The Role of The Hydrogen Bond in Molecular Crystals

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20th May, Muğla, Turkey

End of 146 B.C Macedonians of Philip II and Alexander the Great and their dynasty of Macedonian kings occupied by Romans Imperia

A.D. 395 division of of the Roman Empire, Macedonia came under Byzantine rule.
In VI century settled by the Slavs

14th Macedonia under the rule of the Ottoman Imperia during the 5 centuries

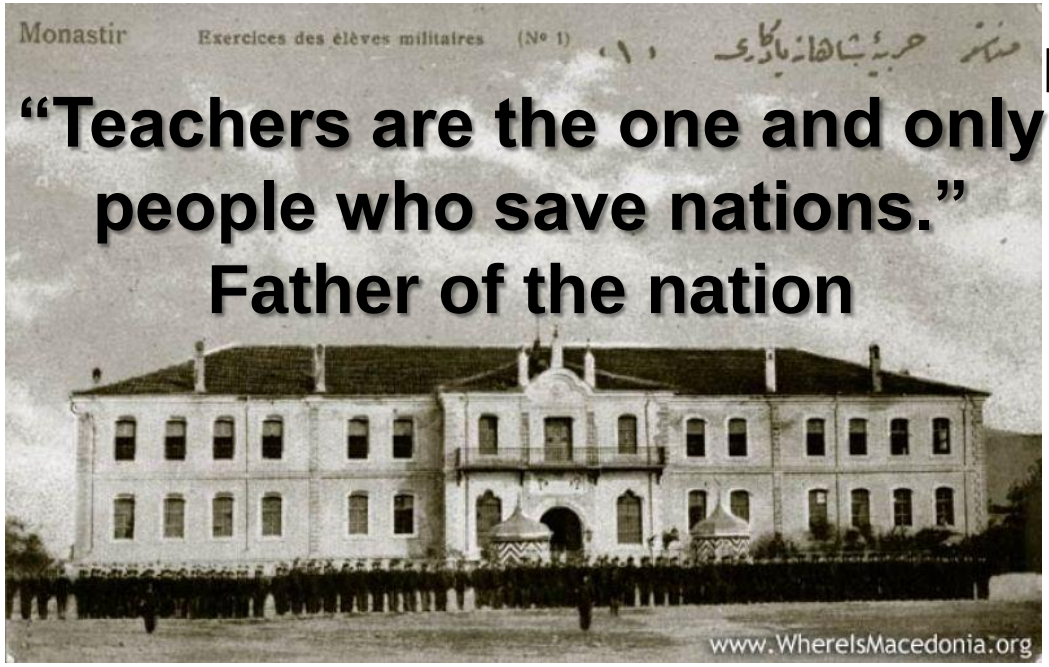
Raising national awareness for independency during the Balkan Wars, World War I and World War II

1944. Becoming independent Republic as a Part of Yugoslav federation

1990 Become Independent state after divorcing of Yugoslavia

Mustafa Kemal Atatürk – Memorial Museum in Bitola (Monastir)

Goce Delcev, Macedonian national hero for national identity



"I understand the world solely as a field for cultural competition among the peoples"

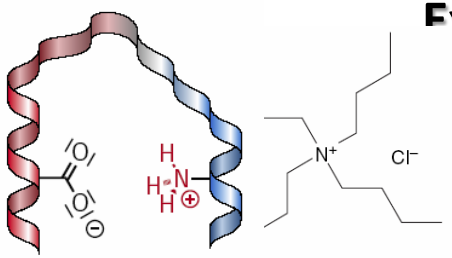
Goce Delcev University, in Stip, born place of Goce Delcev
Second biggest state university in Macedonia

The outlook of the lecture

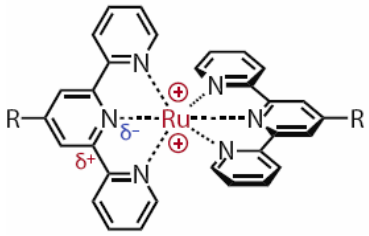
- **Wide spreading and diversity of noncovalent intermolecular interactions**
- **What molecular crystals are and how they are formed**
- **The role of Hydrogen bond (H-bond) in molecular crystals**
- **Introduction to the H-Bond (Historical path in discovery of H-Bond; H-Bond: Classical Definitions; The H-Bond Strength; The H-Bond Puzzle; Two Different Conceptions: The Brønsted and Lewis Acid-Base Theories**
- **The Aim of this Lecture: Comparable both PT and CT visions**
- **"The Brønsted-Based H-Bond Theory"** ***The Dual H-Bond Model***
- **"The Lewis-Based H-Bond Theory"** ***The H-Bond as a CT or EDA***
- **Case Study 1-5 for H-bonds in Molecular crystals of life Sci. relevance (Pharmaceuticals)**

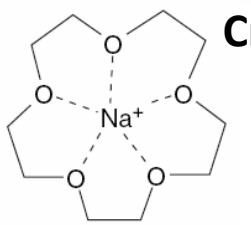
What is the nature of non-covalent interactions?

