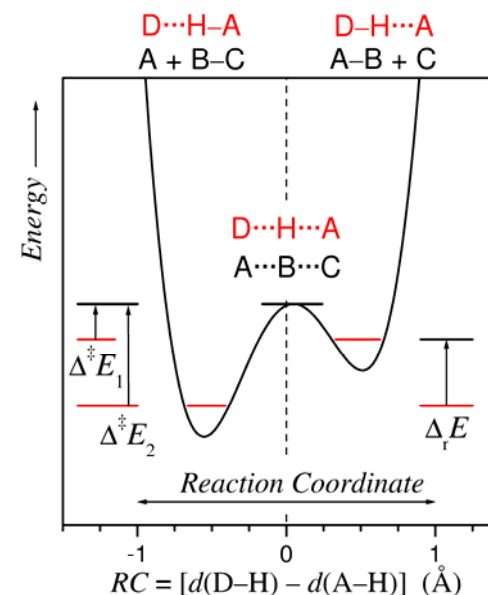
The present communication will try to **solve the puzzle** by re-examining the problem and discussing the most recent methods developed to **make such strength predictions feasible.**

A New Comprehensive H-Bond Model: The Dual H-Bond

The clue of the problem is that
the H-bond is not really a bond
donated by the donor D–H to the acceptor :A but rather
consists of two bonds
formed by a same proton with two acceptors, each carrying an electron pair.

In chemical words, the H-bond **is not a reaction of nucleophilic addition** but rather **of nucleophilic substitution** along the **bimolecular proton-transfer (PT) reaction pathway** leading from D–H···A to D···H–A through the D···H···A transition state.

Hence, what we are used to call H-bond is actually **a minimum (or two minima) along this reaction pathway** which may have quite **different shapes** according to the strength of the H-bond formed.



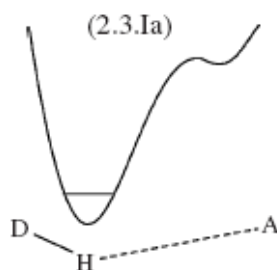
The Dual H-Bond (continued)



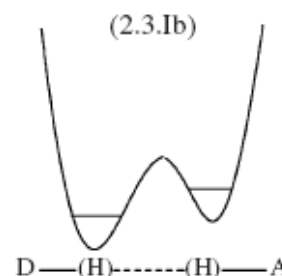
The **possible shapes** the PT reaction pathway may adopt according to the **different strength** of the H-bond formed are essentially of three types:

- (i) only one accessible asymmetric single well (**aSW**) in **weak bonds**;
- (ii) two symmetric or slightly asymmetric double wells (**sDW, saDW**) in **strong bonds** (also called **LBHBs = low-barrier H-bonds**); or
- (iii) one symmetric single well (**sSW**) in **very strong bonds**.

**Weak
HB
(aSW)**



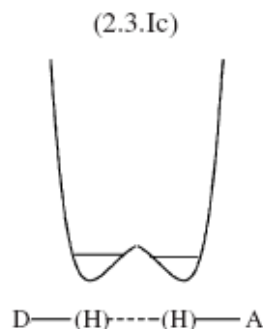
aSW-HB
*Asymmetric single-well
high-barrier H-bond*
Properties:
Weak, long and
strongly dissymmetric.
Ordered both in solution
and in crystals.
Essentially electrostatic.



aDW-MB
*Asymmetric double-well
medium-barrier H-bond*
Properties:
Moderate strength.
Tautomeric exchange
in solution and static
disorder in crystals.
Partially covalent.

**Moderately
Strong HB
(saDW)**

**Strong
HB
(sDW)
(LBHB)**



sDW-LB
*Symmetric double-well
low-barrier H-bond*
Properties:
Strong and short.
Tautomeric exchange
in solution and dynamic
disorder in crystals.
Partially covalent.



sSW-NB
*Symmetric single-well
no-barrier H-bond*
Properties:
Very strong and short.
Symmetric and linear.
Ordered both in solution
and in crystals.
Essentially covalent.

**Very
Strong
HB
(sSW)**

The Dual H-Bond Energy

According to the dual H-bond model, the H-bond energy, E_{HB} , is not properly the $\text{D-H}\cdots\text{A}$ dissociation energy, but rather *the smaller of the two bond-dissociation energies, $D_0(\text{D-H})$ and $D_0(\text{H-A})$* , by which D^- and $:\text{A}$ are competitively bound to the same central proton. If one is stronger, the other is weaker, and **weak** the overall H-bond will be. Accordingly, **strong bonds** will occur only when

$$\Delta D_0 = D_0(\text{D-H}) - D_0(\text{H-A}) = 0$$

or, in terms of affinity for the proton (pa), when

$$\Delta \text{pa} = \text{pa}(\text{D}^-) - \text{pa}(:\text{A}) = 0.$$

These relationships, when expressed as

$$\Delta \text{PA} = \text{PA}(\text{D}^-) - \text{PA}(:\text{A}) \quad (\text{in the gas phase}) \quad \text{or}$$

$$\Delta \text{p}K_a = \text{p}K_{\text{AH}}(\text{D-H}) - \text{p}K_{\text{BH}^+}(\text{A-H}^+) \quad (\text{in condensed phase}),$$

assume the name of *PA/pK_a equalization principle*.

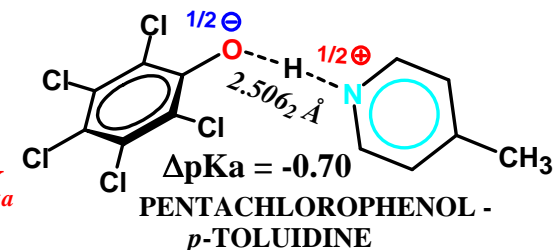
Crystal and thermodynamic data show that **the condition $\Delta D_0 = \Delta \text{pa} \approx 0$** typical of strong H-bonds **can be achieved only in specific chemical circumstances**, normally indicated as the *four strong H-Bond Chemical Leitmotifs*.

A Library of Strong H-bonds: The Chemical Leitmotifs (CLs)

CHARGE-ASSISTED H-BONDS

CL # 1: (\pm)CAHB \Rightarrow S, VS
Double Charge-Assisted HB

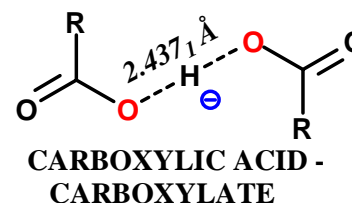
Acid and base having by chance the same PA/pK_a



CL # 2: (-)CAHB \Rightarrow S, VS

Negative Charge-Assisted HB

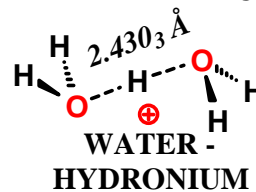
Two acids having lost a proton (same PA/pK_a)



CL # 3: (+)CAHB \Rightarrow S, VS

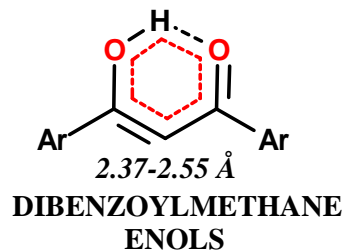
Positive Charge-Assisted HB

Two bases having gained a proton (same PA/pK_a)



**S= Strong, VS= Very Strong,
M= Medium Strong, W= Weak
H-Bond**

σ/π -BOND COOPERATIVE H-BONDS



CL # 4: RAHB \Rightarrow S, VS

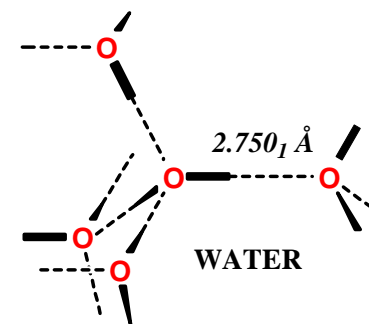
Resonance-Assisted HB or π -Cooperative HB

PA/pK_a Matching by π -Conjugated-Bond Polarization

CL # 5: PAHB \Rightarrow M

Polarization-Assisted HB or σ -Cooperative HB

(Partial) PA/pK_a Matching by σ -Bond Polarization

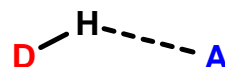


NEITHER CHARGE- NOR RESONANCE/POLARIZATION - ASSISTED H-BONDS

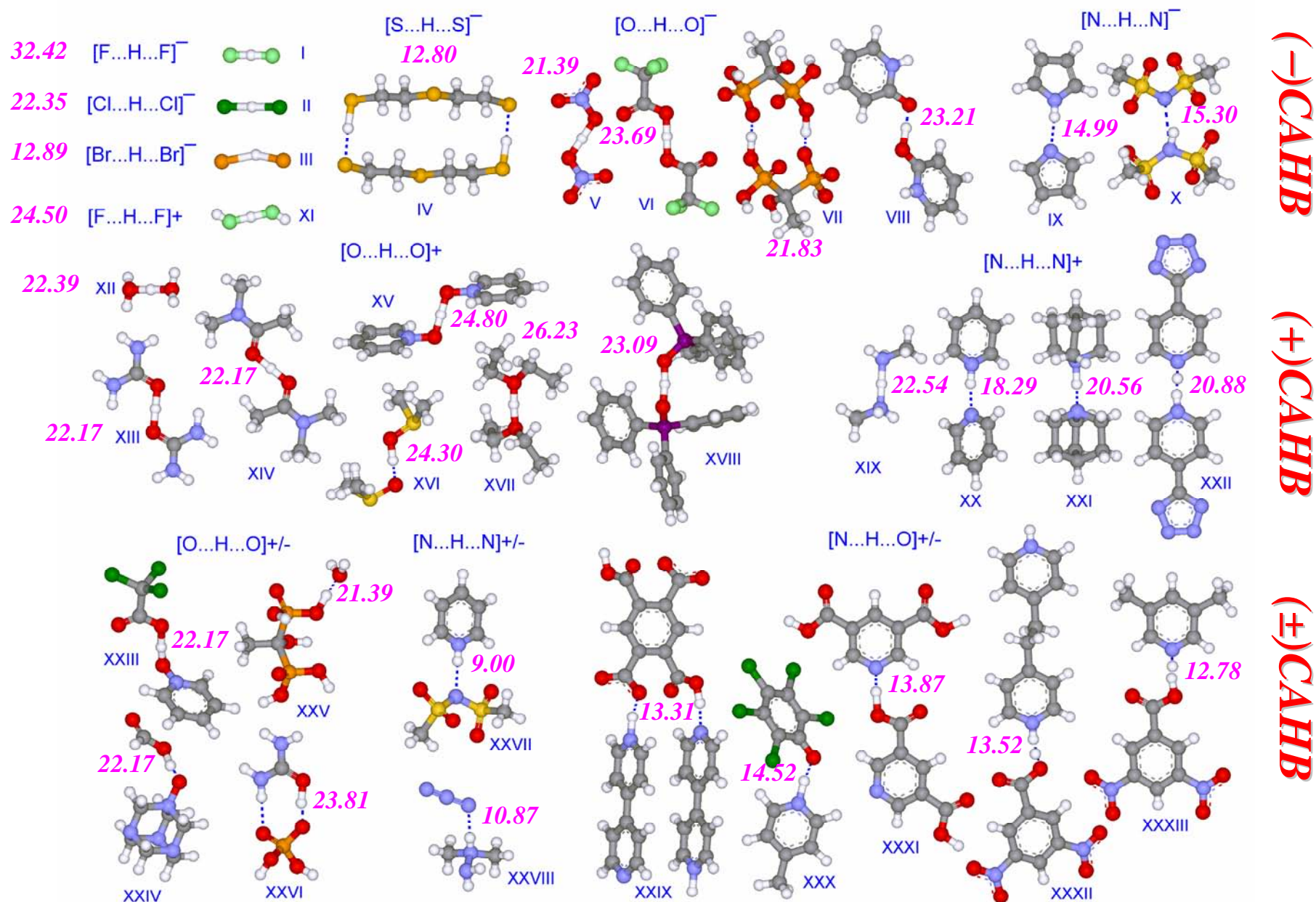
CL # 6: OHB \Rightarrow W

Ordinary HB

No PA/pK_a Matching



A Gallery of the Most Famous Strong H-bonds



P. Gilli et al., *Acc. Chem. Res.* (2009); E_{HB} values (kcal mol⁻¹) calculated by the exponential equation

Towards a comprehensive H-bond theory: Driving Variables and H-Bond Theories

Any **generic H-bond theory** can be written as

$$\text{H-Bond Properties} = F \{ \text{H-Bond Driving Variables} \},$$

where **F** is a **theoretical operator** transforming *variables* into *properties*, such as H-bond geometries, energies, PT barriers, dipole moments, IR frequencies, NMR chemical shifts, etc.

