

Hydrogen bonding and other weak interactions in biopolymers

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What is a hydrogen bond? Textbook definitions

“a type of dipole–dipole interaction” (Brown et al.: *Chemistry: The Central Science*, 12th edn, Prentice Hall: Upper Saddle River, NJ 2012)

“a special type of dipole–dipole interaction” (Burdge: *Chemistry*, 2nd edn, McGraw-Hill: Boston, MA 2011)

“particularly strong dipole–dipole forces” (Zumdahl and Zumdahl: *Chemistry: An Atoms First Approach*, Brooks Cole: Belmont, CA 2012)

“an extreme form of dipole–dipole interaction” (Kotz et al.: *Chemistry and Chemical Reactivity*, 7th edn, Brooks Cole: Belmont, CA 2009)

“especially enhanced dipole–dipole forces” (Siska: *University Chemistry*, Prentice-Hall: Upper Saddle River, NJ 2005),

“a special kind of dipole–dipole force” (Moore et al.: *Chemistry: The Molecular Science*, 4th edn, Brooks-Cole: Belmont, CA, 2010)

“a sort of super dipole–dipole force” (Tro: *Chemistry: A Molecular Approach*, 2nd edn, Prentice-Hall: Boston, MA 2011)

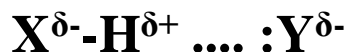
“no more than a particularly strong type of directional dipole-dipole interaction” (J. Israelachvili: *Intermolecular and Surface Forces*, 2nd ed., Academic Press, New York (1991)

Wikipedia (2014):

“The hydrogen bond is the electromagnetic attractive interaction between polar molecules. . . it is not a true bond but a particularly strong dipole–dipole attraction, and should not be confused with a covalent bond”.

Vodíková vazba (vodíkový můstek)

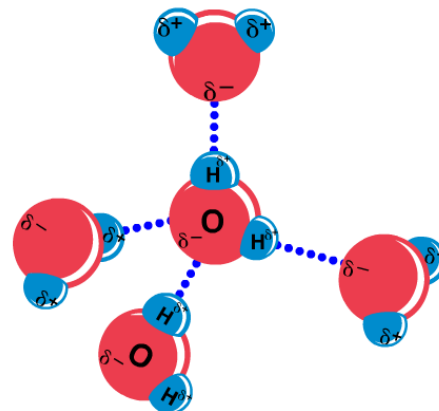
má často silnou elektrostatickou složku:



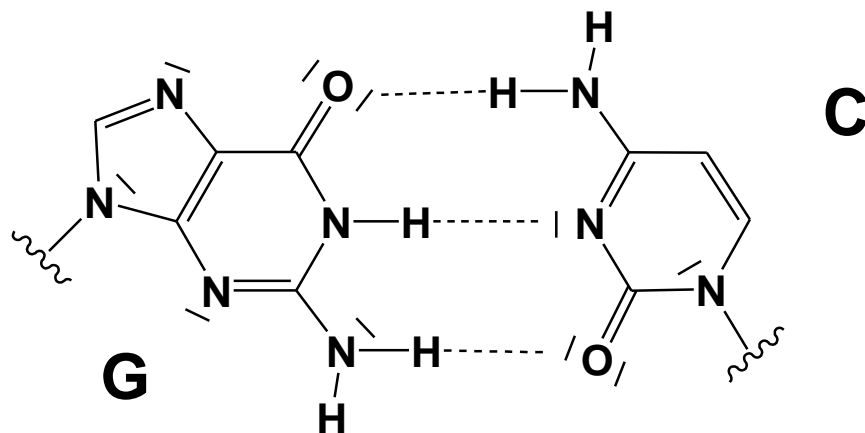
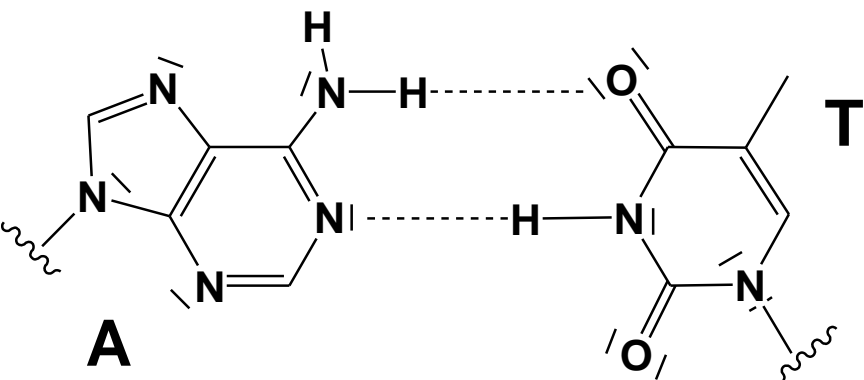
X --- elektronegativní prvek

N,O,F,S,Cl : vazba X-H je polární, na H parciální kladný náboj

Y --- nositel parciálního záporného náboje ve volném elektronovém páru
v biologických makromolekulách hlavně O,N



příklad: vodíkové můstky svazují páry bazí DNA:



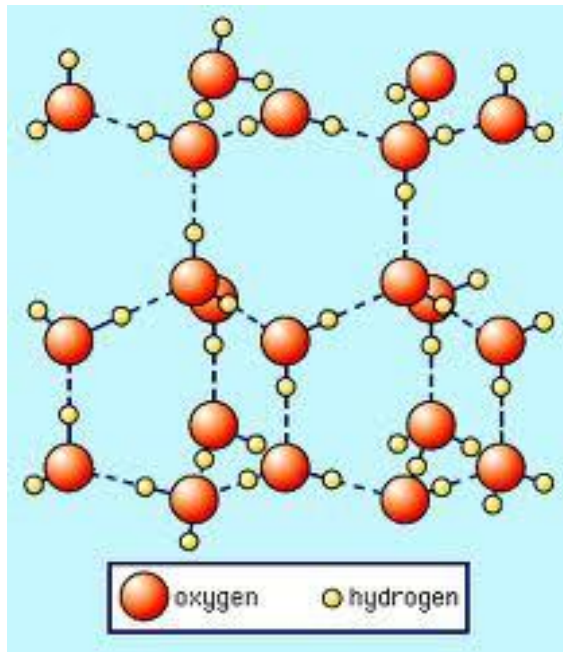
Vodíkové můstky určují krystalovou strukturu ledu.

Maximalizace počtu vodíkových můstků vede k poměrně malé hustotě

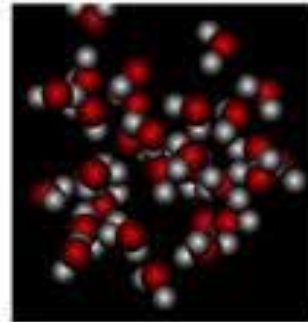
→ Led plave na vodě

→ Kanálky v mřížce ledu může difundovat kyslík

→ Vodíkové můstky mají zásadní význam pro život na Zemi.

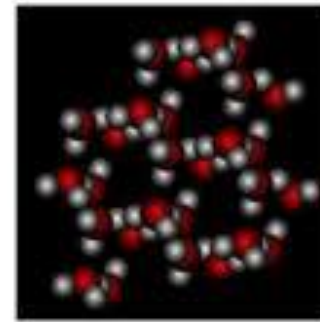


liquid (water)

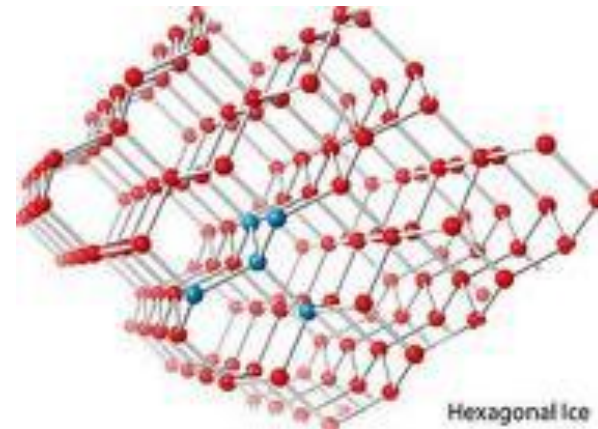


Fewer Hydrogen Bonds

solid (ice)



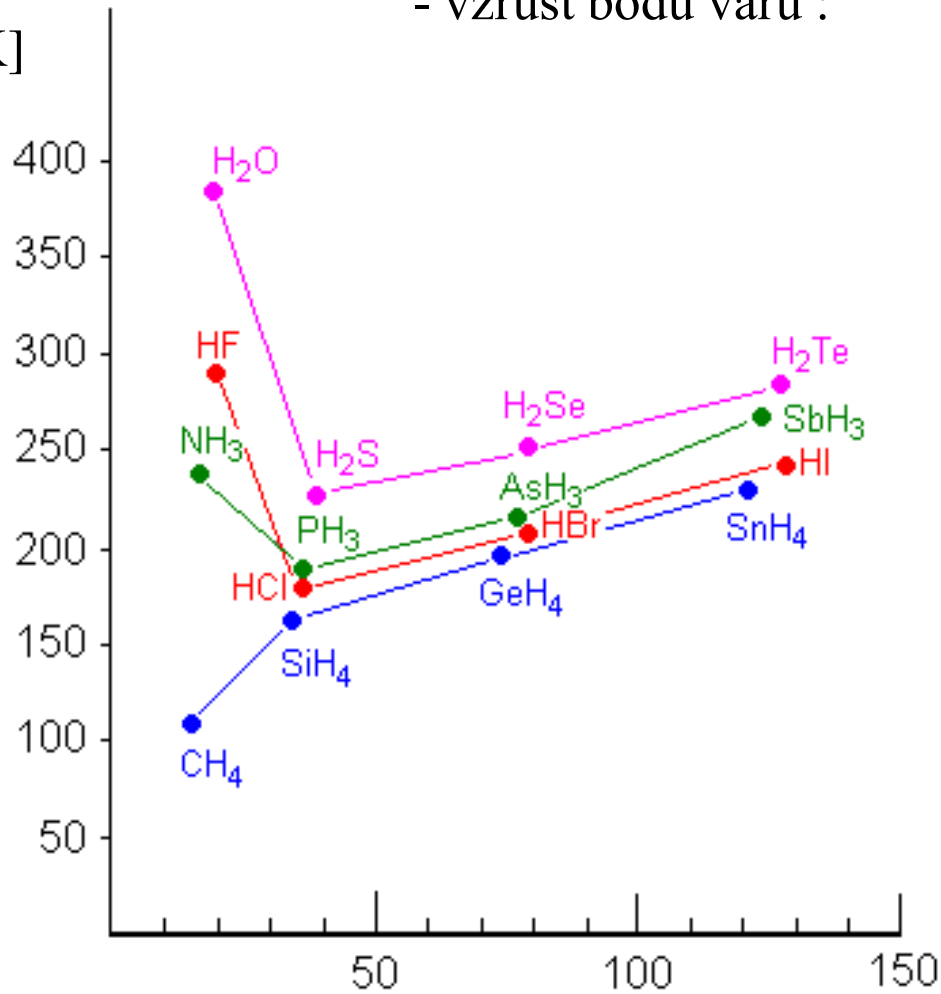
More Hydrogen Bonds



Hexagonal ice

Projevy přítomnosti vodíkové vazby v kapalinách
- vzrůst bodu varu :

Bod varu [K]

