Weak hydrogen bonds in crystal engineering

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What is crystal engineering?

The understanding of intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design of new solids with desired physical and chemical properties.

Crystal Engineering: The Design of Organic Solids,
Elsevier, Amsterdam, **1989**

Crystal engineering

The practical question

Given the molecular structure of an organic compound what is its crystal structure?

The problem

- Intermolecular interactions in organic molecular solids are weak
- A functional group forms interactions with other groups but its exact behaviour during crystallisation depends on the nature and positioning of all the other functional groups in the molecule
  - In supramolecular chemistry, hydrocarbon residues also count as functional groups.
- Therefore crystal structures are not related to molecular structures in simple ways
- The goal is to find families of crystal structures that are related to the molecular structures in simple, easily understandable ways, based on well known chemical principles

How would we expect molecular and crystal structures to be related?

Could we relate molecular and crystal structure through structural units of an intermediate size?

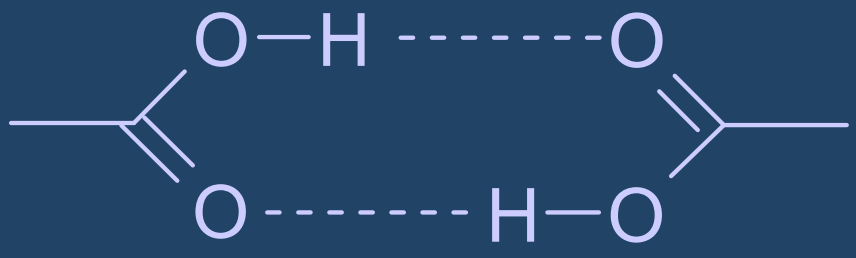
These units would need to be simple enough that they are understood in terms of the most favoured intermolecular interactions possible for the molecule, but complex enough that they represent core features of the crystal packing.

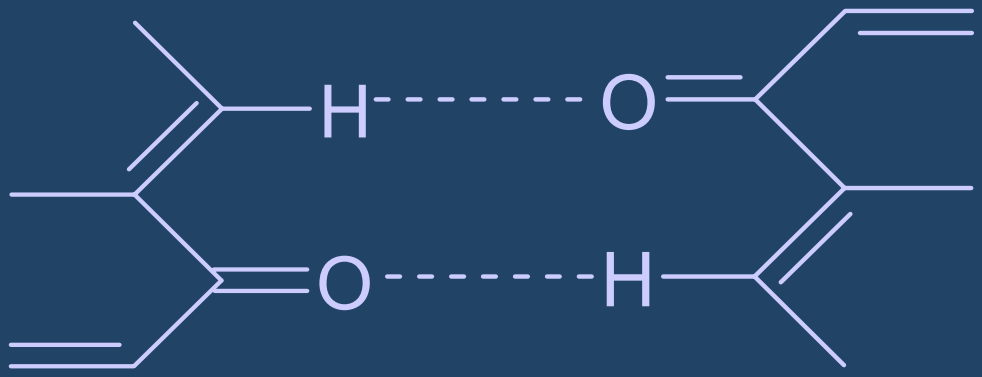
Such units would have kinetic significance

Supramolecular synthons are structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions

Desiraju (1995)

What synthons are possible?





C–H···N Hydrogen Bonds

Linear Motifs and Structural Insulation

···N≡C–H···N≡C–H···N≡C–H···

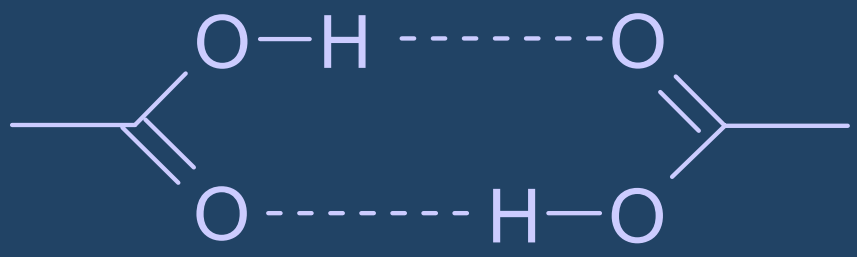
Dulmage and Lipscomb, Acta Cryst., 4, 330, **1951**

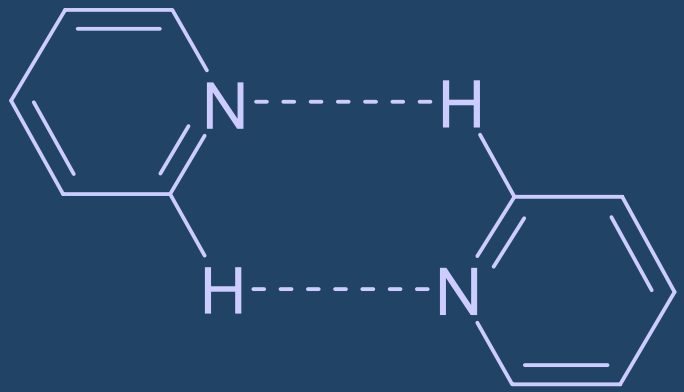
···N≡C–C≡C–H···N≡C–C≡C–H···N≡C–C≡C–H···

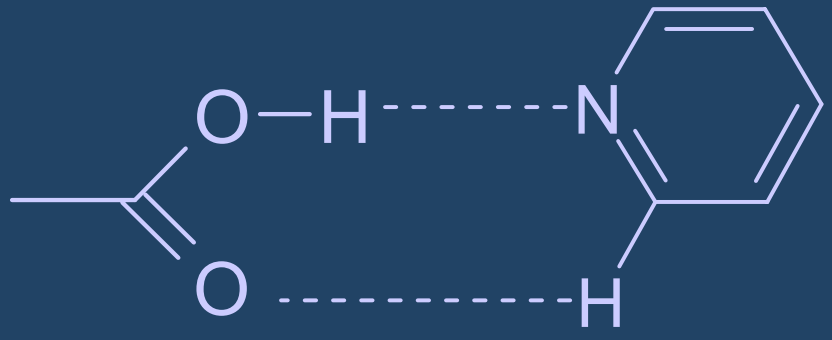
Shallcross and Carpenter, Acta Cryst, 11, 490, **1958**

