

Six Lectures on the Nature of the Hydrogen Bond
Lecture 3

CAHB (Charge-Assisted Hydrogen Bond)
and PA/pKa Equalization Principle

Edited by

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

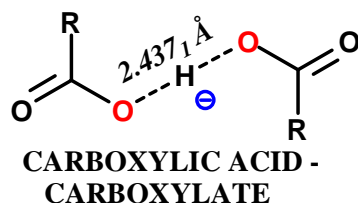
CUSO Summer School 20-24 August 2012
2012 Villars sur Ollon,
on Hydrogen Bonding Switzerland

Six Lectures on the Nature of the Hydrogen Bond
Gastone Gilli

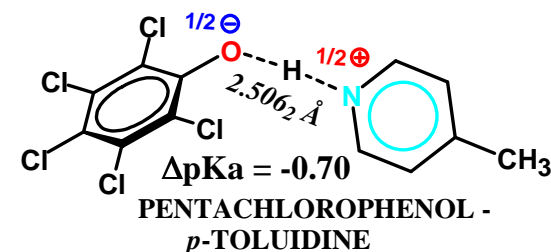
The Six HB Chemical Leitmotifs (CLs)

CHARGE - ASSISTED HBs

CL # 1: (+/-)CAHB \Rightarrow SHB, VSHB
Double Charge-Assisted HB
Direct Acid-Base PA/pK_a Matching



CL # 2: (-)CAHB \Rightarrow SHB, VSHB
Negative Charge-Assisted HB
Acid-Base PA/pK_a Matching by Proton Loss

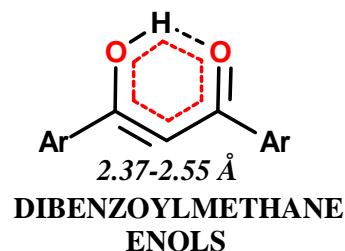


CL # 3: (+)CAHB \Rightarrow SHB, VSHB
Positive Charge-Assisted HB
Acid-Base PA/pK_a Matching by Proton Gain

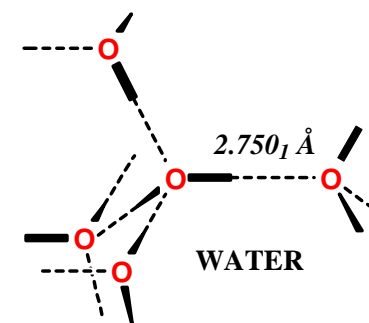


Σ/Π-BOND POLARIZATION - ASSISTED HBs

CL # 4: RAHB \Rightarrow SHB, VSHB
Resonance-Assisted or π-Cooperative HB
PA/pK_a Matching by π-Conjugated-Bond Polarization

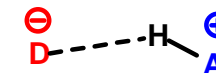
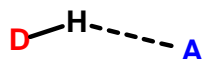


CL # 5: PAHB \Rightarrow MHB
Polarization-Assisted or σ-Cooperative HB
(Partial) PA/pK_a Matching by σ-Bond Polarization



NEITHER CHARGE- NOR Σ/Π-BOND POL.-ASSISTED HBs

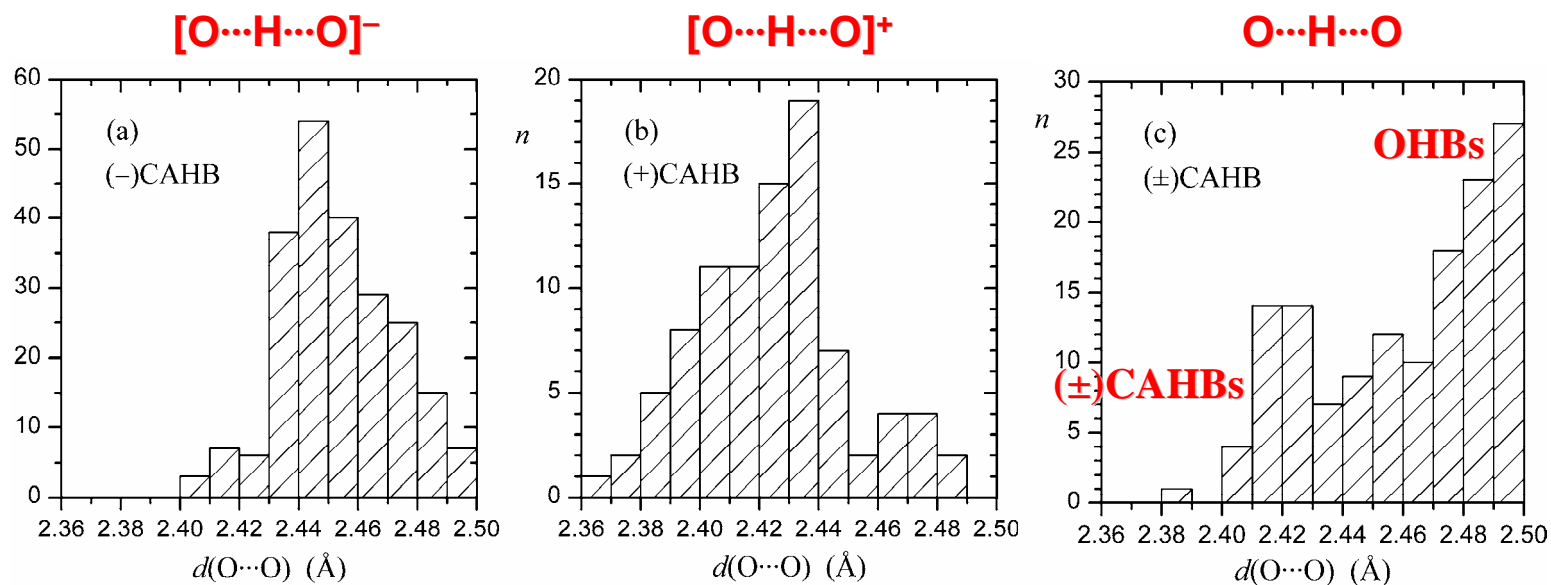
CL # 6: OHB \Rightarrow W
Ordinary HB
No PA/pK_a Matching



Lecture 3. PART 1

Completing the H-Bond Classification: The Chemical Leitmotifs

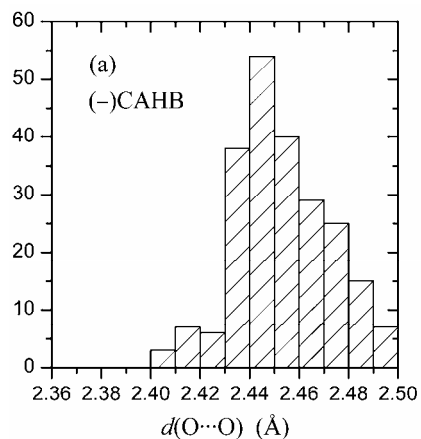
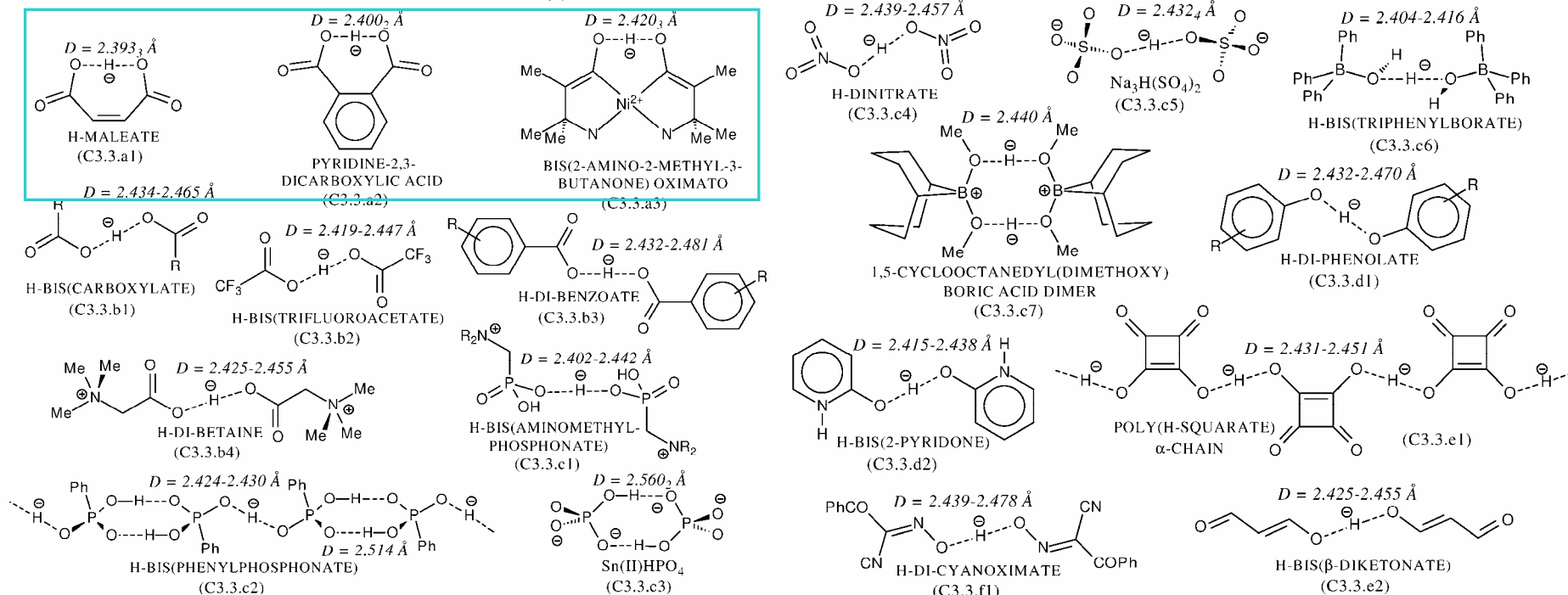
CSD Classification of the O-H...O System



Histograms of the $d(\text{O}\cdots\text{O})$ distances derived from the CSD analysis for the **three CAHB classes** considered: *(a)* homomolecular (-)CAHBs; *(b)* homomolecular (+) CAHBs; and *(c)* from (\pm)CAHBs to OHBs.