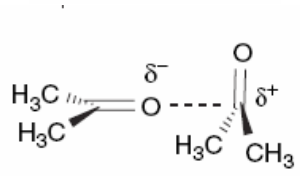
Interactions	Energy/Strength	Examples
Ion-Ion	Strong 200-300 KJ/mol	
Ion - Dipole	Moderate 50 – 200 KJ/mol	Crown ether
Dipole – Dipole	Week 5 - 50 KJ/mol	Specific orientation of polar solvent/acetone
Cation – π	relatively weak 5 - 5 KJ/mol	
π – π interactions	weak 5 - 50 KJ/mol	π – π In DNA

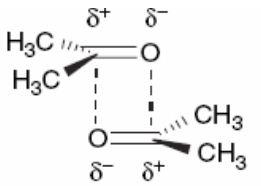


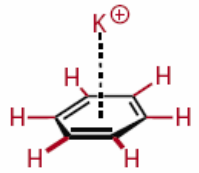
Organometal complex

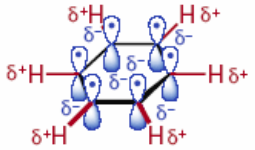


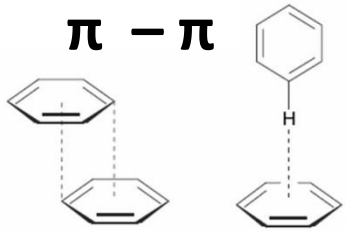


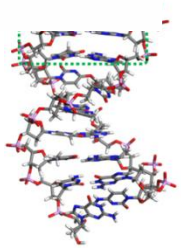


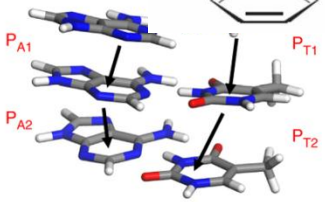






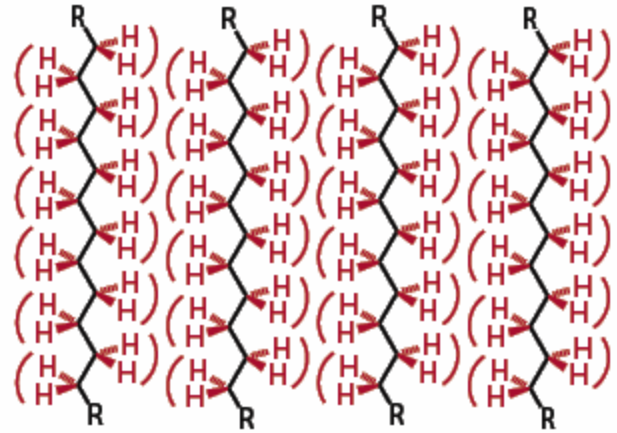




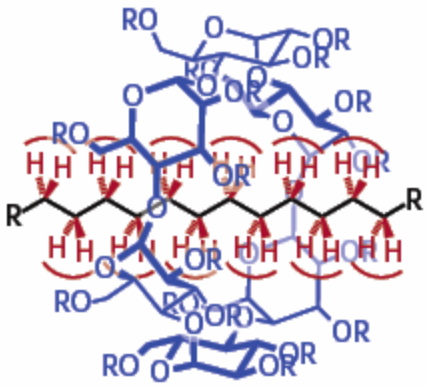


van der Waals interactions

week interactions



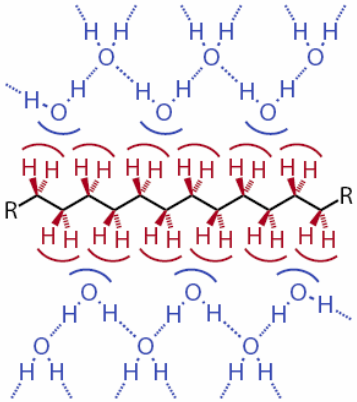
aliphatic chains
e.g., in lipid membranes