Thaimattam et al, New. J. Chem., 1307, **1998**

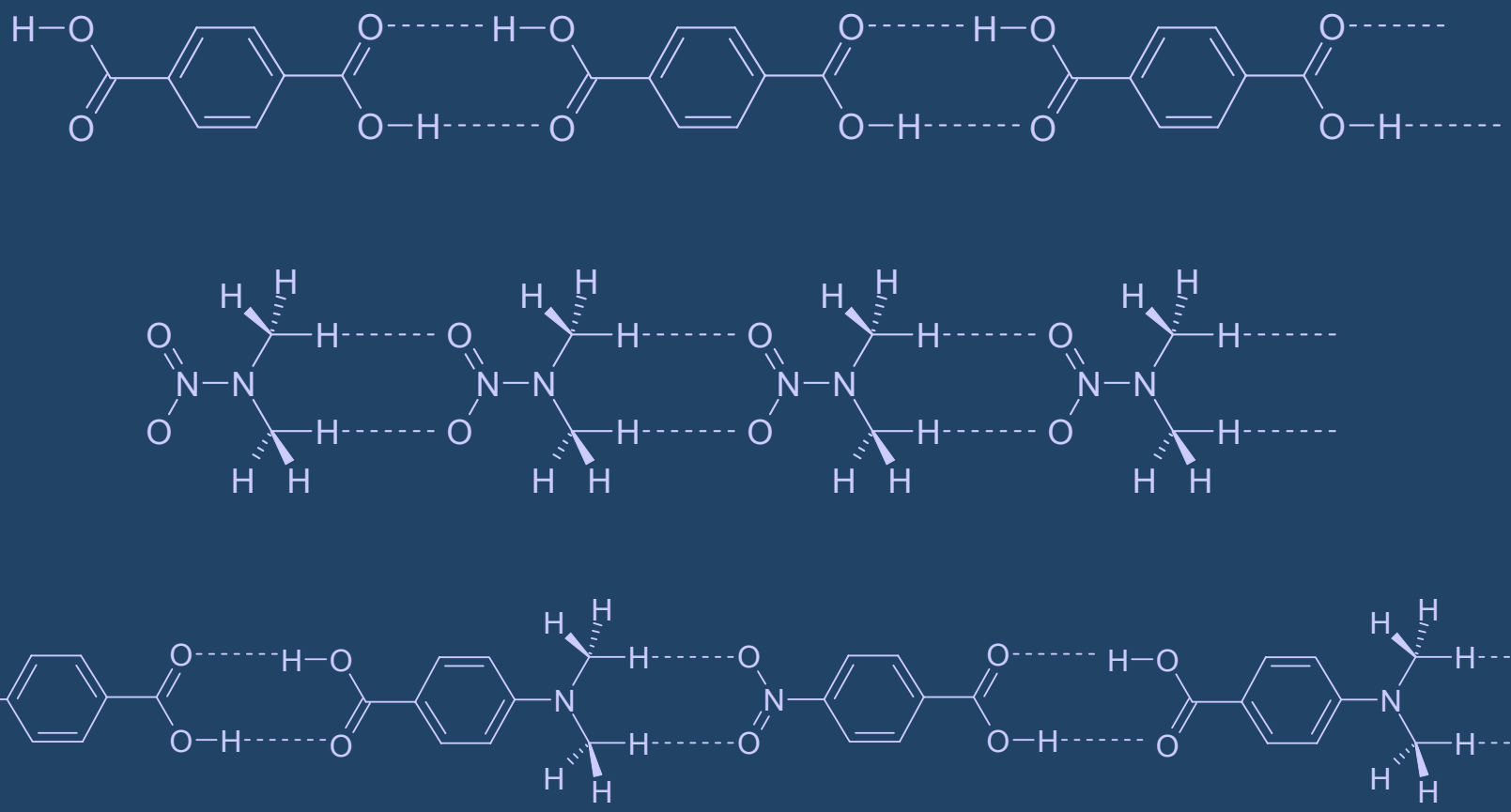
Synthon hierarchy





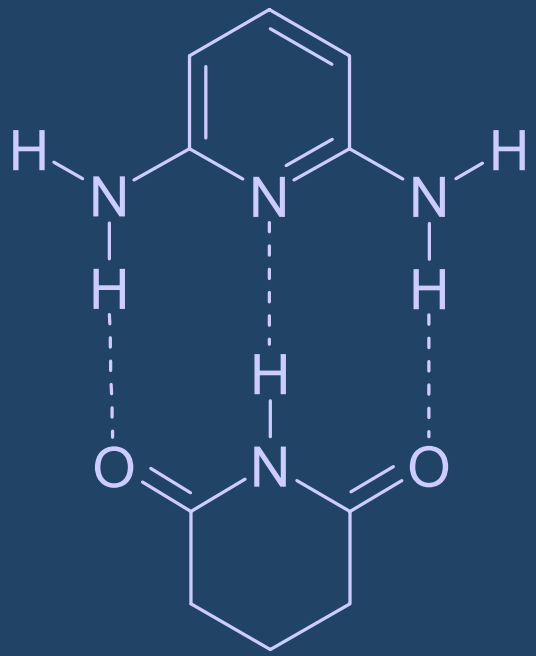


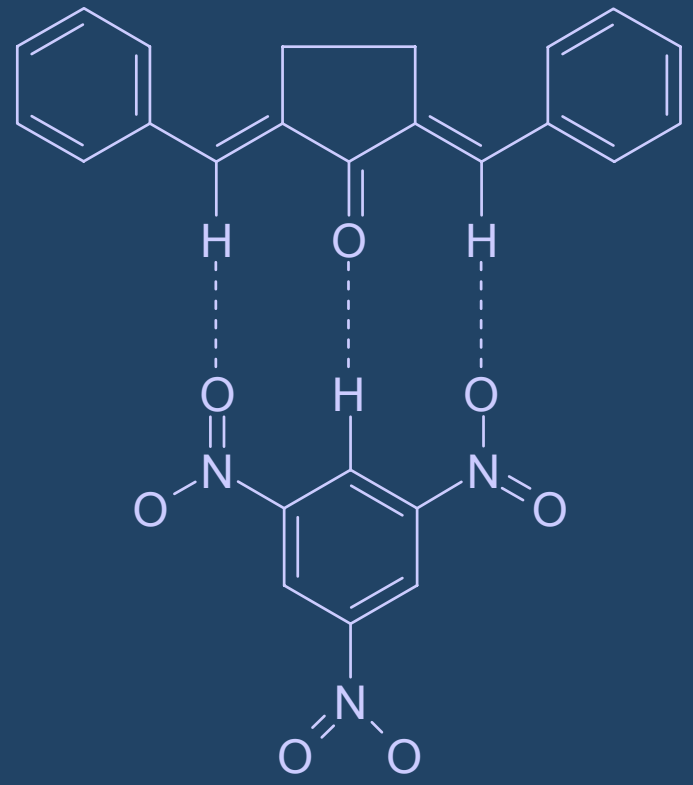
Structural insulation



C.V.K. Sharma et al., J. Chem. Soc., Chem. Commun.,832, **1992**

Multipoint recognition

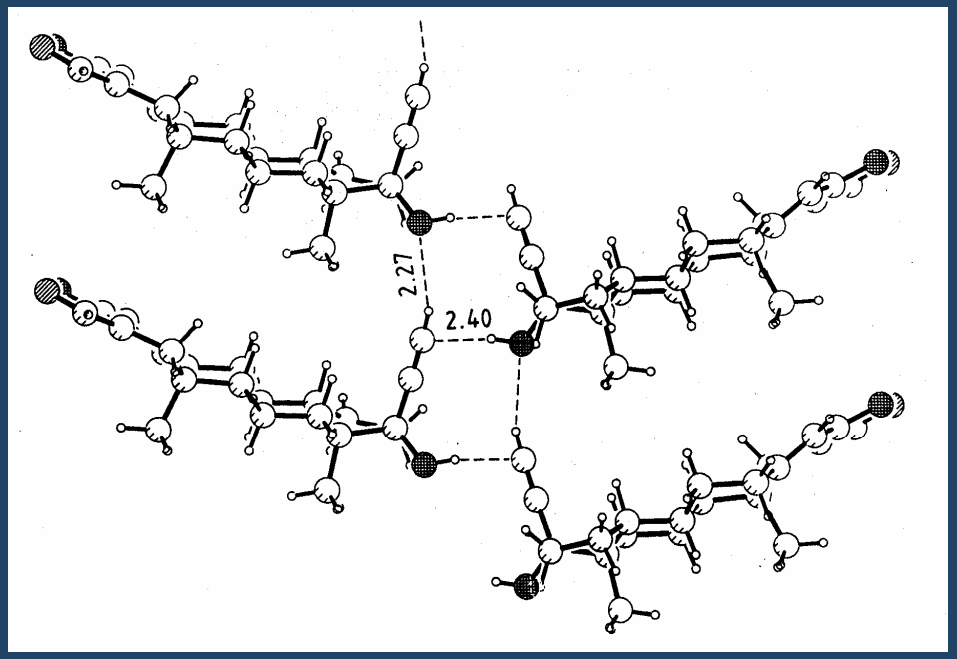


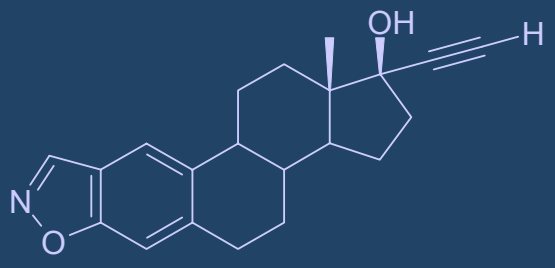


K. Biradha et al., J. Chem. Soc., Chem. Commun.,1473, **1993**

