Dalle molecole ai cristalli molecolari: proprietà collettive e polimorfismo – Nuove sfide per la diffrattometria

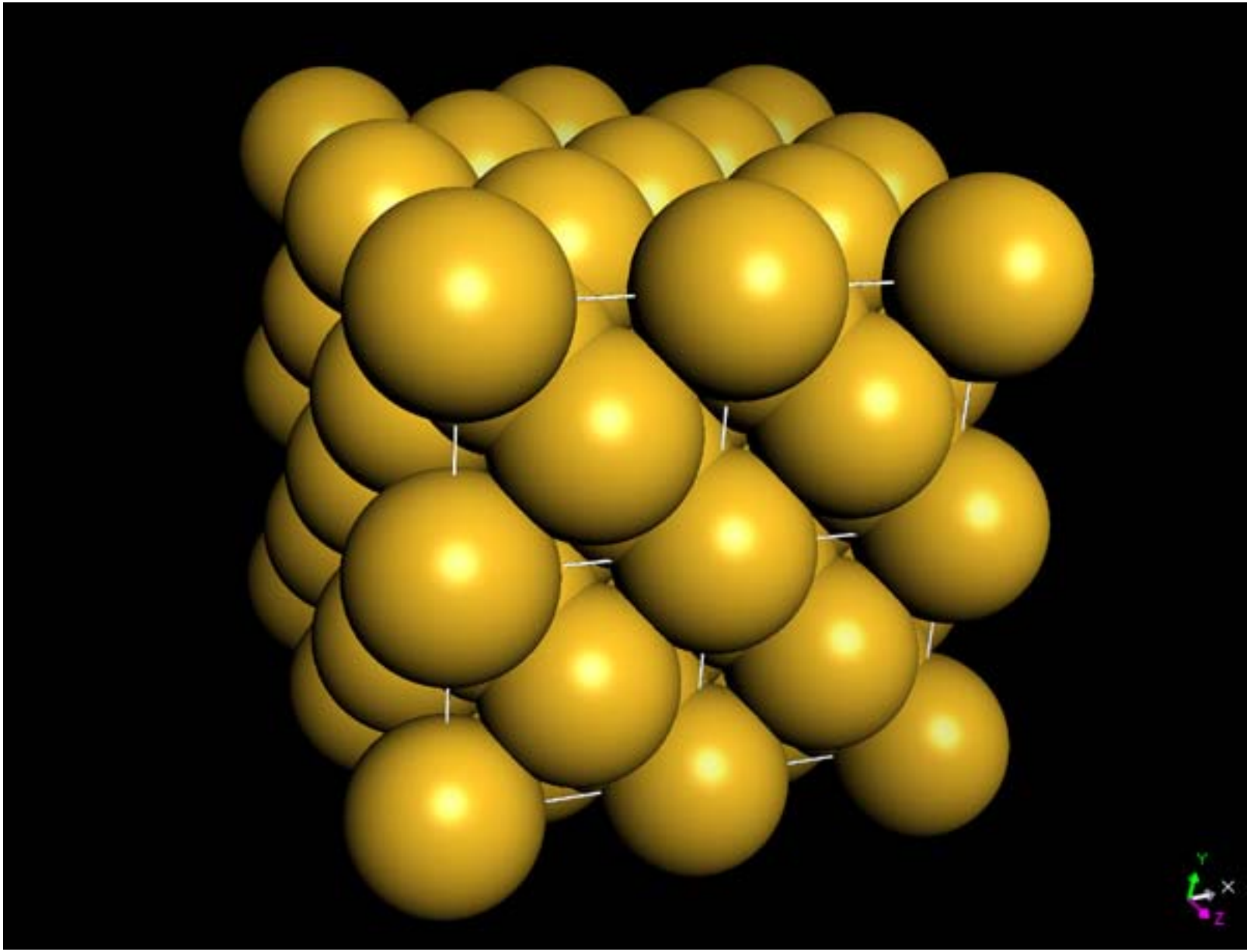
Dario Braga Modena 2005

Le tre regole di un seminario:

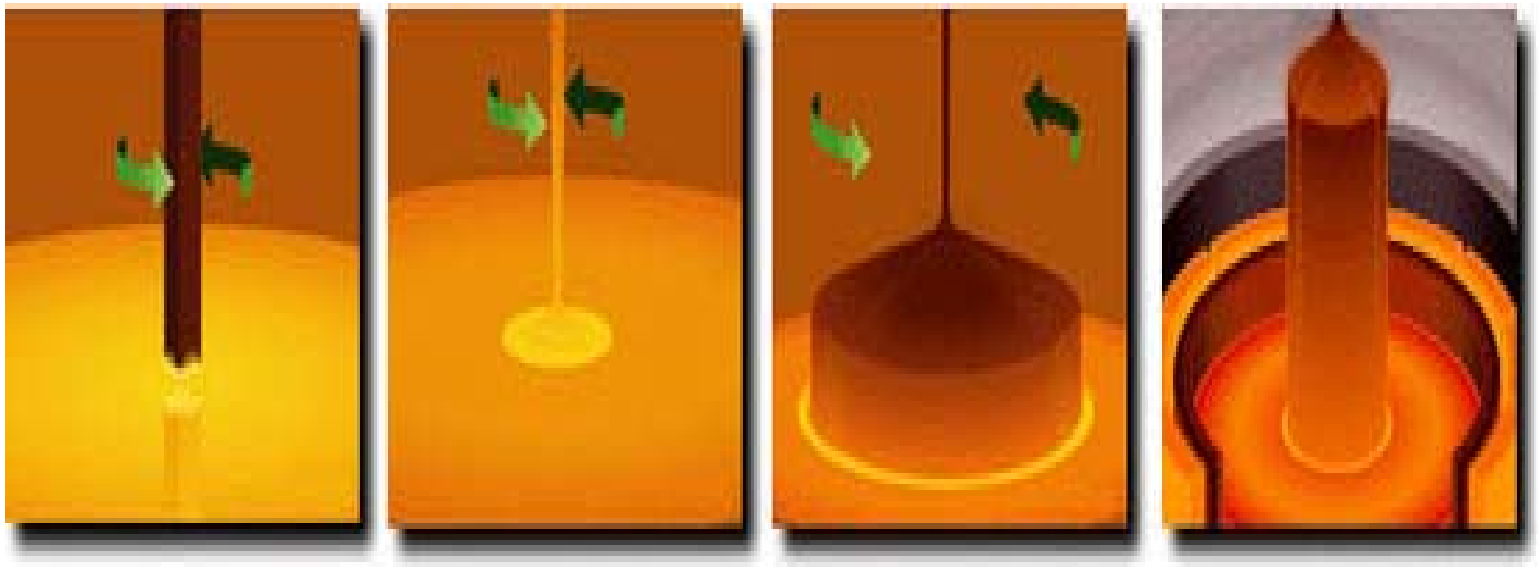
1. *Tell them*
   what you want to tell them
2. *Tell them*
3. *Tell them*
   what you told them

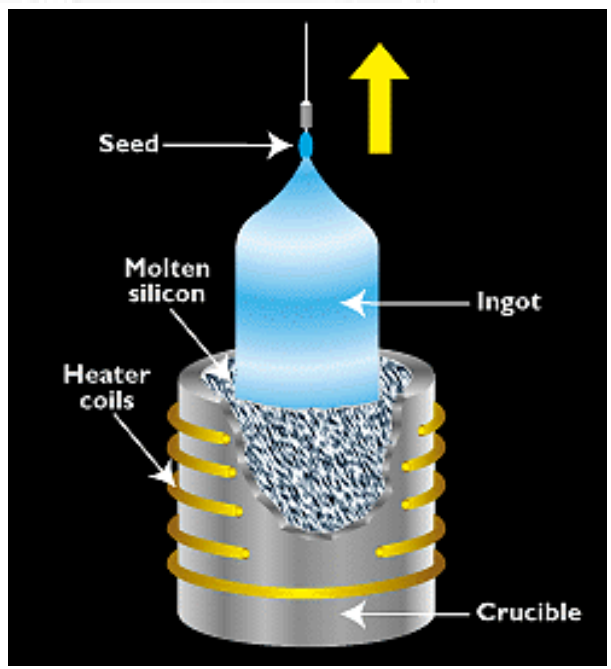
1. What is a crystal? (glass, crystals, instruments)
2. What is diffraction and diffractometry (a briefing)
   Some important single crystal cases
3. Crystallographic Databases
4. Crystal engineering – making crystals with a purpose
5. The Bologna's experience
6. Polymorphism: the nemesys of crystal engineering
   and a big commercial issue
7. Tricky diffraction special applications

Crystalline Silicon

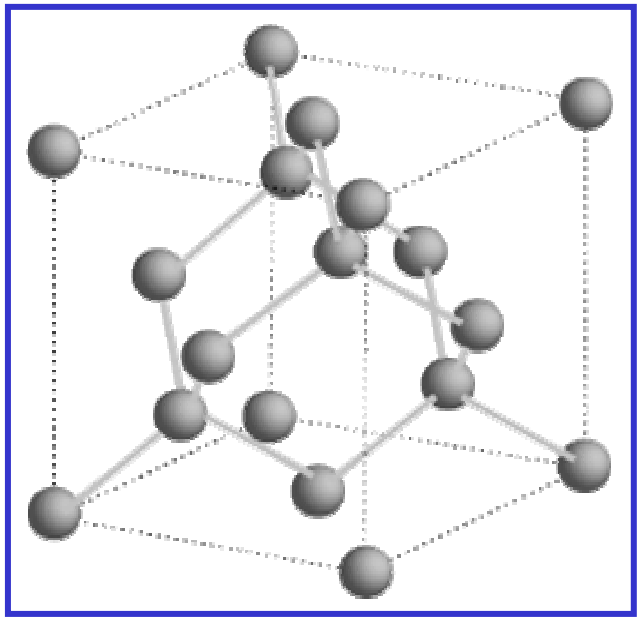


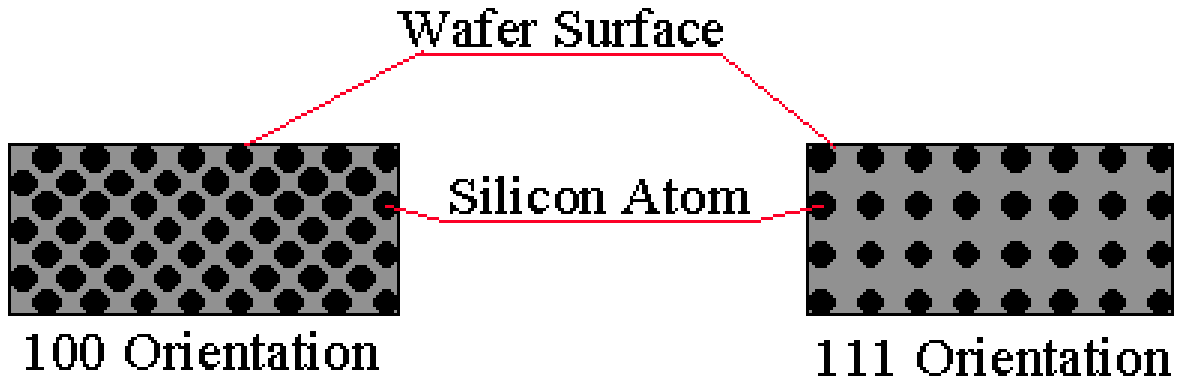
The integrated circuit technology requires SILICON SINGLE CRYSTALS



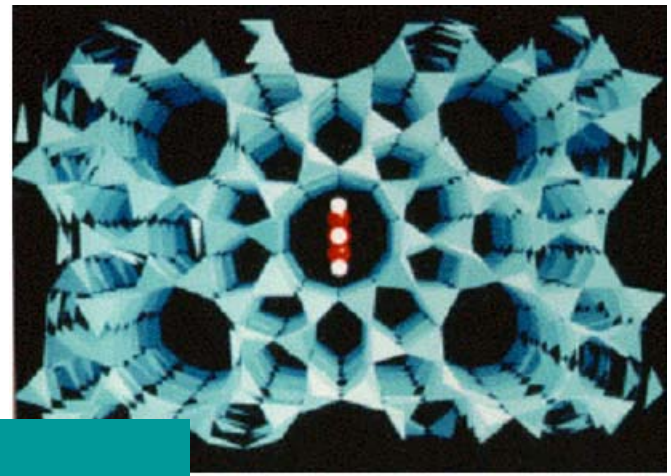


- The Czochralski Process is a Technique in Making Single-Crystal Silicon
- A Solid Seed Crystal is Rotated and Slowly Extracted from a Pool of Molten Si

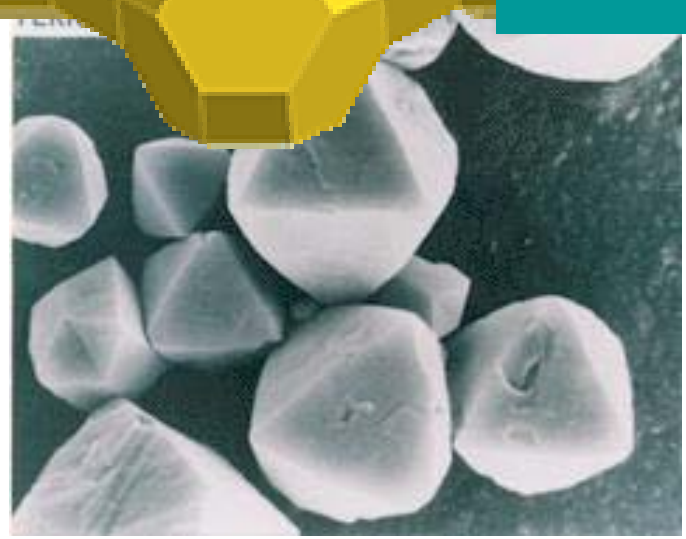


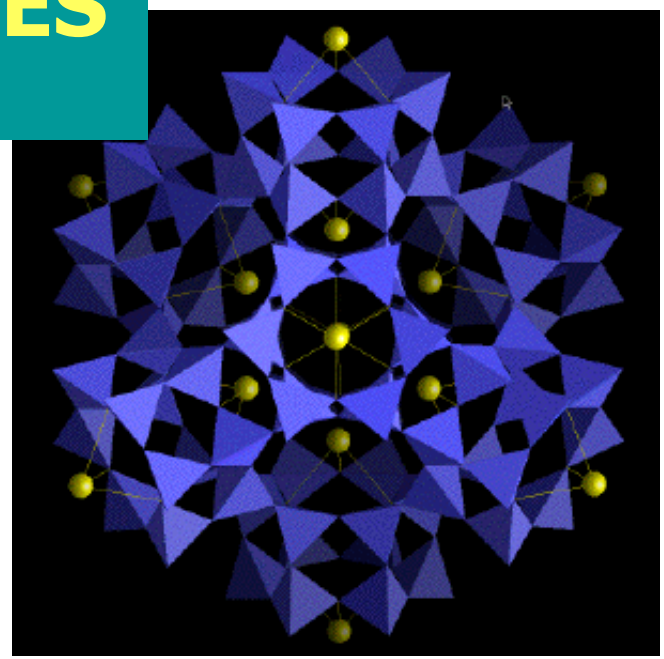

Wafer Surface
Silicon Atom
100 Orientation
111 Orientation

http://faculty.washington.edu/finlayso/Fluidized_Bed/FBR_Intro/trends_scroll.htm



ZEOLITES



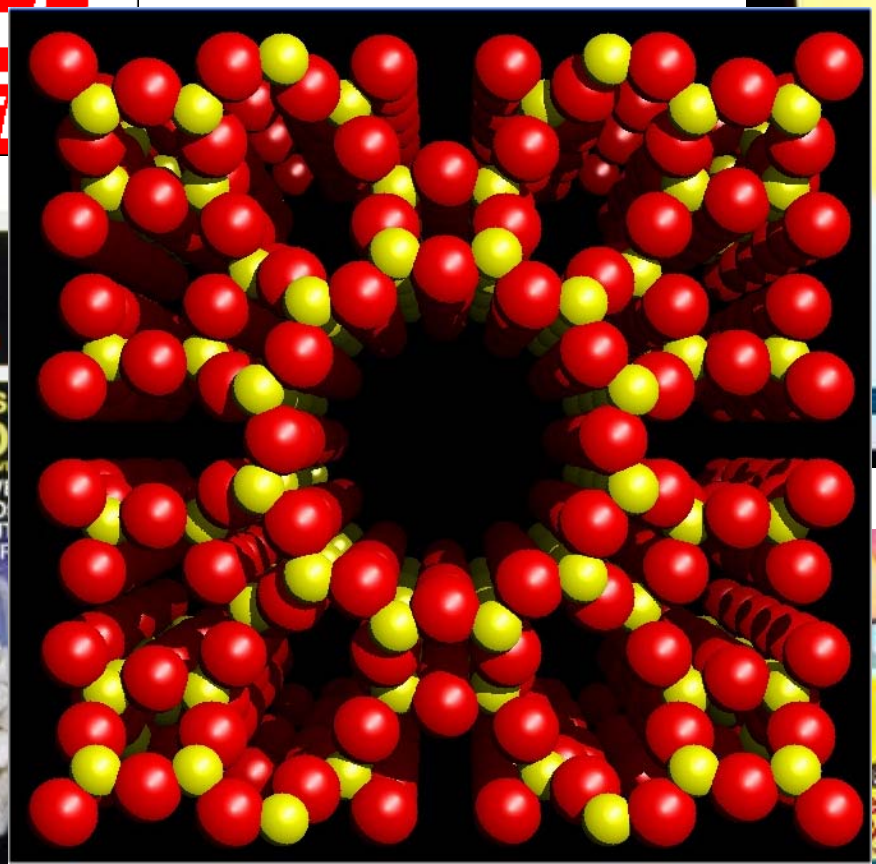


http://ens.lycos.com/ens/aug2000/2000L-08-15-07.html

ZEOLITES


ARIEL


ZEO
CRYSTAL
SOLAR CRYSTALS™
Naturally and Rapidly
Eliminates Odors
Solar Renewable
MONEY BACK GUARANTEE!




Lee's
AQUARIUM & PET PRODUCTS
TWO PREMIUM DISPOS
ZEOLITE CARTRID
Solves the common
problem of ammonia
build-up that fouls


ZEO
SOLAR CRYSTALS
Eliminates Odors
FRIDGE FRESH
Eliminates Odors &

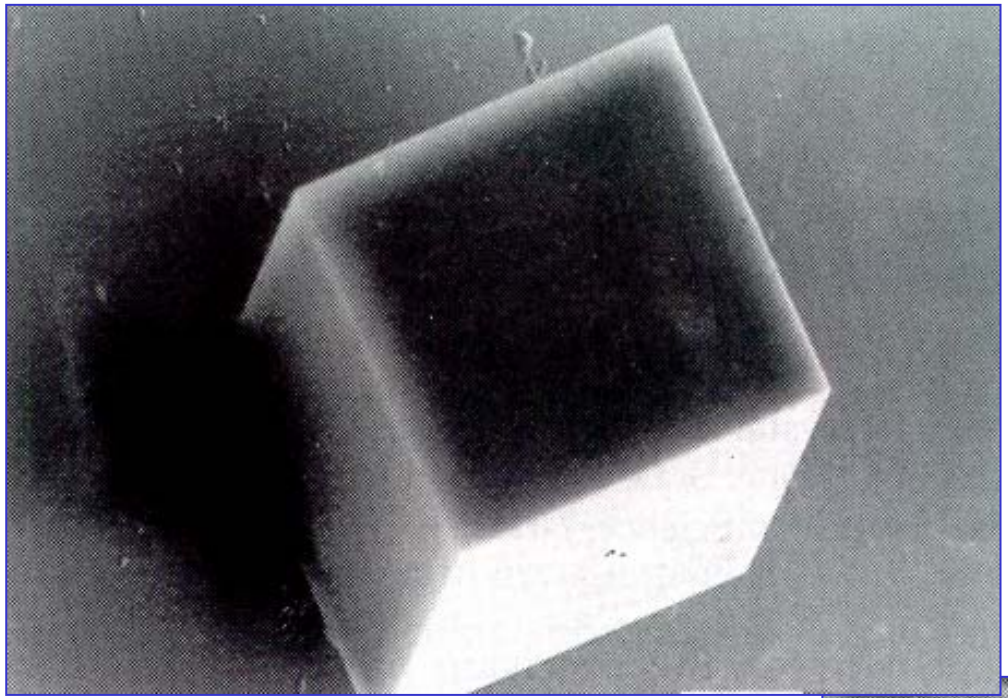
aragonite

Calcium Carbonate

$CaCO_3$

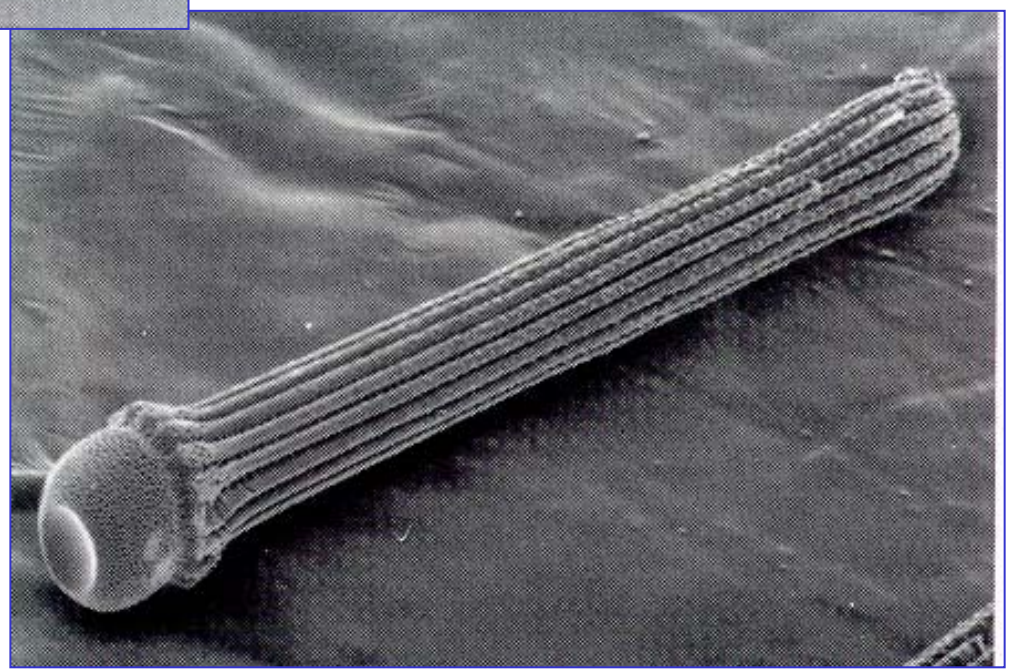
calcite

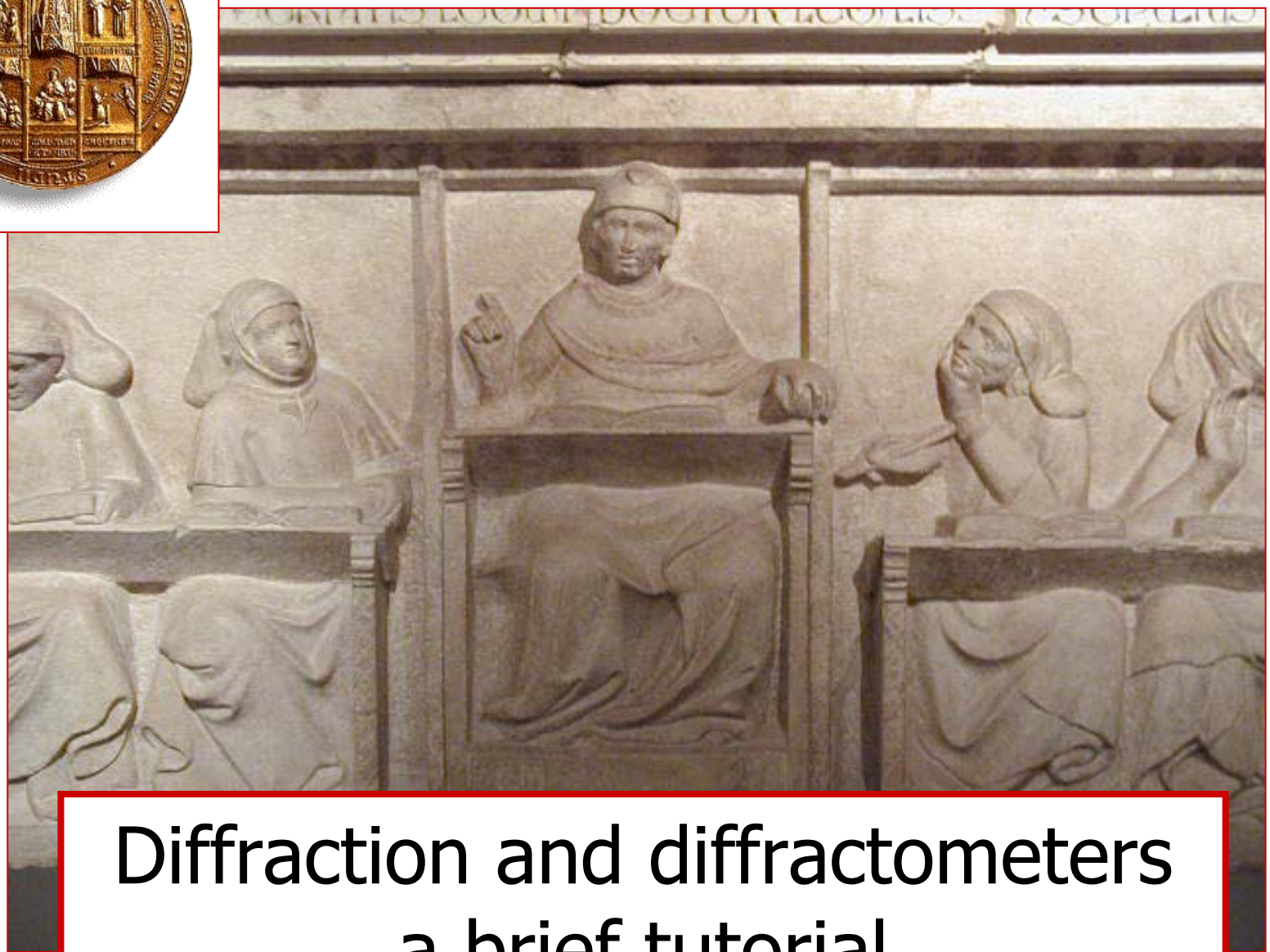
$CaCO_3$
biogenic aragonite



$CaCO_3$
Laboratory
calcite

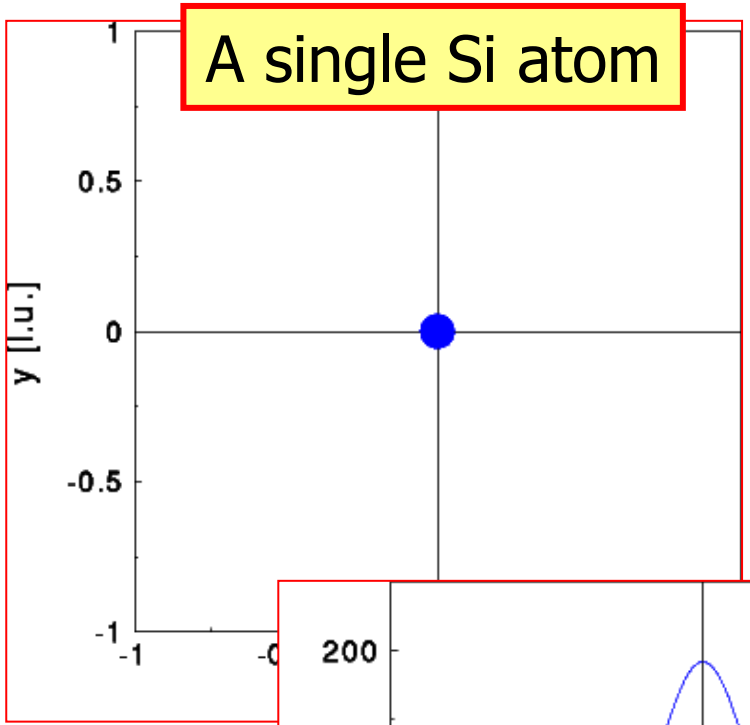
$CaCO_3$
Biogenic
calcite



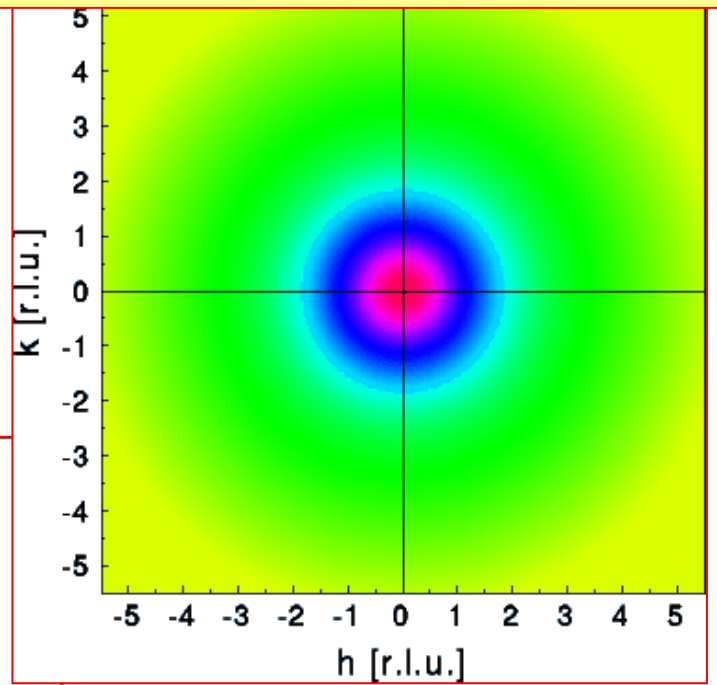


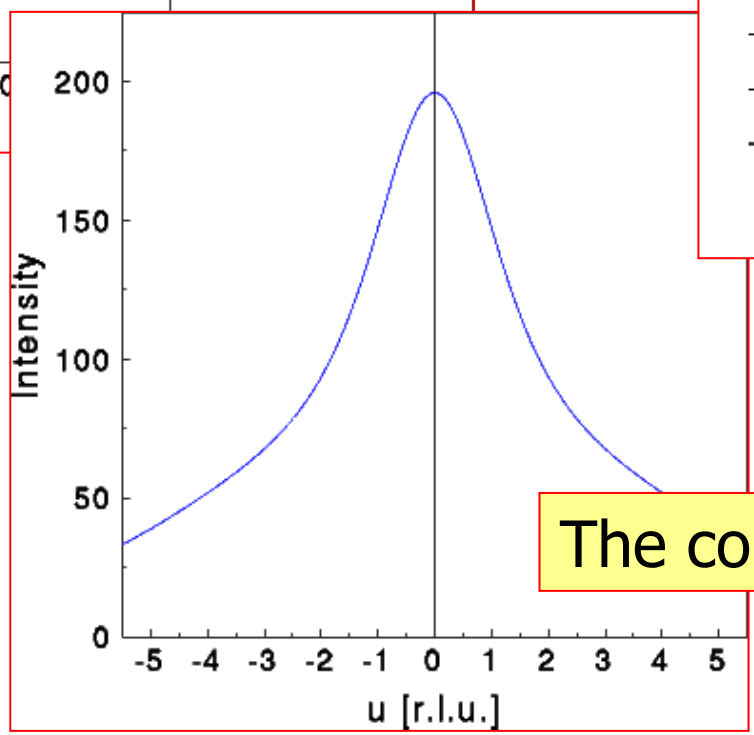
Diffraction and diffractometers
a brief tutorial