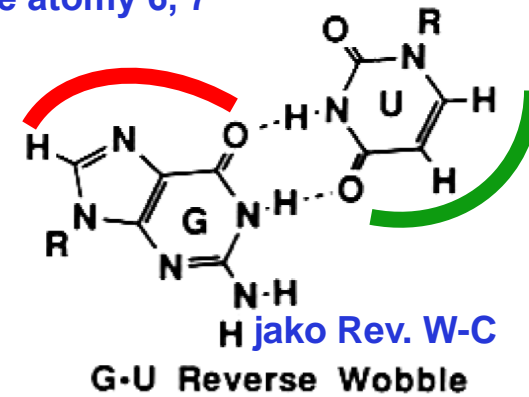
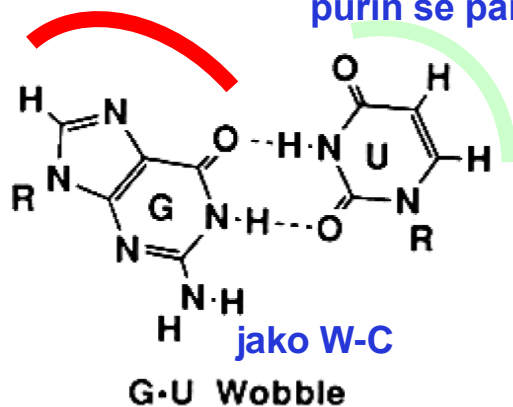
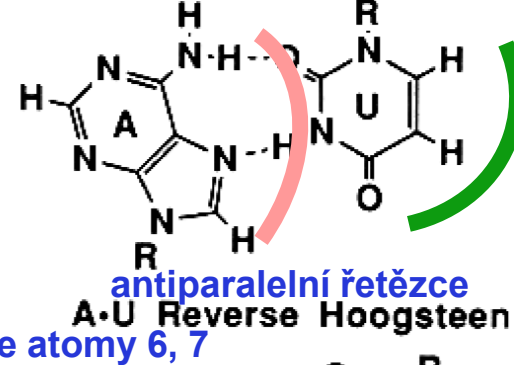
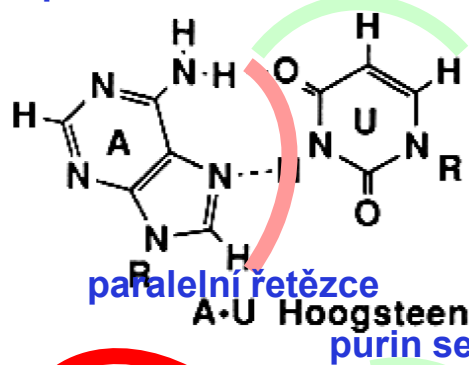
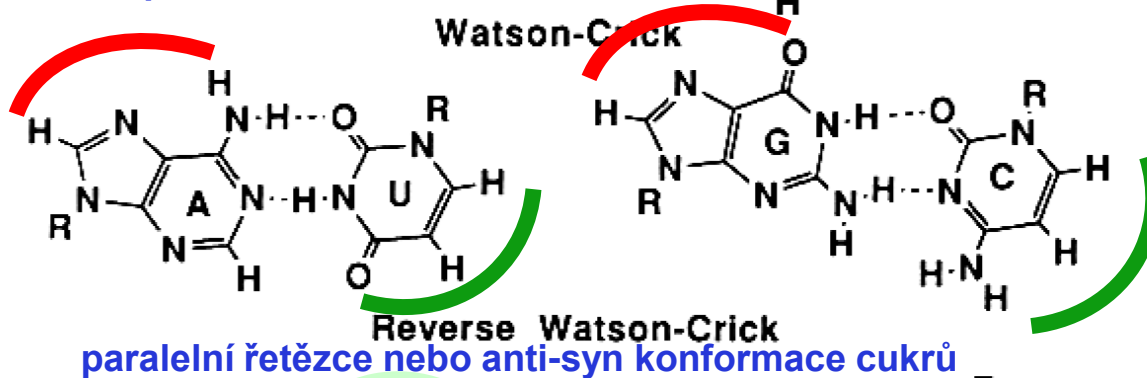
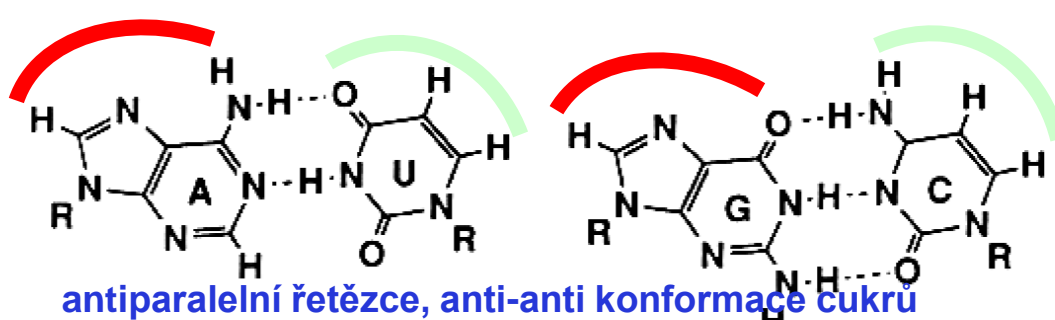


relativní molekulová hmotnost

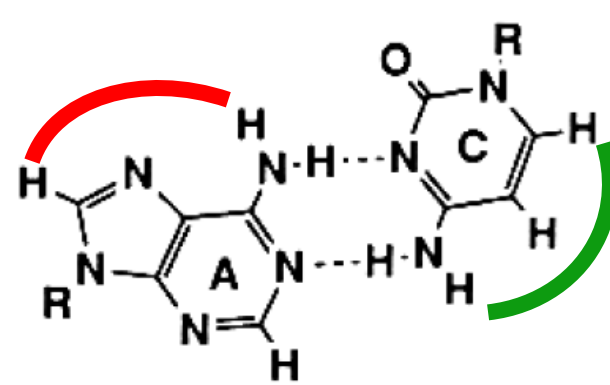
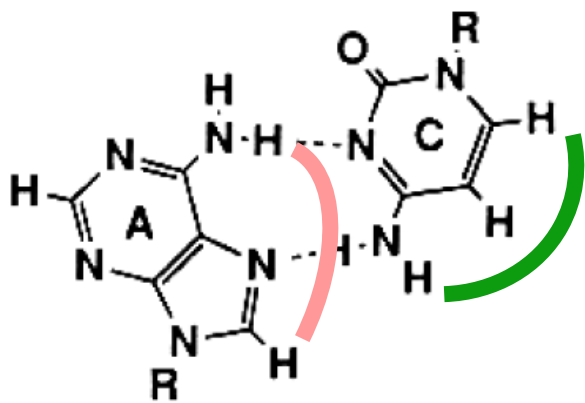
Show B-DNA pdb code 3BSE
Highlight resid 13 and 26

The Base Pair Directory

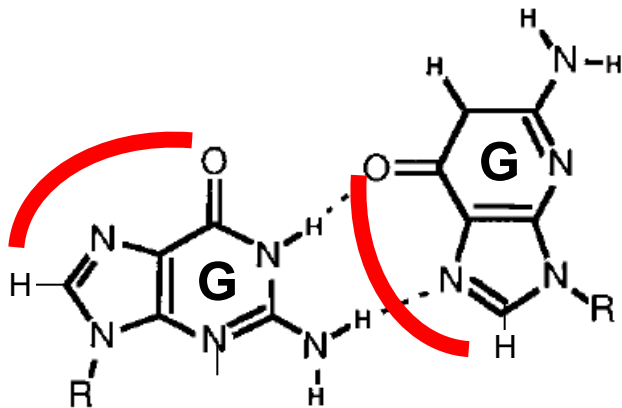
Oblouky označují atomy nacházející se ve velkém žlábkku kanonické B-DNA.
Tmavá barva: pohled ze strany 5' na nukleotid *anti*
Světlá barva: pohled ze strany 3' na nukleotid *anti*
Červená: puriny
Zelená: pyrimidiny



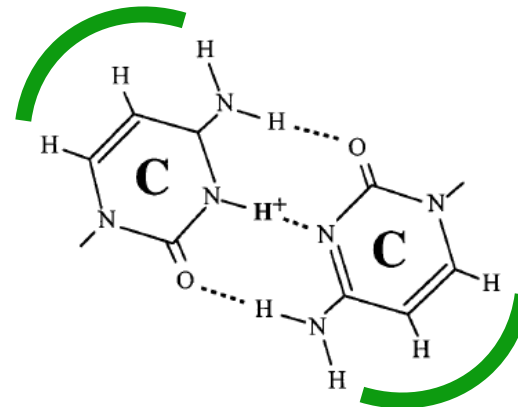
I. Tinoco, Jr. In Appendix 1 of: *The RNA World*, Cold Spring Harbor Laboratory Press, 1993, pp. 603-607.



pKa of N3 of cytosine is 4.7.

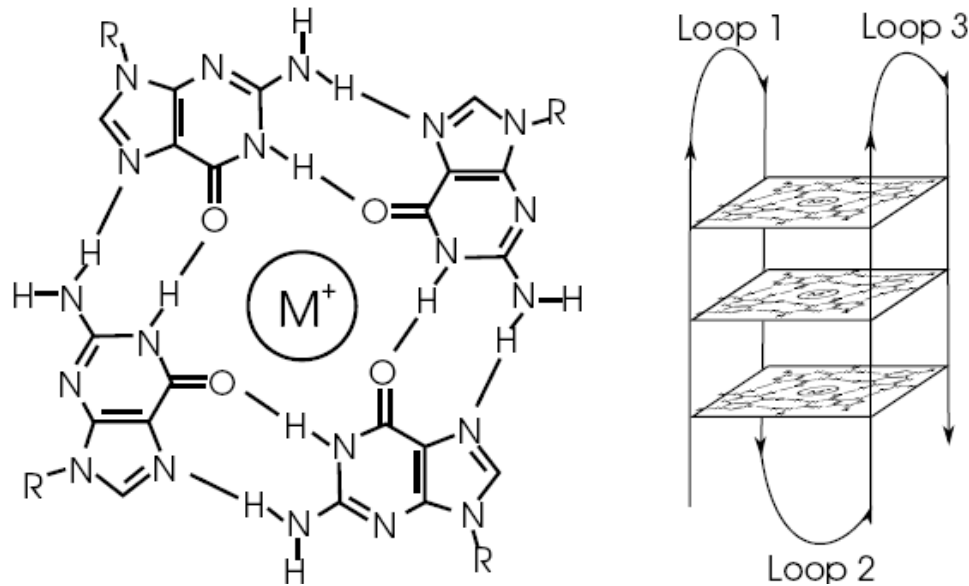


G-G Hoogsteen



C-C⁺ pair (in i-motifs)

Cvičení: vyzačte zóny velkého a malého žlábků a pomocí modelu B-DNA určete, zda na bázi nahlížíme ze strany 5' nebo 3'.



