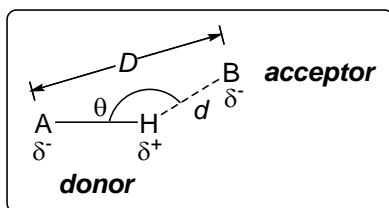
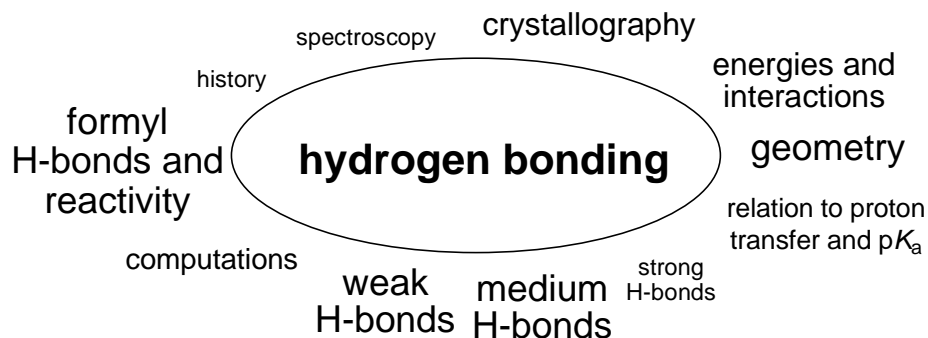


Introduction to Hydrogen Bonding

Eugene E. Kwan

An Evans Group Afternoon Seminar
September 11, 2009

Scope of Seminar

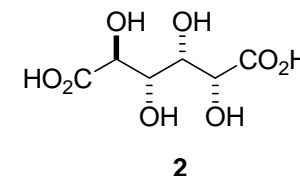
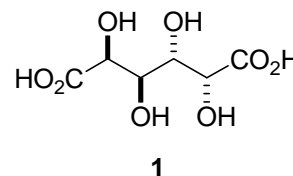


Key Questions

1. What is a hydrogen bond? What are typical experimental observations?
2. What are typical bond dissociation energies? What bonding interactions are involved? **Is hydrogen bonding primarily electrostatic in nature?**
3. How long are hydrogen bonds? **What are the angular requirements on the acceptor and donor?**
4. What can computations tell us?
5. Do formyl hydrogen bonds exist? **What is their role in reactivity?**

Problem of the Day

Galactaric acid (**1**) (melting point, 206 °C) has an unusually low solubility in water for an unsubstituted carbohydrate. By contrast, its epimer, glucaric acid (**2**) (mp, 125 °C) is deliquescent. Please propose an explanation.

Jeffrey *Carb. Res.* **1982**, *108*, 255-211.

Selected References

1. "An Introduction to Hydrogen Bonding." Jeffrey, G.A. New York: Oxford University Press, **1997**. (**general introduction**)
2. "The Hydrogen Bond in the Solid State." Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 48-76. (**geometrical constraints, crystallography**)
3. "'Strong' Hydrogen Bonds in Chemistry and Biology." Perrin, C.L.; Nielson, J.B. *Annu. Rev. Phys. Chem.* **1997**, *48*, 511-544. (**strong H-bonds**)
4. "Hydrogen-Bond Structure in Carbohydrate Crystals." *Acc. Chem. Res.* **1978**, *11*, 264-270. (**medium H-bonds**)
5. "The C-H...O Hydrogen Bond in Crystals: What Is it?" Desiraju, G. **1991**, *24*, 290-296. (**weak H-bonds**)
6. "The Weak Hydrogen Bond in Structural Chemistry and Biology." in *IUCr Monographs on Crystallography, Vol. 9*. Desiraju, G.R.; Steiner, T. New York: Oxford University Press, **1999**. (**weak H-bonds**)
7. "Hydrogen Bonding: A Theoretical Perspective." Scheiner, S. New York: Oxford University Press, **1997**. (**computations**)
8. "Predicting Hydrogen-Bond Strengths from Acid-Base Molecular Properties." Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. *Acc. Chem. Res.* **2009**, *42*, 33-44. (**pKa**)
9. "The Formyl C-H...O Hydrogen Bond as a Critical Factor in Enantioselective Lewis-Acid Catalyzed Reactions of Aldehydes." Corey, E.J.; Lee, T.W. **2001**, *Chem. Commun.* 1321-1329. (**formyl H-bonding and reactivity**)
10. "Unrolling the Hydrogen Bond Properties of C-H...O Interactions." Steiner, T. *Chem. Commun.* **1997**, 727-734. (**weak H-bonds**)

The late 19th and early 20th century contain numerous observations which, in hindsight, were evidence of hydrogen bonding. Both the Germans and British might lay claim to the "discovery of the hydrogen bond."

1902-1914: Werner, Hantzsch, and Pfeiffer use the terms *nebenvalenz* (near valence) and *innere kompleksalzbildung* to describe H-bonding

1912: Moore and Winmill use the term *weak union* to describe amines in aqueous solutions

According to Linus Pauling, the concept of the hydrogen bond should be attributed to Huggins and independently to Latimer and Rodebush in 1920.

Huggins: claims he was the first, and refers to an advanced inorganic chemistry course at the University of California.

Latimer and Rodebush: "the hydrogen nucleus held by two octets constitutes a weak bond"

The first mention of the descriptor "hydrogen bond" appears after 1930.

1931: Pauling writes a general paper on the nature of the chemical bond, describing the hydrogen bifluoride anion as involving a *hydrogen bond*

1935-1936: Four influential papers are published on hydrogen bonding in water and ice (Pauling), metallic hydroxides, minerals, and water (Megaw and Bernal), hydrogen bridges in organic compounds (Huggins), and proton transport in water and ice (Huggins)

1939: Pauling publishes *Nature of the Chemical Bond*, which introduces the concept of hydrogen bonding to the broader chemical community

"Under certain conditions, an atom of hydrogen is attracted by rather strong forces to two atoms instead of only one, so that it may be considered to be acting as a bond between them. This is called a hydrogen bond."

By the late 1930s, infrared spectroscopy and crystallography were used extensively to study hydrogen bonding, a trend which continues today.

Linus Carl Pauling

born: February 28, 1901 (Portland, OR)

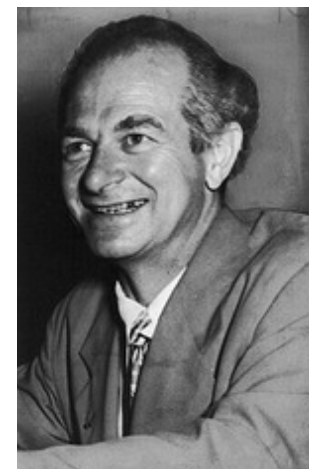
died: August 19, 1994, aged 93 (Big Sur, CA)

religion: atheist as an adult

Nobel Prizes: chemistry (1954) and peace (1962)

education: Caltech, physical chemistry and mathematical physics (1925)

career: Caltech, UCSD, Stanford



key research: tetravalency of carbon, concept of electronegativity, structure of the atomic nucleus, X-ray crystallography, protein structures, molecular clocks in protein evolution

influential textbooks: *The Nature of the Chemical Bond* (1939)
General Chemistry (1947)

doctoral students:

Jerry Donohue: DNA paper in *Nature* by Watson and Crick says "we are much indebted to Dr. Jerry Donohue for constant advice and criticism especially on interatomic distances."

Martin Karplus: NMR, ESR, molecular dynamics simulations

Edgar Wilson: advisor of Dudley Herschbach, molecular spectroscopy, rotational/microwave spectroscopy

William Lipscomb: X-ray structure of boranes and carboranes, structure of proteins and enzymes

A Contrast: Polywater and C-H Hydrogen Bonding

"Polywater." Franks, F. Cambridge: MIT Press, **1981**.

"Science: Doubts about Polywater." *Time Magazine* (Oct. 19, **1970**).

"'Pathological Science' is not Scientific Misconduct (nor is it pathological)."

Bauer, H.H. *Int. J. Phil. Chem.* **2002**, 8, 5-20.

In the 1960s, science began a somewhat dubious and expensive flirtation with a substance known as *polywater*. An obscure Soviet scientist named Nikolai Fedyakin found that water which had been condensed in or repeatedly passed through quartz capillaries had astounding properties: it froze below -40 °C; boiled above 150 °C; and had a density of 1.1 to 1.4 g/cm². Although it was quickly published in Soviet journals and English summaries appeared in *Chemical Abstracts*, the work went unnoticed.

In 1966, Boris Derjaguin, the director of the Laboratory for Surface Physics at the institute for Physical Chemistry in Moscow and an internationally respected scientist, took up the experiments. He travelled to Nottingham for the Discussions of the Faraday Society. This time, "anomalous water" was noticed. A prominent American spectroscopist, Ellis Lippincott, termed the mysterious substance "polywater," for polymerized water. Frank Donahoe, of Wilkes College, proposed that polywater might pose a grave danger to all life on Earth. If polywater turned normal water into polywater, then the resulting chain reaction might turn the Earth into "a reasonable facsimile of Venus." Of course, he conceded, the danger was probably slight, but caution was in order. Could Vonnegut's *Cat's Cradle* be an uncanny harbinger of a ghastly future?

Chaos ensued. The extraordinary findings were reproduced by some, but not all. Doubts were cast and particular attention was given to the possibility of contamination. Intense scrutiny revealed that, under rigorously clean conditions, polywater could not be synthesized. In one dramatic demonstration, Dennis Rousseau, of Bell Labs, played a vigorous game of handball, wrung out his shirt, and collected the perspiration. After evaporation, the substance had infrared spectroscopic and other properties which were suspiciously similar to those of polywater.

So what went wrong? Were scientists negligent or worse, the nefarious perpetrators of fraud? In my estimation, no. As it turns out, people are surrounded by a haze of organic materials and salts. These aerosols are typically exhaled from the lungs or evaporated from the skin, collect on the pores of laboratory glass, and were probably concentrated by the repeated actions of undoubtedly earnest experimenters. Accordingly, polywater could never be synthesized on polyethylene. In fact, the Soviets used quartz precisely because glass was known to release impurities into water, while quartz was not.

In hindsight, it is easy to judge the polywater scientists as careless, if not fraudulent. However, the levels of contamination required to give anomalous results was rather low, and indeed, comparable with the limits of detection at the time. The first American publication on the subject, for example, noted that there was no spectroscopic evidence of contamination. If poor laboratory practices were not responsible, then should polywater have been excluded on purely theoretical grounds instead? Richard Feynman remarked that if polywater was more stable than normal water, then organisms would be able to use normal water as food. They would ingest normal water, excrete polywater, and use the energy difference as food! Unfortunately, such reasoning is invalid, as it confuses thermodynamics with kinetics. For example, one could not reasonably argue that organisms should be ingesting graphite, and excreting diamonds, as there is (to my knowledge) no trivial way to convert one to the other. A priori, it was not clear at all that polywater is impossible.

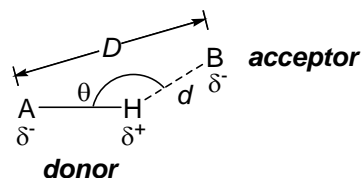
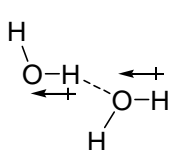
"Pathological Science." Langmuir, I., as edited by Hall, R.N. *Physics Today*. **1989**, 36-48.

In 1953, Langmuir gave a famous talk in which he described what he termed "pathological science: the science of things that aren't so." He gave six characteristics:

- (1) The causative agent is of barely detectable intensity, but the magnitude of the effect is substantially independent of the intensity of the cause.
- (2) The effects are barely detectable or many observations must be averaged together to detect the effect.
- (3) There are claims of great accuracy.
- (4) Fantastic theories contrary to experience are suggested.
- (5) Criticisms are met by *ad hoc* excuses.
- (6) The ratio of supporters to critics rises up to near 1:1 and then falls to 0.

Was polywater pathological science? Is the concept itself a useful way of thinking about science, or is it merely "an epithet applied to potentially revolutionary discoveries that did not pan out?" Without prejudice, there are striking parallels between polywater and the C-H...O bond: both are (allegedly) hydrogen bonding phenomena, both claims were extraordinary and unusual, and both were highly controversial. However, while polywater turned out to be a fictional substance thought to be real, the C-H...O bond turned out to be a real interaction thought to be fictional.

Classification of Hydrogen Bonds



	strong	medium	weak
bond energy (kcal/mol)	14-40	4-14	0-4
interaction type	mostly covalent	mostly electrostatic	electrostatic
bond lengths (A)	A---H = H...B	A---H < H...B	A---H << H...B
A---B	2.2 - 2.5	2.5 - 3.2	3.2 - 4.0
H...B	1.2 - 1.5	1.5 - 2.2	2.2 - 3.2
bond angle (°)	175-180	130-180	90-150
reduction in IR stretch frequency	25%	10-25%	<10%
examples	proton sponges, HF complexes, hydrated protons	carboxylic acids, alcohols, biomolecules	C-H...O/N O/N-H...π

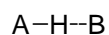
Some Energies

Hydrogen bonds can have a wide range of energies: 0.2-40 kcal/mol.

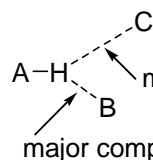
Dimer	Energy (kcal/mol)
[F-H-F] ⁻	39
[H ₂ O-H-OH ₂] ⁺	33
[H ₃ N-H-NH ₃] ⁺	24
[HO-H-OH] ⁻	23
NH ₄ ⁺ ... OH ₂	19
NH ₄ ⁺ ... Bz	17
HOH ... Cl ⁻	13.5
O=C-OH ... O=C-OH	7.4
HOH ... OH ₂	4.7; 5.0
N≡C-H ... OH ₂	3.8
HOH ... Bz	3.2
F ₃ C-H ... OH ₂	3.1
Me-OH ... Bz	2.8
F ₂ HC-H ... OH ₂	2.1; 2.5
NH ₃ ... Bz	2.2
HC≡CH ... OH ₂	2.2
CH ₄ ... Bz	1.4
FH ₂ C-H ... OH ₂	1.3
HC≡CH ... C≡CH ⁻	1.2
HSH ... SH ₂	1.1
H ₂ C=CH ₂ ... OH ₂	1.0
CH ₄ ... OH ₂	0.3; 0.5; 0.6; 0.8
C=CH ₂ ... C=C	0.5
CH ₄ ... F-CH ₃	0.2

Computed gas-phase energies from ref. [2].

