

Six Lectures on the Nature of the Hydrogen Bond
Lecture 1

*Introduction to the Hydrogen Bond:
Basic Concepts and Summary of Our First Studies
from 1989 to 2002*

Edited by

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



**23rd
European
Crystallographic
Meeting**

*6-11 August 2006
Leuven, Belgium*

Modern Hydrogen Bonding Theory
Gastone 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

The Birth of the H-Bond

The first idea of HB was devised in the laboratory of **Gilbert Newton Lewis** at the end of 1920s while he was writing his famous book *Valence and the structure of atoms and molecules* (1923).

The final assessment of the HB concept is accredited to **M.L. Huggins** and, independently, to **W.M. Latimer** and **W.H. Rodebush**, three young men working there.

The first paper was: **W.M. Latimer and W.H. Rodebush**. *Polarity and ionization from the standpoint of the Lewis theory of valence. J Am Chem Soc 42: 1419-1433, 1920.*

The first book is due to Pauling who made the HB known to the wider chemical community: **Pauling, L.** *The Nature of the chemical bond and the structure of molecules and crystals. An introduction to modern structural chemistry. Cornell University Press, Ithaca, N.Y., 1939, 1940, 1960, Chapter 12, 55 pages.*

The definition of HB has not changed over the years. What I like best was proposed by: **Vinogradov, S.N. and Linnel, R.H.** *Hydrogen bonding. Van Nostrand-Reinhold, New York, 1971.*

Hydrogen Bond Definitions

A Three-Center-Four-Electron Interaction



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

Alternatively:

A Proton Sharing Interaction



between **two electron pairs**

located on two adjacent electronegative atoms

Two Important HB Properties

- ◆ The HB acceptor is not an atom but an electron pair located on that atom
- ♠ Since both D and A must be more electronegative than H, all HBs have polarity

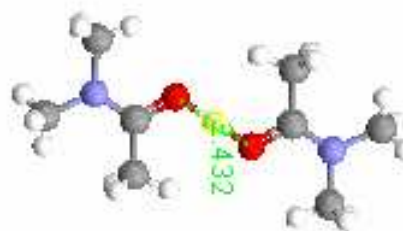
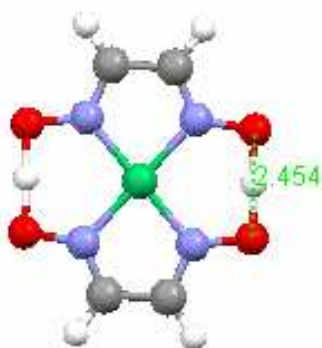


Electrostatic and Covalent HBs: The Pauling's Model

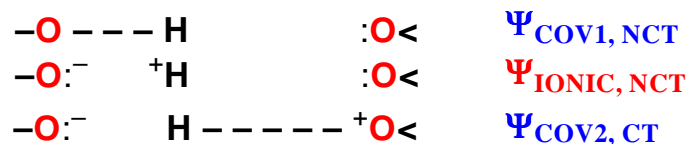
In *The Nature of the Chemical Bond*, L. Pauling describes two types of HBs:

◆ **Weak and dissymmetric HBs of electrostatic nature.** "It is recognized that the hydrogen atom, with only one stable orbital (the 1s orbital), can form only one covalent bond, that the hydrogen bond is largely ionic in character, and that it is formed only between the most electronegative atoms." (HB Chapter, p. 1)

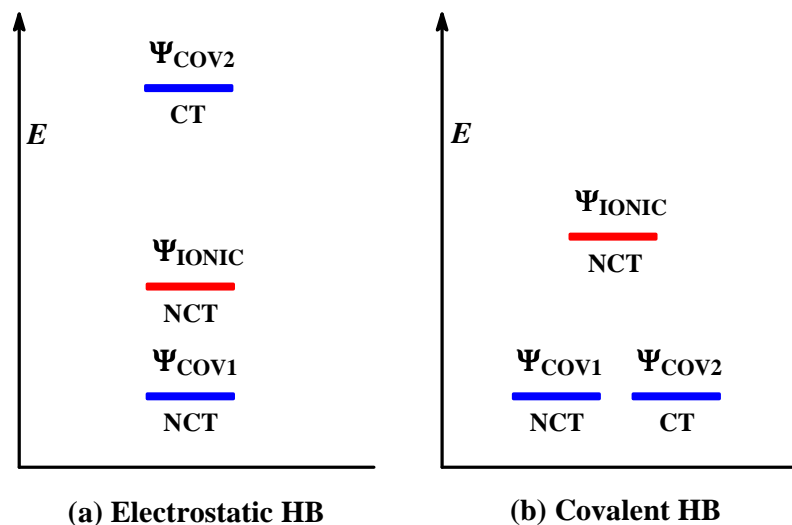
♣ **Strong and symmetric HBs of covalent nature: The "exceptions".** These exceptions are described in terms of VB theory as: "... the hydrogen bond in the $[\text{HF}_2]^-$ ion lies midway the two fluorine atoms and may be considered to form a half-bond with each." (HB Chapter, p. 49)



The Coulson's VB Treatment. The Standard HB Model



Pauling's ideas acquired theoretical weight with the VB treatment by **Coulson and Danielsson (1954)** where the O-H...O bond is depicted as a mixture of three main VB forms, two covalent and one ionic.



This line of thought was also adopted by **Pimentel and McClellan** in their famous book *The Hydrogen Bond (1960)*.

They wrote: “At the **1957 Ljubljana Conference** one of the important points of fairly general accord was that the electrostatic model does not account for all of the phenomena associated with H bond formation”.

The Birth of the Simple Electrostatic Paradigm

For reasons difficult to understand, the Standard HB Model was discarded in the mid-sixties and the HB became **the weak electrostatic interaction not stronger than some 4-5 kcal mol⁻¹** everyone has read of in elementary textbooks, while strong HBs just disappeared from the chemical horizon. The effect of this choice was disastrous and it took more than twenty years to put it right.

Why the Standard Model was Abandoned

The most probable reason can be ascribed to the bizarre way in which Pauling had arranged his famous HB chapter in *The Nature of the Chemical Bond*.

♣ Weak electrostatic HBs are quoted on p. 1 of the chapter, while strong covalent ones only on p. 49. **Since most people read only the first few pages of anything**

♦ On p. 50, strong HBs are called “**exceptions**”. Most readers may have thought: **Why to bother about exceptions when there are already so many regular HBs to bother about? These are things for specialists!**

♥ On p. 1, the Pauling’s statement “**the hydrogen atom ... can form only one covalent bond...**” was quite unclear and, in consequence, was systematically misinterpreted. In correct VB terms it cannot be said that the H atom can form only one bond because, in fact, it may also form **any combination of two bonds whose bond orders sum up to one**, from (1,0) to (0,1) through (1/2, 1/2).

Another Unsolved Problem: The HB Puzzle

Bond lengths and energies of normal chemical bonds are determined by the nature of the interacting atoms and weakly perturbed by the environment.

On the contrary, **binding energies (E_{HB})** and **$\text{D}\cdots\text{A}$ distances ($d_{\text{D}\cdots\text{A}}$)** of **$\text{D}-\text{H}\cdots\text{A}$ H-bonds** do not simply depend on the donor (**D**) and acceptor (**:A**) nature, but *show very large variations even for the same donor-acceptor couple*.

This is what we have often called, for the sake of brevity,
the HB Puzzle.

An extreme example of this behavior comes from the effects produced on **the $\text{O}-\text{H}\cdots\text{O}$ bond** by the changing **acid-base properties** of its environment.