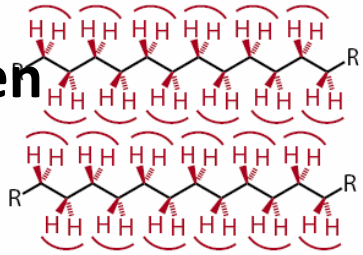
cyclodextrin
inclusion complexes

Hydrophobic effects-

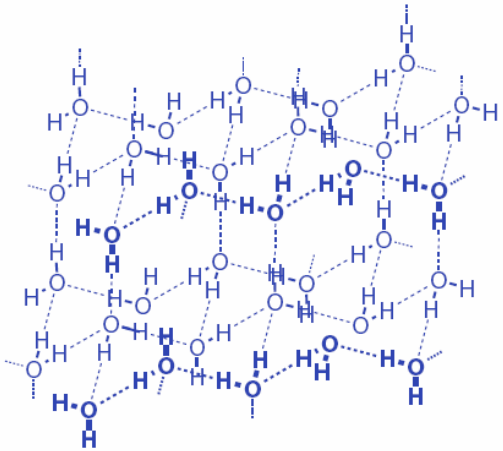
Enthalpy/ entropy driven

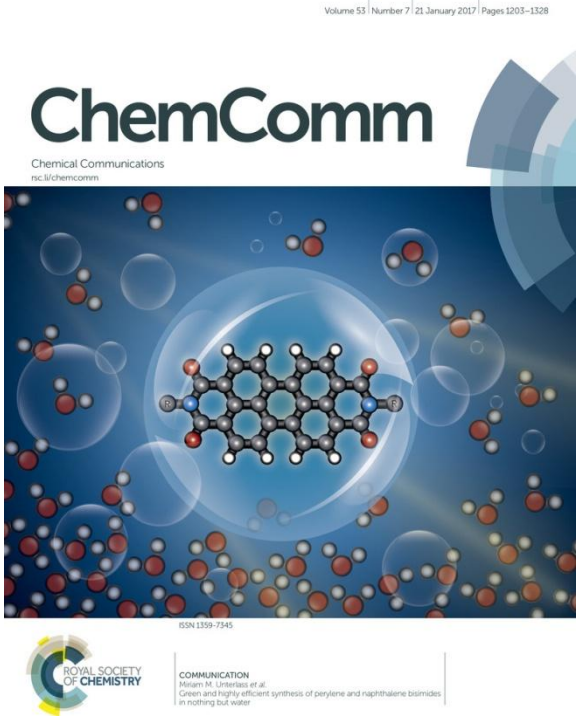


$\Delta G = \Delta H - T\Delta S$

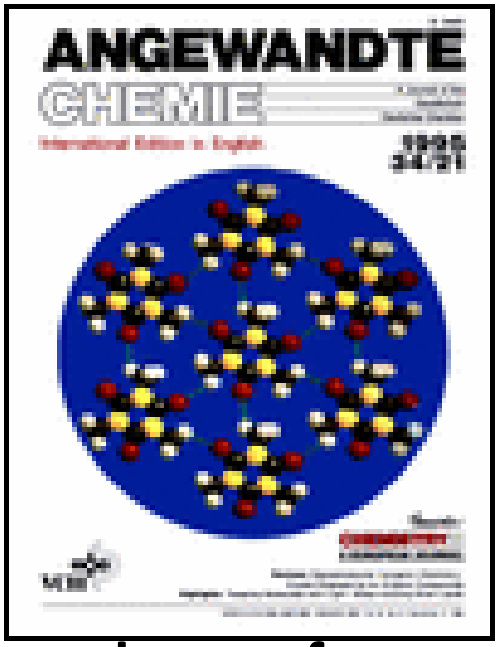


phase segregation, interface minimization

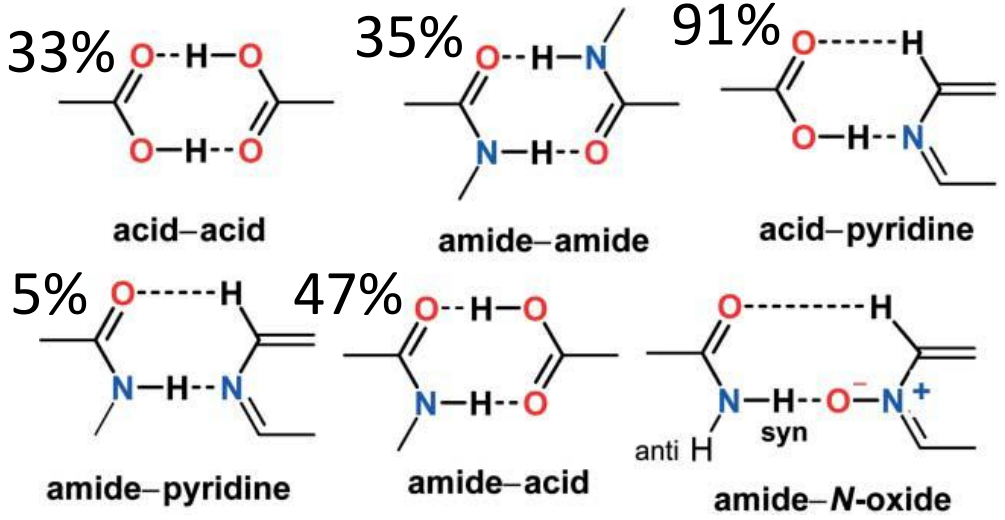




How do molecules interplay?