Bonding Terminology



normal hydrogen bond
(two-centered)



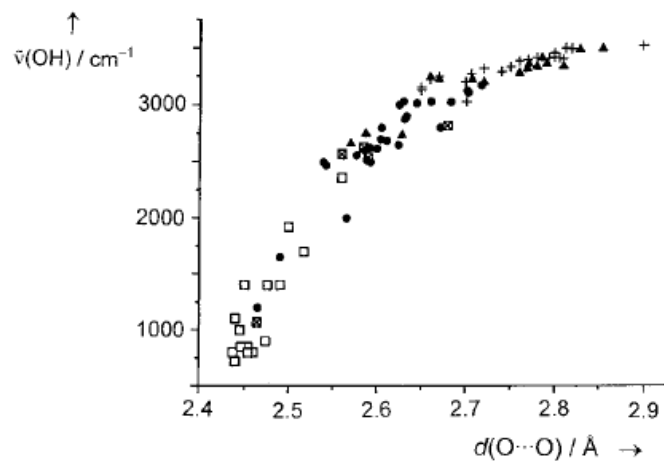
minor component

bifurcated hydrogen bond
(three-centered)

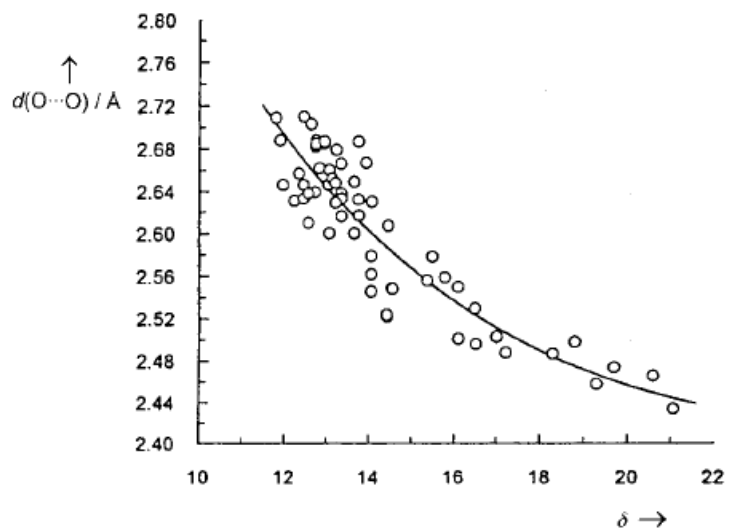
major component

- over 25% of H-bonds in carbohydrates are multifurcated; more in amino acids and proteins

IR Stretches



NMR Chemical Shift



[ref 2]

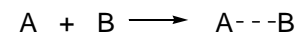
Computed Properties

Consider the IR stretches of the water dimer:

monomer	dimer
1743	1751, 1789
3958	3870, 3970
4109	4073, 4116
	130, 167
	174, 210
	416, 761

What Are The Relevant Interactions?

In general, the total energy change ΔE for the reaction

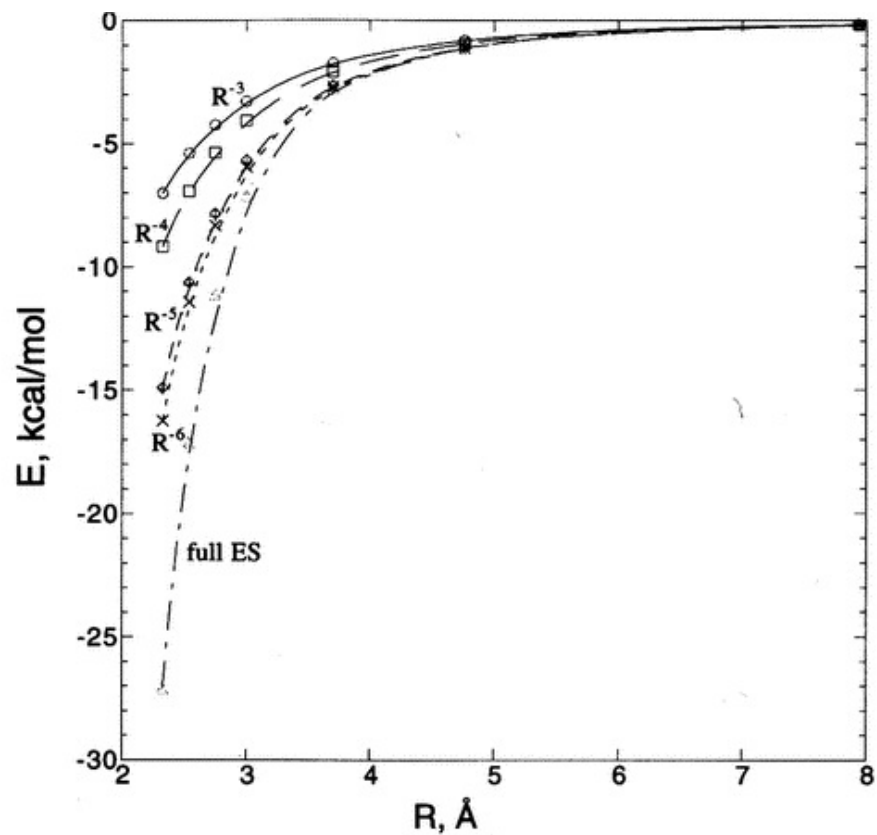


is $E(\text{complex}) - E(A) - E(B)$. As two molecules approach each other, they have a distribution of electron density. The Coulombic force can be written as a "multipole series:"

interaction	distance dependence	
charge-charge	$1/r$	} "electrostatic"
charge-dipole	$1/r^2$	
dipole-dipole	$1/r^3$	
dipole-quadrupole	$1/r^4$	"polarization"
van der Waals, dispersion	$1/r^6$	

In general, **the electrostatic component dies off the slowest.**

interaction energy for the water dimer:



Kitaura-Morokuma Scheme

$$E_{\text{total}} = E_{\text{electrostatic}} + E_{\text{polarization}} + E_{\text{charge transfer}} + E_{\text{mixing}} + E_{\text{exchange}}$$

Results for the Water Dimer

SCF calculations show that the water dimer is *primarily electrostatic*:

increasing basis set size →

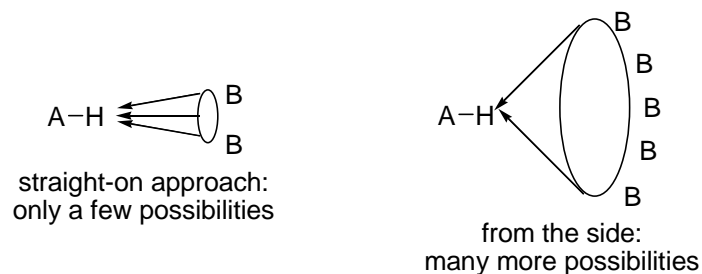
energy/basis set	STO-3G	4-31G	6-31G**
electrostatic	-4.2	-8.9	-7.5
exchange	4.0	4.2	4.3
polarization	-0.1	-0.5	-0.5
charge transfer	-4.8	-2.1	-1.8
mixing	0.1	-0.3	-0.1
total	-5.1	-7.7	-5.6

Values in kcal/mol.

[ref 7]

Must hydrogen bonds be linear? No.

- location of electron density and dipoles not necessarily the same
- multiple hydrogen bonds or other geometric requirements can force compromises
- conic correction factor:

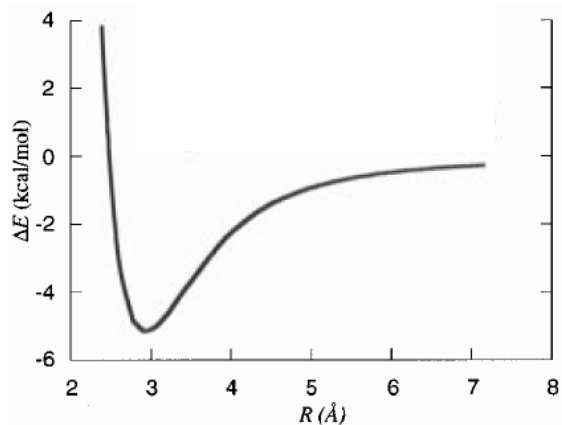


Water Dimer



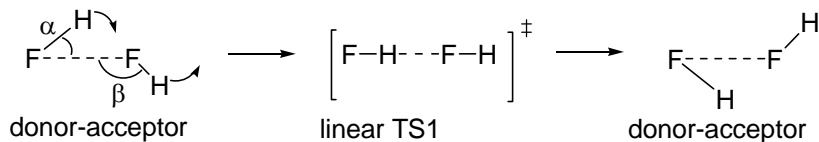
Computed binding energy: ~5 kcal/mol (actual value, 3.5?)
 Experimental Geometry: D , 2.98 Å
 angle of the acceptor to plane, $123^\circ \pm 10^\circ$

Attractive Doesn't Mean Stabilizing



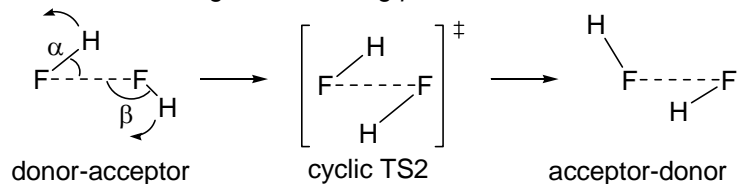
HF Dimer

Path 1: Decreasing α , increasing β

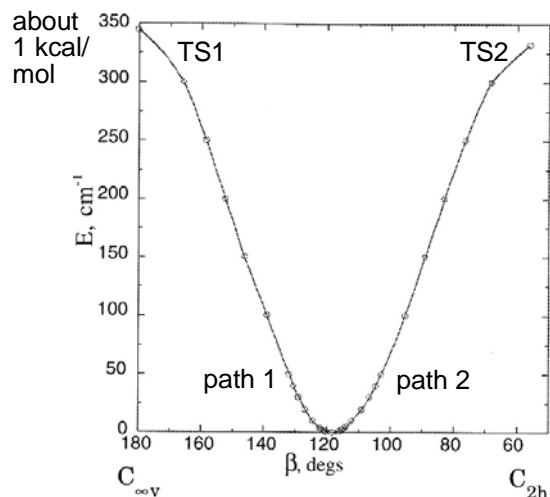


- hydrogens: change sides of F-F axis
- donor/acceptor roles: *not* interchanged

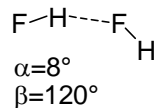
Path 2: Increasing α , decreasing β



- hydrogens: stay on same side of F-F axis
- donor/acceptor roles: interchanged



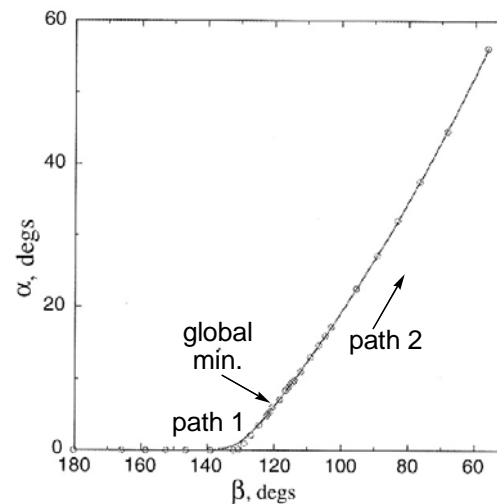
The minimum:



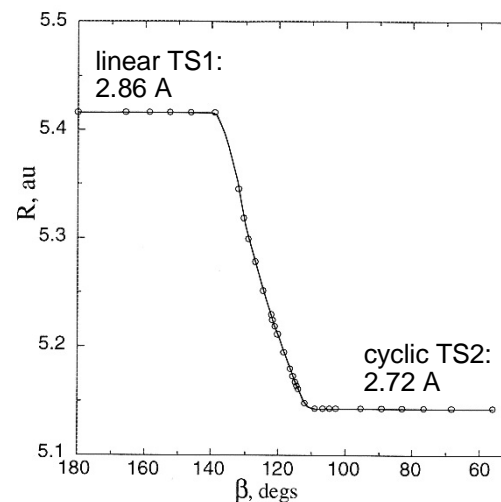
TS1: 345 cm^{-1}
TS2: 332 cm^{-1}

Bunker *J Chem Phys* **1988** 89 3002 and ref 7

α and β along the minimum-energy pathways:



interfluorine distance along the minimum-energy pathways:

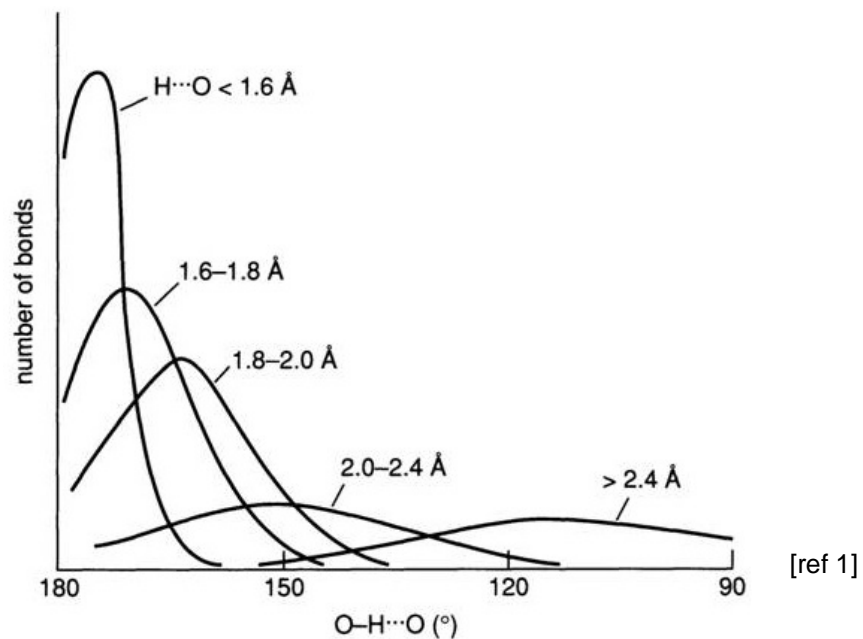


- both pathways are rather sharp, rising to a maximum energy within 20° of the minimum

1 kcal = 350 cm^{-1}
1 au = 0.529 Å

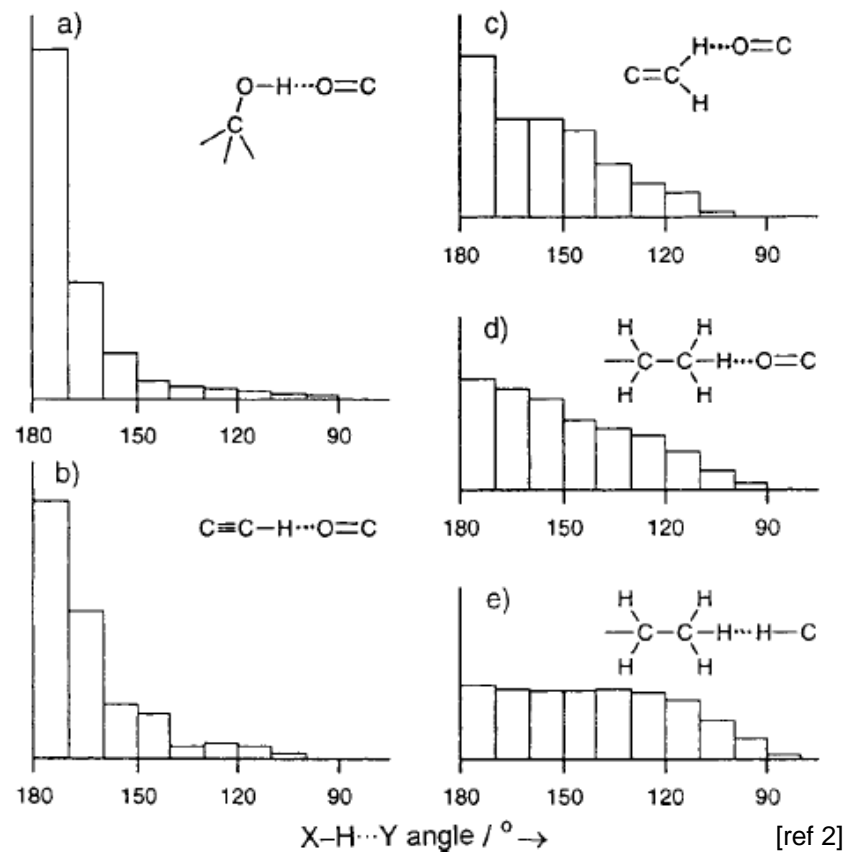
Donor Directionality

The donor directionality decreases as the strength of the bond decreases:



As the polarization of the donor decreases, the angular dependence decreases (see right; conic correction has been applied).