Following the **dual H-bond logic**, the driving variables can be traced back to **two proton affinities**, $\text{pa}(\text{D}^-)$ and $\text{pa}(\text{:A})$, or better to their linear combinations, **sum** $[\Sigma\text{pa}]$ and **difference** $[\Delta\text{pa}]$, which are the only quantities to have a clear physical meaning. The eq above becomes

$$\text{H-Bond Properties} = F \{ [\Sigma\text{pa} = \text{pa}(\text{D}^-) + \text{pa}(\text{:A})]; [\Delta\text{pa} = \text{pa}(\text{D}^-) - \text{pa}(\text{:A})] \}$$

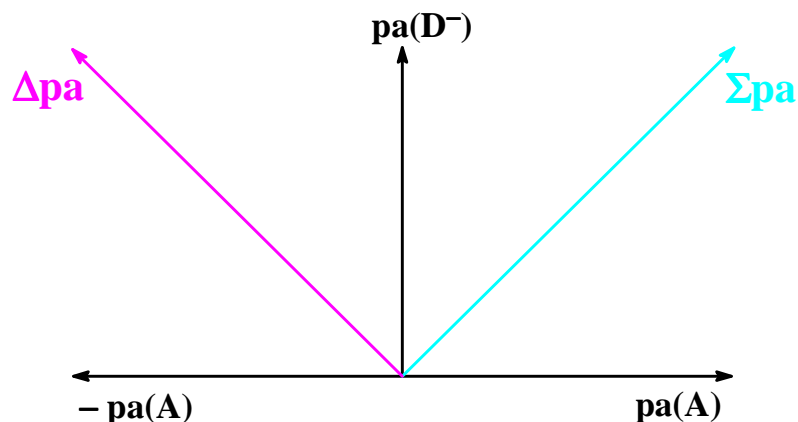
where

$$\text{Sum} = \Sigma\text{pa} \approx [\chi(\text{D}) + \chi(\text{A})]/2 = \text{Average electronegativity of D and A}$$

Difference = Δpa = Reaction energy, $\Delta_r E$, or any of its LFER-related quantities (ΔPA , $\Delta\text{p}K_a$)

This equation will be now analyzed for two special cases:

- (1) Σpa variable for $\Delta\text{pa} = 0$; and
- (2) Δpa variable for $\Sigma\text{pa} = \text{constant}$.



Case study 1. Σpa variable for $\Delta pa = 0$:
1.1 The Importance of Electronegativity

$$H\text{-Bond Properties} = F \{[\Sigma pa = pa(D^-) + pa(:A)]; [\Delta pa = 0]\}$$

Homomolecular (-)CAHBs and (+)CAHBs of the type $[X\cdots H\cdots X]^-$ (X = F, O, Cl, N, Br, S) and $[X\cdots H\cdots X]^+$ (X = O, N) are

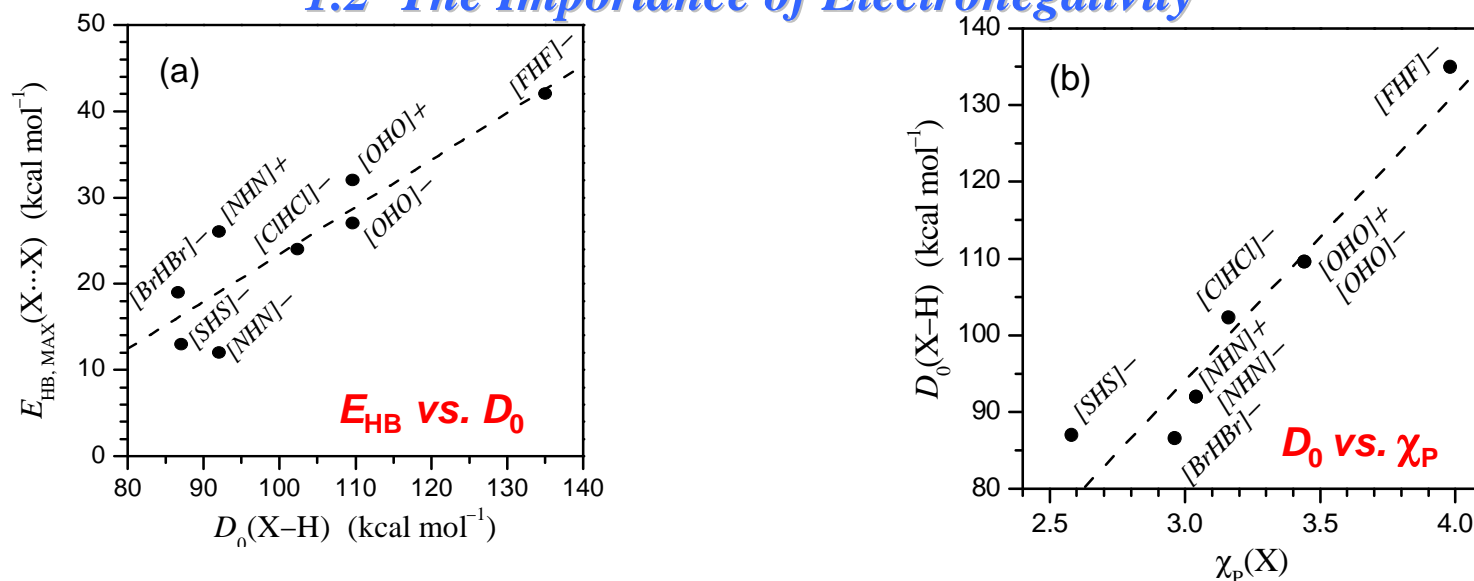
couples of two identical acids or bases

which have $\Delta pa = 0$ by definition, and whose energy, E_{HB} , then corresponds to the maximum observable energy $E_{HB,MAX}(X\cdots X)$.

This $E_{HB,MAX}$ quantity plays an important role in H-bond theories, because a small number of very accurate $E_{HB,MAX}$ values can be recovered from the NIST database as **gas-phase dissociation enthalpies, ΔH_{DIS} , of simple $X\cdots H\cdots X$ homomolecular complexes** and then directly correlated with the corresponding **bond-dissociation energies, $D_0(X-H)$.**

Case study 1. Σpa variable for $\Delta pa = 0$ (continued):

1.2 The Importance of Electronegativity



The following regression equation is obtained

$$E_{\text{HB,MAX}} \equiv \Delta H_{\text{DIS}}(\Delta pa = 0) = -31.3 + 0.55 D_0(\text{X-H})$$

(kcal mol⁻¹; $r = 0.900$, $n = 8$)

which shows that **maximum H-bond energies** are nearly proportional to one half of the X-H bond-dissociation energies, in complete agreement with the VB concept that strong H-bonds are **three-centre-four-electron covalent interactions** splitting a single bond in two half bonds with bond numbers $n = 1/2$.

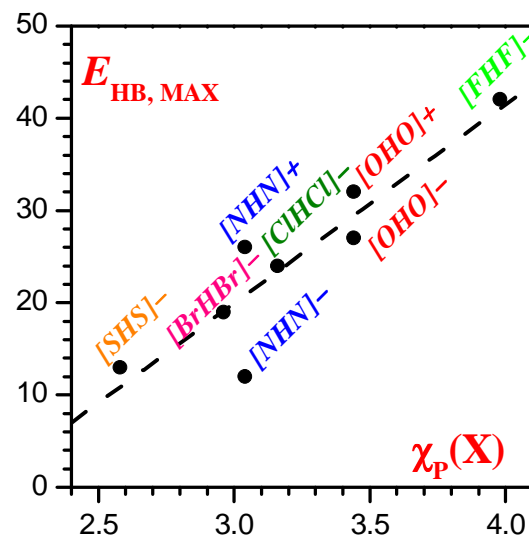
On the other hand, also $D_0(\text{X-H})$ and the electronegativity $\chi_p(\text{X})$ are linearly related

$$D_0(\text{X-H}) = -18.2 + 37.4 \chi_p(\text{X})$$

(kcal mol⁻¹; $r = 0.956$, $n = 8$),

Case study 1. Σpa variable for $\Delta pa = 0$ (continued):

1.3 The Importance of Electronegativity



Finally, the following regression equation is obtained

$$E_{HB,MAX} \equiv \Delta H_{DIS}(\Delta pa = 0) = -44.8 + 21.6 \chi_P(X)$$

(kcal mol⁻¹; $r = 0.907$, $n = 8$),

which, for the first time in the history of the H-bond, shows that *the maximum energy for any given $X \cdots H \cdots X$ bond is a linear function of the electronegativity of X.*

Case study 1. $\Sigma\chi$ variable for $\Delta\chi=0$ (continued):
1.4 H-Bond Electronegativity Classes, $EC(D,A)$

In Summary:

- There may not be a unique energy scale for all H-bonds;
- For any generic D–H···A bond, **any different (D,A) couple** will generate its own specific *H-bond electronegativity class, $EC(D,A)$* ;
- **Each class** will be fully characterized by a **specific couple of linearly related values**, that is
 $[E_{\text{HB,MAX}}(\text{D}\cdots\text{A}) / \Sigma\chi(\text{D,A})]$.

A Quite Useful Energy-Geometry Relationship

It has been recently shown by VB methods (Gilli et al., *Acc Chem Res* 2009) that **all bonds belonging to a same $EC(D,A)$** are characterized by well-definite **ranges of energies and D···A distances**, which are mutually **related by the following VB exponential equation**

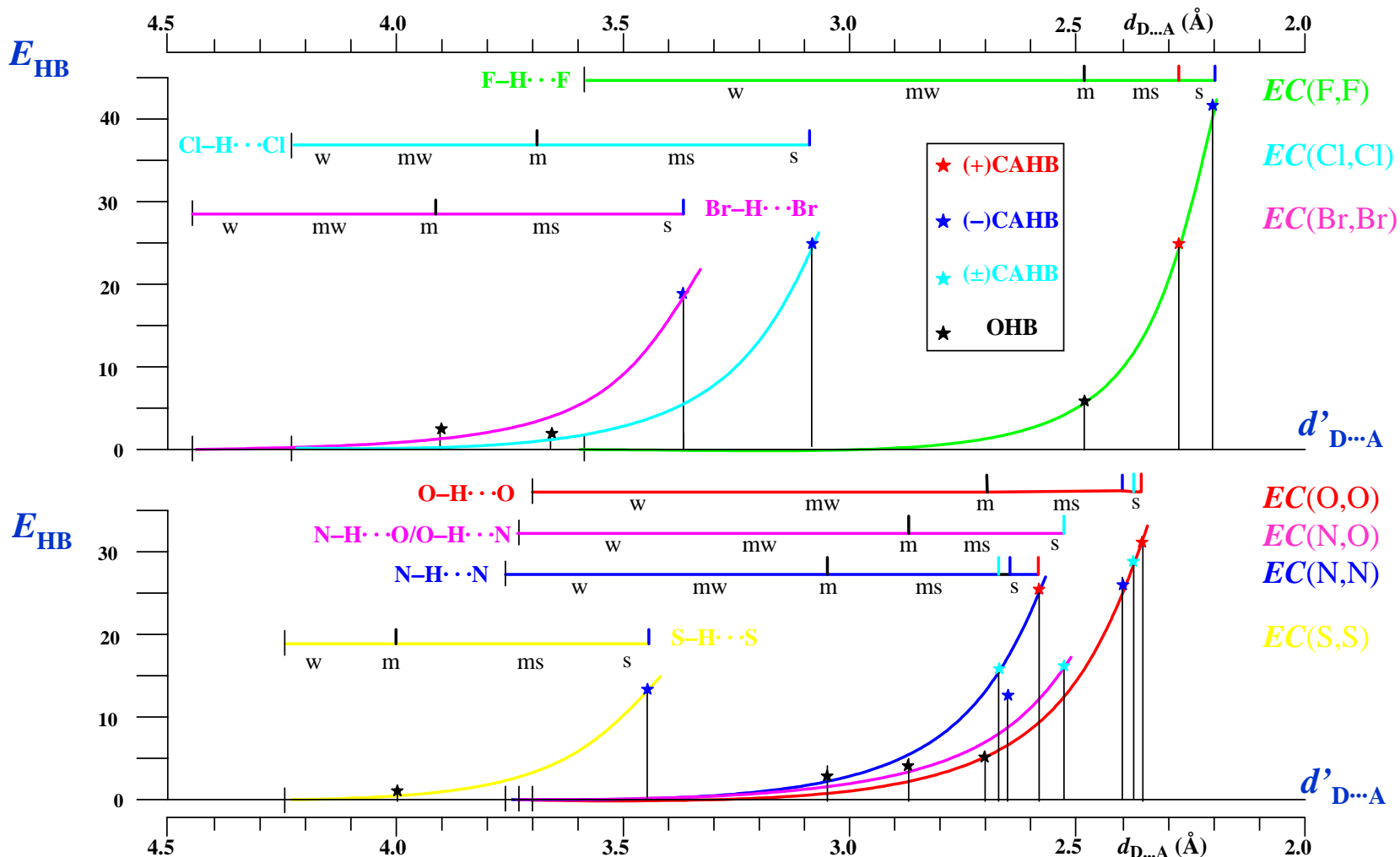
$$E_{\text{HB}} = E_{\text{HB,MAX}} \exp[-k (d'_{\text{D}\cdots\text{A}} - d'_{\text{D}\cdots\text{A,min}})]$$

where $E_{\text{HB,MAX}}$ is the maximum energy associated with the minimum $d'_{\text{D}\cdots\text{A,min}}$ distance, and k an empirical constant ranging from 5 to 7.