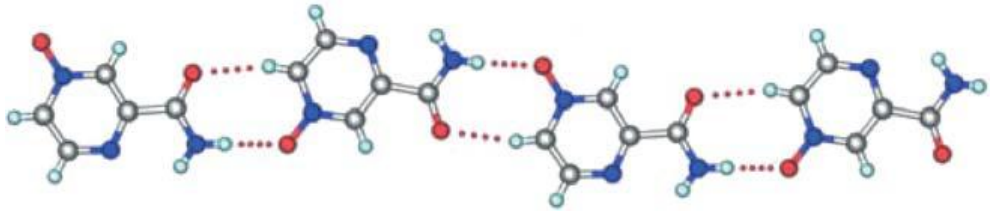


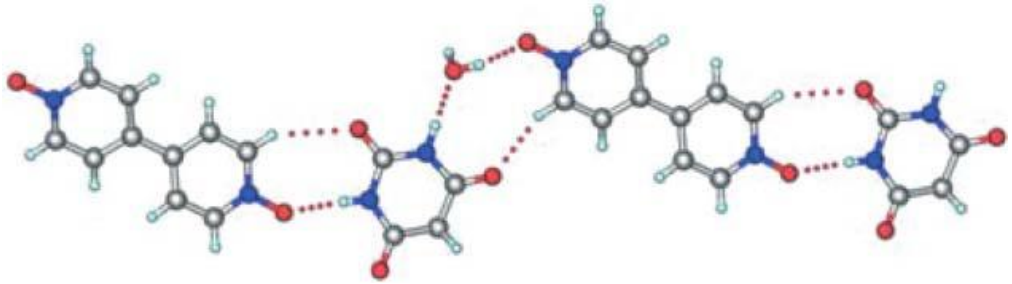
(Molecular dating)



Prevalence of occurrence of structural unites: homo- & hetero synthons

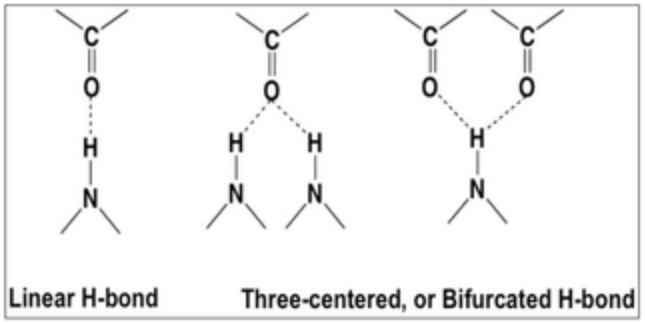
***Angew. Chem. Int*. Ed. (1995) Engl. 21, pp. 2328.**

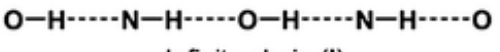




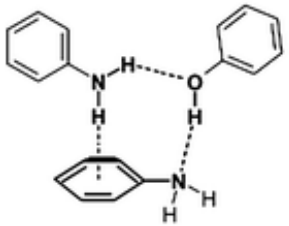
Chem. Commun., 2006, 1369–1371

Patterns (Molecular interactions)

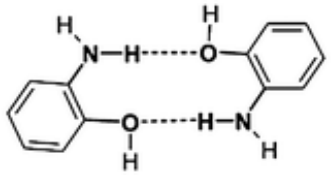




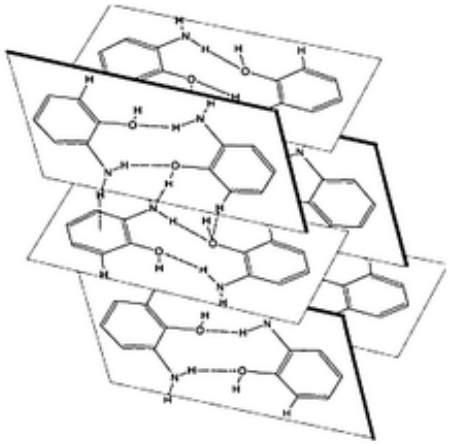
Infinite chain (I)



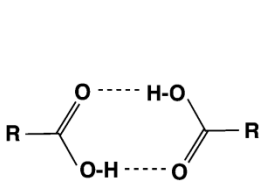
Trimer (II)

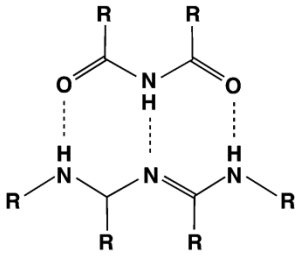


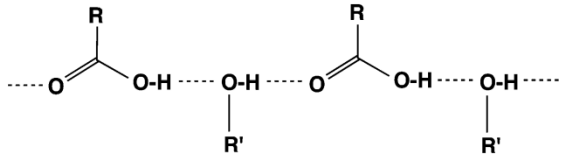
Dimer (III)

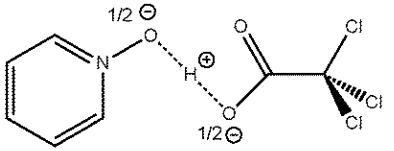


Dimer herringbone (IV)

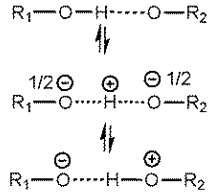




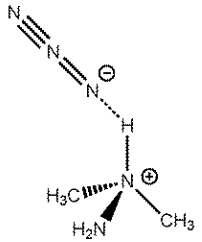




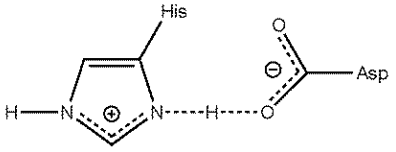
(a) Pyridine-N-oxide-trichloroacetic acid