The weak $\text{HO}-\text{H}\cdots\text{OH}_2$ bond in water [$E_{\text{HB}} \approx 5 \text{ kcal mol}^{-1}$; $d_{\text{O}\cdots\text{O}} \approx 2.70\text{-}2.75 \text{ \AA}$] is transformed, in acidic or basic medium, into **the very strong $[\text{H}_2\text{O}\cdots\text{H}\cdots\text{OH}_2]^+$ or $[\text{HO}\cdots\text{H}\cdots\text{OH}]^-$ bonds** with E_{HB} up to 30-31 kcal mol⁻¹ and $d_{\text{O}\cdots\text{O}}$ down to 2.38-2.42 Å.

How to Tackle the HB Puzzle: the Problem of the Driving Variable

The **Electrostatic Paradigm** cannot explain the HB Puzzle.
Neither the **Standard Model** provides a complete interpretation of it;
it just suggests that H-bonds increase their strength with their increasing
covalency but without suggesting any specific mechanism for it.

To put the problem in more general terms, there are a dozen of physicochemical variables commonly measured in HB studies (energies, geometries, IR frequencies, NMR chemical shifts, NQR couplings, isotopic effects, not to speak of the intrinsic properties of the interacting molecules) and most, if not all, appear to be systematically intercorrelated.

But, **what's the driving variable?**
**What's the variable which, among the many intercorrelated ones,
drives the transformation from weak and electrostatic
to strong and covalent HB?**

A Proposal: The PA/pK_a Equalization Principle

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

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

OR

$$\text{acidic constants: } \Delta\text{p}K_{\text{a}} = \text{p}K_{\text{AH}}(\text{D-H}) - \text{p}K_{\text{BH}^+}(\text{A-H}^+)^*$$

-
- Ault, B.S. and Pimentel, G.G. *J Phys Chem* 79: 615 (1975).
 - Kebarle, P., *Ann Rev Phys Chem* 28: 445–476 (1977).
 - Meot-Ner (Mautner) M., *J Am Chem Soc* 106: 1257–1264 (1984).
 - Huyskens, P.L. and Zeegers-Huyskens Th., *J Chim Phys* 61: 81 (1964).
 - Malarski, Z., M. Rospenk, and L. Sobczyk *J. Phys. Chem.* 86: 401–406 (1982).

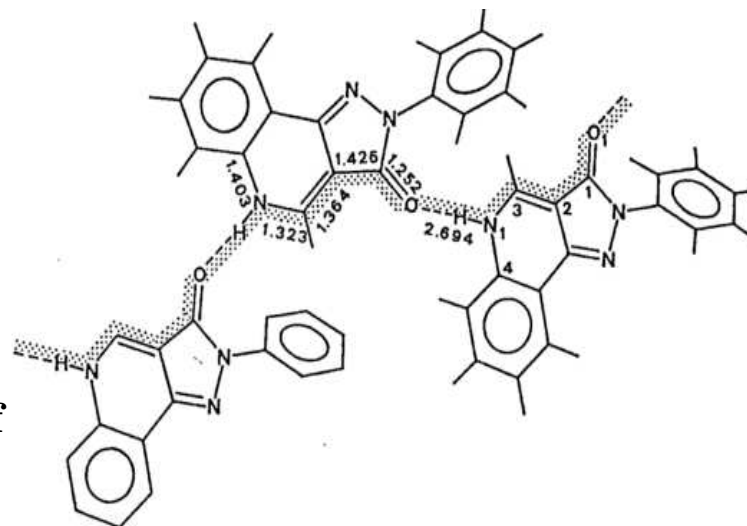
Our First Steps into the HB

As usual, we entered the HB field by chance. In 1985, during a study on the ligands of the benzodiazepine receptor, we determined the structure of **CGS8216** and noticed something strange: a quite short N–H...O bond of 2.694 Å in association with an interleaving β -enaminone \cdots O=C–C=C–NH \cdots fragment which was almost completely π -delocalized.

It was the first indication of a possible correlation between π -delocalization and H-bond strengthening – what we later called the **Resonance-Assisted H-Bond (RAHB)**

(Gilli, Bellucci, Ferretti & Bertolasi, *JACS*, 1989; Bertolasi, Gilli, Ferretti & Gilli, *JACS*, 1991).

Since, at the time, the very few crystal structures of β -enaminones were known, the work started on the analogous class of β -enolones (or β -diketone enols), compounds already known to give strong O–H...O bonds in association with the equally resonant \cdots O=C–C=C–OH \cdots fragments.



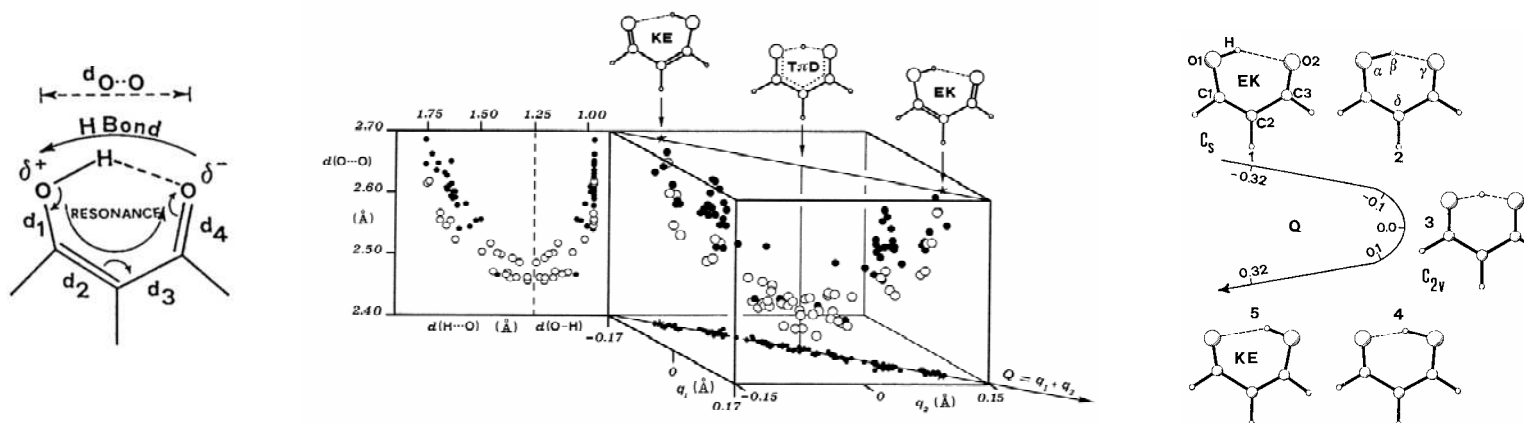
Structural Databases and Crystal Structure Correlation Methods

The correlation between π -delocalization and *H-bond strengthening* is essentially a problem of geometrical nature: What has to be proved is an intercorrelation between **HB strength** (as measured by the **O...O** or **O-H distances**) and π -delocalization of the resonant fragment (as measured by the **d₁-d₄ distances**).

This was the beginning of our intense interest for:

♣ **Structural Databases** in general and **Cambridge Structural Database (CSD)** in particular (Allen, Kennard..., 1979, 2002).

♣ Structural data interpretation by the so called **Crystal Structure Correlation (CSC) Method** (Bürgi, 1973, 1975; Bürgi and Dunitz, 1983), a method for obtaining information on the dynamic behavior of molecules from the inevitably rather static crystal data geometries.



Some sample applications of CSC to the study of RAHB in β -diketone enol structures.