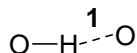
Number of Structures vs. Angle



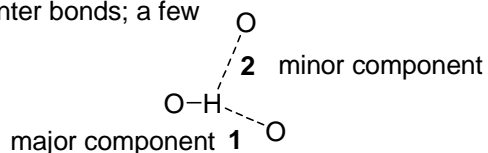
Donor Directionality: O-H...O Contacts

This class of group-pair interactions has been extensively studied by neutron diffraction. Six distinct regions are visible to the right:

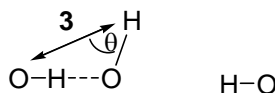
- (1) directional two-center bonds; major components of three center bonds



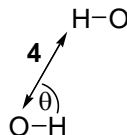
- (2) minor components of three center bonds; a few four center bonds



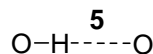
- (3) non-bonding next neighbors



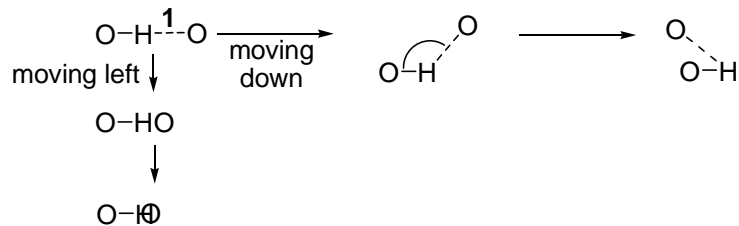
- (4) non-bonding second neighbors



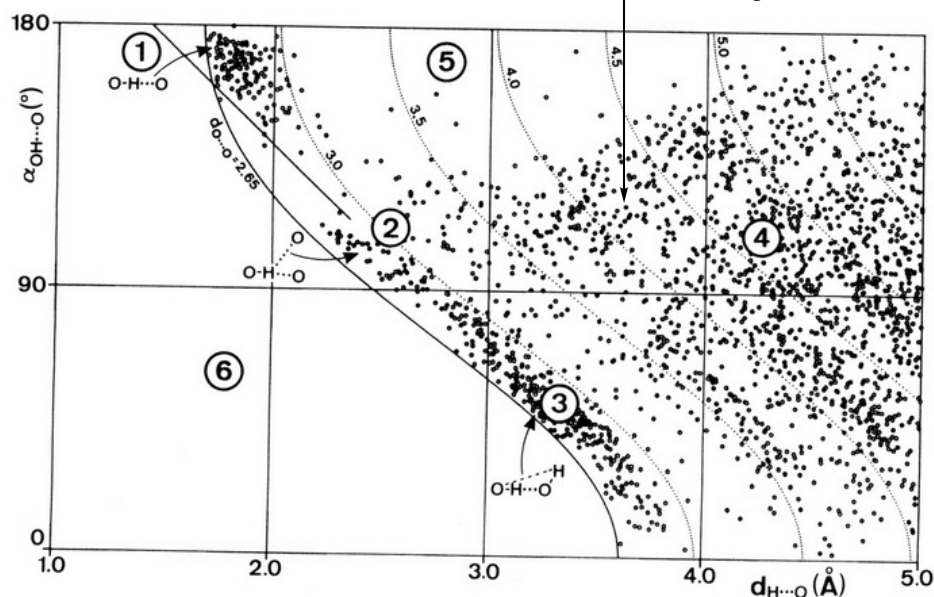
- (5) stretched two-center bonds (poorly-populated)



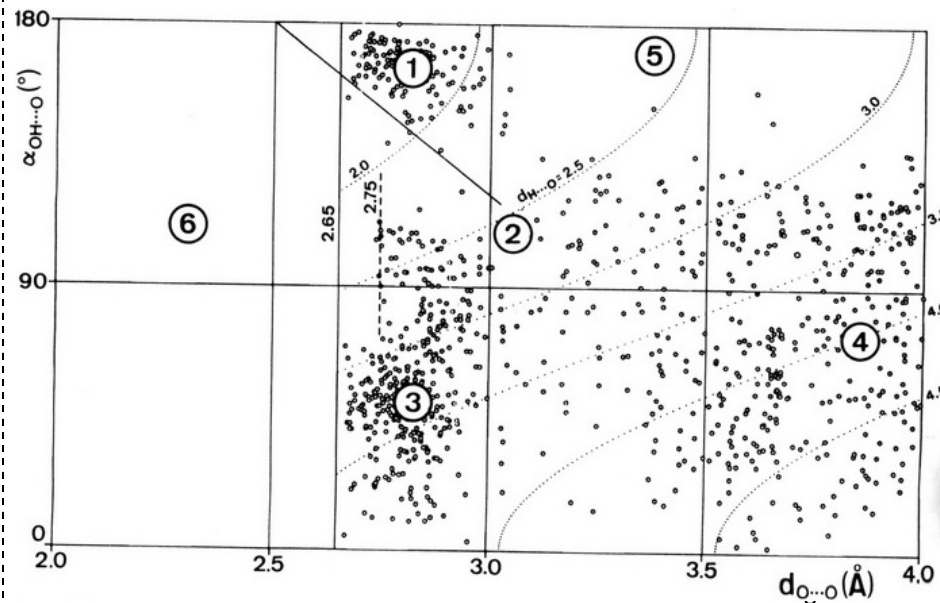
- (6) "the excluded region" (O...O repulsions)



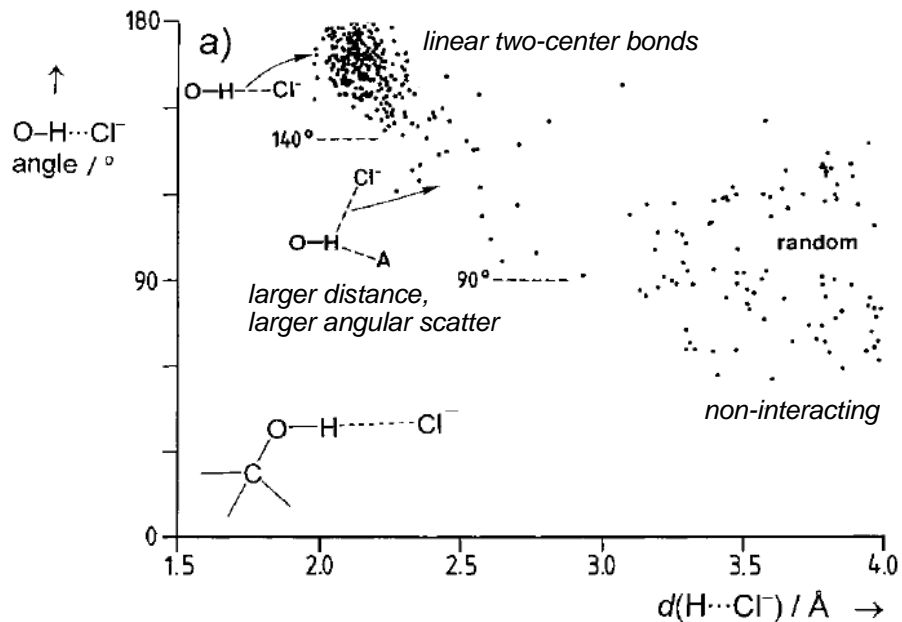
Angle vs. H...O Distance



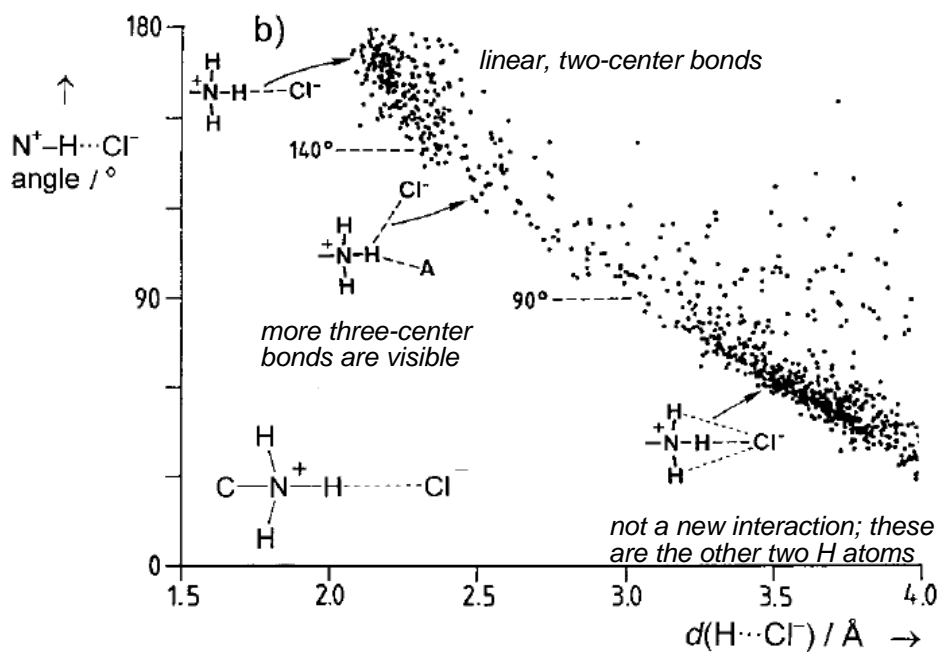
Angle vs. O...O Distance



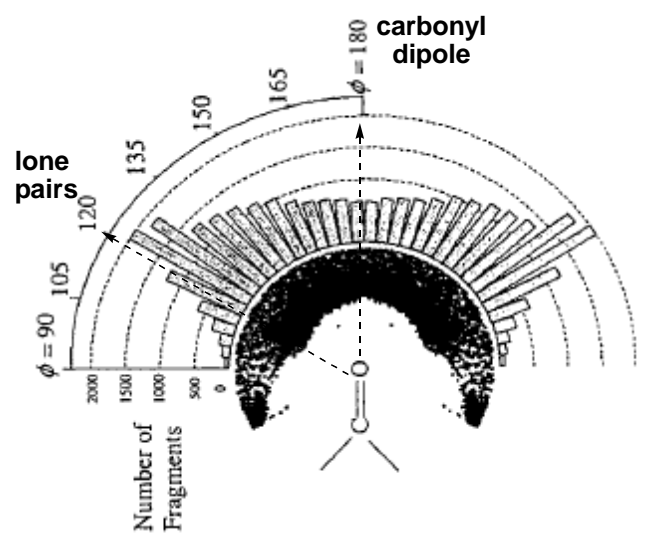
Donor Directionality: Other Systems [ref 2]



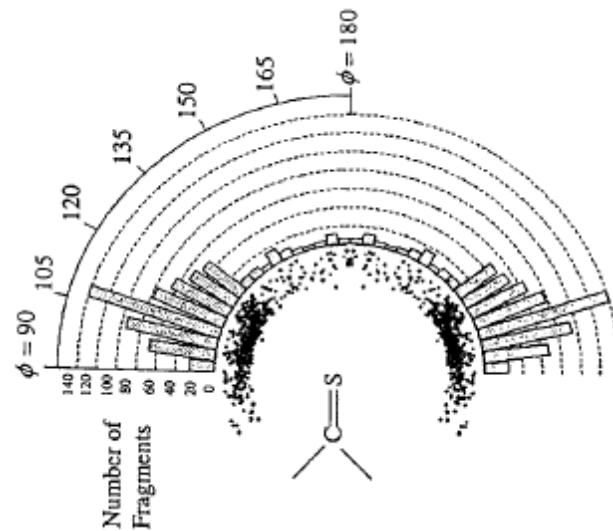
With a more complex donor, such as ammonium, more features are visible:



Acceptor Directionality



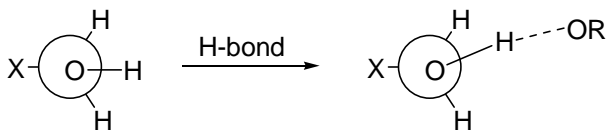
- tradeoff: align with
dipole or lone pairs?



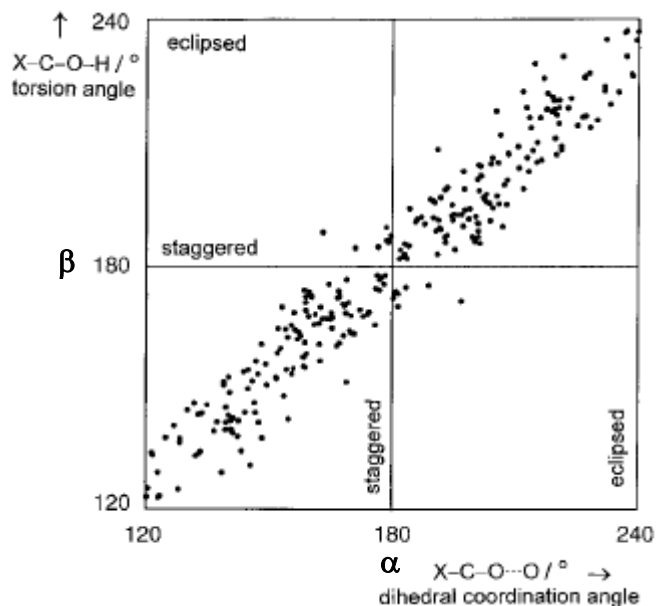
- thiocarbonyl is less
polar
- more emphasis on
lone pairs

Torsional Effects

When hydrogen bonding occurs, it causes other subtle changes. For example:

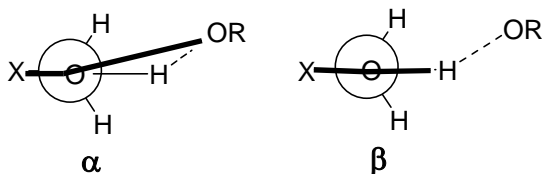


Hydrogen bonding may even occur at the expense of an eclipsing interaction:



Weak hydrogen bonds, such as $C_{sp^3}-H...O$ interactions, are usually not strong enough to cause eclipsing interactions, but rotations of up to 15° have been detected.