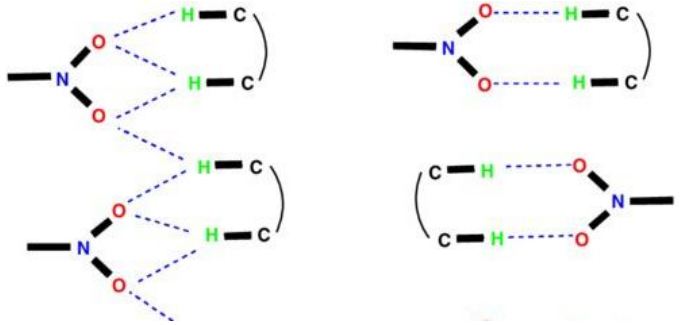
(b) neutral, shared and ionic forms of the H-bond



(c) 1,1-dimethylhydrazine-hydrazoic acid

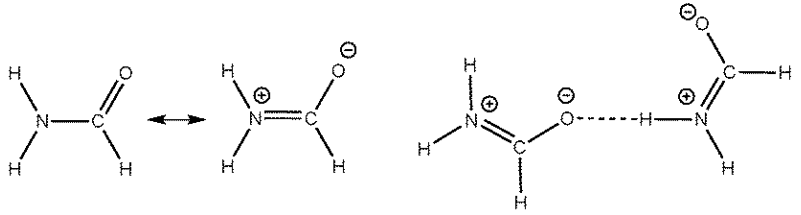


(d) low barrier H-bond in enzymic catalysis



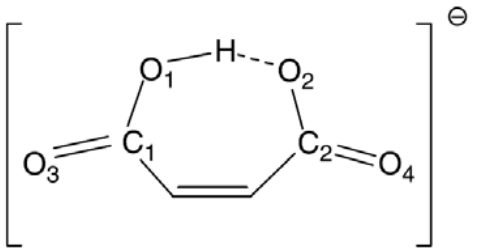
chelated C-H···O hydrogen bonding synthon-I forming catemer.

cyclic C-H···O hydrogen bonded dimer synthon-I

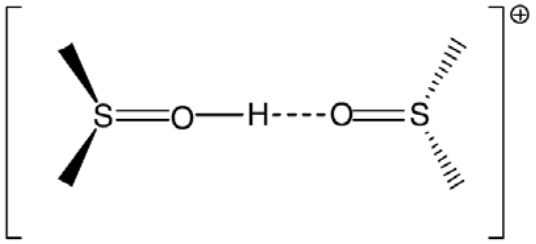


(e) resonance assisted H-bond

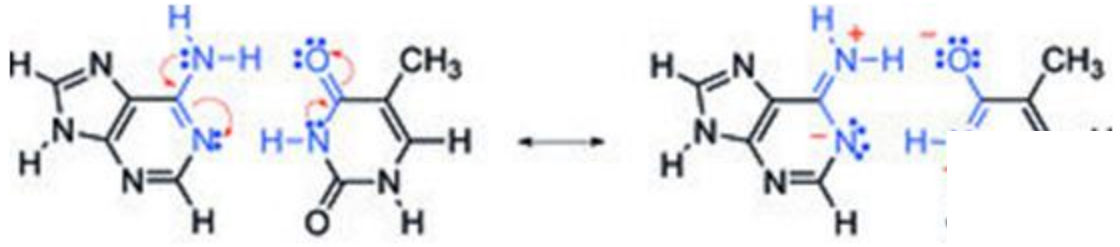
Negative charge assisted hydrogen bond [(–)



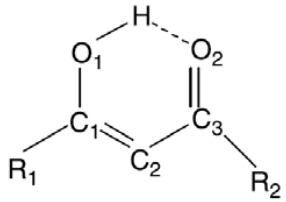
Positive charge assisted hydrogen bond [(+)

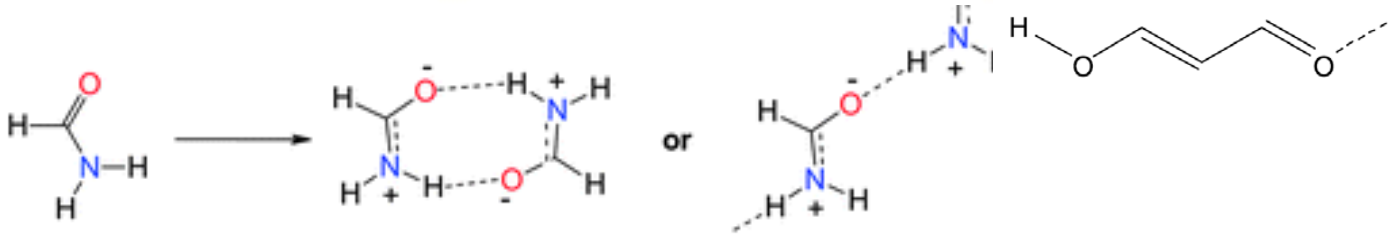


Resonance-assisted hydrogen bonding in adenine–thymine (AT)