G-kvartet (též **guaninový kvartet** nebo **G-tetráda**) je rovinný systém čtyř **guaninových** bází, navzájem pootočených o 90° a pospojovaných **vodíkovými můstky**. Patří mezi nekanonické (neobvyklé) typy sekundární struktury nukleových kyselin. G-kvartety jsou běžně k nalezení v **GC-bohatých** oblastech **RNA**, ale i v **DNA** (především v **promotorových** oblastech některých **genů**, na koncích telomer)^[1] a v některých oblastech genů pro těžké řetězce imunoglobulinů.^[2] Vyskytuje-li se nad sebou hned několik G-kvartetů, útvar se někdy označuje jako **G-kvadruplex**.^[1] Pro vznik G-kvartetů je zásadní existence tzv. **hoogsteenovského párování** – klasické párování bází by neumožnilo vznik této neobvyklé struktury.^[3]

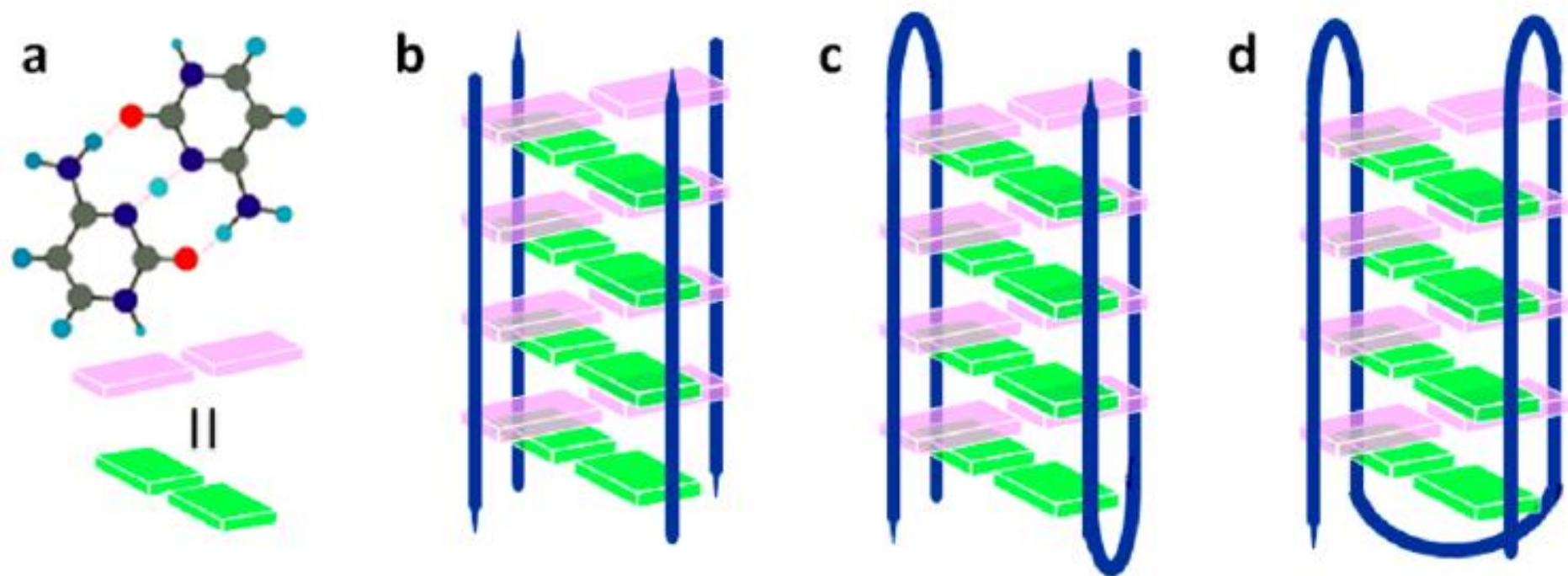
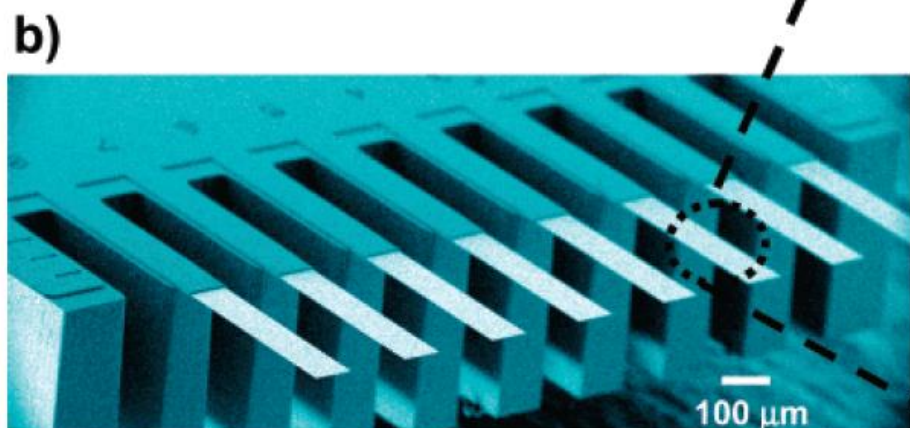
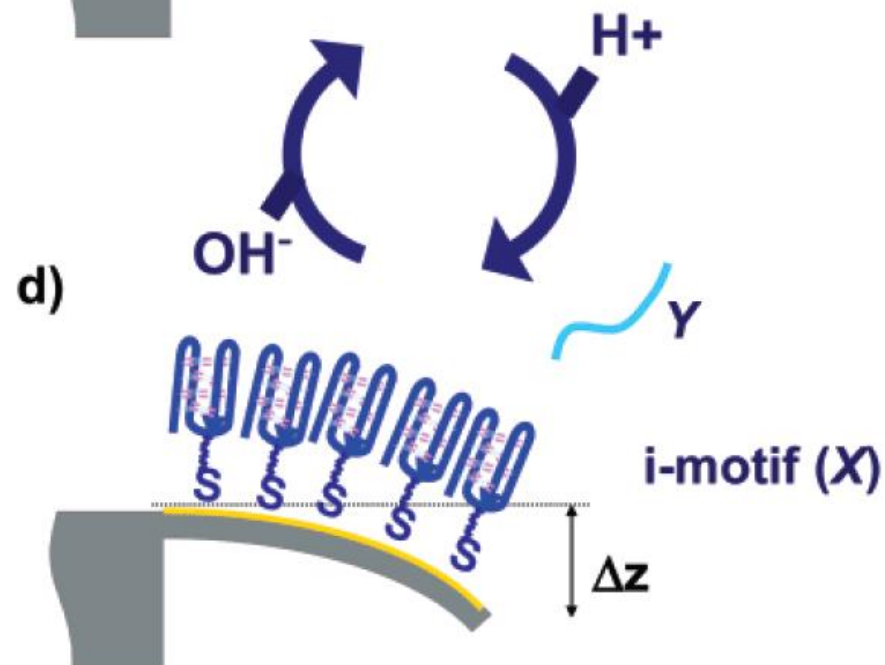
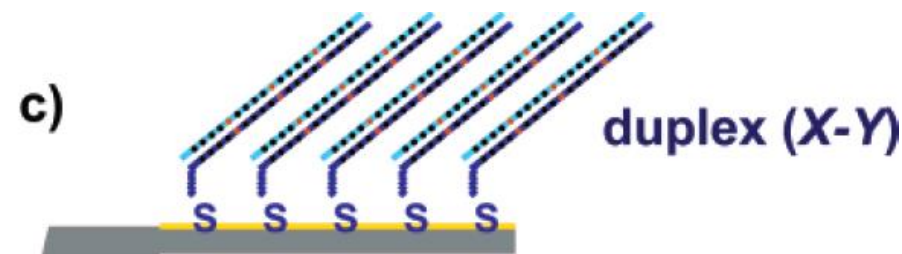
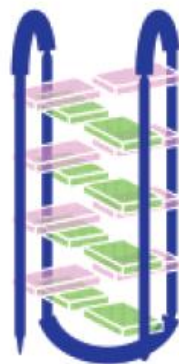
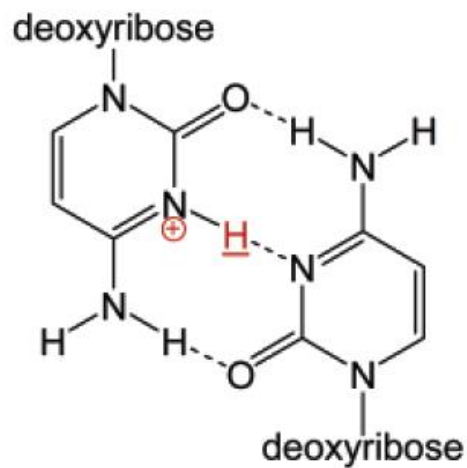


Figure 1. Schematic illustration of i-motif conformations: (a) C·CH⁺ pairs; (b) tetramer i-motif structure; (c) dimer i-motif structure; (d) intramolecular i-motif structure.

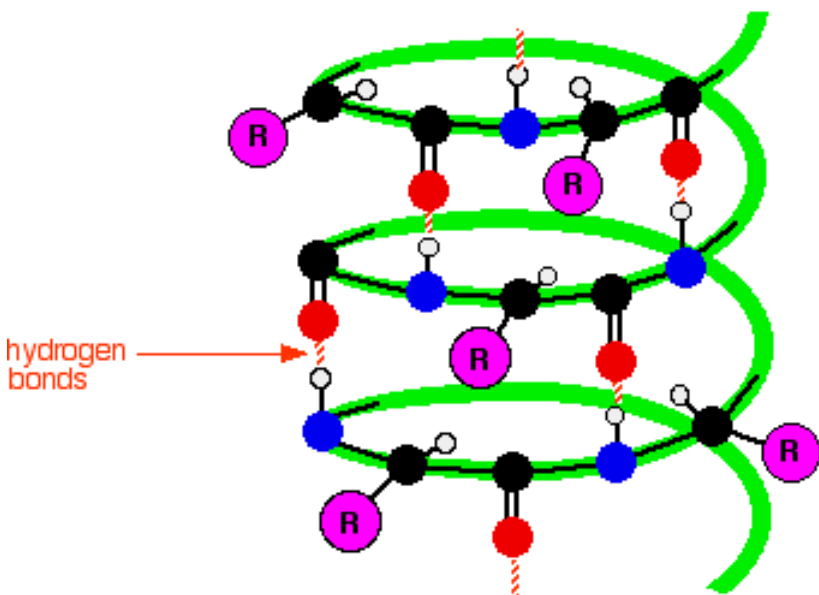
DNA Molecular Motor Driven Micromechanical Cantilever Arrays