CSD Classification of the O-H...O System: (-)CAHB

CHART 3.3. HOMONUCLEAR AND HOMOMOLECULAR O-H...O NEGATIVE CHARGE-ASSISTED HB, (-)CAHB

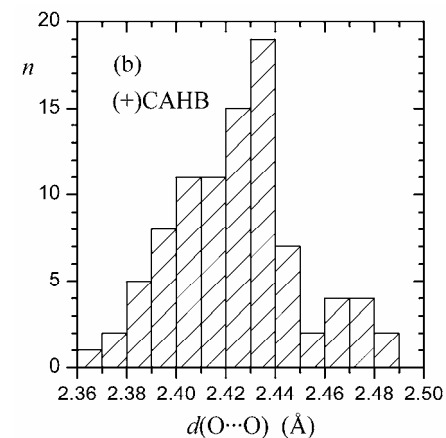
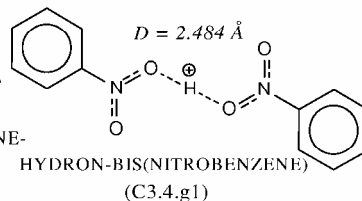
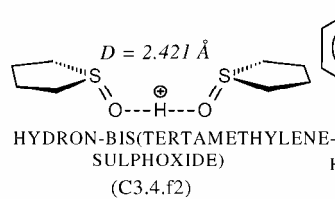
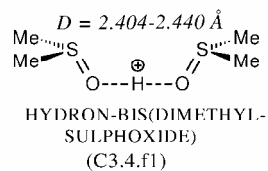
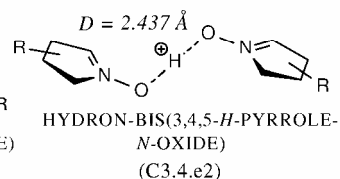
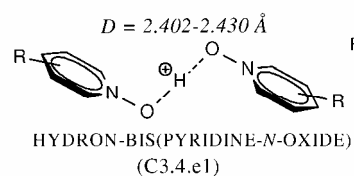
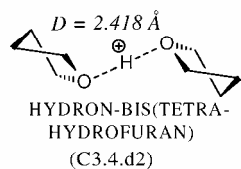
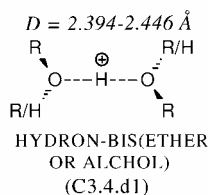
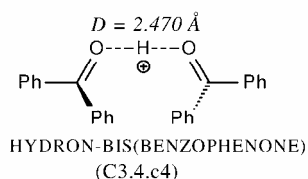
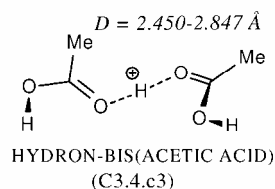
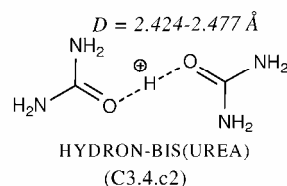
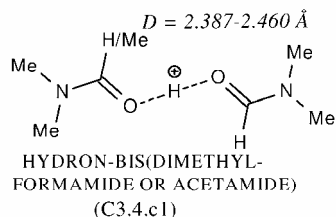
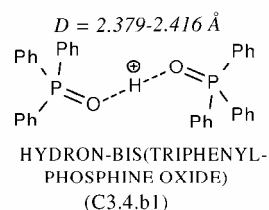
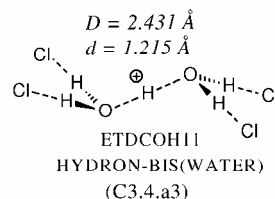
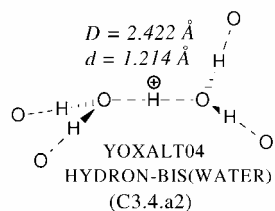
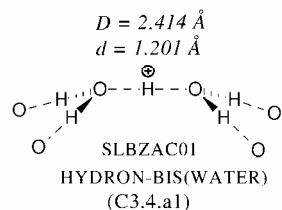


Very few cases of **intramolecular** bonds, such as the **H-maleate anion**, one of the most studied molecules by both diffraction and QM methods. The major part are **intermolecular** and occur in both **organic and inorganic acid salts**.

There are indications that (-)CAHBs become **increasingly short and proton centred** with the **increasing acidity** of the molecules involved (*cfr.* trifluoroacetates with carboxylates).

CSD Classification of the O-H...O System: (+)CAHB

CHART 3.4. HOMONUCLEAR AND HOMOMOLECULAR O-H...O POSITIVE CHARGE-ASSISTED HB, (+)CAHB

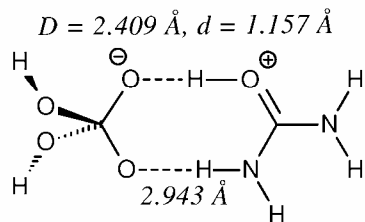


(+)CAHBs can be considered H-bonds formed by **two R=O bases that have captured a proton** from an external strong acid.

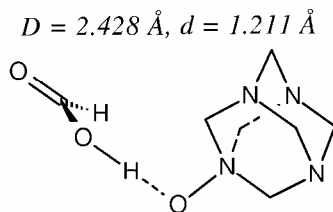
They are essentially **intermolecular** and, in the majority of cases, **homomolecular**. This is due to the fact that, when we mix **two different bases A and B** in solution, the two homomolecular forms **AA** and **BB** will be inevitably more stable and easier to crystallize than the mixed form **AB**, for evident reasons of better pK_a matching.

CSD Classification of the O-H...O System: (+/-)CAHB

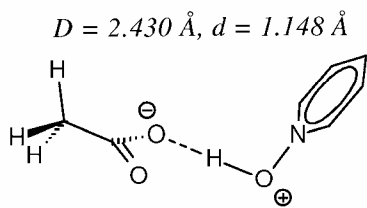
CHART 3.5. HOMONUCLEAR O-H...O DOUBLE CHARGE-ASSISTED HB, (\pm)CAHB



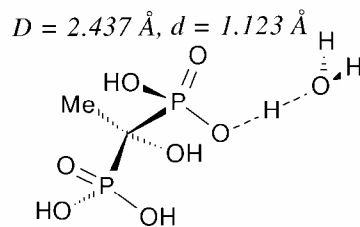
CRBAMP01, N-100K, $\Delta pK_a = 2.1$
PHOSPHORIC ACID - UREA
(C3.5.a1)



HMT0FA07, N-100K, $\Delta pK_a = -0.9$
FORMIC ACID - HMTA-N-OXIDE
(C3.5.a2)

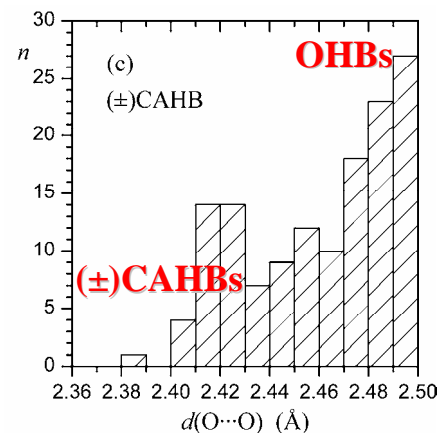


PYOTCA01, N-100K, $\Delta pK_a = -1.3$
TRICHLOROACETIC ACID -
PYRIDINE-N-OXIDE
(C3.5.a3)

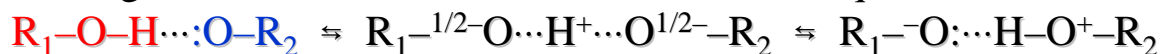


ETHDPH01, N-293K, $\Delta pK_a = 3.3$
(OH)-ETHANE-1,1-DIPHOSPHORIC
ACID - WATER
(C3.5.a4)

3. When ΔpK_a tends to vanish, very strong and proton-centred H-bonds develop which could be represented as $R_1^{-1/2}-O...H^+...O^{1/2}-R_2$ as well as $R_1^{-1/2}-O...H...O^{1/2+}-R_2$ and that, for the presence of a double charge inside the bond, have been called **double charge-assisted H-bonds** or (\pm)CAHBs (Gilli and Gilli, 2000).



This last class of strong CAHBs can be related to the acid-base equilibrium



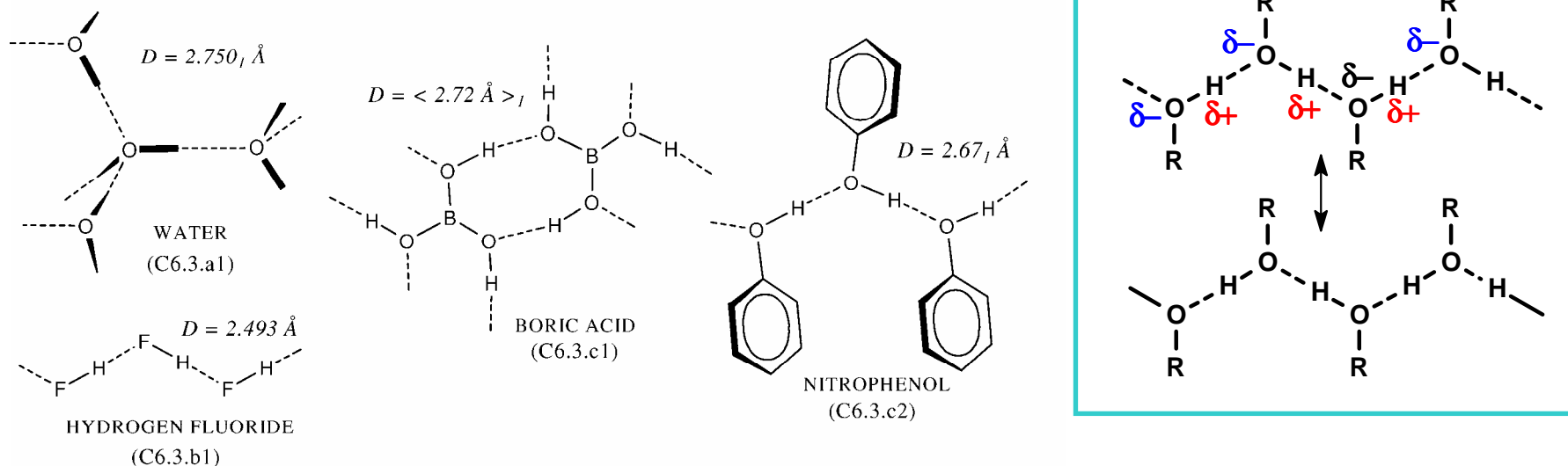
between an **acid**, R_1-O-H , and a **base**, $:O-R_2$, whose conjugated acid is $H-O^+-R_2$.