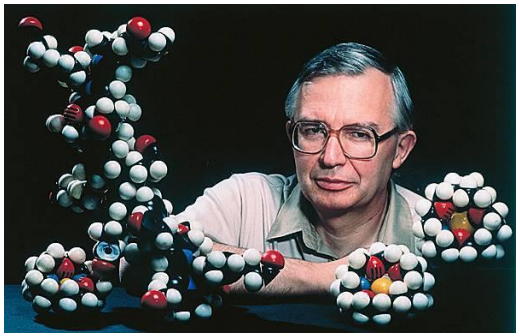
ChemistryOpen (2015) 4(3)





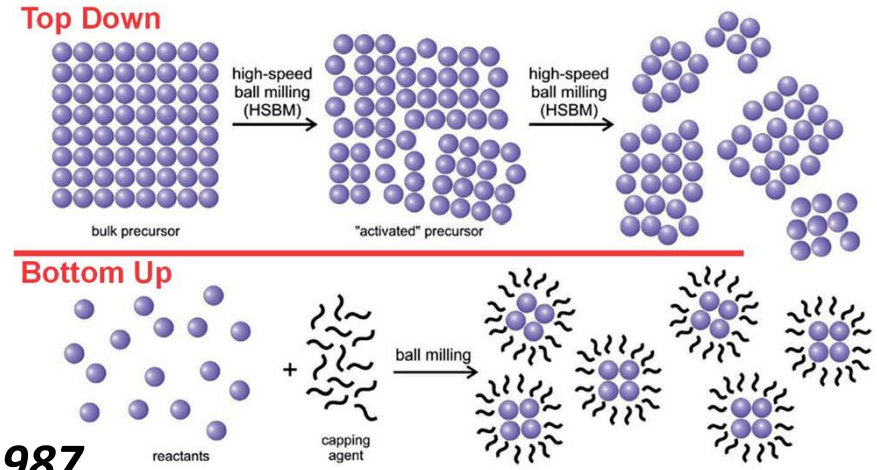
CrystEngComm, **2012,**14, 2571-2578

Chemistry beyond molecules (Supramolecular chemistry)