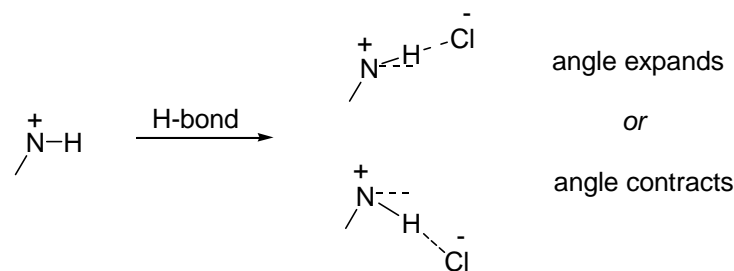
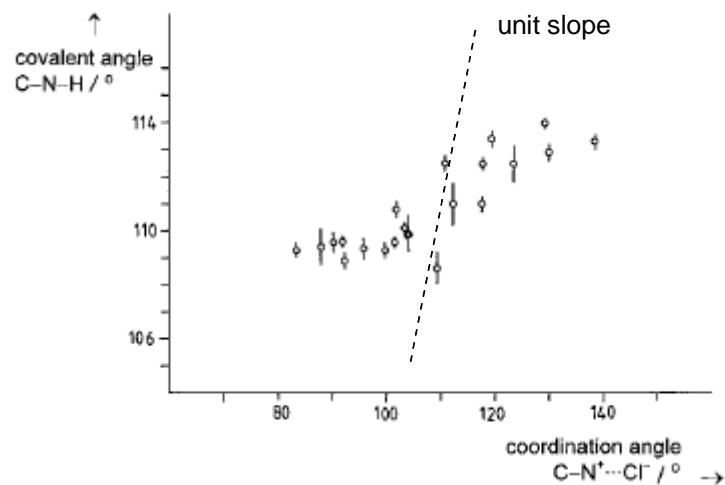
The linear correlation of unit slope shown above means that angles α and β are always the same:



scatter in graph reflects adjustment of H-bonding to torsional or other geometric constraints

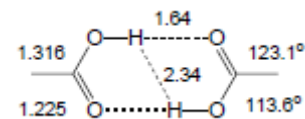
Geometric Relaxation

Hydrogen bonding can have more remote effects. For example, the bond angles next to the donor can change:



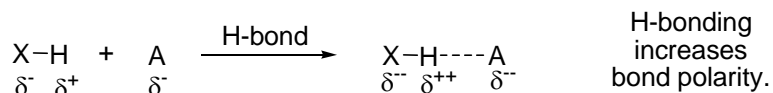
Repulsive Contacts

Hydrogen bonding can be stabilizing overall, but cause locally repulsive contacts:

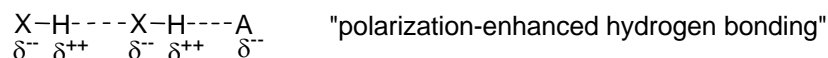


σ-Bond Cooperativity

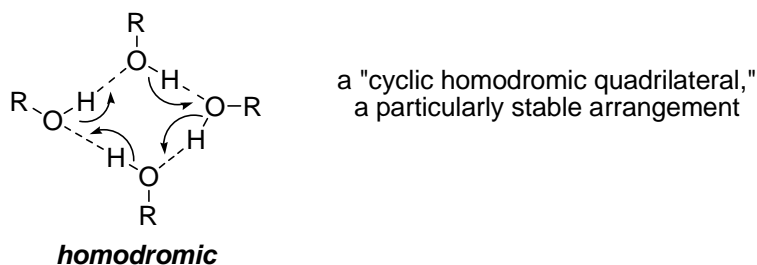
Do two proximal hydrogen bonds influence each other? Yes.



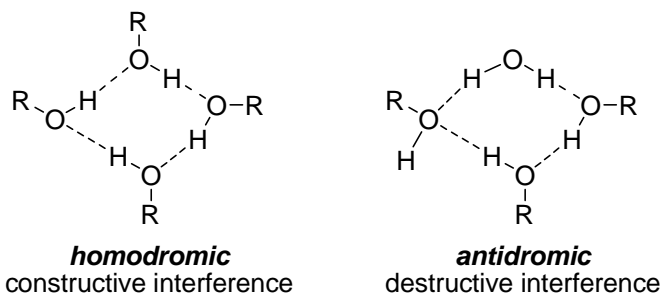
Therefore, a chain of two hydrogen bonds increases the strength of both bonds:



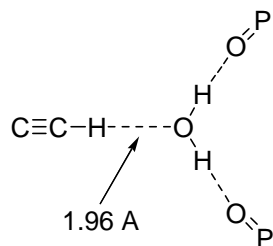
One can also use resonance arrows to analyze such patterns:



Destructively interfering patterns are also possible:



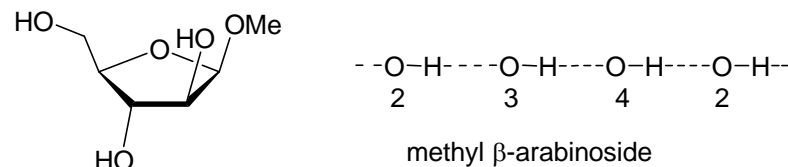
For example, this is an unusually short C-H...O interaction:



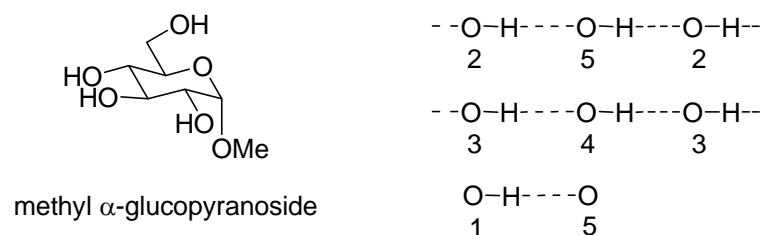
Carbohydrates

Networks of hydrogen bonding in carbohydrate crystals have been mapped extensively with "graph set theory." Arrays of head-to-tail chains, like pencils in a box, are common. There are four basic patterns:

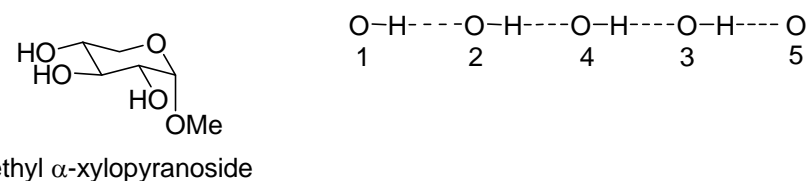
(1) Infinite chains, ring and glycosidic oxygens excluded



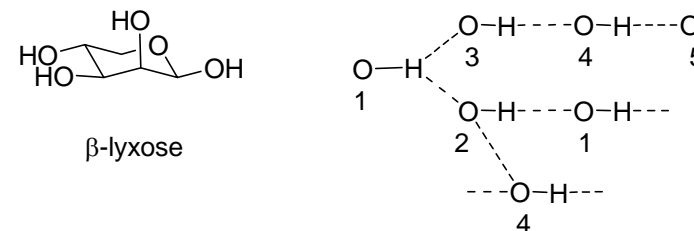
(2) Infinite chains with finite chains which terminate in O_{ring} or O_{glyco}



(3) Finite chains, terminating with O_{ring} or O_{glyco}



(4) Infinite chains, with O_{ring} or O_{glyco} as minor components of 3-center bonds

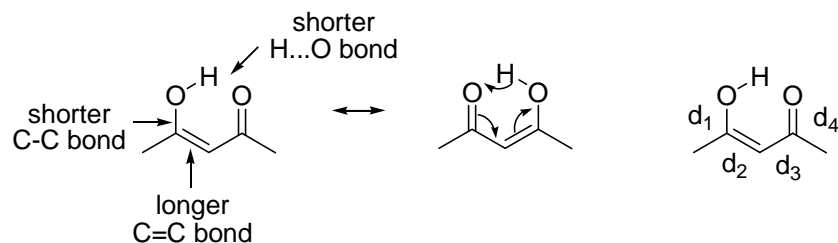


- idea was originally introduced by Jeffrey

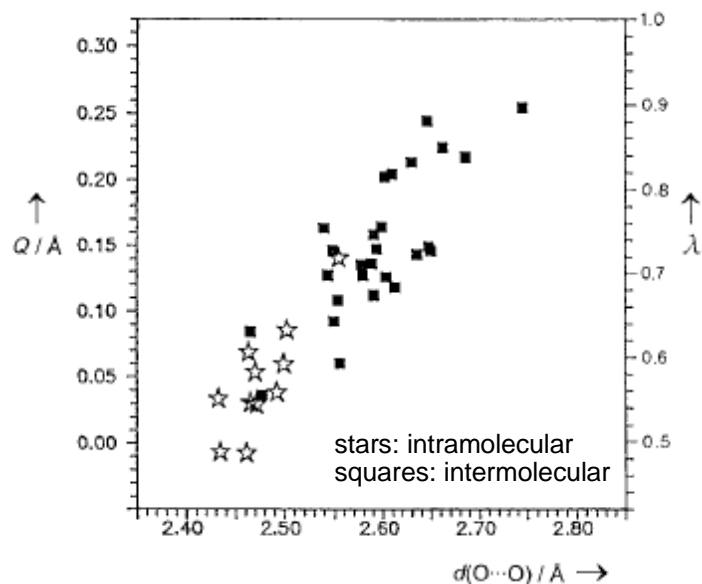
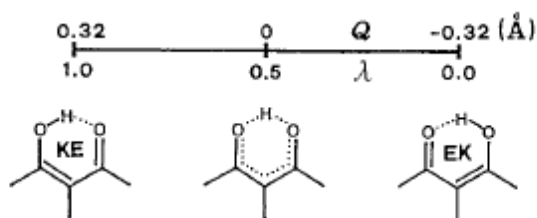
[ref 1]

π -Bond Cooperativity

Gilli and coworkers have introduced an analogous concept for π -cooperativity:

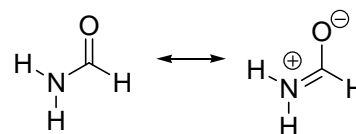
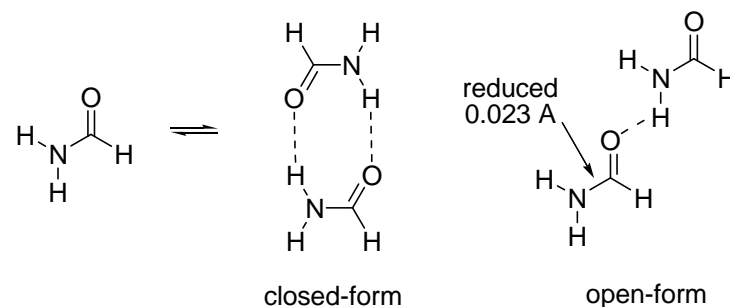


One can define a delocalization parameter $Q = d_1 - d_4 + d_3 - d_2$ which correlates with the O...O contact distance for a range of 1,3-diketones:



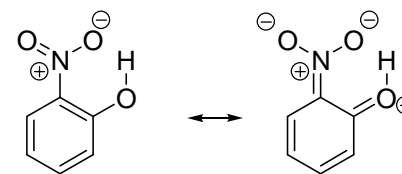
In the limit of full delocalization, all the bond lengths are equal and Q goes to 0.

The cooperative effect in amides is particularly important in proteins. As a model, consider the open- and closed-form dimers of formamide:

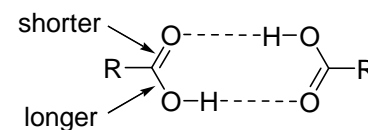


One can think of hydrogen bonding as increasing the importance of the charge-separated resonance form.

Similarly, π -cooperativity is responsible for the unusually strong hydrogen bond in *o*-nitrophenol:

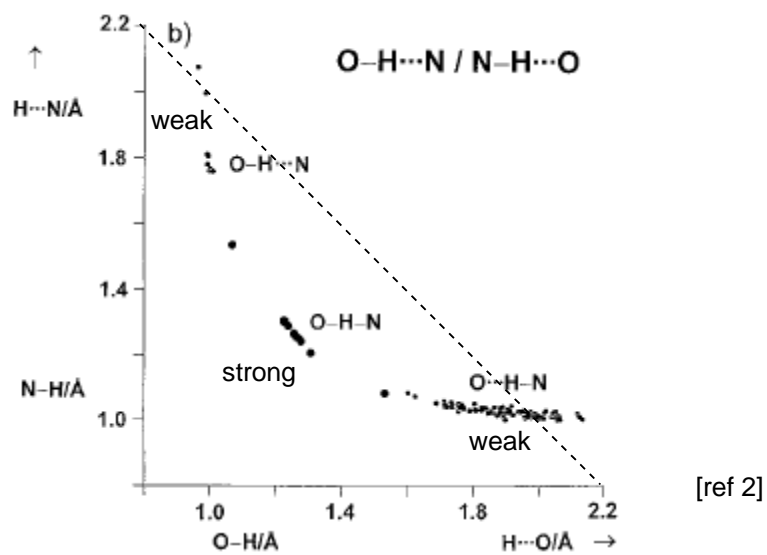


Carboxylic acids are another example:



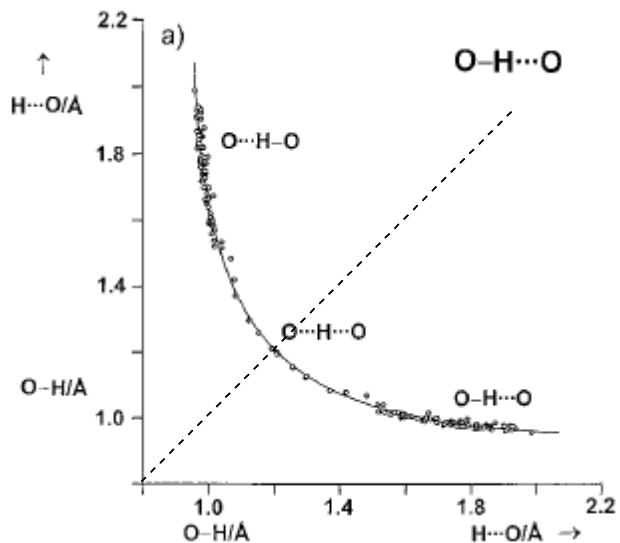
Where is the Hydrogen Atom?