J. AM. CHEM. SOC. 2005, 127, 17054–17060

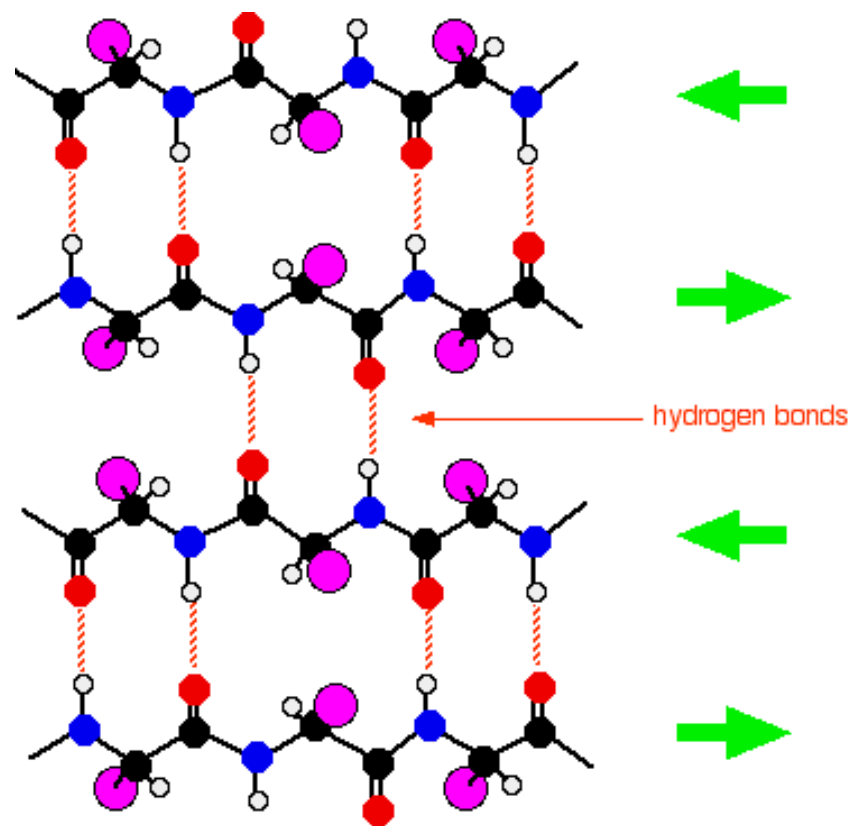


Classical hydrogen bonds stabilizing canonical protein structures

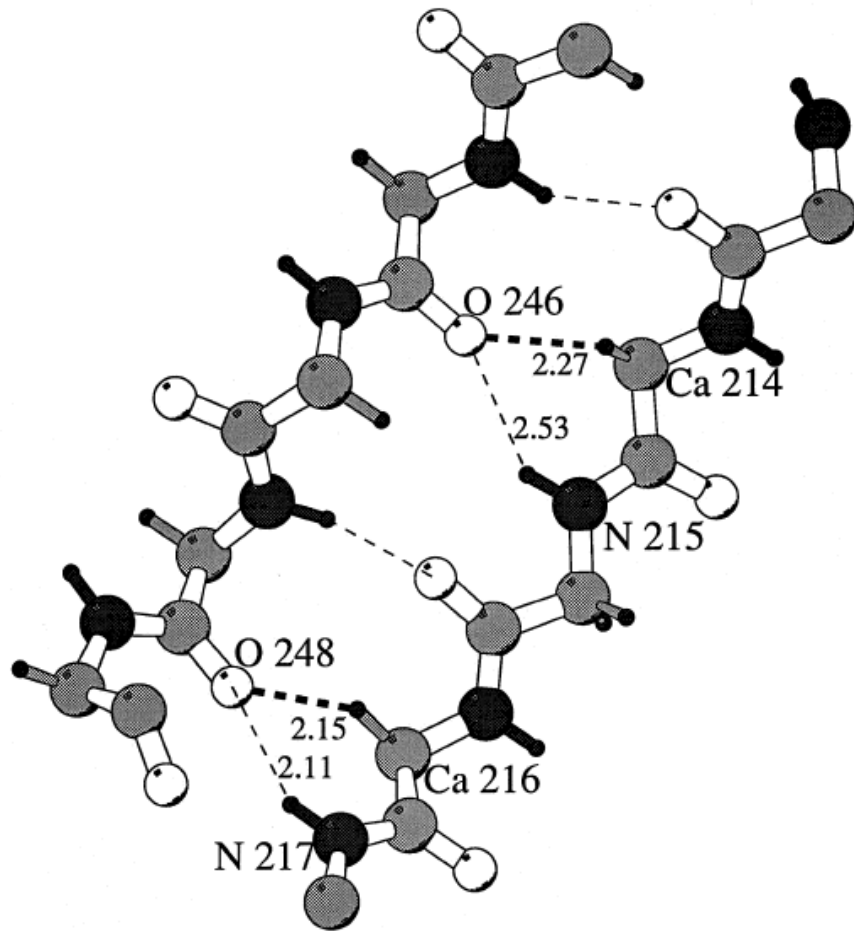
$\text{N-H}\cdots\text{O}=\text{C}$



α -helix

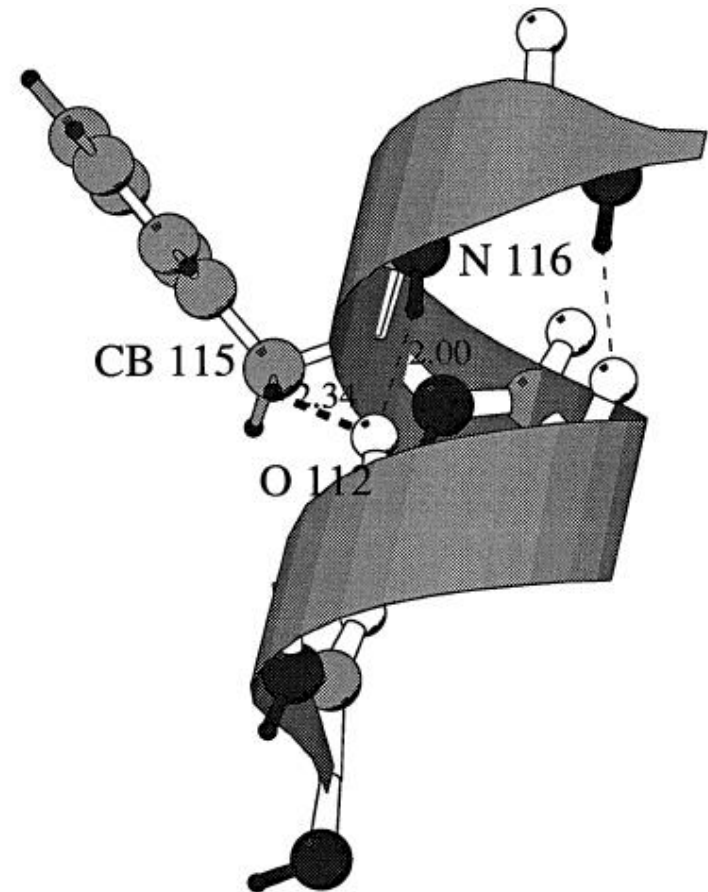


β -sheet



antiparallel β -sheet

Geotrichum lipase (1THG)



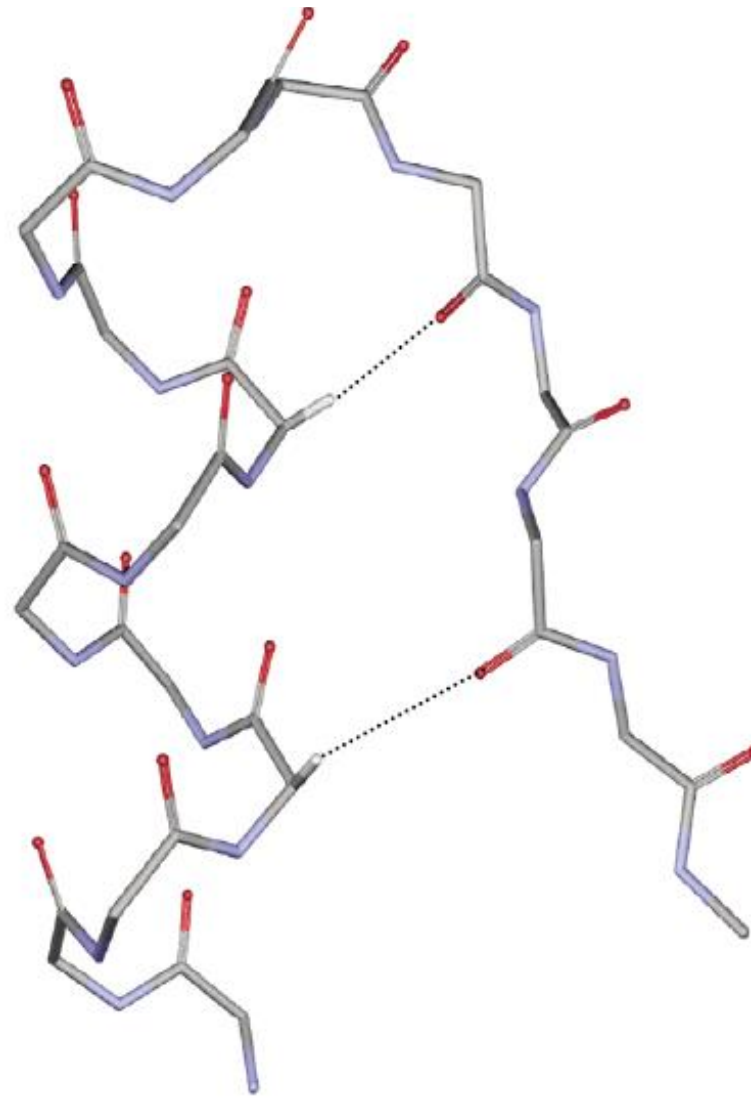
α -helix

Myoglobin (1MBA)

A C–H...O Hydrogen Bond Stabilized Polypeptide Chain Reversal Motif at the C Terminus of Helices in Proteins

J. Mol. Biol. (2002) **322**, 871–880

M. Madan Babu, S. Kumar Singh and P. Balaram*



The C α —H...O hydrogen bond: A determinant of stability and specificity in transmembrane helix interactions



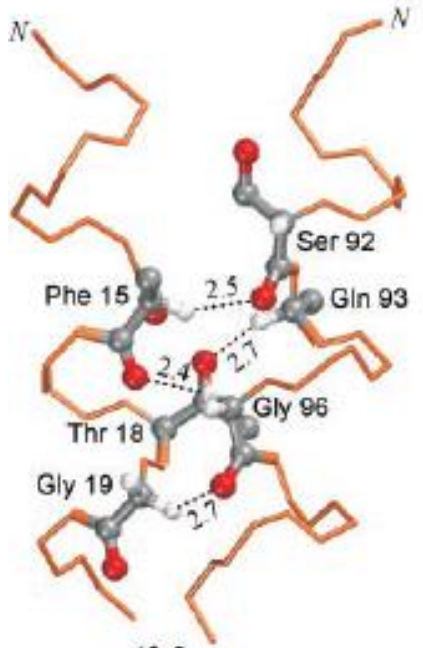
Glycerol facilitator (GlpF)
(1fx8)



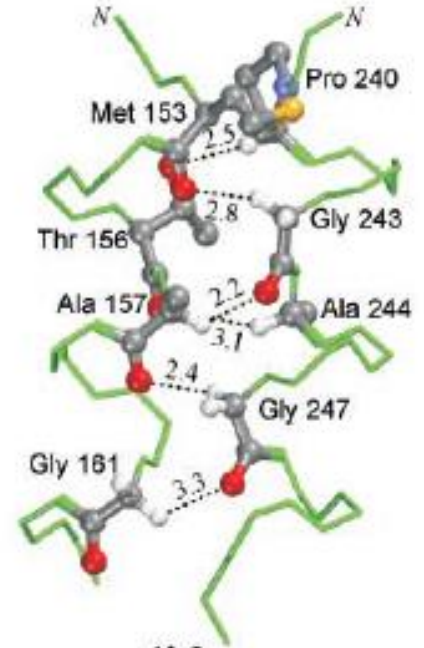
Calcium ATPase
(1eul)



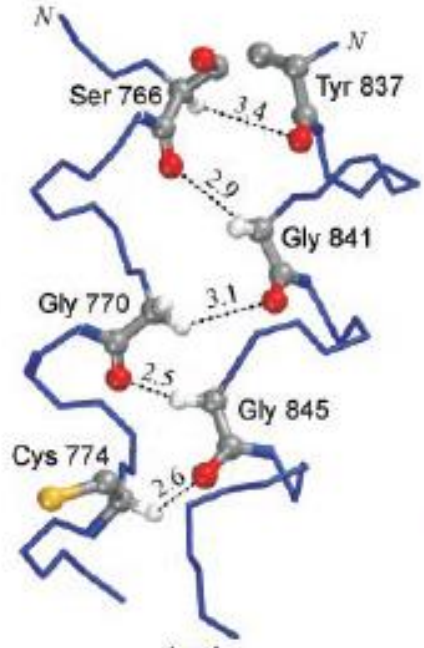
Glycophorin A (GpA)
(1afo)