The Development of the O–H····O RAHB

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Evidence for Resonance-Assisted Hydrogen Bonding from
Crystal-Structure Correlations on the Enol Form of the
 β -Diketone Fragment

Gastone Gilli,* Fabrizio Bellucci, Valeria Ferretti, and Valerio Bertolasi

*Contribution from the Centro di Strutturistica Diffraattometrica and Dipartimento di Chimica,
Università di Ferrara, 44100 Ferrara, Italy. Received May 4, 1987.*

Revised Manuscript Received September 14, 1988

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Evidence for Resonance-Assisted Hydrogen Bonding. 2.^a
Intercorrelation between Crystal Structure and Spectroscopic
Parameters in Eight Intramolecularly Hydrogen Bonded
1,3-Diaryl-1,3-propanedione Enols

Valerio Bertolasi, Paola Gilli, Valeria Ferretti, and Gastone Gilli*

*Contribution from the Centro di Strutturistica Diffraattometrica and Dipartimento di Chimica,
Università di Ferrara, 44100 Ferrara, Italy. Received October 19, 1990*

The O–H····O RAHBs



Very interesting

Class of Strong HBs

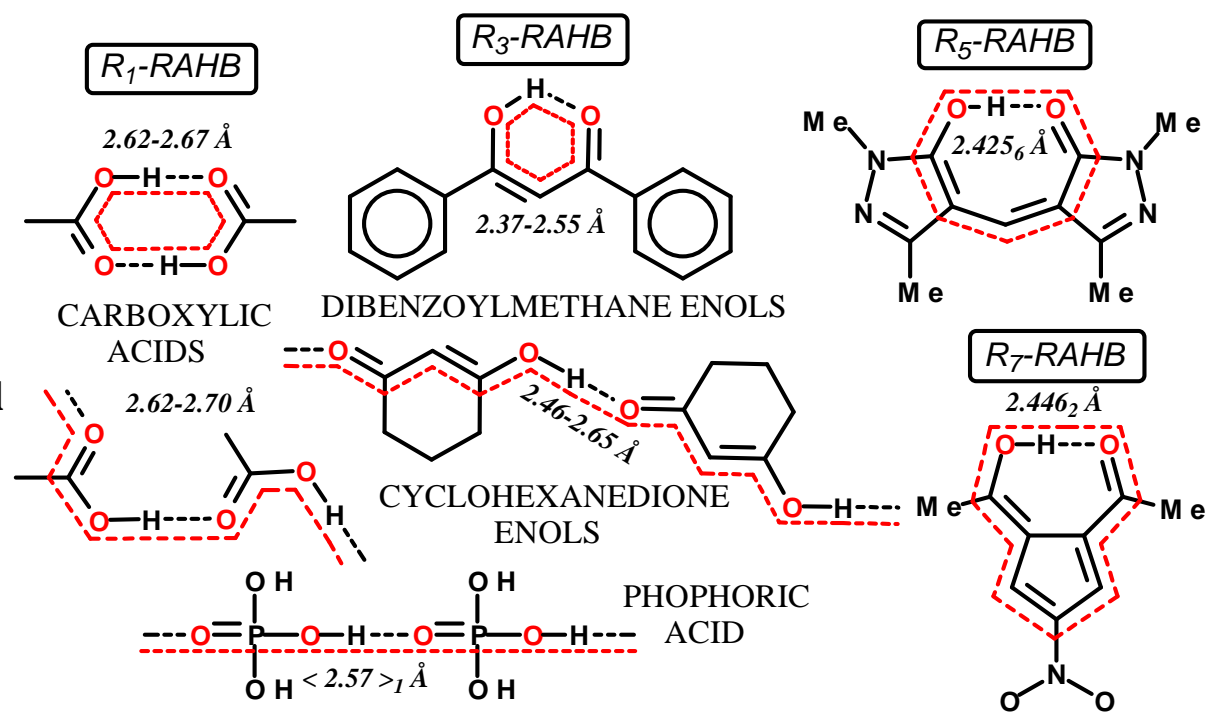
Different lengths of the
resonant spacer R_n

($n = 1, 3, 5, 7$)

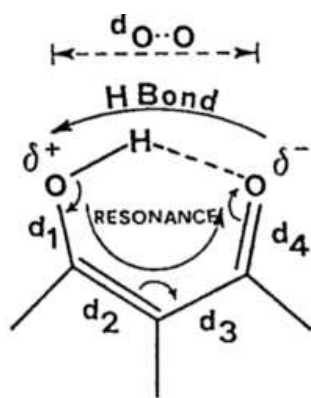
The HBs formed were all
much stronger than normal
(non-resonant) O–H····O
bonds, with

$d(\text{O}\cdots\text{O})_{\text{INTRA}} =$
2.39-2.55 Å

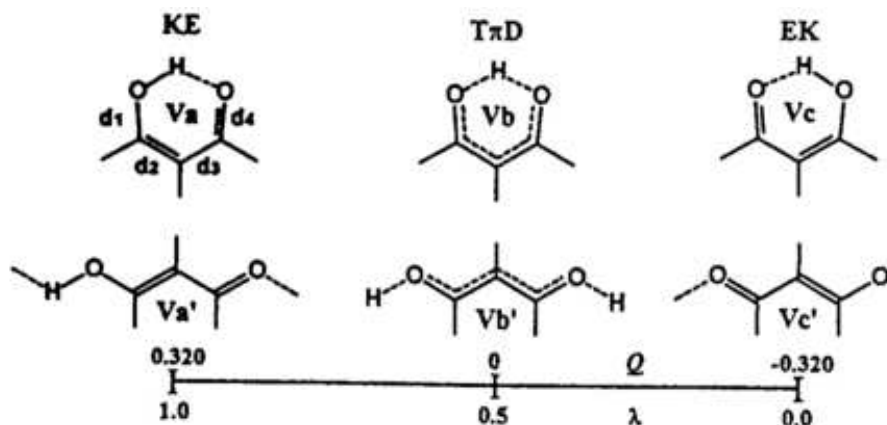
$d(\text{O}\cdots\text{O})_{\text{INTER}} =$
2.46-2.65 Å



A Model for RAHB: Electrostatic or Covalent?



RAHB Electrostatic Model



RAHB Covalent Model

The RAHB Electrostatic Model (JACS, 1989). (a) The resonance causes delocalization of the π -conjugated system and sets up opposite charges on the terminal oxygens. (b) The charges have the correct sign for strengthening the H-bond (O \cdots O shortening and O-H lengthening). (c) Moving the proton to the right is equivalent to moving the electron to the left. Previous charges are cancelled out, π -delocalization can proceed generating new charges, and the H-bond is further strengthened. (d) Iteration of this imaginary process will inevitably lead to the full delocalization of the π -conjugated system and to a very short O \cdots H \cdots O bond with centered proton.

The RAHB Covalent Model (JACS, 1994, 2004). Based on the VB enolketo \leftrightarrow ketoenol resonance, it has become later the Standard Model for RAHB interpretation .

Initial incongruities (wrong spin parity of the resonant forms) of the model were later mended (2004) by its fusion with the **State Correlation (or Avoided-Crossing) Diagrams (Shaik et al, 1992).**

Starting Again: The Empirical Approach

The substantial success obtained in assessing and interpreting the **O–H···O** RAHB aroused our interest in a more general problem: RAHB gives often rise to H-bonds which are considerably stronger than ordinary bonds (say, 15-20 against the usual 4-5 kcal mol⁻¹). But then, **how many classes of strong H-bonds are there?**

To tackle this problem, in 1994 we decided **to change approach** and **to restart to investigate the O-H...O bond from the very beginning** by adopting a **purely empirical strategy**:

- (i) *Suspend any previous ideas on the **electrostatic or covalent** nature of the HB;*
- (ii) *Suspend what we had already learned on **O–H···O** RAHB;*
- (iii) *Define the **O–H···O** bond as a simple **topological structure** where a H atom is connected to two or more oxygen atoms;*
- (iv) *Collect all **crystal structures** having **O–H···O** bonds with $d(\text{O}\cdots\text{O}) \leq 2.70 \text{ \AA}$;*
- (v) *Collect all available **IR $\nu(\text{O-H})$** and **NMR $\delta(\text{H})$** data of H-bonded protons;*
- (vi) *Collect all available **HB energy data** from thermodynamic measurements in gas phase and non-polar solvents;*
- (vii) *Try to infer a conclusion on the very nature of the **O–H···O** bond from the ensemble of the data collected.*