A single Si atom

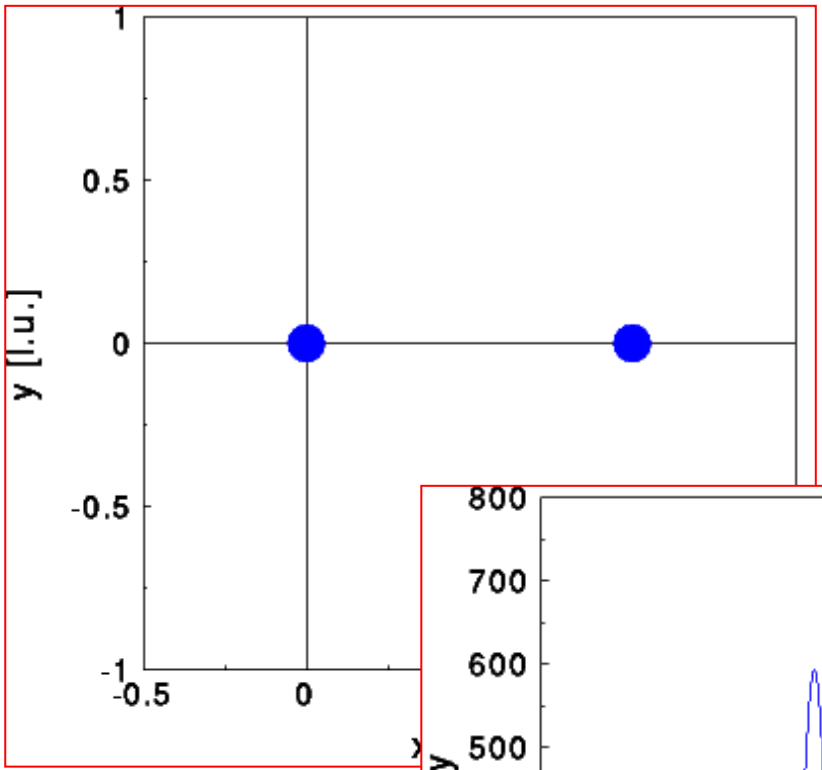


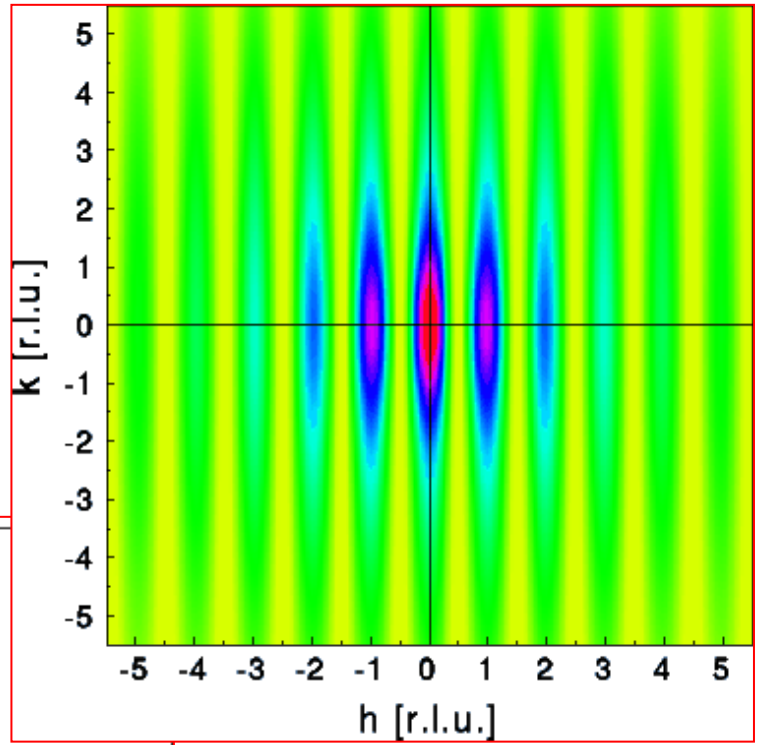
and 2D Fourier transform

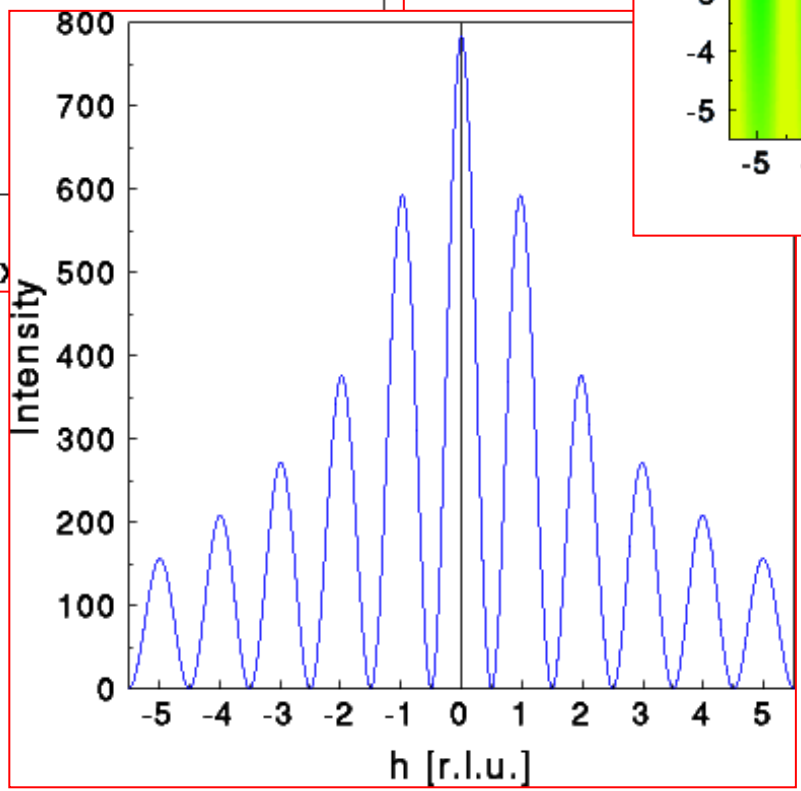




The corresponding 1D

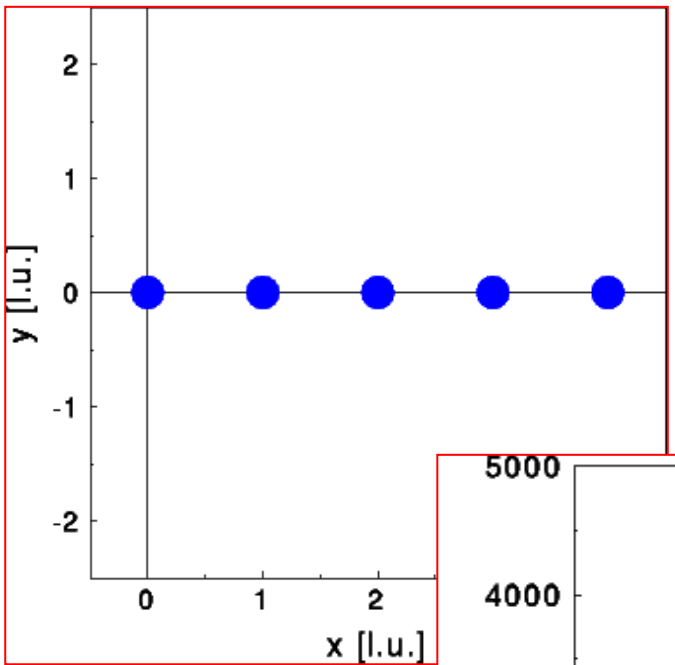


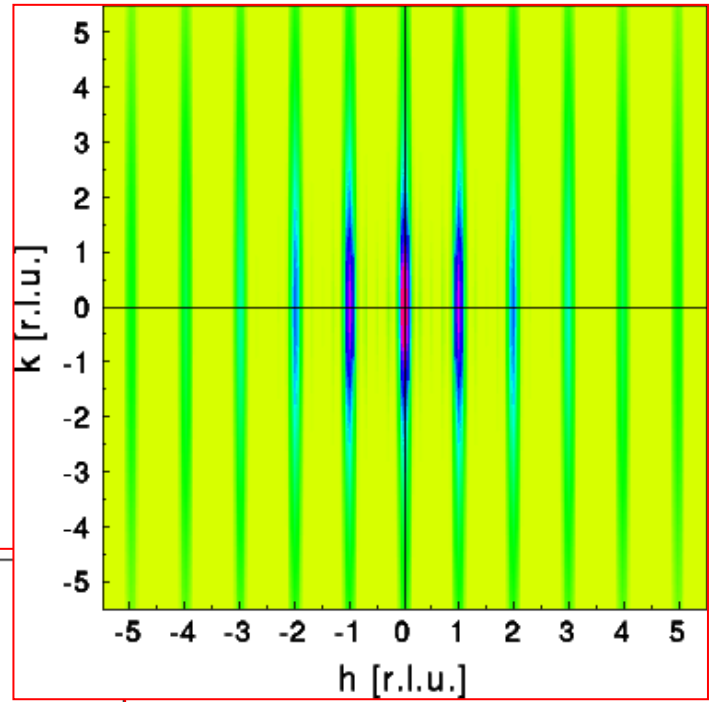


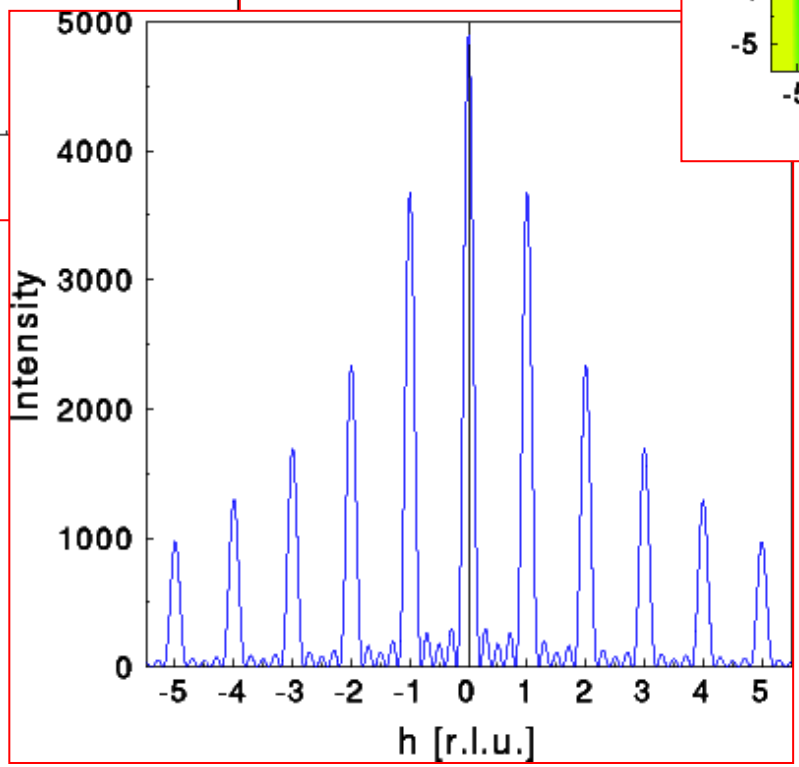


A pair of atoms

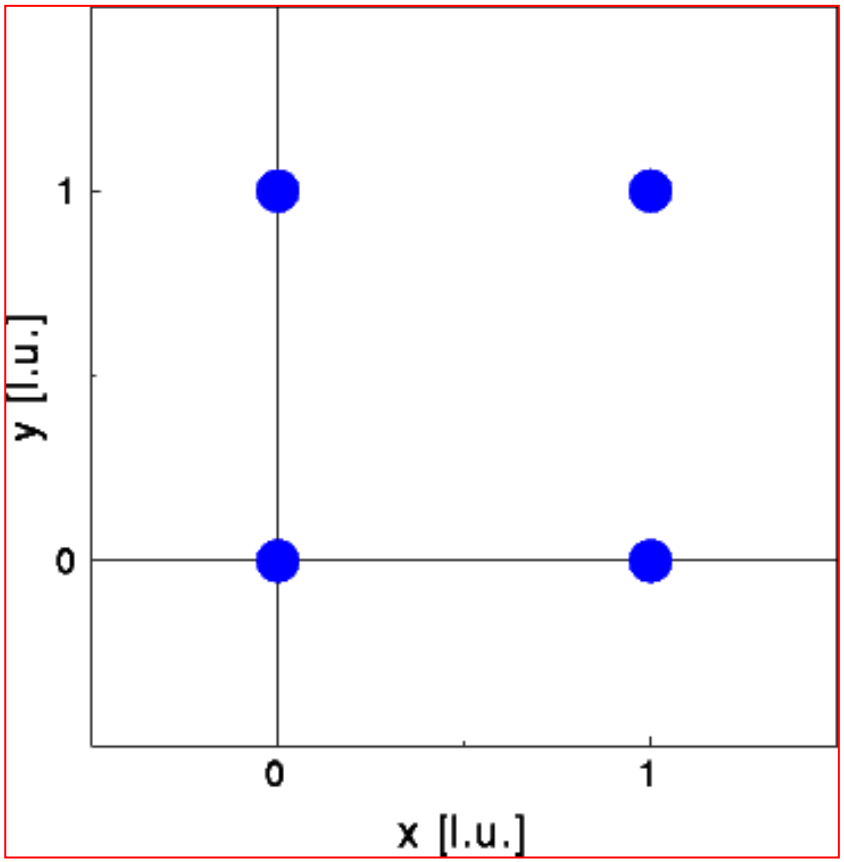
1D crystal

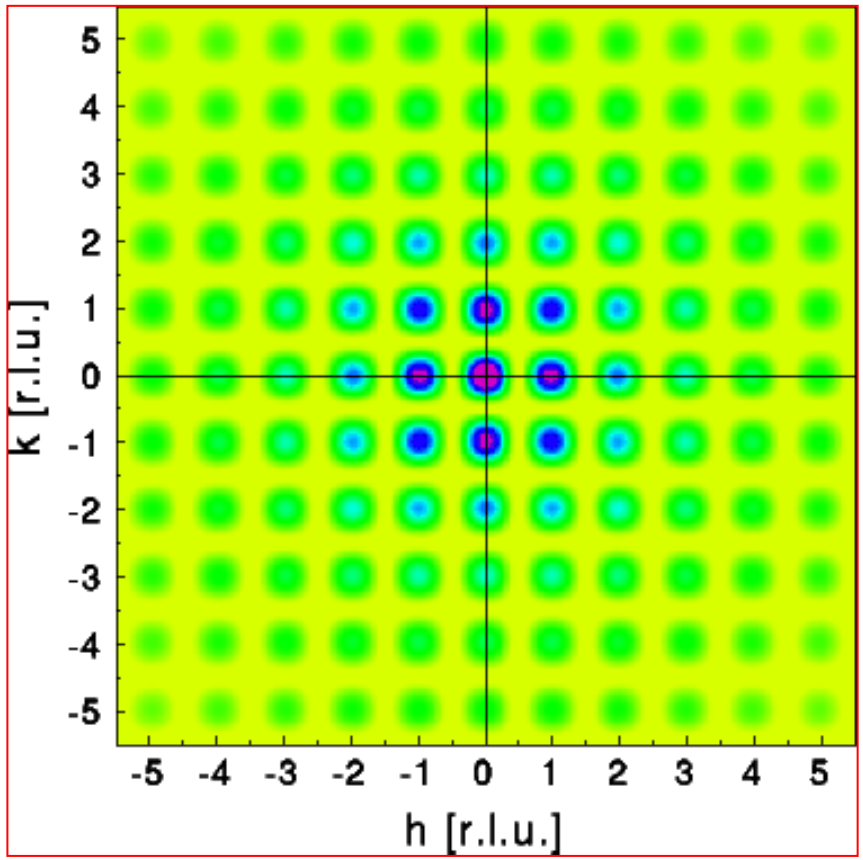

y [l.u.]
x [l.u.]
2
1
0
-1
-2
0
1
2


k [r.l.u.]
h [r.l.u.]
5
4
3
2
1
0
-1
-2
-3
-4
-5

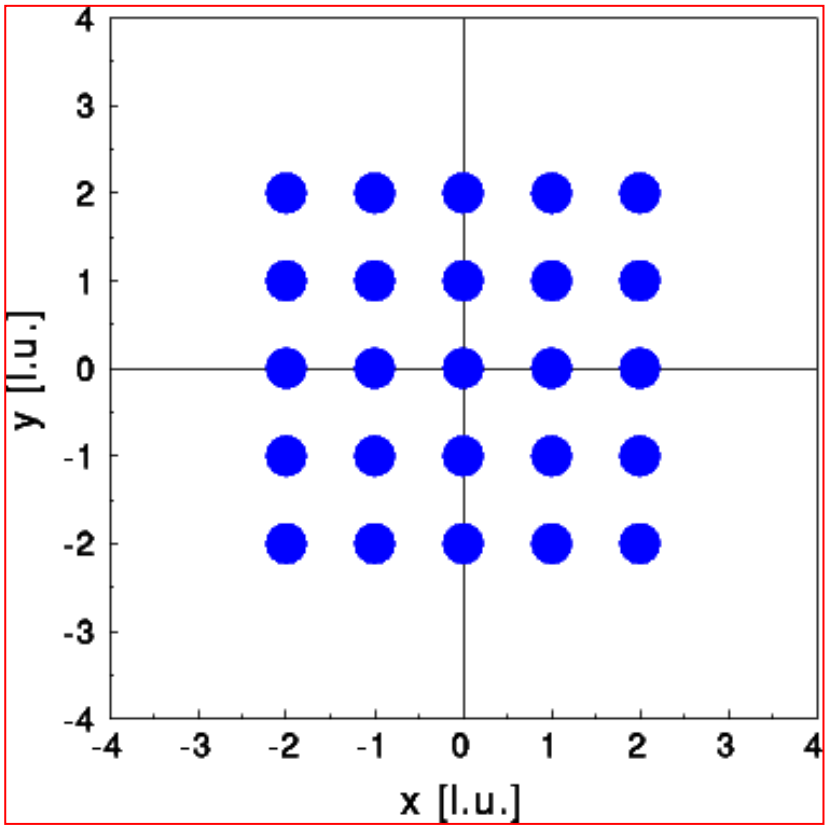

Intensity
h [r.l.u.]
5000
4000
3000
2000
1000
0
-5
-4
-3
-2
-1
0
1
2
3
4
5

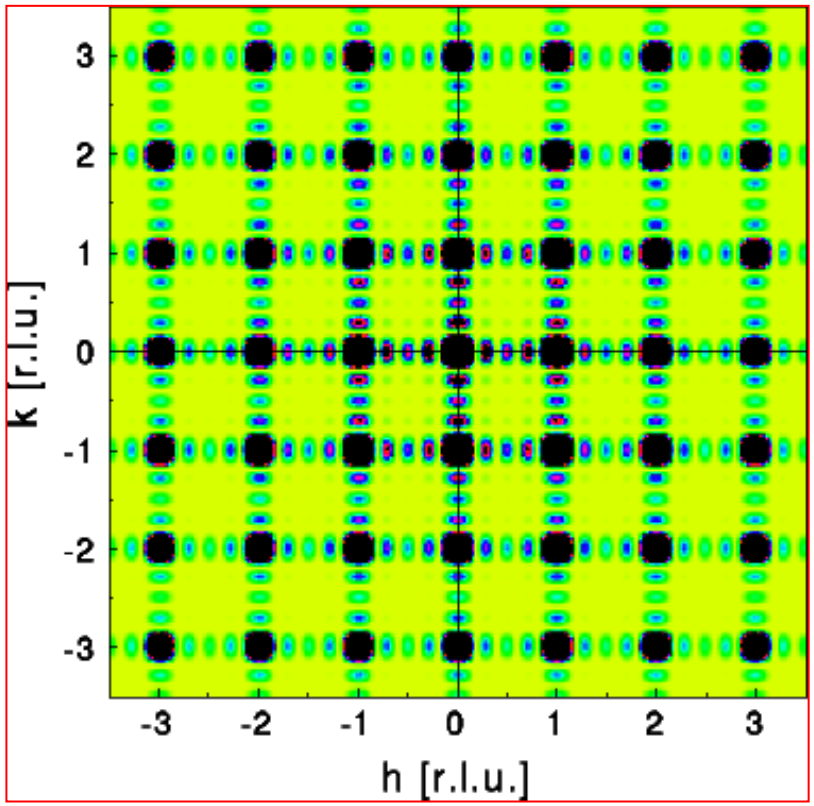
A bidimensional crystal



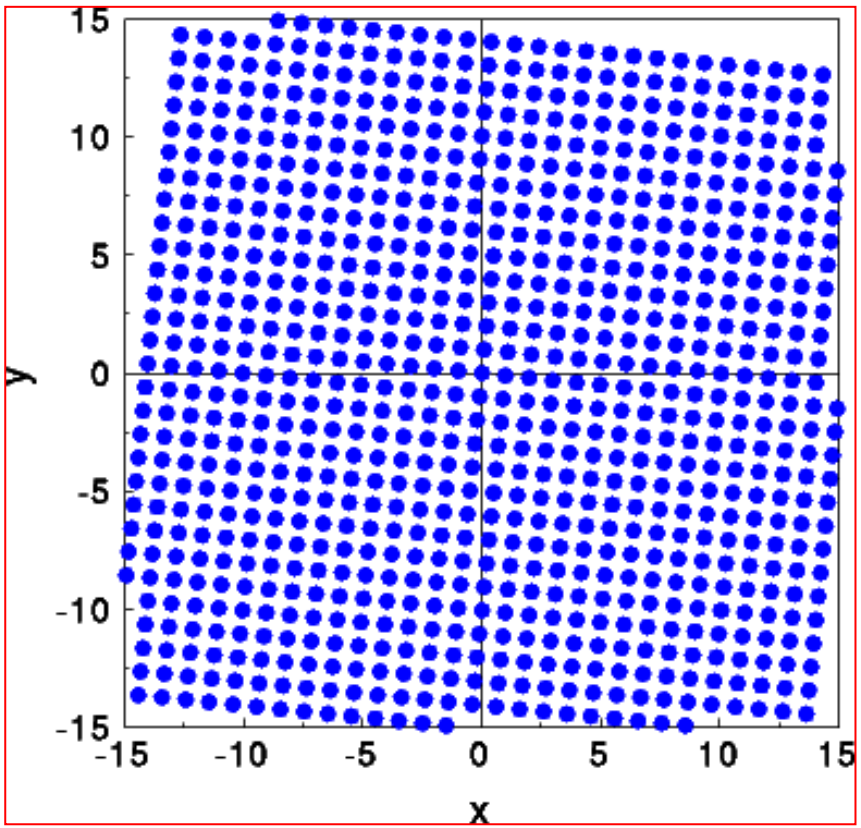


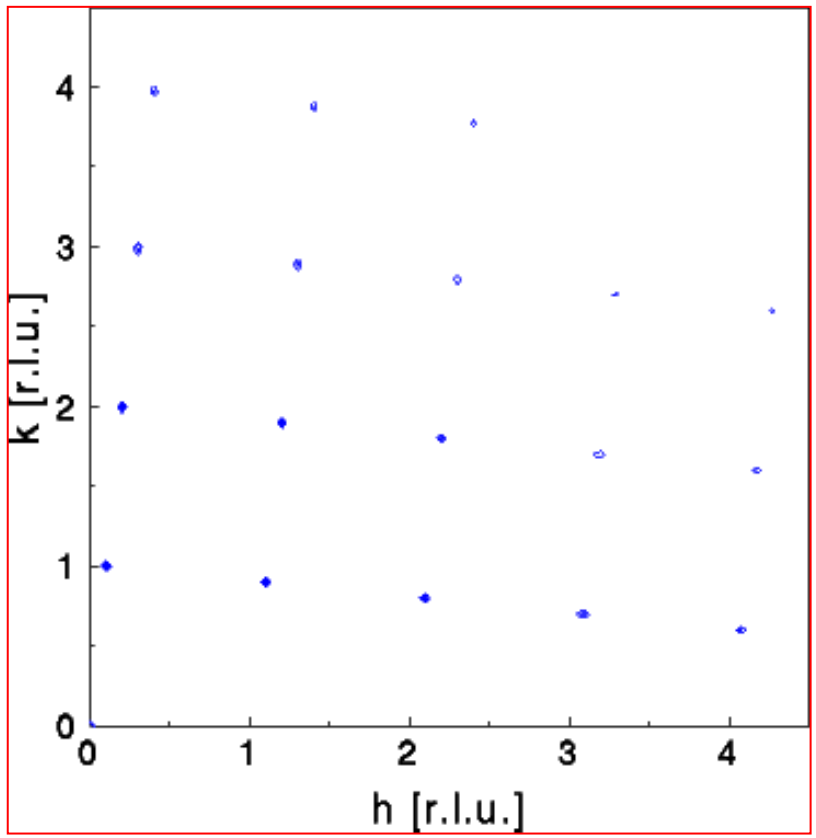
Finited crystal, limited by a square box



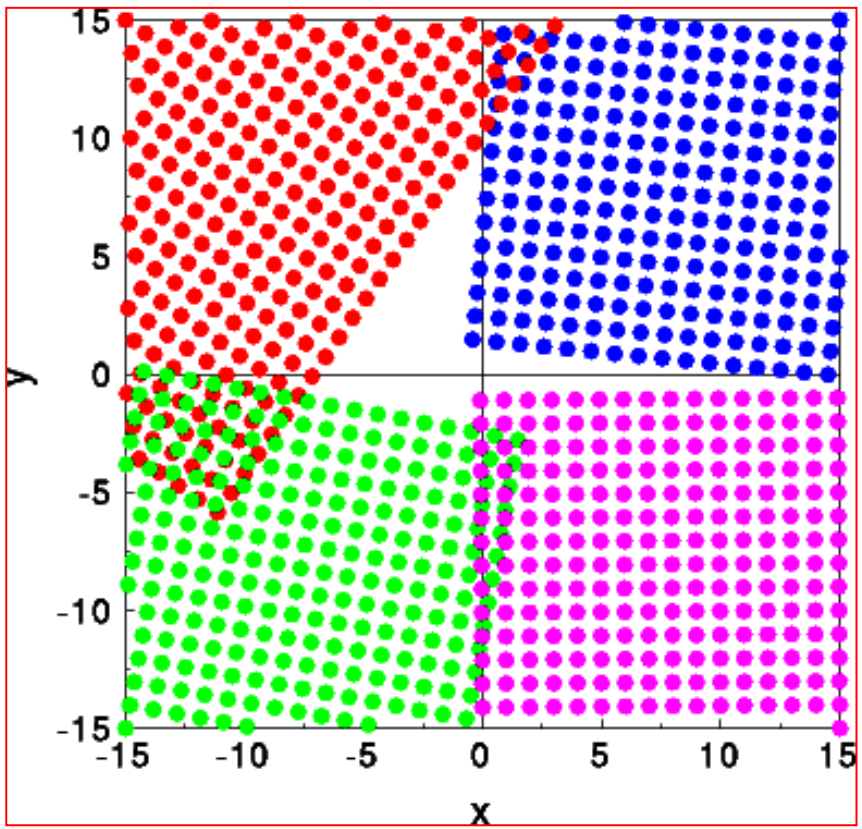


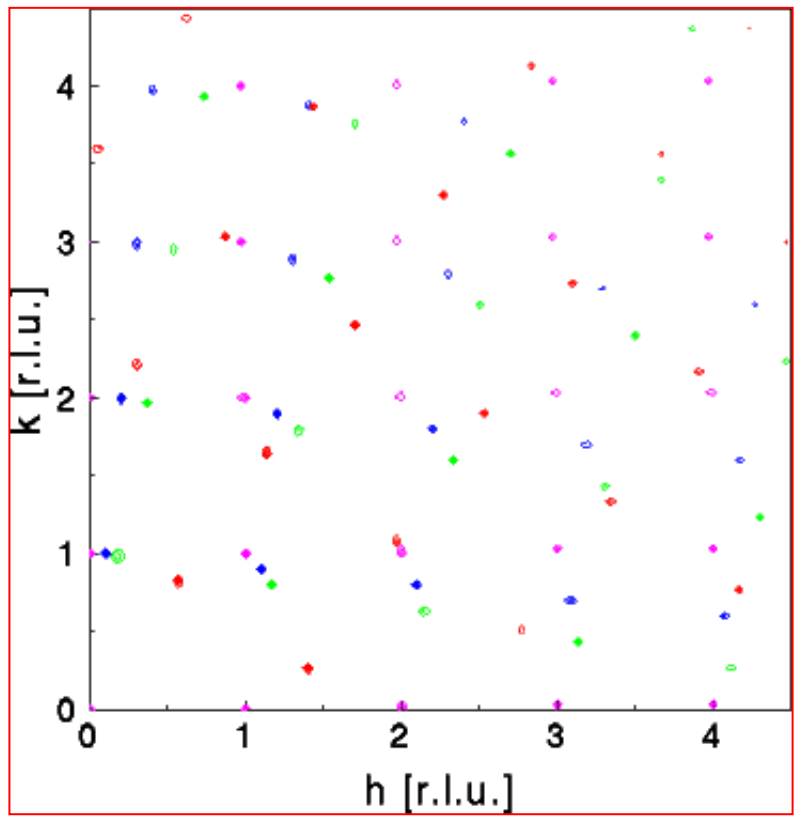
A single crystal at random orientation (i.e. rotated by a random angle) and its corresponding diffraction pattern



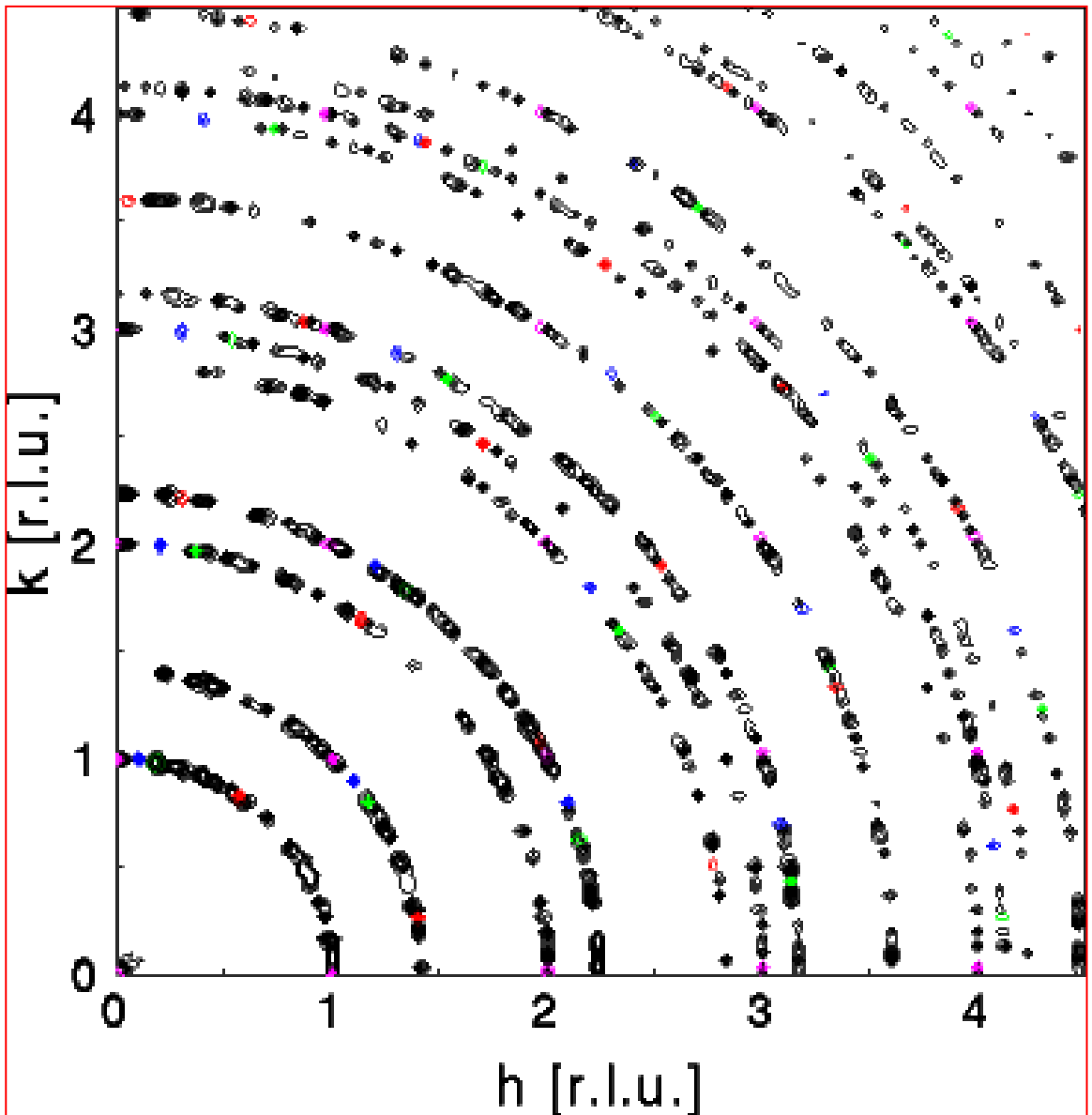


A “powder” composed of 4 single crystals in random Orientation and the corresponding diffraction pattern (same colours as the crystals)

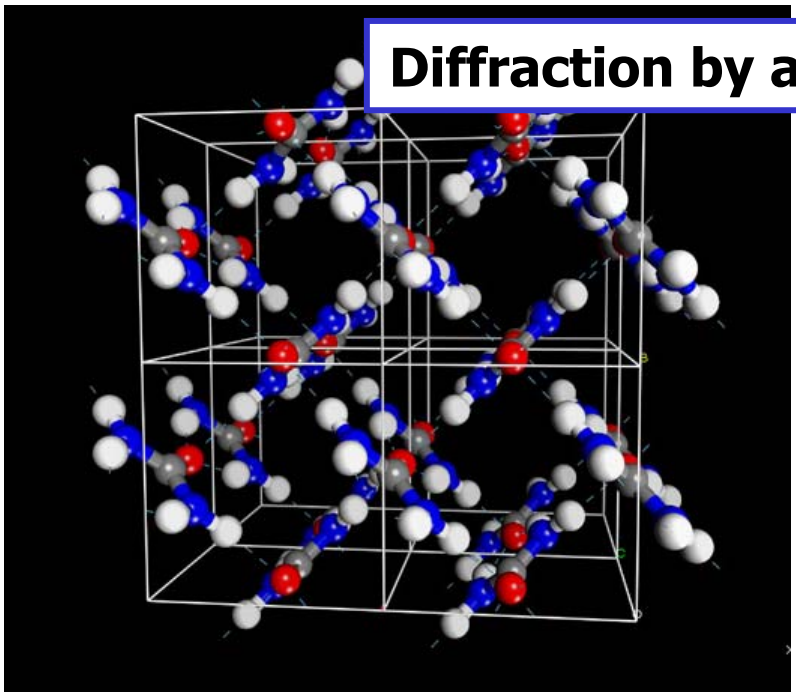


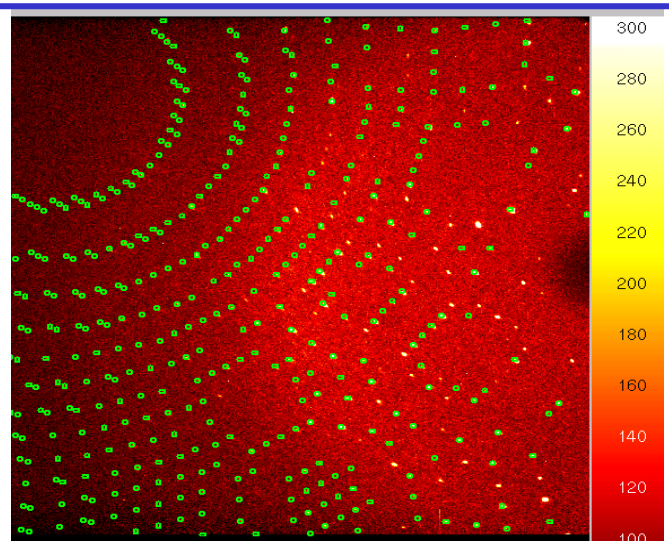


Diffraction pattern of *40* single crystals

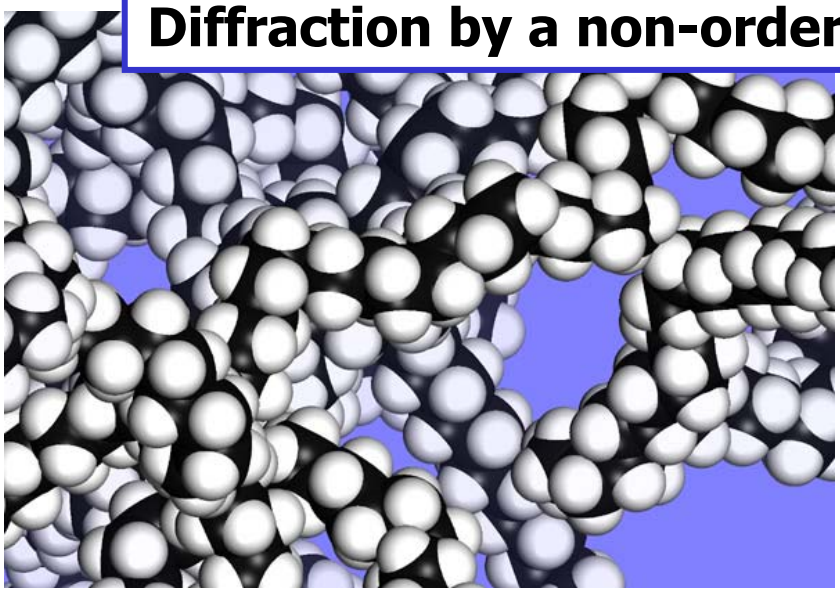


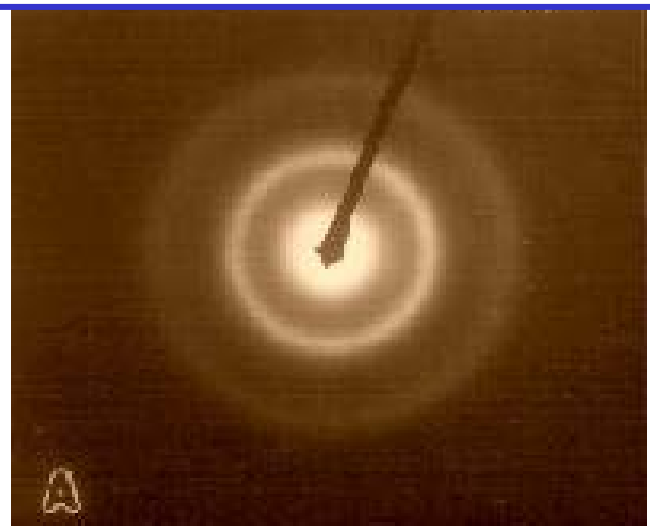
Diffraction by an ordered material, a crystal