The Next Figure

displays the general correlation for **all $EC(D,A)$'s** for which sufficient data are available.

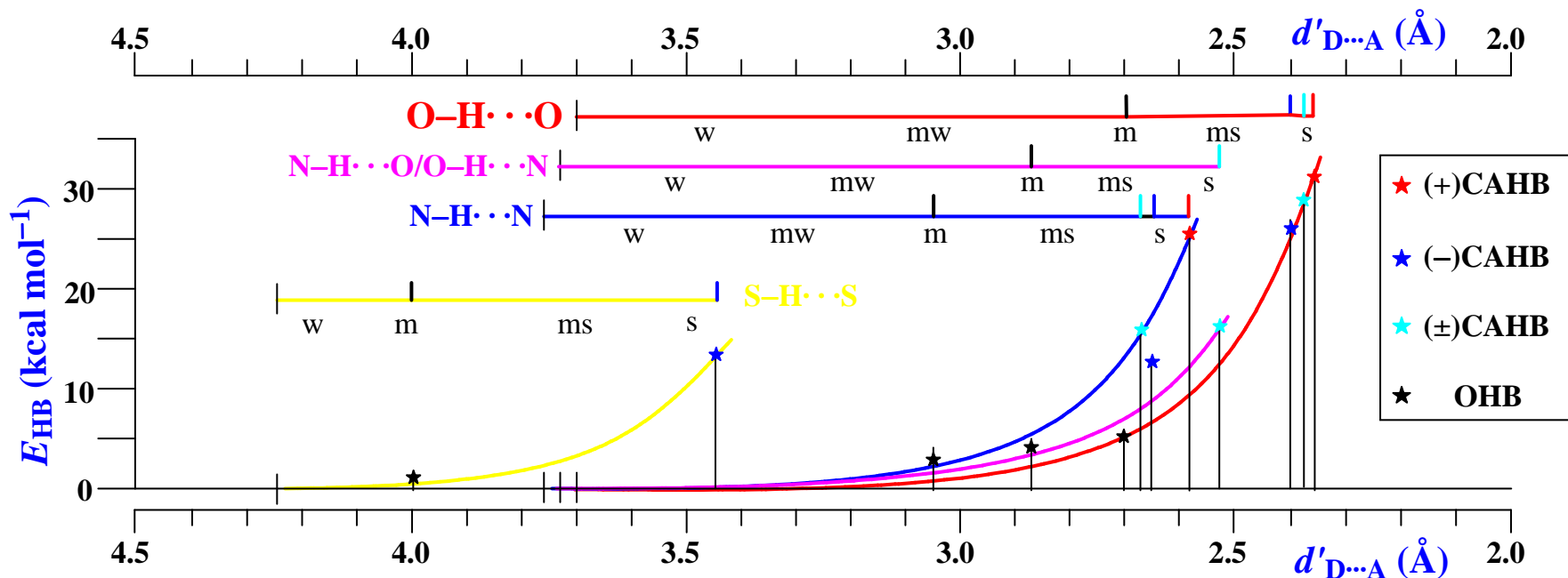
$$E_{\text{HB}} = E_{\text{HB,MAX}} \exp[-k (d'_{\text{D}\cdots\text{A}} - d'_{\text{D}\cdots\text{A,min}})]$$



The general correlation for all EC(D,A)'s for which sufficient data are available

- The different colors of curves and horizontal lines indicate the different EC(D,A)'s
- Six are homonuclear and just one heteronuclear (N-H...O/O-H...N)

$$E_{\text{HB}} = 32.0 \exp[-5.1 (d'_{\text{D}\cdots\text{A}} - 2.360)] \quad (\text{red figures set for the O-H}\cdots\text{O bond})$$



Let's take the homonuclear O-H...O bond as an example:

The **red horizontal line** indicates the **full range of O...O distances** ever found, from the longest distance corresponding to the sum of the vdW radii (**3.70 \AA** for E_{HB} set to **zero**) to the shortest one of **2.36 \AA** observed in the $[\text{H}_2\text{O}\cdots\text{H}\cdots\text{OH}_2]^+$ water complex having $E_{\text{HB,MAX}} = \mathbf{32.0 \text{ kcal mol}^{-1}}$

The **red curve** corresponds to the **exponential equation above**. It is seen to fit well the experimental points, that is the four $E_{\text{HB}}/d'_{\text{D}\cdots\text{A}}$ couples measured for the neutral (OHB) and the three charge-assisted (CAHB) bonds marked in the legend

Case study 2. Δp_a variable for $\Sigma p_a = \text{constant}$:

The PA/ pK_a Equalization Principle

$$H\text{-bond Properties} = F \{[\Sigma p_a = \text{constant}]; [\Delta p_a = p_a(D^-) - p_a(:A)]\}$$

For a given EC(D,A), Σp_a is constant, so that the H-bond properties depend only on Δp_a . The specific nature of $p_a(D^-)$ and $p_a(:A)$ depends, however, on the choice of F and we have already described three different but interconsistent ways for doing it:

(i) In the *electrostatic-covalent H-bond model (ECHBM)*, F is the H-bond Coulson's VB formalism, the duality is expressed by the $D-H\cdots A \leftrightarrow ^-D\cdots H-A^+$ resonance, and $\Delta p_a = \Delta E = E[\Psi(^-D\cdots H-A^+)] - E[\Psi(D\cdots H-A)]$ is the energy difference between the two VB wavefunctions. (Gilli et al., *JACS* 1994; for a short review see: Gilli & Gilli, *J. Mol. Struct.* 2000).

(ii) In the *transition-state H-bond theory (TSHBT)*, F is the traditional TST, the duality arises from the tautomeric $D-H\cdots A \rightleftharpoons D\cdots H\cdots A \rightleftharpoons D\cdots H-A$ equilibrium, and Δp_a is the classical reaction energy $\Delta_r E = E(D-H\cdots A) - E(D\cdots H-A)$. (Gilli et al., *JACS* 2002, 2005; for a short review see: Gilli et al., *J. Mol. Struct.* 2006).

(iii) Finally, the *PA/ pK_a equalization principle* represents a TSHBT version where $\Delta_r E$ is empirically evaluated by extrathermodynamic quantities, in particular:

- the donor/acceptor acid-base parameters PA and pK_a , so that Δp_a becomes

$$\Delta p_a = \Delta PA = PA(D^-) - PA(:A) \text{ in the gas phase or}$$
$$\Delta p_a = \Delta pK_a = pK_{AH}(D-H) - pK_{BH^+}(A-H^+) \text{ in condensed phase}$$

(Gilli et al., *Acc. Chem. Res.* 2009; for a short review see: Gilli & Gilli, *J. Mol. Struct.* 2010).

Practical Evaluation of the H-bond Strength: Predicting H-bond Strengths from Molecular Properties

- (i) **VB methods (ECHBM)** are of prevalent theoretical interest. Their main application is the well-known **Lippincott & Schroeder method (1955, 1957)** which does not predict H-bond strengths but just calculates them starting from H-bond geometries; its last formulation is the exponential function $E_{\text{HB}} = E_{\text{HB,MAX}} \exp[-k (d'_{\text{D}\cdots\text{A}} - d'_{\text{D}\cdots\text{A,min}})]$
- (ii) **TSHBT** needs to evaluate $\Delta_r E$ by complex QM simulations of PT pathways and their interpretation in terms of the Marcus' rate-equilibrium theory;
- (iii) conversely, **PA/pK_a equalization methods** are easily accessible if proper advantage is taken of the extensive **PA and pK_a compilations** presently available.

The thermodynamics of the **PA/pK_a equalization methods** has been recently analyzed (**Gilli et al., J. Mol. Struct. 2007; Acc. Chem. Res. 2009**) showing that:

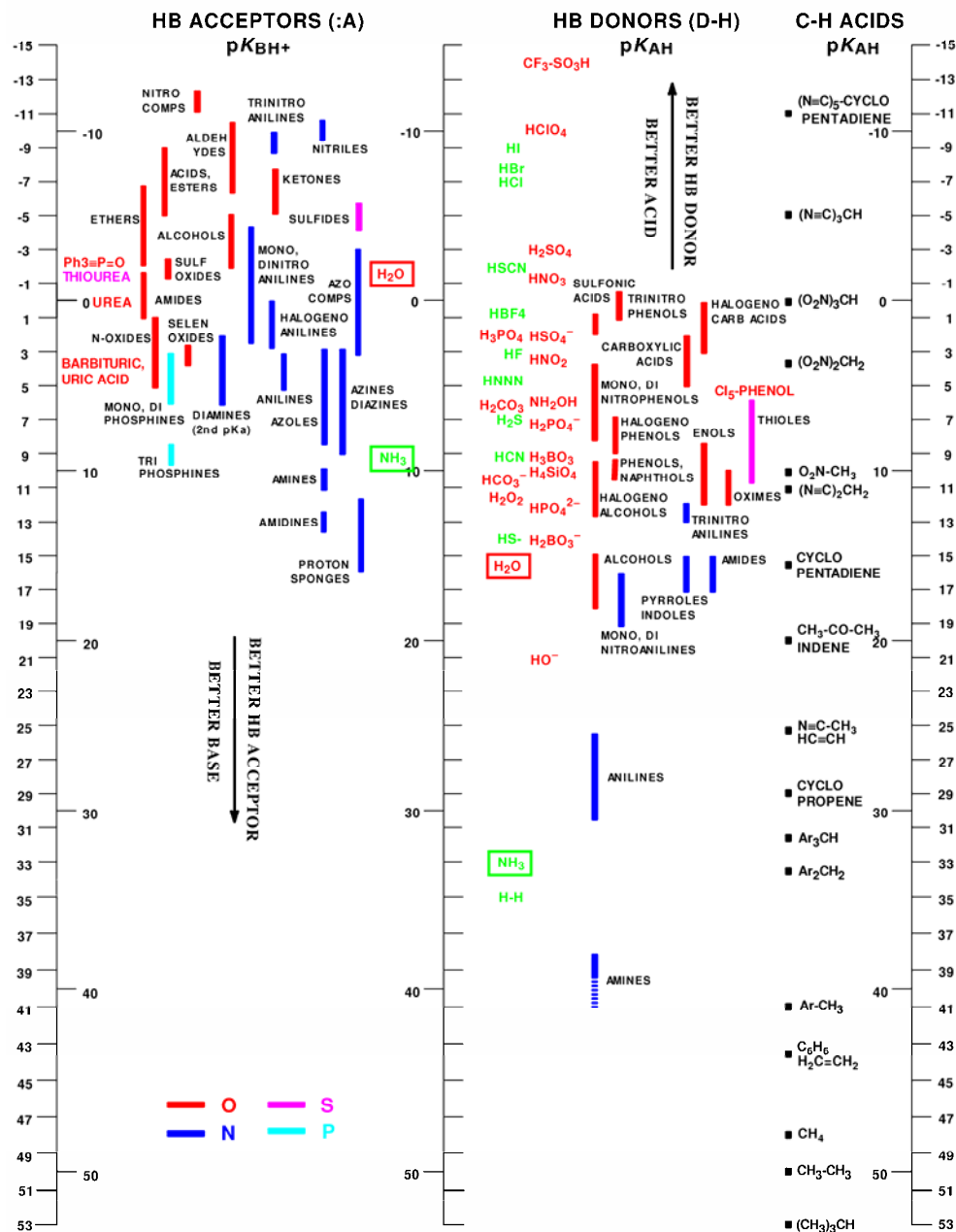
- **ΔPA's** can properly treat only **(-)CAHBs** and **(+)CAHBs**, while
- **ΔpK_a's** are compatible with all H-bonds [**OHBs**, **(±)CAHBs**, **(-)CAHBs**, and **(+)CAHBs**]
- with the only exception of **RAHBs**, whose correct **ΔpK_a** values cannot be evaluated because of the perturbations induced by the **π-delocalization** effects.