A Full Classification of Strong HBs

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Covalent Nature of the Strong Homonuclear Hydrogen Bond Study of the O—H---O System by Crystal Structure Correlation Methods¹

Paola Gilli, Valerio Bertolasi, Valeria Ferretti, and Gastone Gilli*

*Contribution from the Centro di Strutturistica Diffraattometrica and Dipartimento di Chimica
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*Received July 7, 1993**



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Towards an unified hydrogen-bond theory

G. Gilli*, P. Gilli

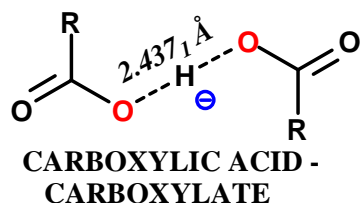
Dipartimento di Chimica and Centro di Strutturistica Diffraattometrica, University of Ferrara, Via Borsari 46, I-44100 Ferrara, Italy

Received 22 November 1999; received in revised form 25 January 2000; accepted 7 February 2000

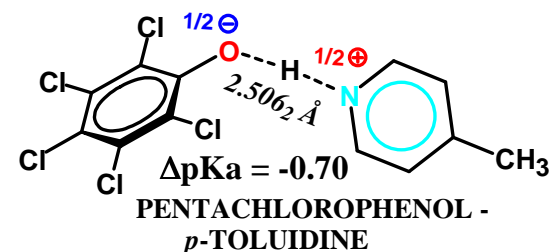
The Six HB Chemical Leitmotifs (CLs)

CHARGE - ASSISTED HBs

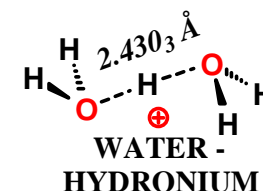
CL # 1: (\pm)CAHB \Rightarrow SHB, VSHB
Double Charge-Assisted HB
Direct Acid-Base PA/pK_a Matching



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

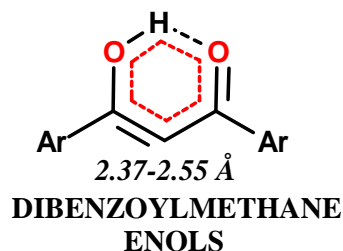


CL # 3: (+)CAHB \Rightarrow SHB, VSHB
Positive Charge-Assisted HB
Acid-Base PA/pK_a Matching by Proton Gain

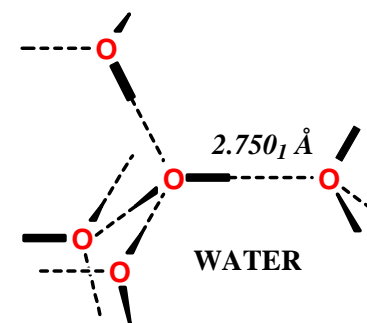


Σ/Π -BOND POLARIZATION - ASSISTED HBs

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

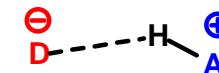
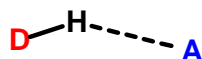


CL # 5: PAHB \Rightarrow MHB
Polarization-Assisted or σ -Cooperative HB
(Partial) PA/pK_a Matching by σ -Bond Polarization



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

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



The Five HB Chemical Leitmotifs (CLs)

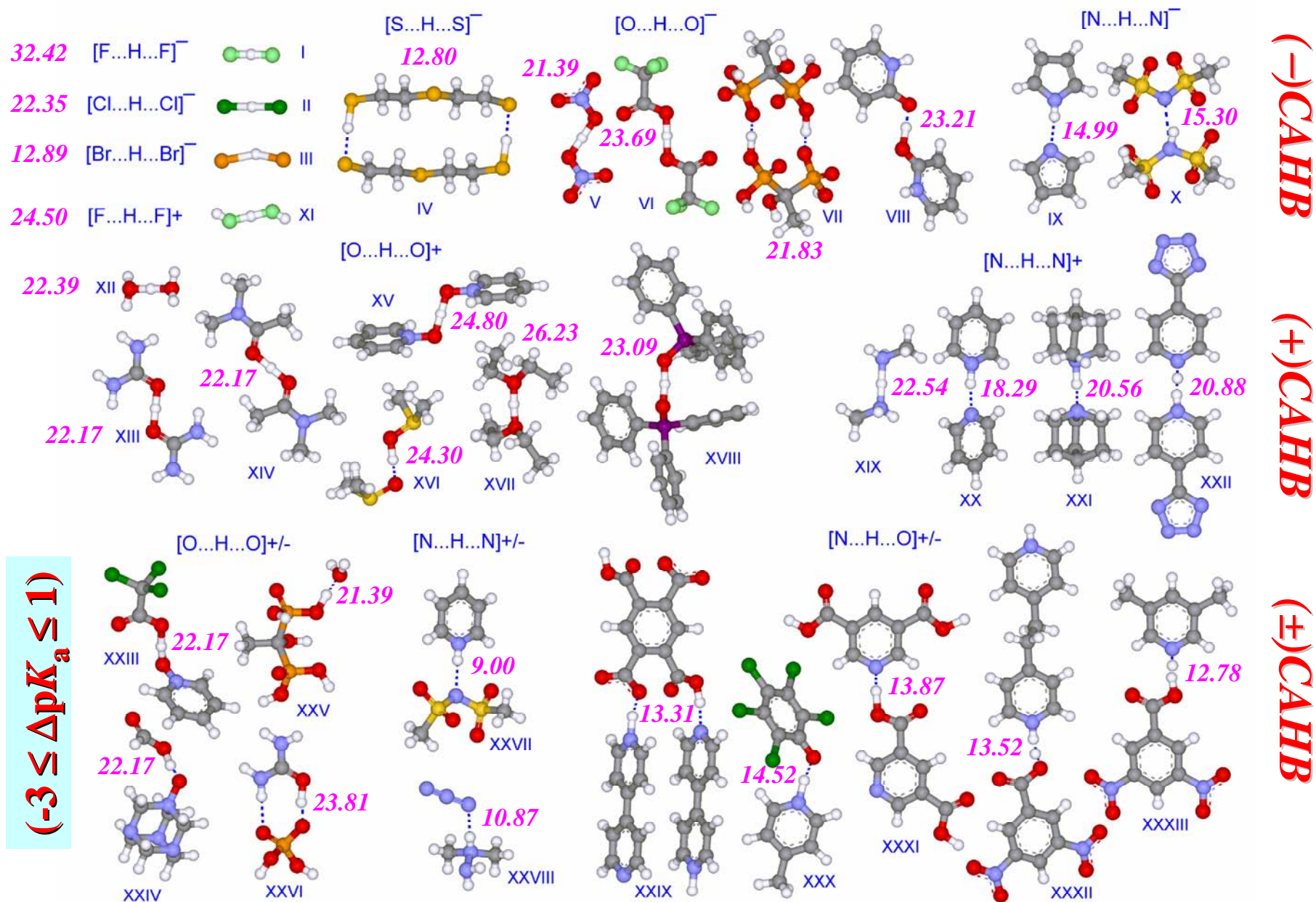
The most interesting aspect of a HB classification based on HB strength is that strong HBs belong only to a small number of chemical schemes that we have called **Chemical Leitmotifs**.