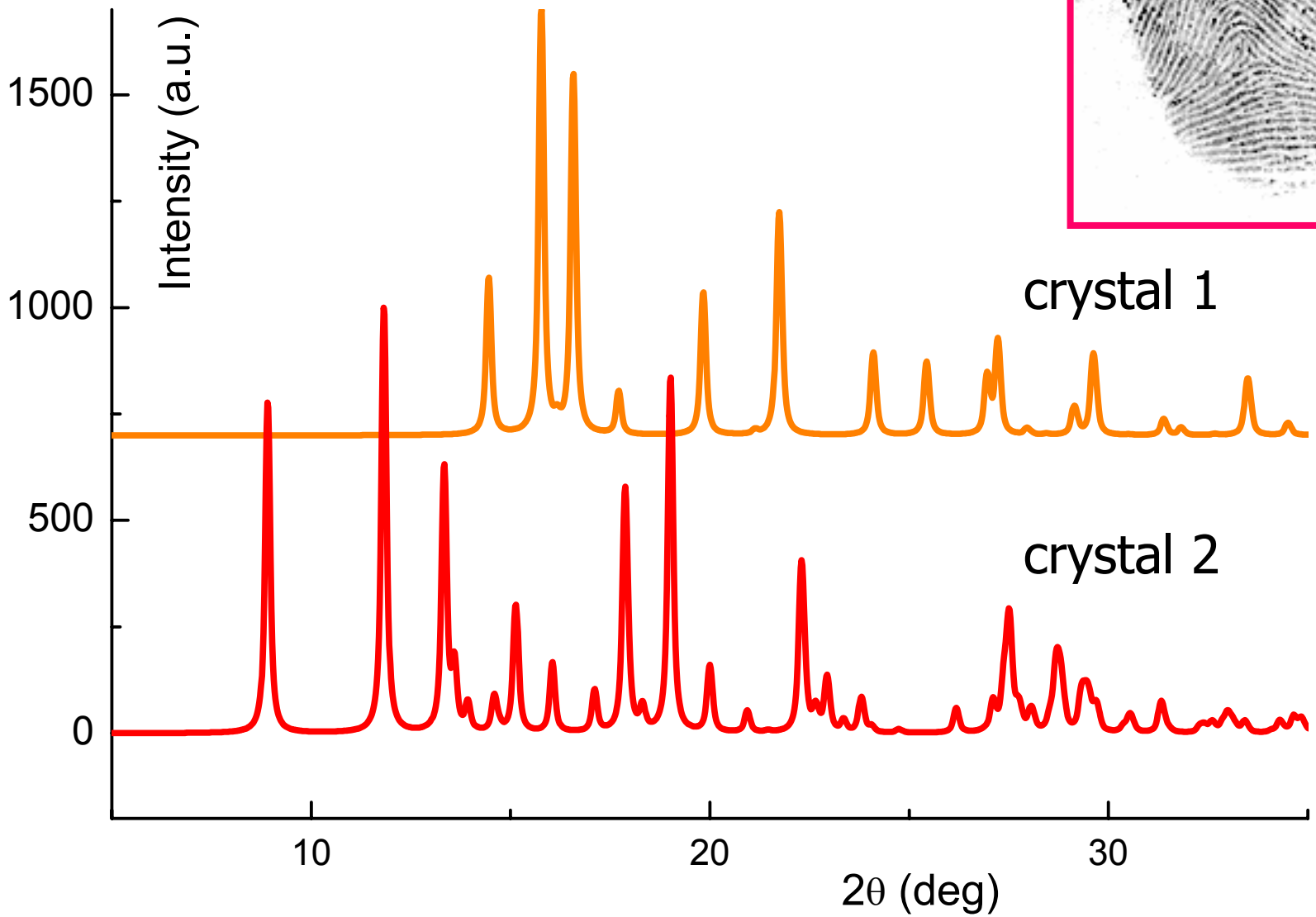


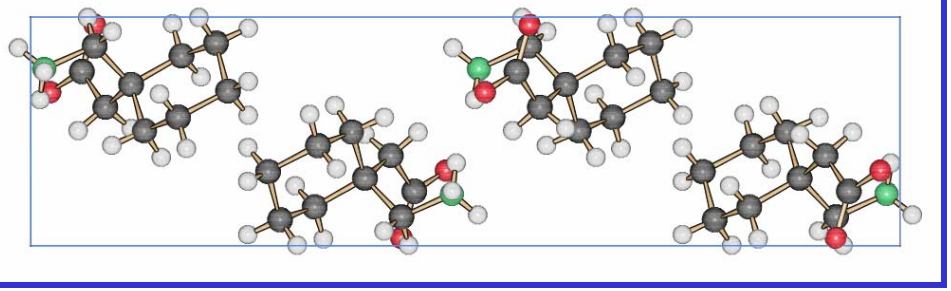
Diffraction by a non-ordered material, an amorphous

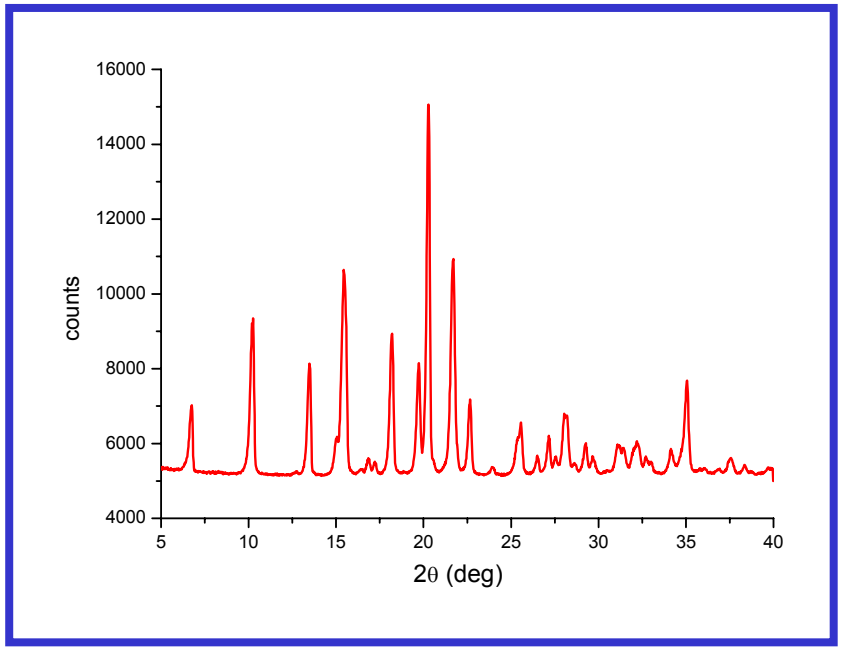


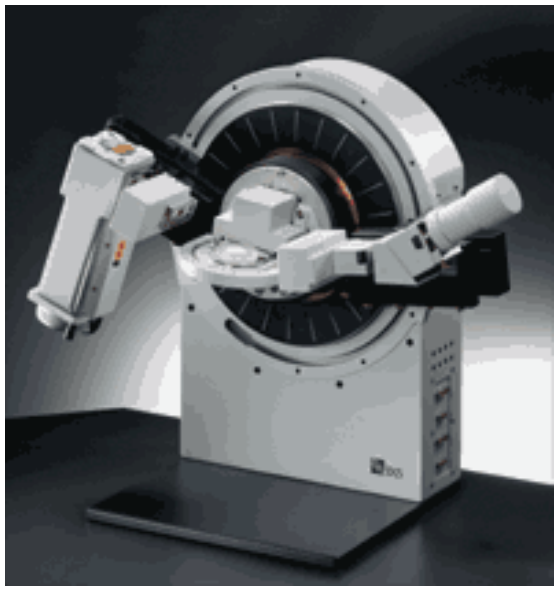


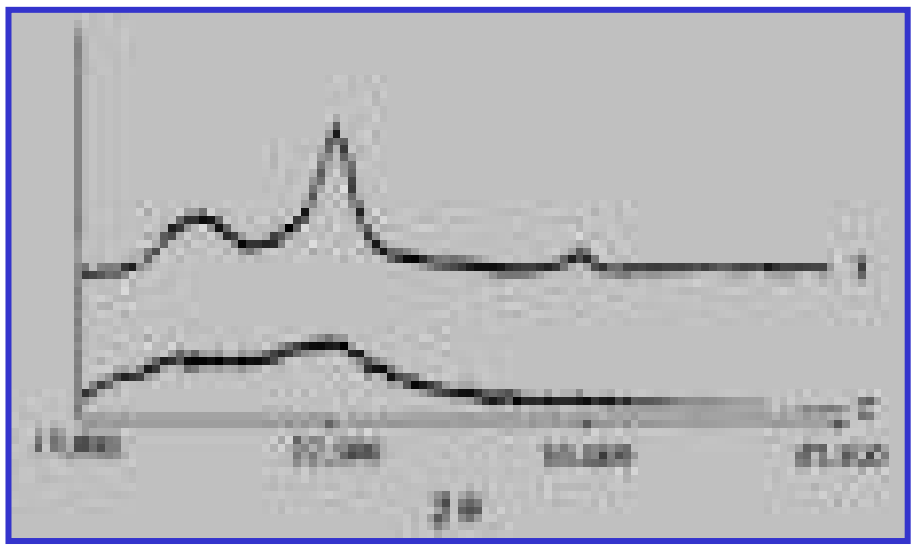
Powder diffraction pattern = fingerprint

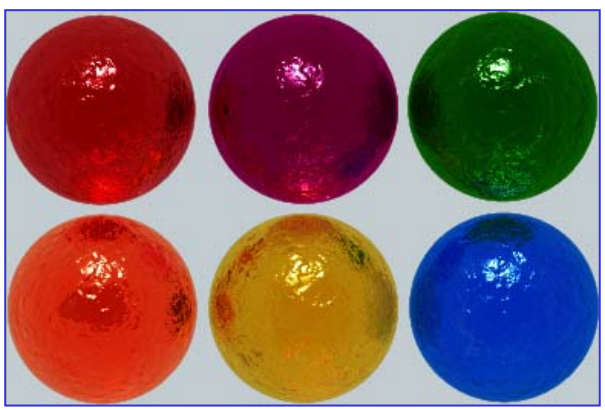




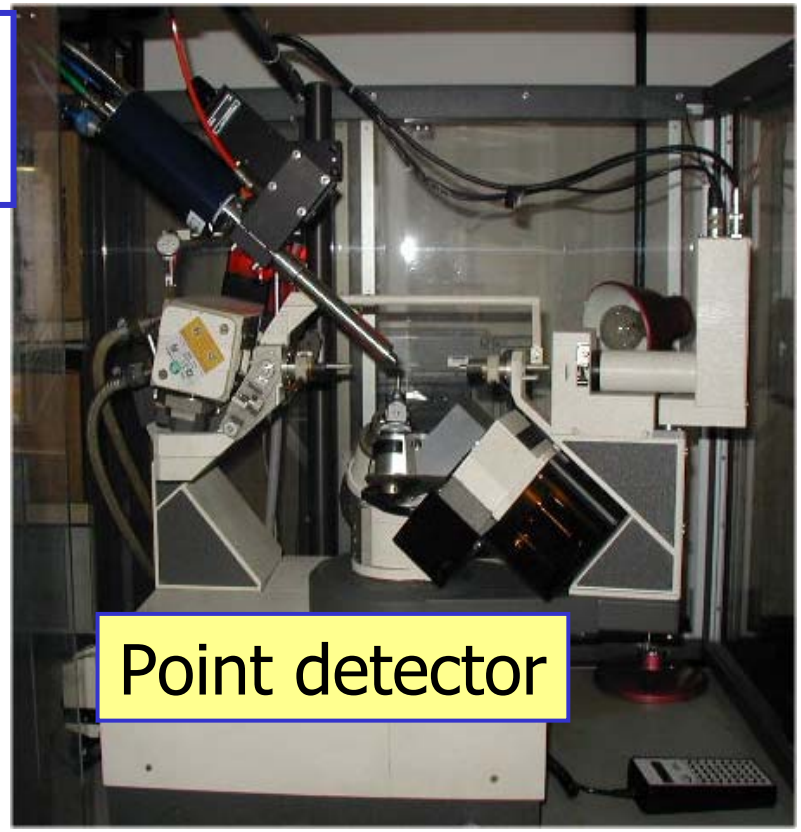

16000
14000
12000
10000
8000
6000
4000
counts
5
10
15
20
25
30
35
40
2θ (deg)







An average data collection takes 4-5 days



An average data collection takes ca.12-24 hours

Banche Dati Cristallografiche

Cambridge Structural Database http://www.ccdc.cam.ac.uk

circa 300 000 strutture di cristalli molecolari e ionici contenenti molecole organiche e complessi di coordinazione ed organometallici

Protein Data Bank http://www.rcsb.org/pdb/

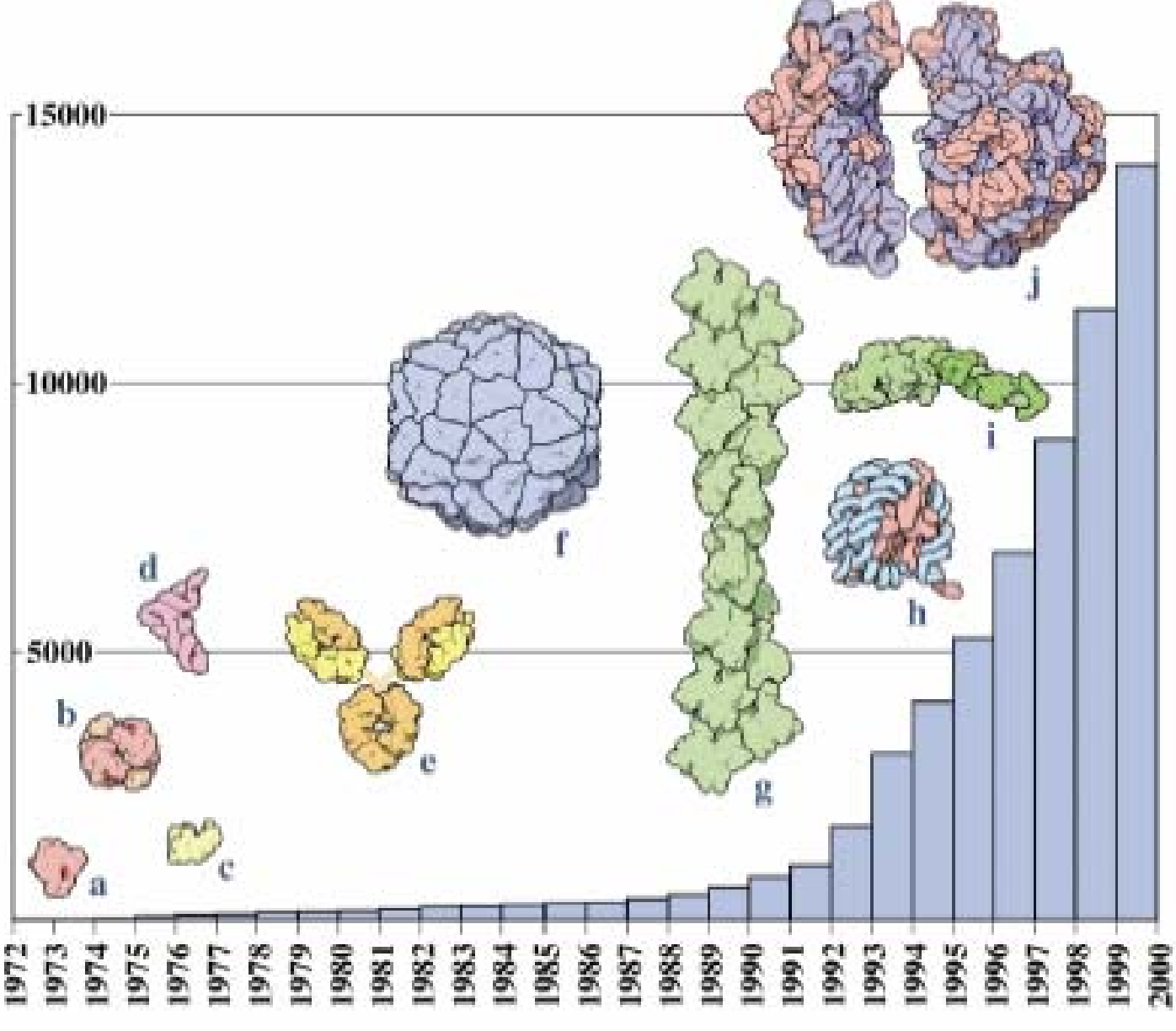
circa 20 000 strutture di proteine, acidi nucleici, virus e carboidrati

Inorganic Crystal Structure Database http://icsd.fiz-karlsruhe.de

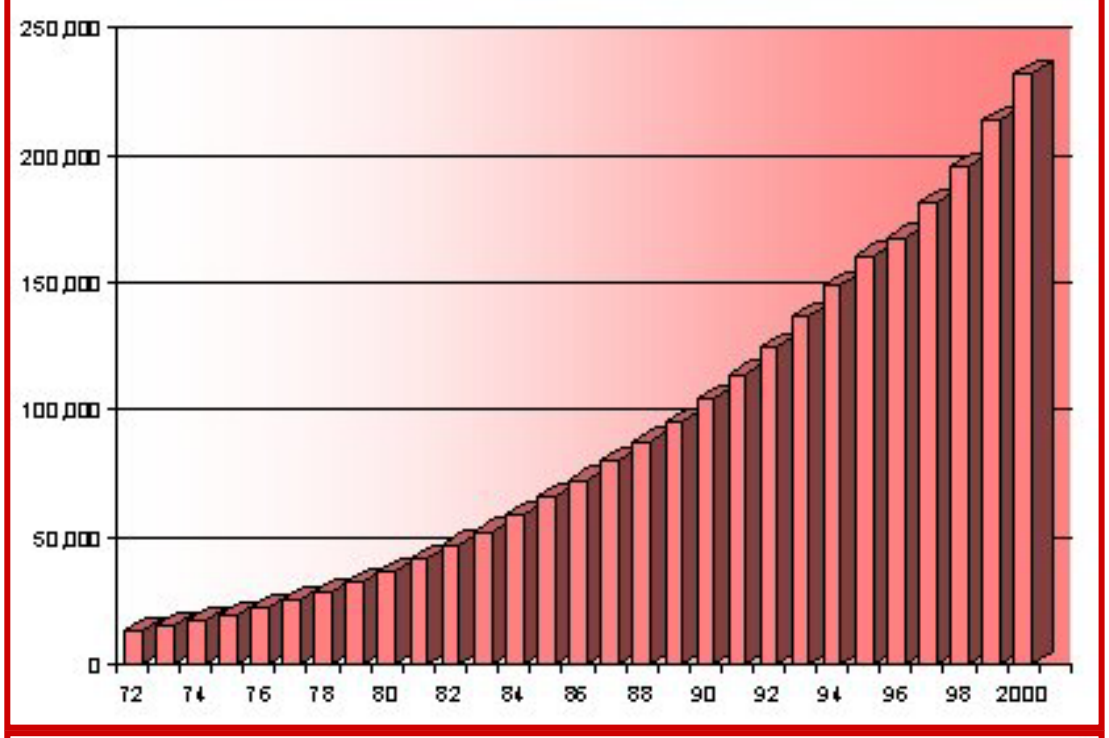
ca. 80 000 strutture i composti inorganici, ceramici, minerali, elementi puri, pubblicati dal 1915 in avanti

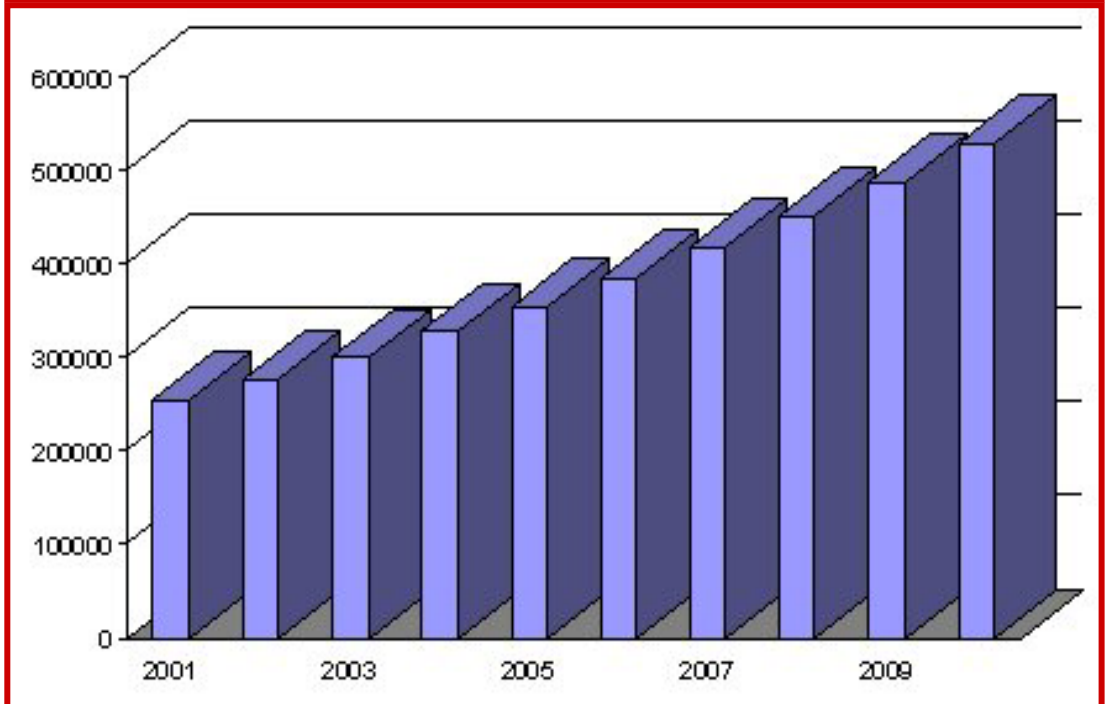
Powder Diffraction Files http://www.icdd.com

272 000 set di dati di diffrazione di polveri



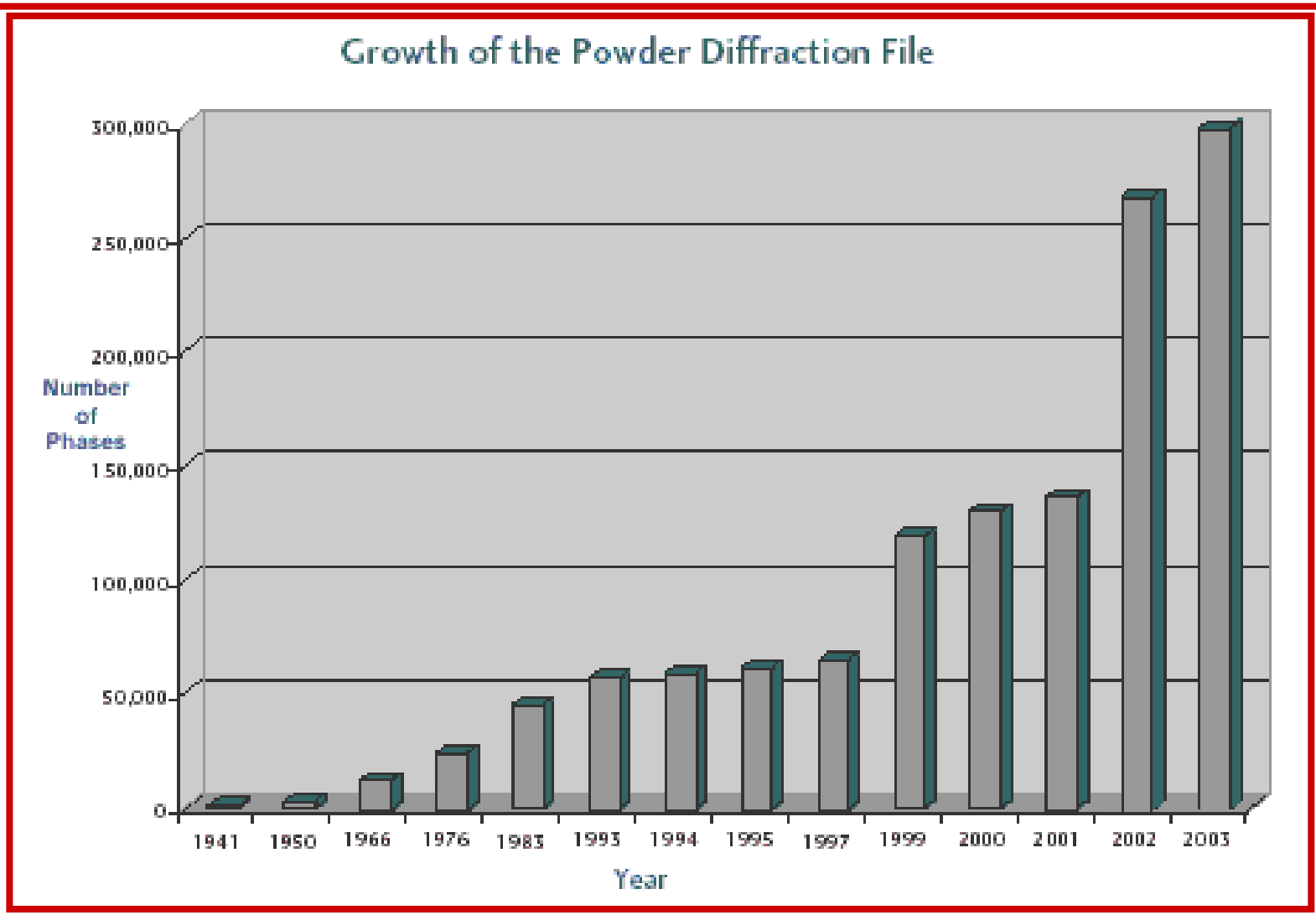
La PDB Protein Data Bank contiene circa 20000 strutture di proteine, acidi nucleici, virus, e carboidrati determinate sperimentalmente mediante diffrazione di raggi-X o NMR.

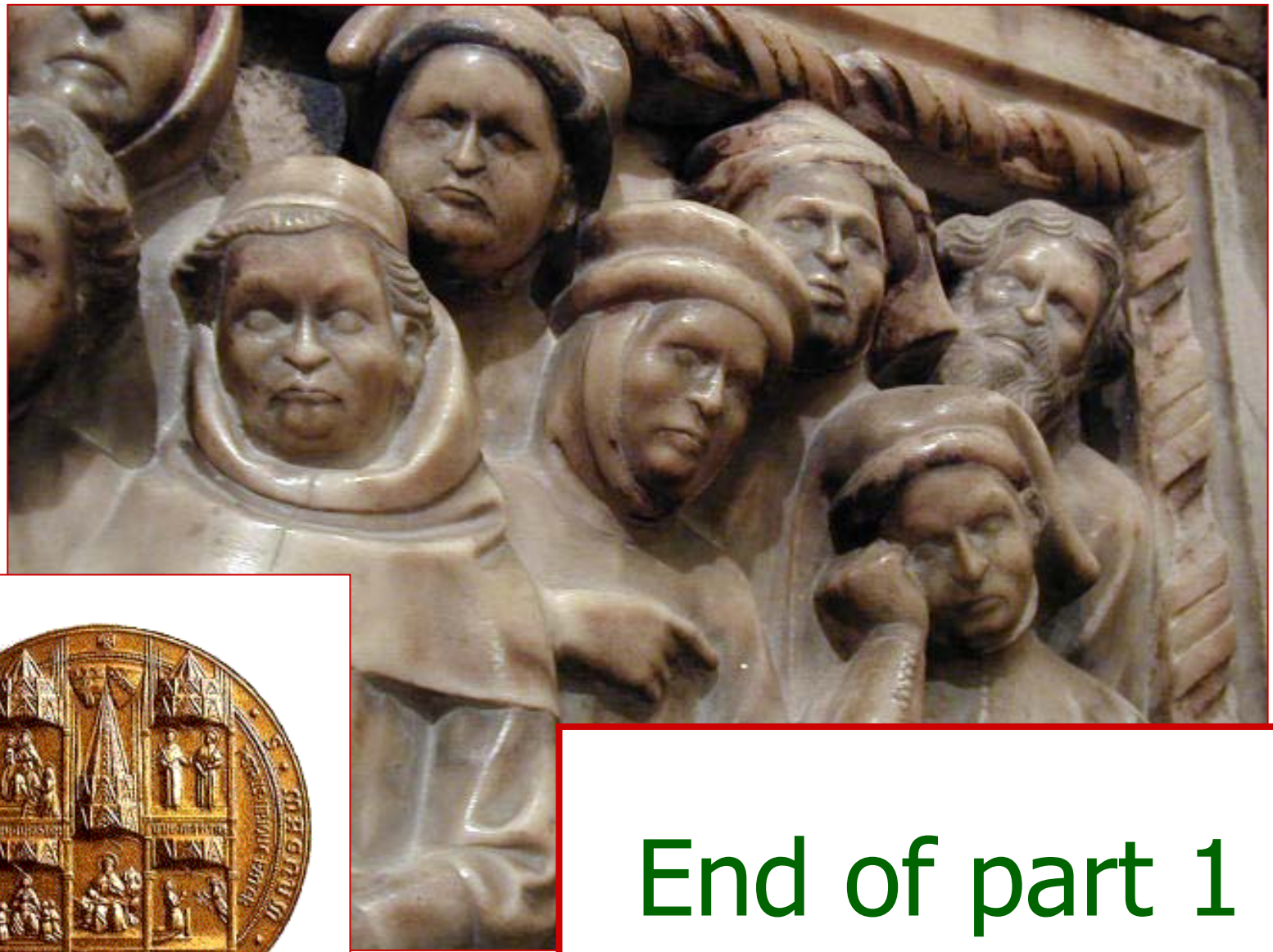




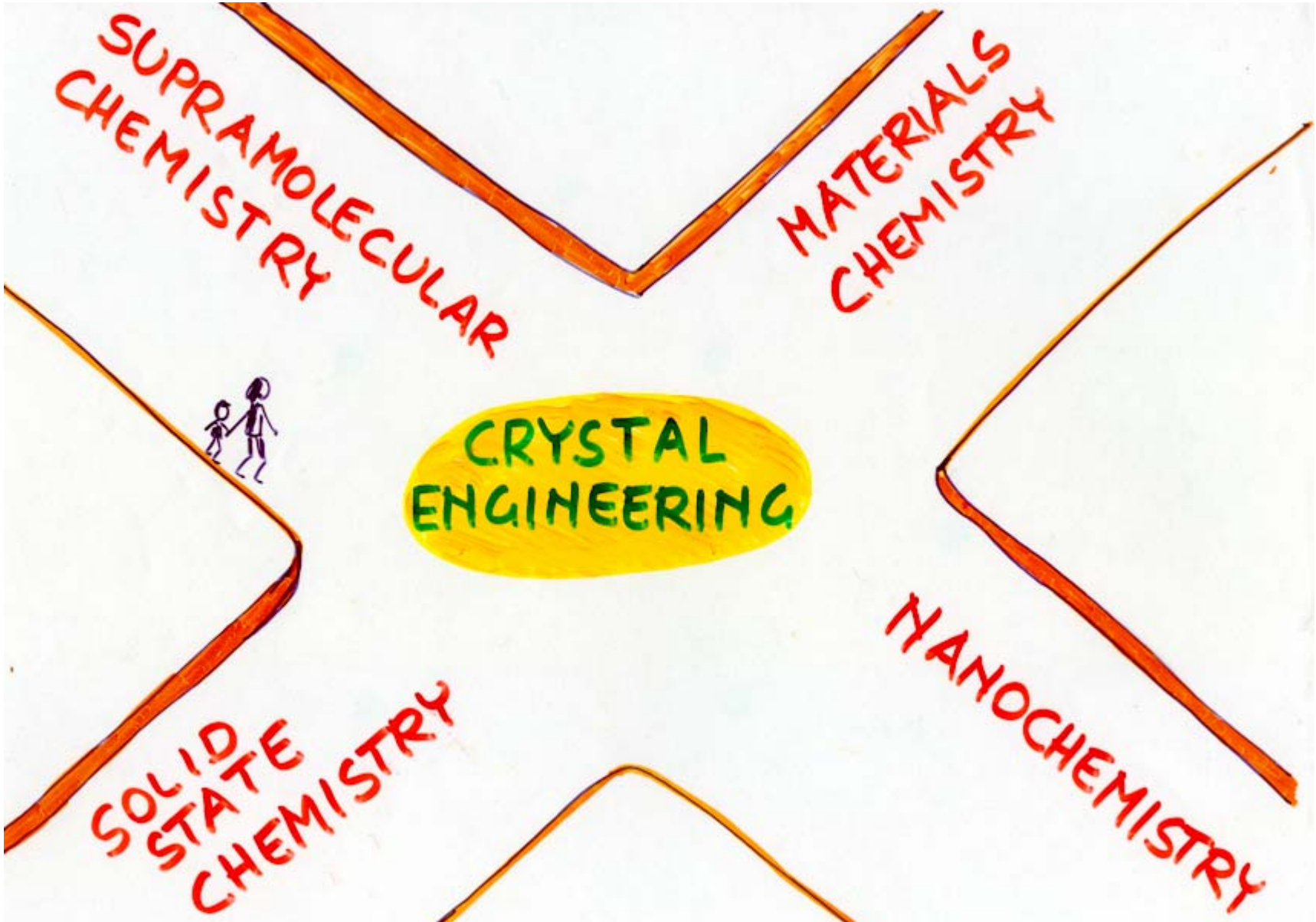
La CSD (Cambridge Structural Database) contiene ca. 300000 strutture determinate mediante diffrazione di raggi X e di neutroni di composti contenenti almeno un atomo di carbonio

Il PDF **Powder Diffraction File** contiene 272000 set di dati di diffrazione di polveri, spesso integrati con i diffrattogrammi calcolati sulla base delle strutture determinate mediante diffrazione di raggi X da cristallo singolo.