*In conclusion, pK_a-matching is the method of election
for predicting H-bond strengths,*

provided we have collected the **pK_a(H₂O) values** of all most common **H-bond donors and acceptors**, a not simple task because these values span the considerable range **-15 ≤ pK_a ≤ 53**.

The results of our work in the field has been summarized in form of a bar-chart called

the pK_a slide rule



The pK_a Slide Rule

is a tool for fast graphical evaluation of the approximate ΔpK_a differences:

$$\Delta pK_a = pK_{AH}(\text{donor}) - pK_{BH+}(\text{acceptor})$$

- Data are arranged in two columns: **D-H donors** (or A-H acids) on the right, and **A: acceptors** (or B bases) on the left,
- pK_a values are given for chemical classes
- different colors indicate the atoms involved

•••••

Strong (\pm)CAHBs occur when **an acid and a base** lie on a same horizontal line.

In general:

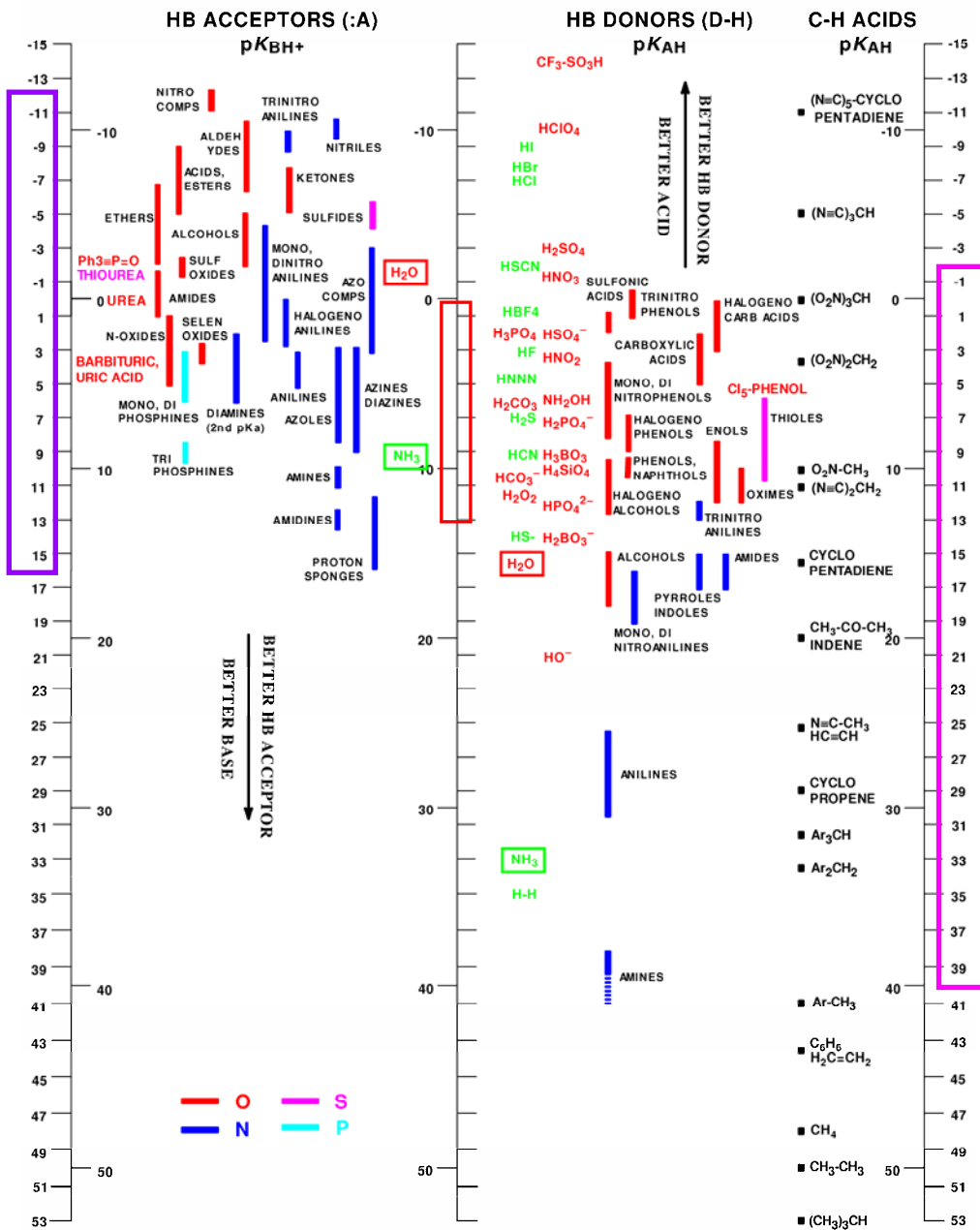
$\Delta pK_a \gg 0$: D-H...A, weak & neutral

$\Delta pK_a \approx 0$: D...H...A, strong & centered

$\Delta pK_a \ll 0$: -D...H-A⁺, weak & charged

Strong (-)CAHBs occur when **two acids** (on the right) lie on a same horizontal line,

Strong (+)CAHBs occur when **two bases** (on the left) lie on a same horizontal line.



The pK_a Slide Rule

Organic donors (-1 ≤ pK_a ≤ 40) are shifted in regard to organic acceptors (-12 ≤ pK_a ≤ 16), so that a large group of acceptors (nitro and carbonyl compounds, nitriles, ethers, alcohols, and sulfoxides) fall in a region facing some inorganic acids but no organic donors and are then expected to form only weak H-bonds.

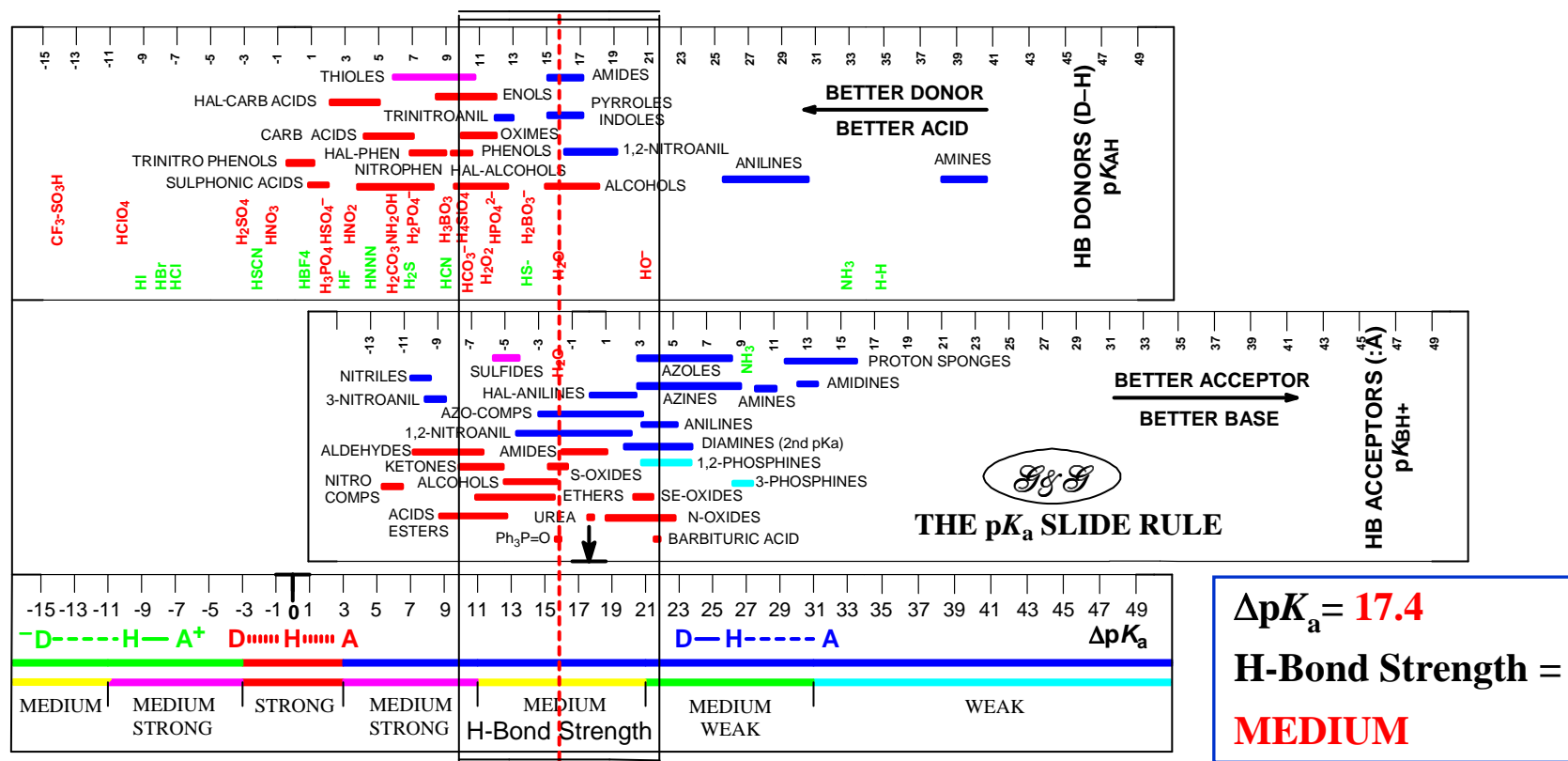
The same happens for weak donors (amines, anilines, and alcohols) which do not face any known acceptor.

Maximum overlap between organic donors and acceptors occurs in the interval 0 ≤ pK_a ≤ 14 where the greatest number of strong H-bonds are expected.