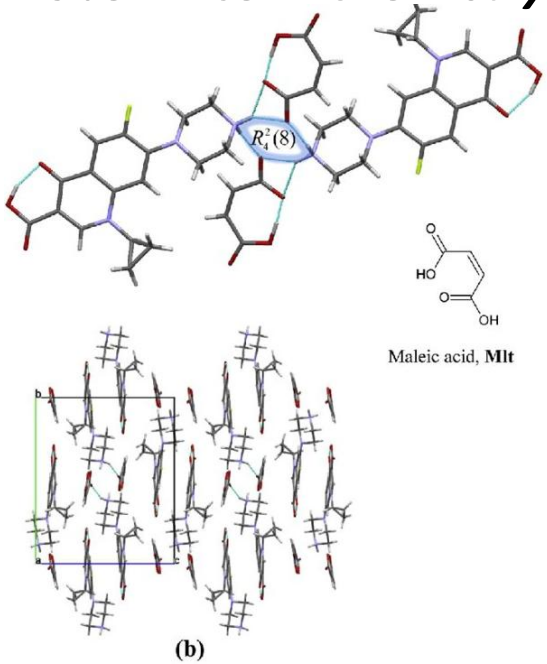


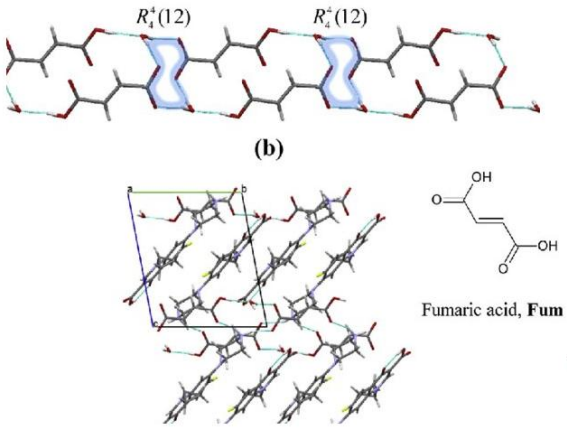
Jean-Marie Lehn,

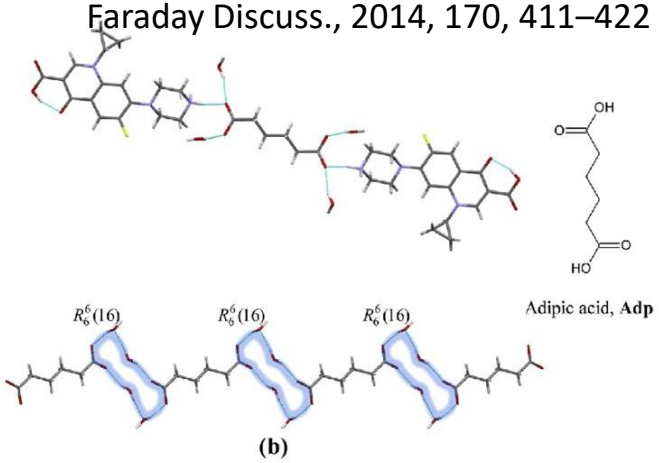
Nobel Price in Chemistry 1987

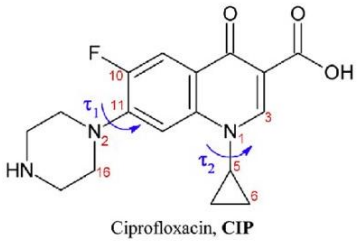


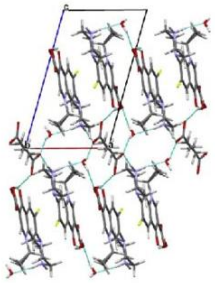
Faraday Discuss., 2014, 170, 411–422







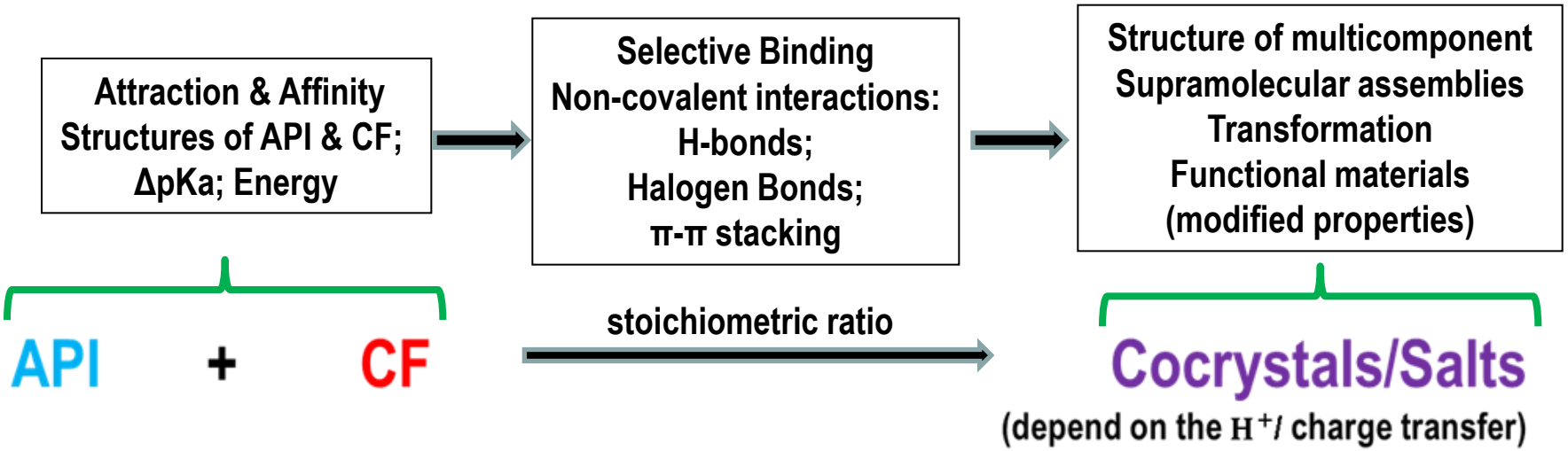




Eur. J. Pharm.Sci (2015) 77, 112–121

Driving forces for molecular cocrystal formation

"Molecular recognition is selective binding with a purpose"