This equilibrium is known to give three extreme outcomes (plus an infinite number of intermediate ones) modulated the value of $\Delta pK_a = pK_a(R_1-O-H) - pK_a(H-O^+-R_2)$.

1. When ΔpK_a is large and positive weak and neutral OHBs are formed ($O-H \cdots O$).
2. When ΔpK_a is large and negative always weak but charged OHBs are obtained ($^-O \cdots H-O^+$).

CSD Classification of the O-H...O System: PAHB

CHART 3.6. HOMONUCLEAR AND HOMOMOLECULAR O-H...O σ -COOPERATIVE OR POLARIZATION-ASSISTED HB, PAHB



O-H...O σ -Bond Cooperative or Polarization-Assisted H-bond (PAHB)

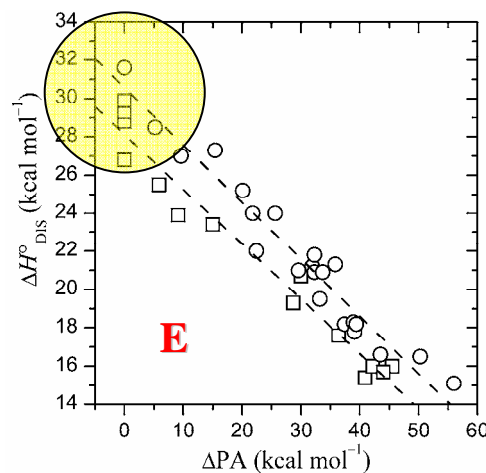
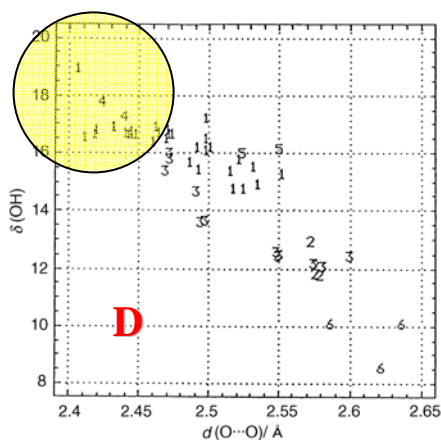
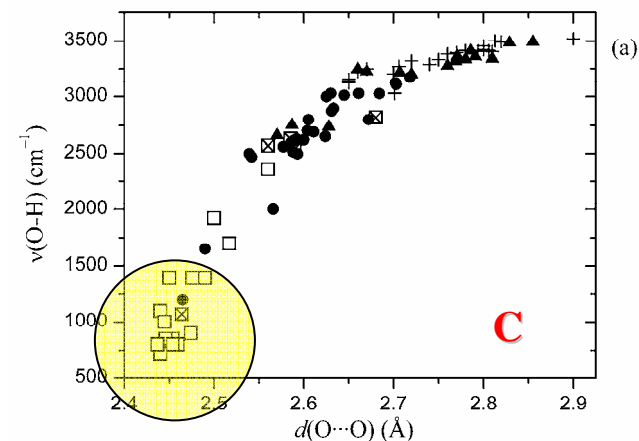
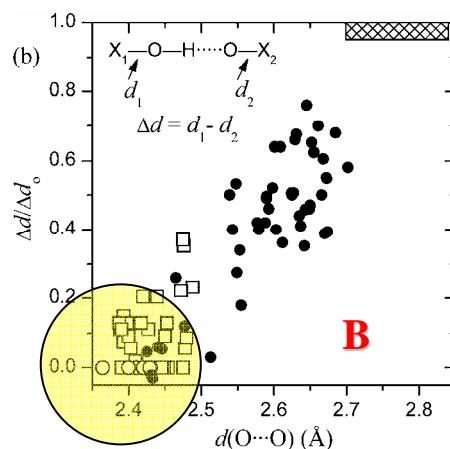
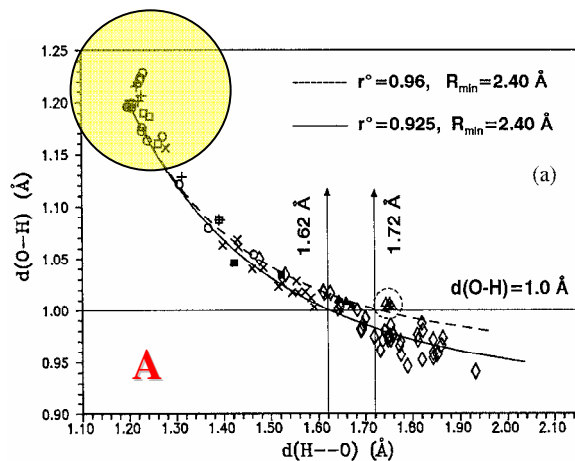
The concept of σ -bond cooperativity was firstly suggested by Jeffrey and Saenger (1991) in relation to the hypothesis that H-bonds within long chains of waters (or alcohols or phenols) should be stronger than ordinary O-H...O bonds because the **increased O-H bond polarization** induced by the chain has the **correct sign** for **further strengthening the bond**.

Later on, the bonds were added to the list of the Chemical Leitmotifs with the name **Polarization-Assisted H-bond or PAHB** (Gilli *et al.*, 2000).

The few typical cases above clearly show that **the bond shortening is small**, certainly because of the **too small polarizability of the σ -bond**, but sufficient to keep the O...O distances slightly below the shortest distances normally associated with the ordinary O-H...O bond (some 2.70 - 2.75 Å).

CSD Classification of the O-H...O System

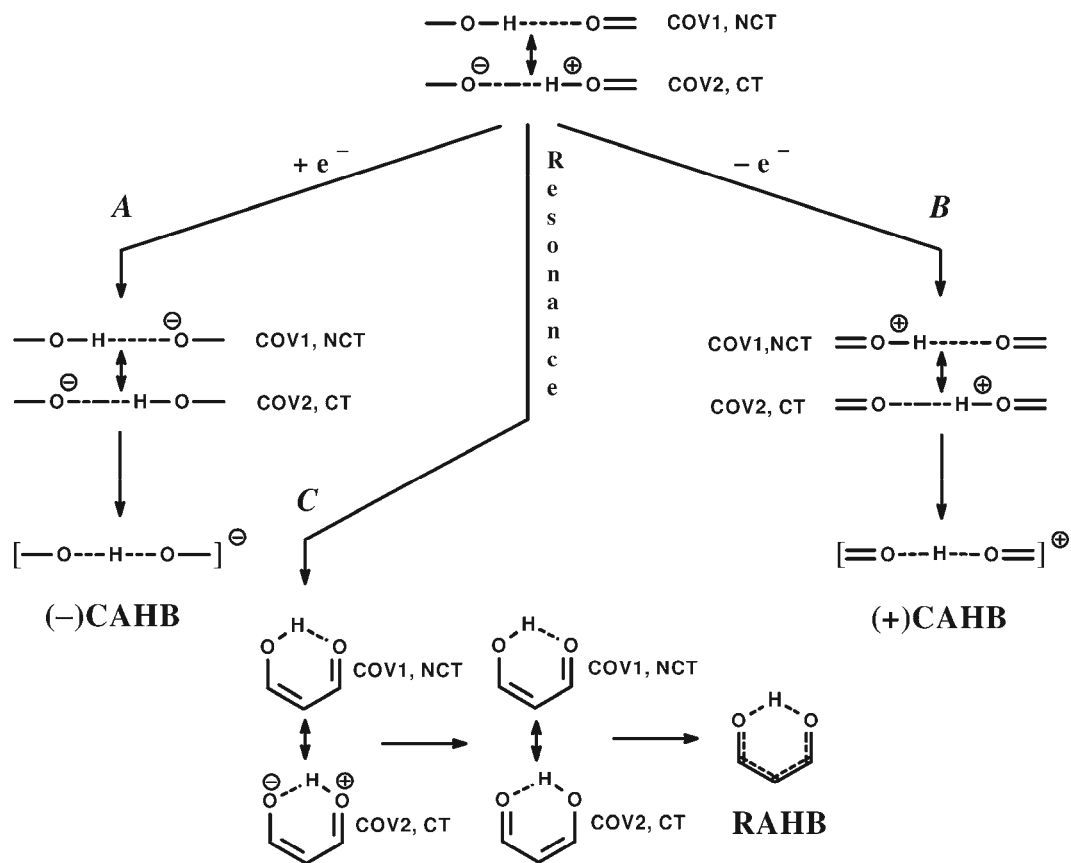
CAHB & RAHB: Symmetrization of Physical Properties



- (c)
- A.** $d(\text{O-H})$ vs. $d(\text{H}\cdots\text{O})$ (Å): RAHB, CAHB; N/A
 - B.** $\Delta d/\Delta d_0$ vs. $d(\text{O}\cdots\text{O})$ (Å): *idem*
 - C.** IR $\nu(\text{O-H})$ (cm^{-1}) vs. $d(\text{O}\cdots\text{O})$ (Å): *idem*
 - D.** ^1H NMR $\delta(\text{OH})$ vs. $d(\text{O}\cdots\text{O})$ (Å): RAHB. N/A
 - E.** Gas-phase H-bond dissociation enthalpies $\Delta H^\circ_{\text{DIS}}(\text{O-H}\cdots\text{O})$ vs. ΔPA (kcal mol^{-1}), (difference of proton affinities): CAHB

CSD Classification of the O-H...O System

CAHB & RAHB: Automatic Equalization of VB Resonance Forms



The three ways for making iso-energetic the two VB resonance forms **COV1,NCT** and **COV2,CT**:

(A) by adding an electron;

(B) by removing an electron;

(C) by connecting the two oxygens by a π -conjugated chain.