Systematic Applications of the pK_a -Equalization Methods:

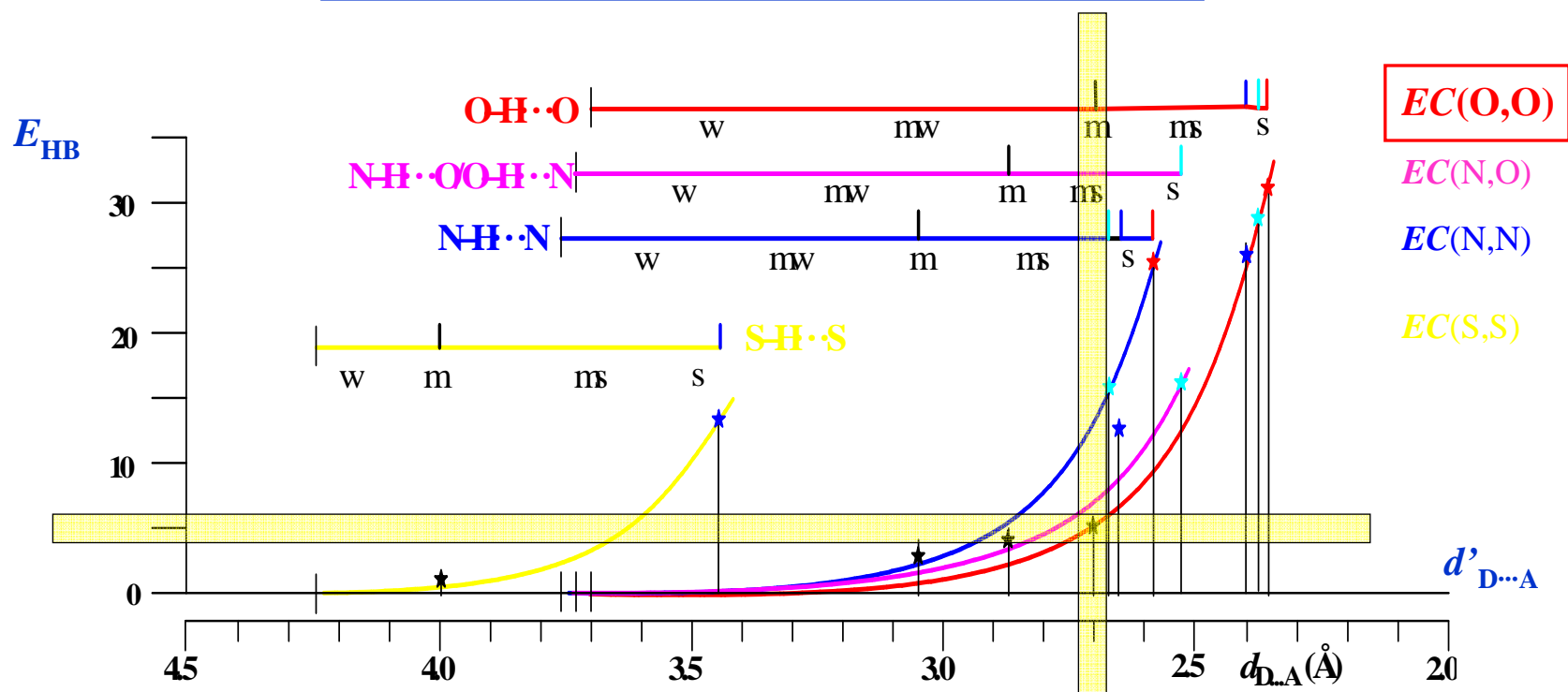
1.1. Practical Use of the pK_a Slide Rule: *The Water-Water Dimer*

- The pK_a slide rule can be redrawn as a **true slide rule** by allowing the donor and acceptor scales to **shift reciprocally** so to bring into coincidence the donor and acceptor molecules.
- In this example the slide rule is set in such a way to permit graphical ΔpK_a evaluation and empirical strength appreciation for the **O–H \cdots :O bond in the water dimer**.



Systematic Applications of the pK_a -Equalization Methods:
1.2. Practical Use of the pK_a Slide Rule: *The Water-Water Dimer*

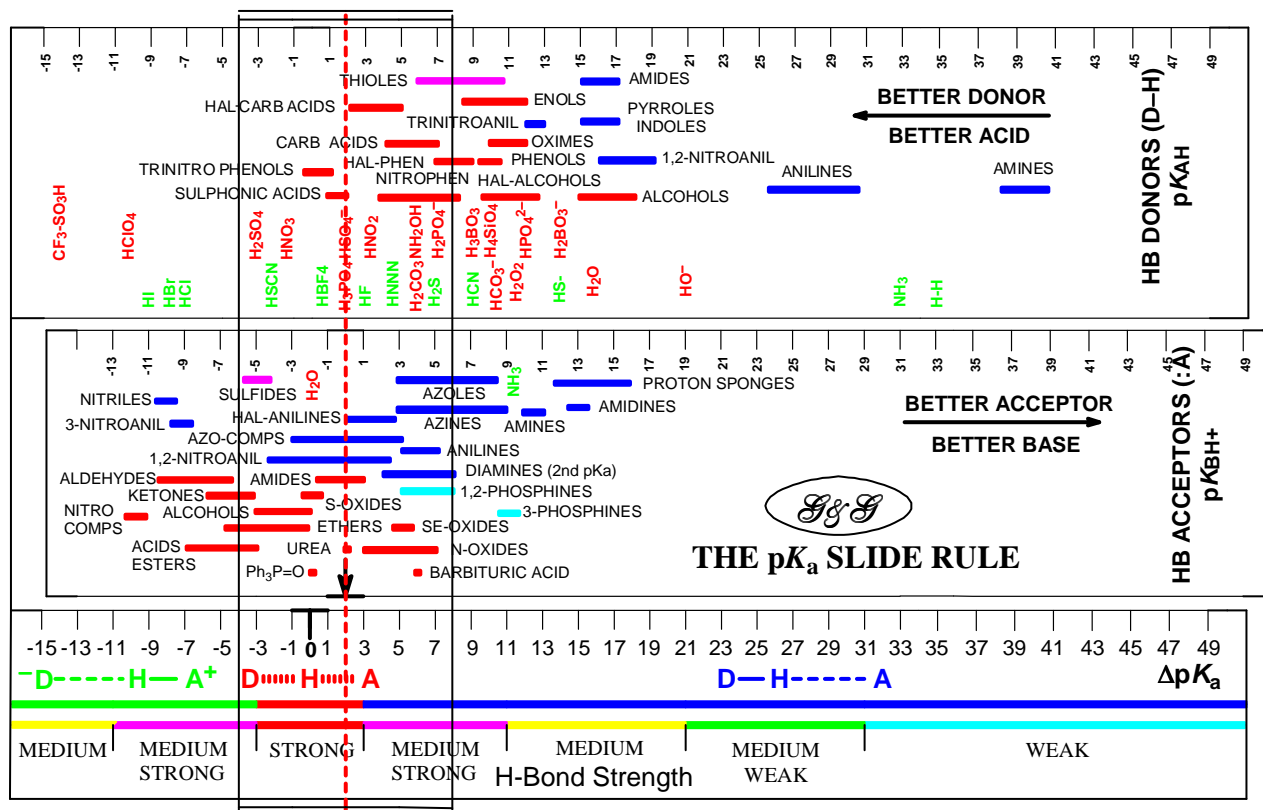
$$E_{\text{HB}} = E_{\text{HB,MAX}} \exp[-k (d'_{\text{D}\cdots\text{A}} - d'_{\text{D}\cdots\text{A,min}})]$$



Diagnosis for the Water Dimer:
 $d'_{\text{O}\cdots\text{O}} \approx 2.70 \text{ \AA}$
 $E_{\text{HB}} \approx 5 \text{ kcal mol}^{-1}$

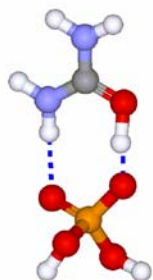
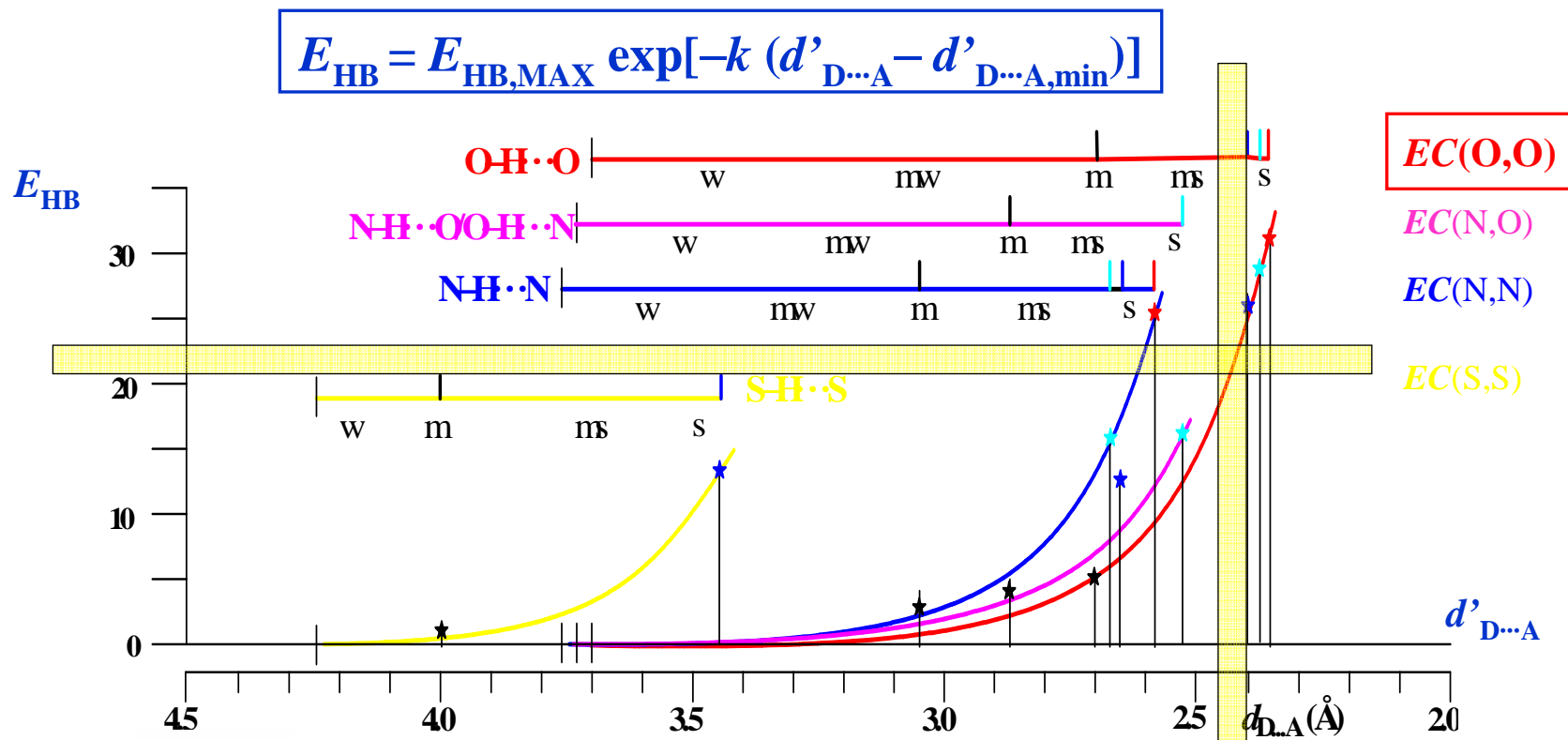
Systematic Applications of the pK_a -Equalization Methods:

2.1. Practical Use of the pK_a Slide Rule: Urea-Phosphoric Acid



$\Delta pK_a = 2.1$
H-Bond Strength = STRONG

Systematic Applications of the pK_a -Equalization Methods:
 2.2. Practical Use of the pK_a Slide Rule: Urea-Phosphoric Acid



CRBAMP01:
 N-100K
 $d'_{\text{O}\cdots\text{O}} \approx 2.409 \text{ \AA}$

Diagnosis for Urea-Phosphoric Acid:
 $d'_{\text{O}\cdots\text{O}} \approx 2.42 \text{ \AA}$
 $E_{\text{HB}} \approx 22 \text{ kcal mol}^{-1}$

Systematic Applications of the pK_a -Equalization Methods:

3.1. N–H···O/O–H···N Bonds are ΔpK_a -Modulated over the Full ΔpK_a Range

When evaluated from the pK_a slide rule, **the total ΔpK_a range is enormous: $-30 \leq \Delta pK_a \leq 65$.**

- **The problem is now:** Does the ΔpK_a predict H-bond strengths over the full ΔpK_a range?
- We have tried to verify this point through an extended analysis of the **N–H···O/O–H···N bonds** found in the Cambridge Structural Database (CSD).

Procedure:

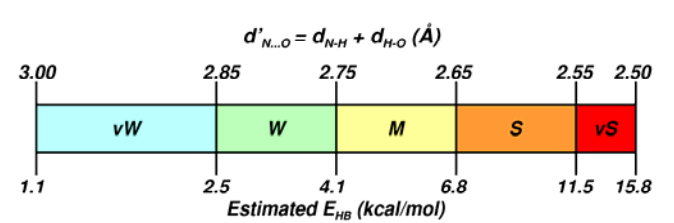
- In a first CSD search, the **functional groups** of known pK_a range most frequently involved in N–H···O/O–H···N bonds were identified.
- Next, **10 classes of donors and 11 of acceptors were selected** and the search was restarted for each separate donor-acceptor couple.
- **Altogether, 8681 bonds were analyzed (3968 N–H···O, 2295 O–H···N and 2418 $^-\text{O}\cdots\text{H}-\text{N}^+$).**
- N···O distances were evaluated as $d'_{\text{N}\cdots\text{O}} = d_{\text{N}-\text{H}} + d_{\text{H}-\text{O}}$ to account for N–H–O angle changes and, for each group, **minimum and average distances** were registered.
- These geometrical values were compared (next slide) with **the acid-base features of the donors** (pK_{AH} range), of the **acceptors** (pK_{BH^+} range), and with **their combinations** (ΔpK_a range).