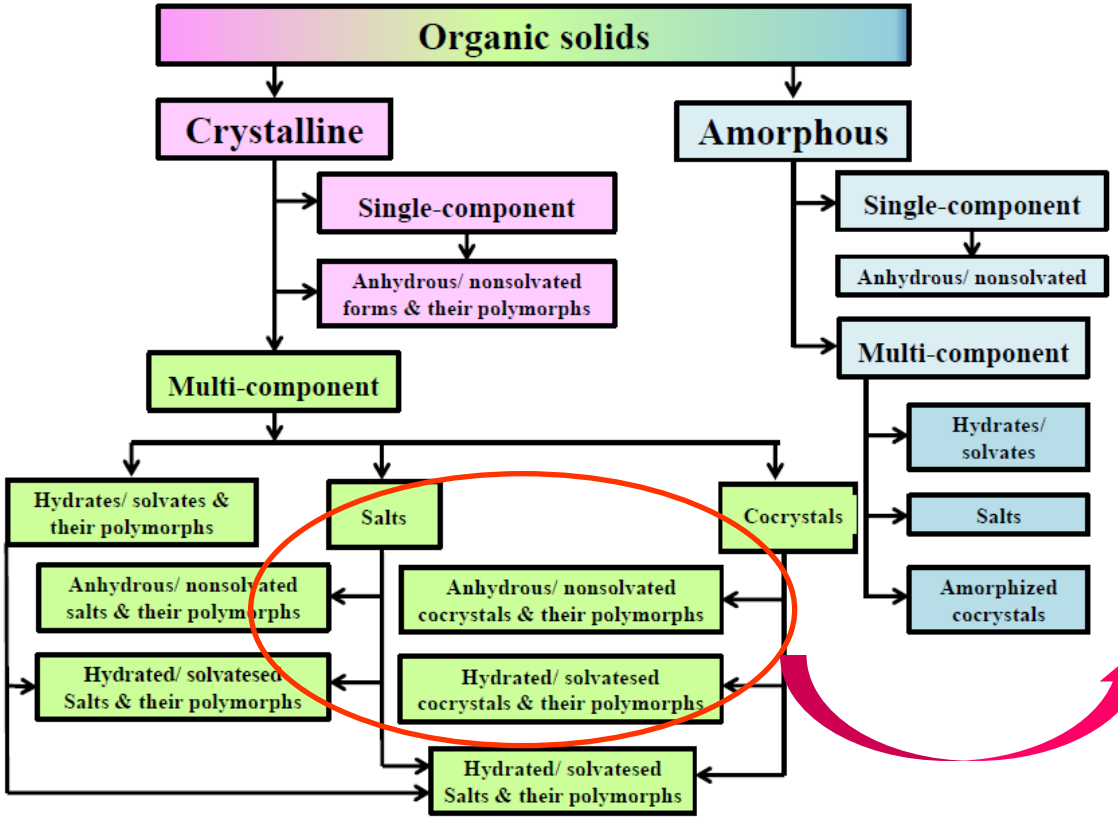


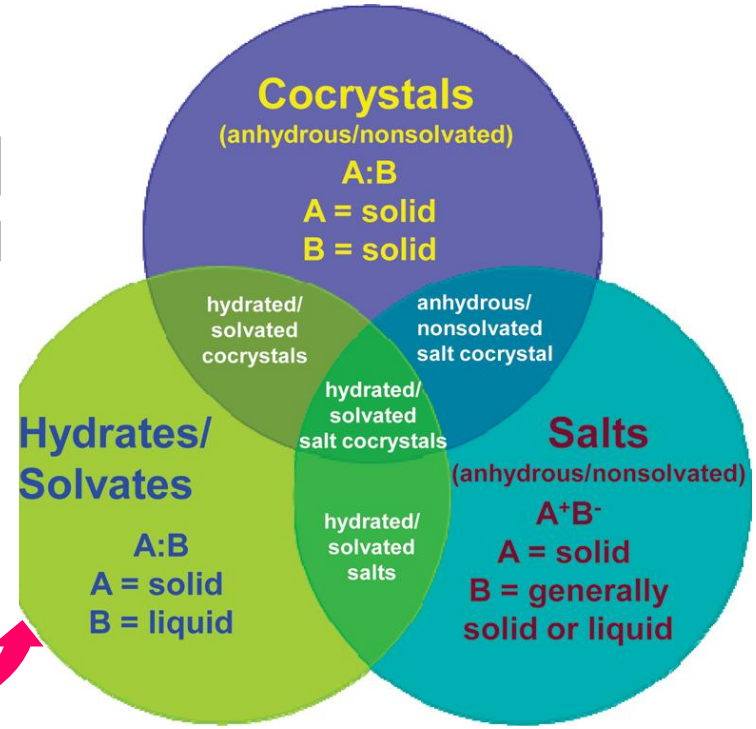
A – Active Pharmaceutical Ingredient (API):
neutral or polar ionizable;
solid or liquid

B – Coformers (CF)

J.-M. Lehn, *Pure Appl. Chem.* 1978, *50*, 871.

Where is the place of Molecular Cocrystals among the Solid Forms?



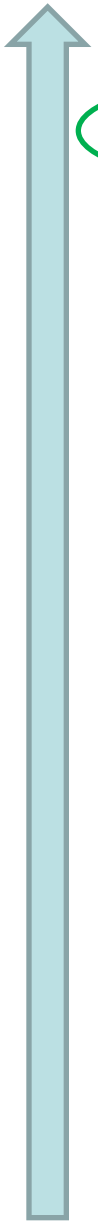


Multi-Component Solid Forms Inherently Overlap with One Another and in Addition They Can Exhibit Polymorphism

Cocrystals are solid crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio.

Aitipamula, S. *et al.* , Polymorphs, Salts, and Cocrystals: What's in a Name?, *Cryst. Growth Des.* 2012, *12*, 2147−2152

A Timeline for Progress in Defining Molecular Cocrystals



Ionic-Cocrystals; Zwitterionic Cocrystals, Chiral Cocrystals

2011-2013

Braga, D., *Cryst.Growth Des.*, 2011,
CrystEngComm, 2012, 14
Smith ,AJ Mol Pharm. 2013,
Tilborg, A., *CrystGrowth Des.*, 2013,
Chen, S., *CrystEngComm*, 2010,12,

Multi-component molecular crystals, assembled by any type or combination of intermolecular interactions

2008

Nangia, A., New J. Chem. 32

Multi-component molecular crystals, each component being an atom, ionic compound, or molecule

2007

Stahly, G. P., Cryst. Growth Des. 7
Bond, A. CrystEngComm .9
Childs, S. L. Cryst. Growth Des. 7

Neutral molecular constituents linked within crystalline lattice through H-bonds

2006

Jones, W.MRS Bull.,,
Zaworotko, M. J., J. Pharm. Sci. 95

Structurally homogeneous crystalline solids made by solid components at ambient temperature

2005

Aakeröy, C. B., (2005),
CrystEngComm7

Molecular complexes, Multi-component crystals

2003

Desiraju, G. R, CrystEngComm 5
Dunitz, J. D. CrystEngComm 5