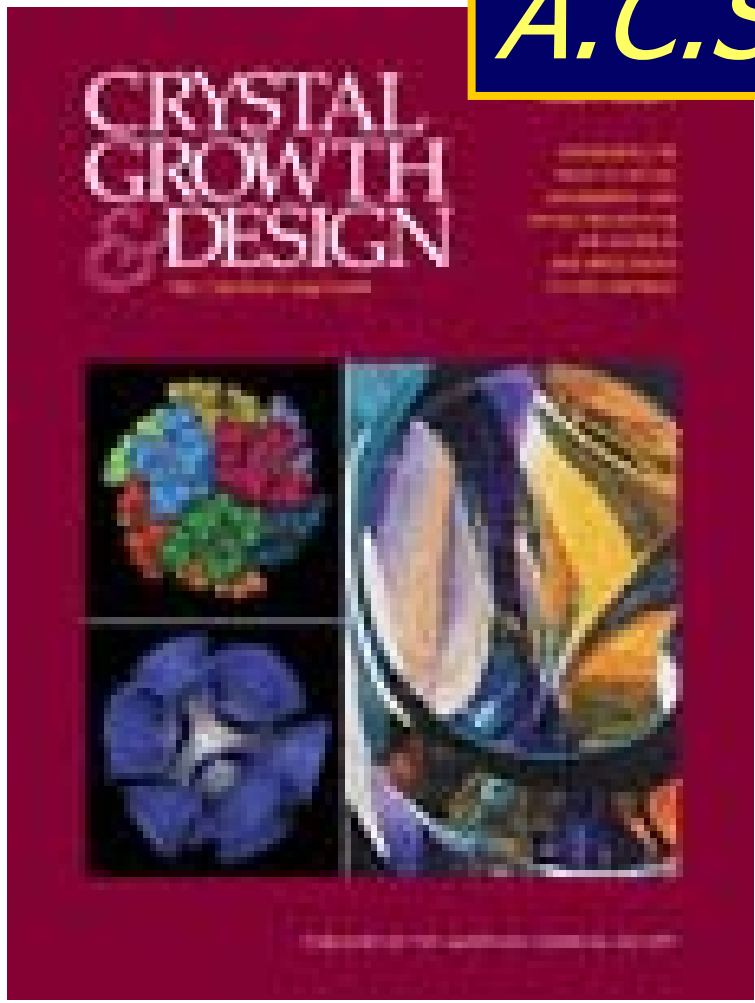
End of part 1



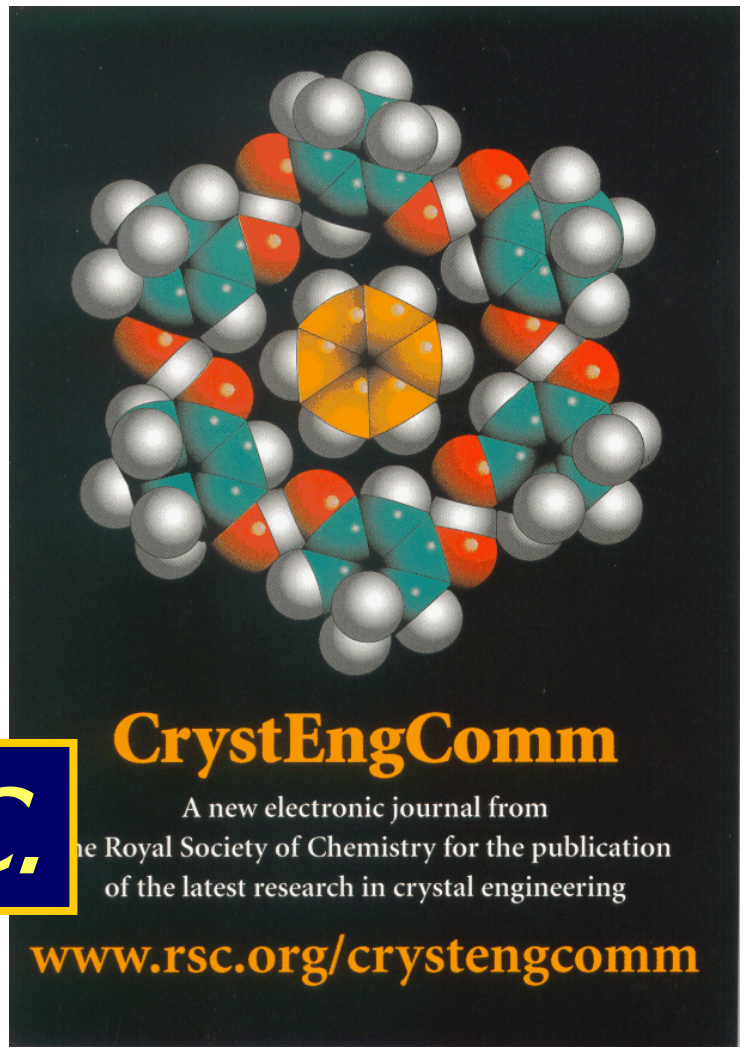
Crystal Engineering is at the intersection of supramolecular and materials chemistry with solid state chemistry and nanochemistry

Journals.....

A.C.S.



R.S.C.



PHOTODIMERIZATION IN THE SOLID STATE

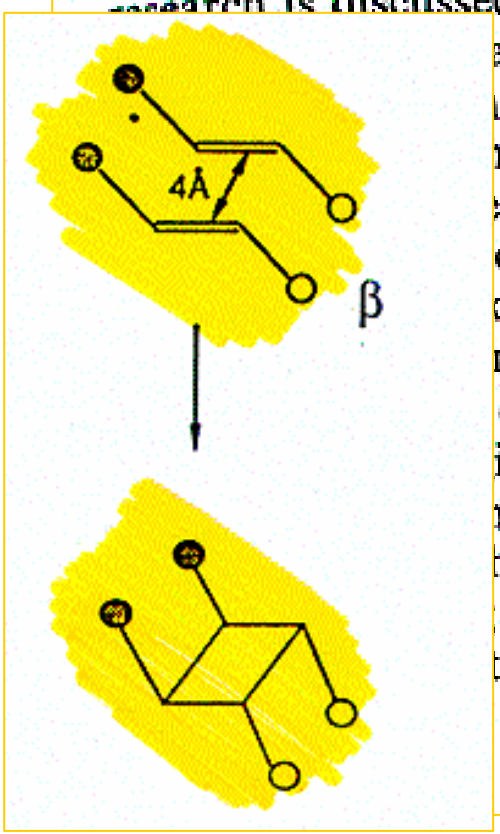
G. M. J. SCHMIDT

Department of Chemistry, Weizmann Institute of Science
Rehovot, Israel

Schmidt, G.M.J.,
Pure Appl. Chem.
1971, *27*, 647.

ABSTRACT

Following a brief historical review of solid-state pho
research is discussed under four parallel headings: first, analysis of the *topo-*
according to which the course of the solid-state reaction
istry of the photodimer (if any) can be predicted from the
nearest-neighbour geometry of closest monomer molecules
; secondly, the study of the *locus of the reaction*, that is the
ourse of the reaction or (dimerization, *cis* → *trans* isomeriza-
ture (dislocation, grain and phase boundaries); thirdly, a
ng of the *packing principles of organic molecules* in their
enable us to construct photoreactive (or lightstable) crystal
iven monomer as well as mixed crystals of potentially co-
ners for synthetic purposes or energy-transfer studies.
hes to t
sed on general-
modes of primary amides and of dichlorophenyl derivatives
their application to a *systematic photochemistry of the solid state* discussed.



NATURE VOL. 335 15 SEPTEMBER 1988

J. Maddox 1988 - NATURE -

Crystals from first principles

A new calculation of the polymorphs of silica appears to have broken new ground in derivi structure from chemical composition. But X-ray crystallographers need not worry — yet.

ONE of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition. Who, for example, would guess that graphite, not diamond, is the thermo-

In 1987 **Margareth Etter** wrote: "*Organizing molecules into predictable arrays is the first step in a systematic approach to designing organic solid-state materials*".

In 1989 **Gautam R. Desiraju** wrote "Crystal engineering is.. …*the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties*".

Supramolecular Chemistry—Scope and Perspectives Molecules, Supermolecules, and Molecular Devices (Nobel Lecture)**

By Jean-Marie Lehn*

1. From Molecular to Supramolecular Chemistry

Molecular chemistry, the chemistry of the covalent bond, is concerned with uncovering and mastering the rules that govern the structures, properties, and transformations of molecular species.

Supramolecular chemistry may be defined as "chemistry beyond the molecule," bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces. Its development requires the use of all resources of molec
lat
lecular entities, supermolecules possessing features as well

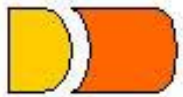
What is a (molecular) crystal if not an "organised entity of higher complexity held together by intermolecular forces" ?

Le proprietà di insiemi di molecole sono proprietà ***collettive***

risultanti dalla ***convoluzione*** delle proprietà del ***singolo componente*** (atomo/molecola) con le ***regole*** di aggregazione e ripetizione dell'insieme di appartenza

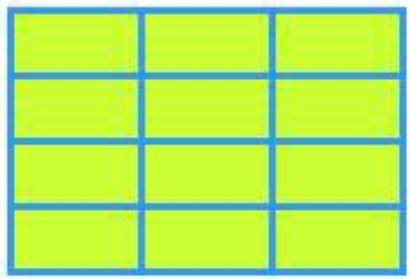
Paradigms

Non-covalent interactions



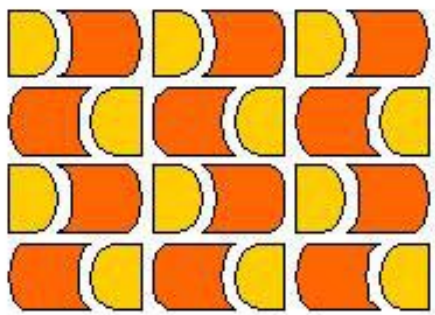
Supermolecule

Periodicity



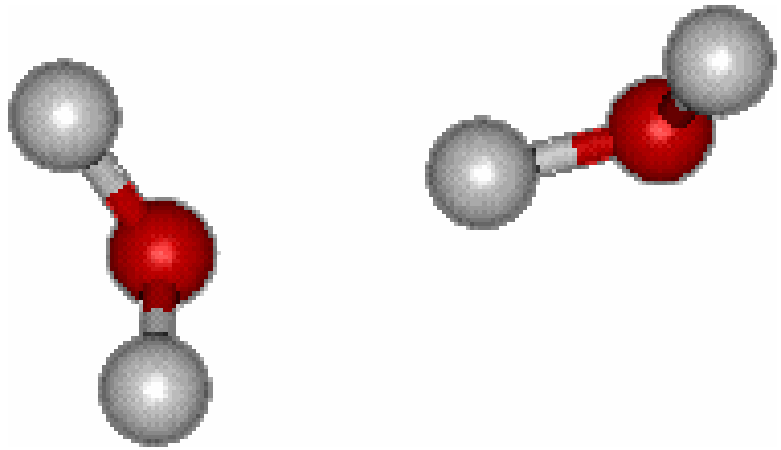
Crystal

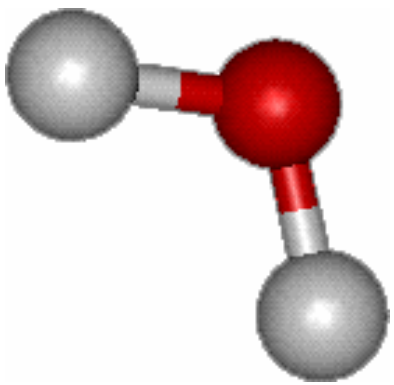
Periodical distribution of
non-covalent interactions



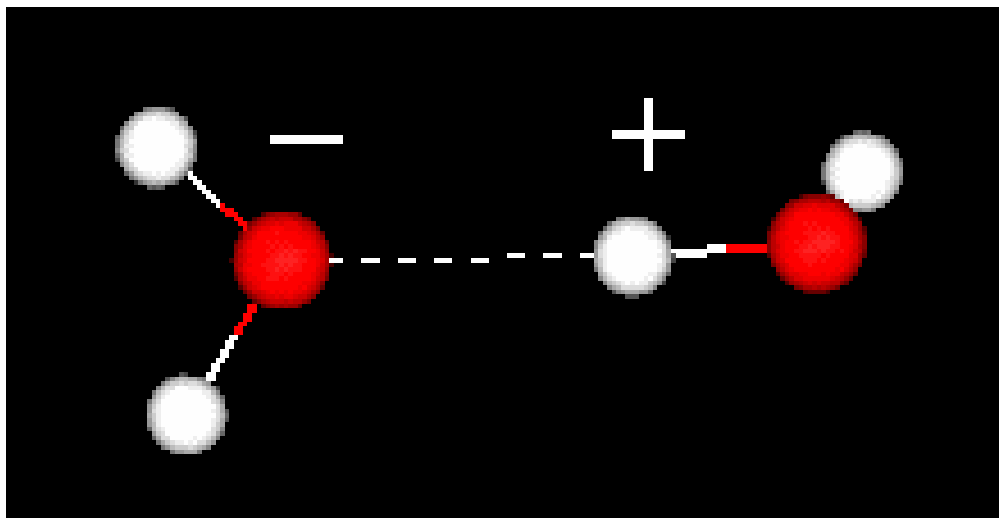
Periodical supermolecule

Ad esempio, una singola molecola d'acqua non bolle e non gela...





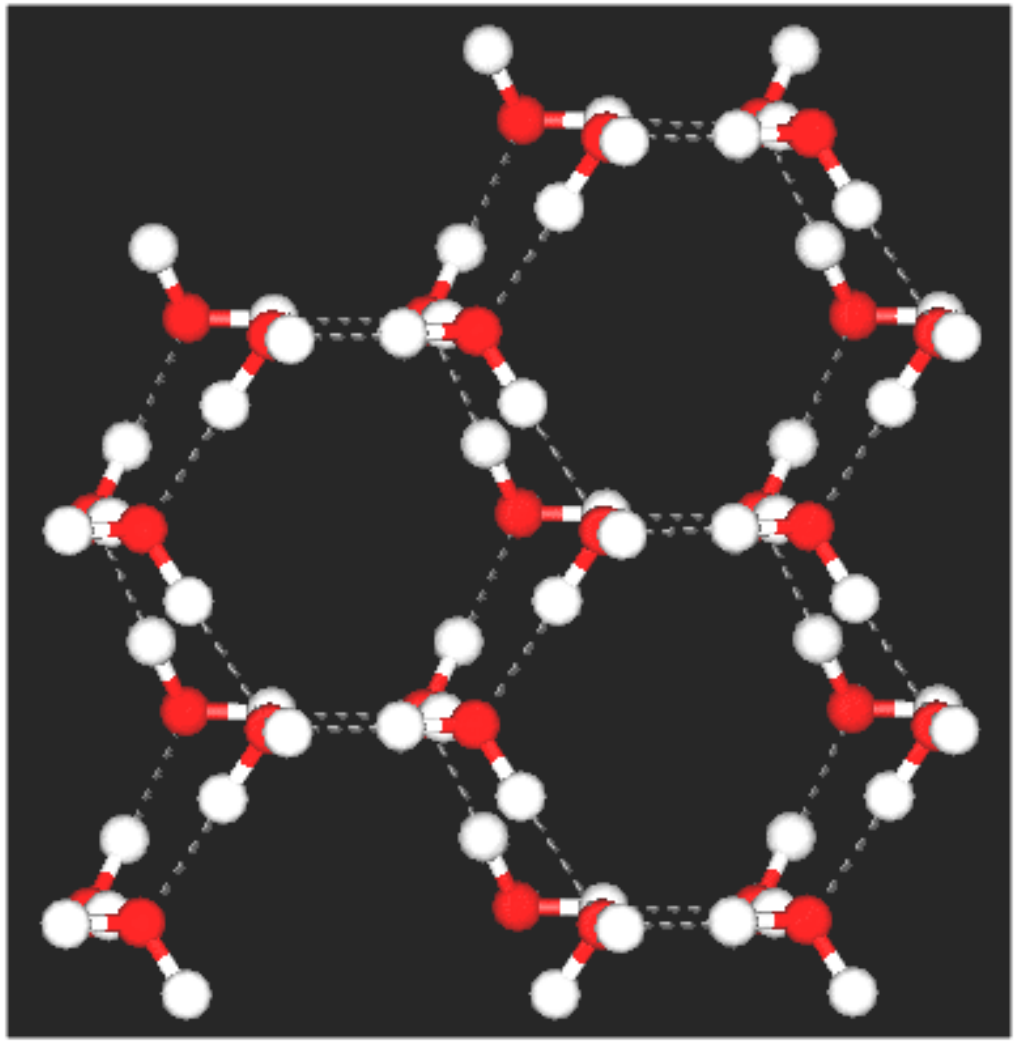
water



Il *legame a ponte di idrogeno* è responsabile di molte proprietà *collettive* dell'acqua

quali, ad esempio

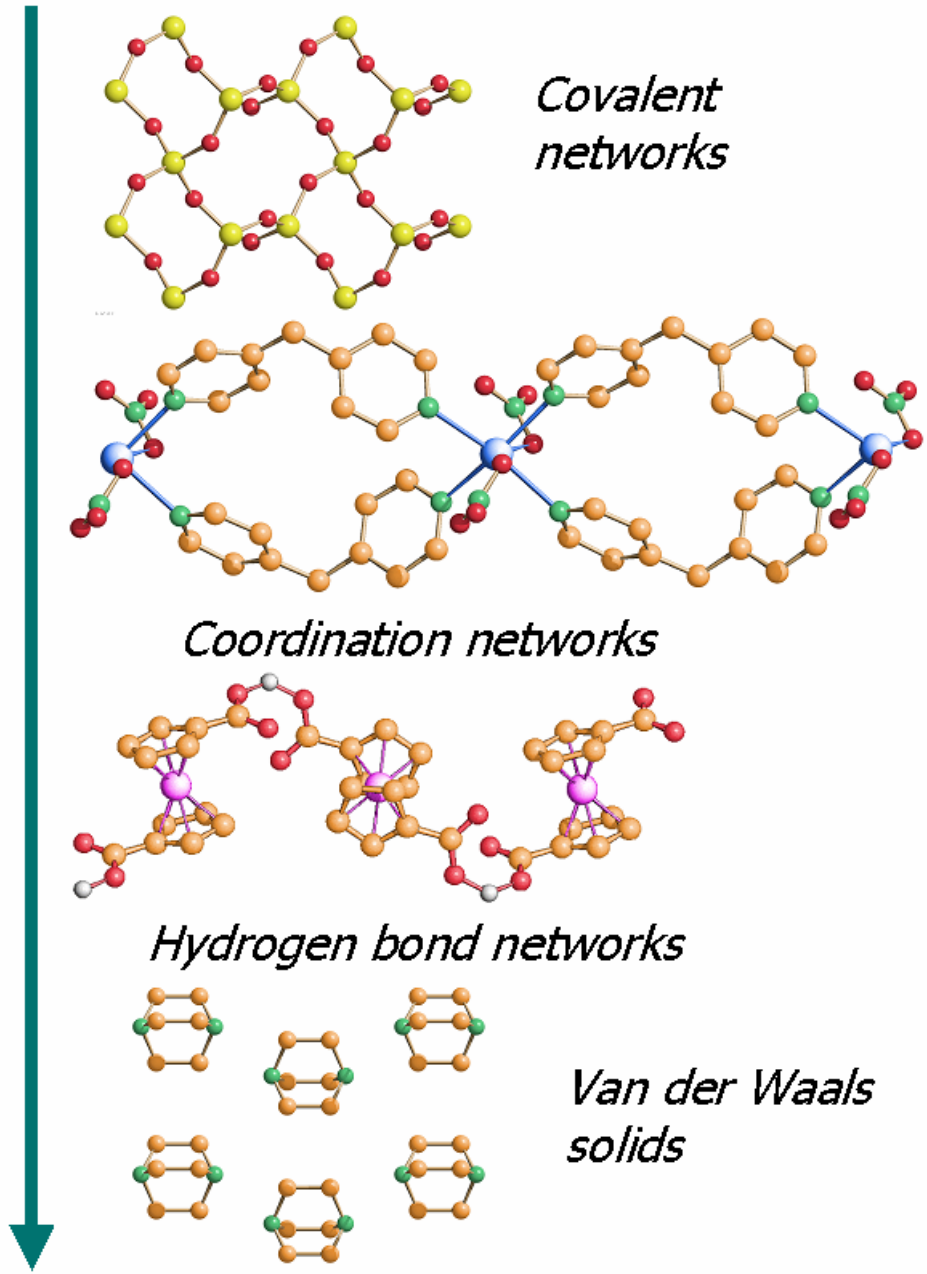
- l'intervallo di temperatura e pressione in cui essa è liquida
- il fatto che la densità della fase solida (ghiaccio) sia inferiore di quella della fase liquida



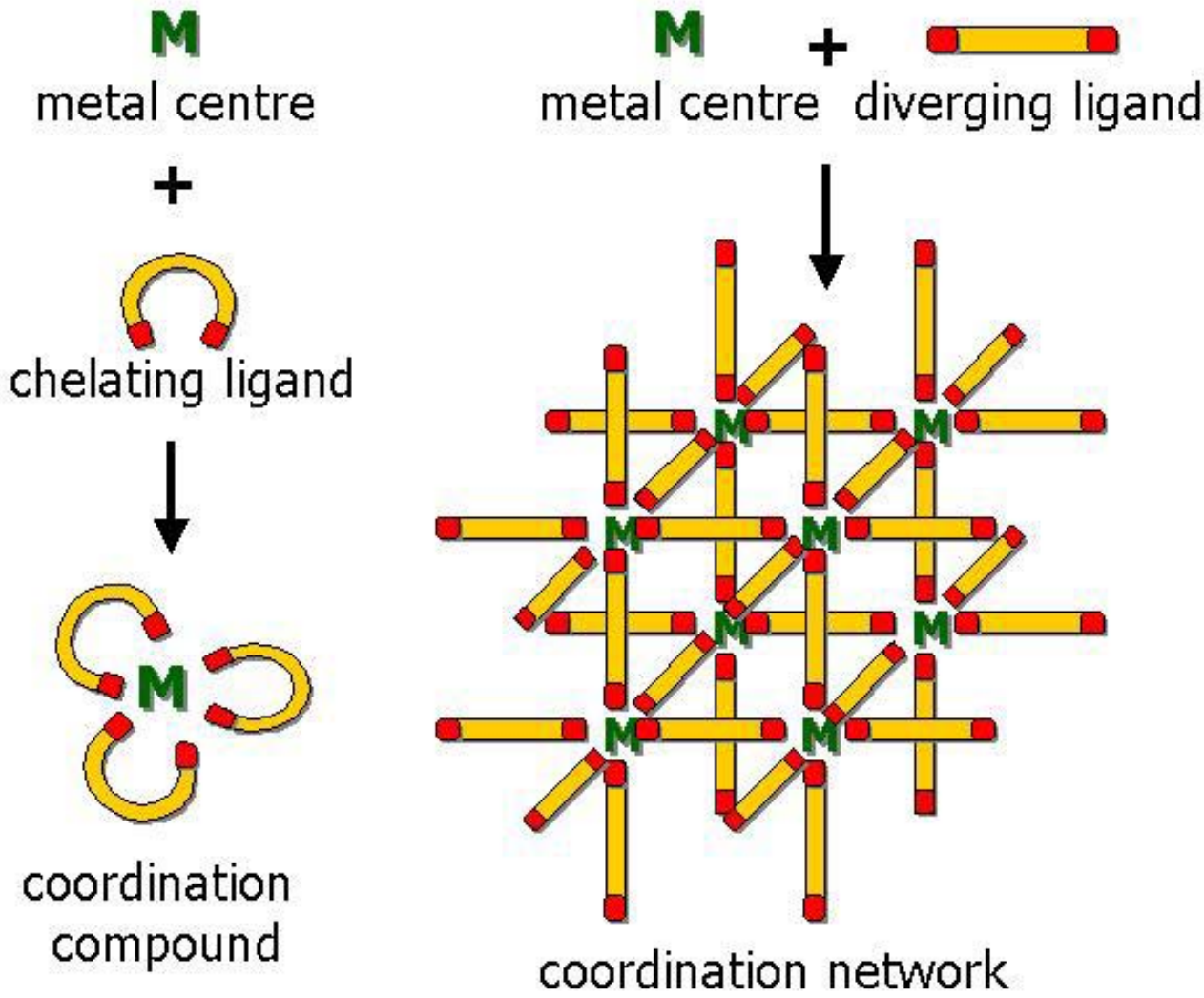
Il ghiaccio galleggia sull'acqua: un iceberg può essere visto come un immensa "super-molecola" di acqua tenuta insieme da legami idrogeno

L’acqua è un materiale da costruzione ?

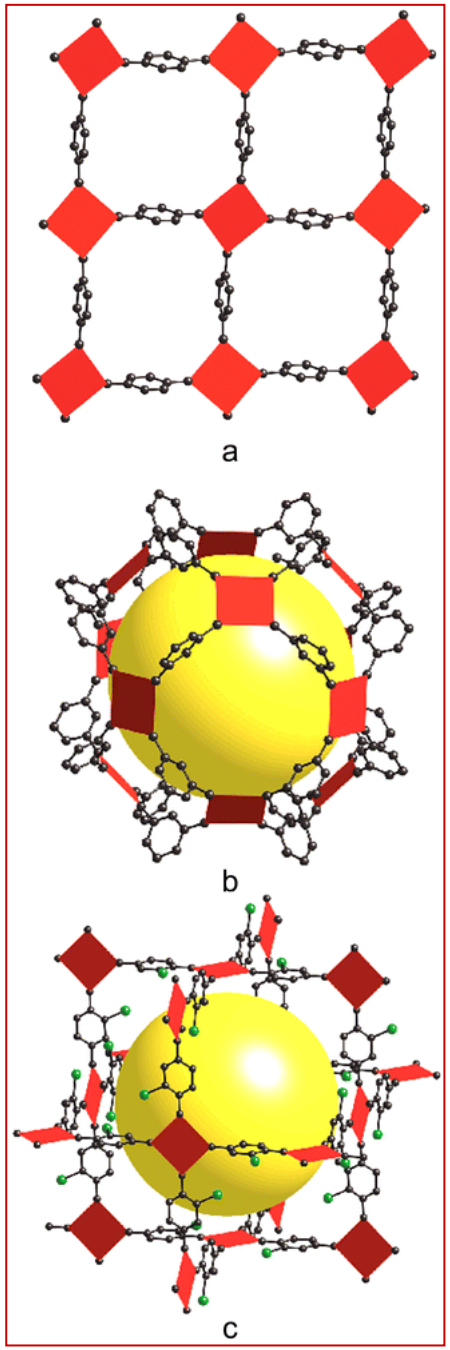
Bonding interactions between building blocks span a very wide energy range: the difference in bonding types offers a practical way to differentiate target materials, and hence synthetic strategies, as a function of the energy involved in the bond breaking-bond forming processes that lead from building block to superstructure.



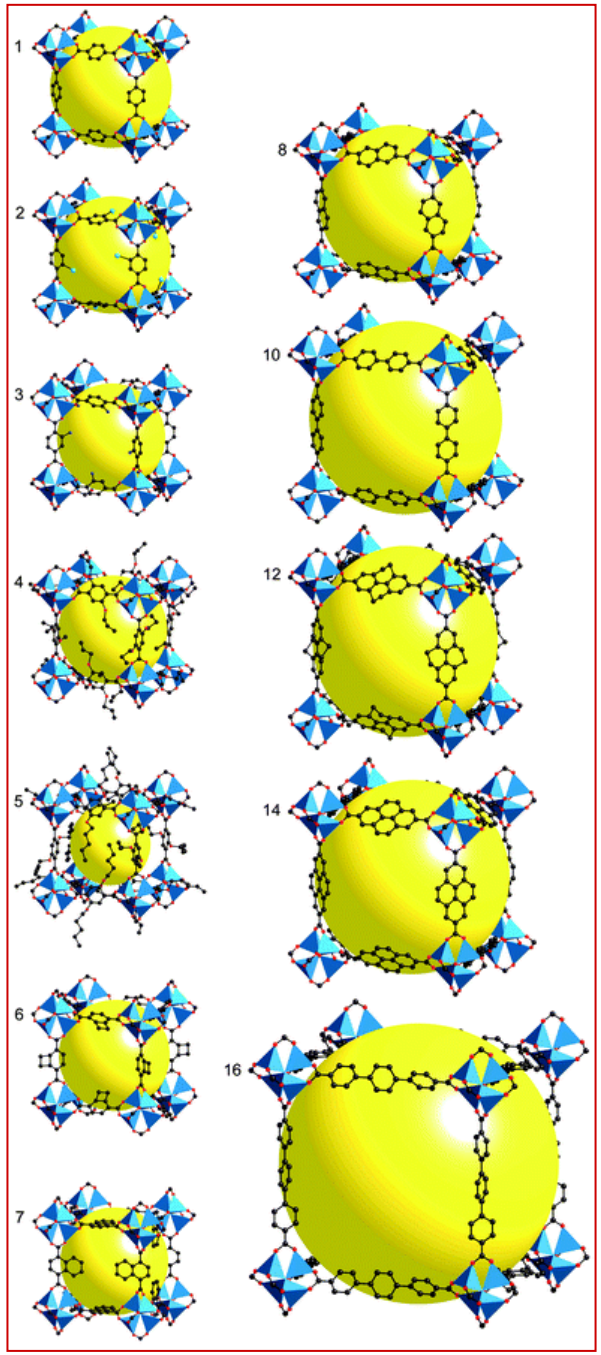
Braga D., Chem. Commun. 2003



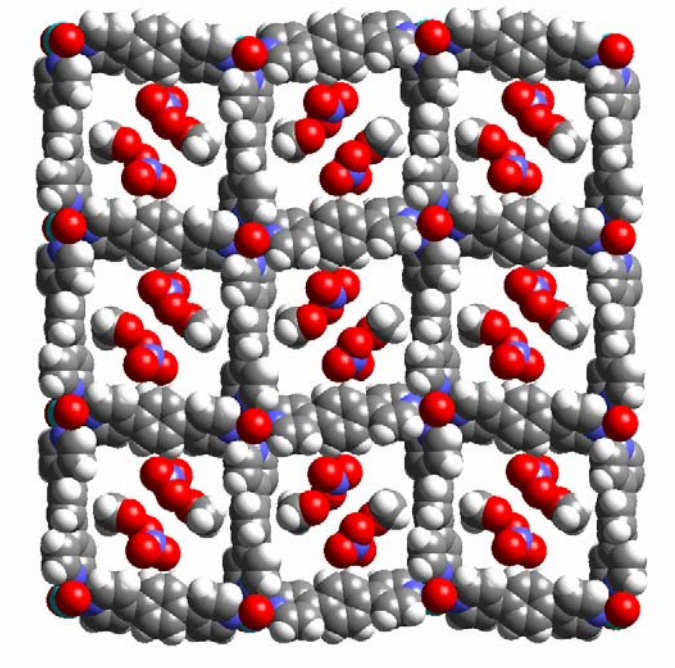
The transition from molecular to periodical coordination chemistry. From coordination complexes (top) to coordination networks (bottom): the use of bidentate ligand spacers allows construction of *periodical* coordination complexes.