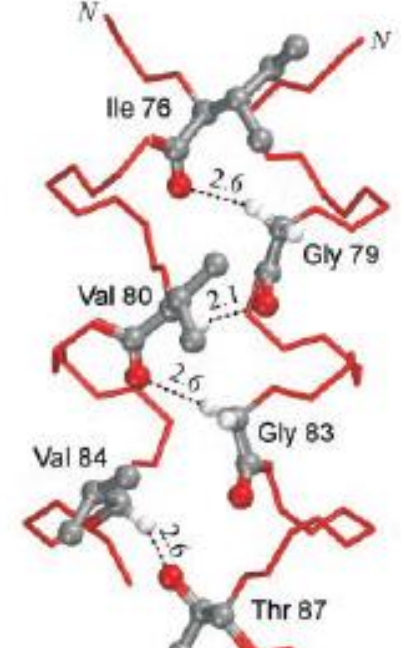
1fx8
helix 1 - helix 4



1fx8
helix 5 - helix 8



1eul
helix 5 - helix 7



1afo

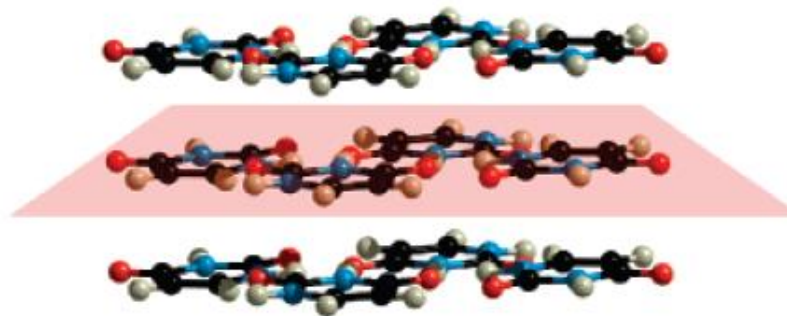
Crystal structure of uracil

J. AM. CHEM. SOC. 2008, 130, 945–954

N-H...O

C-H...O

a



b

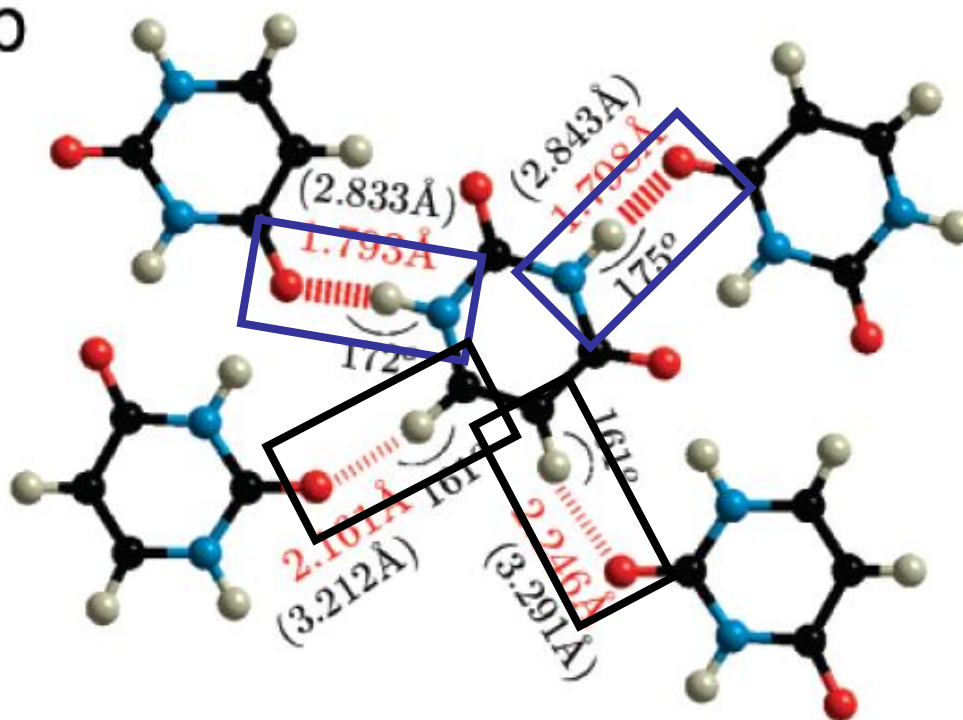
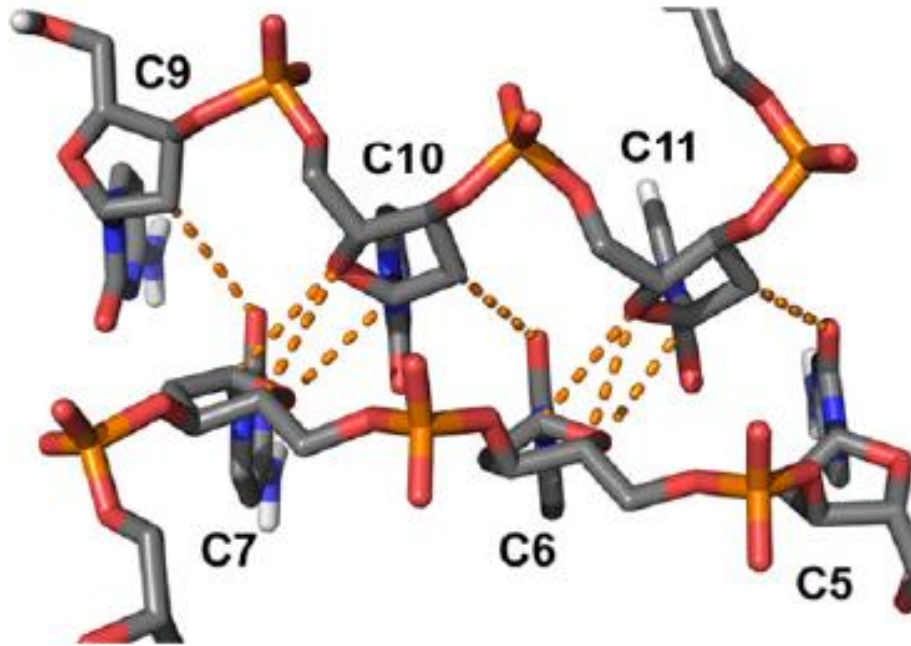


Figure 1. Crystal structure adopted by uracil. (a) Planar arrangement. (b) Conventional N–H...O and weak C–H...O hydrogen bonding within a plane. Color coding: C black, O red, N blue, H gray. The XHY angle, the H...X distance (in red), and the XY distance (in brackets) are indicated.

Crystal structure of intercalated four-stranded d(C₃T) at 1.4 Å resolution

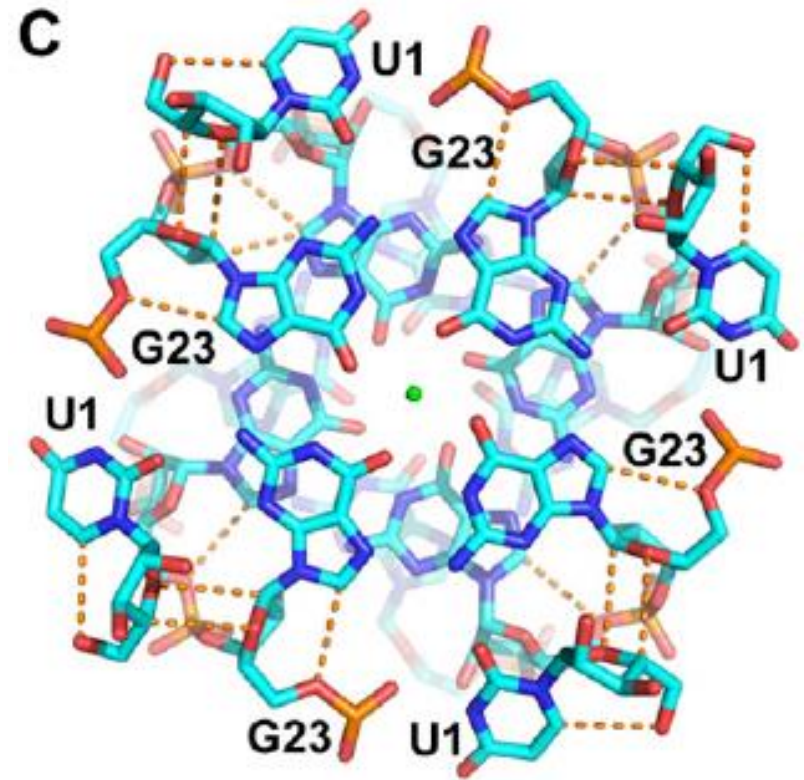
A. Rich et al., PNAS 91, 1994, 11636



Extensive CHO hydrogen bonding in the DNA i-motif

X-ray analysis of an RNA tetraplex (UGGGGU)₄ at 0.6 Å resolution

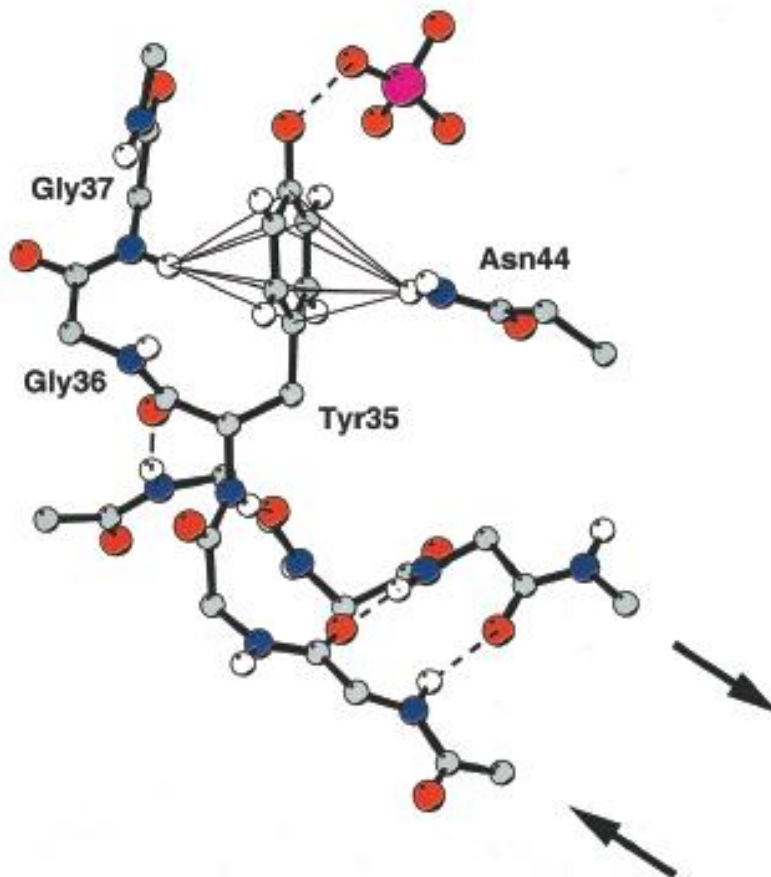
M. Sundaralingam et al., PNAS 98, 2001, 13665