Interaction interference

Danazole



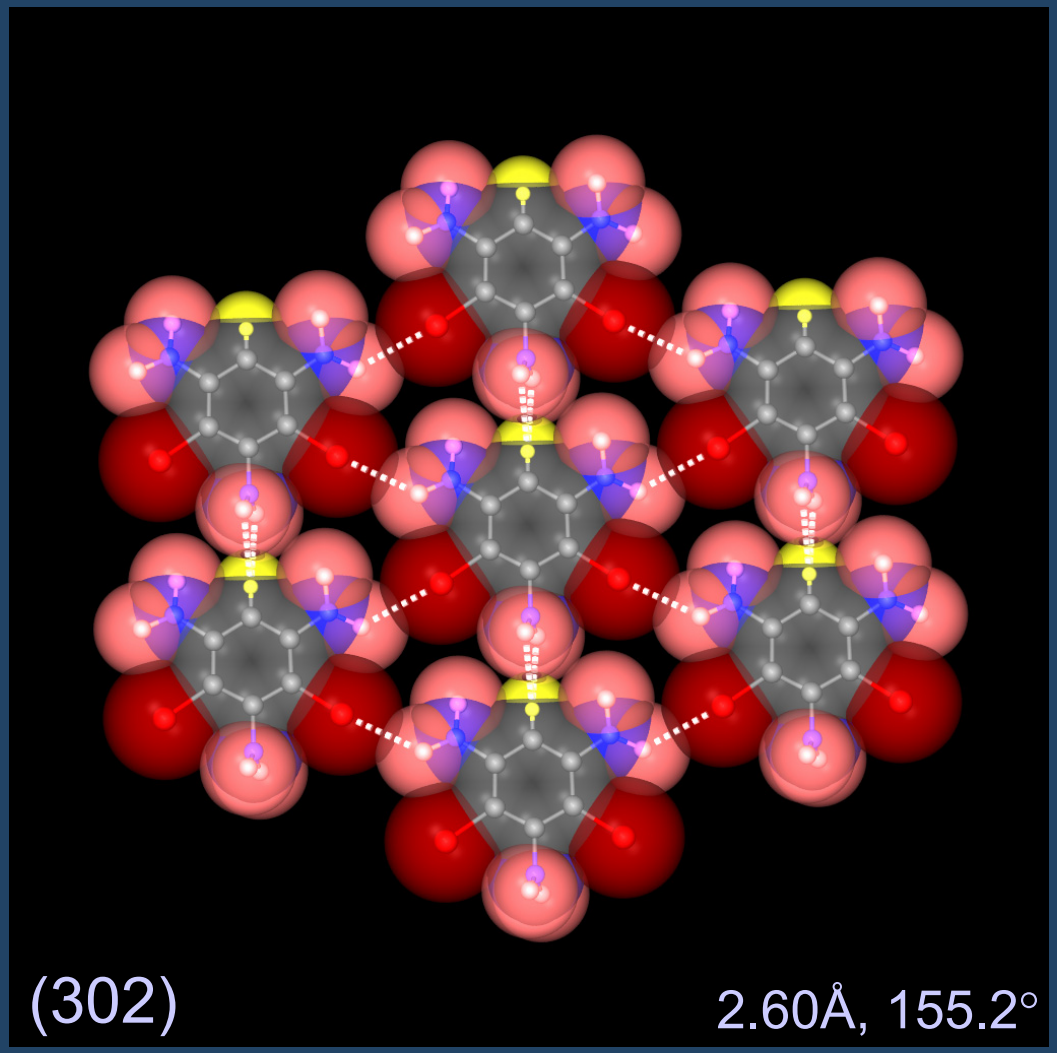


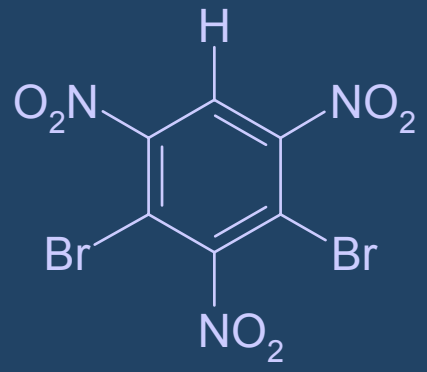
Expected
O–H…O–H…O–H…

Found
O–H…π and C–H…O

M. A. Viswamitra et al., J. Am. Chem. Soc., 115, 4868, **1993**

A functional crystal





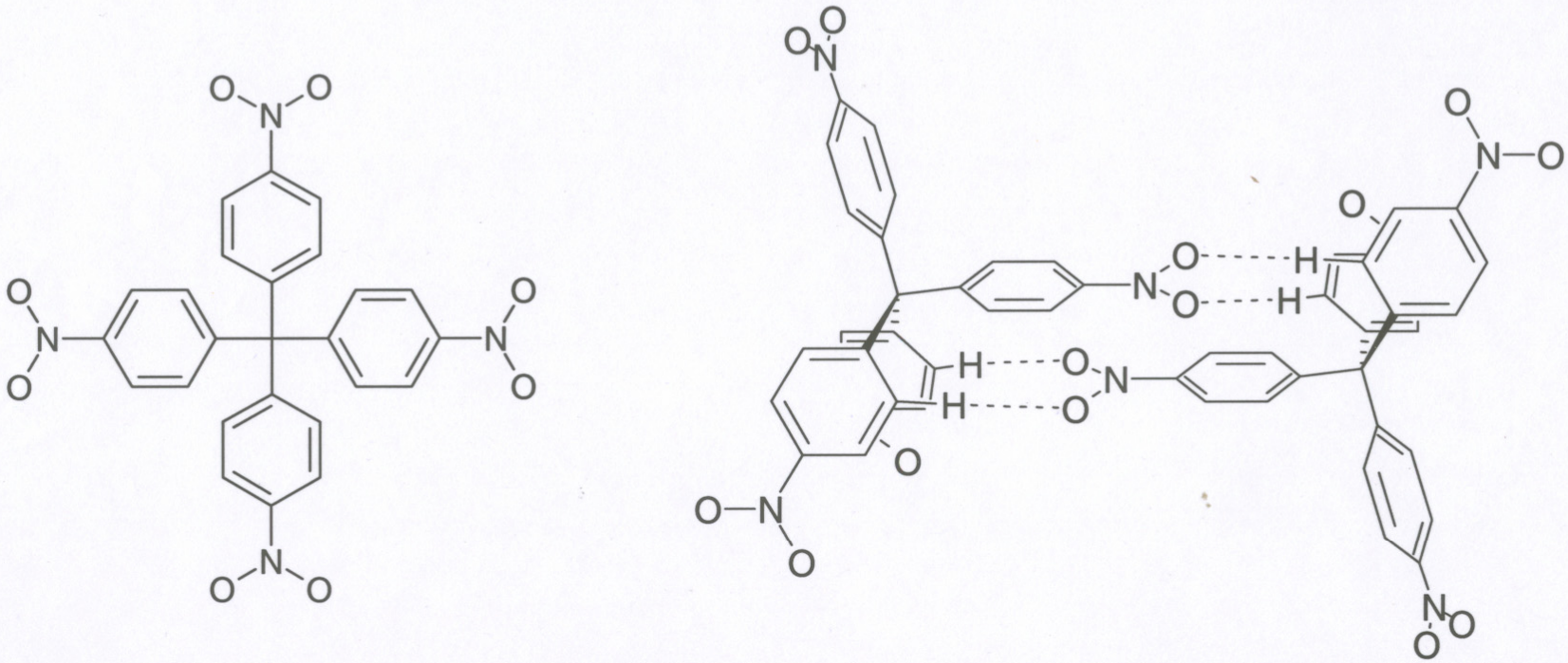
Space group *C2*

Intense powder SHG signal at 1.06 μm

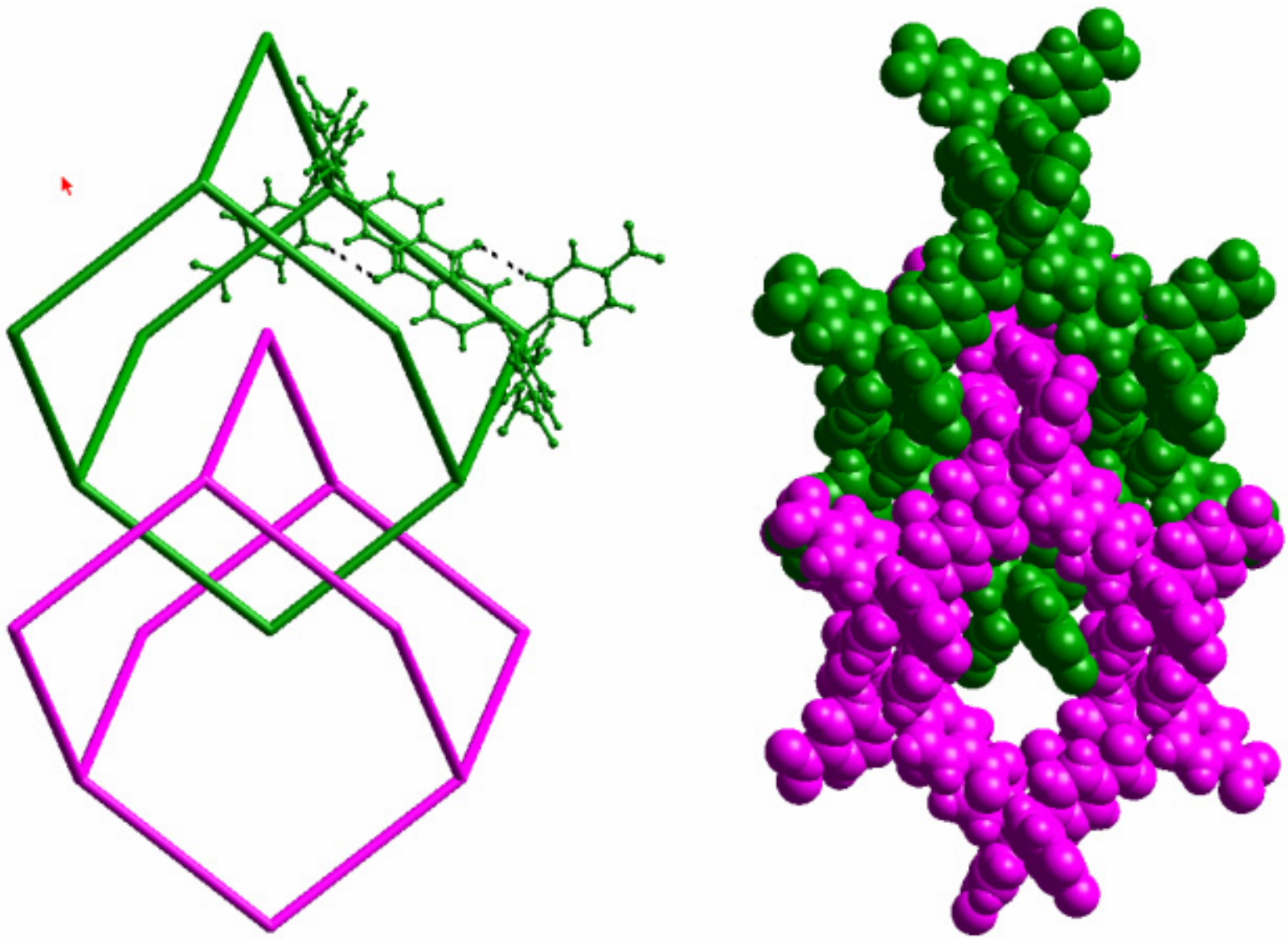
P. K. Thallapally et al., Chem. Commun., 1052, **2002**