(Gilli and Gilli, 2000)

CSD Classification of the O-H...O System: CAHB & RAHB: Automatic PA/pKa Equalization

Chemical Leitmotif # 2:

(-)CAHB

[R-D...H...A-R]⁻

Chemical Leitmotif # 3:

(+)CAHB

[R-D...H...A-R]⁺

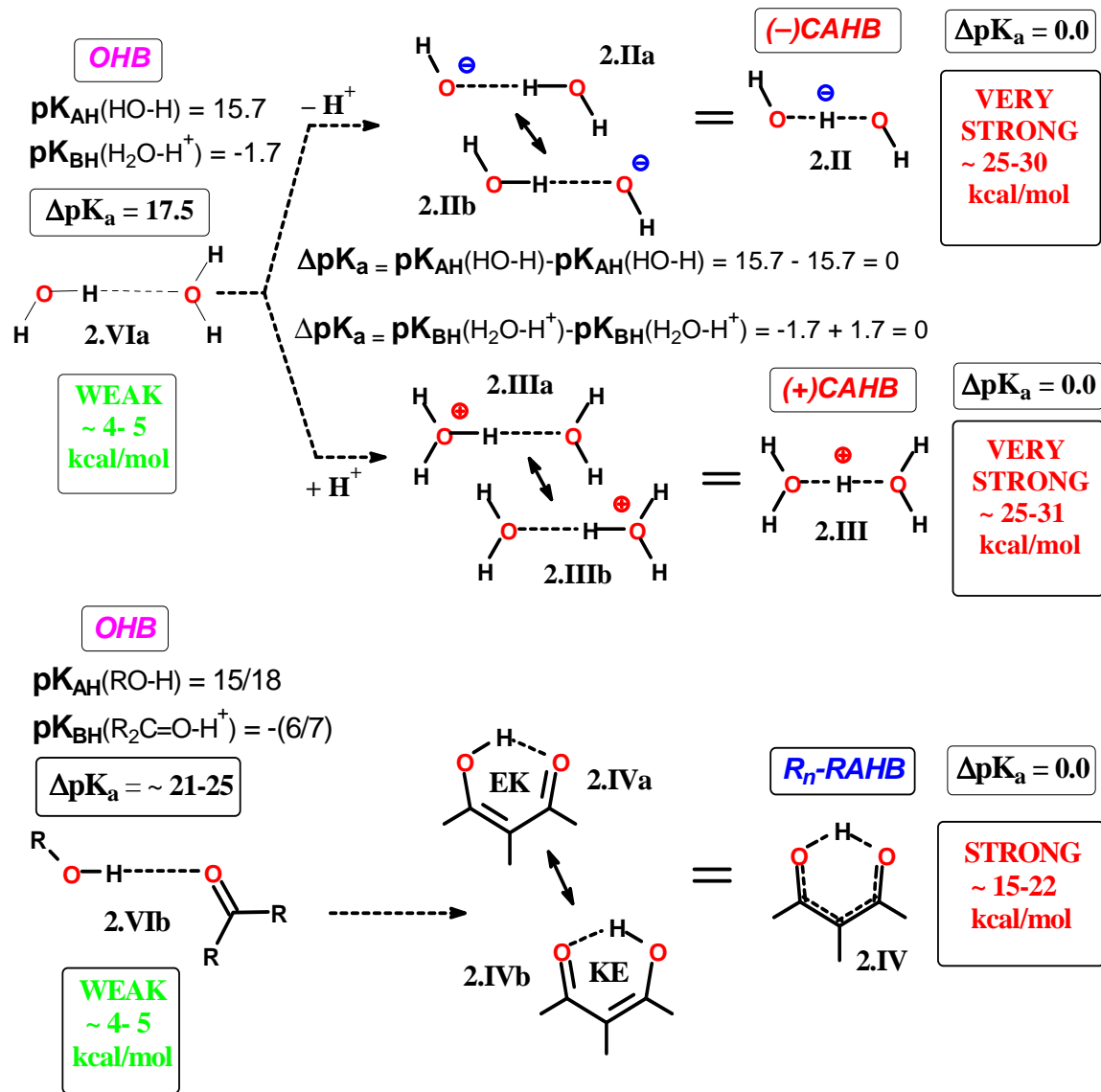
Chemical Leitmotif # 4:

RAHB

R-D-H...A=R

\rightleftharpoons

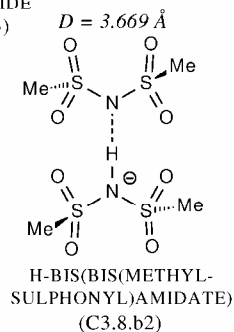
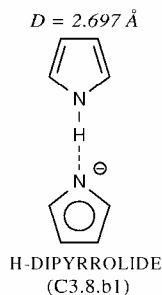
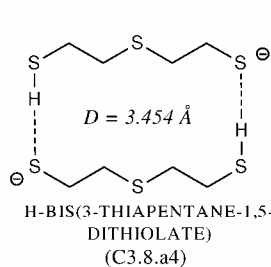
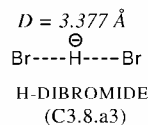
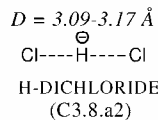
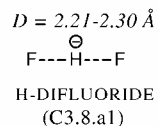
R=D...H-A-R



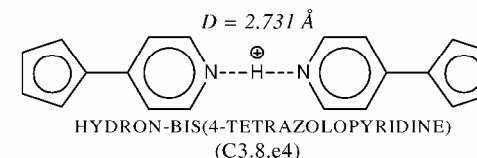
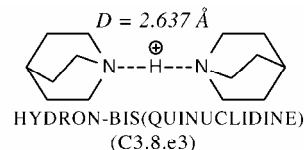
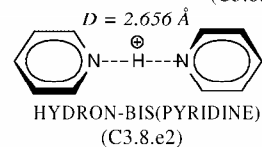
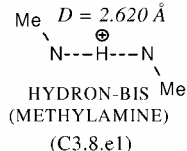
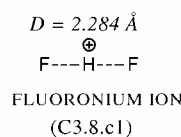
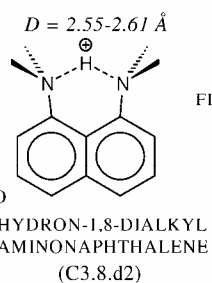
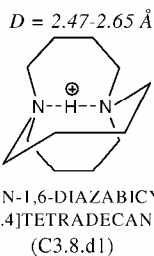
CSD Classification of Other Homonuclear Systems: (-) and (+)CAHB

CHART 3.8. HOMONUCLEAR X-H...X (X = F, Cl, Br, S, N)
CHARGE-ASSISTED HBs, CAHBs

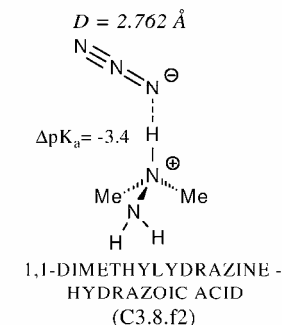
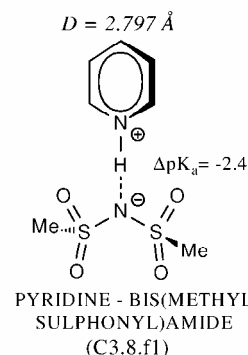
(-)CAHB



(+)CAHB



(+/-)CAHB



The considerations made for O-H...O can be extended to **other homonuclear X-H...X bonds**, provided **X is sufficiently electronegative** and the bond formed belongs to a proper Chemical Leitmotif.

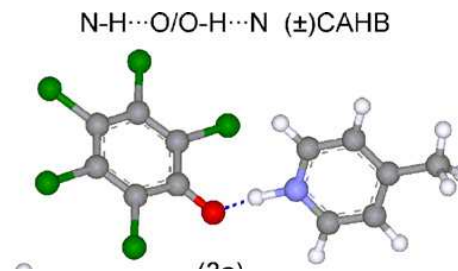
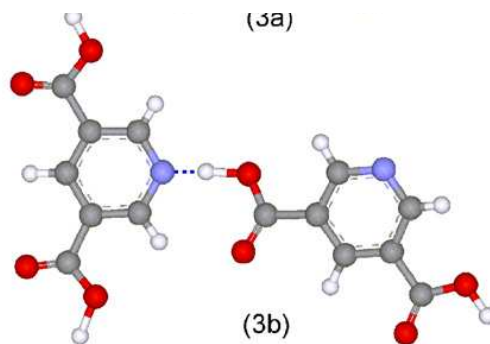
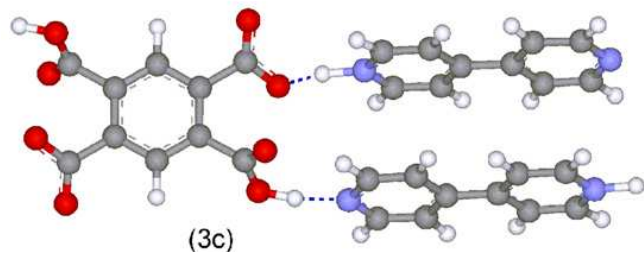
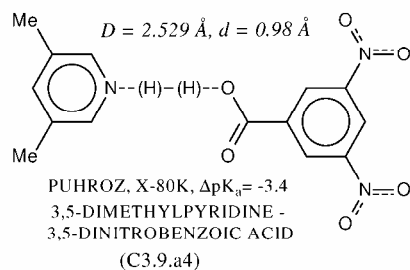
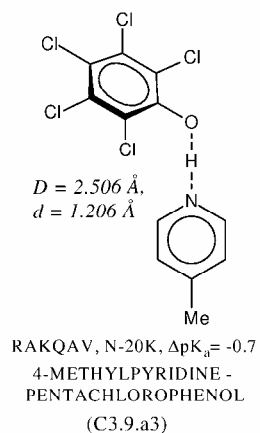
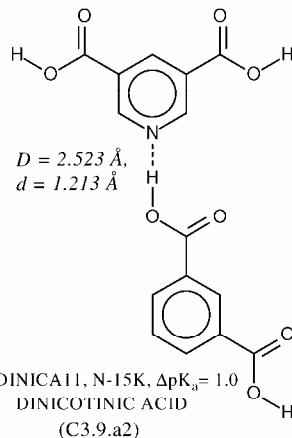
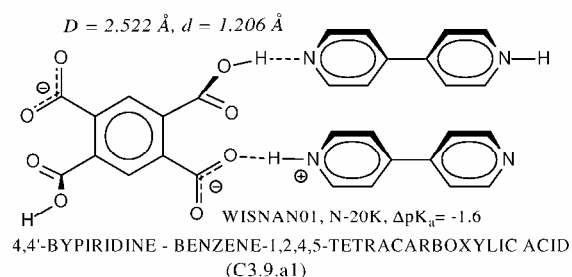
Typical (-)CAHBs include [Hal...H...Hal]⁻ (Hal = F, Cl, Br), a single case of [S...H...S]⁻, and a few [N...H...N]⁻ bonds, while [F...H...F]⁺ is the only (+)CAHB known to involve halogens.