*The Alchemic Piper plays the
Five Magic Tunes that make any
Hydrogen Bond stronger:*

The Chemical Leitmotifs

A Gallery of the Most Famous Strong H-Bonds



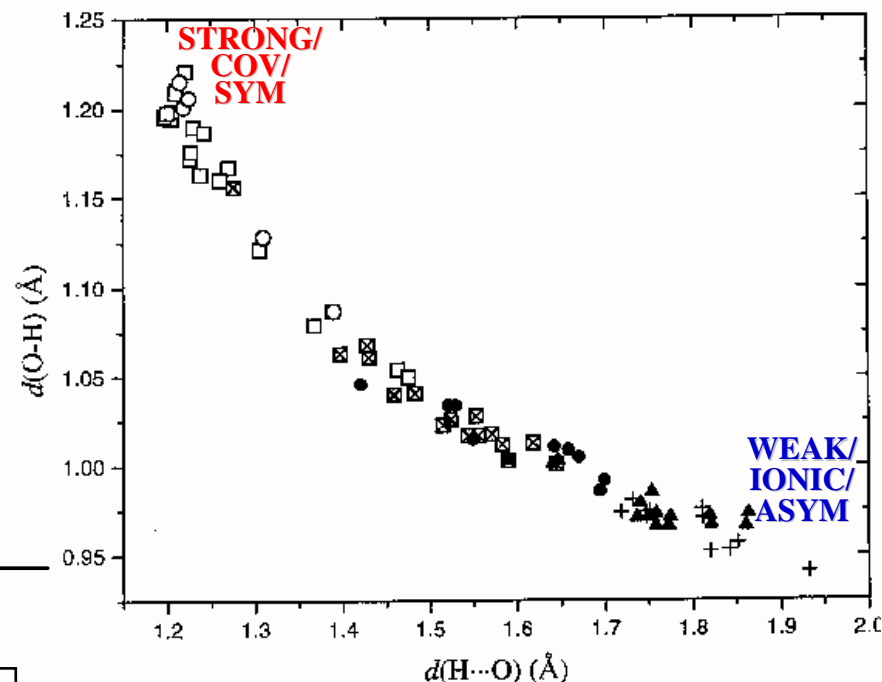
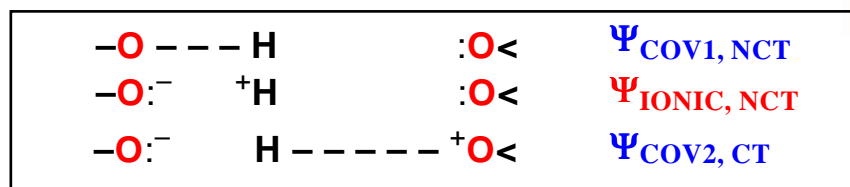
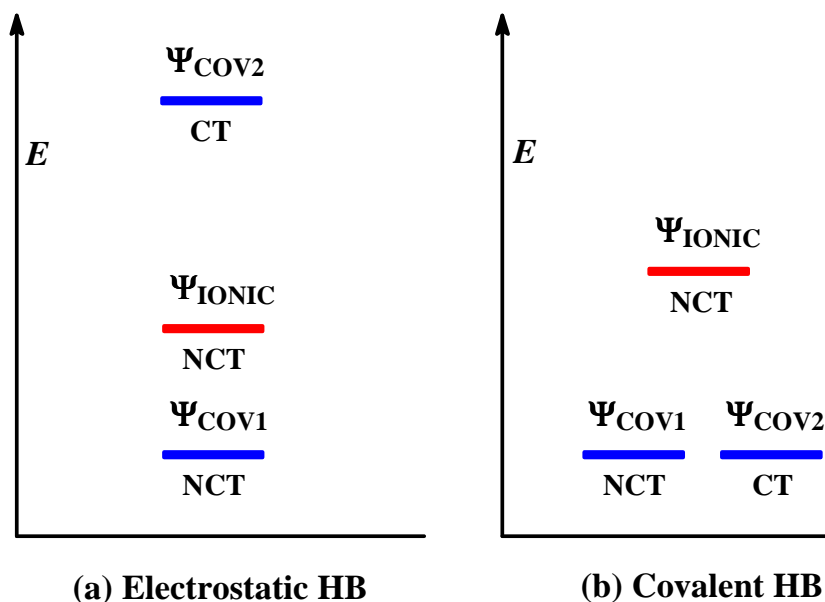
P. Gilli et al., *Acc. Chem. Res.* (2009); E_{HB} values (kcal mol⁻¹) calculated by the exponential equation

Symmetry and Covalency (1)

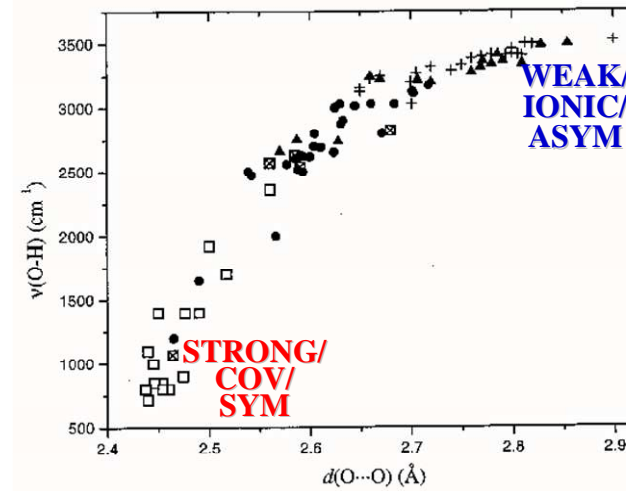
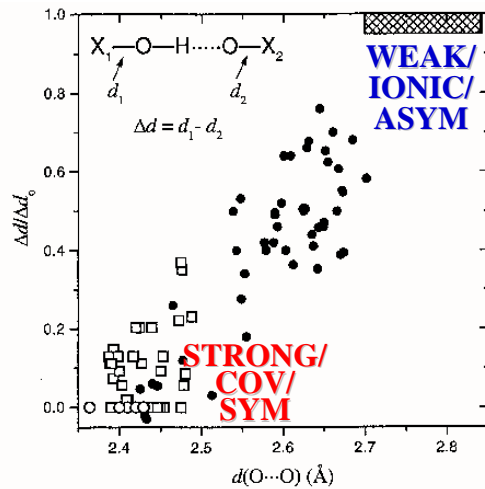
Not surprisingly, **Chemical Leitmotifs** became the main theme of our research, and the first topic systematically studied was, still not surprisingly, their **Covalent or Electrostatic Nature**.

The covalent nature of the strong O–H···O bond was mainly assessed by reinterpreting the experimental results in terms of the Coulson's VB formalism.

We cannot measure covalency but can evaluate molecular symmetry, the Coulson's model being the **algorithm** able to translate one concept into the other because the **total symmetry across the HB** implies **energy equivalence between its two covalent VB forms**, *i.e.* $E(\Psi_{\text{COV1}}) = E(\Psi_{\text{COV2}})$, which is just the situation associated with formation of the covalent HB.



Symmetry and Covalency (2)



In summary,

- H-bonds are neither **electrostatic or covalent** but rather **a mixture of the twos**
- the **degree of covalency** increases with the H-bond strength and reaches a maximum when the bond is **perfectly symmetric**, which maximizes the $\text{O}-\text{H}\cdots\text{O} \leftrightarrow ^-\text{O}\cdots\text{H}-\text{O}^+$ VB mixing
- the symmetry displacement is measured by the VB variable $\Delta E = E(\Psi_{\text{COV}2}) - E(\Psi_{\text{COV}1})$, a quantity which is quite difficult to be evaluated in practice
- the **ΔE term**, however, can be tentatively estimated in terms of extra-thermodynamic quantities, wiz **Proton Affinities (PA)** and related **Acid-Base Dissociation Constants (ΔpK_a)**

Symmetry and Covalency (3)

The ECHBM (Electrostatic-Covalent HB Model)

The PA/pKa Equalization Principle

Empirical analysis of experimental data joined with homeopathic doses of VB theory has led us to formulate the **ECHBM (Electrostatic-Covalent HB Model; Gilli & Gilli, J. Mol. Struct., 2000)** that can be summarized as follows:

♦ *Any given D-H...A system* may form HBs in a *wide range of strengths, lengths, symmetries and proton locations*, the two extremes being represented

by the

weak, long, dissymmetric and proton-out-centred HB of electrostatic nature

and by the

**very strong, very short, symmetric and proton-centred HB
classifiable as a true 3-center-4-electron covalent bond.**

♠ **The driving variable** able to transform strong into weak HBs is **an energy** (the ΔE term of the VB theory) that can be semiempirically evaluated as

– the difference of proton affinities [$\Delta PA = PA(D^-) - PA(A)$]) or

– the difference of acid-base constants [$\Delta pK_a = pK_{AH}(D-H) - pK_{BH^+}(A-H^+)$]

between the donor (D) and acceptor (:A) of the D–H...:A bond.