Systematic Applications of the pK_a -Equalization Methods:

3.2. $N-H\cdots O/O-H\cdots N$ Bonds are ΔpK_a -Modulated over the Full ΔpK_a Range

← Increasing Acidity of the Protonated $A-H^+$ Acceptor
 Increasing Basicity of the $:A$ Acceptor →

| | Acceptors HB | Nitro Cmps | Carbonyl Cmps | Ethers | Alcohols/ Phenols | Amides | Nitriles | Anilines | Azines | Diamines (2 nd pK_a) | Azoles | Amines |
|--|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------------------|---------------------------|---------------------------|
| | | | | | | | | | | | | |
| | HB Donors | -11 ÷ -12 | -5 ÷ -10 | -2 ÷ -7 | -2 ÷ -5 | 1 ÷ -2 | -10 ÷ -11 | 5 ÷ -4 | 7 ÷ 1 | 6 ÷ 2 | 8 ÷ 3 | 11 ÷ 8 |
| ΔpK_a large & positive | Amines | 5 | 42 | 11 | 83 | 13 | | | | | | |
| | $R-N-H$ | 2.94 3.19 ₉ | 2.77 3.06 ₃ | 2.96 3.23 ₅ | 2.79 3.10 ₂ | 2.98 3.17 ₄ | | | | | | |
| | 40 ÷ 38 | 52 ÷ 49 | 50 ÷ 43 | 47 ÷ 40 | 45 ÷ 40 | 42 ÷ 37 | | | | | | |
| | Anilines | 104 | 109 | 27 | 21 | 21 | | | | | | |
| | $Ar-N-H$ | 2.91 3.21 ₁ | 2.87 3.07 ₁ | 2.91 3.13 ₂ | 3.00 3.12 ₂ | 2.80 3.07 ₃ | | | | | | |
| | 31 ÷ 25 | 43 ÷ 36 | 41 ÷ 30 | 38 ÷ 27 | 36 ÷ 27 | 33 ÷ 24 | | | | | | |
| | Pyrroles/ Indoles | 15 | 314 | 35 | 92 | 95 | | | | | | |
| | $>N-H$ | 2.94 3.11 ₃ | 2.78 2.98 ₁ | 2.79 3.07 ₃ | 2.76 2.97 ₁ | 2.81 2.96 ₁ | | | | | | |
| | 17 ÷ 15 | 39 ÷ 26 | 27 ÷ 20 | 24 ÷ 17 | 22 ÷ 17 | 19 ÷ 14 | | | | | | |
| | Amides | 4 | 246 | 33 | 211 | 2487 | | | | | | |
| $-C(O)-N-H$ | 3.04 3.14 ₁ | 2.82 3.03 ₁ | 2.90 3.12 ₅ | 2.80 3.03 ₁ | 2.73 2.97 ₁ | | | | | | | |
| 17 ÷ 15 | 39 ÷ 26 | 27 ÷ 20 | 24 ÷ 17 | 22 ÷ 17 | 19 ÷ 14 | | | | | | | |
| HBs weak & neutral | Alcohols | | | | | | 52 | 8 | 319 | 15 | 267 | 529 |
| | $R-O-H$ | | | | | | 2.77 2.94 ₁ | 2.81 2.90 ₂ | 2.67 2.87 ₁ | 2.82 2.87 ₁ | 2.67 2.87 ₁ | 2.68 2.91 ₁ |
| | 18 ÷ 9 | 29 ÷ 19 | 16 ÷ 5 | 17 ÷ 2 | 16 ÷ 2 | 15 ÷ 1 | 10 ÷ -2 | | | | | |
| | Oximes | 8 | | 42 | | 17 | 12 | | | | | |
| | $=N-O-H$ | 2.81 2.90 ₂ | | 2.66 2.75 ₁ | | 2.65 2.76 ₂ | 2.68 2.77 ₂ | | | | | |
| | 12 ÷ 10 | 23 ÷ 20 | 16 ÷ 5 | 11 ÷ 3 | 10 ÷ 4 | 9 ÷ 2 | 4 ÷ -1 | | | | | |
| | Phenols/ Naphthols | 65 | 37 | 279 | 51 | 25 | 34 | 100 | | | | |
| | $Ar-O-H$ | 2.75 2.92 ₂ | 2.68 2.81 ₁ | 2.52 2.79 ₁ | 2.52 2.70 ₂ | 2.57 2.69 ₁ | 2.58 2.74 ₁ | 2.64 2.79 ₁ | | | | |
| | 12 ÷ 4 | 23 ÷ 14 | 16 ÷ -1 | 11 ÷ -3 | 10 ÷ -2 | 9 ÷ -4 | 4 ÷ -7 | | | | | |
| | Carboxylic Acids | 6 | 2 | 95 | 399 | 193 | 6 | 39 | 73 | 217 | 1441 | |
| $R-COO-H$ | 2.76 2.79 ₁ | 2.66 2.71 ₁ | 2.65 2.88 ₂ | 2.52 2.67 ₁ | 2.53 2.73 ₂ | 2.62 2.65 ₁ | 2.53 2.77 ₁ | 2.58 2.72 ₁ | 2.54 2.78 ₁ | 2.59 2.86 ₁ | | |
| 5 ÷ 0 | 16 ÷ 10 | 9 ÷ -5 | 4 ÷ -7 | 3 ÷ -6 | 2 ÷ -8 | 3 ÷ -11 | | | | | | |
| Increasing Acidity of the D-H Donor | Trinitro Phenols | | 8 | 27 | 7 | 32 | 99 | | | | | |
| | $Ar-O-H$ | | 2.70 2.77 ₃ | 2.62 2.74 ₂ | 2.58 2.71 ₃ | 2.63 2.80 ₂ | 2.69 2.88 ₁ | | | | | |
| | 1 ÷ 0 | 12 ÷ 10 | 5 ÷ -5 | 0 ÷ -7 | -1 ÷ -6 | -2 ÷ -8 | -7 ÷ -11 | | | | | |
| | Sulfonic Acids | | 16 | 18 | | 9 | 167 | | | | | |
| | $R-SO_2-O-H$ | | 2.71 2.89 ₅ | 2.67 2.86 ₄ | | 2.76 2.93 ₇ | 2.70 2.97 ₁ | | | | | |
| | 3 ÷ 0 | 14 ÷ 10 | 7 ÷ -5 | 2 ÷ -7 | 1 ÷ -6 | 0 ÷ -8 | -5 ÷ -11 | | | | | |



HB-strengths
← color code

HBs weak
& charged

ΔpK_a large
& negative

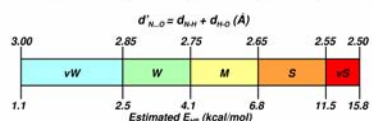
From: P. Gilli et al., *Acc. Chem. Res.* 42: 33-44 (2009)

Systematic Applications of the pK_a -Equalization Methods:

3.3. $N-H\cdots O/O-H\cdots N$ Bonds are ΔpK_a -Modulated over the Full ΔpK_a Range

| Acceptors HB | Nitro Cmps R-N ₂ ⁺ O ₂ ⁻ | Carbonyl Cmpds C=O | Ethers R-O-R | Alcohols/ Phenols R-OH | Amides N-C=O | Nitriles R-C≡N | Anilines Ar-N ₂ | Azines N=N | Diamines (2 nd pK _a) N-N | Azoles N=N | Amines R-N |
|---|---|----------------------------------|---------------------------------|----------------------------------|-----------------------------------|---------------------------------|---------------------------------|----------------------------------|---|----------------------------------|-----------------------------------|
| Donors | -11 to -12 | -5 to -10 | -2 to -7 | -2 to -5 | 1 to -2 | -10 to -11 | 5 to -4 | 7 to 1 | 6 to 2 | 8 to 3 | 11 to 8 |
| Amines R ₂ N-H | 5 2.94 3.19 ₂ | 42 2.77 3.06 ₂ | 11 2.96 3.23 ₂ | 83 2.79 3.10 ₂ | 13 2.99 3.17 ₂ | | | | | | |
| 40 + 38 | 52 + 49 | 50 + 43 | 47 + 40 | 45 + 40 | 42 + 37 | | | | | | |
| Anilines N ₂ H | 104 2.91 3.21 ₂ | 109 2.87 3.07 ₂ | 27 2.91 3.12 ₂ | 21 3.00 3.07 ₂ | 21 2.80 3.07 ₂ | | | | | | |
| 31 + 25 | 43 + 36 | 41 + 30 | 38 + 27 | 36 + 27 | 33 + 24 | | | | | | |
| Pyrroles >N-H | 15 2.94 3.11 ₂ | 314 2.78 2.98 ₂ | 35 2.79 3.07 ₂ | 92 2.76 2.97 ₂ | 95 2.81 2.96 ₂ | | | | | | |
| 17 + 15 | 39 + 26 | 27 + 20 | 24 + 17 | 22 + 17 | 19 + 14 | | | | | | |
| Amides N-H | 4 3.04 3.14 ₂ | 246 2.82 3.03 ₂ | 33 2.90 3.12 ₂ | 211 2.80 3.03 ₂ | 2487 2.73 2.97 ₂ | | | | | | |
| 17 + 15 | 39 + 26 | 27 + 20 | 24 + 17 | 22 + 17 | 19 + 14 | | | | | | |
| Alcohols R-O-H | | | | | | 52 2.77 2.94 ₂ | 8 2.81 2.90 ₂ | 319 2.67 2.87 ₂ | 15 2.82 2.87 ₂ | 267 2.67 2.87 ₂ | 529 2.68 2.91 ₂ |
| 18 + 9 | | | | | | 29 + 19 | 22 + 4 | 17 + 2 | 16 + 2 | 15 + 1 | 10 + -2 |
| Oximes =N-O-H | | | | | | 8 2.81 2.90 ₂ | 42 2.66 2.75 ₂ | | | 127 2.65 2.76 ₂ | 12 2.68 2.77 ₂ |
| 12 + 10 | | | | | | 23 + 20 | 16 + 5 | 11 + 3 | 10 + 4 | 9 + 2 | 4 + -1 |
| Phenols/ Naphthols Ar-O-H | | | | | | 65 2.75 2.92 ₂ | 37 2.68 2.81 ₂ | 231 2.78 2.89 ₂ | 25 2.62 2.65 ₂ | 34 2.58 2.72 ₂ | 100 2.64 2.79 ₂ |
| 12 + 4 | | | | | | 23 + 14 | 16 + -1 | 11 + -3 | 10 + -2 | 9 + -4 | 4 + -7 |
| Carboxylic Acids R-COOH | | | | | | 8 2.76 2.79 ₂ | 21 2.66 2.71 ₂ | 95 2.65 2.88 ₂ | 6 2.62 2.74 ₂ | 39 2.58 2.72 ₂ | 1441 2.59 2.88 ₂ |
| 5 + 0 | | | | | | 16 + 10 | 9 + -5 | 4 + -7 | 3 + -6 | 2 + -8 | 3 + -11 |
| Trinitro Phenols Ar-O-H | | | | | | | 8 2.70 2.77 ₂ | 27 2.62 2.74 ₂ | 7 2.59 2.71 ₂ | 32 2.63 2.80 ₂ | 99 2.69 2.88 ₂ |
| 1 + 0 | | | | | | 12 + 10 | 5 + -5 | 0 + -7 | -1 + -6 | -2 + -8 | -7 + -11 |
| Sulfonic Acids R-SO ₃ -H | | | | | | | 16 2.71 2.89 ₂ | 19 2.67 2.86 ₂ | | 9 2.76 2.93 ₂ | 167 2.70 2.97 ₂ |
| 3 + 0 | | | | | | 14 + 10 | 7 + -5 | 2 + -7 | 1 + -6 | 0 + -8 | -5 + -11 |

| Donor Class | | Acceptor Class | | Sample Size |
|---|---|----------------|-----|--------------------------|
| $pK_{a, \text{donor}}$ range | $pK_{a, \text{acceptor}}$ range | n | n | |
| $d_{N\cdots O}(\text{min})$ | $d_{N\cdots O}(\text{min})$ | n | n | Minimum $d'_{N\cdots O}$ |
| $d_{N\cdots O}(\text{mean})$ (Neutral) | $d_{N\cdots O}(\text{mean})$ (Ionized) | n | n | |
| Average $d'_{N\cdots O}$ with subscripted esd | | | | |
| ΔpK_a range | | | | |



All strong H-bonds are located in a same position (orange-red block) associated with complexes of phenols and carboxylic acids with azines, azoles, and second aminic moieties of monoprotonated diamines, which form strong H-bonds because their global ΔpK_a range (from 11 to -8) encompasses the zero, and therefore a consistent fraction of them is expected to fall within the interval of true pK_a matching.