- highly symmetric bonds are strong

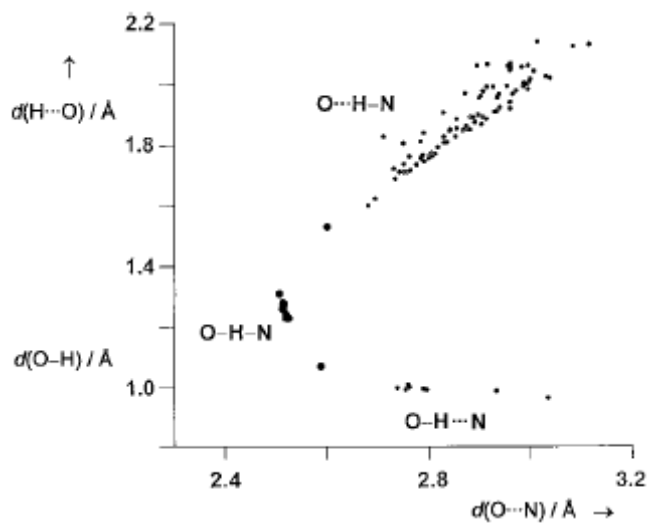


[ref 2]

A similar pattern is observed in O-H...O contacts:



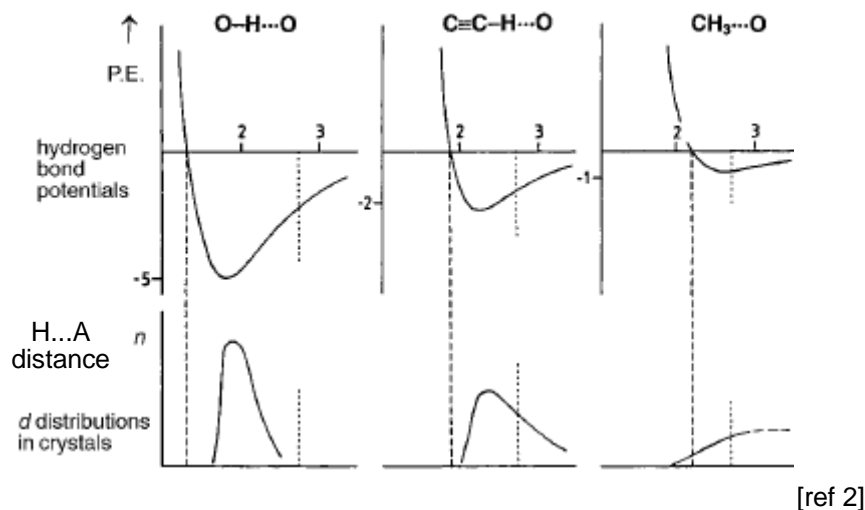
Here is the same information, presented in a different format:



A Word of Caution

Are the shortest hydrogen bonds the strongest? No.

- a hydrogen bond of the same length between two charged objects is stronger than one between two neutral ones
- not necessarily valid even for comparisons between contacts of the same type
- strongest hydrogen bonds are the ones closest to their optimal geometry



These distributions look Boltzmann-type, but the analogy is tenuous:

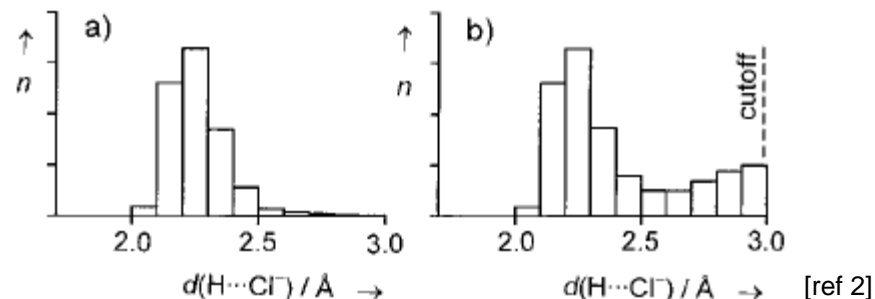
"An ensemble of structural parameters obtained from chemically different compounds in different crystal structures does not even remotely resemble a closed system at thermal equilibrium and does not therefore conform to the conditions necessary for the application of the Boltzmann distribution."

Burgi and Dunitz *Acta Cryst Sect B* **1988**, 44, 445

- hydrogen bonding can actually *shorten* the X-H bond (more later)

Statistical Analysis of H...A Bond Lengths

Solid state bond lengths can be displayed in a histogram format if a cutoff angle is defined:



H...A bond lengths for $-\text{NH}_3^+ \dots \text{Cl}^-$ contacts

(a) cutoff of $135^\circ \dots 180^\circ$

(b) cutoff of $90^\circ \dots 180^\circ$

Functional Group Donor and Acceptor Ability

Here are some rough trends:

donor strength

$\text{O-H} > \text{N-H} > \text{S-H} > \text{C-H}$

- of course, there are exceptions: alkyne (strong C-H) is better than N-NH₂
- donor strength is increased by electron withdrawing groups:

$\text{H}_3\text{O}^+ > \text{O}=\text{C}-\text{OH} > \text{Ph}-\text{OH} > \text{C}_{\text{sp}^3}-\text{OH} > \text{H}_2\text{O} > \text{OH}^-$

acceptor strength

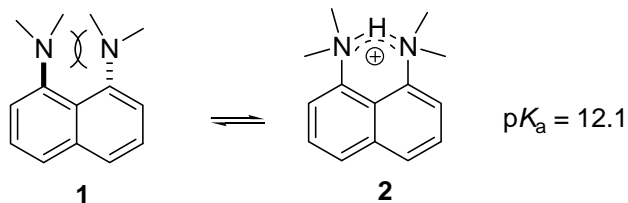
- conversely, electron donating groups increase acceptor strength:

$^-\text{OH} > ^-\text{COO}^- > \text{H}_2\text{O} > \text{C}_{\text{sp}^3}-\text{OH} > \text{Ph}-\text{OH} > \text{C}-\text{NO}_2 > \text{M}-\text{CO}$
 $\text{F}^- > \text{M}-\text{F} > \text{BF}_4^- > \text{C}-\text{F}$

Thus, a natural question is: **what is the relationship between hydrogen bonding and acidity?**

Proton Sponges

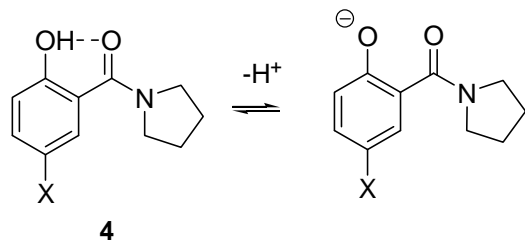
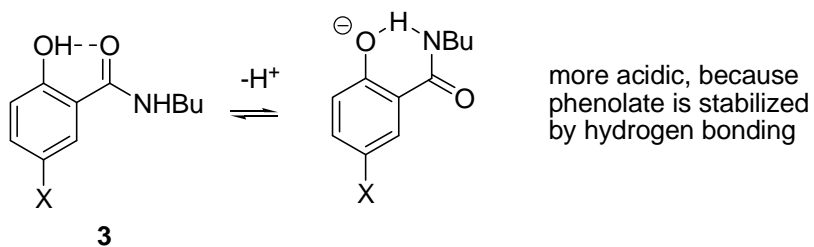
- exceptional basicity due to relief of steric strain upon protonation
- in **1**, the naphthalene ring is distorted such that the two nitrogen atoms are on 0.4 Å either side of a mean plane giving a repulsive N-N distance of 2.79 Å.



- strong H-bond in **2**
- with BF_4^- counterion,
 N...N distance: 2.56 Å
 H...N distance: 1.31 Å
 θ : 159°

[ref 1]

Phenols



Mock JCS PT2 1995 2069

	$pK_a(3)$	$pK_a(4)$	
X = NO_2	5.10	5.93	- values in water
X = Br	7.26	8.45	
X = H	8.03	9.28	
X = OMe	8.31	9.75	
X = Me	8.48	9.73	

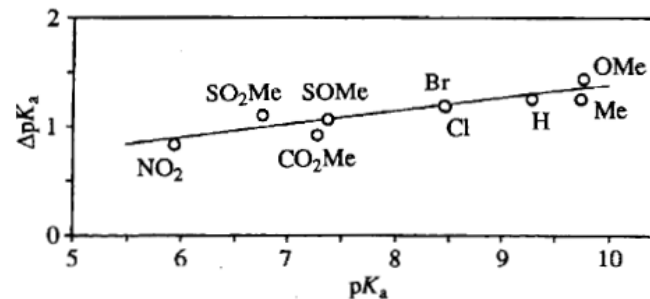


Fig. 1 Plot of ΔpK_a (pK_a of **2** minus pK_a of **1**) versus pK_a of **2**. Least-squares regression line has a slope of 0.12 (± 0.02), intercept 0.14 (± 0.18).

H-Bond Strength and Acidity

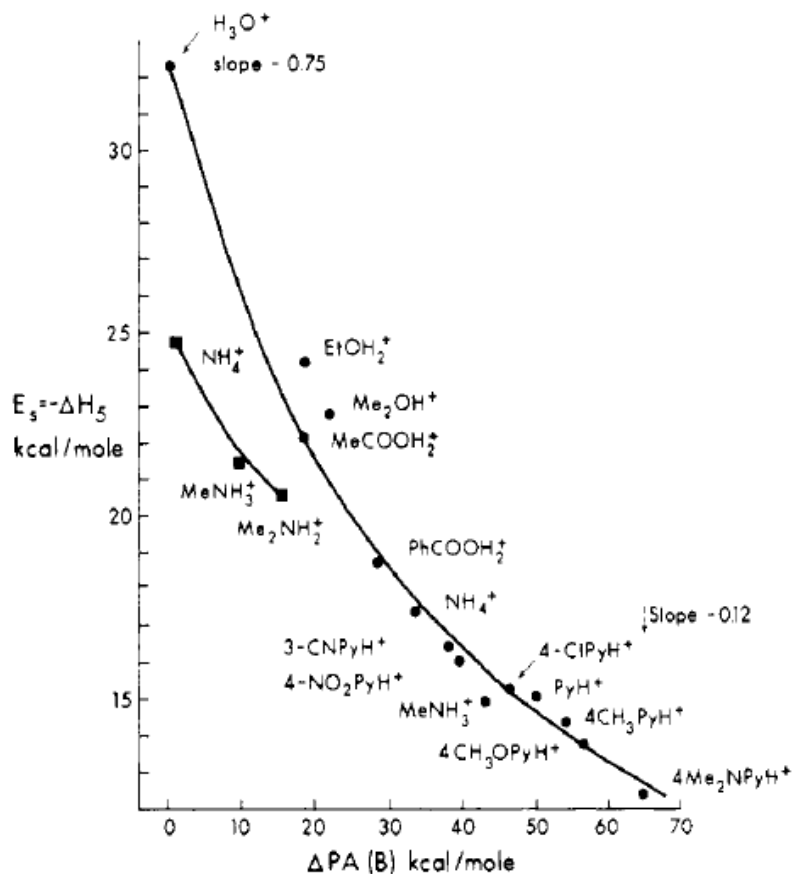


Figure 3. Relationship between the hydrogen bond energies in $BH^+ \cdots B_0$ and the proton affinity difference $PA(B) - PA(B_0)$: ●, $B_0 = H_2O$; ■, $B_0 = NH_3$. ΔH_s is equal to enthalpy change for gas-phase reaction: $BH^+ \cdots B_0 = BH^+ + B_0$. Data for pyridine hydrates from this work; other data from ref 2. $PA(H_2O) = 168$ kcal/mol, $PA(NH_3) = 202$ kcal/mol.² Results show that the hydrogen bond in $BH^+ \cdots B_0$ is maximum for $\Delta PA(B) = 0$ and decreases as the acidity of BH^+ is decreased.

Estimation of Hydrogen Bond Strengths

- Gilli and coworkers have correlated H-bond strengths and acidity
- proxies: length for H-bond strength, pK_a (water) for acidity
- caveats:
 - extrapolation from crystal structures to solution
 - why use water, a high dielectric solvent?
- nonetheless:
 - optimal H-bonding strength occurs when pK_a 's are matched***

[ref 8]

Acceptors HB	Nitro Cmps	Carbonyl Cmps	Ethers	Alcohols/ Phenols	Amides	Nitriles	Anilines	Azines	Diamines (2 nd pK _a)	Azoles	Amines					
HB Donors	<chem>R-N(=O)=O</chem> -11 + -12	<chem>C=O</chem> -5 + -10	<chem>R-O-R</chem> -2 + -7	<chem>R-O-H</chem> -2 + -5	<chem>N-C=O</chem> 1 + -2	<chem>R-C#N</chem> -10 + -11	<chem>Ar-N</chem> 5 + -4	<chem>N=C</chem> 7 + 1	<chem>N</chem> 6 + 2	<chem>N</chem> 8 + 3	<chem>R-N</chem> 11 + 8					
Amines <chem>R-N-H</chem> 40 ÷ 38	5 2.94 3.19 ₉	42 2.77 3.06 ₃	11 2.96 3.23 ₅	83 2.79 3.10 ₂	13 2.98 3.17 ₃	<p style="text-align: center;">$d'_{N...O} = d_{N-H} + d_{H-O}$ (Å)</p> <p style="text-align: center;">Estimated E_{HB} (kcal/mol)</p> <p style="text-align: center;"> N-H...O O-H...N N[⊖]-H...O[⊖] </p>										
Anilines <chem>Ar-N-H</chem> 31 ÷ 25	104 2.91 3.21 ₁	109 2.87 3.07 ₁	27 2.91 3.13 ₂	21 3.00 3.12 ₂	21 2.80 3.07 ₃											
Pyrroles/ Indoles <chem>N-H</chem> 17 ÷ 15	15 2.94 3.11 ₃	314 2.78 2.98 ₁	35 2.79 3.07 ₃	92 2.76 2.97 ₁	95 2.81 2.96 ₁											
Amides <chem>-C(O)-N-H</chem> 17 ÷ 15	4 3.04 3.14 ₁	246 2.82 3.03 ₁	33 2.90 3.12 ₅	211 2.80 3.03 ₁	2487 2.73 2.97 ₁											
Alcohols <chem>R-O-H</chem> 18 ÷ 9	52 2.77 2.94 ₁	8 2.81 2.90 ₂	319 2.67 2.87 ₁	15 2.82 2.87 ₁	267 2.67 2.87 ₁							529 2.68 2.91 ₁				
Oximes <chem>=N-O-H</chem> 12 ÷ 10	29 ÷ 19	22 ÷ 4	17 ÷ 2	16 ÷ 2	15 ÷ 1							10 ÷ -2				
Phenols/ Naphthols <chem>Ar-O-H</chem> 12 ÷ 4	8 2.81 2.90 ₂	42 2.66 2.75 ₁	17 2.65 2.76 ₂	12 2.68 2.77 ₂	23 ÷ 20							16 ÷ 5	11 ÷ 3	10 ÷ 4	9 ÷ 2	4 ÷ -1
Carboxylic Acids <chem>R-C(O)O-H</chem> 5 ÷ 0	65 2.75 2.92 ₂	37 2.68 2.81 ₁	279 2.52 2.79 ₁	51 2.52 2.70 ₁	25 2.57 2.69 ₁							34 2.58 2.74 ₁	100 2.64 2.79 ₁			
Trinitro Phenols <chem>Ar-O-H</chem> 1 ÷ 0	23 ÷ 14	16 ÷ -1	11 ÷ -3	10 ÷ -2	9 ÷ -4							4 ÷ -7				
Sulfonic Acids <chem>R-SO₂O-H</chem> 3 ÷ 0	6 2.76 2.79 ₁	2 2.66 2.71 ₁	95 2.65 2.88 ₂	399 2.52 2.67 ₁	193 2.53 2.73 ₁							6 2.62 2.65 ₁	38 2.53 2.77 ₁	73 2.58 2.72 ₁	217 2.54 2.79 ₁	1441 2.59 2.86 ₄
	16 ÷ 10	9 ÷ -5	4 ÷ -7	3 ÷ -6	2 ÷ -8	3 ÷ -11										
	8 2.70 2.77 ₃	27 2.62 2.74 ₂	7 2.58 2.71 ₃	32 2.63 2.80 ₂	99 2.69 2.88 ₁											
	12 ÷ 10	5 ÷ -5	0 ÷ -7	-1 ÷ -6	-2 ÷ -8	-7 ÷ -11										
	16 2.71 2.89 ₅	18 2.67 2.86 ₄	9 2.76 2.93 ₇	167 2.70 2.97 ₁												
	14 ÷ 10	7 ÷ -5	2 ÷ -7	1 ÷ -6	0 ÷ -8	-5 ÷ -11										