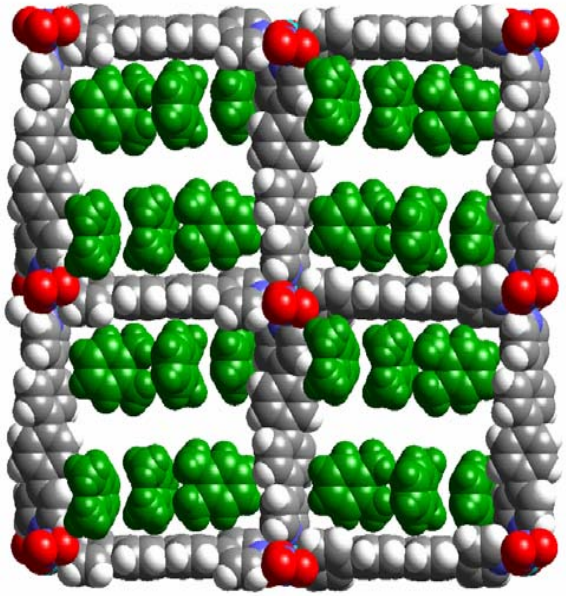


Omar Yaghi: coordination polymers based on copper acetate bridges



$[Ni(PyPhPy)_2(H_2O)_2]\cdot benzene\cdot 5MeOH\cdot 2(NO_3)_2$

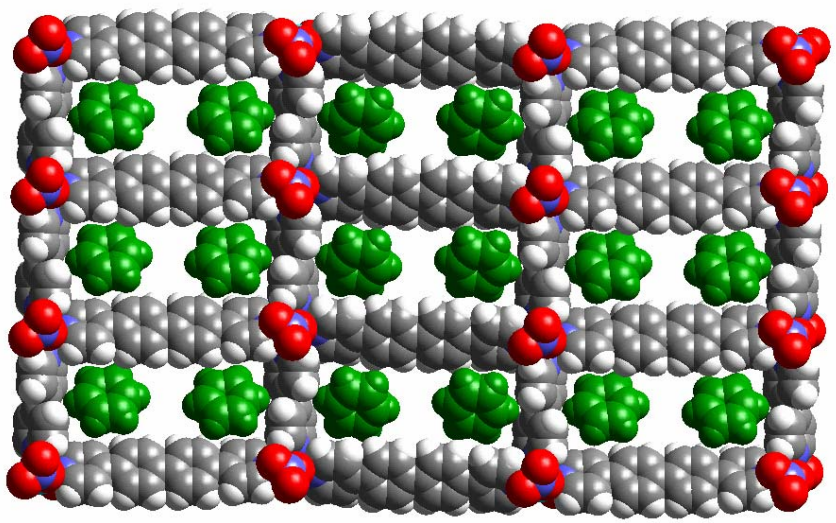


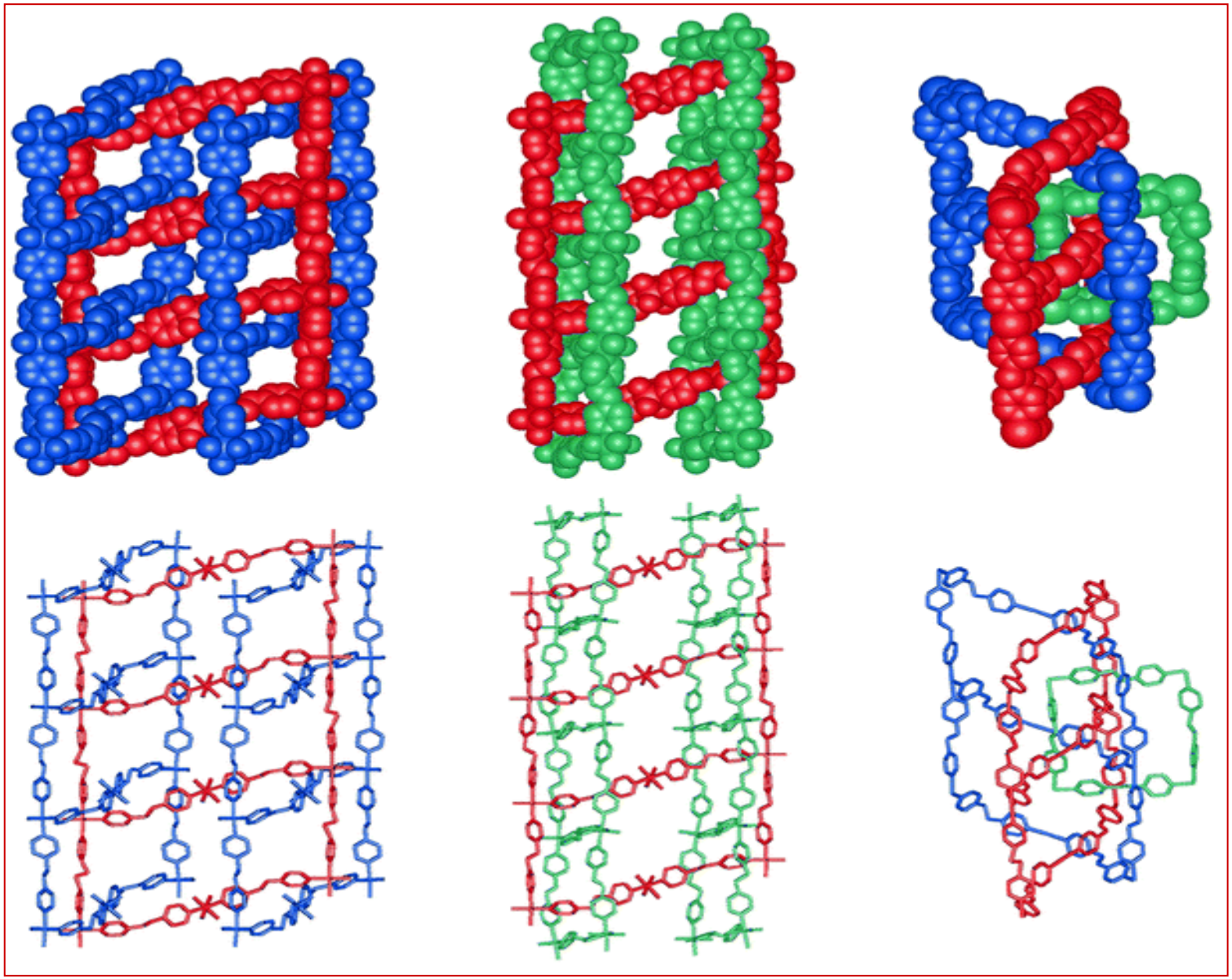


$[Ni(PyPh_2Py)_2(NO_3)_2]\cdot 4(o\text{-xylene})$

Makoto Fujita 2001

$[Ni(Py_2)(PyPh_2Py)(NO_3)_2]\cdot 8(benzene)$





Lucia Carlucci, Gianfranco Ciani*, Davide M. Proserpio and Silvia Rizzato, *CrystEngComm 2003*

Crystal engineering in Bologna

Making and using metal containing building blocks for
> Supramolecular Complexes, Coordination networks

Hydrogen bonding between ions
> Protonic conductivity in fuel cell

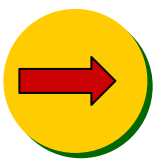
Crystal polymorphism and pseudo polymorphism
> Pharmaceutical compounds, Molecular Alloys

(Solvent-free) Molecular Solid <-> Gas Reactions
> Gas Trap

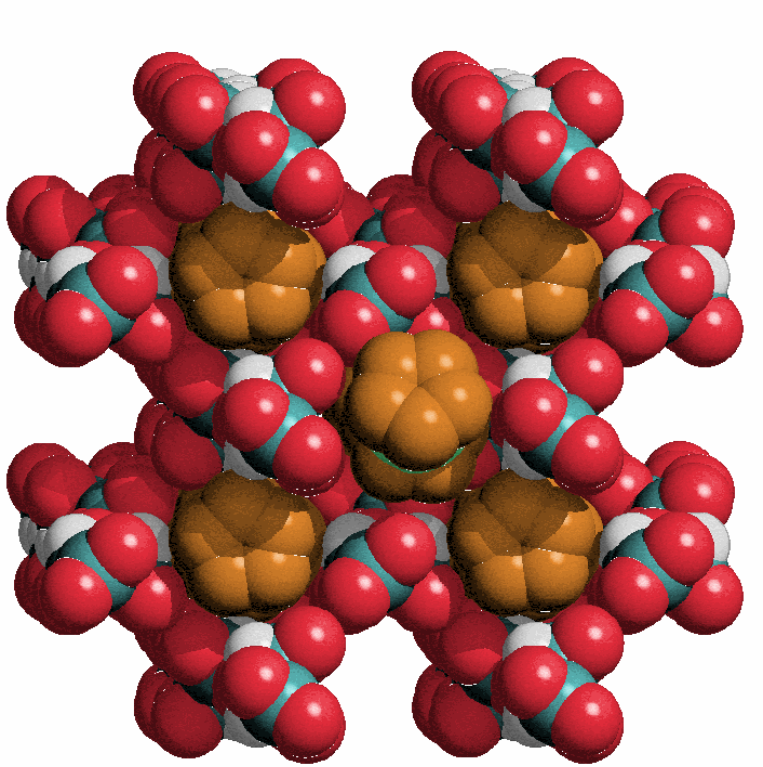
(Solvent-free) Molecular Solid-Solid Reactions **>**
Mechanochemistry

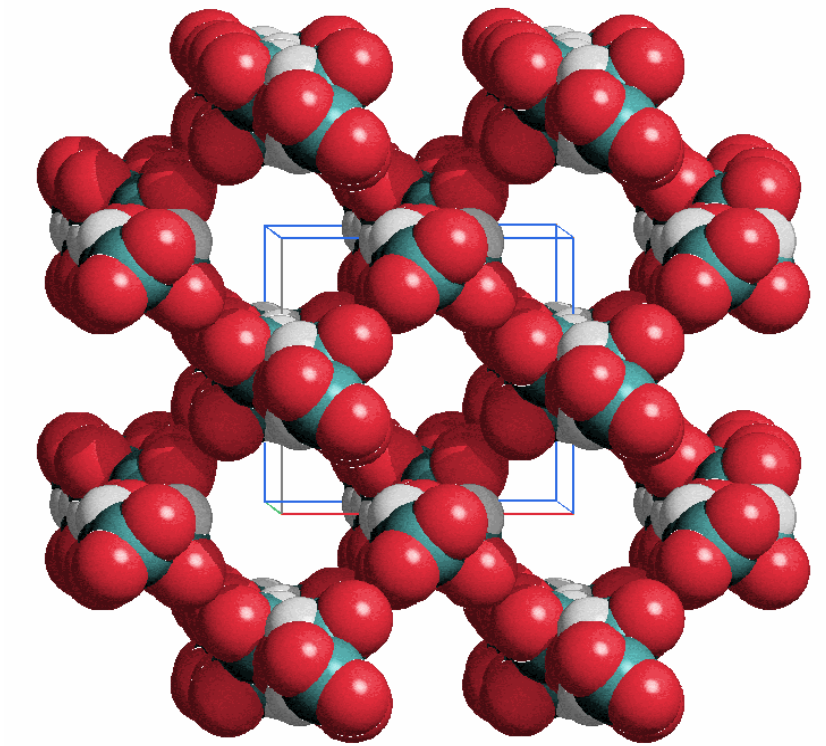
Making and using metal containing building blocks

Hydrogen bonded coordination networks



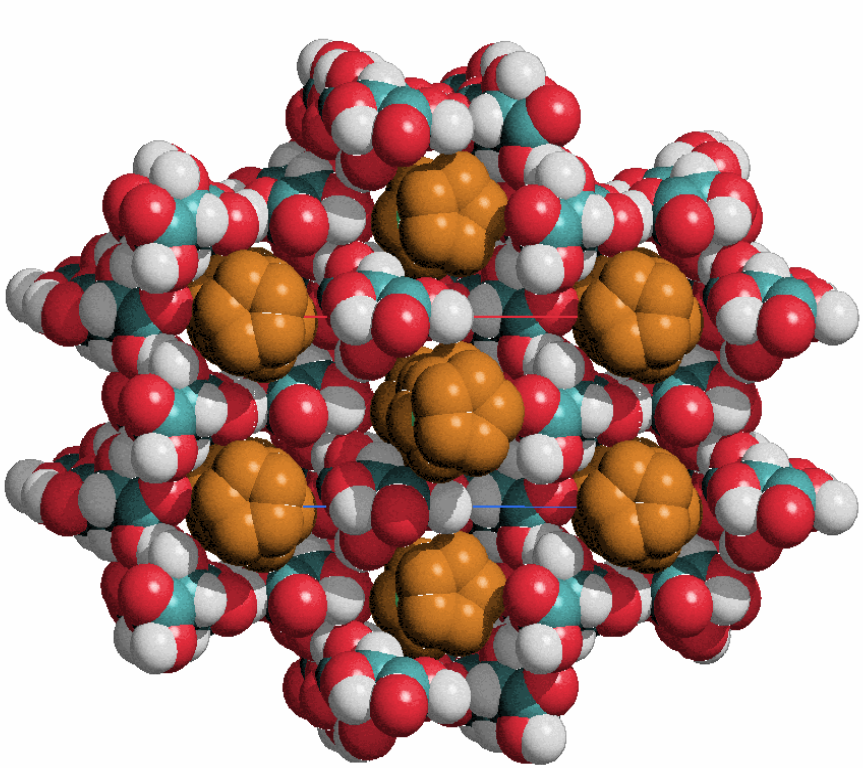
Chiral frameworks with "nanosize" channels

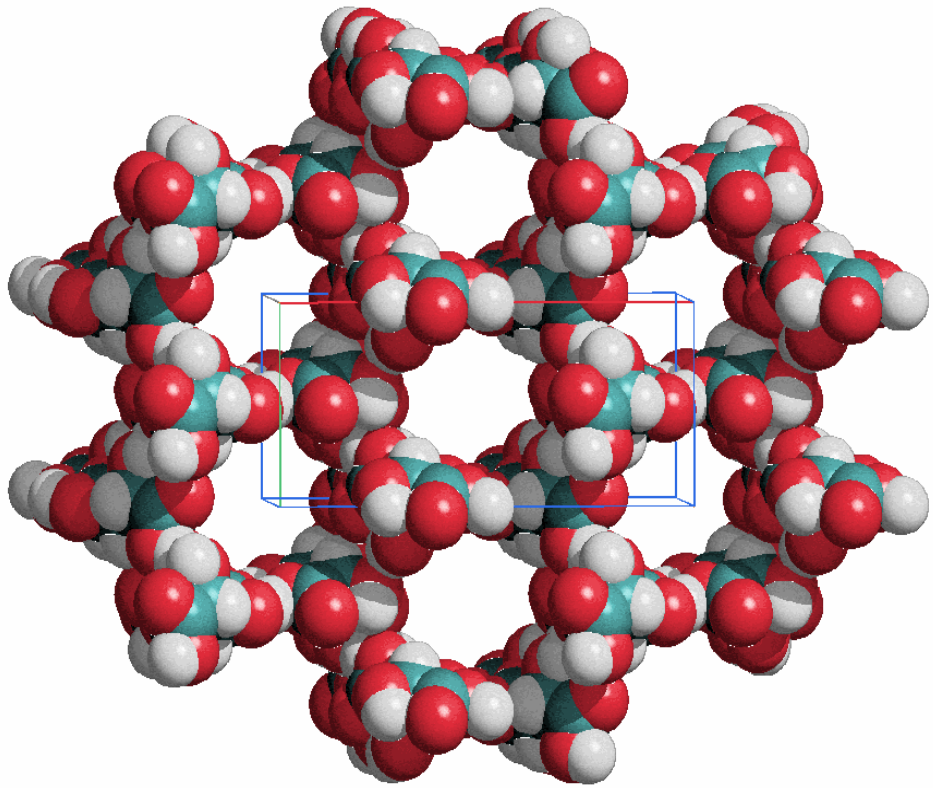




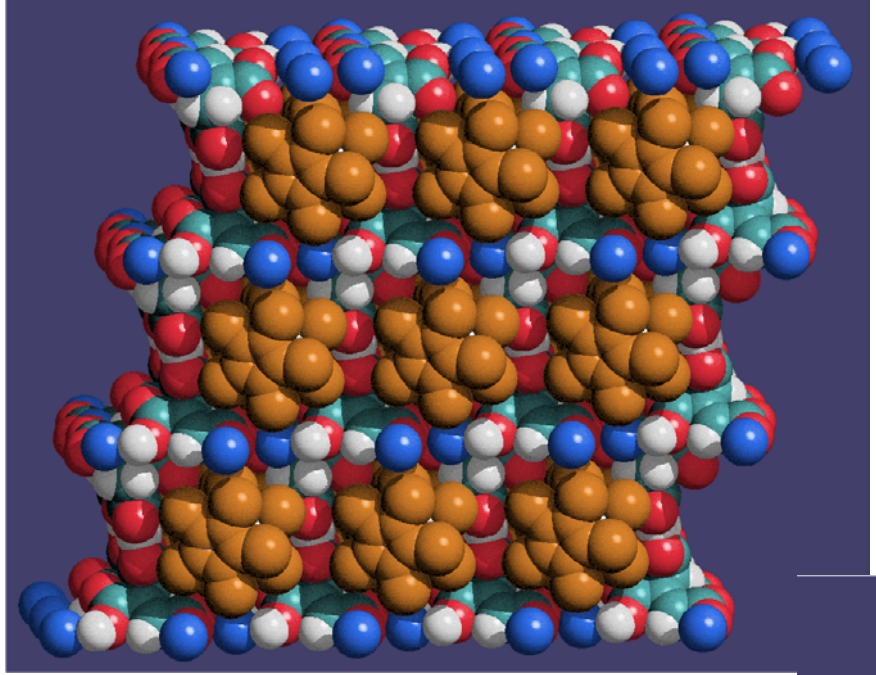
$[(C_5H_5)_2Co]^+$ [L-tartaric acid]$^-$

Honeycomb/zeotype frameworks



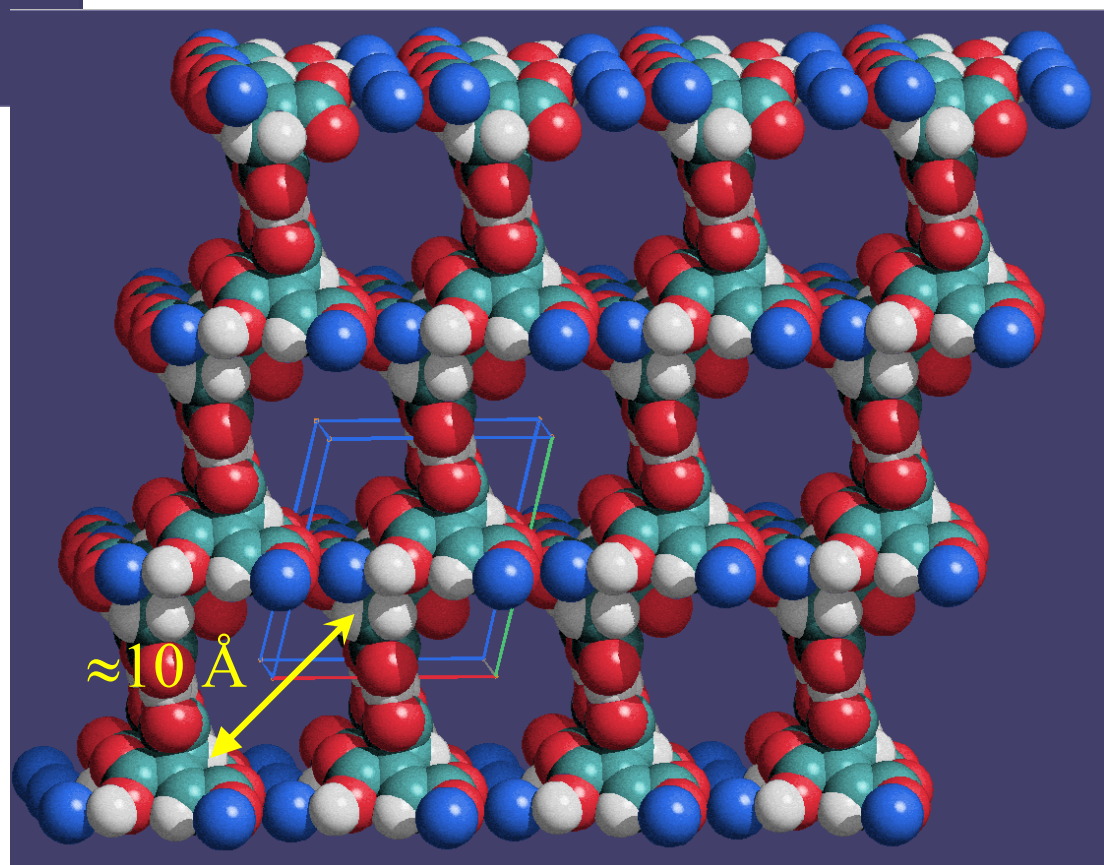


$[(C_5H_5)_2Co]^+ [D,L\ tartaric\ acid]^-$



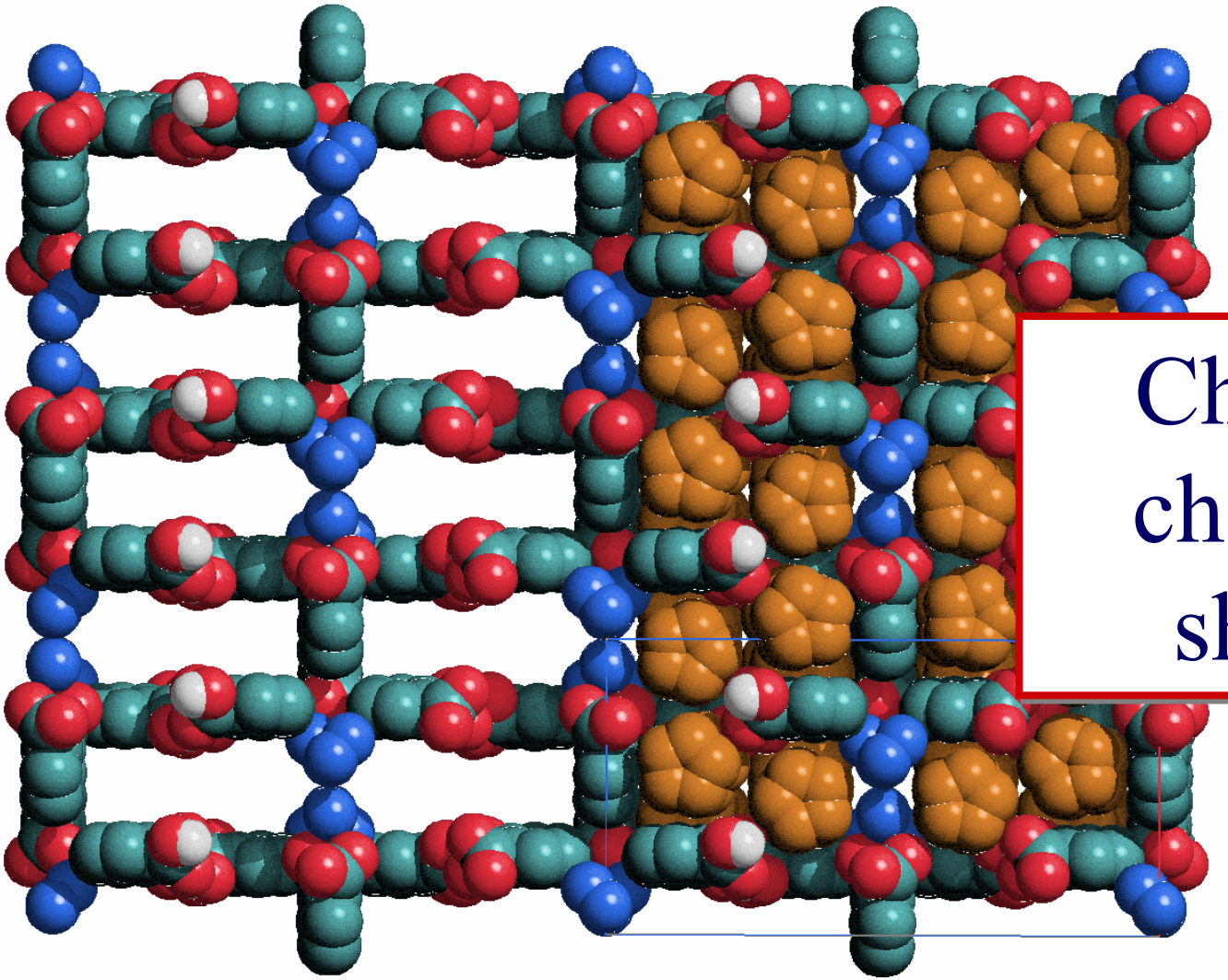
Increase channel size

$[(C_5Me_5)_2Co]^+$
[*trans*-acotinic acid]$^-$



Rectangular channels

$[(C_5H_5)_2Co]^+$ [hydrogenphthalate]$^-$ [water]