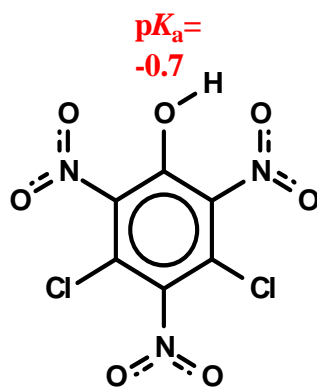
- To notice that the information obtained is **statistical** because individual pK_a 's are unknown and, accordingly, $d'_{N\cdots O}$ distances can only be compared with the average ΔpK_a intervals of each donor-acceptor group.
- Notwithstanding, the many regularities observed definitely support the idea that H-bond strengths are essentially ΔpK_a -driven in the complete range of ΔpK_a values.

Systematic Applications of the pK_a -Equalization Methods:

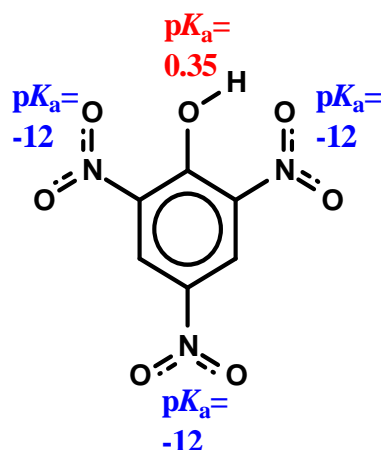
4.1. $\Delta pK_a / E_{HB} / d'_{D...A}$ Relationships in Nitro- and Halogeno-Phenols

A second verification of the complex $\Delta pK_a / E_{HB} / d'_{D...A}$ relationships comes from the study of the H-bonds formed by **nitro- and halogeno-phenols** with various **N- and O-bases**, a class of compounds with a good pK_a matching already studied for many years by the Wrocław (Sobczyk, Malarski, Lis, Grech, Majersz, Koll, ...) and Poznań (Szafran, Dega-Szafran, Katrusiak, ...) groups and for which we have recently determined (Gilli, Bertolasi & Gilli) the X-ray structures of 18 new complexes.

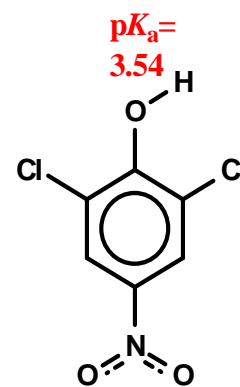
Hence, this system constitutes a **well-documented group of structures** where $d'_{D...A}$ values range from 2.40 to 3.55 Å, E_{HB} values (as evaluated by the Lippincott & Schroeder method) from 0.1 to 24 kcal mol⁻¹, and whose thermodynamic pK_a parameters are often known with sufficient precision.



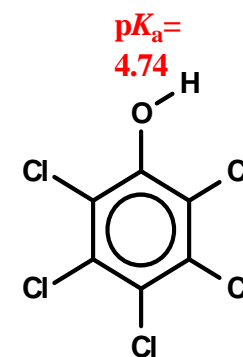
Dichloropicric acid



Picric acid



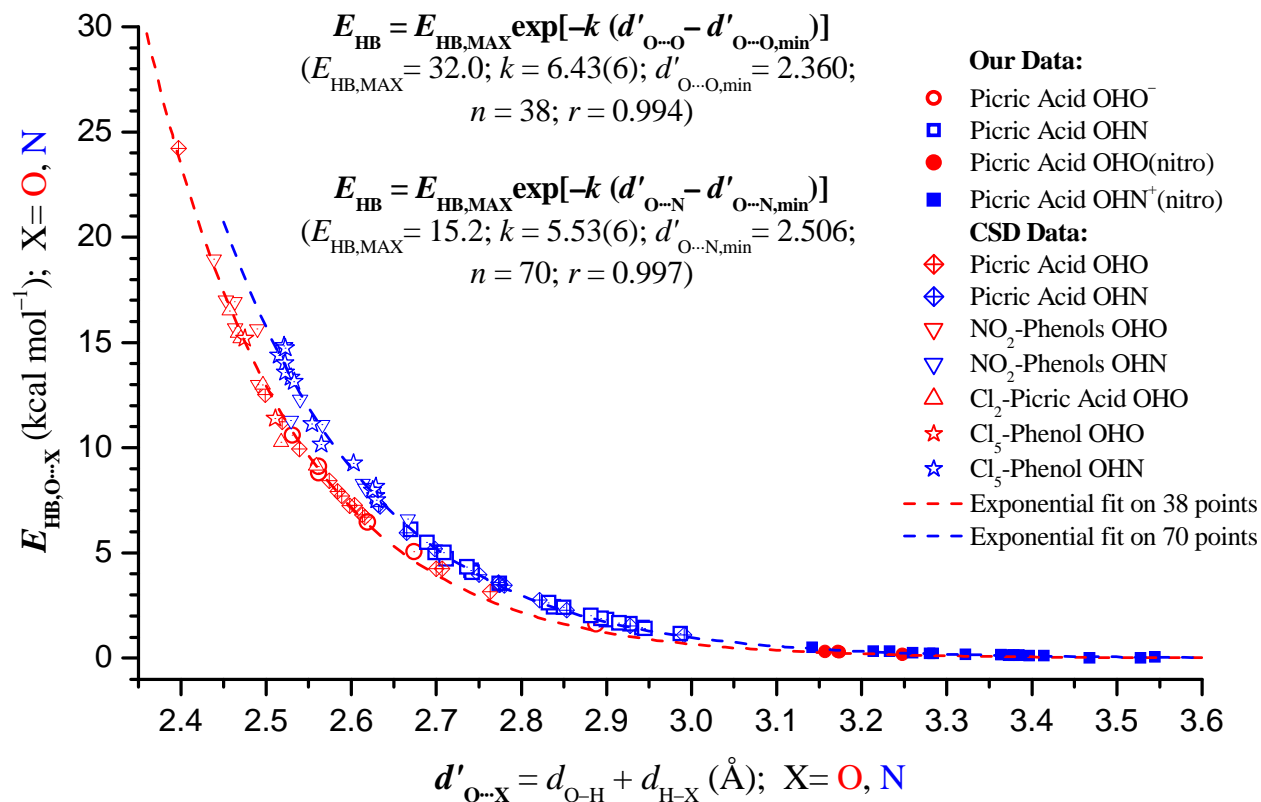
2,6-Dichloro-4-nitrophenol



Pentachlorophenol

Systematic Applications of the pK_a -Equalization Methods:
4.2. $\Delta pK_a / E_{HB} / d'_{D...A}$ Relationships in Nitro- and Halogeno-Phenols

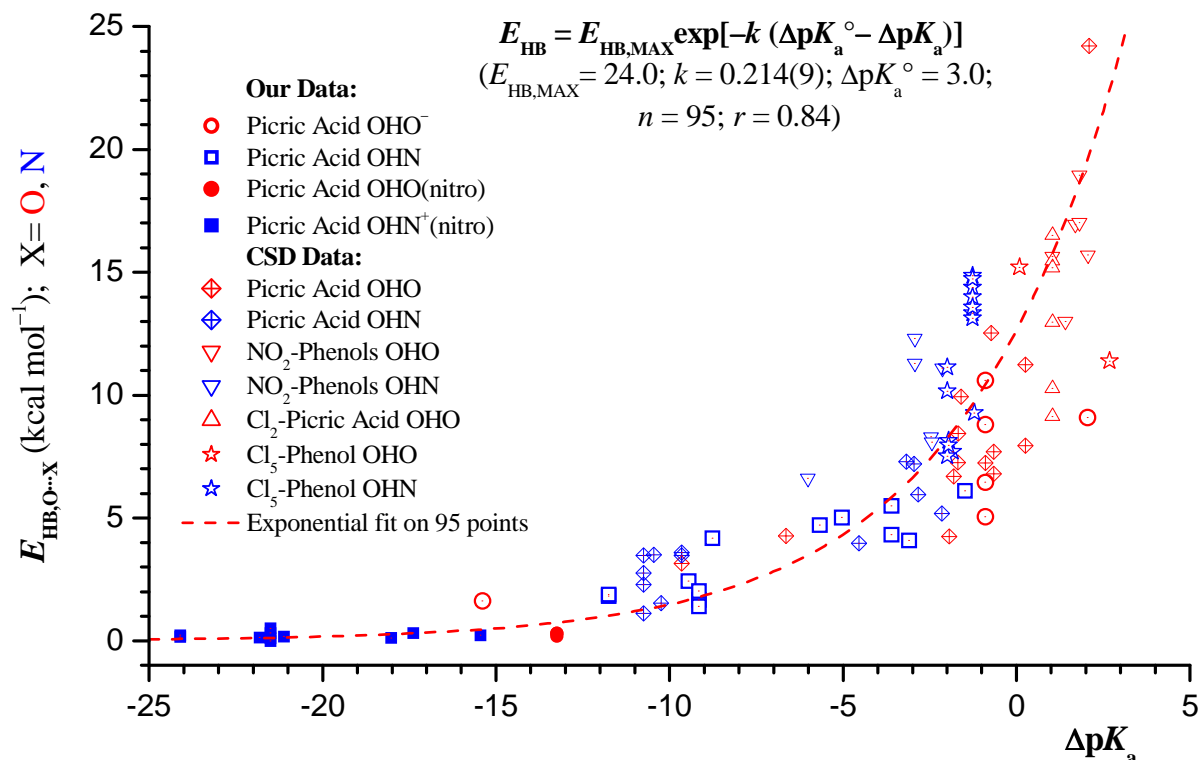
E_{HB} versus $d'_{D...A}$ Scatterplot



- **Open symbols** = HBs donated by phenols; **Full symbols** = HBs accepted by the NO₂ groups
- **O–H...O** bonds are intrinsically stronger than **N–H...O** ones (different electronegativity class) and the E_{HB} versus $d'_{D...A}$ curve has the expected exponential form discussed above with reasonably similar exponential factor, k .
- **Note:** All E_{HB} values are computed by the *Lippincott & Schroeder* method.

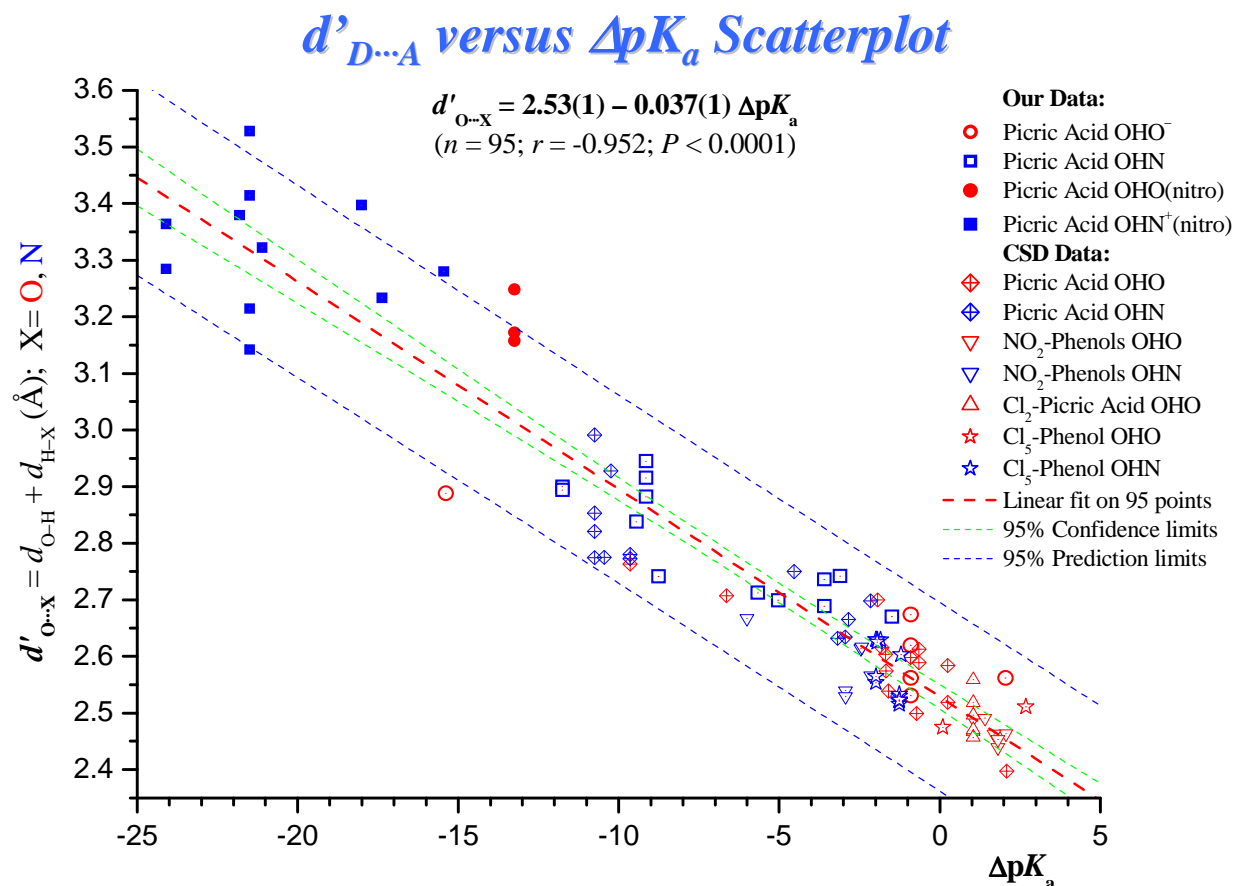
Systematic Applications of the pK_a -Equalization Methods:
4.3. $\Delta pK_a / E_{HB} / d'_{D...A}$ Relationships in Nitro- and Halogeno-Phenols