Donor Class	Acceptor Class		Sample Size
	pK_{BH} range		
	n	n	
	d_{N...O} (min)	d_{N...O} (min)	
pK_{AH} range	d_{N...O} (mean)	d_{N...O} (mean)	Minimum d'_{N...O}
	(Neutral)	(Ionized)	
ΔpK_s range			Average d'_{N...O} with subscripted esd

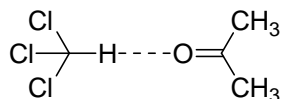
C-H...O Hydrogen Bonding

"The Weak Hydrogen Bond in Structural Chemistry and Biology." in *IUCr Monographs on Crystallography, Vol. 9*. Desiraju, G.R.; Steiner, T. New York: Oxford University Press, **1999**.

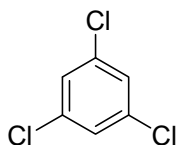
1935: the behavior of HCN is analogous to hydrogen-bonded substances such as HF, ethylene glycol, and aliphatic carboxylic acids (Kumler)

arrangements of $\text{---H-C}\equiv\text{N-H-C}\equiv\text{N-}$ are specifically suggested, which was later found in the corresponding crystal structure (1951)

1937: first formal introduction of "weak hydrogen bond" in literature (Glasstone) mixtures of chloroform/acetone were investigated and found to have anomalous colligative properties



1939: IR studies show smaller C-H stretching frequencies; large shifts of up to 100 cm^{-1} are noted for alkynes and other C-H bonds next to electronegative groups



C-H stretch reduced by 35 cm^{-1} in the presence of pyridine

In general, C-H hydrogen bonds are weaker than classical hydrogen bonds; therefore, crystallography became more important than spectroscopy.

1953: crystal structure of dimethyl oxalate shows C-H...O contacts and may demonstrate why it has a mp of $54\text{ }^\circ\text{C}$ ($100\text{ }^\circ\text{C}$ greater than for similar carboxylic acid esters), the first evidence for a $\text{CH}_3\cdots\text{O}$ H-bond (Jeffrey)

1962: Sutor systematically reviews purine and pyrimidine crystal structures and finds many structures have contacts below the van der Waals distance of 2.6 \AA for an H...O contact

theophylline, 2.25 \AA
 caffeine, 2.12 \AA
 uracil, 2.20 and 2.27 \AA

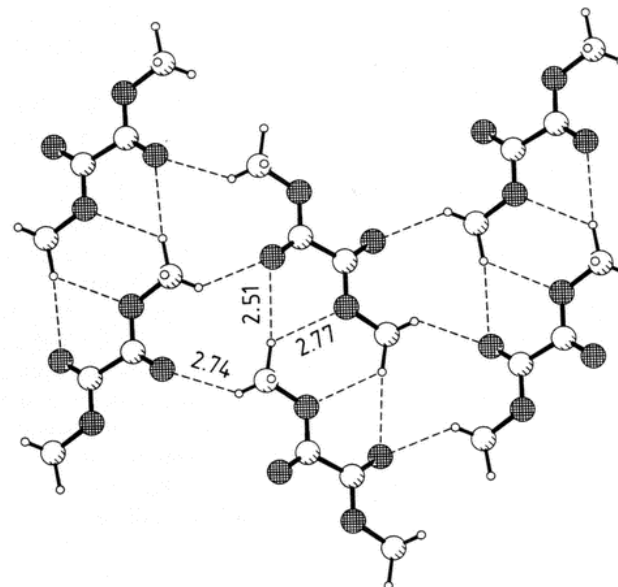
1968: Donahue questions the use of 2.6 \AA ; using previously suggested values of $2.20\text{--}2.40\text{ \AA}$, he finds no evidence of hydrogen bonding; the stricter criteria were suggested merely to alert crystallographers to the possibility of unusually short H...O separations with carbon donors

Between 1968-1982, a few papers are published, but the field became very wary of C-H...O hydrogen bonding.

1982: Taylor and Kennard publish a sophisticated review of the Cambridge Structural Database and find:

- (1) statistically, short C-H contacts are much more likely when the acceptors is oxygen, rather than carbon or hydrogen
- (2) these C-H...O contact distances are frequently less than the van der Waals distance of 2.6 \AA , in fact, $<2.4\text{ \AA}$ is common
- (3) short C-H...O contacts have similar geometrical constraints as typical O-H...O hydrogen bonds

Since then, C-H hydrogen bonding has become an accepted non-covalent interaction.



the crystal structure of dimethyl oxalate (updated crystal structure from Jones); contact from CH_3 to next layer was 2.62 \AA ; obviously weak bonds, but presumably a large number of them

General Considerations

Interactions

- van der Waals (vdW), electrostatic, and covalent interactions
- in weak H-bonds, mostly electrostatic, some vdW contribution
- electrostatic forces diminish slowly with distance, so C-H...O interactions can deviate easily from their optimal geometry
- as C-H polarization decreases, the directional electrostatic component becomes less important than the isotropic vdW interaction, so the overall interaction becomes less directional
- classical H-bond polarization: C(δ^-)-H(δ^+)...O(δ^-)
- alternative polarization C(δ^+)-H(δ^+)...O(δ^-)

Bond Energy

- although difficult to determine experimentally, computations provide insights
- consensus: 0-2 kcal/mol (gas phase)

Some Calculated BDEs for C-H...O Bonded Dimers (gas phase, MP2)

System	Energy/ kcal mol ⁻¹
H-C≡C-H...O=CH ₂	-1.15
H-C≡C-H...OH ₂	-2.19
N≡C-H...OH ₂	-3.79
CH ₄ ...OH ₂	-0.59
CH ₄ ...OH ₂	-0.53
NH ₂ -CH ₃ ...OH ₂	-0.61
NH ₃ ⁺ -CH ₃ ...OH ₂	-9.3

Geometrical Requirements

Donor Directionality

- weak H-bonds are less directional than moderate H-bonds
- linear bonds are preferred for short contacts (histogram a)
- conic correction has been applied for the right hand histograms

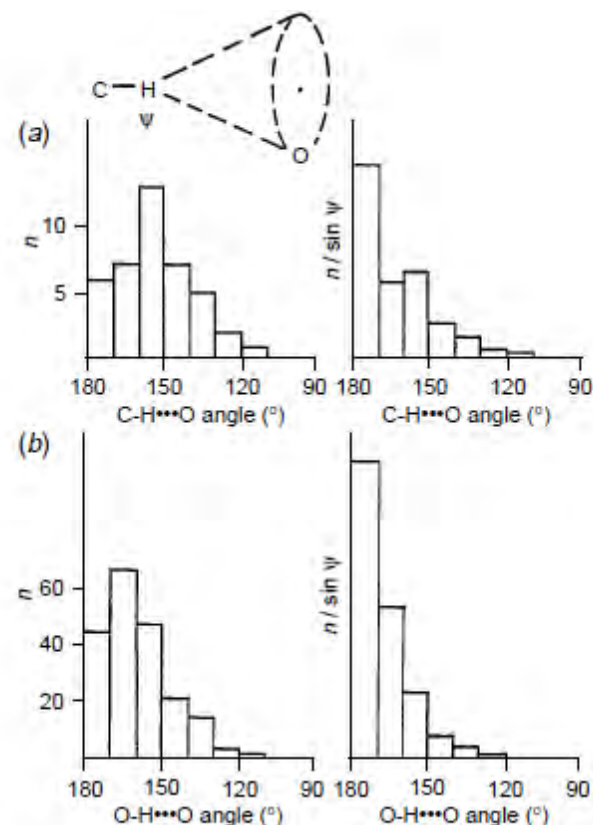
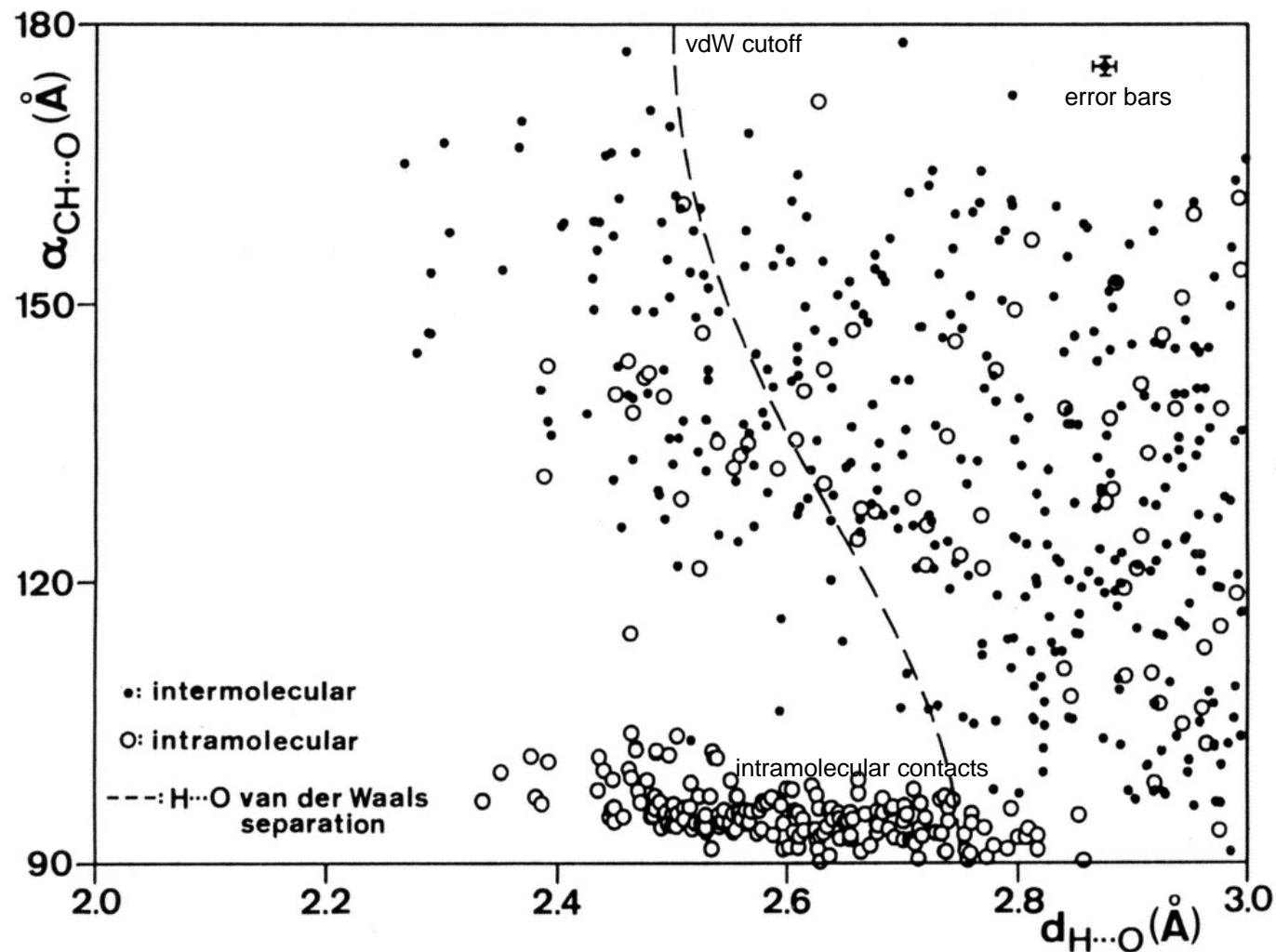


Fig. 7 Frequency distribution of X-H...O angles (ψ) in crystal structures: (a) 41 intermolecular C-H...O contacts with H...O < 2.4 Å in organic neutron crystal structures (ref. 23); (b) 196 O-H...O hydrogen bonds in carbohydrate X-ray crystal structures (ref. 24). The inset illustrates the 'cone correction' (ref. 24) (weighting by $1/\sin \psi$) that relates the left and the right histograms. The idea to show C-H...O and O-H...O histograms in one figure was adapted from a lecture of J. Kroon (Utrecht, Sept. 5, 1995).

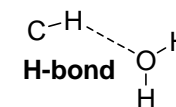
Scatterplot Analysis



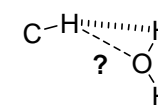
- data from neutron diffraction studies from carbohydrates

- impossible to tell between:

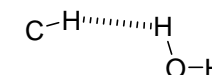
bonding



uncertain



coincidental/repulsive contact



- cluster of intramolecular contacts: *syn*-diaxial interactions: "forced contacts," possibly even repulsive

- no evidence of directionality

- cooperative effects possible but not well studied

Figure 5.7. Scatterplot of the angle C—H...O against $d_{\text{H}\cdots\text{O}}$. (●) intermolecular contacts; (○) intramolecular contacts; (---) H...O van der Waals separation based on a spherical O atom with $r \approx 1.50 \text{ \AA}$ and a spheroidal H atom with a side-on radius $r_s \approx 1.25 \text{ \AA}$ and a head-on radius $r_h \approx 1.0 \text{ \AA}$. The "classical" van der Waals separation would be a vertical line at $d_{\text{H}\cdots\text{O}} \approx 2.6 \text{ \AA}$. The error bars of the top right point represent the typical experimental uncertainty $\pm 0.01 \text{ \AA}$ and $\pm 1^\circ$ (from Steiner and Saenger, 1992c, reprinted with permission).