Conversely, [N...H...N]⁺ (+)CAHBs are quite frequent because they constitute the class of **proton sponges**, compounds with a variety of chemical applications that, for this reason, have been extensively studied from a structural point of view (Adler, 1990; Staab and Saupe, 1988; Llamas-Saiz *et al.*, 1994).

Finally, about thirty N-H...N (±)CAHBs short enough to suggest a strict PA/pK_a matching have been retrieved, which would deserve a more detailed thermodynamic study. Only two examples are shown.

CSD Classification of Heteronuclear Systems: (\pm)CAHB

CHART 3.9. HETERONUCLEAR
N-H...O/O-H...N DOUBLE CHARGE-ASSISTED HB, (\pm)CAHB



(\pm)CAHBs, whose strength simply depends on the more or less accidental donor/acceptor PA/pK_a matching, are not expected to be seriously affected by the **heteronuclearity** of the bond.

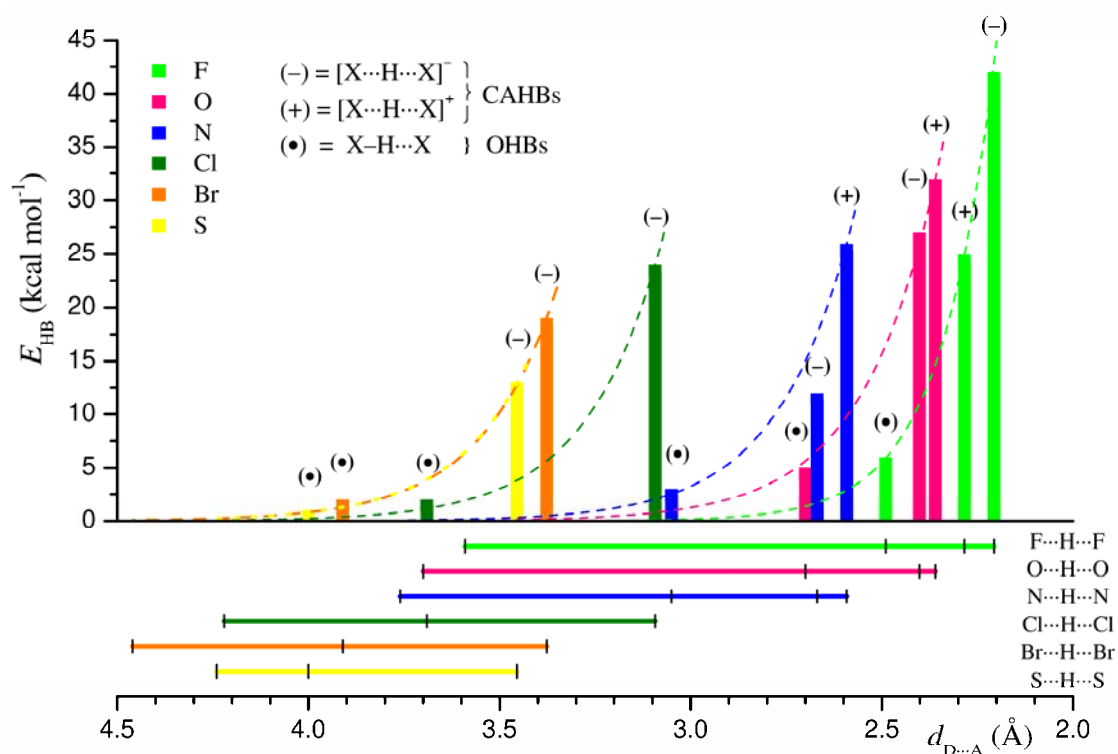
As a matter of fact, a systematic CSD study (Gilli and Gilli, 2000) carried out on **318** strong N-H...O/O-H...N bonds with $d(N\cdots O) \leq 2.66 \text{ \AA}$ has singled out

265 (\pm)CAHBs (192 N-H⁺...O⁻ and 73 O-H...N),
29 (+)CAHBs (29 N-H⁺...O), and only
7 (-)CAHBs (5 N-H...O⁻ and 2 O-H...N⁻).

Summary of D...A Distances: OHBs against CAHBs (1)

D-H...A	χ_P (vdW)	$d(D\cdots A)$ <i>OHB</i>	$d(D\cdots A)$ <i>OHB</i>	SHR% <i>OHB</i>	E_{HB}	$d(D\cdots A)$ <i>CAHB</i>	SHR% <i>CAHB</i>	E_{HB}
[F...H...F] ⁻	3.94	3.59	2.49	-31	≈ 6	2.207	-38	42(3)
[O...H...O] ⁻	3.44	3.7	2.7	-27	≈ 5	2.402	-35	27(1)
[Cl...H...Cl] ⁻	3.16	4.22	3.69	-13	≈ 2	3.093	-30	24(3)
[N...H...N] ⁻	3.04	3.76	3.05	-19	≈ 3	2.669	-29	12(-)
[Br...H...Br] ⁻	2.96	4.46	3.91	-12	≈ 2	3.377	-24	19(3)
[S...H...S] ⁻	2.58	4.24	4	-6	≈ 1	3.454	-18	13(1)
[F...H...F] ⁺	3.98	3.59	2.49	-31	≈ 6	2.284	-36	25(2)
[O...H...O] ⁺	3.44	3.7	2.7	-27	≈ 5	2.36	-36	32(2)
[N...H...N] ⁺	3.04	3.76	3.05	-19	≈ 3	2.592	-31	26(2)
[O...H...O] [±]	3.44	3.7	2.7	-27	≈ 6	2.381	-36	<u>28.7</u>
[N...H...O] [±]	<3.24>	3.73	2.87	-23	≈ 4	2.506	-33	-
[N...H...N] [±]	3.04	3.76	3.05	-19	≈ 3	2.682	-29	<u>16.4</u>

Summary of D...A Distances: OHBs against CAHBs (2)



Full range of **H-bond energies**, E_{HB} , and **D...A contact distances** spanned by the most common OHB or CAHBs homonuclear bonds.

Horizontal lines on the bottom show the full ranges of the D...A distances from the longest (Σ , vdW) to the shortest value.

The dashed curves represent the exponential dependence of E_{HB} from $d_{D \cdots A}$ (Gilli et al., 2008).

(Slide to be discussed below in Lecture 4)

Lecture 3. PART 2
The PA/pKa Equalization Principle
Modelling the H-Bond by Thermodynamic Methods

A Proposal

Two very similar proposals come from the early thermodynamic or spectroscopic investigations on the HB and are both centered on the **matching of the acid-base properties of the HB donor and acceptors moieties**, what we like to call, for the sake of brevity, the **PA/pK_a Equalization Principle**.

With reference to any generic **D–H···A bond**, this principle states that the HB is the stronger the smaller becomes the difference of the donor-acceptor

proton affinities: $\Delta PA = PA(D^-) - PA(A)^*$

or

acidic constants: $\Delta pK_a = pK_{AH}(D-H) - pK_{BH^+}(A-H^+)^*$

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

1975. Ault, B.S. and Pimentel, G.G. *J Phys Chem* 79: 615 (1975).

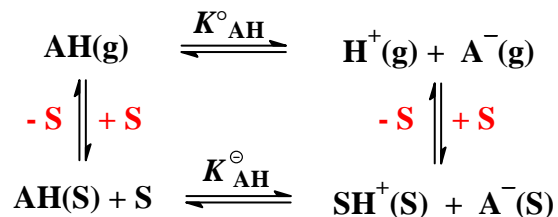
1977. Kebarle, P., *Ann Rev Phys Chem* 28: 445–476 (1977).