C-H···O Diamondoid Networks

Tetrakis(4-nitrophenyl)methane

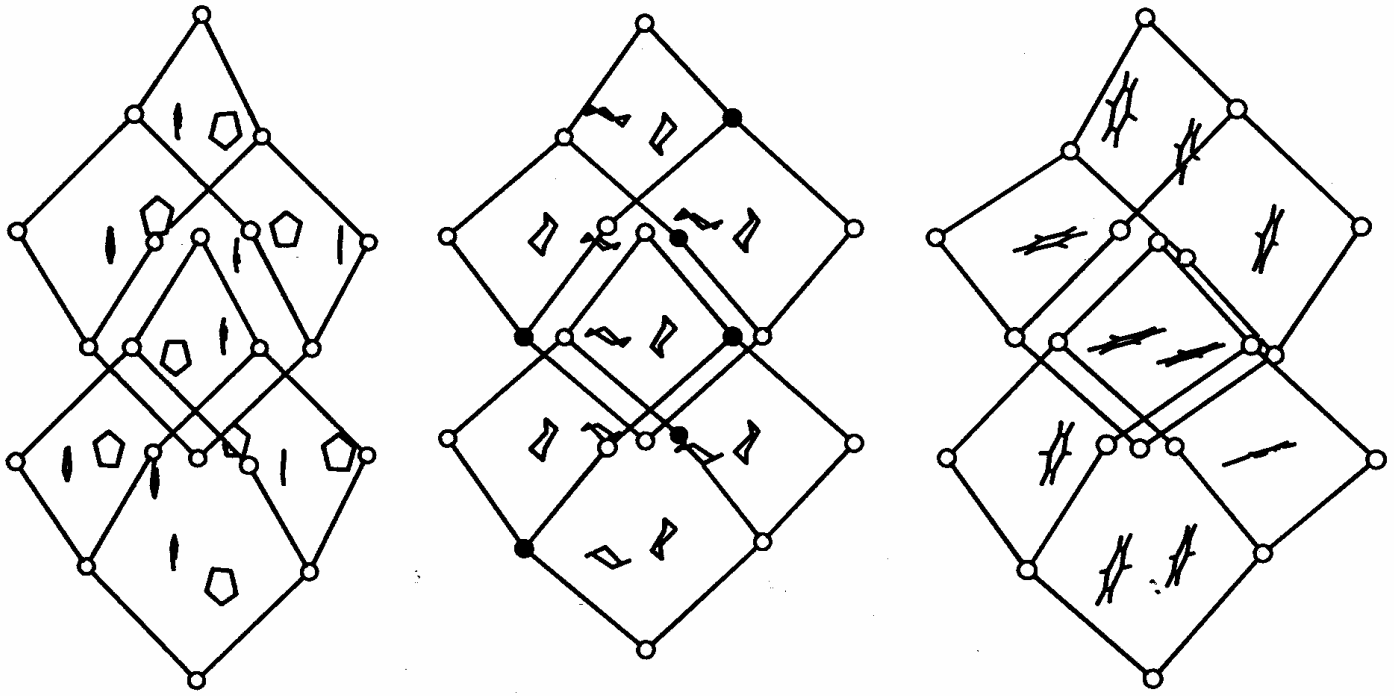


R. Thaimattam, F. Xue, J. A. R. P. Sarma, T. C. W. Mak and G. R. Desiraju
J. Am. Chem. Soc. **2001**, *123*, 4432–4445



C–H···O Diamondoid Networks

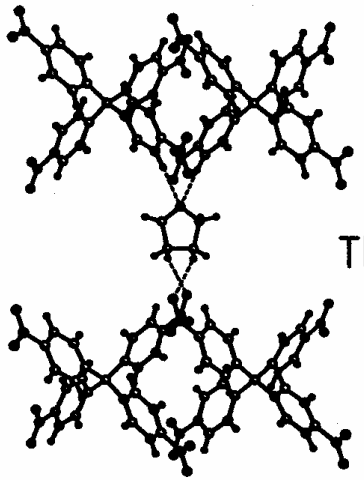
Tetrakis(4-nitrophenyl)methane



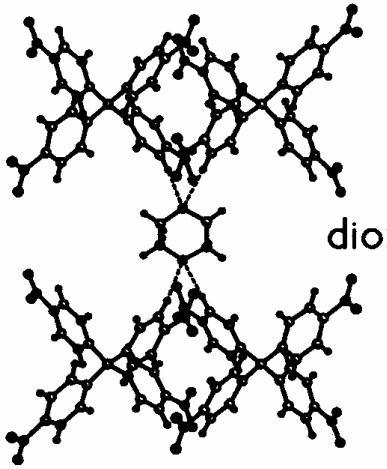
*Fdd*2	$P4_2/n$	*Pbcn*
THF	dioxane nitrobenzene	4-bromoanisole, anisole phenetole, *p*-xylene chlorobenzene

Guest Location in the Host Channel

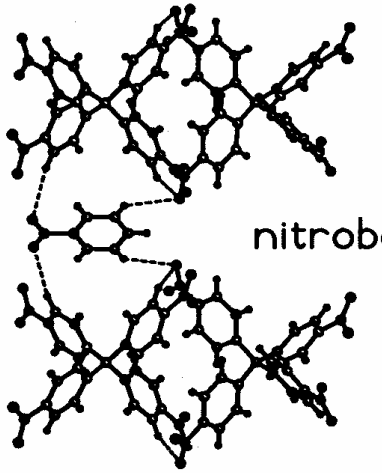
Tetrakis(4-nitrophenyl)methane



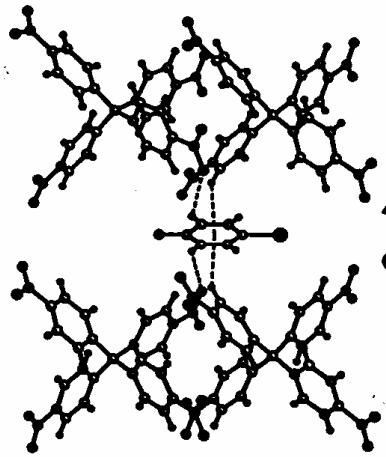
THF



dioxane



nitrobenzene



4-bromo-
anisole

C–H···O 2.45–2.65 Å

C–H···π 2.60–2.66 Å

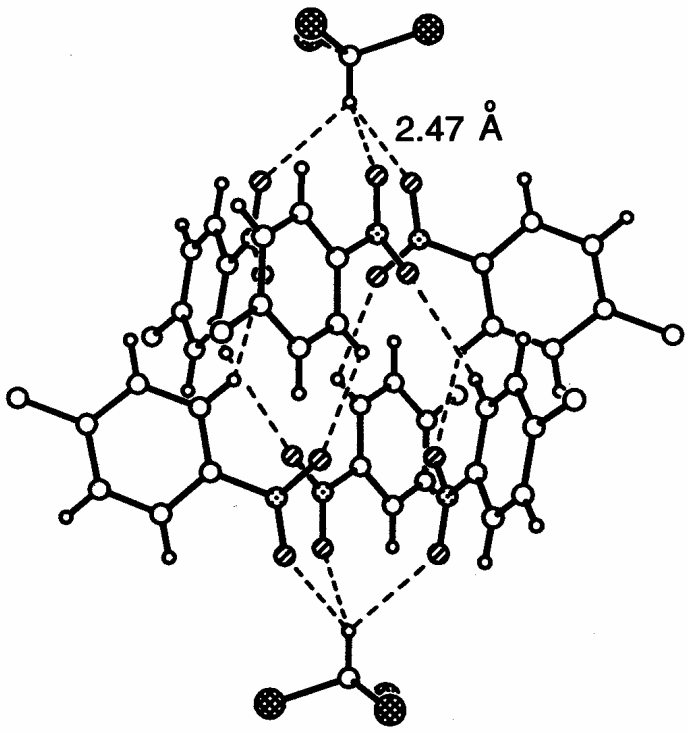
Host–Guest Complexes

Tetrakis(4-nitrophenyl)methane

Guest rich	Host rich	Guest excess
THF, 1:1	Chloroform, 3:1	Mesitylene, 1:2
Dioxane, 3:2	Bromoform, 3:1	Collidine, 1:2
Nitrobenzene, 3:2	DMF, 3:1	o-Xylene, 2:2
4-Bromoanisole, 2:1		
Anisole, 2:1		
Phenetole, 2:1		
p-Xylene, 2:1		
Chlorobenzene, 2:1		