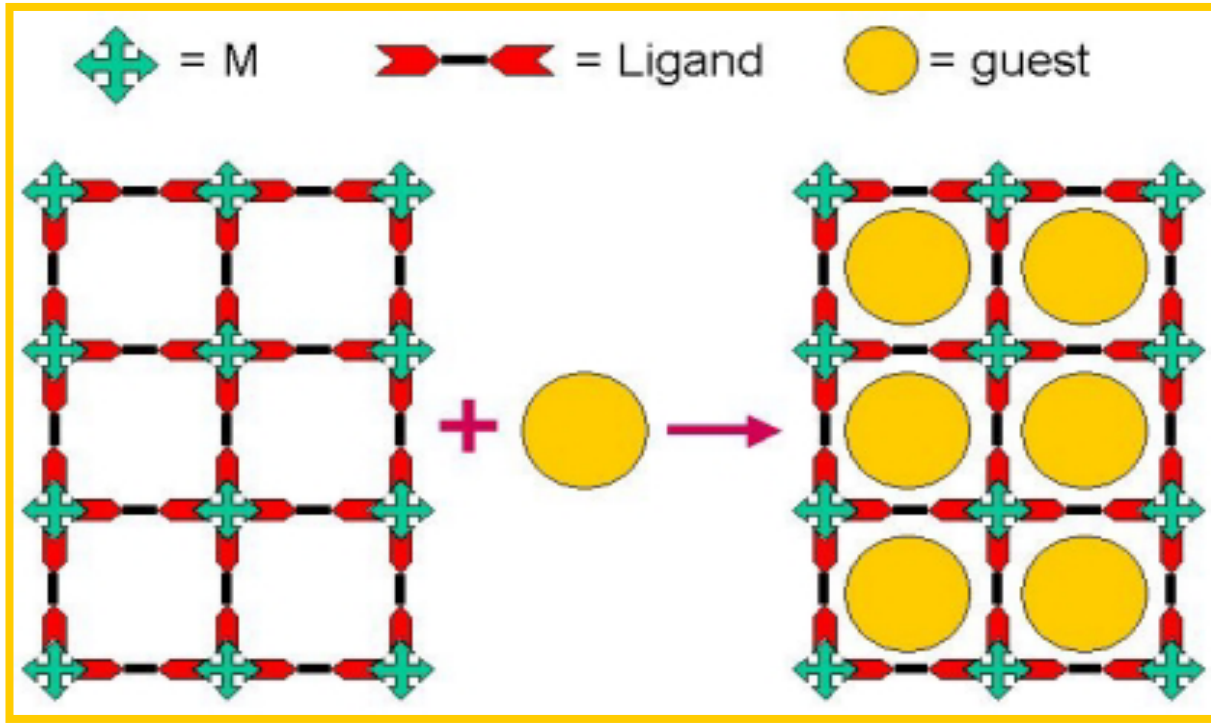


Change channel shape

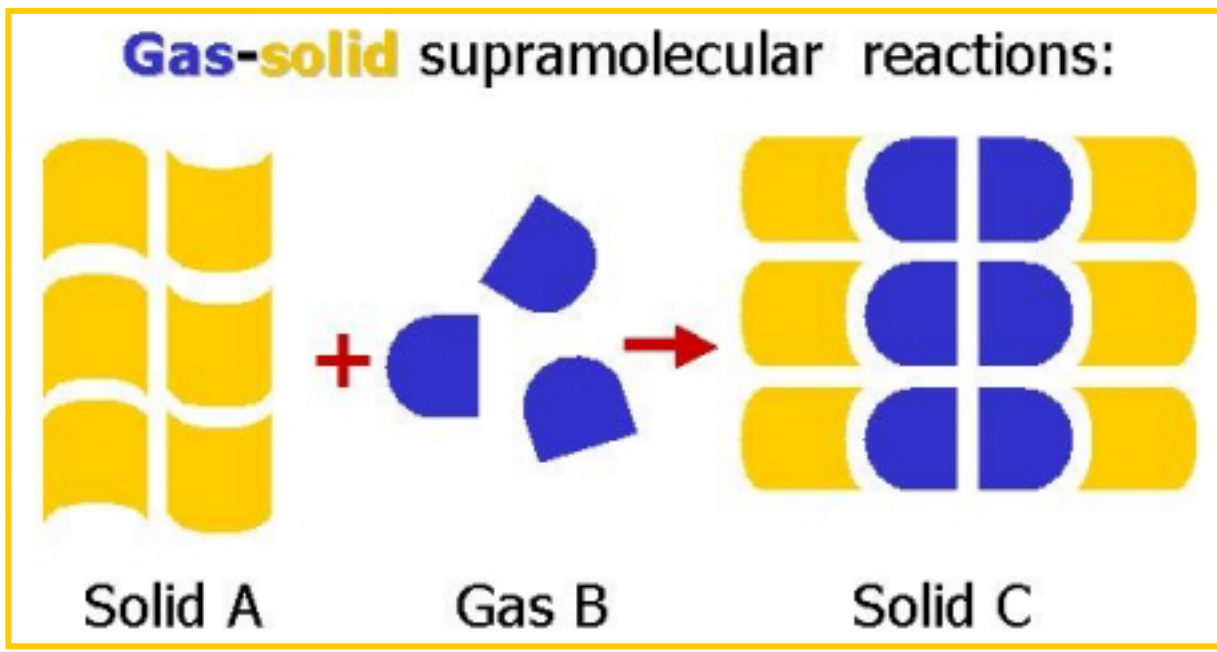
Solvent-Free

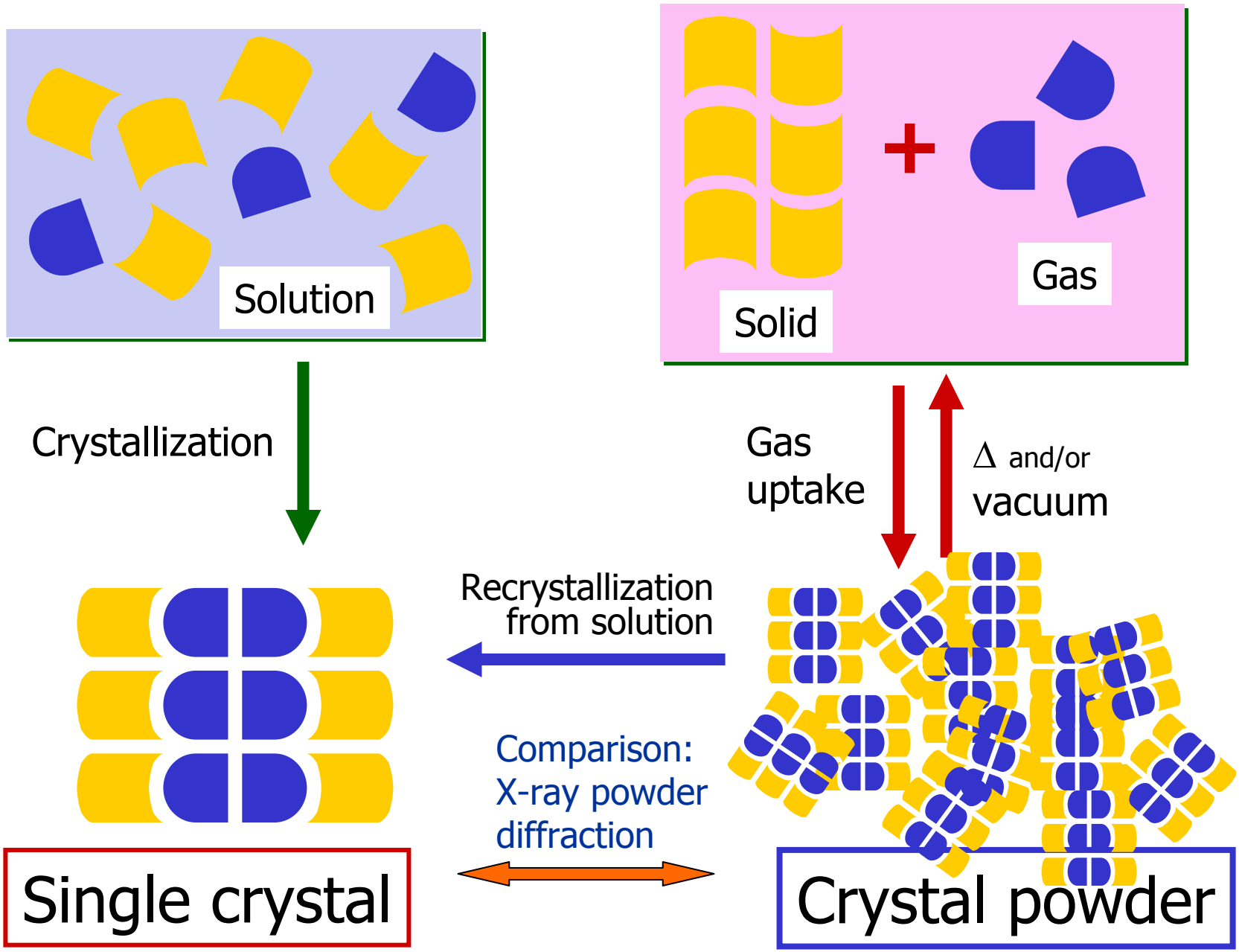
solid-solid or solid-gas reactions

NANO-POROSITY



GAS-SOLID REACTION

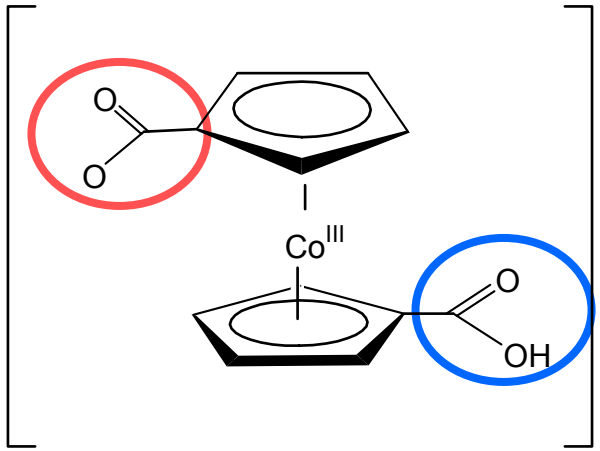




All processes monitored by TGA, IR, X-ray, CPMAS ^{13}C NMR

$[Co^{III}(C_5H_4COOH)_2]Cl \cdot H_2O$ → $[Co^{III}(C_5H_4COOH)(C_5H_4COO)]$

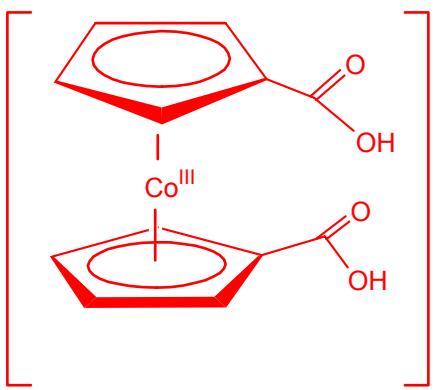
Crystalline Solid



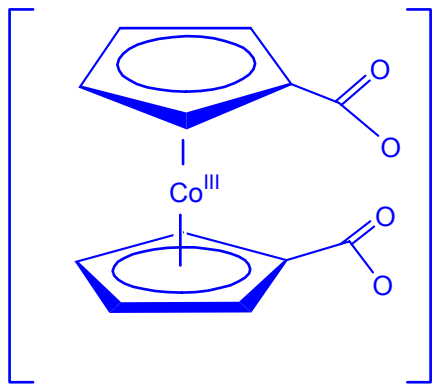
+ Acid vapour

+ Base vapour

An amphoteric Vapour Trap



A^-



BH^+

Chem Comm. 2001, 2272

solution of A + B

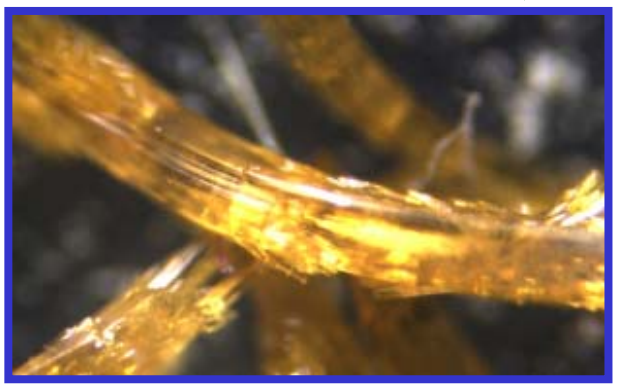
Crystallization

Seeding

solid A + vapour B

Gas uptake

Δ and/or vacuum



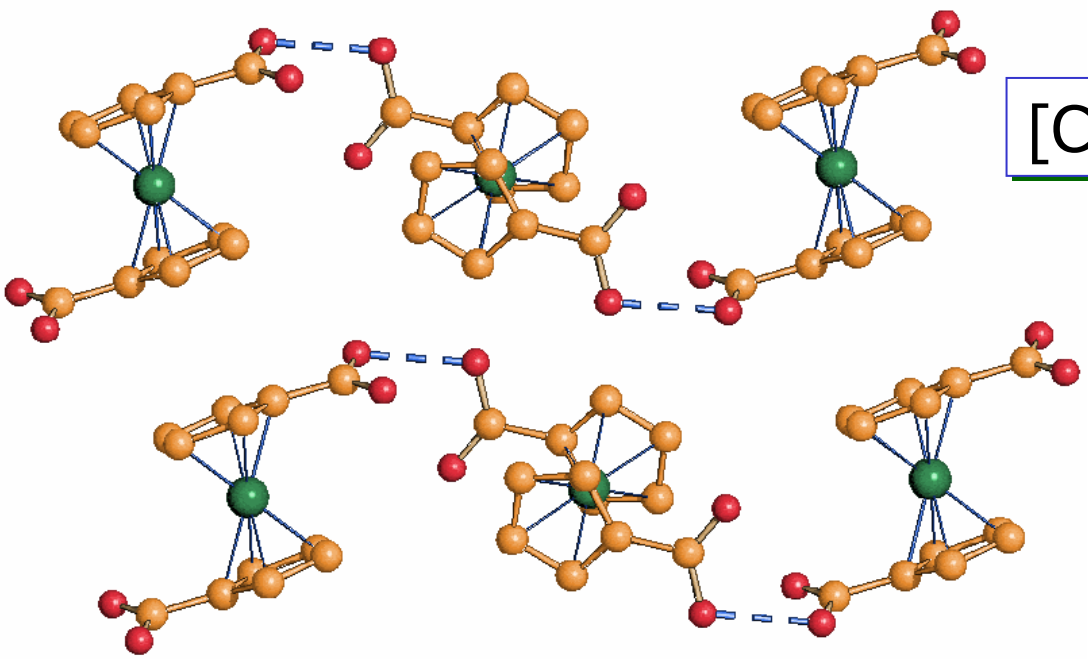
Single crystal of C

Comparison calculated and measured XPD

Crystalline powder C

processes monitored by TGA, IR, X-ray, CPMAS ^{13}C NMR

Reaction with HCl

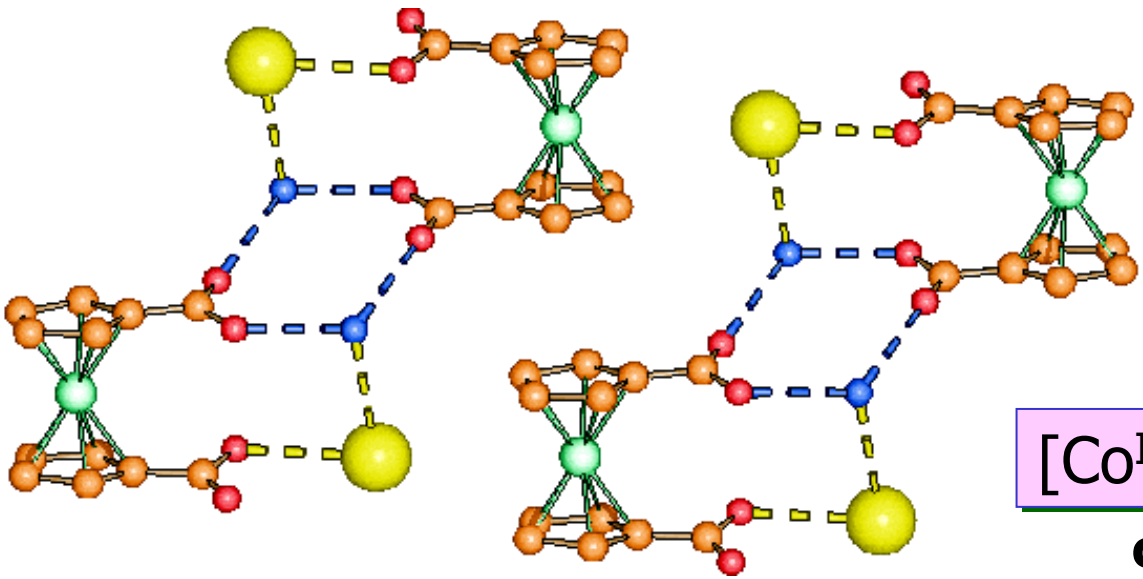


$[Co^{III}(C_5H_4COOH)(C_5H_4COO)]$

crystalline powder

Δ
vacuum

+ HCl hydrated vapour

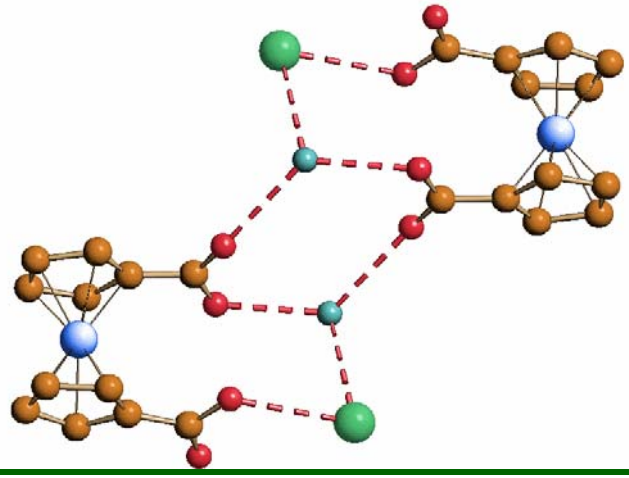


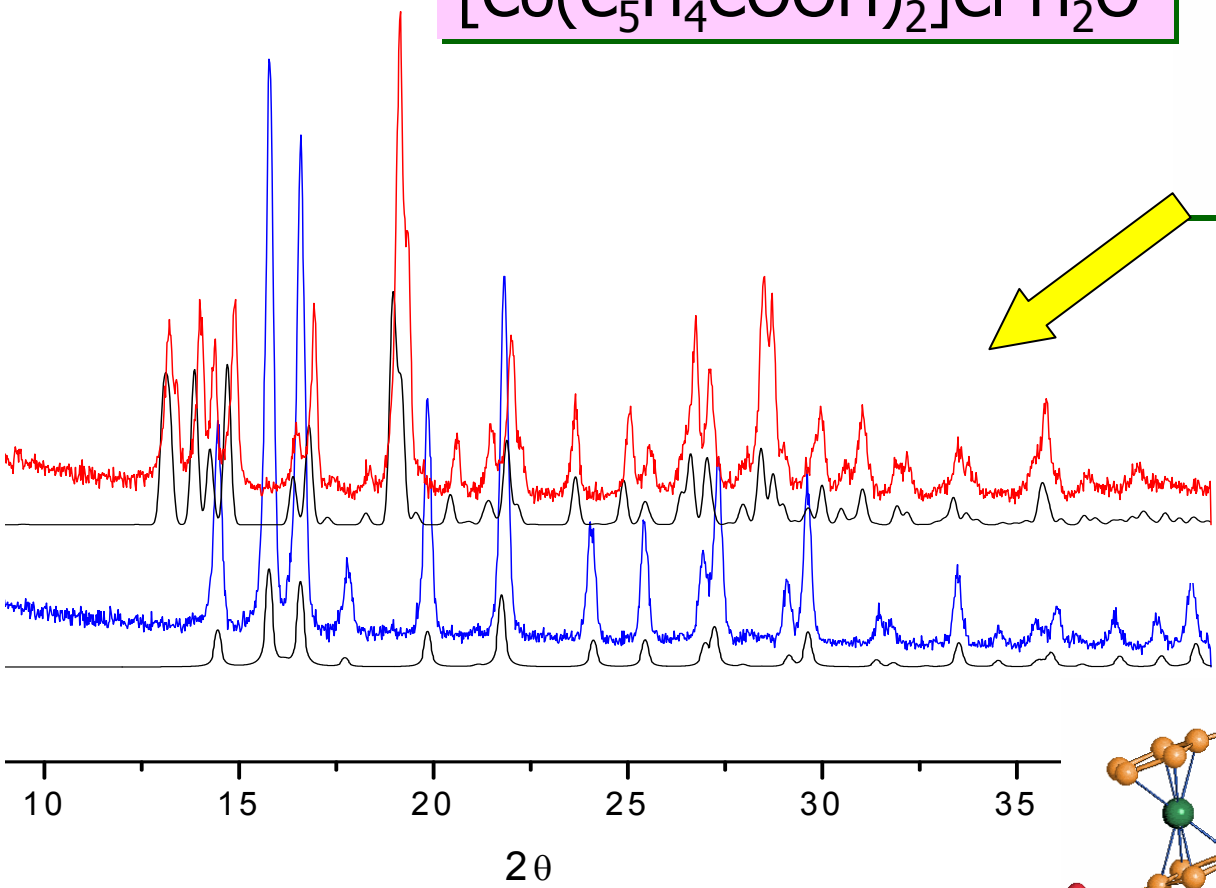
$[Co^{III}(C_5H_4COOH)_2]Cl \cdot H_2O$

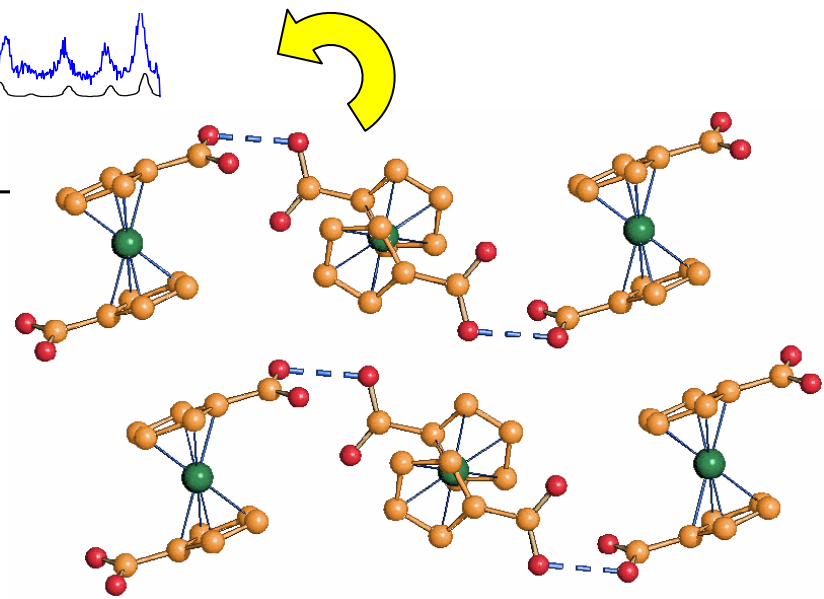
crystalline powder

Reaction with HCl

$[Co(C_5H_4COOH)_2]Cl \cdot H_2O$



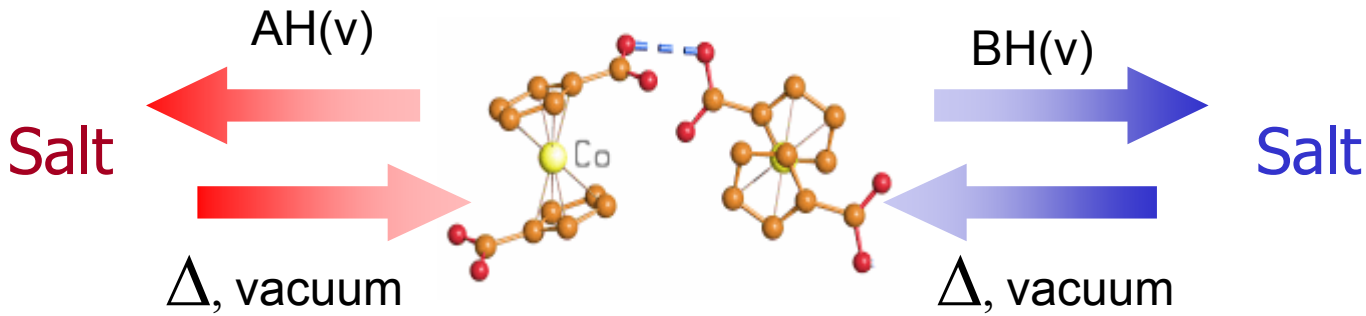




$[Co(C_5H_4COOH)(C_5H_4COO)]$

Heterophase reactions of

$[Co^{III}(C_5H_4COOH)(C_5H_4COO)]$

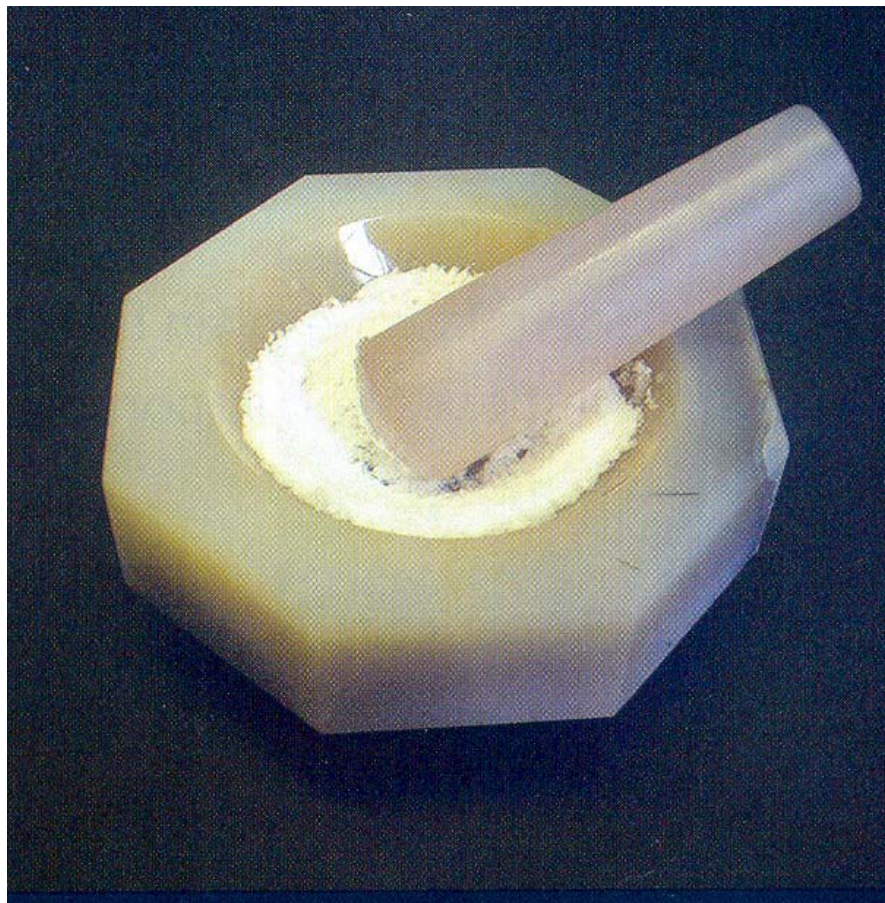


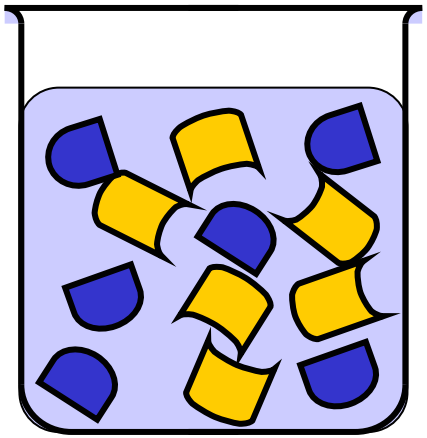
- Easy to make, high yield, low cost
- High thermal stability (500K)
- No decomposition after several absorption-desorption cycles
- No formation of amorphous phase
- Amphoteric behaviour
- Versatile (salts or co-crystals)

heterogenous reactions with ACID vapours	heterogenous reactions with BASE vaps
HCl	NH_3
BF_4	$(CH_3)NH_2$
CF_3COOH	$(CH_3)_3N$
CHF_2COOH	
CH_2FCOOH	
HCOOH	

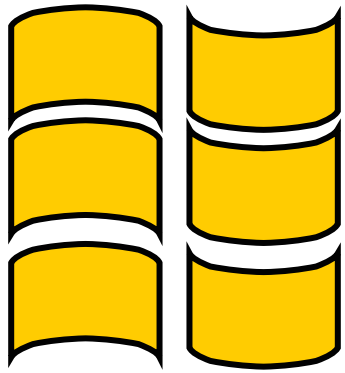
Solid-solid reactions

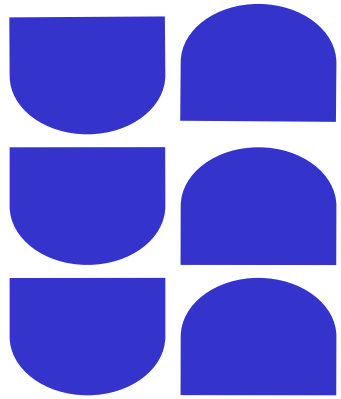
"mechanochemistry"





solution of A + B



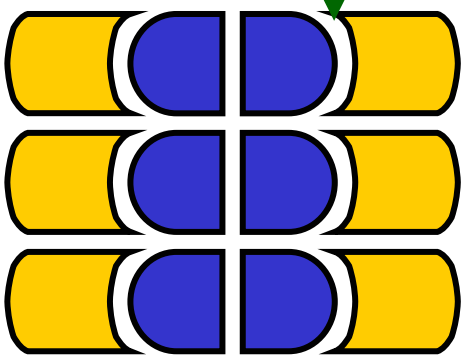


solid A + solid B

Crystallization

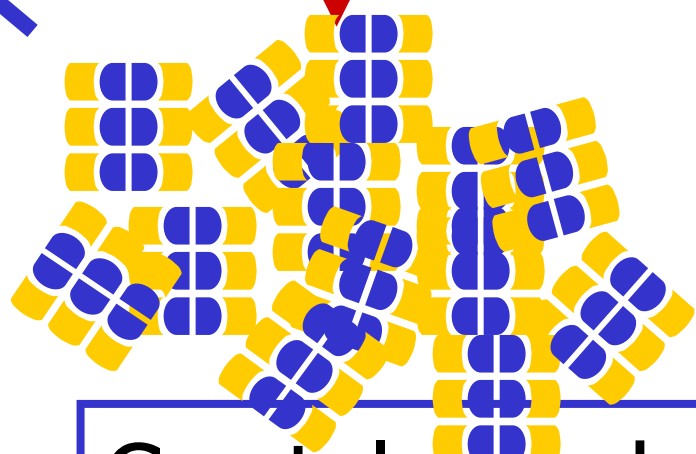
Seeding

Grinding



Single crystal

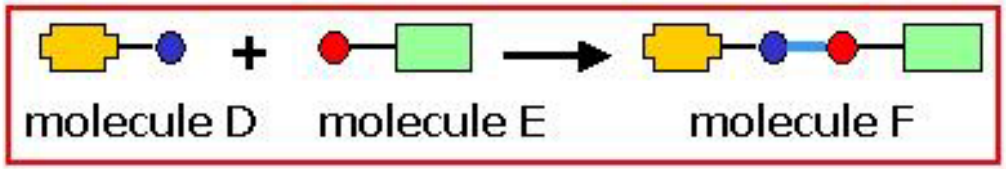
Comparison:
X-ray powder
diffraction

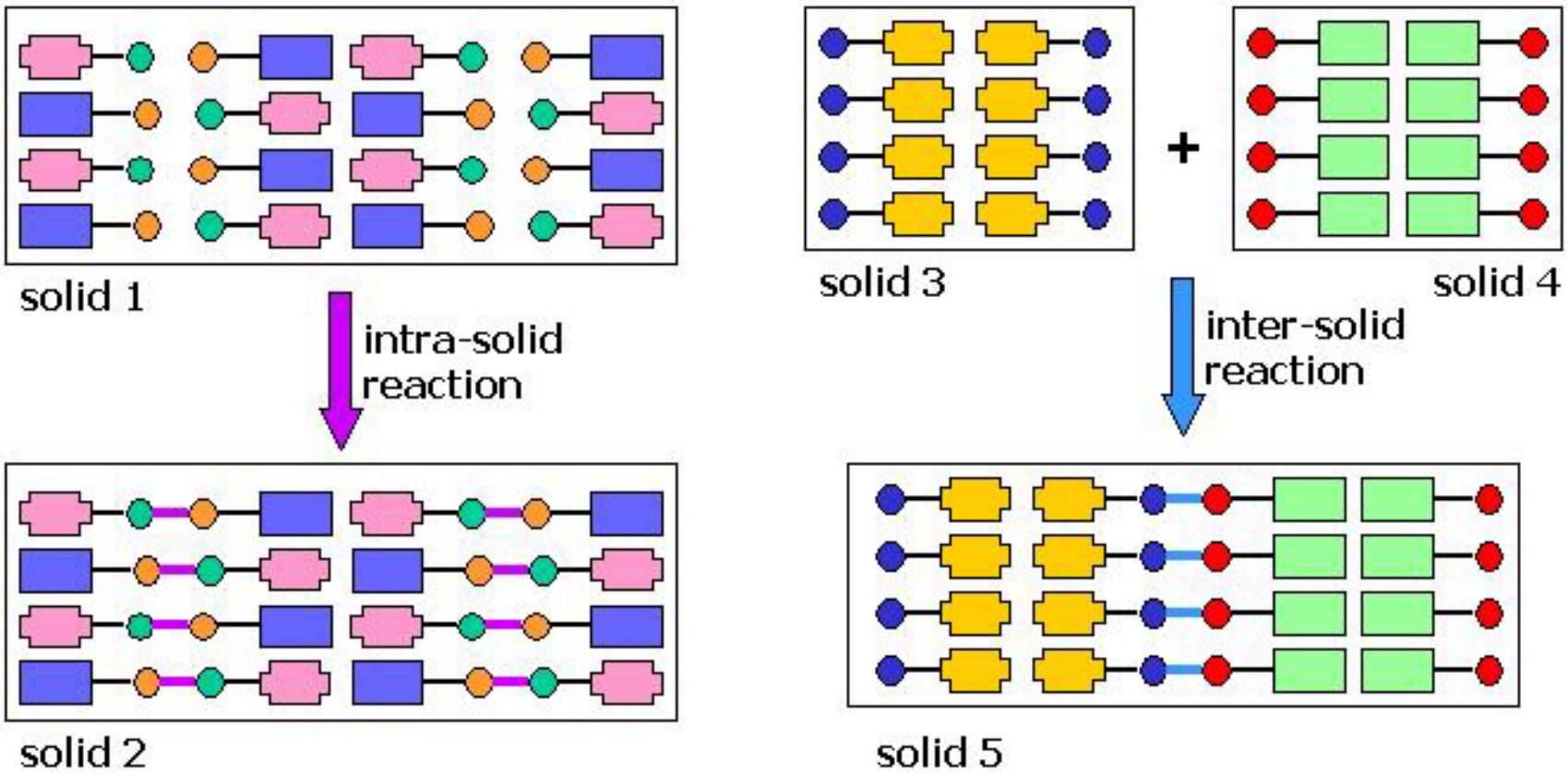


Crystal powder

processes monitored by TGA, IR, X-ray, CPMAS ^{13}C NMR

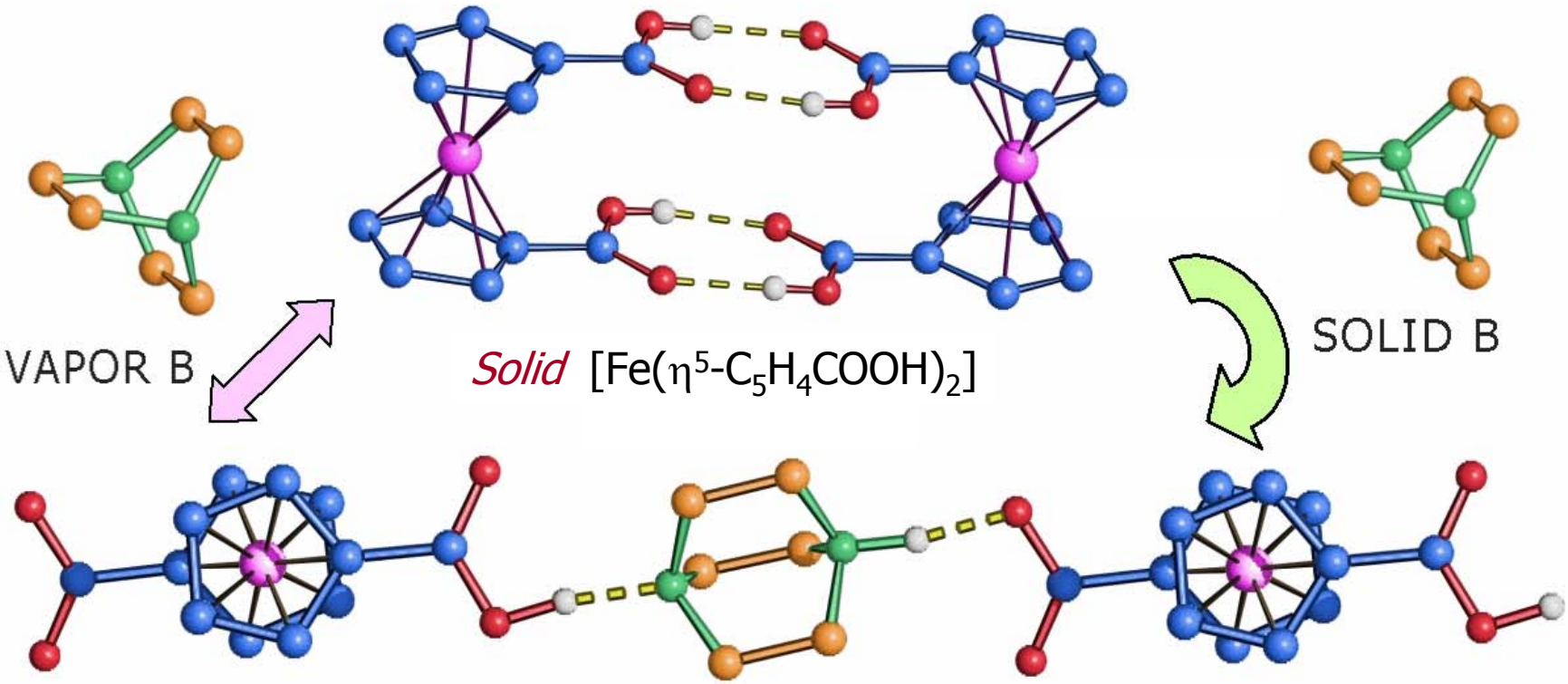
Intra solid *versus* inter solid reactions





See "*Reactions between or within molecular crystals*" Braga and Grepioni Angew. Chem. 2004, 43, 2-11

Mechanochemical Assembly of Hydrogen Bonded Organic-Organometallic Solid Compounds

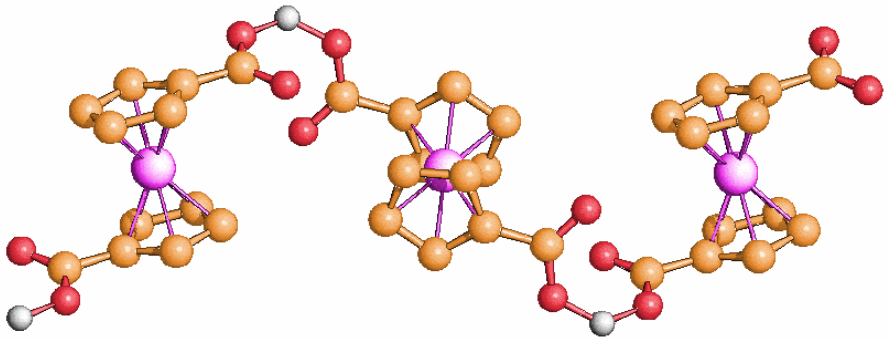


Solid $[Fe(\eta^5\text{-}C_5H_4COOH)_2]$

Solid $[Fe(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)][HDABCO]$

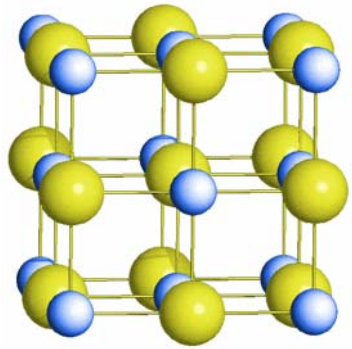
[B: 1,4-diazabicyclo[2.2.2]octane (DABCO)]

Chem Comm 2002



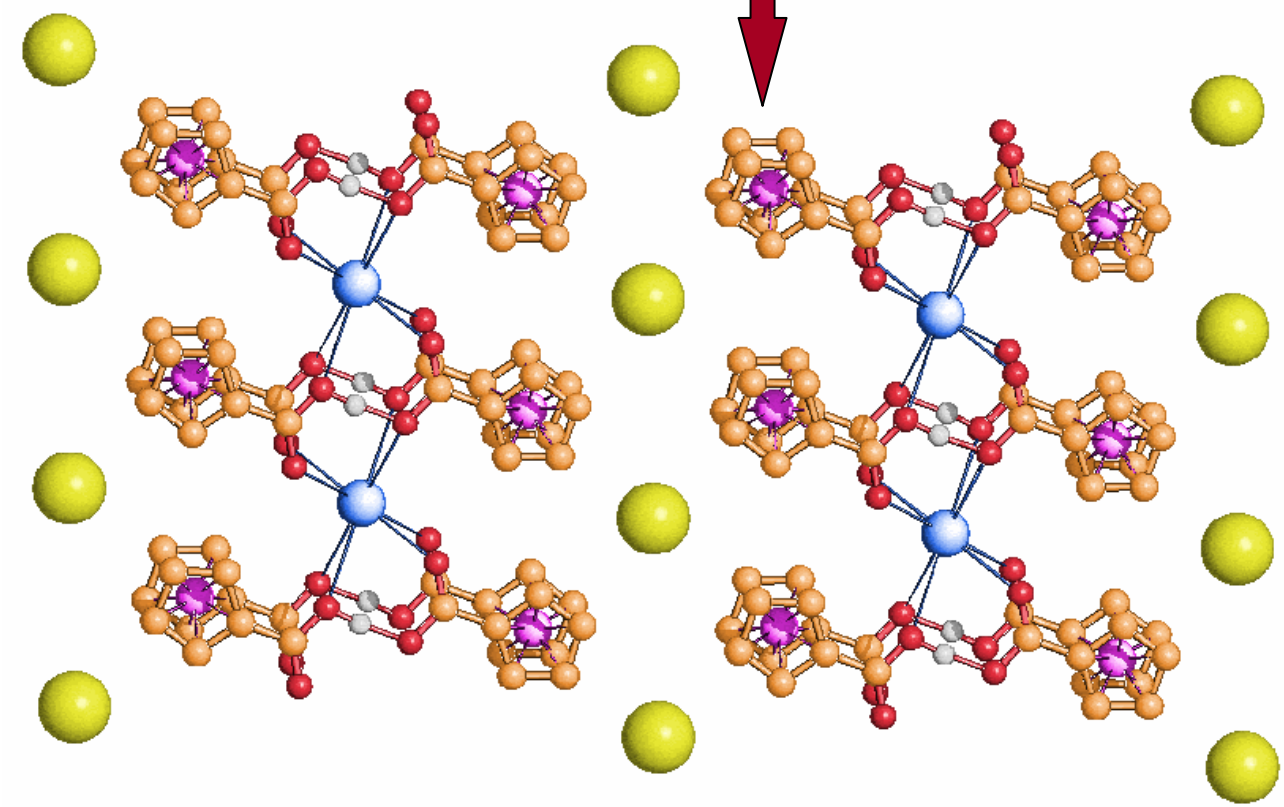
Solid $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]$