1982. Malarski, Z., M. Rospenk, and L. Sobczyk *J. Phys. Chem.* 86: 401–406 (1982).

1984. Meot-Ner (Mautner) M., *J Am Chem Soc* 106: 1257–1264 (1984).

Modelling the H-Bond by Thermodynamic Methods

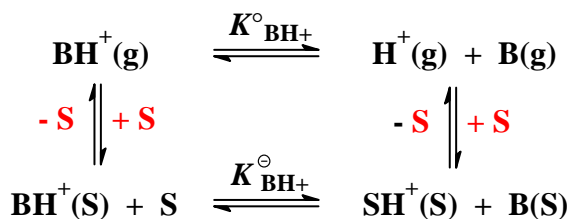
Thermodynamic Equations



$$\begin{aligned}
 \Delta_{\text{AH}}G^{\circ} &= \Delta_{\text{AH}}H^{\circ} - T \Delta_{\text{AH}}S^{\circ} = -RT \ln K_{\text{AH}}^{\circ} \\
 &= \text{gas-phase acidity of AH} = \text{gas-phase basicity of A}^{-};
 \end{aligned}$$

$$\Delta_{\text{AH}}H^{\circ} = \text{proton affinity of A}^{-} = \text{PA(A}^{-});$$

$$\begin{aligned}
 \Delta_{\text{AH}}G^{\bullet} &= \Delta_{\text{AH}}H^{\bullet} - T \Delta_{\text{AH}}S^{\bullet} = -RT \ln K_{\text{AH}}^{\bullet} \\
 &= 2.303 RT \text{p}K_{\text{AH}} = 1.364 \text{p}K_{\text{AH}} \text{ (kcal mol}^{-1} \text{ at 25}^{\circ}\text{C)}
 \end{aligned}$$



$$\begin{aligned}
 \Delta_{\text{BH}^{\text{+}}}G^{\circ} &= \Delta_{\text{BH}^{\text{+}}}H^{\circ} - T \Delta_{\text{BH}^{\text{+}}}S^{\circ} = -RT \ln K_{\text{BH}^{\text{+}}}^{\circ} \\
 &= \text{gas-phase basicity of B};
 \end{aligned}$$

$$\Delta_{\text{BH}^{\text{+}}}H^{\circ} = \text{proton affinity of B} = \text{PA(B)};$$

$$\begin{aligned}
 \Delta_{\text{BH}^{\text{+}}}G^{\bullet} &= \Delta_{\text{BH}^{\text{+}}}H^{\bullet} - T \Delta_{\text{BH}^{\text{+}}}S^{\bullet} = -RT \ln K_{\text{BH}^{\text{+}}}^{\bullet} \\
 &= 2.303 RT \text{p}K_{\text{BH}^{\text{+}}} = 1.364 \text{p}K_{\text{BH}^{\text{+}}} \text{ (kcal mol}^{-1} \text{ at 25}^{\circ}\text{C)}
 \end{aligned}$$

The **PA/pK_a equalization (or PA/pK_a matching) principle** is the hypothesis that the D–H···A bond strength can be accounted for in terms of the differences

$$\Delta\text{PA} = \text{PA(D}^{-}) - \text{PA(:A)} \quad \text{or} \quad \Delta\text{p}K_{\text{a}} = \text{p}K_{\text{a}}(\text{D-H}) - \text{p}K_{\text{a}}(\text{A-H}^{\text{+}}).$$

PA and **pK_a** are defined by the thermodynamic equations above, respectively in the gas phase or in a solvent (S), most frequently dimethylsulphoxide (DMSO) or water (H₂O).

Modelling the H-Bond by Thermodynamic Methods

Non-Homogeneity of the Thermodynamic Indicators

Starting from the 1960', there have been numerous attempts to rationalize H-bond strengths in terms of PA/pK_a matching, with particular reference to the PA interpretation of matrix-isolation IR, ICR (ion cyclotron resonance), and PHPMS (pulsed high-pressure mass spectrometry) spectroscopies. Though many of these studies were quite successful in interpreting limited series of compounds, no general rule valid for all possible types of H-bonds has never been produced.

The reasons have been only recently recognized (*Gilli, Pretto, and Gilli, J Mol Struct, 2007*) in defects of the previous thermodynamic treatment, whose correction has led to single out a number of new specific and important factors:

H-bonds are not thermodynamically homogeneous but **belong to four distinct thermodynamic classes**, each of which must be treated in a slightly different way:

Though **PA and pK_a values** are strictly correlated, they **are endowed with different thermodynamic properties** that hinder the application of the PA/pK_a equalization principle to some classes of chemical leitmotifs;

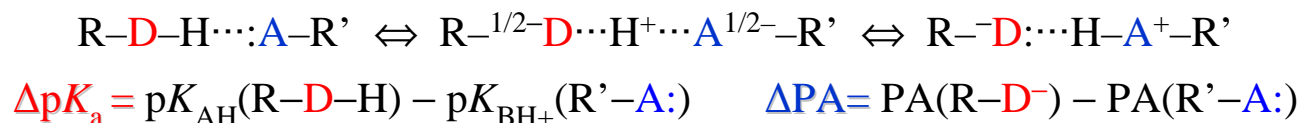
The interpretation of thermodynamic data is often tricky and requires much attention to be correctly performed.

Modelling the H-Bond by Thermodynamic Methods

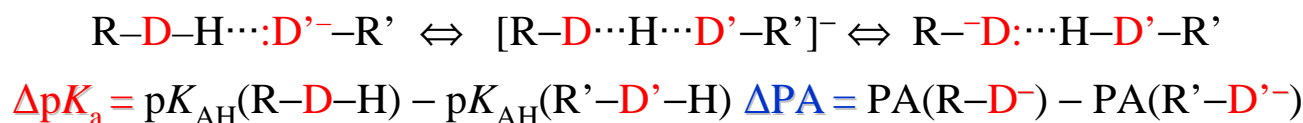
Thermodynamic H-Bond Classes

RAHBs: RAHBs cannot be treated by PA/pK_a equalization methods because π-delocalization modifies the PA/pK_a's of the donor and acceptor moieties.

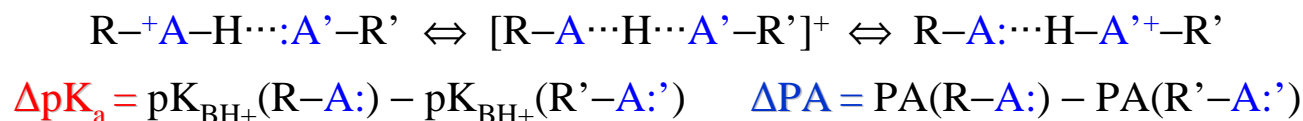
(+/-)CAHBs, PAHBs, or OHBs: A *proton transfer* from an acid (HB donor) to a base (HB acceptor)



(-)CAHBs: A *proton sharing* between two acids (HB donors)



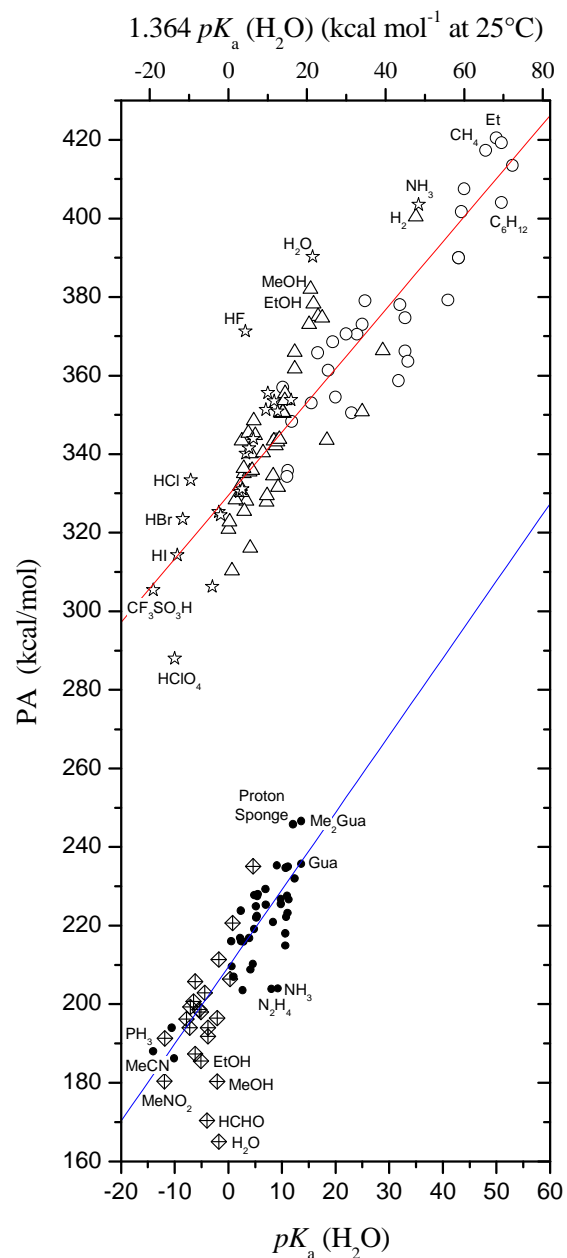
(+)CAHBs: A *proton sharing* between two bases (HB acceptors)



Whenever **(-)** and **(+)**CAHBs are both homonuclear (D = D' or :A = :A') and homomolecular (R = R'), the matching condition $\Delta\text{p}K_{\text{a}} = 0$ will hold irrespective of the actual pK_a's of the two interacting moieties. In this case, all HBs formed will be strong!

Modelling the H-Bond by Thermodynamic Methods

Differences between PA and pK_a Quantities



The plot shows the intercorrelation between PA and pK_a values. Data are arranged in two subsets for **A-H acids** and **:B bases** with correlation equations (with removed outliers)

$$PA(A-) = 329(2) + 1.61(7) pK(AH, H_2O)$$

$$PA(B:) = 210(1) + 2.0(1) pK(BH, H_2O).$$

The two lines are reciprocally shifted by an amount of energy that, at the zero of pK_a , is $\Delta = \Delta(329 - 210) = 119\ kcal\ mol^{-1}$.

What does this energy difference represent?

Considering the dissociation reactions of the **acid** and the **base** in the gas phase



it is evident that Δ represent **the work needed to take the two charges $H^+(g)$ and $A^-(g)$ from the H-bond distance (say, R) to the infinity (the zero of all charged quantities).**

Since $\Delta \cong 119\ kcal\ mol^{-1}$, an approximate value of the H-bond distance can be calculated as $\langle R \rangle = 332.15/1999 = 2.23\ \text{\AA}$, a value that, though fairly reasonable from a physical point of view, is too inaccurate for being of practical use.