Rhombohedral $CHCl_3$ Solvate

Strong Host–Guest interactions



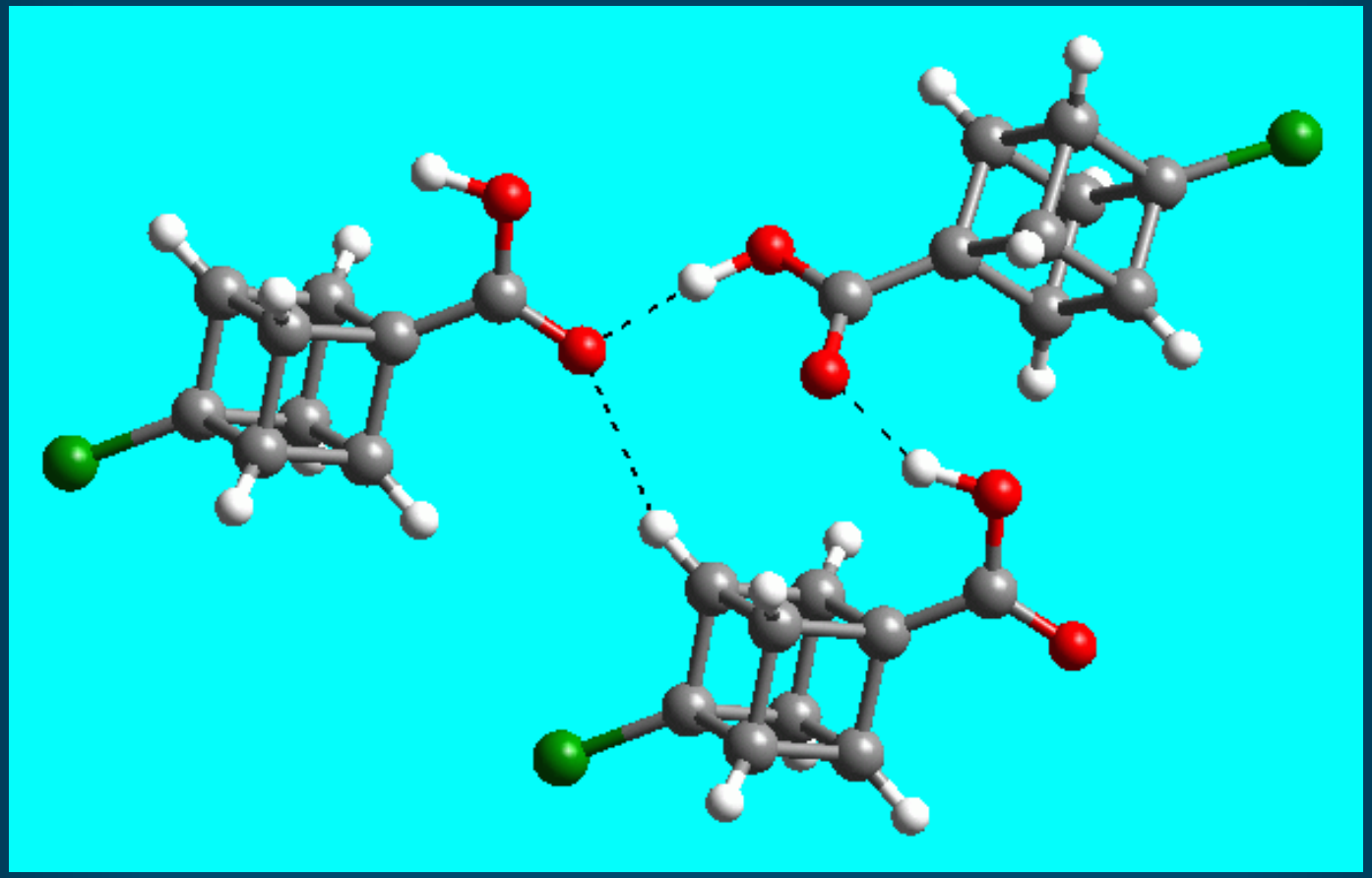
Reversible host framework deformation

Desolvation – Solvation

THF Solvate

Diamondoid form	△, < 100°C 2 mm Hg, 2h →	Rhombohedral form
Fdd2	← THF soaking 10 days, 0°C	$R\bar{3}$
Diamondoid form	△, > 109°C 2 mm Hg, 2h →	Rhombohedral form

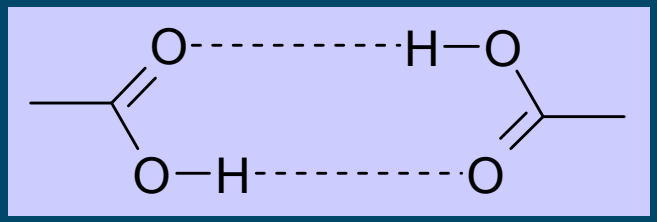
syn-anti Catemer in 4-chlorocubanecarboxylic acid



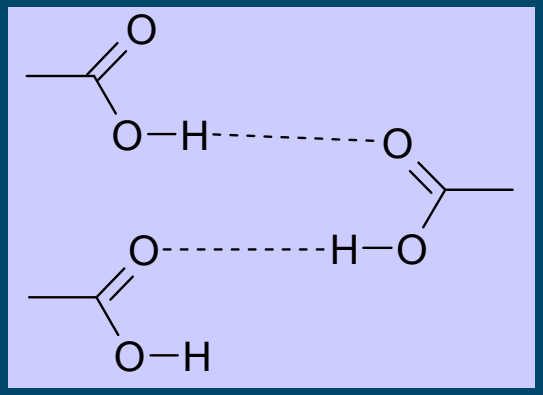
Supportive C–H···O bond

Kuduva et al, JACS, 121, 1936, **1999**

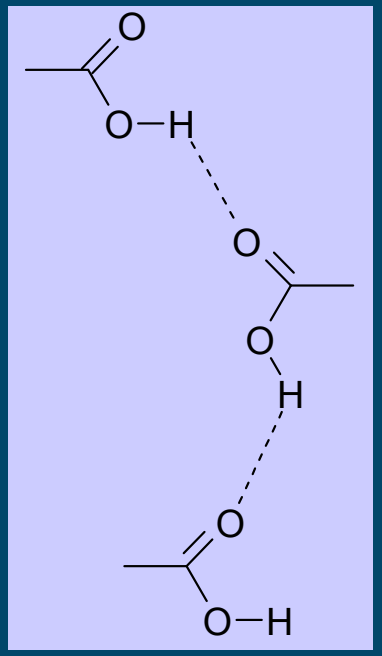
What do carboxylic acids do in the solid state?



Dimer



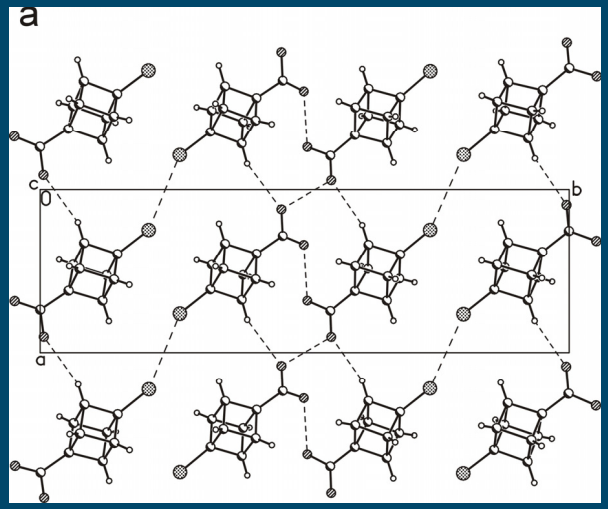
syn-Catemer

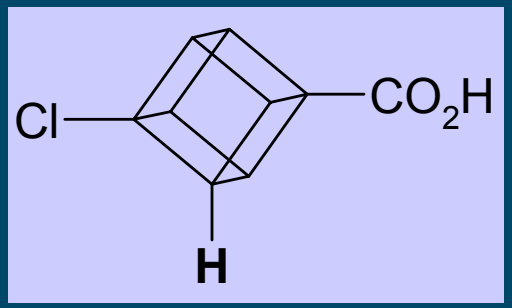


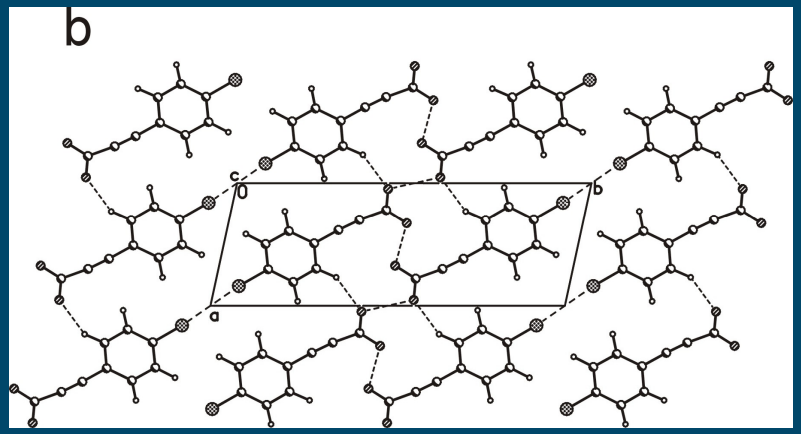
syn,anti-Catemer

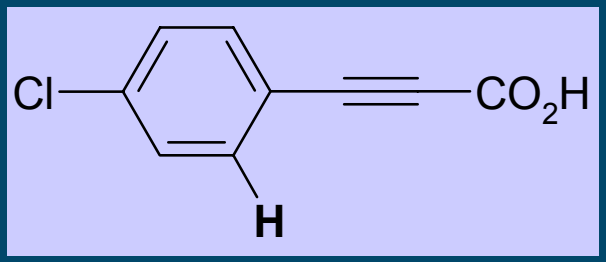
Different molecules, same crystal structure