Cutoff Criteria

- no critical distance where interaction changes from "H-bonding" to "vdW"
- strict vdW radii criteria for H-bonding incorrect; smooth distribution of points on both sides of cutoff

vdW radii: Bondi *J Chem Phys* **1964**, 68, 441

Acceptor Directionality

- carbonyl donors: X-H vectors prefer to point at carbonyl lone pairs

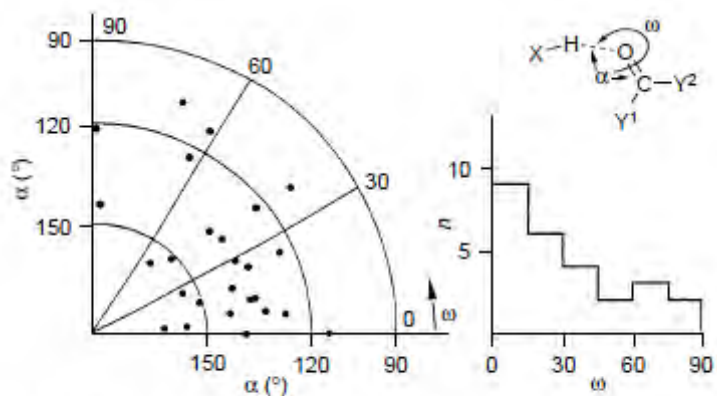


Fig. 12 Approach of acidic and sterically unhindered C-H donors to C=O acceptors (26 data points) (ref. 32). Geometrical definitions are shown in the inset. The data are indicative of soft but significant acceptor directionality.

- α is the H-O-C angle; ω is the H-O-C-Y dihedral angle
- left-hand histogram shows a preference for slightly less than linear contacts
- right-hand histogram shows a preference for in-plane contacts

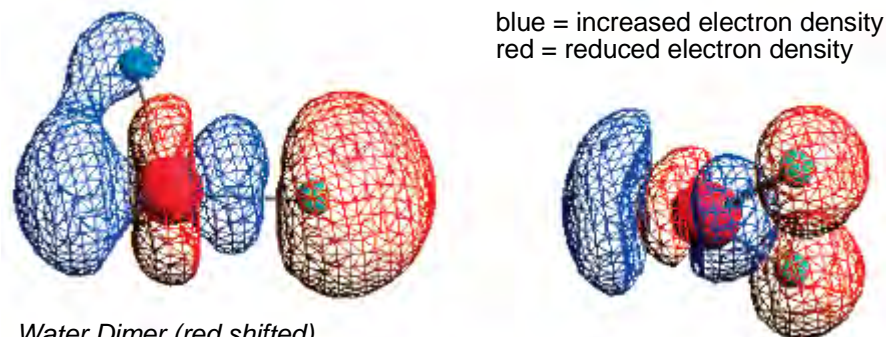
[ref 10]

Red- vs. Blue-Shifted IR Stretches

- usually, H-bonding weakens donor bond, increases band intensity
- occasionally, H-bonding *strengthens* donor bond: "blue shifted H-bonds"
- evidence suggests that there is nothing special about these H-bonds

"Red- versus Blue-Shifting Hydrogen Bonds: Are There Fundamental Distinctions?" Scheiner, S.; Kar, T. *J. Phys. Chem. A* **2002**, 106, 1784-1789.

Electron Density Analysis



Water Dimer (red shifted)

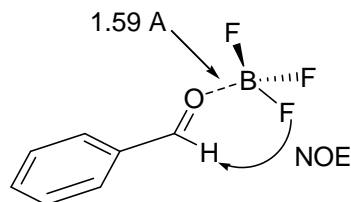


$F_3C-H...OH_2$ (blue shifted - calculated change in C-H bond length: -1.6 mÅ)

- no apparent difference in electron density patterns

Aldehyde-BF₃ Complexes

- X-ray, NMR: *anti* complex
- note that the B-F bond eclipses the aldehyde plane

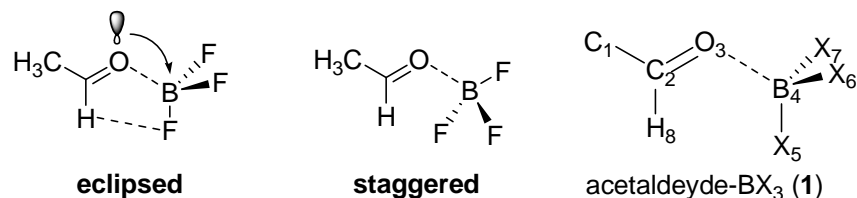


- related B-O distances for comparison: B(OH)₃, 1.36; KB(OAc)₄, 1.47

Reetz *JACS* **1986** 108 2405

Conformational Analysis (Liu and Guo *J Chem Phys A* **2004** 108 9196)

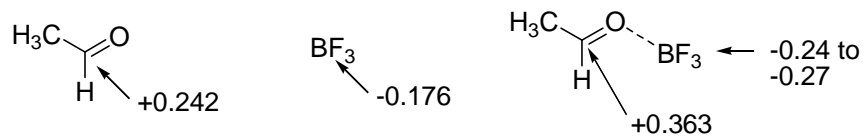
- sterics predict staggered conformation



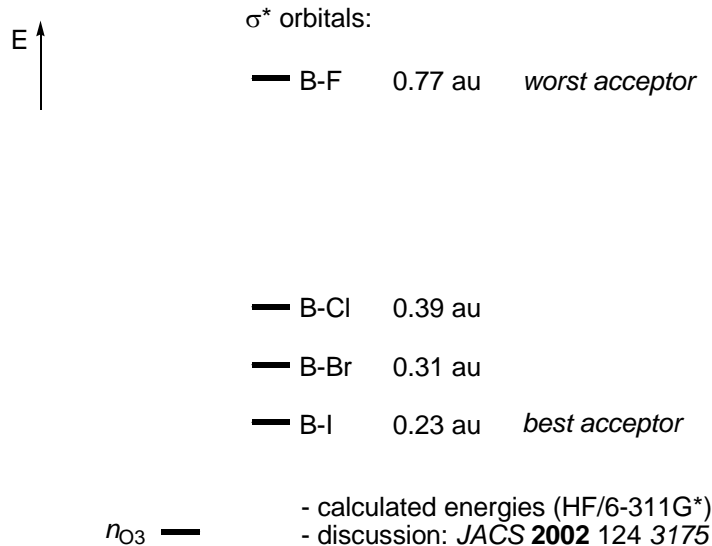
Sterics favor the staggered conformation; larger penalty for X=Cl over X=F.

Hyperconjugation favors the eclipsed conformation, assuming the $n_{O3} - \sigma^*_{B-X}$ interaction is important; more important for X=Cl over X=F.

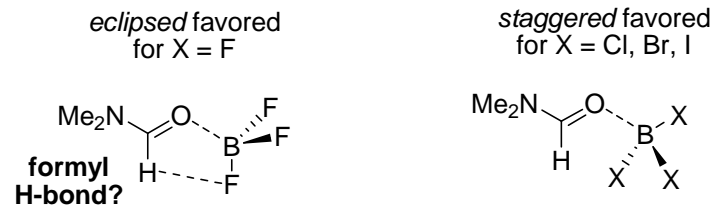
Formyl hydrogen bonding (if present) favors the eclipsed conformation; more important for X=F than X=Cl. This is attractive, given the polarizing effect of the Lewis acid.



(MINDO)



X-ray structures of DMF-BX₃ (Corey *TL* **1997** 38 33):

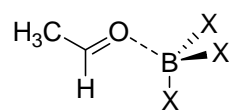


HCBF dihedral angle: 10°
 H...F distance: 2.36 Å

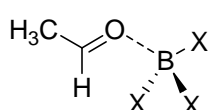
Are sterics and C-H...O H-bonding more important than hyperconjugation?

Natural Bond Order (NBO) Method

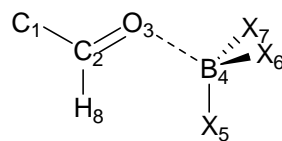
- HF/6-311++G(2d,p) calculations



eclipsed



staggered



acetaldehyde-BX₃ (1)

Steric Energy

For X=F, the cost of eclipsing the B-F bond is 3 kcal/mol.
For X=Cl, the cost of eclipsing the B-Cl bond is 15 kcal/mol.

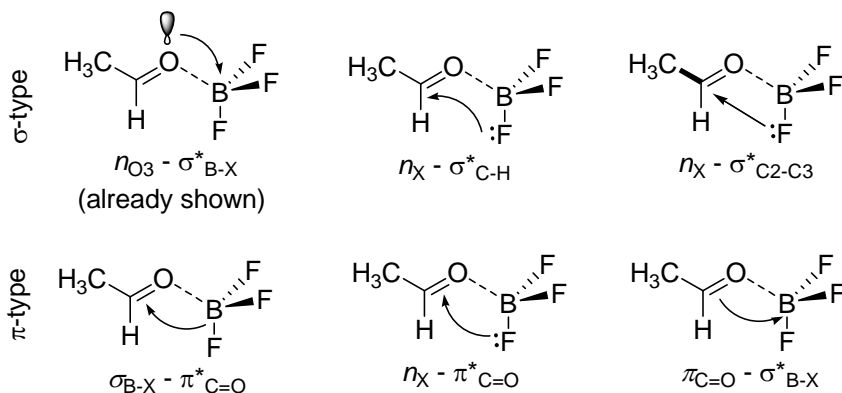
Hyperconjugative Interactions

- eclipsed conformation is always preferred

For X=F, there is 3 kcal/mol eclipsed-staggered energy difference.
For X=Cl, there is a 11 kcal/mol eclipsed-staggered energy difference.

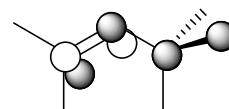
- other calculations (Gung *JOC* **1992** 57 1370) also show a preference for the eclipsed geometry, with a cooperative effect from MeCHO to PhCHO

- other interactions are important:

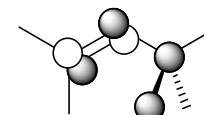


- π -type interactions more important than σ -type
- every interaction prefers eclipsed conformation
- exception: $n_X - \sigma^*_{C2-C3}$ interaction (not important -- σ^*_{C2-C3} too high in energy)

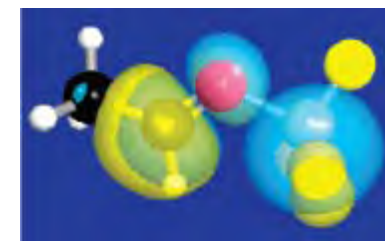
What is special about the eclipsed conformation for the π -type interactions?



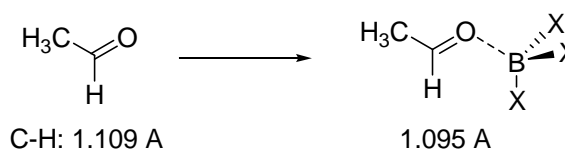
eclipsed (in phase)



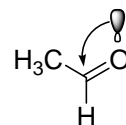
staggered (out of phase)



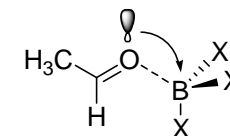
A Blue-Shifted Formyl Hydrogen Bond



- calculated bond lengths show blue-shifted formyl C-H bond
- lengths do not depend on X or eclipsed/staggered



free aldehyde:
 $n_O - \sigma^*_{C-H}$ important,
bond lengthened



bound aldehyde:
 n_O involved in
other interactions,
bond not lengthened
as much

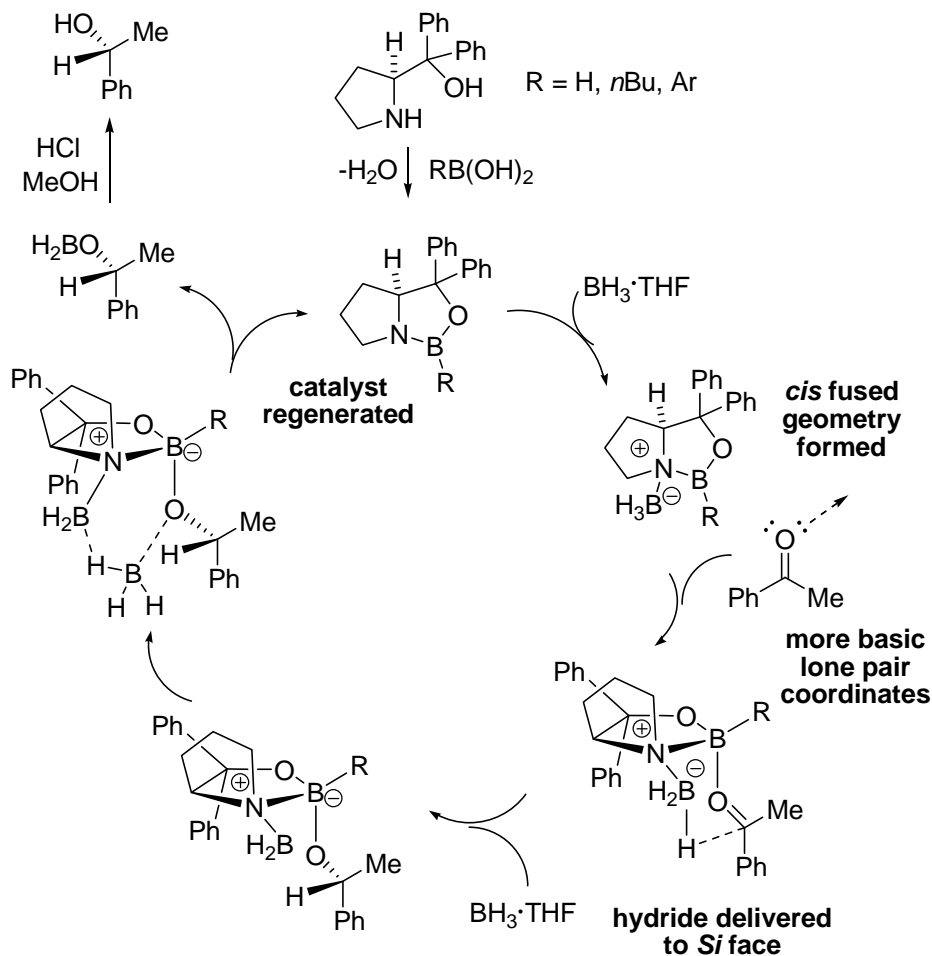
Key References

"The Formyl C-H...O Hydrogen Bond as a Critical Factor in Enantioselective Lewis-Acid Catalyzed Reactions of Aldehydes." Corey, E.J.; Lee, T.W. *Chem. Commun.* **2001**, 1321-1329.

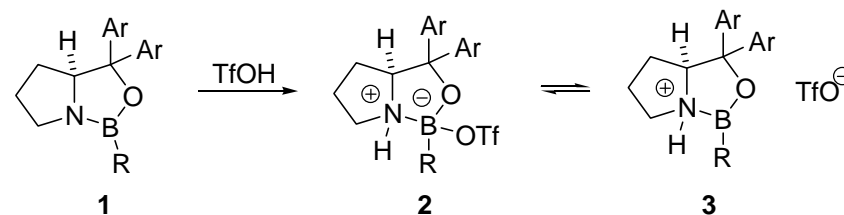
"Cationic Oxazaborolidines." Corey, E.J. *ACIE* **2009** 48 2100-2117.