+

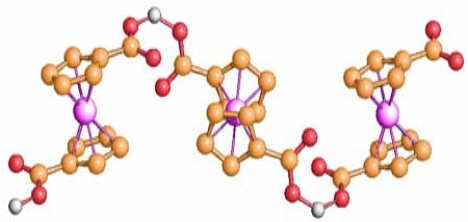


Solid KBr

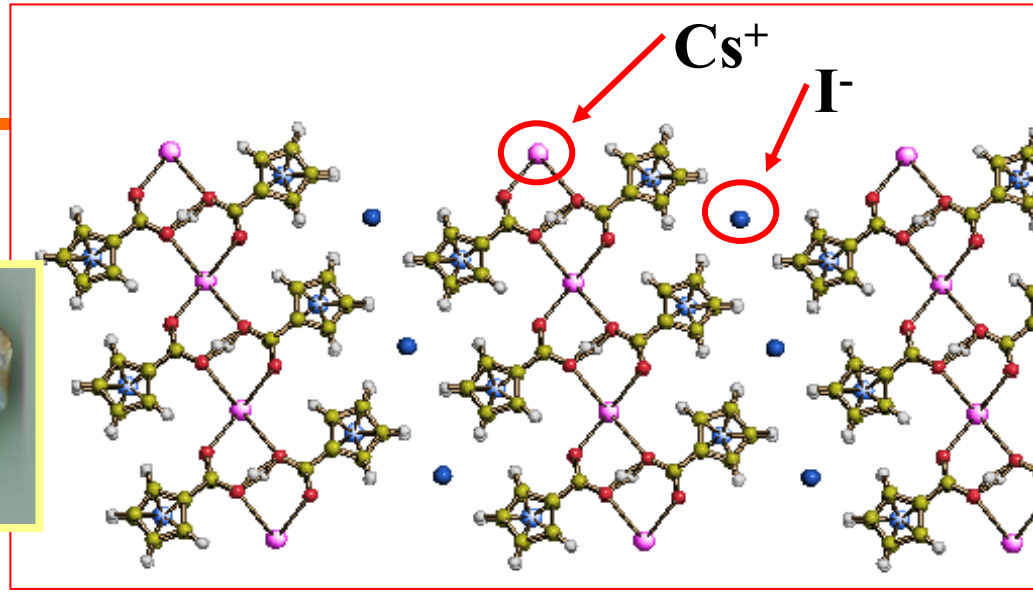
GRINDING

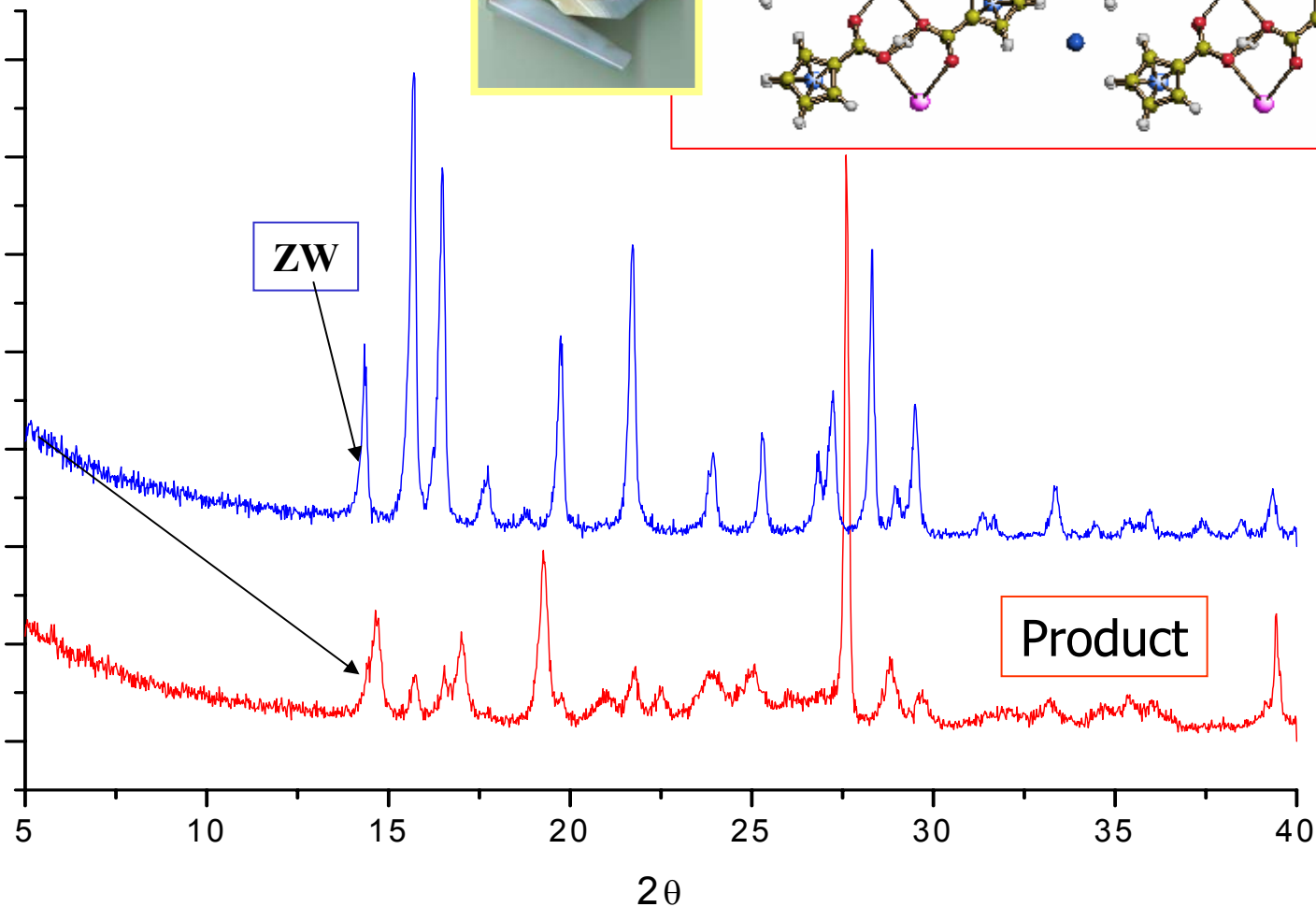


Solid $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]_2 \cdot K^+Br^-$



+ CsI



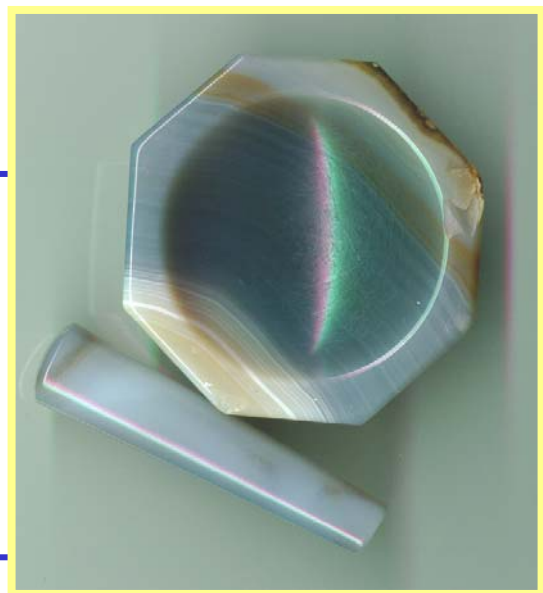


Mechanochemical Preparation of Coordination Polymers

Homo-phase solid-solid reactions

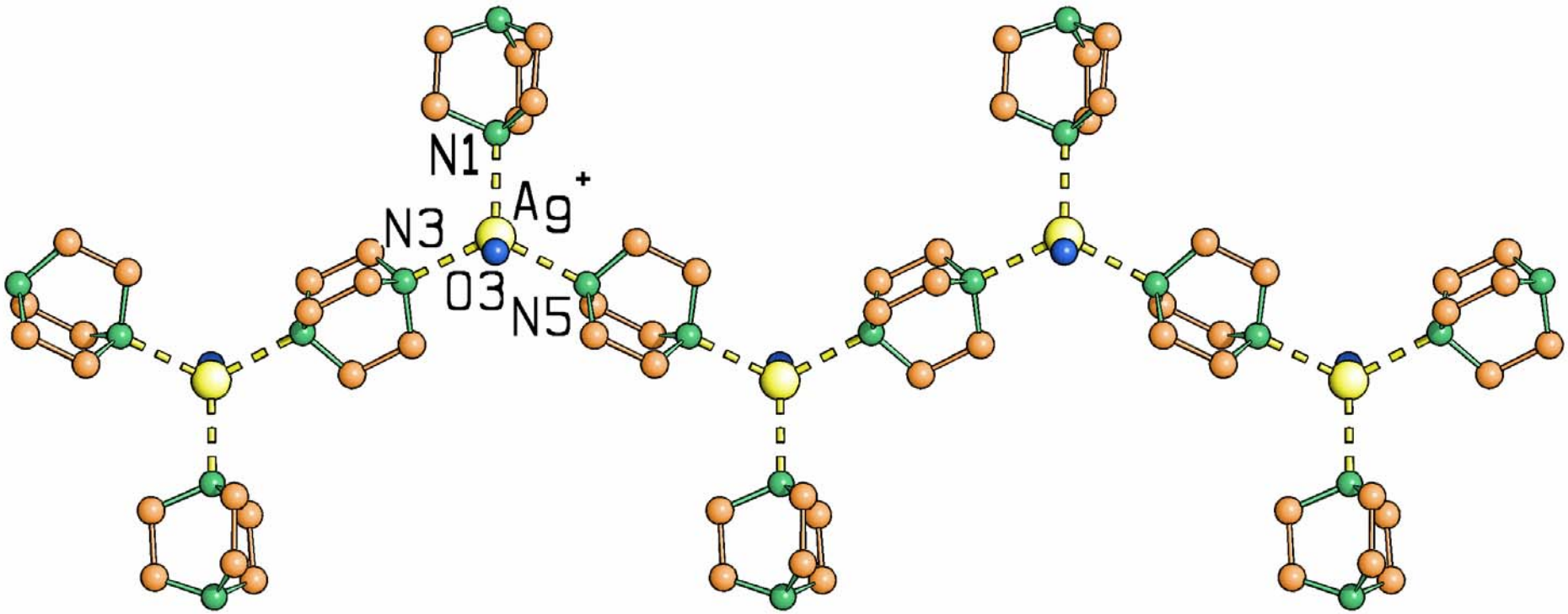
$Ag[CH_3COO](s) + 2[N(CH_2CH_2)_3N]_2(s)$

$ZnCl_2\,(s) + [N(CH_2CH_2)_3N]\,(s)$



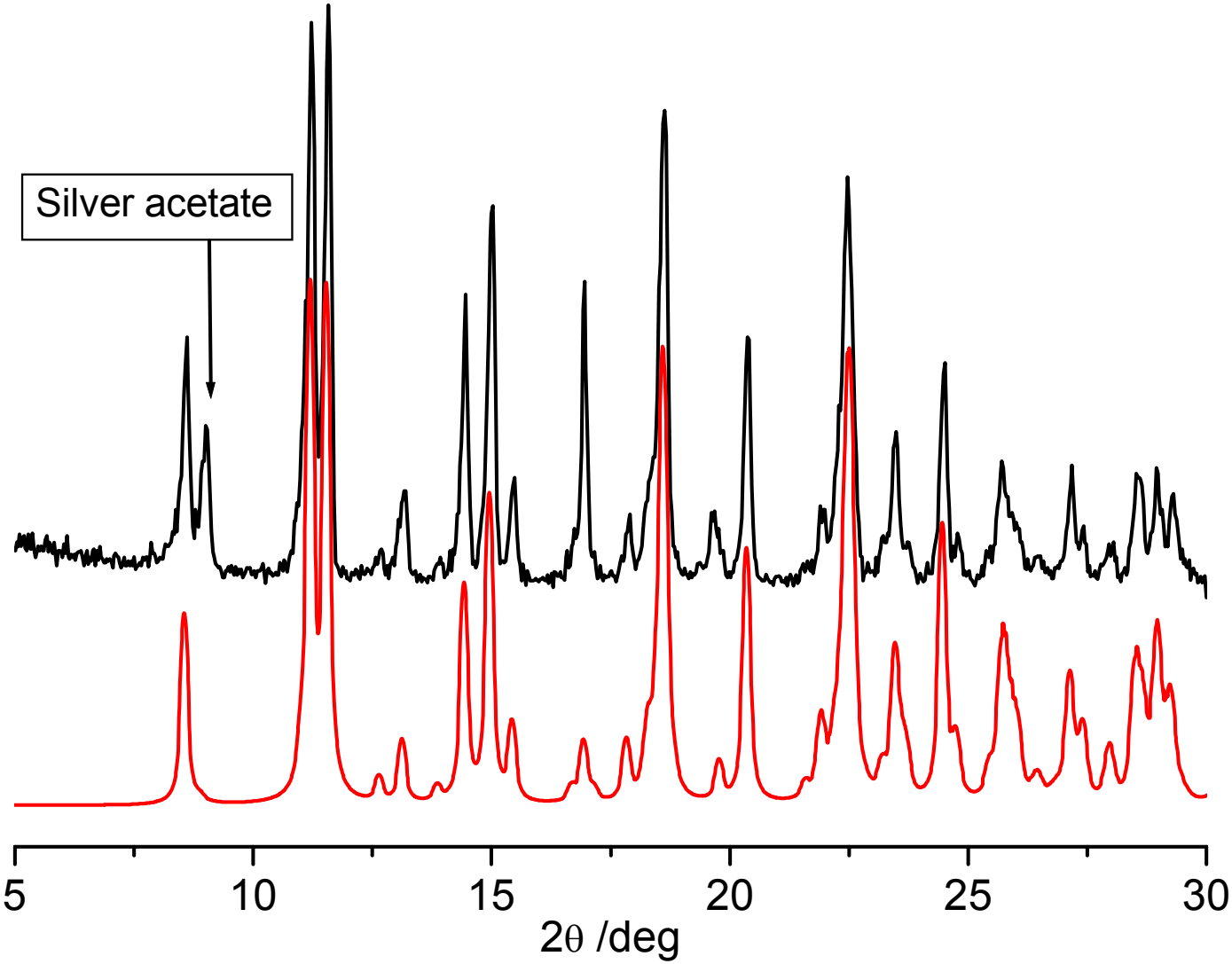
CrystEngComm. 2004

$Ag[N(CH_2CH_2)_3N]_2[CH_3COO]\cdot 5H_2O$.

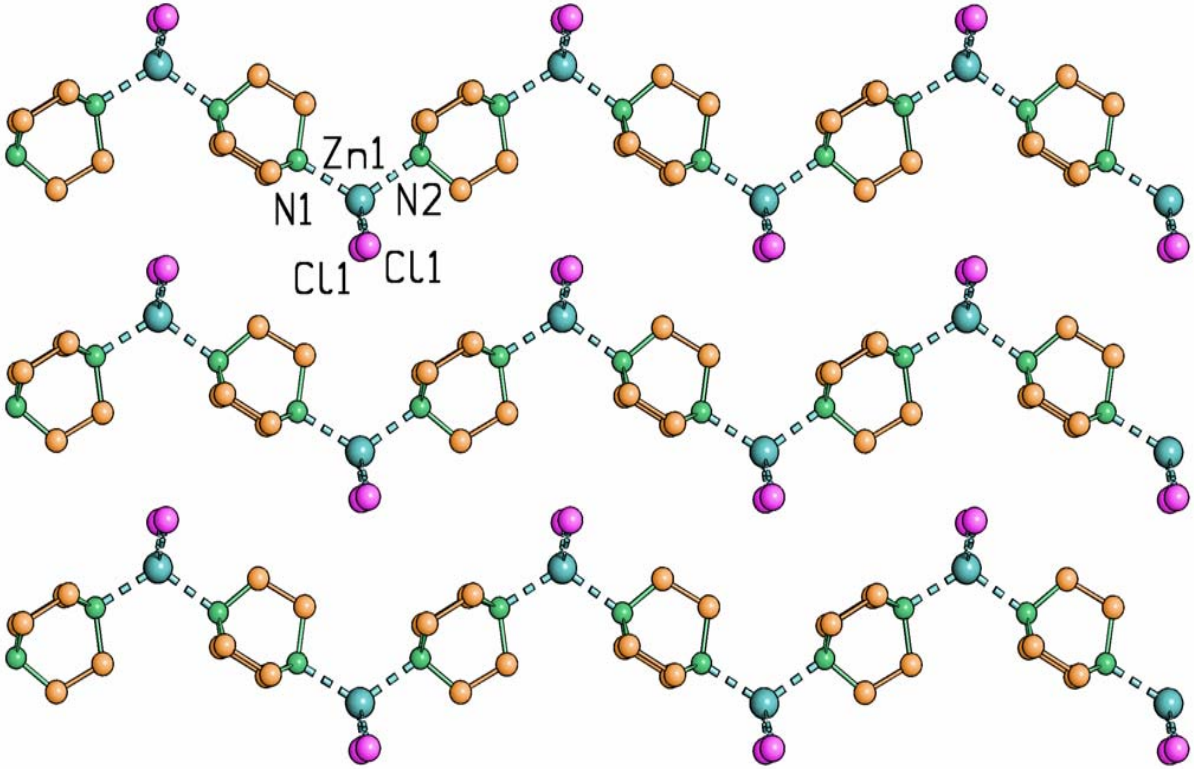


The coordination network in $Ag[N(CH_2CH_2)_3N]_2[CH_3COO]\cdot 5H_2O$.

The chain of $Ag^{(+)}$---$[N(CH_2CH_2)_3N]$---$Ag^{(+)}$---$[N(CH_2CH_2)_3N]$---$Ag^{(+)}$ with each silver cation carrying an extra pendant $[N(CH_2CH_2)_3N]$ ligand and a coordinated water molecule in tetrahedral coordination geometry.

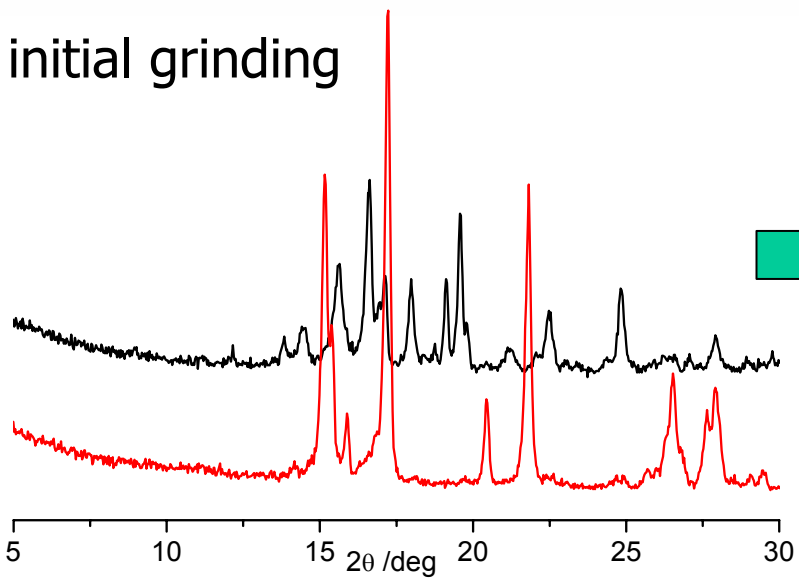


$Ag[N(CH_2CH_2)_3N]_2[CH_3COO]\cdot 5H_2O$: comparison between calculated and measured X-ray powder diffractograms

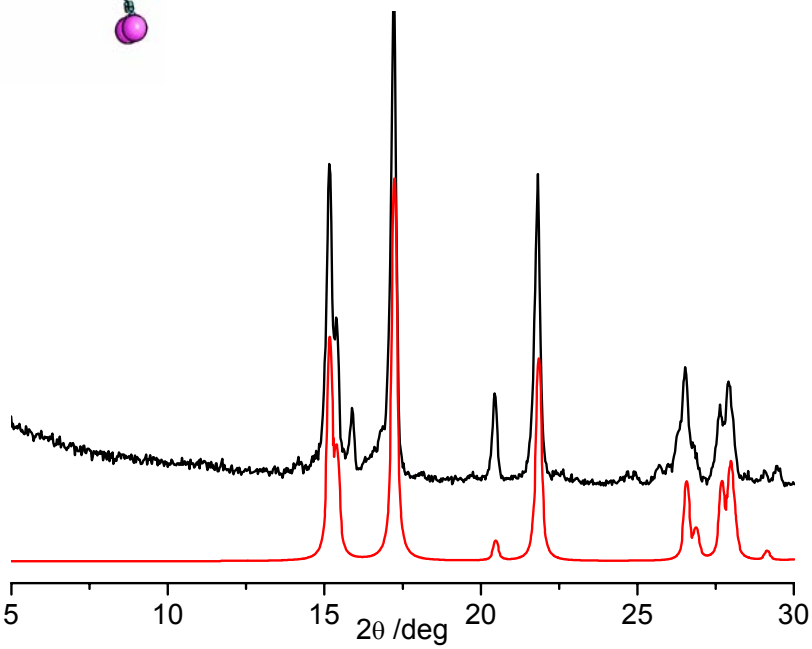


The one-dimensional coordination network in crystalline $Zn[N(CH_2CH_2)_3N]Cl_2$

initial grinding



10 min "vigorous grinding"



..tell them what you told them…

- **Solid-gas** and **solid-solid** reactions with/between crystalline molecular solids can be used to make new materials
- **Pros**: easy, unexpensive, often quantitative and lead to thermodynamic products (useful new "tools" for crystal engineering)
- **Cons**: difficult product characterization, requires a combination of solid state techniques (…patience, and good luck!)


Lucia


Dario
Crystal Engineering Lab


Michele
Crystal Engineering Lab


Marco


Silvia
Giorgiana
Stefano
Marco


Fabrizia
Fabio

End of part 2

Il polimorfismo nei farmaci

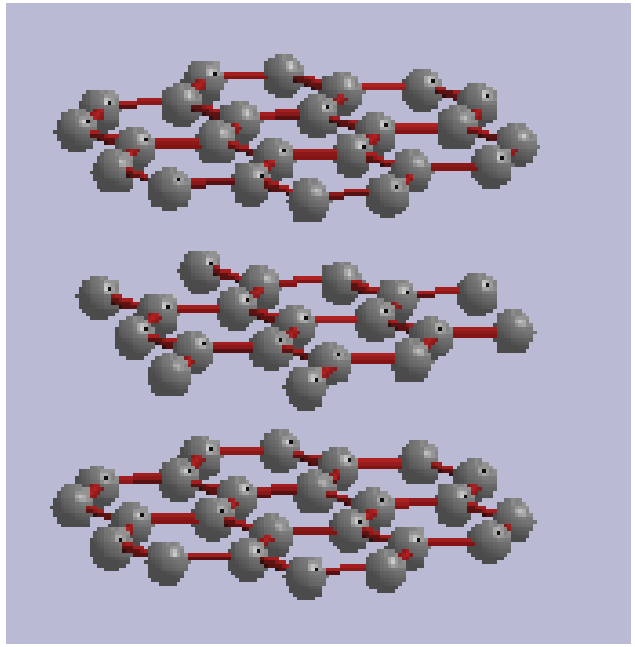
1) Definizioni
2) Rilevanza del polimorfismo in campo farmaceutico
   Casi "storici"
3) La diffrazione di polveri – method of choice
4) Esempi tratti dai brevetti attuali
5) Pitfalls and shortcomings, pseudopolimorfismo, amorfi etc.

Che cos'è un polimorfo?

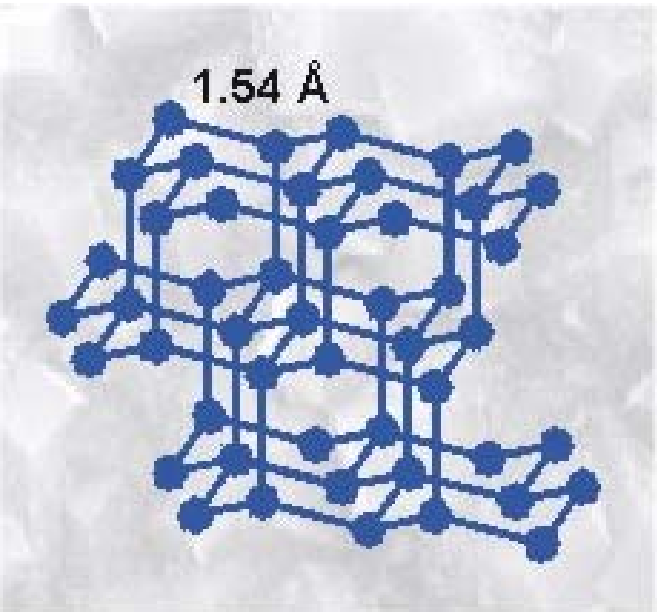
cristalli diversi* della stessa sostanza sono detti polimorfi

*cristalli diversi = diverse distribuzioni nello spazio delle molecole, ioni o atomi che compongono la sostanza. Se si tratta di elementi, si parla anche di allotropi

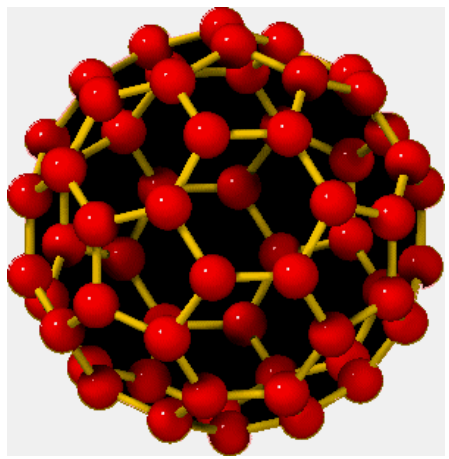
C (grafite)



C (fullerene)



C (diamante)



Form a cocoa mass by fermenting, drying and roasting cocoa beans before removing their shells and grinding the beans

Mix with sugar (and milk)

Refine – grind the particles

Add additional cocoa butter and flavourings

Conch – mix and beat the mixture to let any undesirable volatile flavours escape and to coat all the particles (eg sugar) in chocolate

Temper – heat and cool the chocolate while stirring to ensure that stable crystals form

Chocolate crystals

Cocoa butter is composed of a mixture of saturated and unsaturated fats (triglycerides). Some of the unsaturated triglycerides in cocoa butter have low melting points, making it partly liquid at room temperature.

The fat crystals form polymorphs. The chocolate industry labels these polymorphs forms I to VI and aims to get the cocoa butter to crystallise in a stable form V to give the chocolate a glossy appearance and a good snap.

Per le caratteristiche richieste agli imballaggi, data la natura dei prodotti da contenere e proteggere, il settore farmaceutico è particolarmente interessato alla commercializzazione di solidi cristallini.
Nel 2002, le confezioni vendute hanno raggiunto un totale di 1.701 milioni, ripartite secondo le diverse tipologie di prodotti:

- forme farmaceutiche liquide (iniettabili, orali, oftalmici, ecc.): 525,5;
- **forme farmaceutiche solide (compresse, capsule, polveri, ecc.): 1.042;**
- altre forme (pomate, gel, spray, ecc.): 133,5.

http://www.italiaimballaggio.it/italiaimballaggio/05_03/sezioni/01_mark/art1_mark.html

A Molecular Crystal is formed by chemical entities (molecules or molecular ions) that retain their chemical identity in gas phase and/or in solution

Solid drugs are generally in the form or molecular crystals

Polimorfismo dei farmaci

Se *la stessa* molecola – il principio attivo – si aggrega in *solidi differenti*, questi possono comportarsi come *farmaci differenti*

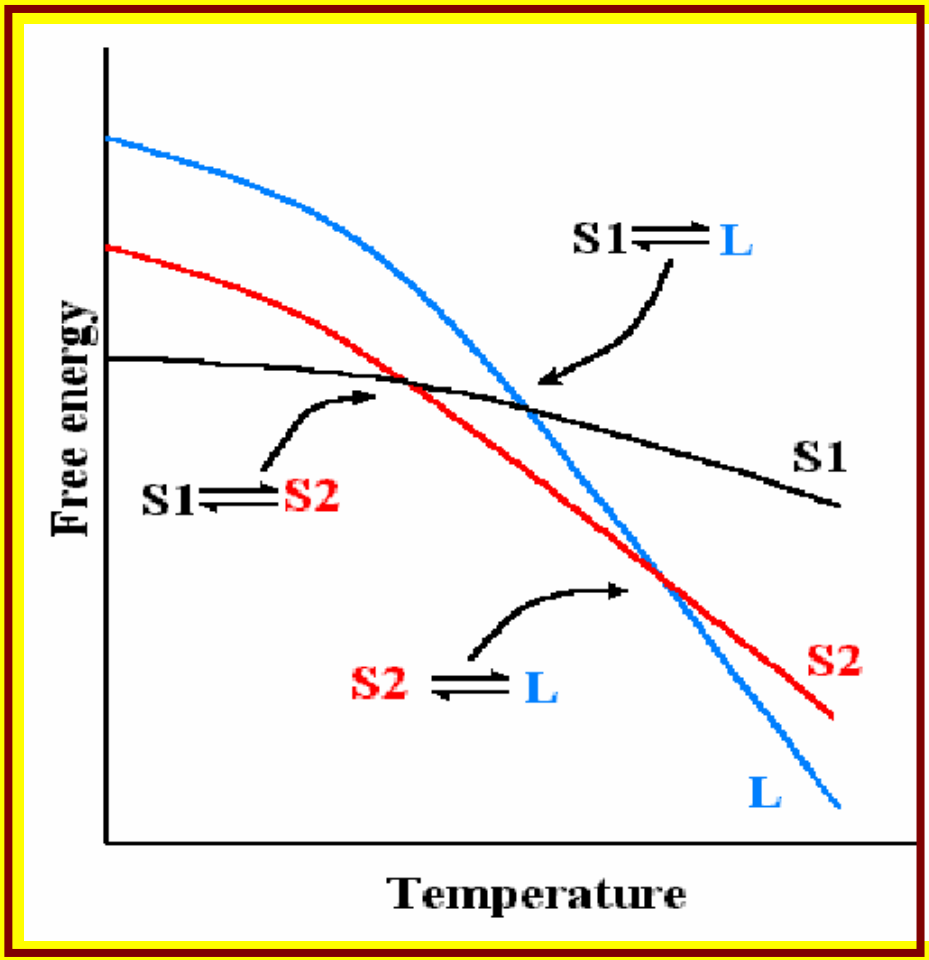
Forme polimorfe dello stesso composto hanno **proprietà differenti** quali:

- Stabilità termica
- Melting point
- Granulometria
- Solubilità (=> biodisponibilità)

Principi attivi solidi:

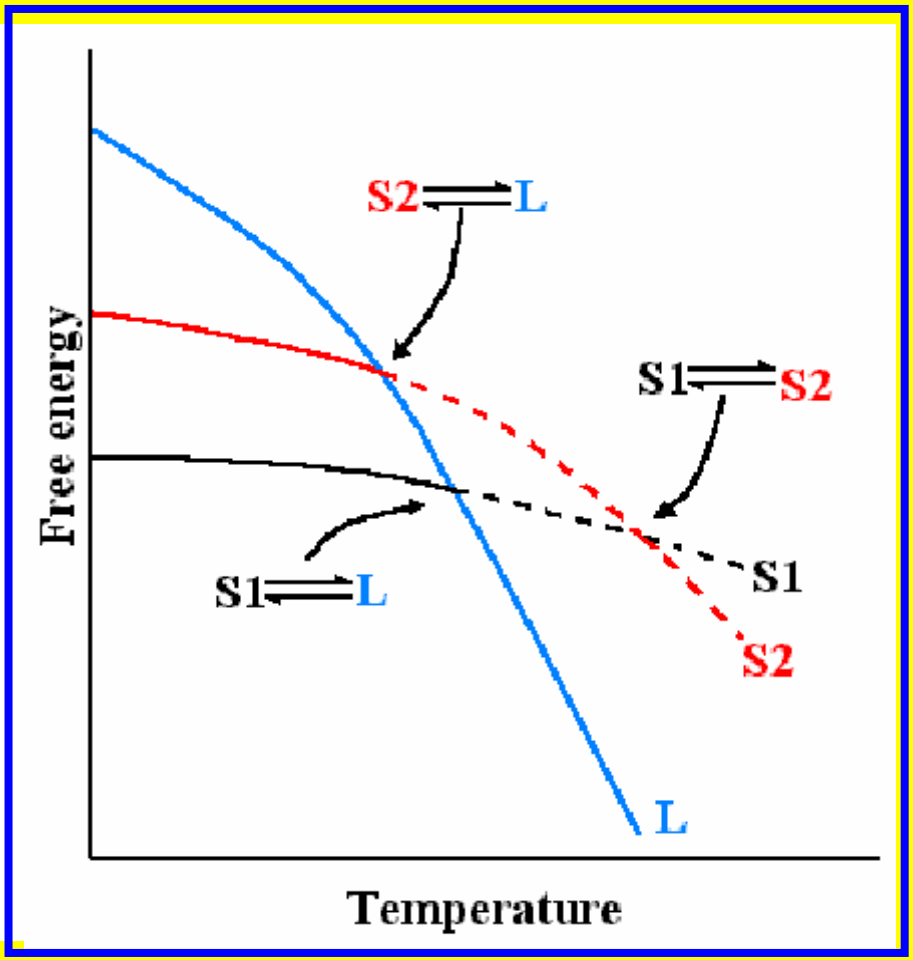
- Più stabili
- Meglio immagazzinabili
- Facilmente trasportabili

ENANTIOTROPIC SYSTEM



interconversion before melting

MONOTROPIC SYSTEM



melting before the solid-solid transition

Polymorphism: hystoricals and case studies

Disappearing (and reappearing?) Polymorphs

Example: **RITONAVIR**

In the summer of 1998 NORVIR semi-solid capsules supplies were threatened as a result of the appearance of a new much less soluble crystal form of ritonavir.

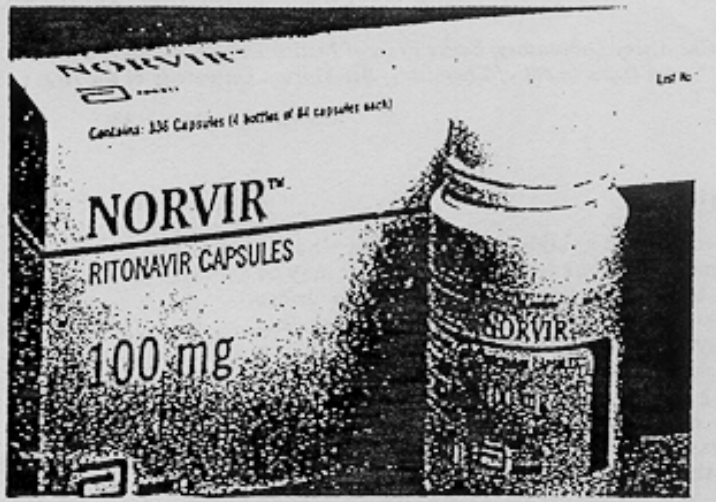
Ritonavir exhibits conformational polymorphism, the most stable form II can only be obtained from highly supersaturated solutions

Manufacturing problems hit Abbott's HIV drug ritonavir

Ritonavir

Capsules of Abbott Laboratories' protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.

Production of Norvir oral solution is being increased to compensate for the likely capsule shortage. The solution is bioequivalent to the capsule formulation, with the recommended 600mg twice daily dosage of ritonavir corresponding to 7.5ml twice daily of the solution.



Capsules unlikely to be available from mid-August

There is said to be no problem with the capsules that are already on the market.

The problem relates to "undesirable" crystal formation. Abbott says that a series of recent production batches of Norvir capsules failed the approved test for dissolution, and were not released for marketing. Investigation of the reason for the failure showed the presence of a new crystalline form of ritonavir which affects the way it dissolves, and possibly its absorption. Retained samples from a number of marketed batches of capsules were examined and there was no evidence of the unwanted crystalline form.

Mr Mark Haywood (managing director, Abbott Laboratories) said that teams were working round the clock to try to resolve the issue, but at present the company had no idea why the problem was occurring.

The vast majority of sales of Norvir are of the capsules rather than the oral solution. The solution is normally more expensive than the capsules but Abbott says that, while the capsules are unavailable, the solution will be sold at the capsule price.

Norvir oral solution has a bitter taste. This can be reduced by mixing with chocolate milk, Abbott says.

The company has set up a helpline (0800 0183340) for patients and health professionals. A letter explaining the situation will be given to health professionals for them to issue to patients if they wish.

FDA enquiry on Ritonavir

Q: *You are a large multinational company. Your scientists are obviously smart. How could this happen?*

A: *A company's size and the collective IQ's of their scientists have no relationship to this problem…*

…. There are many ***misteries of Nature*** we have not solved. Hurricanes, for example, continue to occur and often cause massive devastation. Meteoroligists cannot predict months in advance when and with what velocity a hurricane will strike a specific community.
Polymorphism is a parallel phenomenon. We know that it will probably happne. But not why or when.
Unfortunately, there is nothing that we can do today to prevent a hurricane from striking any community or polymorphism from striking any drug."

Ritonavir

"… We [Abbott] tried everything: we conducted countless experiments. We reconditioned our facilities: We rebuilt facilities and new lines. We looked at alternative sites. We visited a number of other organizations around the World… to see if we could start clean in a new environment free of form II…"

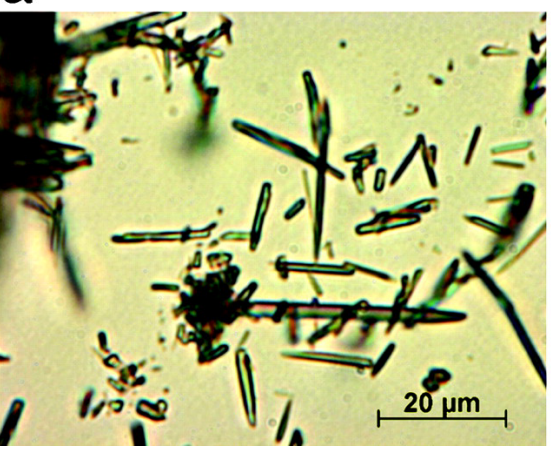
"… In a matter of weeks – maybe five or six weeks, every place became contaminated with form II crystal…"

"… While we have speculated on the cause of this chemical transformation, we don't have conclusive proof what happened…"

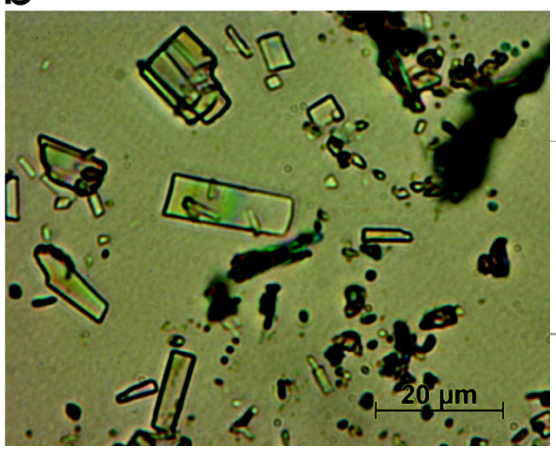
Table 2. Comparison of physical parameters of ritonavir crystal forms

Form	Melting point, °C	H_{fus}, J/g	Solid-state structure
I*	**122-125***	78.2	Monoclinic
II*	**122**	87.8	Orthorhombic
III	**78-82**	60.3	Monoclinic
IV	**116**	59.8	Not assigned
V	**97**	32.0	Monoclinic

a



b



Solubility in ethanol/water (mg/mL)

Form I 170 (75/25)

Form II 30 (75/25)

Chemburkar et al Organic Proc Res & Develp 2000, **4**, 413

Reprinted from ACCOUNTS OF CHEMICAL RESEARCH, 1995, 28.