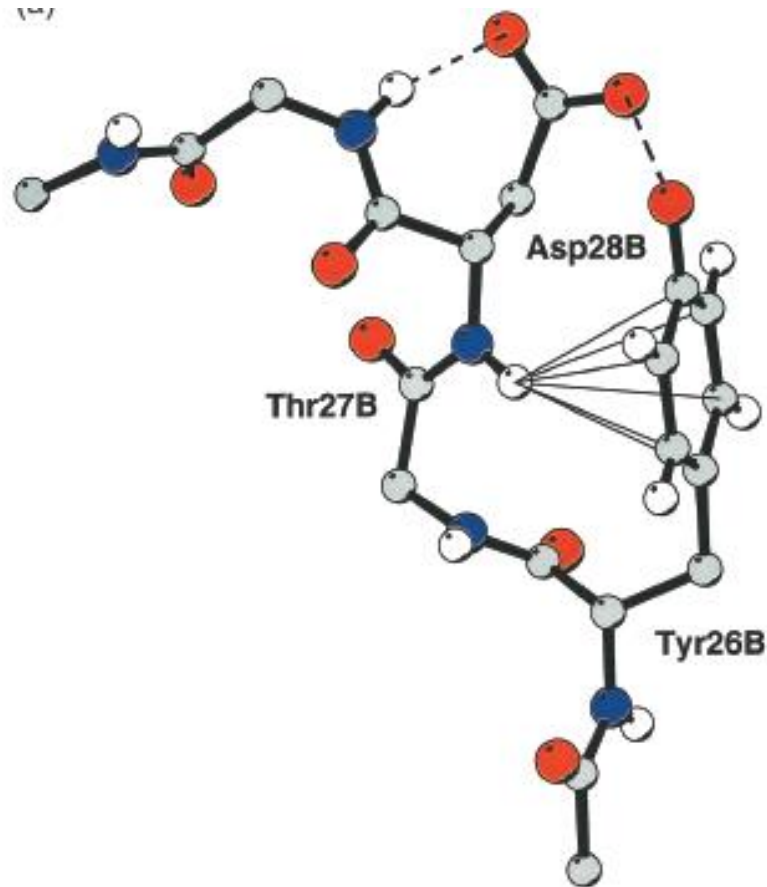
in an RNA G4 tetraplex

X-H... π hydrogen bonds

N-H... π hydrogen bonds in protein crystal structures



Bovine pancreatic trypsin inhibitor
Pdb code 5pti



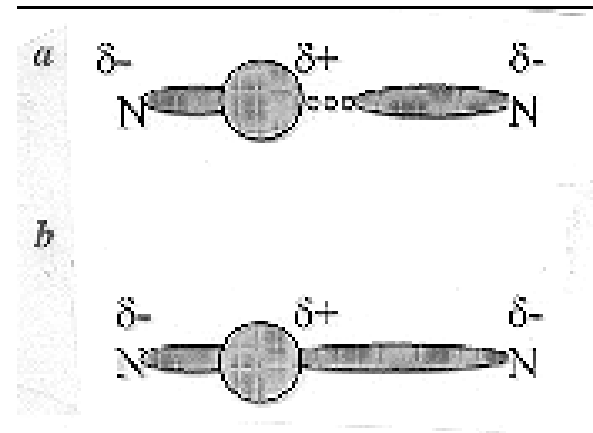
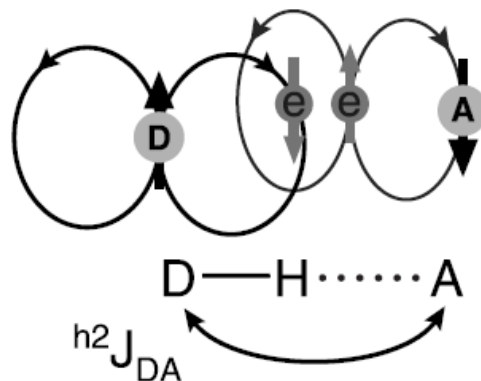
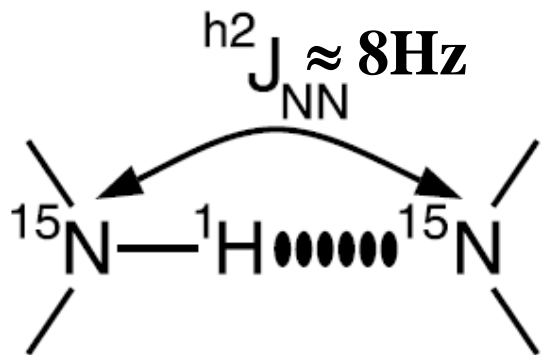
B28Asp insulin
Pdb code 1zeg

International Union of Pure and Applied Chemistry (IUPAC) Compendium of Chemical Terminology (1997):

“. . . a form of association between an electronegative atom and a hydrogen atom attached to a second, relatively electronegative atom. It is best considered as an electrostatic interaction, heightened by the small size of hydrogen, which permits proximity of the interacting dipoles or charges.“

However,....

Dingley and Grzesiek observe J coupling between two ^{15}N nuclei ($^2J_{\text{NN}}$) connected through an H bond, $\text{N}-\text{H}\cdots\text{N}$, in nucleic acid–base pairs
 → Evidence for orbital overlap and thus support for covalent component of H-bonding
J. Am. Chem. Soc., 1998, **120**, 8293.

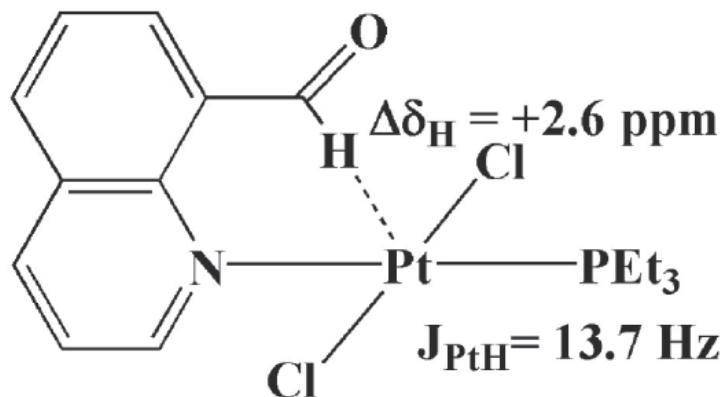


Quantum-Chemical Characterization of Nuclear Spin–Spin Couplings Across Hydrogen Bonds

C. Scheurer and R. Brüschweiler* *J. Am. Chem. Soc.* **1999**, *121*, 8661

In conclusion, we have shown that the recently detected trans-hydrogen nuclear spin–spin couplings in proteins and nucleic-acid base pairs can be explained by quantum chemical calculations indicating that they have a predominantly scalar J coupling character.

Note: ${}^2J_{\text{PtH}}$ across Pt...H hydrogen bonds were reported many years before, but the work of Dingley & Grzesiek is widely quoted as the 1st NMR evidence for H-bond covalency.

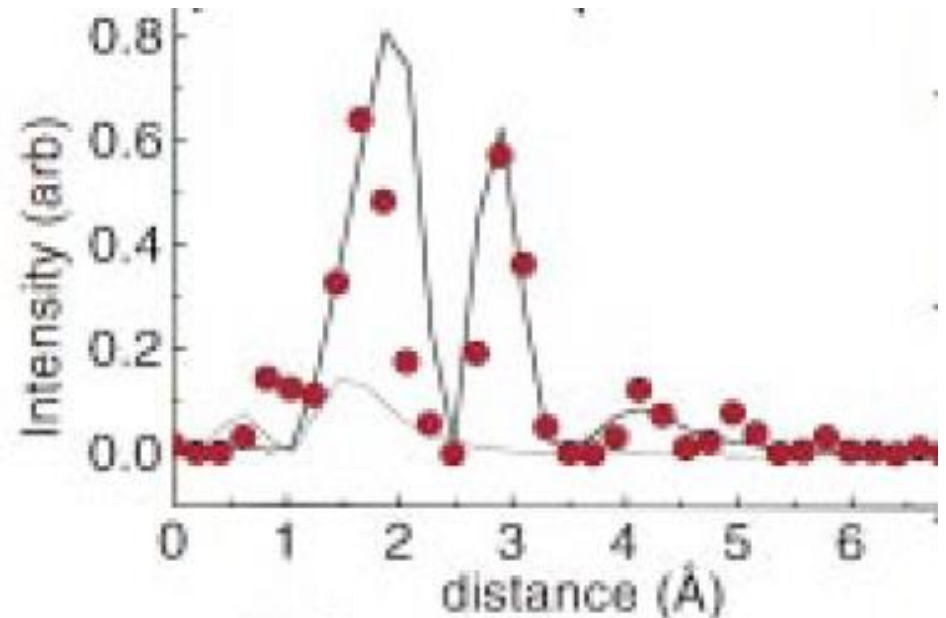
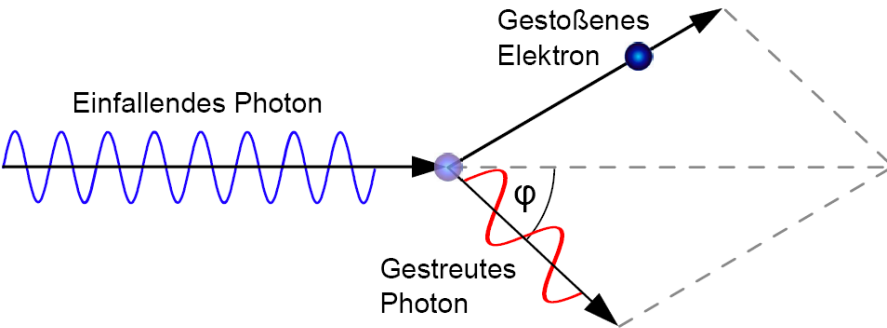


Albinati A, Pregosin PS et al. *Inorg Chem* **26**:503 (1987)

Covalency of the Hydrogen Bond in Ice: A Direct X-Ray Measurement

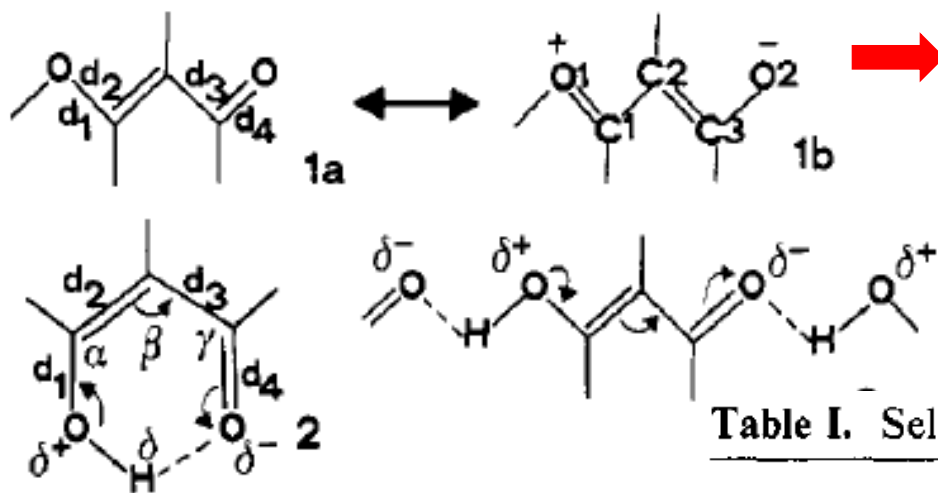
E. D. Isaacs, A. Shukla, P. M. Platzman, D. R. Hamann, B. Barbiellini, and C. A. Tulk,
Phys. Rev. Lett. **82**, 600 (1999)

Periodic intensity variations in the measured Compton profile anisotropies of ordinary ice *Ih* correspond to distances of 1.72 and 2.85 Å, which are close to the hydrogen bond length and the nearest O-O distance, respectively. We interpret this as direct evidence for the substantial covalent nature of the hydrogen bond. Very good quantitative agreement between the data and a fully quantum mechanical bonding model, and the disagreement with a purely electrostatic (classical) bonding model support this interpretation.



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



O-H...O H-bond has a covalent component!