E_{HB} versus ΔpK_a Scatterplot



- The E_{HB} versus ΔpK_a curve displays an approximate exponential form, a fact that still awaits theoretical interpretation because it apparently violates the rule that all free-energy relationships should be linear (**suggestions from the audience are welcome**).
- According to the PA/ pK_a equalization principle, very strong H-bonds are observed only when ΔpK_a is not far from zero.
- The dispersion of the data is most probably imputable to uncertainties on the pK_a values used.

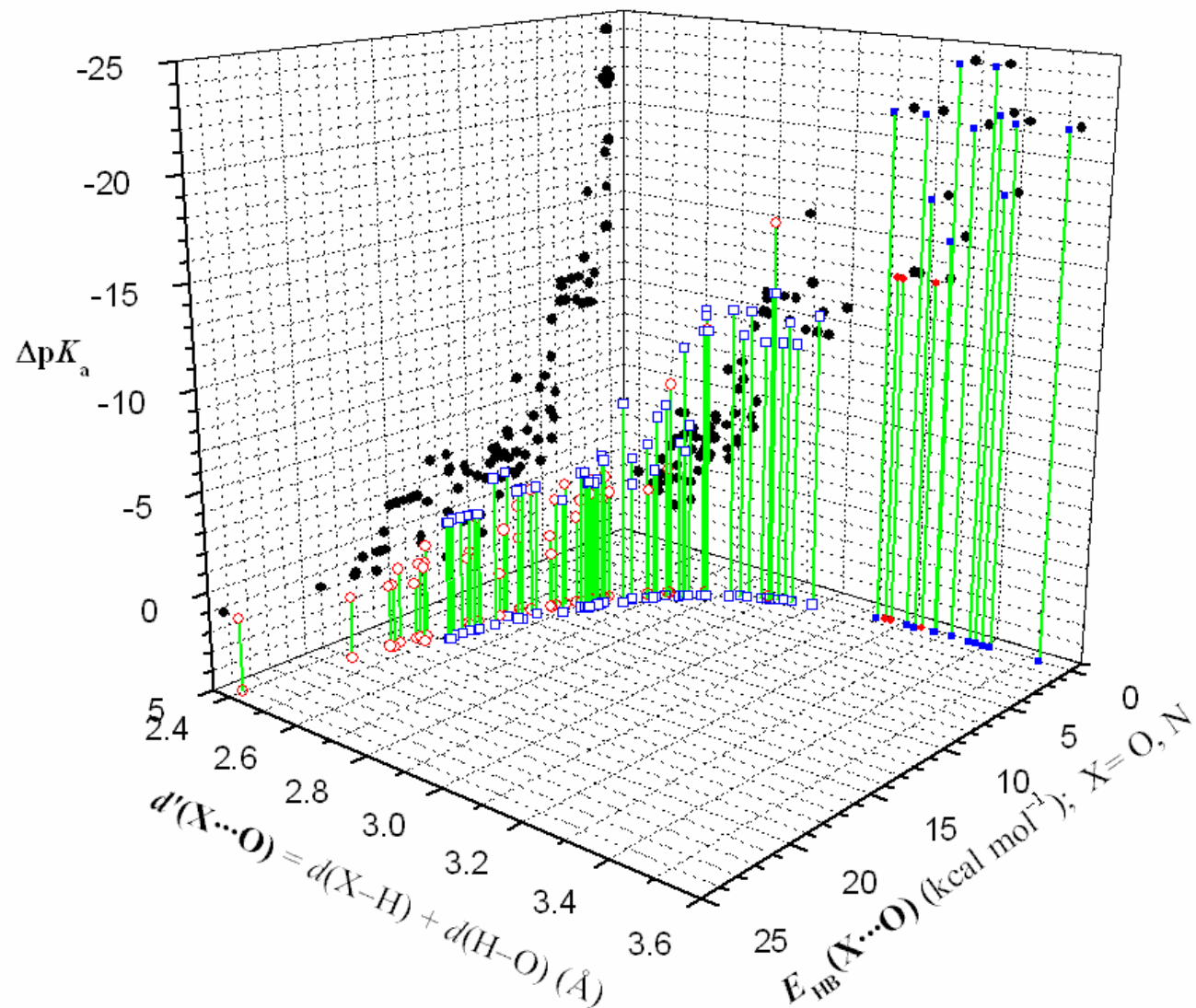
Systematic Applications of the pK_a -Equalization Methods:
4.4. $\Delta pK_a / E_{HB} / d'_{D...A}$ Relationships in Nitro- and Halogeno-Phenols



- The shape of the $d'_{D...A}$ versus ΔpK_a curve is nearly linear. Also this result is surprising because, in chemistry, all energy-distance relationships should be exponential (help from the audience is still welcome).
- The linearity of the plot, anyway, is rather impressive and can only be interpreted as a substantial confirmation that the H-bond geometry is actually modulated by the ΔpK_a over the full ΔpK_a range.

Systematic Applications of the pK_a -Equalization Methods:
4.5. $\Delta pK_a / E_{HB} / d'_{D...A}$ Relationships in Nitro- and Halogeno-Phenols

A 3-Dimensional $\Delta pK_a / E_{HB} / d'_{D...A}$ Correlation



END of LECTURE 4

Note 1. Early Models for a Comprehensive H-Bond Theory

Rather incredibly, **no general model** able to rationalize H-bond behavior over the full range of H-bond energies ($0 \leq E_{\text{HB}} \leq 45 \text{ kcal mol}^{-1}$) has ever been attempted, till very recently.

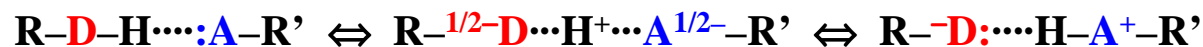
Practically, all **early interpretations** neglect strong H-bonds and remain confined to the rather weak ones, on the ground of the following **paradoxical considerations**:

- Since **strong H-bonds** are quite rare (at least at the age), they are “**exceptions**” which “can be reasonably neglected in the treatment of the much more copious H-bonds of normal strength” (Pauling, *The Nature of the Chemical Bond*, 1939, 1940, 1960);
- “If we discount **such exceptions**, hydrogen bonding may be quite well understood at a qualitative level using simple electrostatic models.” (Coulson, as reported by McWeeny in *Coulson’s Valence*, 1979).
- This is the origin of the well known **Simple Electrostatic Model (SEM)** for which H-bonded molecules can be suitably modeled by a small number of positive and negative point charges or multipoles variously combined with 6-exp or 6-12 atom-atom potentials.
- The first to re-examine critically SEM was, once more, Coulson who, around 1954, suggested an essential **covalent contribution** also to moderately strong H-bonds, so reinventing what we shall later call the **Electrostatic-Covalent H-Bond Model (ECHBM)**.
- The damage was however done! The imaginative idea of a purely electrostatic H-bond was born, leaving ECHBM confined to a restricted number of specialists, until it was revived by us in 1994 (*Covalent nature of the strong homonuclear H-bond...*, Gilli et al., *JACS*, 1994).

*Note 2. Practical Evaluation of H-bond Strengths:
Preliminary Notes on the Correct Use of the pK_a Values*

The use of the **pK_a slide rule** requires some preliminary comments on the classification of all H-bonds with respect to their acid-base properties:

- OHBs and (\pm)CAHBs are *proton-transfer H-bonds* related to the *acid-base* equilibrium

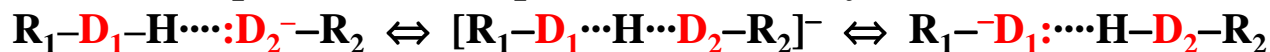


and whose properties are fully controlled by the quantity

$$\Delta pK_a(\text{acid-base}) = pK_a(\text{acid}) - pK_a(\text{base}) = pK_{AH}(R-D-H) - pK_{BH^+}(R'-A-H^+)$$

- • (-)CAHBs and (+)CAHBs are instead *proton-sharing H-bonds* of two different types:

(-)CAHBs are *acid-acid* equilibria whose proton is shared by two H-bond donors (**two acids**)



and whose properties are fully controlled by the quantity

$$\Delta pK_a(\text{acid-acid}) = |pK_{AH}(R_2-D_2-H) - pK_{AH}(R_1-D_1-H)|$$

(+)CAHBs are *base-base* equilibria whose proton is shared by two H-bond acceptors (**two bases**)



and whose properties are fully controlled by the quantity

$$\Delta pK_a(\text{base-base}) = |pK_{BH^+}(R_2-A_2-H^+) - pK_{BH^+}(R_1-A_1-H^+)|$$

- • • To notice that, whenever (-)CAHBs and (+)CAHBs are both homonuclear ($D_1 = D_2$ or $A_1 = A_2$) and homomolecular ($R_1 = R_2$), the matching condition $\Delta pK_a = 0$ will hold irrespective of the actual pK_a of the two interacting moieties

Note 3. Practical Evaluation of H-bond Strengths: Predicting H-bond Strengths from Molecular Properties

ΔpK_a can be considered as a good indicator of pK_a equalization both for proton-transfer and proton-sharing H-bonds, at least in the solvent where the pK_a 's have been measured.

Some peculiarities and minor difficulties connected with the use of pK_a need, however, to be shortly considered.

In theory, the strongest H-bonds are expected to fulfill the condition $\Delta pK_a = 0$. In practice, the pK_a matching does not need to be so perfect and data suggest that **misfits of $\pm 2.5 pK_a$ units** are still compatible with strong H-bond formation.

A further problem arises from the use of the pK_a 's in **water**, a solvent with **high dielectric constant** which tends **to stabilize ionic H-bonds against the neutral ones**, while H-bond strengths are mostly measured in non-polar solvents, in solids and in the gas phase.

Because of that, there are indications that **ΔpK_a (critical)** (the ΔpK_a for which proton transfer amounts to 50%) is not necessarily zero but may assume small negative values depending on the particular environment.

Sobczyk has reported that ΔpK_a (critical) for both ^{35}Cl NQR and diffraction experiments in the solid state is nearly $-1.5 pK_a$ units. This seems to suggest that, in crystal structures, the proton-transfer occurs only for $\Delta pK_a \leq -1.5$ and that the best interval of close pK_a matching is to be shifted to $-4.0 \leq pK_a \leq 1.0$.

P.L. Huyskens, Th. Zeegers-Huyskens., J. Chim. Phys. Phys.-Chim. Biol. 61 (1964) 81.

Z. Malarski, M. Rospenk, L. Sobczyk, J. Phys. Chem. 86 (1982) 401.

P. Huyskens, L. Sobczyk, I. Majers, J. Mol. Struct. 615 (2002) 61.

L. Sobczyk, Ber. Bunsenges. Phys. Chem. 102 (1998) 377.