Two times lucky



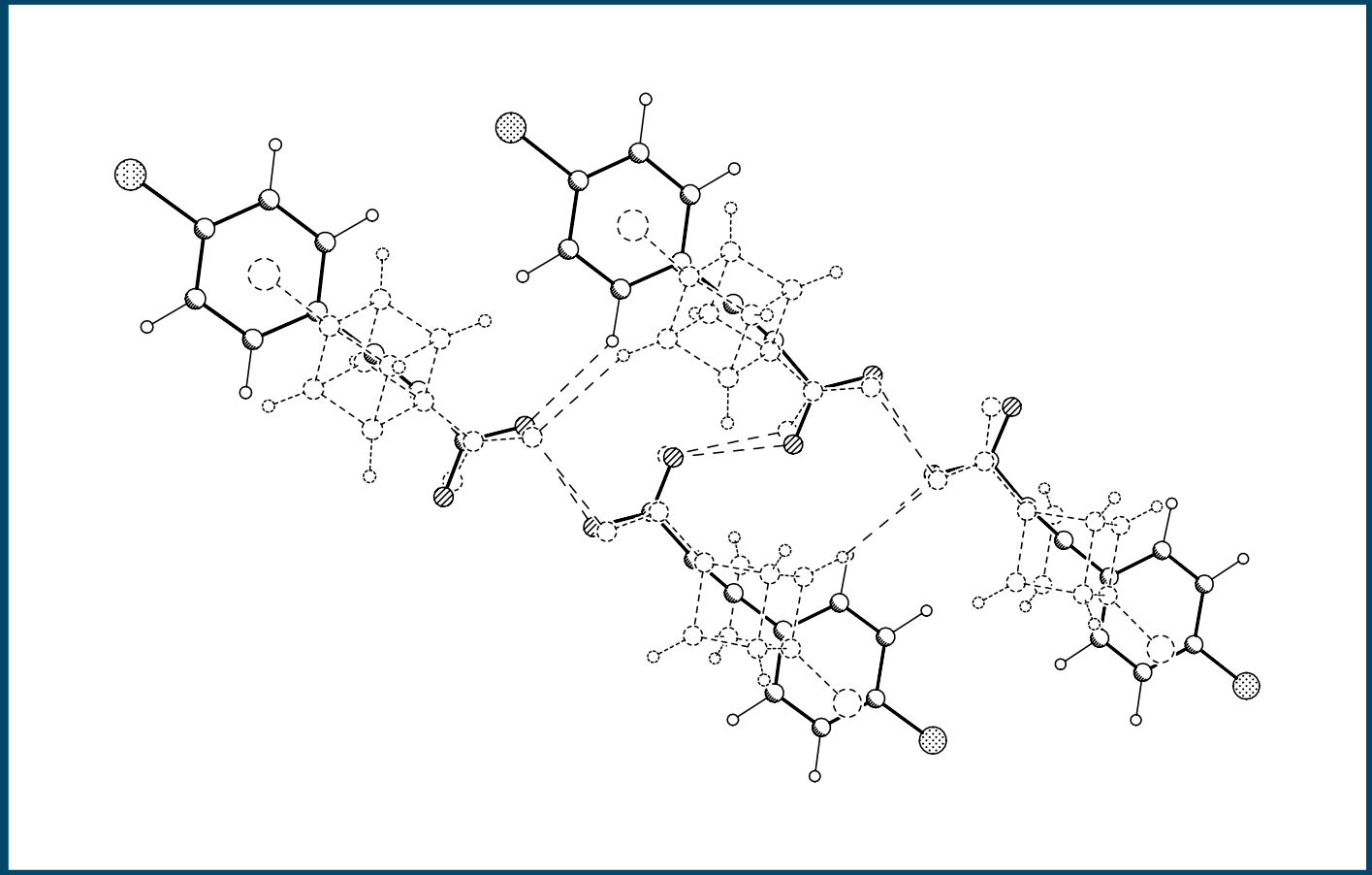




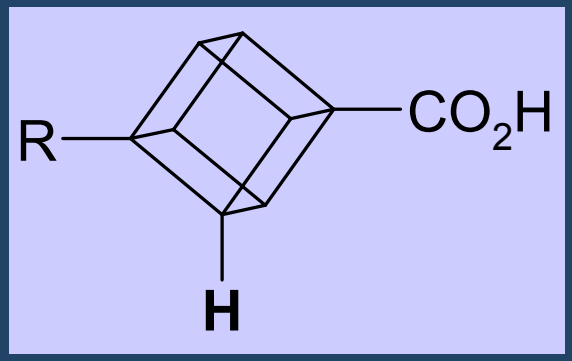


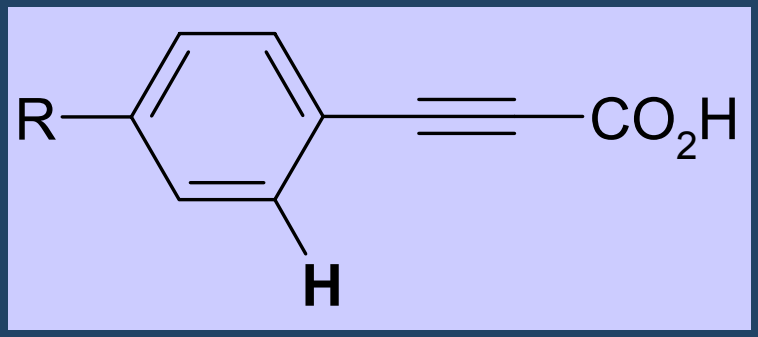
K. V. R. Kishan et al., Chem. Mater., 2, 447, **1990**