25 structures studied by X-ray or neutron diffraction

Table I. Selected Geomtries for the *acacH* Fragment^a

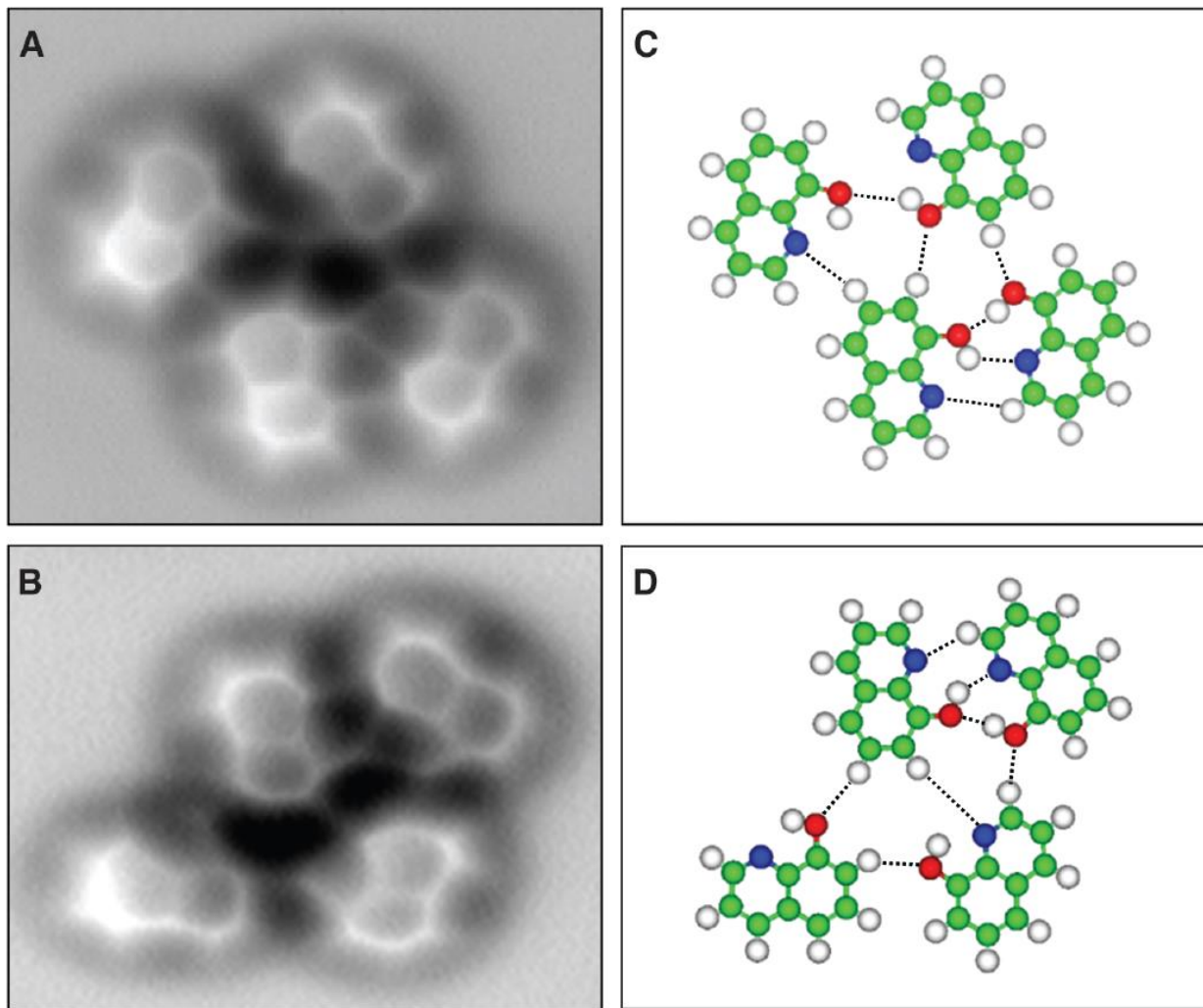
	d_1	d_2	d_3	d_4
standard	1.37	1.33	1.48	1.20
unperturbed	1.353 (4)	1.344 (3)	1.454 (5)	1.225 (3)
extreme perturbations				
intermolecular HB (3)	1.316 (2)	1.372 (2)	1.431 (2)	1.238 (2)
intramolecular HB (2)	1.281 (4)	1.398 (4)	1.410 (4)	1.279 (4)

Effect of O-H...O H-bond formation:
d1 shortens
d2 lengthens
d3 shortens
d4 lengthens

ALL VERIFIED!

Real-Space Identification of Intermolecular Bonding with Atomic Force Microscopy

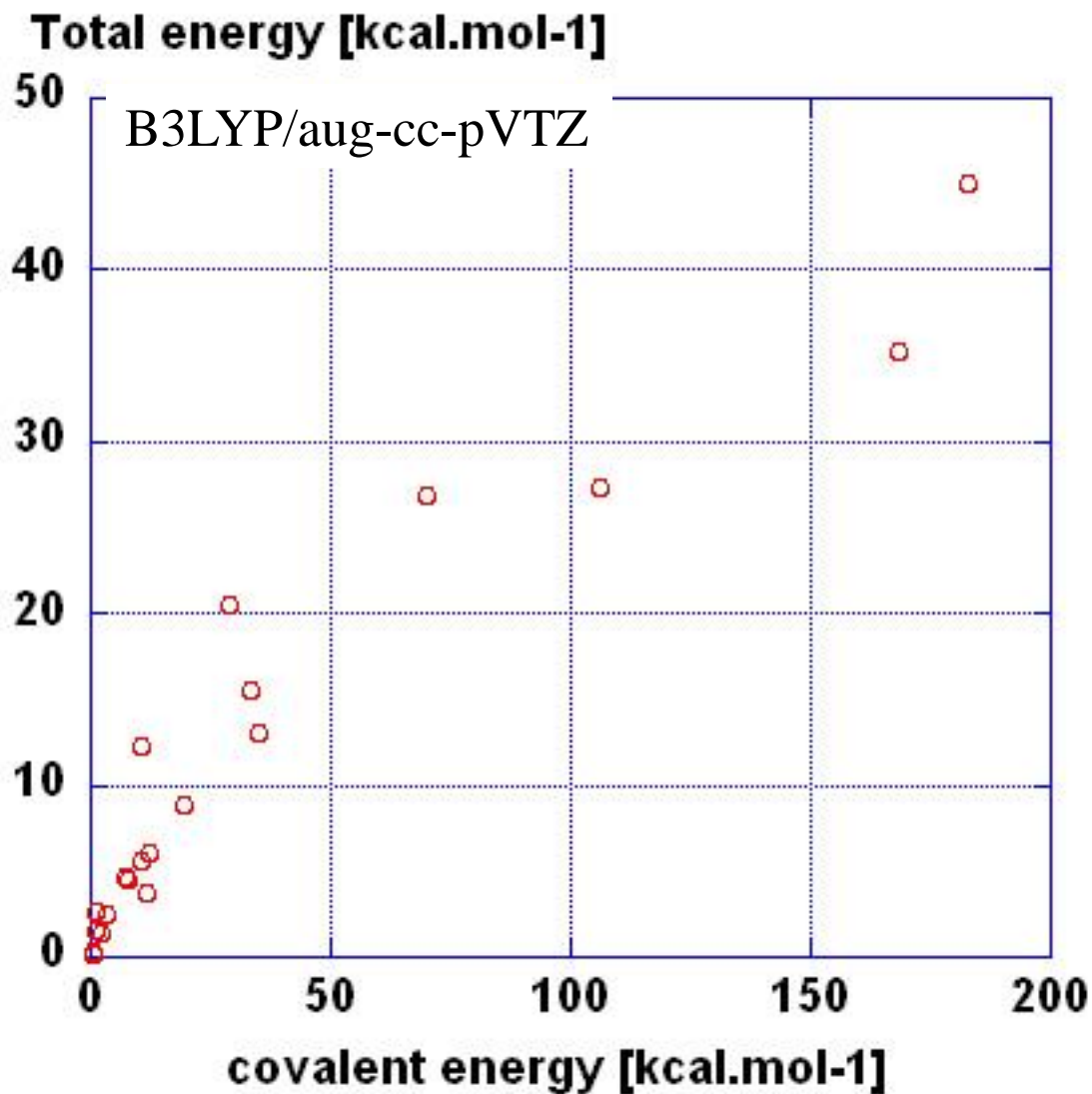
Jun Zhang, Pengcheng Chen, Bingkai Yuan, Wei Ji, Zhihai Cheng, Xiaohui Qiu, Science 342, 611 (2013)



**Hydroxychinolin
na krystalech mědi**

Fig. 2. AFM measurements of 8-hq assembled clusters on Cu(111). (A and B) Constant-height frequency shift images of typical molecule-assembled clusters and their corresponding structure models (C and D). Imaging parameters: $V = 0$ V, $A = 100$ pm, $\Delta z = +10$ pm. Image size: (A) 2.3 by 2.0 nm; (B) 2.5 by 1.8 nm. The dashed lines in (C) and (D) indicate likely H bonds between 8-hq molecules. Green, carbon; blue, nitrogen; red, oxygen; white, hydrogen.

**Korelace mezi celkovou energií H-můstků s jejich kovalentní složkou
⇒ Kovalentní složka je charakteristická vlastnost všech H-můstků**



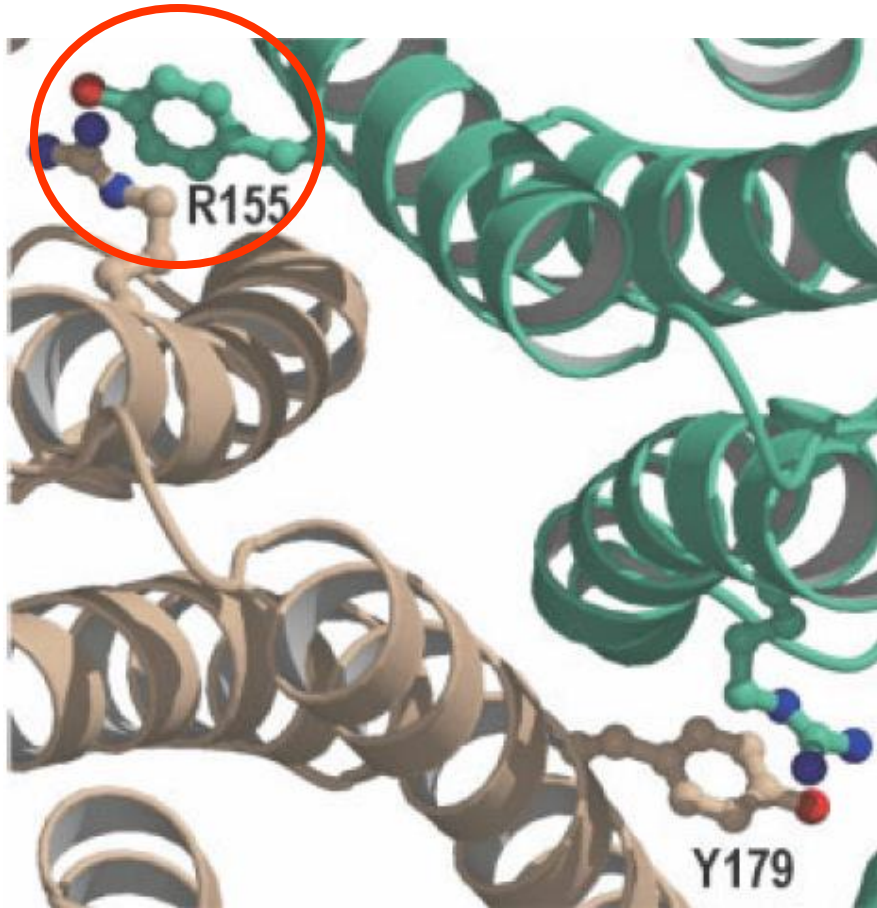
Weinhold & Klein, Mol. Phys. 110: 565 (2012)