- only Diels-Alder reaction considered below

CBS Reagent

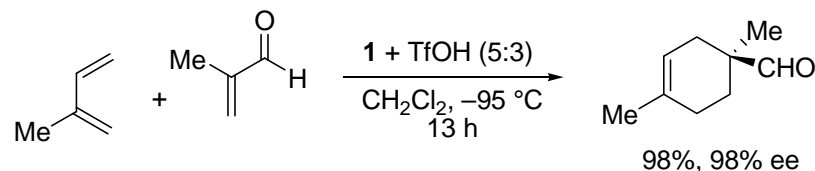


Oxazaborolidinium Catalysts

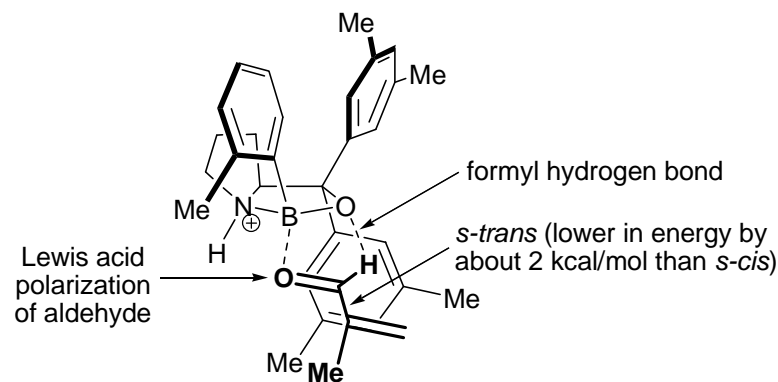


- **3** = very strong Lewis acid; ineffective: MsOH , BF_3 , SnCl_4 , ZnCl_2 , and AlCl_3
- **2** and **3** in rapid equilibrium
- best results: $\text{R} = o\text{-tolyl}$ and $\text{Ar} = 3,5\text{-dimethylphenyl}$ (mexyl)

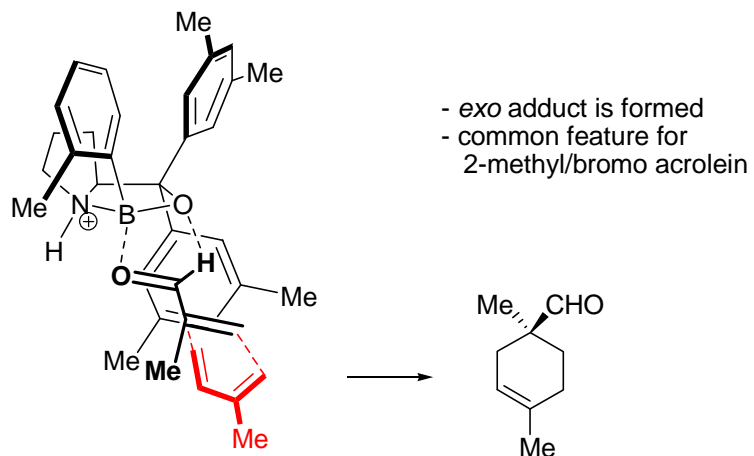
Diels-Alder Reactions



proposed pre-transition state assembly:

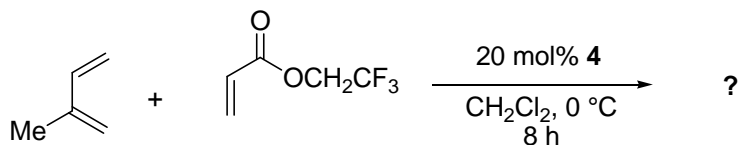


Predicting the Sense of Stereoinduction

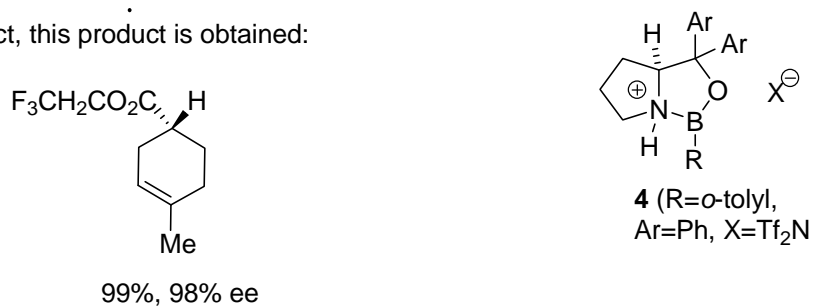


- if $(\text{CF}_3\text{SO}_2)_2\text{NH}$ used instead of TfOH, more stable catalyst generated

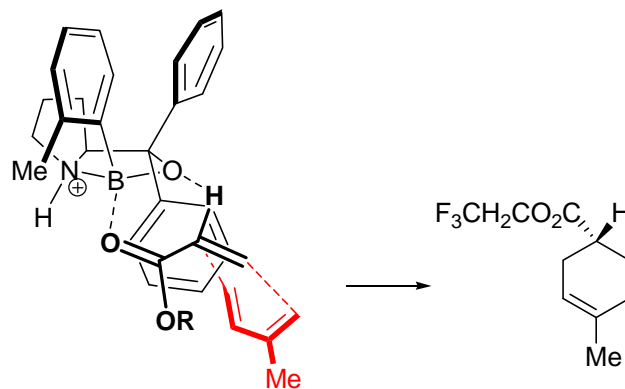
What would one predict for this reaction?



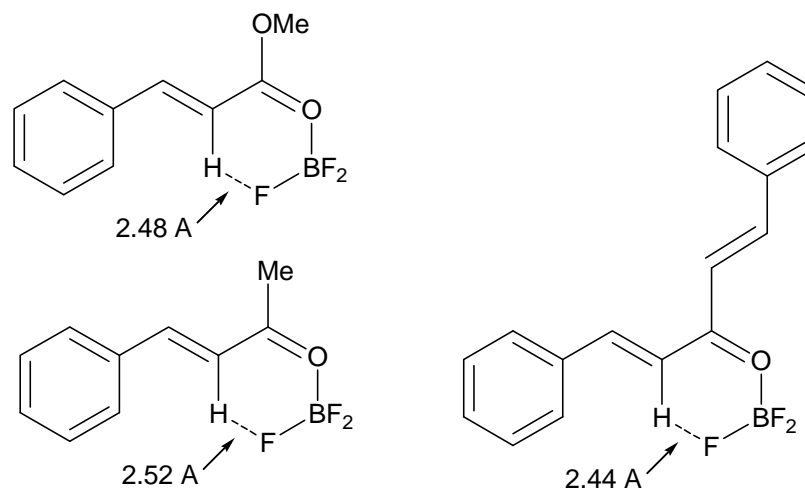
In fact, this product is obtained:



Why the turnover?



X-ray data from enal-BF₃ complexes:
sum of vdW contact radii: 2.67 Å



Computed Energies:

anomeric effect	6 kJ/mol
formyl C-H	9 kJ/mol
α -methyl C-H	12 kJ/mol
β -methyl C-H	4 kJ/mol
α -methylene C-H	8 kJ/mol

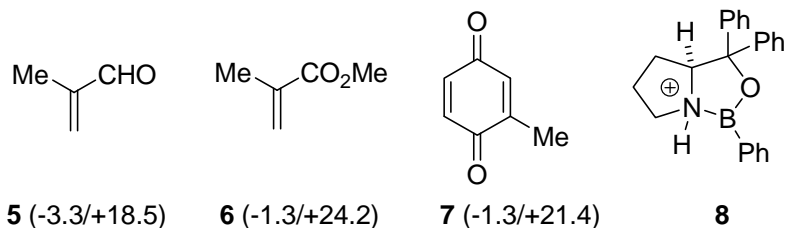
Chem Commun **1997** 2383

Eugene Kwan

Computational Evidence

- DFT calculations with support Corey model
- consider butadiene, catalyst **8**

(catalyst binding energy/activation energy) kcal/mol



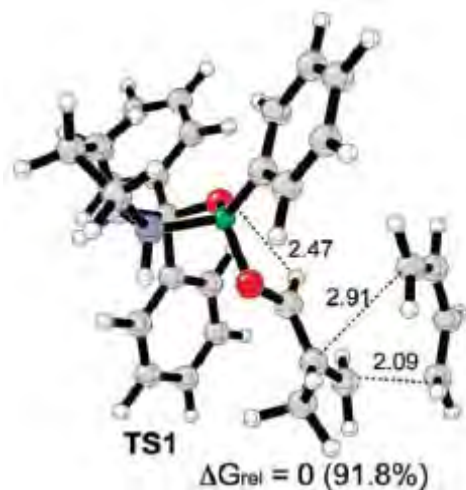
- solvent (PCM model) makes no difference; these are gas phase values

Assumption: Complex formation has a low barrier compared to Diels-Alder reaction.

Corollary: This is a Curtin-Hammett situation.

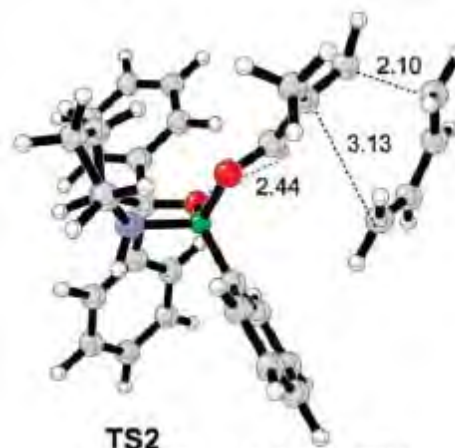
Note: Complex formation is known to be reversible from NMR.

Transition Structures for **5**

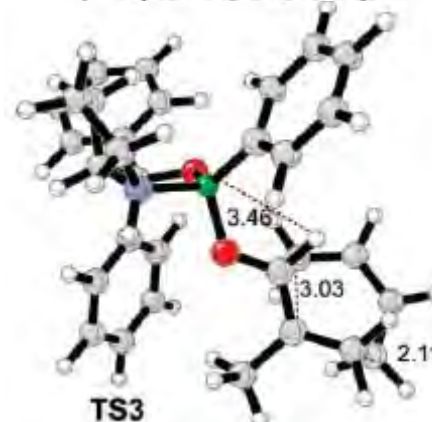


- lowest energy TS (leads to major pdt)
- matches Corey model
- note asynchronous TS

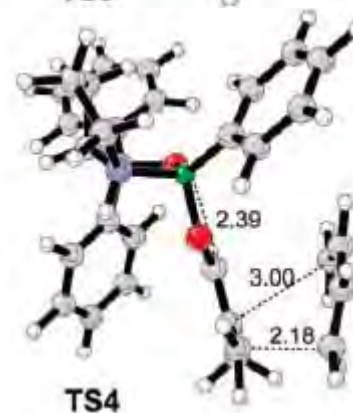
What leads to the minor enantiomer?



- approach from the *endo* face of the catalyst



- rotated dienophile
- no C-H...O bond
- exposes *Si* face of dienophile



- same as TS1, but with *s-cis* dienophile

Computed vs. Observed Selectivities

Entry	Computed Reactions	Enantiomeric Ratio ^a (calculated)	Similar Experimental Examples	Enantiomeric Ratio ^a (experimental)
1		92.4:7.6		98.5:1.5 Ref. 3b
2		84:16		84.5:15.5 Ref. 3a
3		96.8:3.2		97.5:2.5 Ref. 3c
4		94.7:5.3		96.5:3.5 Ref. 3c
5		68.6:31.4 ^b (64:36) ^c		95.5:4.5 Ref. 3d

^a Major enantiomer illustrated. ^b Enantiomer ratio considering only TS geometries with catalyst coordination to the C4 carbonyl. ^c Enantiomer ratio considering TS geometries with catalyst coordination to both carbonyl groups. ^d Enantiomer ratio considering only TS geometries with catalyst coordination to the C1 carbonyl.

- The relatively poor selectivity in entry 2 is presumably due to two possible modes of C-H...O catalyst binding.
- The poor agreement in entry 5 may be related to the relatively weak electron-donating ability of methyl group.

1. *What is a hydrogen bond? What are typical experimental observations?*

- X-H...A = H-bond if: local interaction *and* X-H is a proton donor to A [ref 2]
- X-H gets longer (IR red shift); H goes downfield (NMR)
- reduced thermal motions (X-ray)

2. *What are typical bond dissociation energies? What bonding interactions are involved? Is hydrogen bonding primarily electrostatic in nature?*

Weak (0-4, but usually 0-2 kcal/mol); medium (4-14), strong (14-40).

Electrostatic (directional), van der Waals (isotropic), covalent interactions.

Usually, electrostatics dominate.

3. *How long are hydrogen bonds? What are the angular requirements on the acceptor and donor?*

H...A distances: Weak (2.2-3.2 Å); medium (1.5-2.2); strong (1.2-1.5)

vdW radii cutoffs: suggestive, but not strict criteria.

Linear bonds are preferred (after conic correction), but this depends on the location of electron density, molecular dipole, and other intermolecular forces.

4. *What can computations tell us?*

Bond angles, bond distances, interaction energies, spectroscopic observables, enantiomeric excess(?).

5. *Do formyl hydrogen bonds exist? What is their role in reactivity?*

Very probably. They play an important role in many reactions.

However, there is a relatively small body of evidence for their existence, mostly X-ray crystal structures and computations.

Outlook

These are my personal opinions:

Observation: *There is far more information about hydrogen bonds in the gas and solid states than in the liquid state.*

Comment: We need some new methods to study hydrogen bonds in solution. In particular, ultrafast IR spectroscopy may be useful. Not much is known about hydrogen bonding in transition states except from computations.

Observation: *Computations are now readily accessible and provide many useful insights.*

Comment: Computations can calculate a variety of observables, such as IR frequencies, but perhaps due to experimental limitations, computational studies often do not connect theory and experiment.

Observation: *NMR chemical shifts are correlated with hydrogen bonding, but the nature of the interaction is complex.*

Comment: Perhaps technologies have advanced to the point where it is now feasible to analyze both single crystal X-ray or neutron diffraction patterns *and* solid state NMR chemical shift tensors.

Observation: *Although NMR spectroscopy has now allowed many protein structures to be determined in solution, this approach has not been widely applied to hydrogen bonding in small molecules.*

Comment: Can the same successful approach of analyzing structure-geometry relationships in the solid phase using X-ray and neutron diffraction techniques be applied to the solution phase using NMR or IR? This may depend on the rate of the dynamics involved.

Observation: "Any way you look at it, science is hard." -SJZ

Comment: Understanding the role of hydrogen bonding in reactivity is really hard, but we've made good progress. Asymmetric reactions provide the most rigorous test of our understanding.