Superposition of the two structures



Lucky again



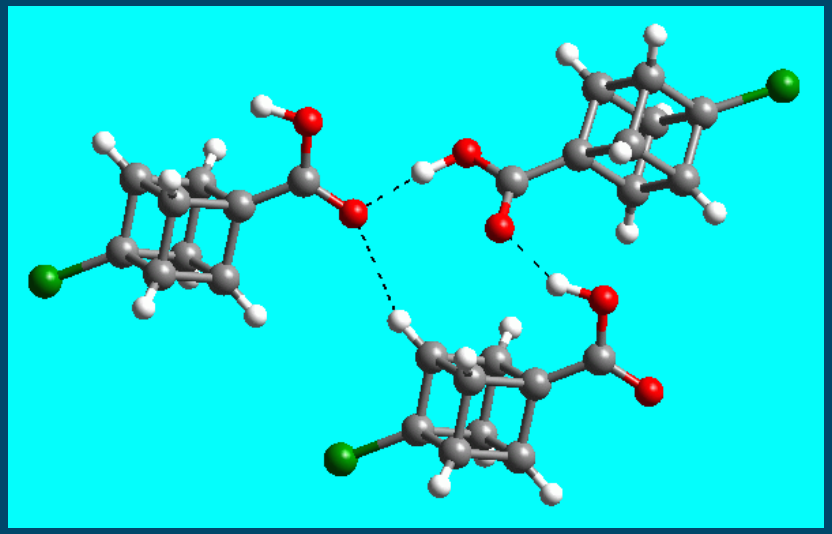


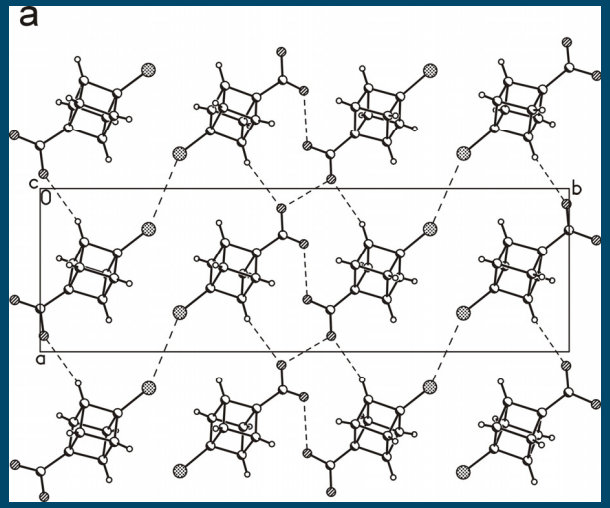
$pK_a \sim 38$

$pK_a \sim 44$

Gives a chance to probe stereoelectronic effects

Hypotheses



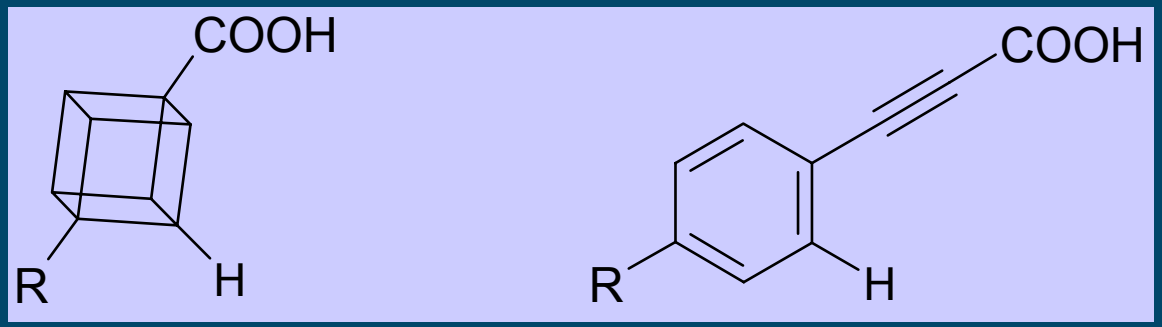


Catemer formation requires two structural features: a sufficiently activated C–H group and a ballast group at the other end of the molecule that provides stabilization via close packing

For the cubane acids, the R-group only needs to provide steric bulk

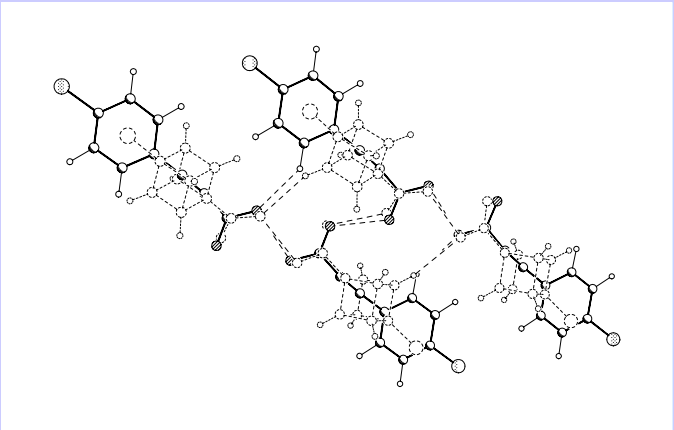
For the phenylpropiolic acids, the R-group needs to provide both steric bulk and electronic activation

Stereoelectronic effects in the solid state



R = H, F, Cl, Br, I, CH_3

D. Das et al, Crystal Growth & Design, 3, 675, **2003**



4-substituent	Cubane	Phenylpropiolic
H	Dimer	Dimer
F	Dimer	Catemer
Cl	Catemer	Catemer
Br	Catemer	Catemer
I	Catemer	Catemer
CH_3	Catemer	Dimer

Hydrogen bond

The master-key of molecular recognition

Strength

Directionality

Weakness

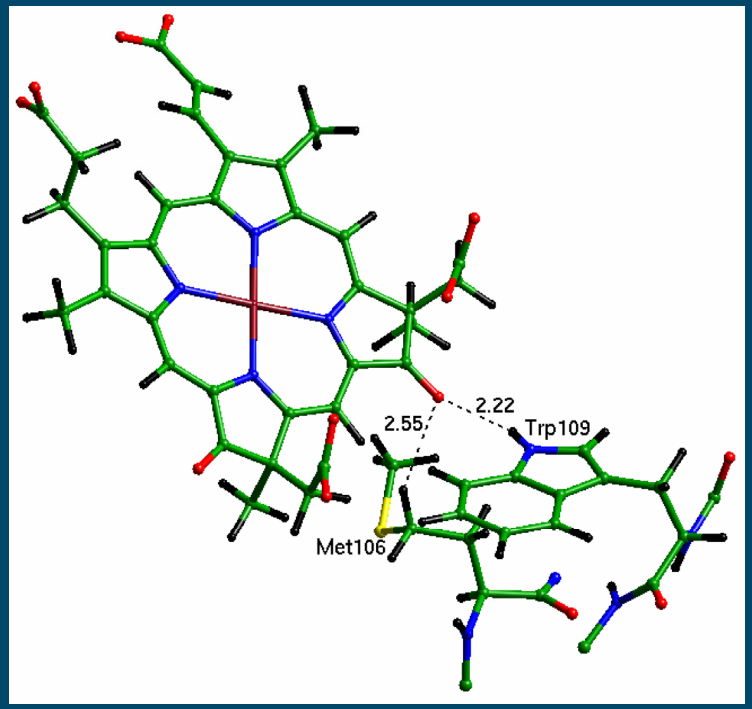
Flexibility

Strong or weak?

Anti-cooperative synthon in
Cytochrome Cd1 nitrite reductase / Heme D/ Heme C

C–H···O (2.55 Å)

N–H···O (2.22 Å)



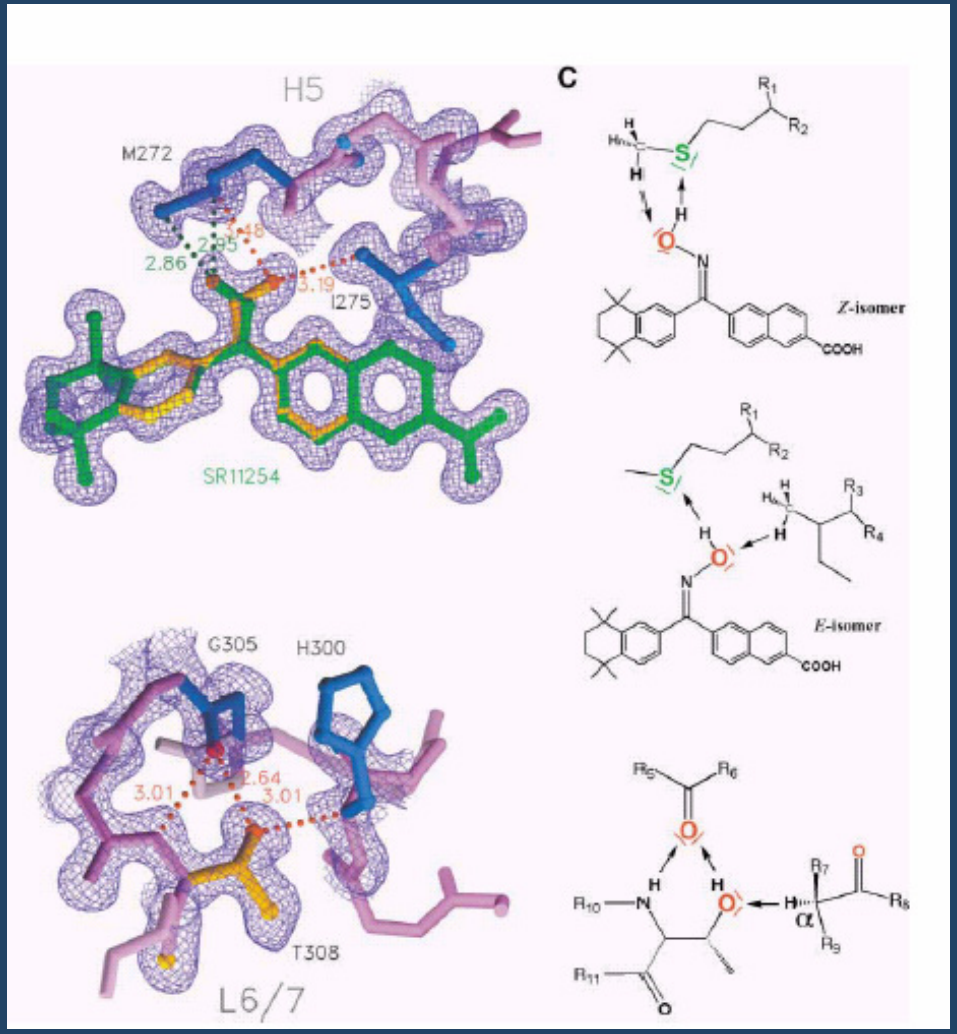
(PDB ID: 1QKS)