X-H---A

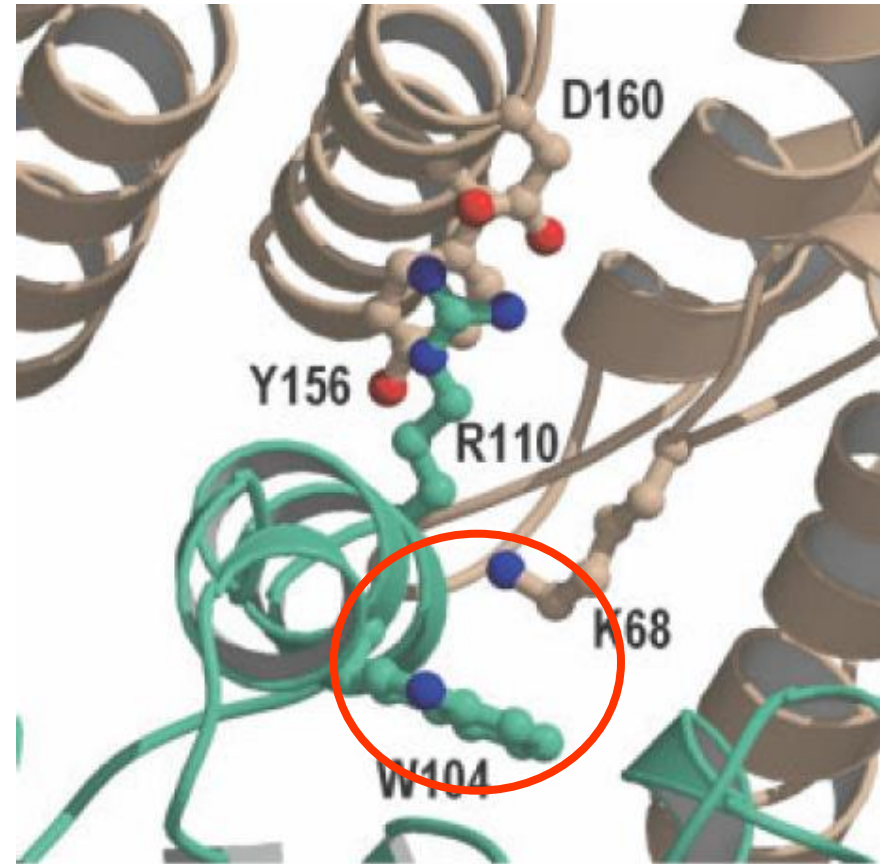
akceptor A má vždy volný elektronový pár
atom X je většinou silně elektronegativní

- zvláštní interakce
- důsledek struktury vodíkového atomu:
neobsazuje p-orbitály, nemůže nést volný (nevazebný) elektronový pár, může se jiným atomům více přiblížit
- Má několik složek:
 - kovalentní spojenou s přenosem náboje z volného el. páru akceptoru do antivazebného orbitálu donoru X-H
 - elektrostatickou, která u silných H-můstků převažuje
 - indukční (dipól X-H polarizuje A)
 - disperzní (všudypřítomná)
 - proti těmto složkám působí překryvová repulze

Cation-p interactions in protein-protein interfaces



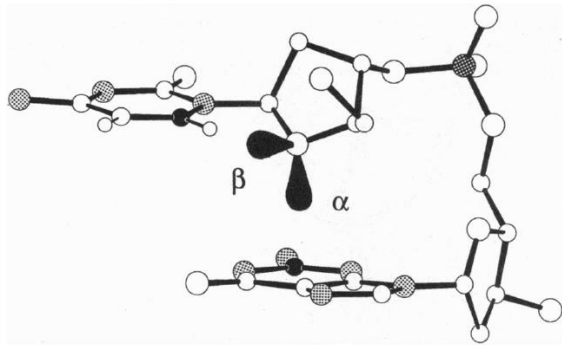
isoprenyl diphosphate synthase (1uby)



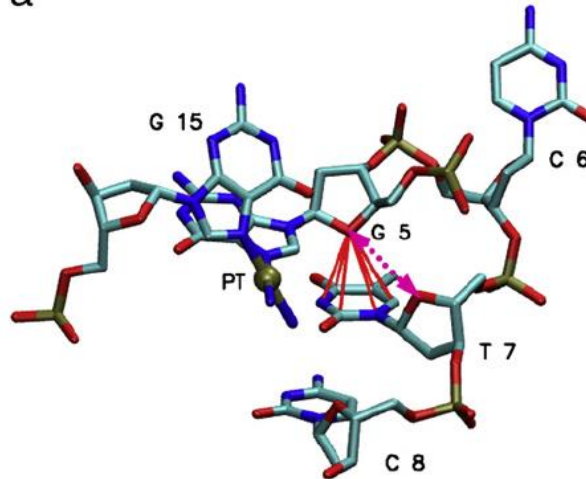
Ran-importin beta (1ibr)
(Ran is a GTPase that regulates diverse cellular processes, including nuclear transport and mitotic spindle assembly. Importin- β Is a GDP-to-GTP Exchange Factor of Ran.)

Experimental observations of « lone-pair- π interactions »

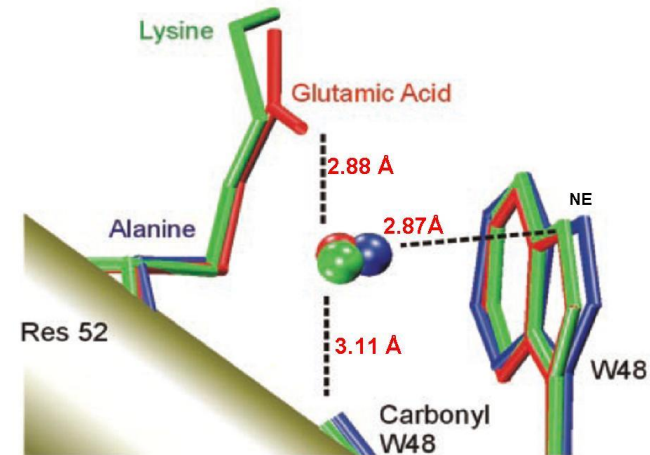
X-ray structures (0.9-1.0 Å) of Z-DNA duplexes, Rich et al., reanalyzed by Egli & Gessner (*Proc. Nat. Acad. Sci. USA* **1995**, 92, 180)



Kozelka et al. (*J. Inorg. Biochem.* **2012**, 108, 69): Re-analysis of the X-ray structure (1.63 Å) of a cisplatin-DNA interstrand crosslink
 Coste et al. (*Nucleic Acids Res.* **1999**, 27, 1837).



X-ray structures (1.9-2.2 Å) of Engrailed homeodomain, Luisi et al., 1998-2003



Lp- π interaction
 responsible for stability of
 the left-handed helix

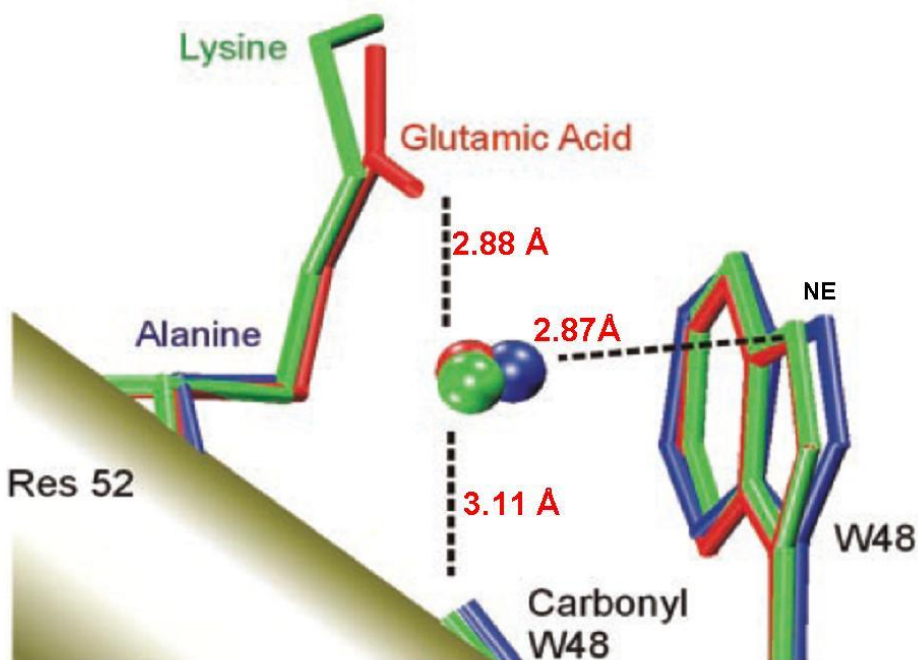
Lp- π interaction
 overcompensates O \cdots O
 repulsion!

Lp- π interaction
 responsible for
 fluorescence quenching
 of trp

Unconventional Interactions Between Water and Heterocyclic Nitrogens in Protein Structures

B. F. Luisi et al., *Proteins: Structure, Function, and Bioinformatics* 57:1–8 (2004)

Charge transfer involved?

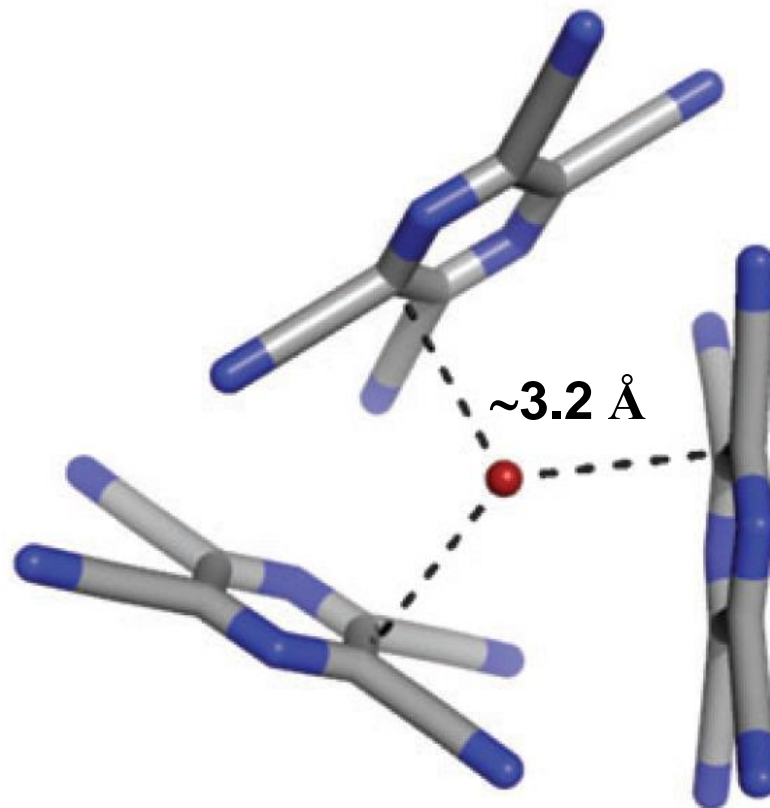


Engrailed homeodomain, **WT**, **K52A**, **K52E**
pdb codes **1ENH**, **1P7I**, **1P7J**)

Charge-transfer complexes between halides and π -receptors observed in solution and solid state

J. K. Kochi et al., *Angew. Chem. Int. Ed.* 2004, 43, 4650, **CSD** code **LAGYIC**

Charge transfer involved



TCP-Br⁻ interaction in solid state

Conclusion of the ab initio analyses

TCB interacts with Cl⁻, forming a strong charge-transfer complex ($\Delta E_{\text{int}} \approx -30$ kcal/mol). The large charge-transfer stabilization energy arises from two properties of this interacting couple:

- the small energy gap between electron donor and acceptor orbitals**
- the large overlap between them**

In contrast, the interacting couple water-indole shows a large gap between the water lone-pair and the lowest p* orbital of indole, in addition, their overlap is small. As a result, the charge-transfer stabilization in this couple is 1-2 orders of magnitude smaller.

In addition to the large CT component, the TCB - Cl⁻ couple profits from a larger electrostatic component, arising from the interaction between the net charge of chloride with the electropositive region around the C-H bonds of TCB.

Take-home message

Structures of nucleic acids and proteins are stabilized by a number of weak interactions. These include:

- Hydrogen bonds**
- Cation- π interactions**
- Lone-pair- π interactions**

Hydrogen bonds are not only electrostatic interactions between dipoles. They contain also a covalent component, which is present in all hydrogen bonds.

C-H...O and X-H... π hydrogen bonds (X = N, O, C) are important interactions stabilizing biopolymers.