♠ Finally, the principle for which all strong HBs must be associated with the condition $\Delta PA / \Delta pK_a \cong 0$ is known as **PA/pKa Equalization Principle** (Gilli *et al.*, JACS, 2004, 2005)

The Origin of the Chemical Leitmotifs according to the PA/pK_a Equalization Principle

Chemical Leitmotif # 1:

(+/-)CAHB

Double Charge-Assisted HB

Direct Acid-Base PA/pK_a Matching

R^{-1/2}-D...H⁺...A^{1/2}-R

The role played by the PA/pK_a equalization in HB strengthening is self-evident for the (±)CAHB chemical leitmotif



which collects, by definition, all strong HBs formed by the acid-base pairs with a pK_a matching within, say, from -3 to +3 ΔpK_a units.



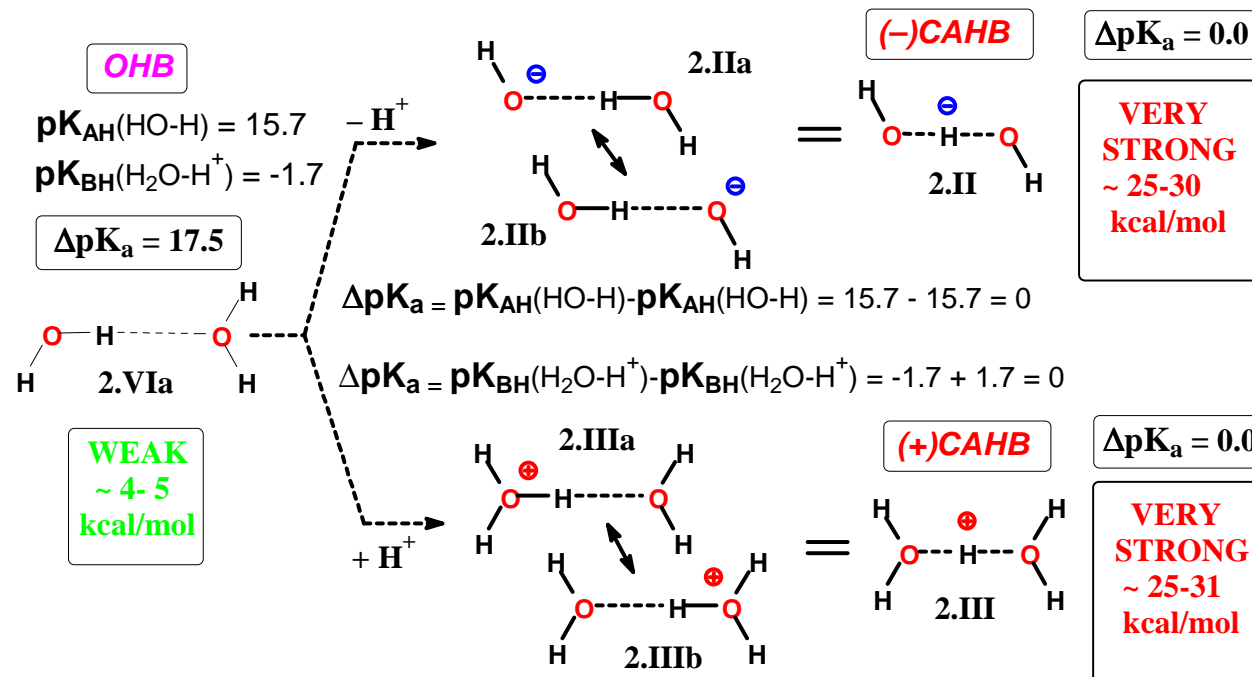
But what about the other leitmotifs? Can we prove that

all chemical leitmotifs are simple artifices
that molecules can use to obliterate the normally
very large ΔpK_a between HB donor and acceptor atoms ?

The Origin of the Chemical Leitmotifs according to the PA/pK_a Equalization Principle

Chemical Leitmotif # 2:
(-)CAHB
Negative Charge-Assisted HB
Acid-Base PA/pK_a Matching
by Proton Loss
[R-D...H...A-R]⁻

Chemical Leitmotif # 3:
(+)CAHB
Positive Charge-Assisted HB
Acid-Base PA/pK_a Matching
by Proton Gain
[R-D...H...A-R]⁺

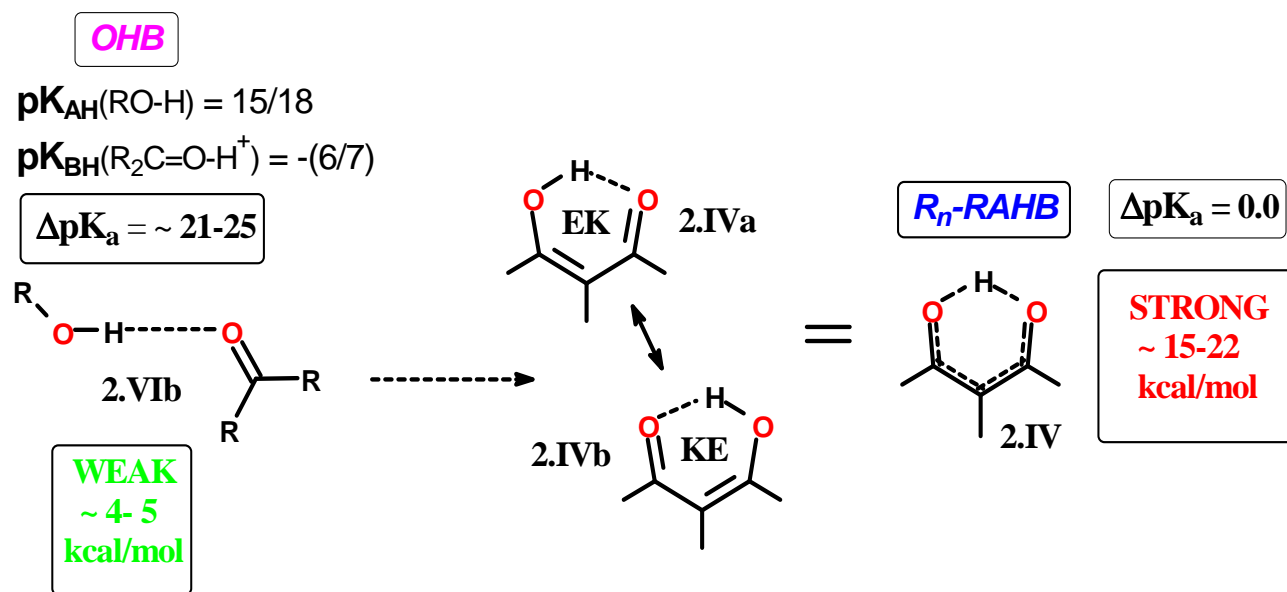
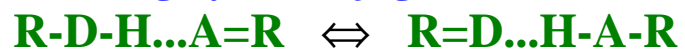


The Origin of the Chemical Leitmotifs according to the PA/pK_a Equalization Principle

Chemical Leitmotif # 4:

RAHB

Resonance-Assisted or π -Bond Cooperative HB
PA/pK_a Matching by π -Conjugated-Bond Polarization



Chemical Leitmotifs and PA/pK_a Equalization Rules

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

(+/-)CAHB is a true *proton transfer from an acid (HB donor) to a base (HB acceptor)*



$$\Delta\text{p}K_a = \text{p}K_{\text{AH}}(\text{R-D-H}) - \text{p}K_{\text{BH}^+}(\text{R}'\text{-A:})$$