S. Sarkhel and G. R. Desiraju, Proteins, 54, 247, **2004**

C–H…O Hydrogen Bonds in the Nuclear Receptor RARγ

Specificity

Reversibility

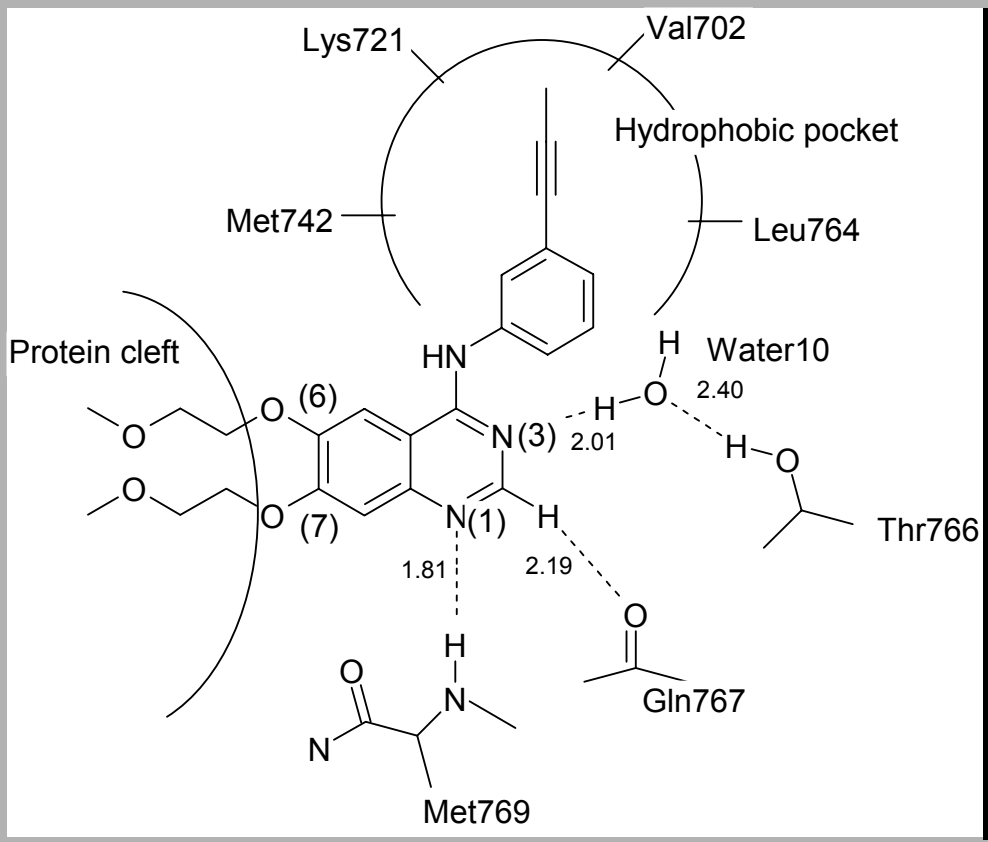


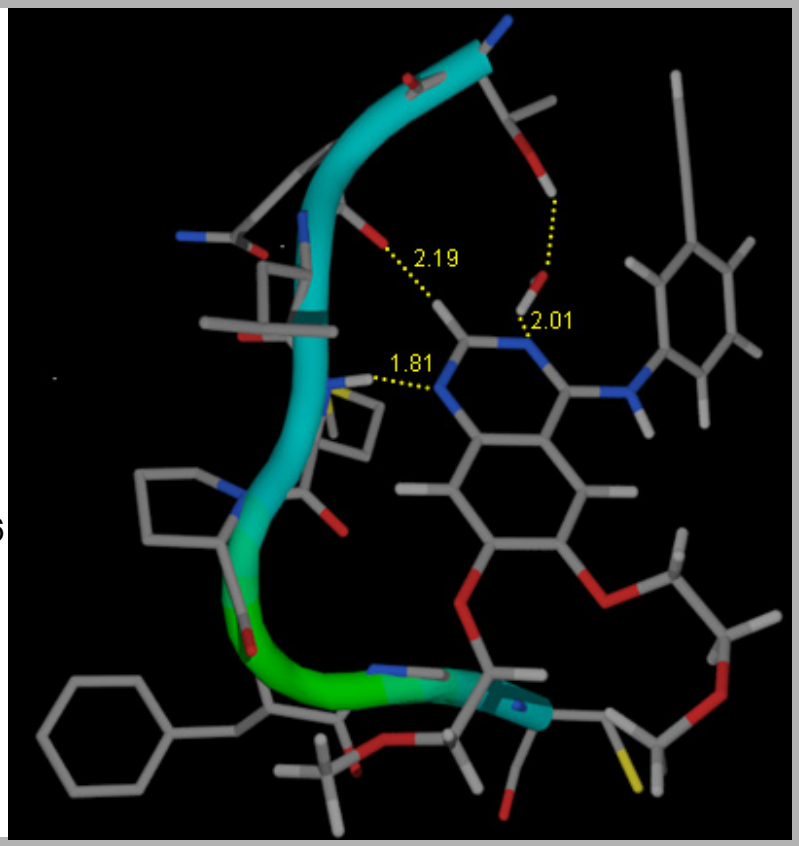
Affinity

Hydrophobicity

Klaholz and Moras, Structure, 10, 1197-1204, **2002**

EGFR Kinase Inhibitor





V. Aparna et al., J. Chem. Inf. Model., 45, 725, **2005**

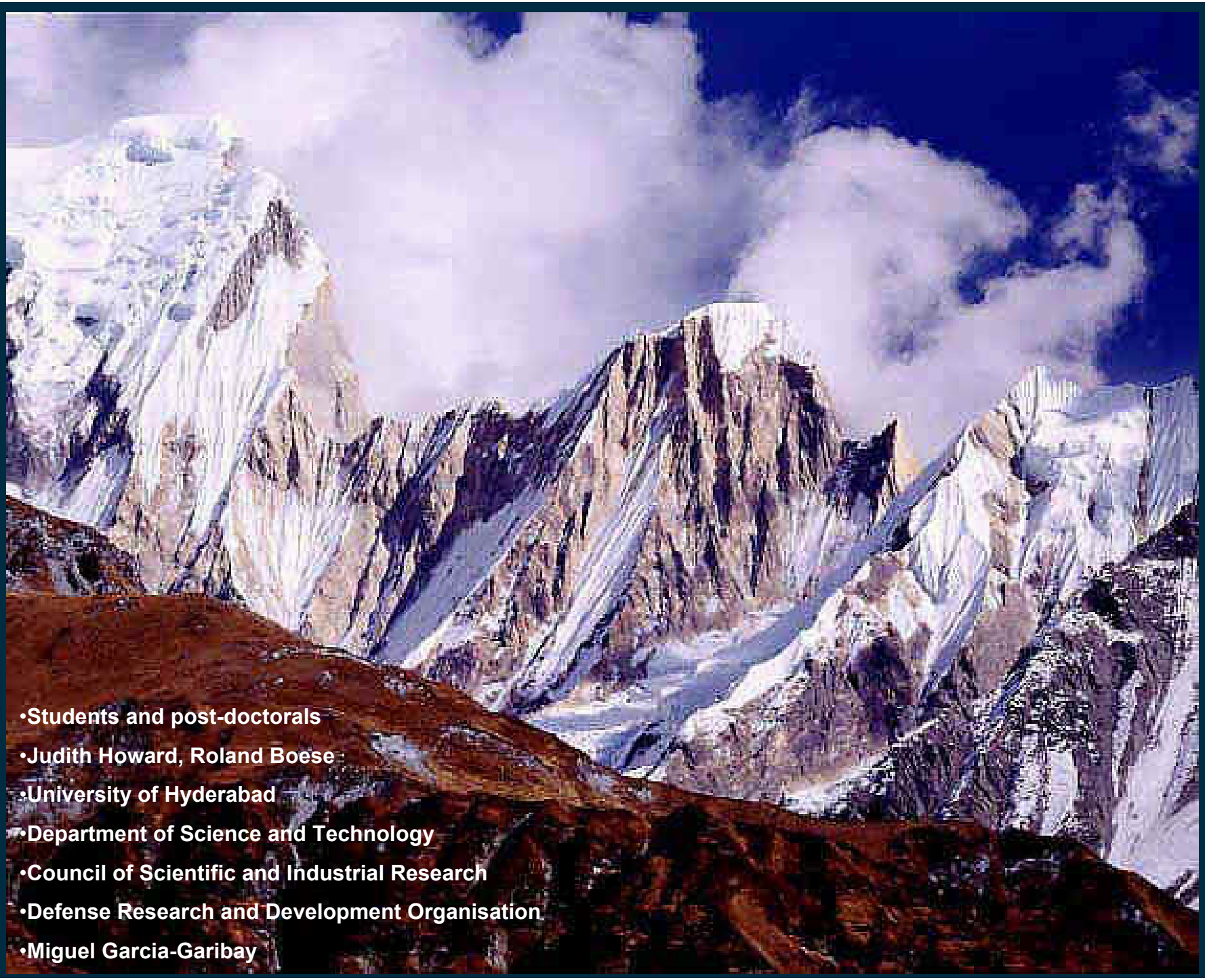
Conclusions

The C–H…O and other ‘weak’ hydrogen bonds are specific interactions with distinct structural consequences

Many C–H…O bonds may be considered to be structure determining

Presence or absence of a single weak interaction may result in a cascade of changes

Different weak interactions may be of varying importance in determining crystal packing


•Students and post-doctorals
•Judith Howard, Roland Boese
•University of Hyderabad
•Department of Science and Technology
•Council of Scientific and Industrial Research
•Defense Research and Development Organisation
•Miguel Garcia-Garibay