Modelling the H-Bond by Thermodynamic Methods

Differences between PA and pK_a Indicators

(+/-)CAHB, PAHB, and OHB: A *proton transfer* from an acid (HB donor) to a base (HB acceptor)

$$\Delta PA = PA(R-D^-) - PA(R'-A:)$$

(-)CAHB: A *proton sharing* between two acids (HB donors)

$$\Delta PA = PA(R-D^-) - PA(R'-D'^-)$$

(+)CAHB: A *proton sharing* between two bases (HB acceptors)

$$\Delta PA = PA(R-A:) - PA(R'-A:')$$

The electrostatic term $\Delta \cong 119 \text{ kcal mol}^{-1}$ is

(i) not present in (+)CAHB (neutral A and A');

(ii) doubly present (charged D^- and D'^-) but mutually canceling out in (-)CAHB;

(iii) present in (+/-)CAHB (charged D^-)

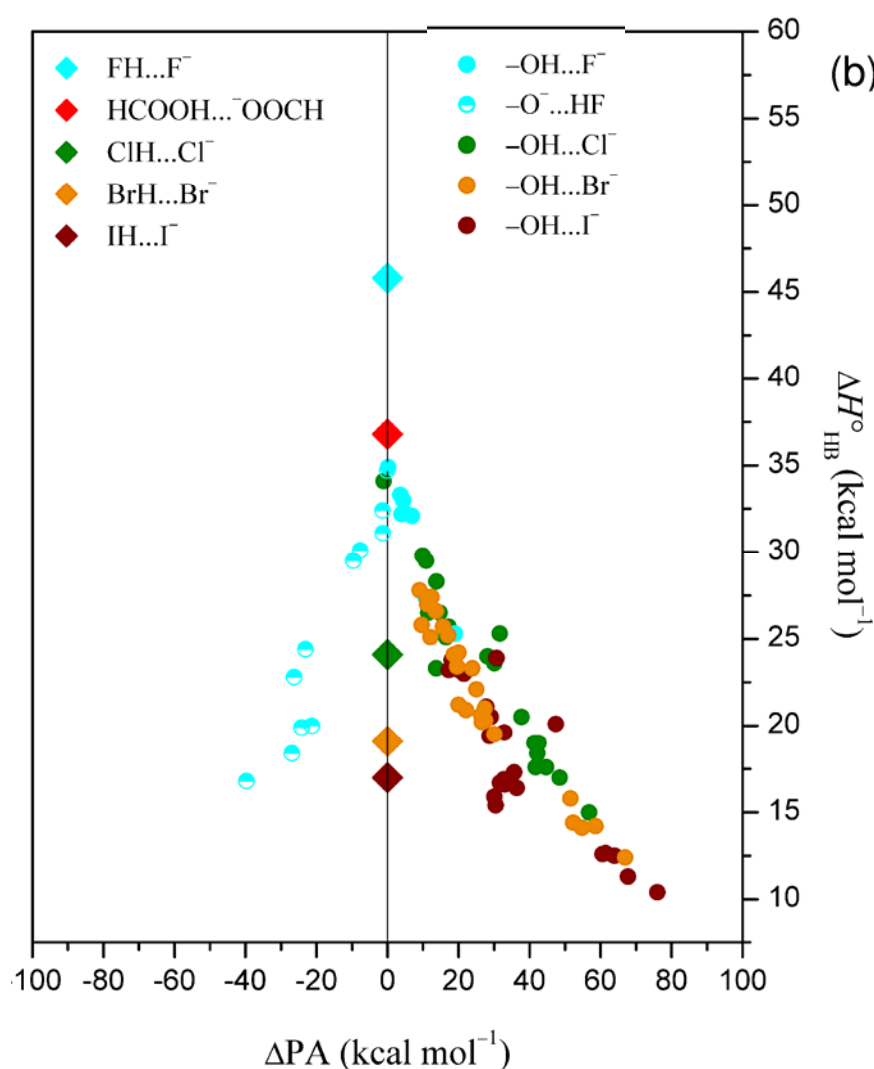
This leads to the conclusion that the values of ΔPA can be actually used for predicting H-bond strengths of the two proton-sharing H-bonds, but cannot be used for the much more frequent proton-transfer ones.

The ΔPA use is therefore limited to (-)CAHBs and (+)CAHBs in the gas phase, a type of application that can be considered of specialized concern and outside the main practical interests of chemistry and biology.

Such difficulties do not subsist **in solution** where no electric work is involved because the proton is exchanged within the close environment of the solvated ions and, accordingly, ΔpK_a turns out to be **the correct indicator of pK_a equalization** for both **proton-transfer** and **proton-sharing** H-bonds.

Modelling the H-Bond by Thermodynamic Methods

A Verification of the PA Equalization Principle



(b) ΔH° vs ΔPA plot for the gas-phase dissociation equilibrium $[-O\cdots H\cdots X]^- \rightleftharpoons O-H + X^-$ studied by *Kebarle and McMahon (1971-1984)*. X represents halide ions (F, Cl, Br, and I) and $-O-H$ a series of organic alcohols and acids. ΔPA values are positive when the dissociated form is $O-H + X^-$ (on the right) and negative when this form is $O^- + H-F$ (blue points on the left).

The points arranged on the vertical line at $\Delta PA = 0$ show, for reference, the well known homonuclear $[X\cdots H\cdots X]^-$ (-)CAHBs.

The plot perfectly follows the PA Equalization Principle, larger association enthalpies being all localized on the vertical line with $\Delta PA = 0$.

Note. The form of the relationship ΔH° versus ΔPA has been investigated by many authors who mostly suggested **linearity** but without achieving any degree of generality. It can be said that, so far, **no theoretical model of this relation has ever been proposed**. **Another important problem to commit to posterity!**

Modelling the H-Bond by Thermodynamic Methods

The pK_a Equalization Principle.

Retrieving a Valid List of pK_a Values

There are two known series of acidity constants that could be a basis for H-bond-strengths prediction, one measured in water, $pK_a(\text{H}_2\text{O})$, and the other in dimethyl-sulphoxide, $pK_a(\text{DMSO})$, but the latter (Bordwell, 2003) is still too limited to be of practical use.

Our work makes exclusive use of $pK_a(\text{H}_2\text{O})$ values. The main difficulty is that the H-bond range of acidities is enormous ($-15 < pK_a < 53$) in comparison with the autoprotolysis range of water ($0 < pK_a < 14$) normally investigated. Hence, measurements must be extended to solvents considerably more acidic or basic than water and then rescaled to water by various awkward methods.

Present values were mostly taken from previous compilations (Maskill, 1985; Cookson, 1974; Smith and March, 2001; Lide, 2006; Martell et al., 2004) and complemented by a number of single values from the literature. Since all data refer to water, the short notation pK_a instead of $pK_a(\text{H}_2\text{O})$ is used, while the symbols pK_{AH} and pK_{BH^+} are used to distinguish between the dissociation of acids and protonated bases. Final data have been arranged in order of chemical functionality:

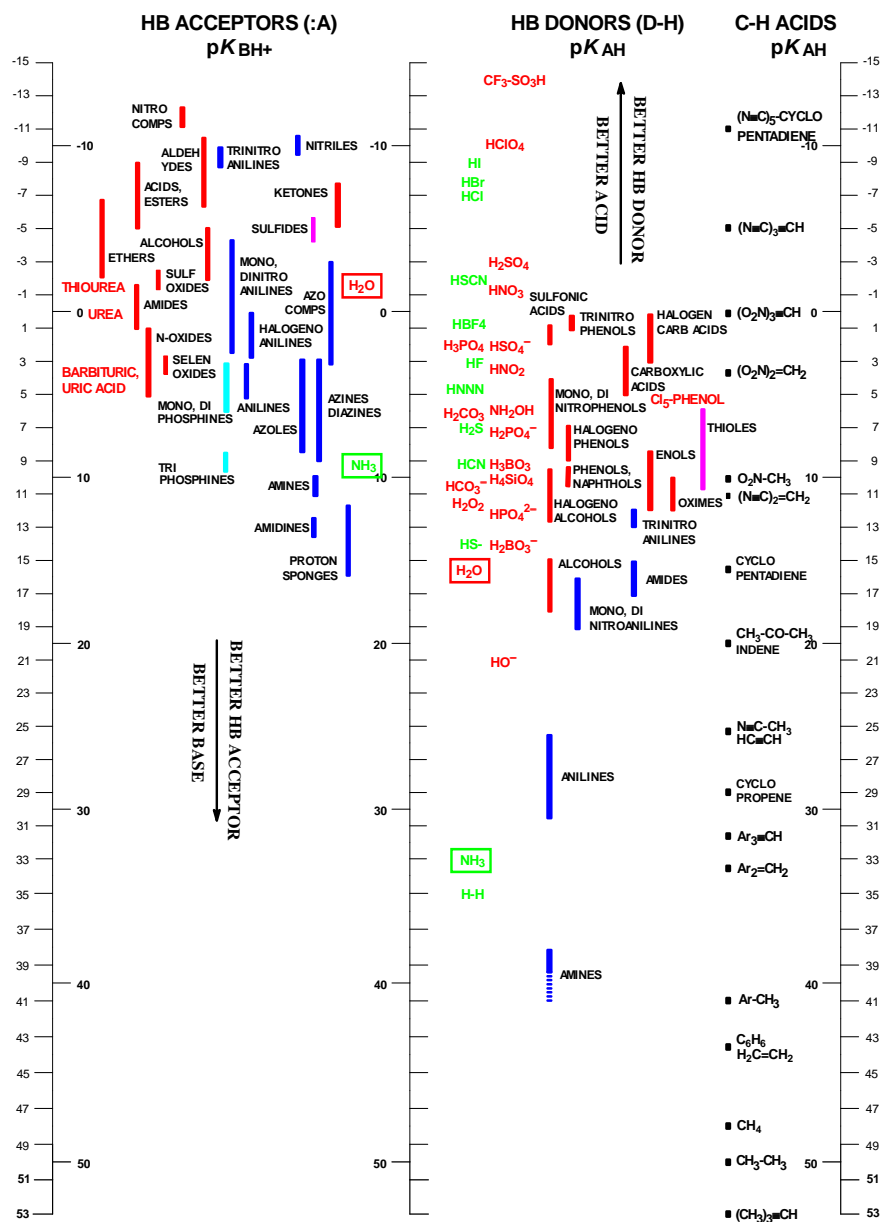
inorganic acids, C–H acids, and organic acids as H-bond donors;

organic oxygen, nitrogen and phosphorous bases as H-bond acceptors.

Extended Tables containing more than 300 chemical classes have been compiled, together with a pictorial representation of the data in form of bar chart, called the

pK_a Slide Rule.