(-)CAHB is a *proton sharing between two acids (HB donors)*



$$\Delta\text{p}K_a = \text{p}K_{\text{AH}}(\text{R-D-H}) - \text{p}K_{\text{AH}}(\text{R-D}'\text{-H})$$

(+)CAHB is a *proton sharing between two bases (HB acceptors)*



$$\Delta\text{p}K_a = \text{p}K_{\text{BH}^+}(\text{R-A:}) - \text{p}K_{\text{BH}^+}(\text{R}'\text{-A:}')$$

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

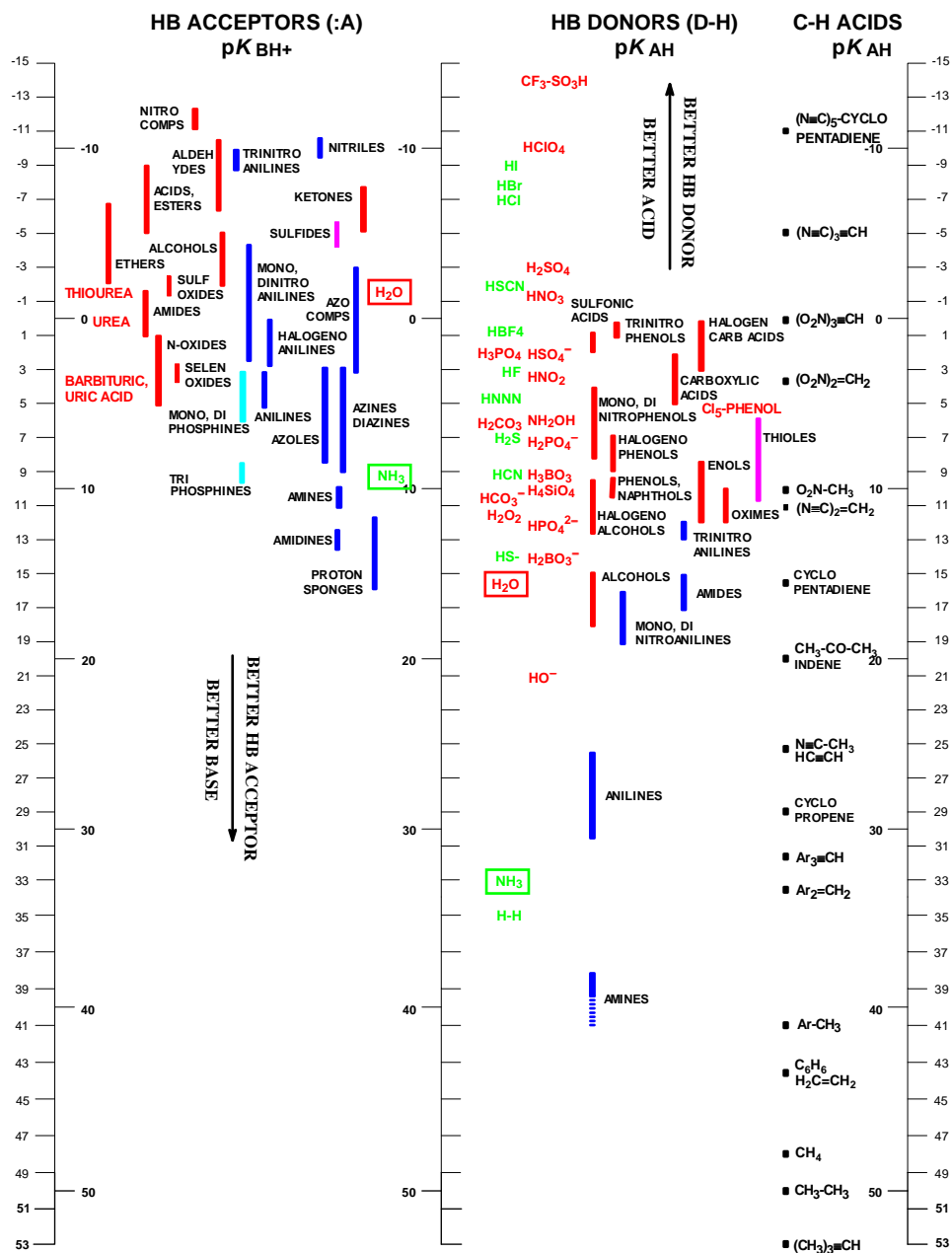
Topics Developed in the Following Lectures

Results obtained from 1989 to 2002

- ♣ Definition of a new type of strong HB: **The Resonance-Assisted HB (RAHB)**
- ◆ Chemical classification of all HBs: **The Chemical Leitmotifs (CAHB, RAHB, PAHB, OHB)**
- ♣ Covalent nature of the strong HB: **The Electrostatic-Covalent HB Model (ECHBM)**
- ◆ Thermodynamic HB driving variable: **The PA/pK_a Equalization Principle**

New Projects from 2002 to 2012

1. Generalization of the **PA/pK_a Equalization Principle** to the most common organic compounds: **The pK_a Slide Rule**
2. Getting over the HB empirical rules and formulation of a comprehensive HB theory: **The Transition-State HB Theory (TSHBT)** and **The Dual H-Bond Model**
3. Redefinition of the **H-bond as a $\sigma^* \leftarrow n$ CT or EDA interaction**. An attempt of unify the forces acting in neutral molecular crystals
4. **H-Bond Patterns in Nature. A Gallery of Functional H-Bonds**



The pKa 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 on the left and
HB Donors on the right.

pK_a values are given for chemical class.

Results expected:

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

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

$\Delta pK_a \ll 0$: $-D \cdots H-A^+$, 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 $0 < pK_a < 14$

The Transition-State HB Theory (TSHBT)

The Dual H-Bond Model

(Gilli et al, J.A.C.S., 2002, 2005; Gilli et al, J. Mol. Struct., 2006; Gilli and Gilli, J. Mol. Struct., 2010)

The basic idea is very simple:

Any D–H...A bond can be considered as a chemical reaction which is bimolecular in both directions

and proceeds *via* transition-state (TS) formation



Changes of nomenclature:

Reaction Pathway \Rightarrow PT-Pathway

Activation Energy, $\Delta^\ddagger E$ \Rightarrow PT-Barrier

Reaction Energy, ΔE_r \Rightarrow $\Delta PA/\Delta pKa$

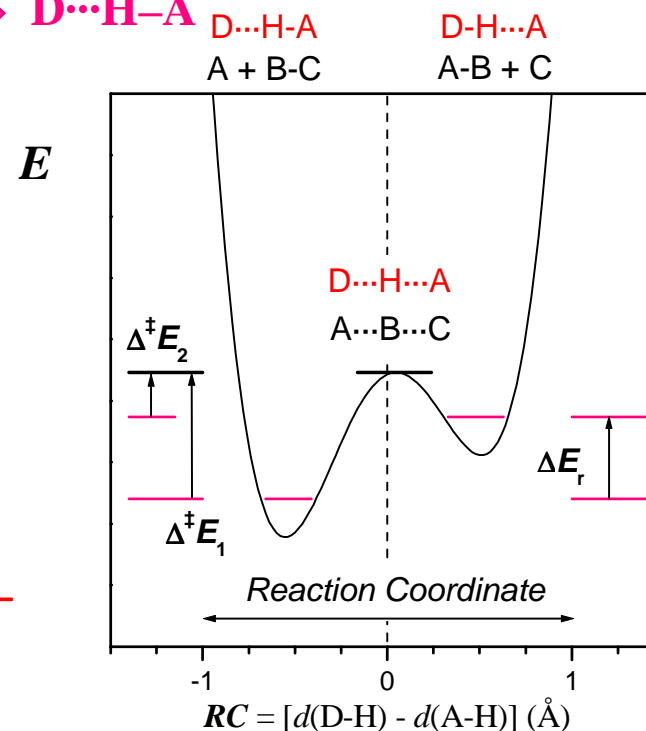
Transition State (TS) \Rightarrow PT-TS

Reaction Coordinate \Rightarrow $RC = [d(D-H) - d(A-H)]$

Experimentals: Variable-Temperature Crystallography

Calculations: DFT-Emulated PT Pathways

Interpretation: Marcus Rate-Equilibrium Theory; Leffler-Hammond Postulate



The H-bond as a $\sigma^* \leftarrow n$ CT or EDA interaction

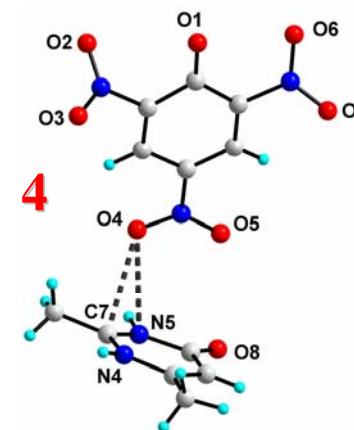
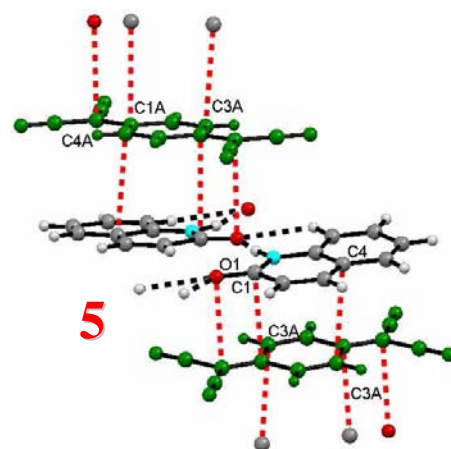
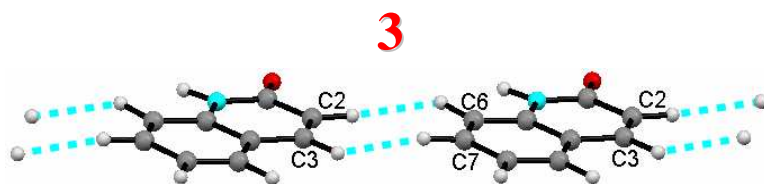
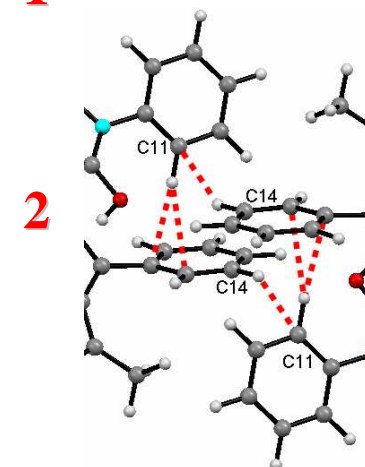
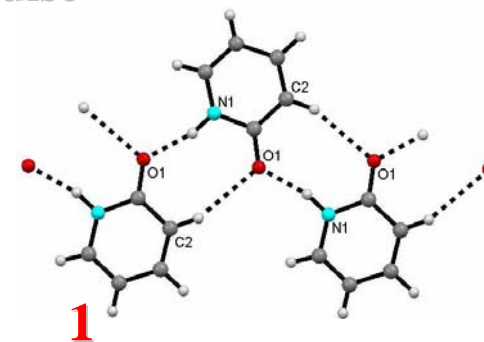
Most EDA Interactions are H-Bonds in Disguise

H-BONDS OF DIFFERENT SPECIES

- 1a. $X-H \leftarrow :Y$ $\sigma^* \leftarrow n$ EDA or $X-H \cdots :Y$ (X, Y = N, O,..) H-Bonds
- 1b. $C-H \leftarrow :Y$ $\sigma^* \leftarrow n$ EDA or weak $C-H \cdots :Y$ (Y = N, O...) H-Bonds
Packing geometry. Planes or ribbons of planar molecules
- 2a. $C-H \leftarrow (C \equiv C)$ $\sigma^* \leftarrow \pi$ EDA or $C-H \cdots : \pi$ (delocalized) H-Bonds
Packing geometry. Herring-bone packing
- 2b. $C-H \leftarrow (C \equiv C)$ $\sigma^* \leftarrow \pi$ EDA or $C-H \cdots : \pi$ (localized) H-Bonds
Packing geometry. Planar or perpendicular packing
3. $C-H \leftarrow H-C$ $\sigma^* \leftarrow \sigma$ EDA or Di-H-Bonds (DHBs)
Packing geometry. Nearly planar packing

NON-H-BONDS

4. $(C,C) \leftarrow :O$ $\pi^* \leftarrow n$ EDA
Packing geometry. Mostly herring-bone packing
5. $C \leftarrow C$ $\pi^* \leftarrow \pi$ EDA
Packing geometry. Parallel stacked packing



A Gallery of Functional H-Bonds

Anticooperative water-without-proton transmission in aquaporin channels

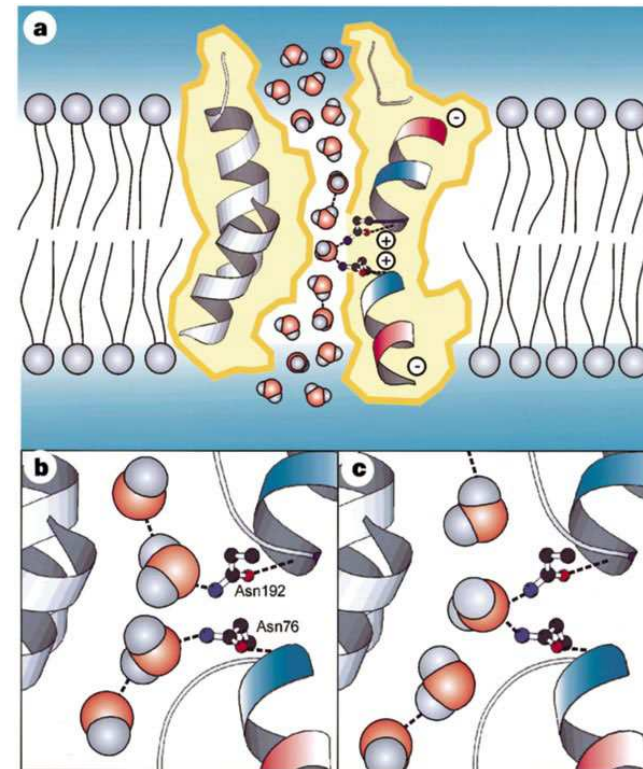
Functional H-Bonds are bonds (usually strong bonds) that are known **to exert a control role** in the working mechanisms of chemical and biological processes (Examples: prototropic tautomerism, acid-base catalysis, enzymatic catalysis, or water transmission in aquaporin biological channels).

Membrane proteins deputed to form **water-specific membrane channels** were firstly discovered in red blood cells and called ***aquaporin-1*** (*AQP1*: Preston, Carrol, Guggino, Agre, **Science 1992**).

The drawing shows a scheme of the structure of ***aquaporin-1*** embedded in the cell membrane (Murata et al., **Nature 2000**, 407:599), cut along the **seven α -helices** at the eight of the **central water channel**.

The partial charges from the **helix dipoles** restrict the **orientation of the waters** passing through the pore **in opposite directions** in the two halves of the chain.

The **inversion of the water-chain direction** is caused by the simultaneous H-bonding of the central water to the **two asparagine residues (Asn76 and Asn192)**, so introducing a single **point of σ -bond anticooperativity** in the chain itself.



Acknowledgments

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and the scientific institutions which made available to us the databases without which this work could not even be started

CCDC
Cambridge Crystallographic Data
Centre
for the use of the
Cambridge Structural Database

NIST
National Institute of Standards and
Technology
for the use of the
NIST Chemistry WebBook

End of Lecture 1