The pKa Slide Rule



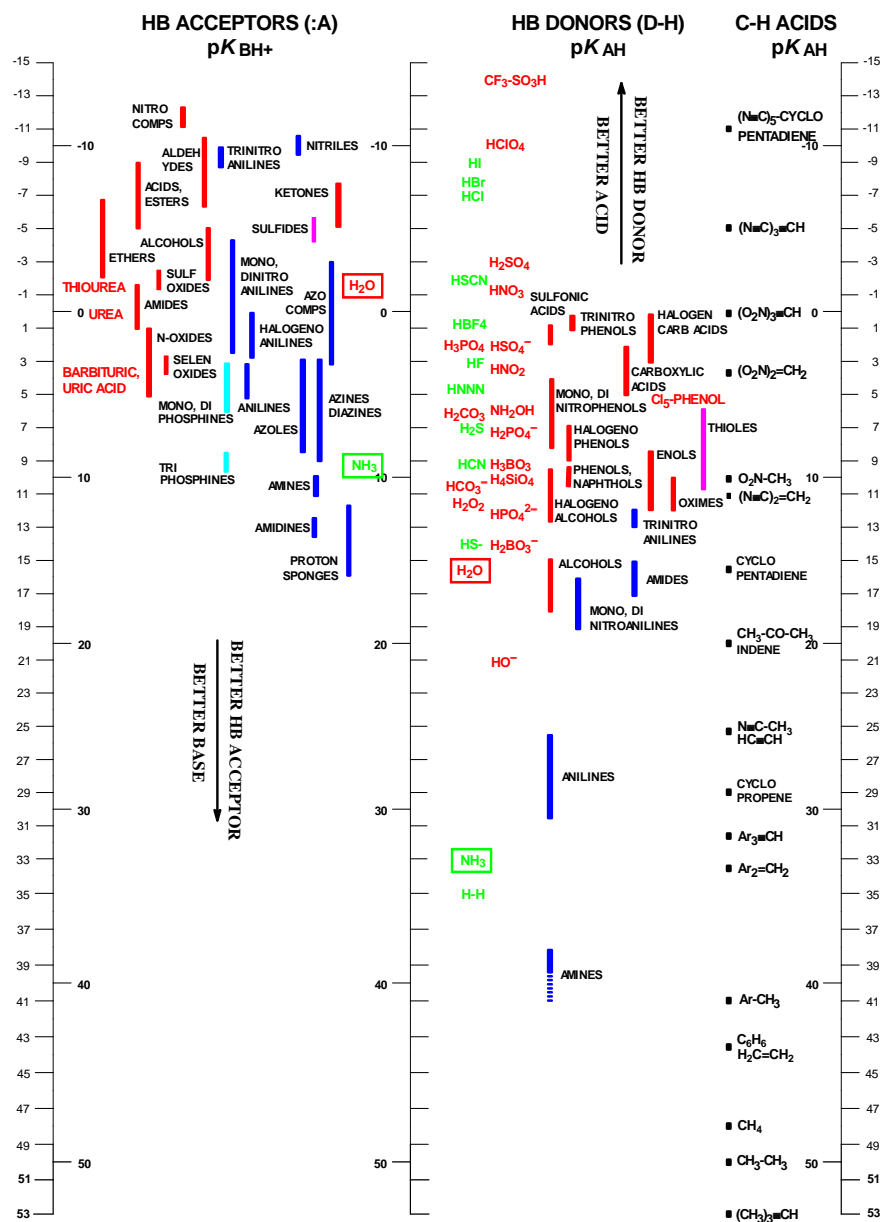
C-H acids display the greatest range of values, $-1 \leq pK_a \leq 53$. Unfortunately, there are very few data for very acidic C-H donors matching the pK_a of carbonyls to form strong $C-H \cdots O$ bonds, the only case (Bock et al., 1993) being the $C-H \cdots O <$ adduct of trinitromethane ($pK_a = 0.0$) with dioxane ($pK_a \approx 2.1$) having $C \cdots O$ distance of 2.936 Å, possibly the shortest ever observed.

Other acids are in the range $-1 \leq pK_a \leq 40$, the strongest being **trinitrophenols** ($-0.7 \leq pK_a \leq 0.33$) and the weakest ones **organic amines** (pK_a around 39-40).

The order of decreasing acidity is **carboxylic acids** > **phenols** > **alcohols** and **amides** > **anilines** > **amines** and, in each class, the acidity is seen to be enhanced by halogenation or nitration.

Thioles ($6.5 \leq pK_a \leq 11$), **enols** ($8.5 \leq pK_a \leq 12$), and **oximes** ($10 \leq pK_a \leq 12$) are significantly more acidic than the corresponding **alcohols** ($15 \leq pK_a \leq 18$).

The pK_a Slide Rule

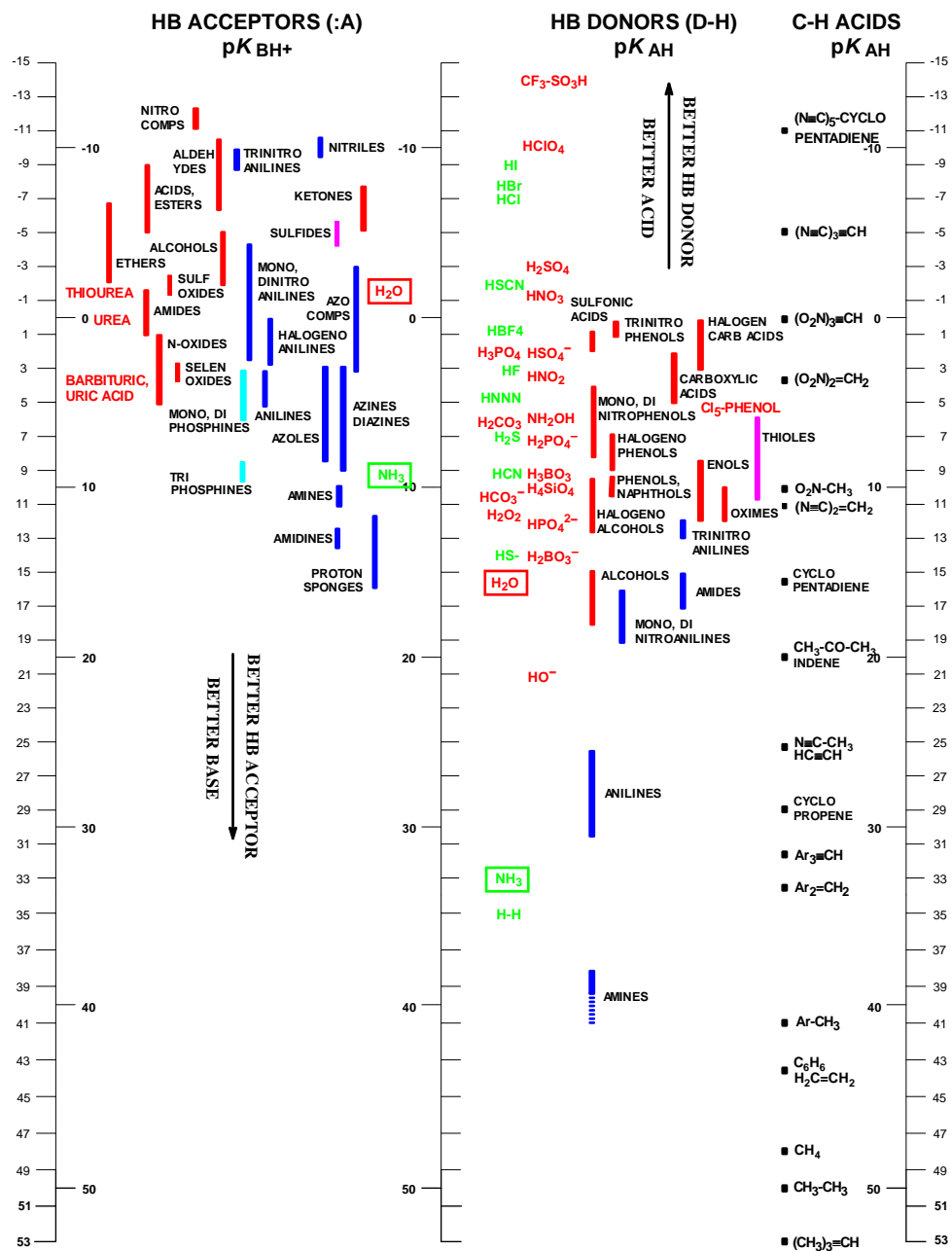


The acceptor range ($-12 \leq pK_a \leq 16$) is shifted upwards with respect to donors, so that **nitro, carbonyl, nitriles, ethers, alcohols, and sulphoxides acceptors** face a **few inorganic acids** but **no organic donors** with which can only form weak H-bonds.

Likewise, the **weakest donors (amines, anilines, and alcohols)** do not face **any known acceptor** and can then form only weak and neutral D-H...:A bonds.

The **maximum donor-acceptor overlap** occurs in the interval of water autoprotolysis ($0 \leq pK_a \leq 14$), where the greatest part of the strong H-bonds are expected.

Finally, the slide rule gives *a new insight* into the most common and familiar types of H-bonds. For instance, we speak without distinction of **amine–nitro, aniline–ketone, water–water, carboxylic acid–pyridine, and perchloric acid–aniline H-bonds** not considering that their ΔpK_a 's are as different as 50, 46, 17.4, -1, and -20 pK_a units corresponding to 67, 61, 23, -1.3, and -27 kcal mol⁻¹ at 25 °C and that this impressive series of numbers actually represent the energy difference between their tautomeric -D:...H-A⁺ and D-H...:A forms.



The pK_a Slide Rule

The pK_a slide rule is a tool for the graphical evaluation of the difference

$$\Delta pK_a = pK_{AH}(D-H) - pK_{BH+}(A-H^+)$$

for the most common classes of organic compounds.

HB Acceptors are on the left and HB Donors on the right.

pK_a values are given for chemical class.

Results expected:

$\Delta pK_a \gg 0$: 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

pK_a ranges of organic compounds:

C-H acids -11 < pK_a < 53

Other Donors -1 < pK_a < 40

Acceptors -12 < pK_a < 16

All -15 < pK_a < 53

pK_a in water 0 < pK_a < 14

End of Lecture 3