Disappearing Polymorphs

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Received November 1, 1994

Introduction

When a compound exhibits polymorphism—the existence of more than one crystal structure—it may be important to obtain a particular polymorph under controlled and reproducible conditions. However, this is not always easy to achieve. Tales of difficulties in obtaining crystals of a particular known form or in reproducing results from another laboratory (or even from one's own!) abound. Indeed, there are cases where it was difficult to obtain a given polymorphic form even though this had previously been obtained routinely over long time periods. Several monographs contain explicit or passing references to these problems,[1] but much of this lore has gone undocumented, especially in the last 30 years or so. In this Account we present and discuss old and new examples.

Crystallization is a process taken for granted by most practicing chemists; the majority of the techniques were developed long ago and are described in all standard laboratory textbooks. It is the standard method for purifying solid compounds, and chemists generally believe that they can control the process, at least when it yields the desired product. What is disturbing about the phenomenon of disappearing or elusive polymorphs is the apparent loss of control over the process: we did the experiment last week and got this result, and now we cannot repeat it! This kind of statement can lead to raised eyebrows or even to outspoken expressions of disbelief. We have ourselves experienced the frustration of not being able to reproduce an experimental result that was undoubtedly obtained earlier.

instance, Faraday[2] observed that molten sulfur in a flask cooled to room temperature did not entirely solidify. When a drop of the fluid material was touched, it immediately crystallized; untouched, some drops were retained for a week in the fluid state. Faraday noted that this supercooled state of sulfur is analogous to that of water cooled below its freezing point, although the temperature difference is much greater (the freezing point of sulfur is 119 °C); De Coppet found that samples of salol (phenyl salicylate) could be kept in the liquid state at room temperature for periods of several years.[3] When nucleation is rapid, the formation of many nuclei leads to many crystals, whereas slow nucleation tends to produce a smaller number of larger crystals. Of course, stirring, shaking, or other disturbances of the liquid phase during the crystallization process can affect the outcome.

A striking case where nucleation was decisive in determining the result of a crystallization experiment has been described recently.[4] Sodium chlorate ($NaClO_3$) crystallizes in the chiral space group $P2_13$; that is to say, individual crystals of this substance may occur in enantiomorphic forms. Normally, crystallization from solution produces the enantiomorphs in roughly equal numbers. Kondepudi, Kaufman, and Singh[5] found, however, that stirring an aqueous solution of this substance leads to a predominance of

Accts. Chem. Res. **28**, 193-200 (1995).

Tipi di brevetto (briefing)

DI PRODOTTO: protegge il prodotto in tutte le sue applicazioni indipendentemente da come viene ottenuto

DI PROCESSO: protegge il prodotto solo se preparato con il processo descritto

DI ATTIVITÀ TERAPEUTICA: protegge l'uso specifico del prodotto

DI FORMULAZIONE FARMACEUTICA: protegge la specifica composizione rivendicata

Per uno stesso prodotto possono coesistere brevetti di processo, di attività e di formulazione ognuno con vita autonoma, anche se saranno sempre ***dominati dal brevetto di prodotto***.

Sono considerati **prodotti diversi**: gli isomeri ottici, gli isomeri geometrici, **i differenti polimorfi**

Types of Polymorphs

International Conference on Harmonization (ICH) Guideline Q6A:

Specifications for new drug substances and Products: October 1999

Polymorphism INCLUDES

Single entity polymorphs

Molecular Adducts (solvates, hydrates)

Amorphous forms (!)

Tempo di vita di un brevetto

Italia	Europa	US
DEPOSIZIONE	**DEPOSIZIONE**	**DEPOSIZIONE**
18 mesi	**6 mesi**	**6 mesi**
PUBBLICAZIONE	**PUBBLICAZIONE**	
	2-5 anni	**2-5 anni**
CONCESSIONE	**CONCESSIONE**	**PUBBLICAZIONE CONCESSIONE**
SCADENZA	**SCADENZA**	**SCADENZA**
20 anni totali dalla concessione	**5 anni max**	**in funzione tempi FDA**
ESTENSIONE	**ESTENSIONE**	**ESTENSIONE**

20 anni

Il periodo di copertura brevettuale – nel caso dei farmaci – include un **periodo di compensazione per il tempo richiesto per la sperimentazione** del farmaco prima della immissione sul mercato

Il **Supplementary Protection Certificate** (CEE n.1768 del 1992) è uguale al periodo, detratto di 5 anni, compreso fra la data della deposizione e la concessione all'immissione in commercio del prodotto; l'estensione non può comunque avere durata superiore ai 5 anni

La scoperta e la commercializzazione di un nuovo farmaco è molto onerosa sotto il profilo economico-finanziario e con risultati caratterizzati da elevata incertezza.

- **Tempi di sviluppo lunghissimi (in media 12 anni)**
- **Costi elevatissimi**
- **Durata effettiva del "monopolio" di brevetto ca. 8 anni**

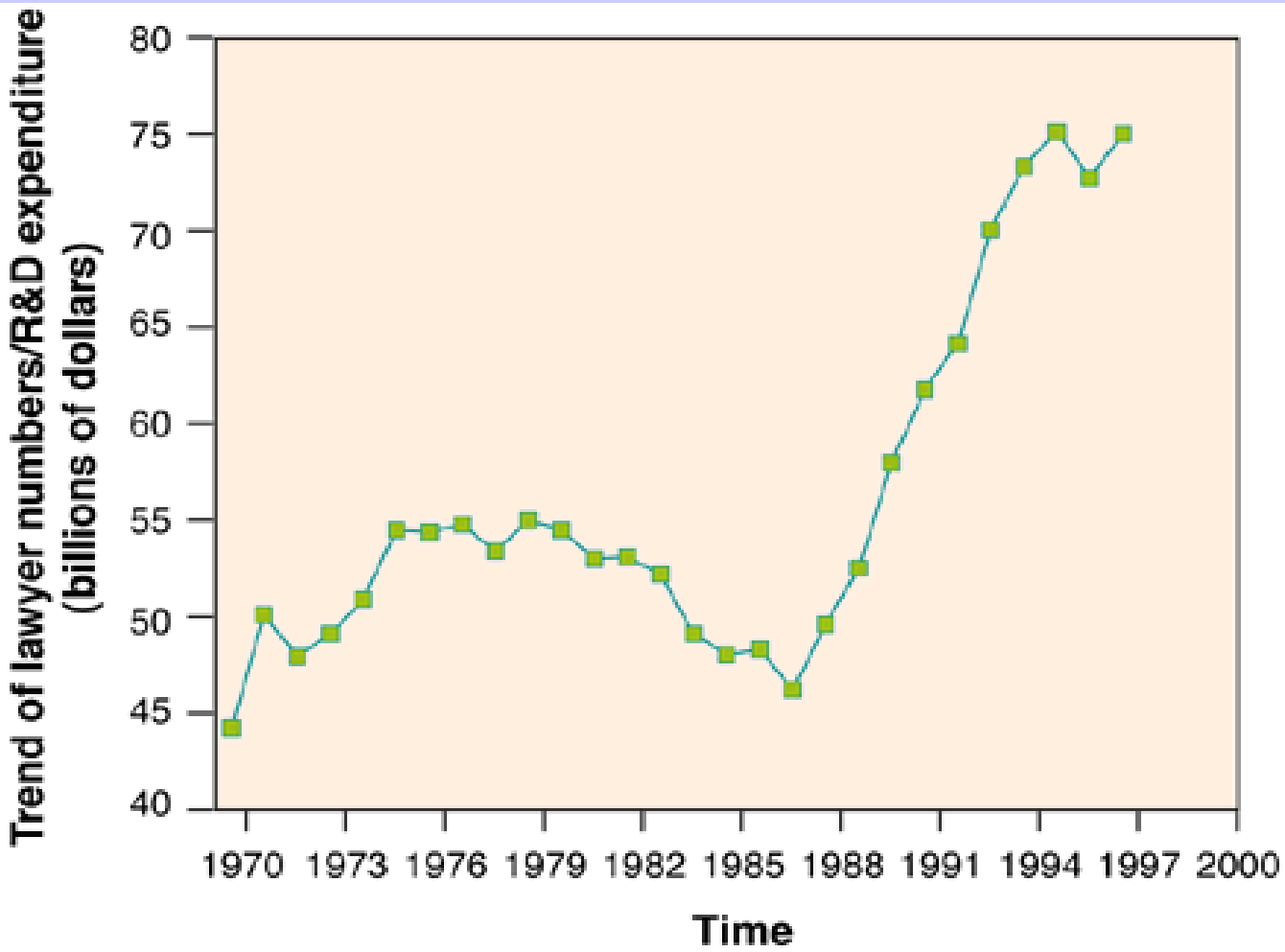
Durante questo periodo l'inventore deve assicurarsi che il prodotto gli consenta di recuperare non solo l'investimento in ricerca necessario per l'ingresso sul mercato, ma anche tutti gli investimenti su altri prodotti che, durante le fasi della ricerca, non hanno superato le prove sperimentali (e non sono perciò divenuti farmaci) (Mossialos, 1993).

Science Mar 17 2000: 1933-1934

Reforming the Patent System

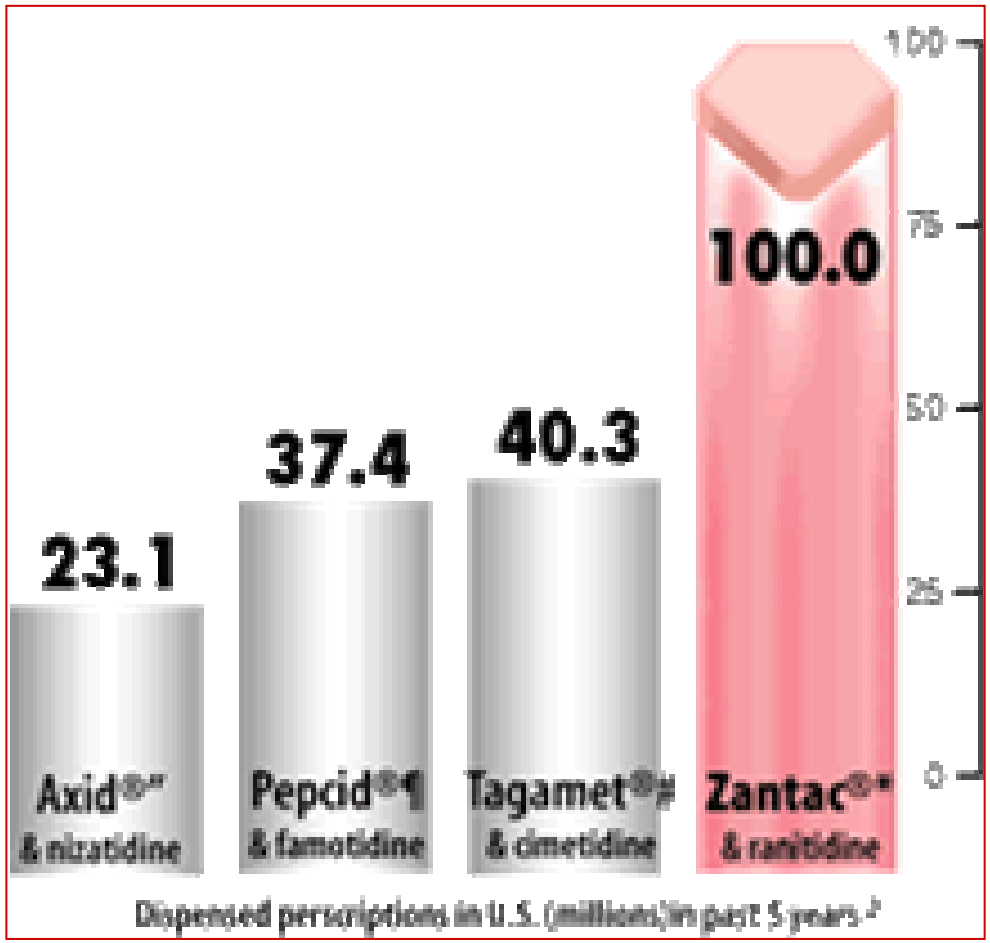
John H. Barton

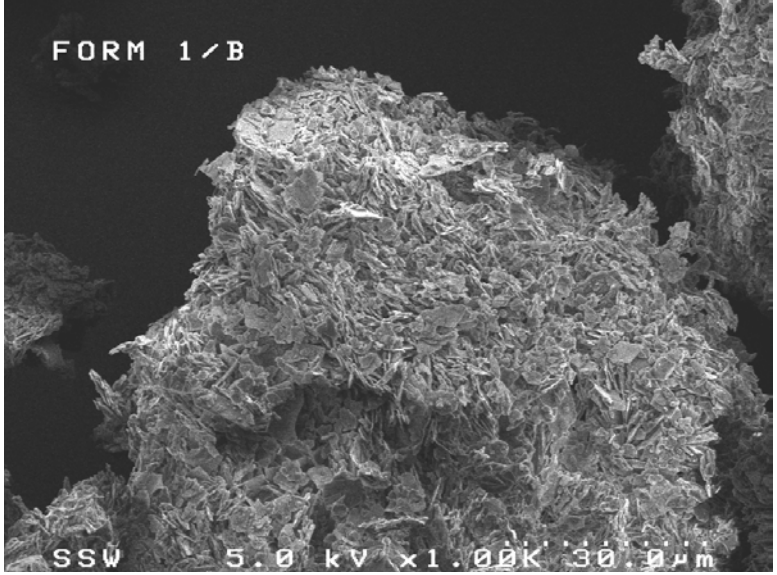
The number of intellectual property lawyers in the United States is growing faster than the amount of research (see figure). This suggests that legal costs are growing as well-and these costs are substantial; lawyer's costs alone approach $10,000 to obtain a patent and $1.5 million (per side) to litigate a patent.

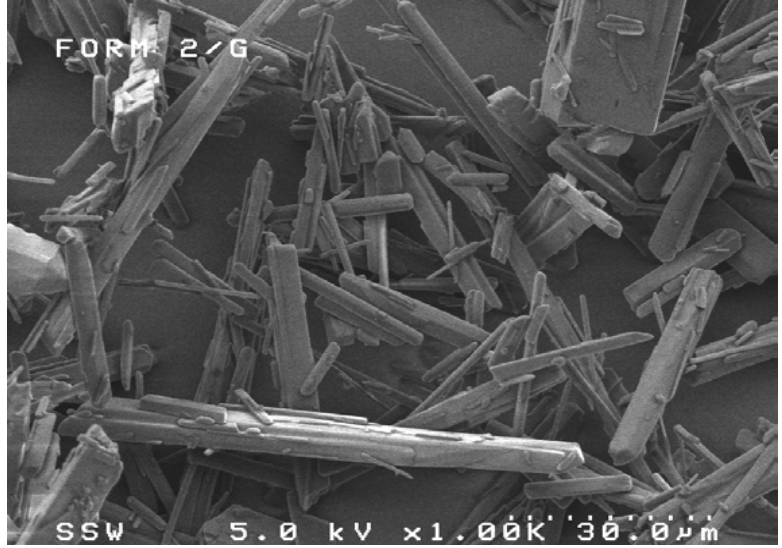


Numbers of intellectual property lawyers per unit of research expenditures in billions of dollars

Zantac is the name brand version of **Ranitidine** which is used to treat and prevent the recurrence of ulcers and to treat other conditions where the stomach makes too much acid. Ranitidine also is used to treat or prevent occasional heartburn, acid indigestion, or sour stomach. It decreases the amount of acid made in the stomach.







GLAXO VS. NOVOFARM

FORM I was patented in 1978, FORM II was discovered and patented in 1981

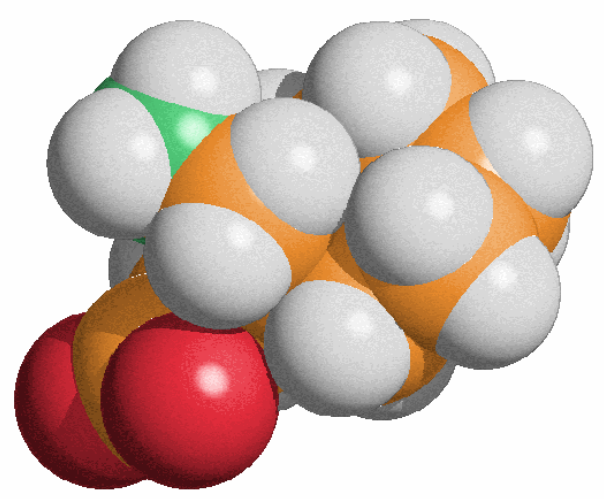
Hence, from 1995 (at the time 17 years for patents in US) form I could be sold without patent infringement as a generic drug
Novofarm attempted preparation of form I but could only get form II, GLAXO suited Novofarn for patent infringement – Novofarm claimed that the patent on form II was not valid because it was not possible to prepare form I according to the patent obtaining invariably form II

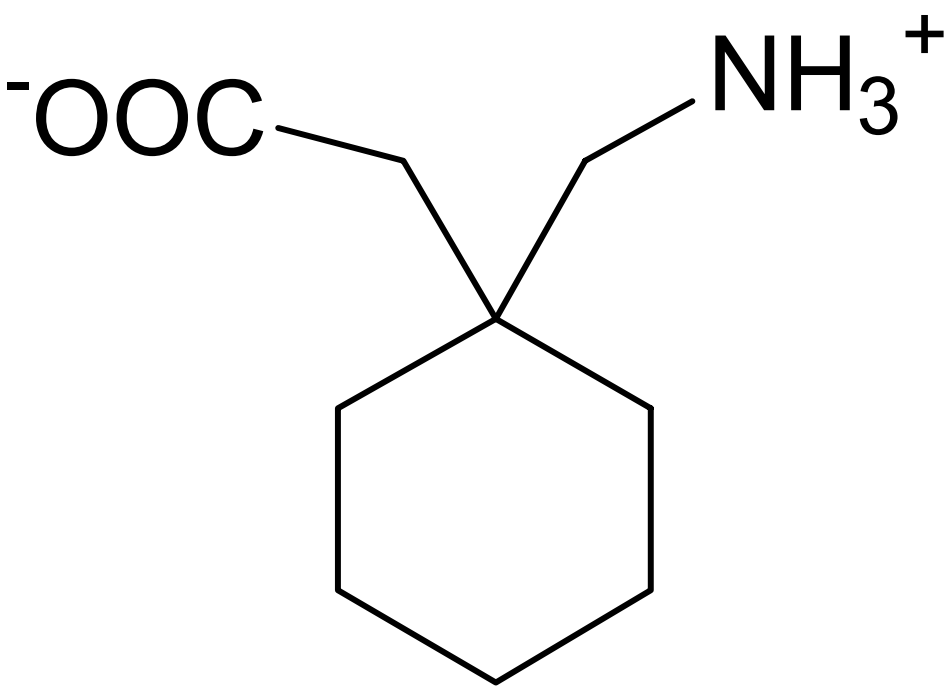
GLAXO successfully demonstrated that form I could indeed be obtained

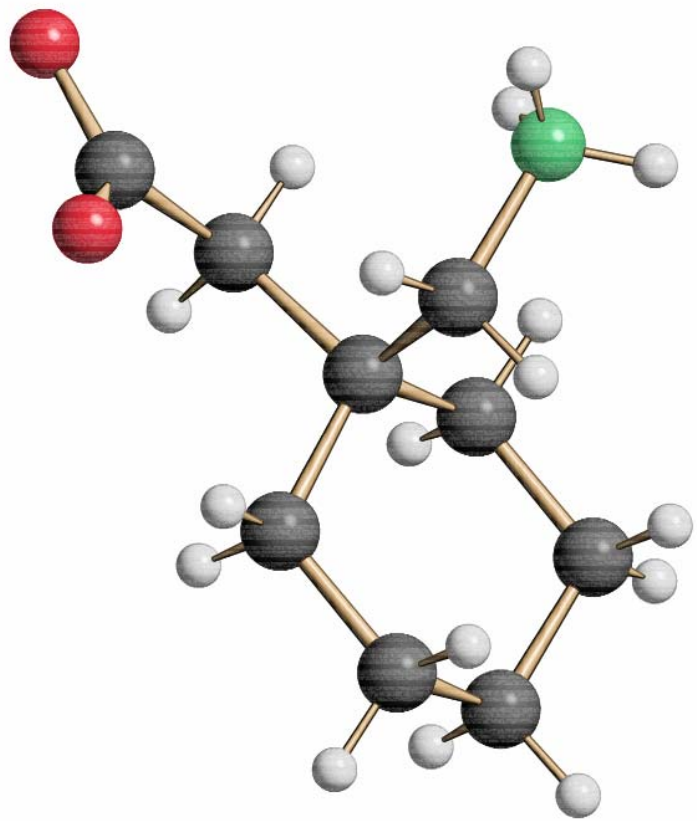
Novofarm then patented a *new process* to obtain form I, GLAXO suited Novofarm claiming that the product contained also form II (covered by the recent patent)

The court granted marketing permission to Novofarm because form II – if present – was present as in impurity in a mixture composed primarily of form I

Gabapentina







Acido 1 aminoetil-1cicloesanacetico

Gabapentina

United States Patent [19]

Satzinger et al.

[11] **4,024,175**

[45] **May 17, 1977**

[54] **CYCLIC AMINO ACIDS**

[75] Inventors: **Gerhard Satzinger**, Denzlingen; **Johannes Hartenstein**, Wittental; **Manfred Herrmann**, St. Peter; **Wolfgang Heldt**, Wasser, all of Germany

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[22] Filed: **Dec. 31, 1975**

[21] Appl. No.: **645,724**

[30] **Foreign Application Priority Data**

Dec. 21, 1974 Germany 2460891

[51] **Int. Cl.**[2] **C07C 101/04**; C07C 101/18

[58] **Field of Search** ..... 260/514 J, 468 J

[56] **References Cited**

OTHER PUBLICATIONS

March, Advanced Organic Chemistry, pp. 816–819 (1969).

Primary Examiner—Robert Gerstl

Attorney, Agent, or Firm—Albert H. Graddis; Frank S. Chow; George M. Yahwak

[57] **ABSTRACT**

The present invention is concerned with new cyclic amino acids and with the preparation thereof.

11 Claims, No Drawings

US006255526B1

(12) **United States Patent**
Pesachovich et al.

(10) **Patent No.: US 6,255,526 B1**
(45) **Date of Patent: *Jul. 3, 2001**

(54) **PREPARATION OF GABAPENTIN**

(75) Inventors: **Michael Pesachovich**, Givat Shmuel; **Claude Singer**, Kfar Saba; **Gideon Pilarski**, Holon, all of (IL)

(73) Assignee: **Teva Pharmaceutical Industries Ltd.**, Petah Tigva (IL)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,024,175	5/1977	Satzinger et al. .	
4,894,476	1/1990	Butler et al.	562/504
4,960,931	10/1990	Butler et al. .	
5,068,413	11/1991	Steiner et al. .	
5,095,148	3/1992	Mettler, et al.	562/507
5,132,451	7/1992	Jennings et al.	562/507

Primary Examiner—Michael L. Shippen
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

Nel brevetto `175 del 1977 viene rivendicata la preparazione e la caratterizzazione di una forma cristallina anidra della gabapentina (chiamata forma II)

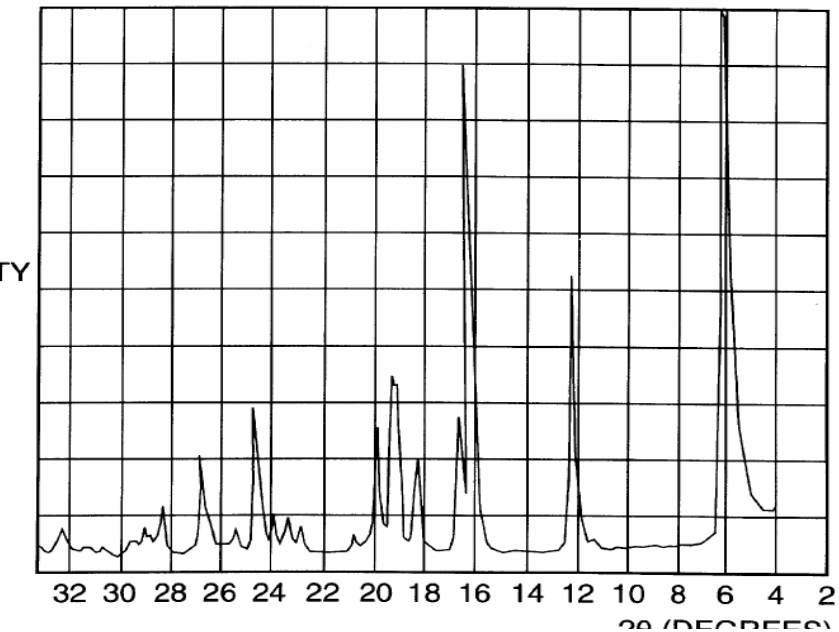
A partire dal 1997 è quindi possibile produrre e commercializzare la forma II come generico

Nel 1999 e nel 2001 vengono brevettati (TEVA) (a) un nuovo processo per produrre la forma II, (b) una nuova forma anidra (III), e (c) una forma monoidrata

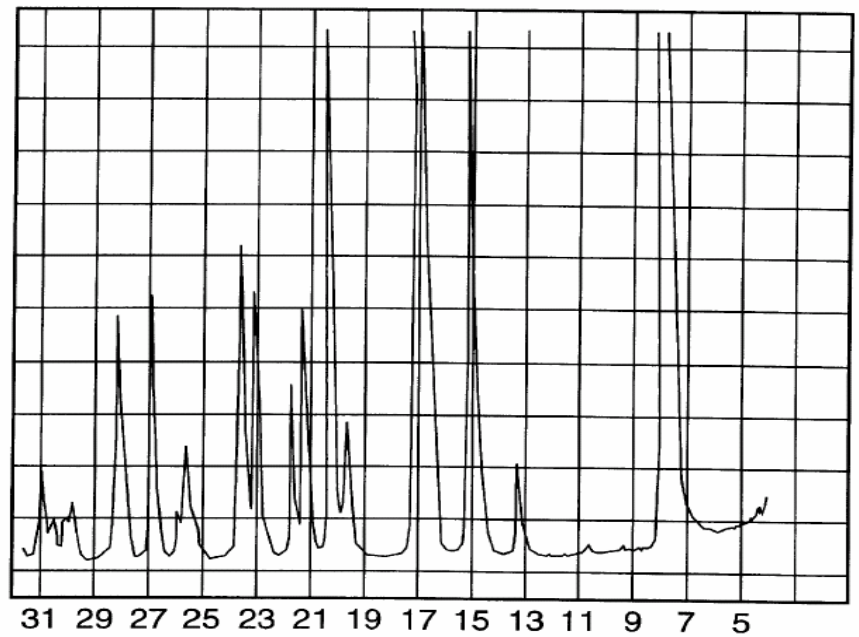
E' quindi essenziale caratterizzare il prodotto del fornitore di gabapentina generica come forma II per non incorrere nel "patent infringment" dei nuovi brevetti

(52) **U.S. Cl.** **562/507**

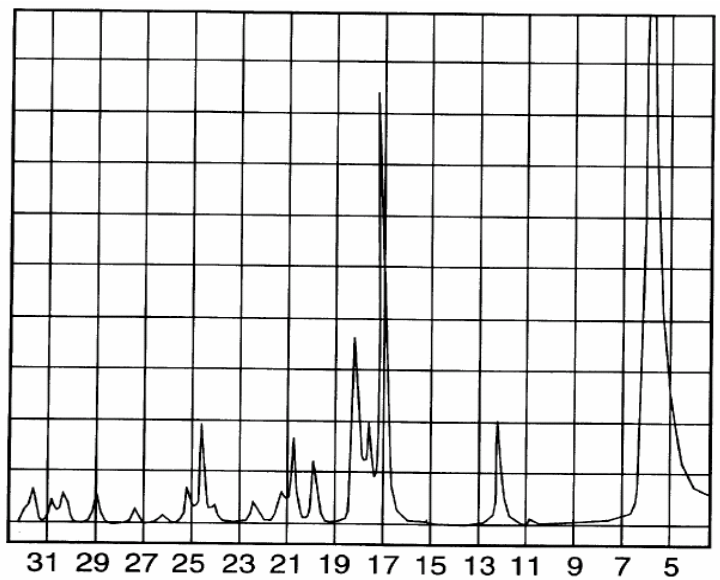
Gabapentina monoidrata (brevetto del 1990) – forma I



Gabapentina anidra (forma II) brevetto del 1977



Gabapentina forma III anidra



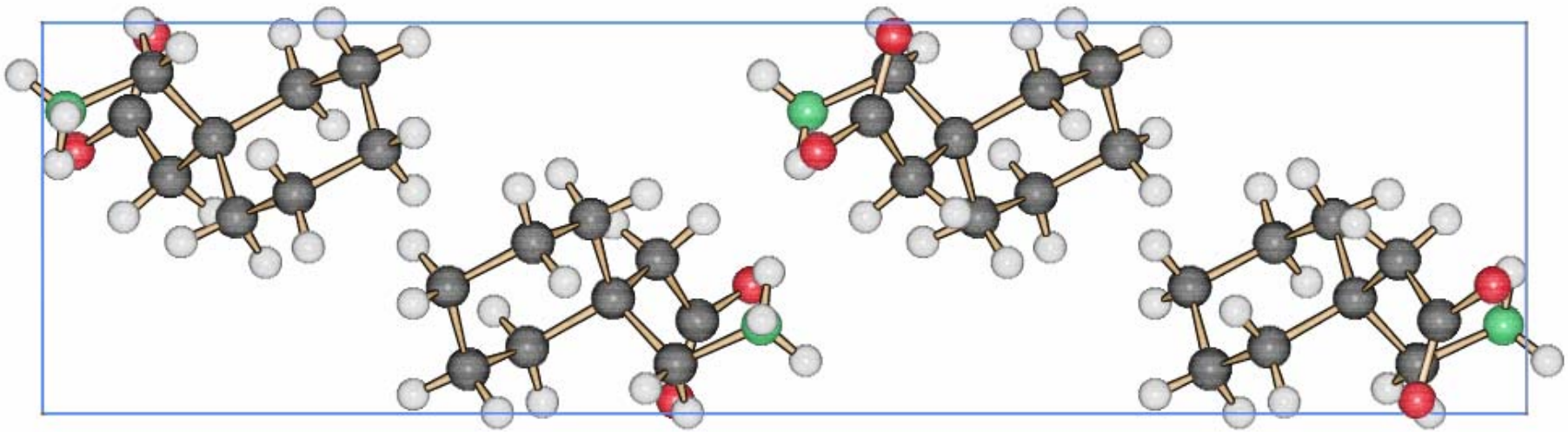
Dati cristallografici – forma II

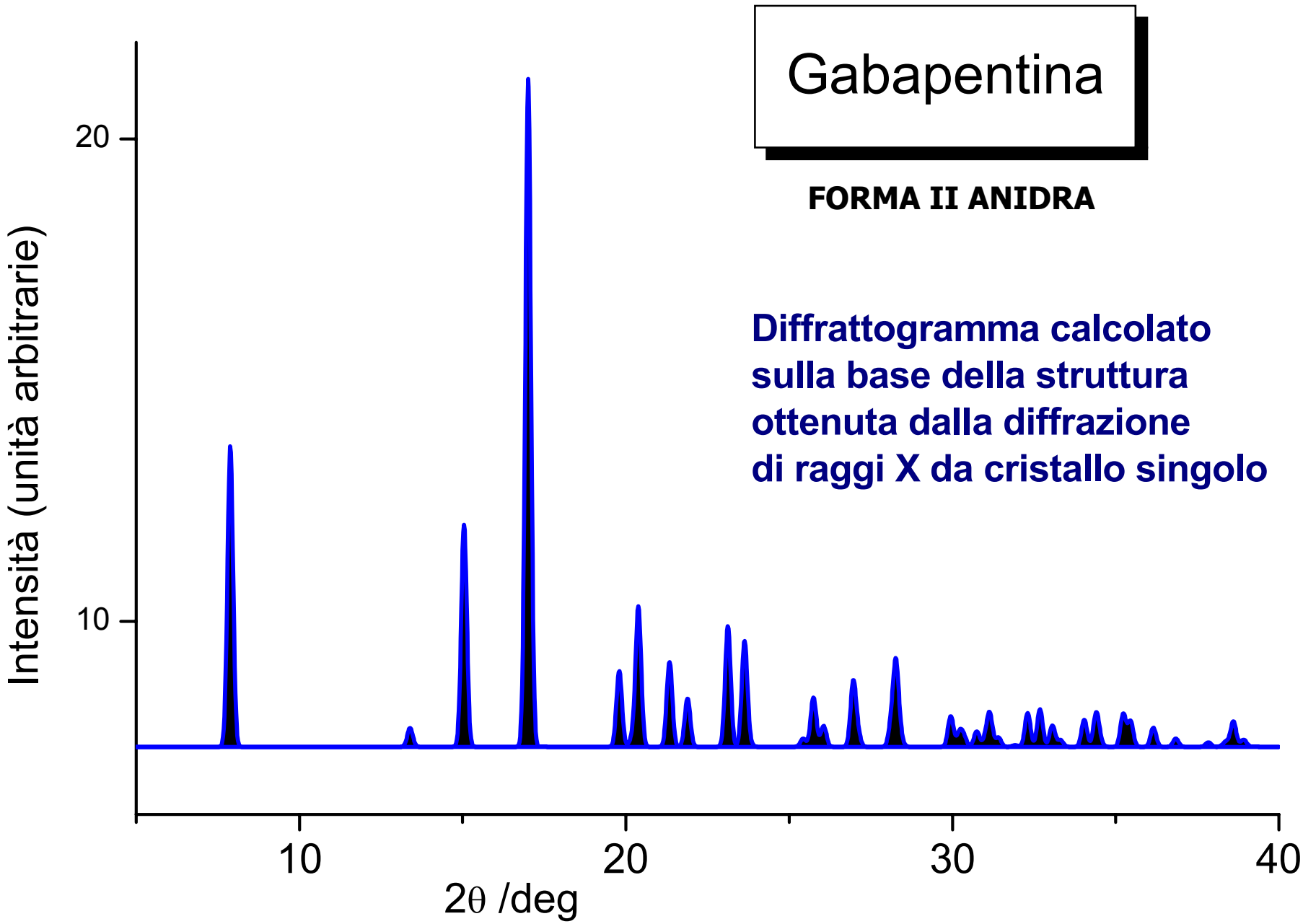
Monoclino $P2_1/c$

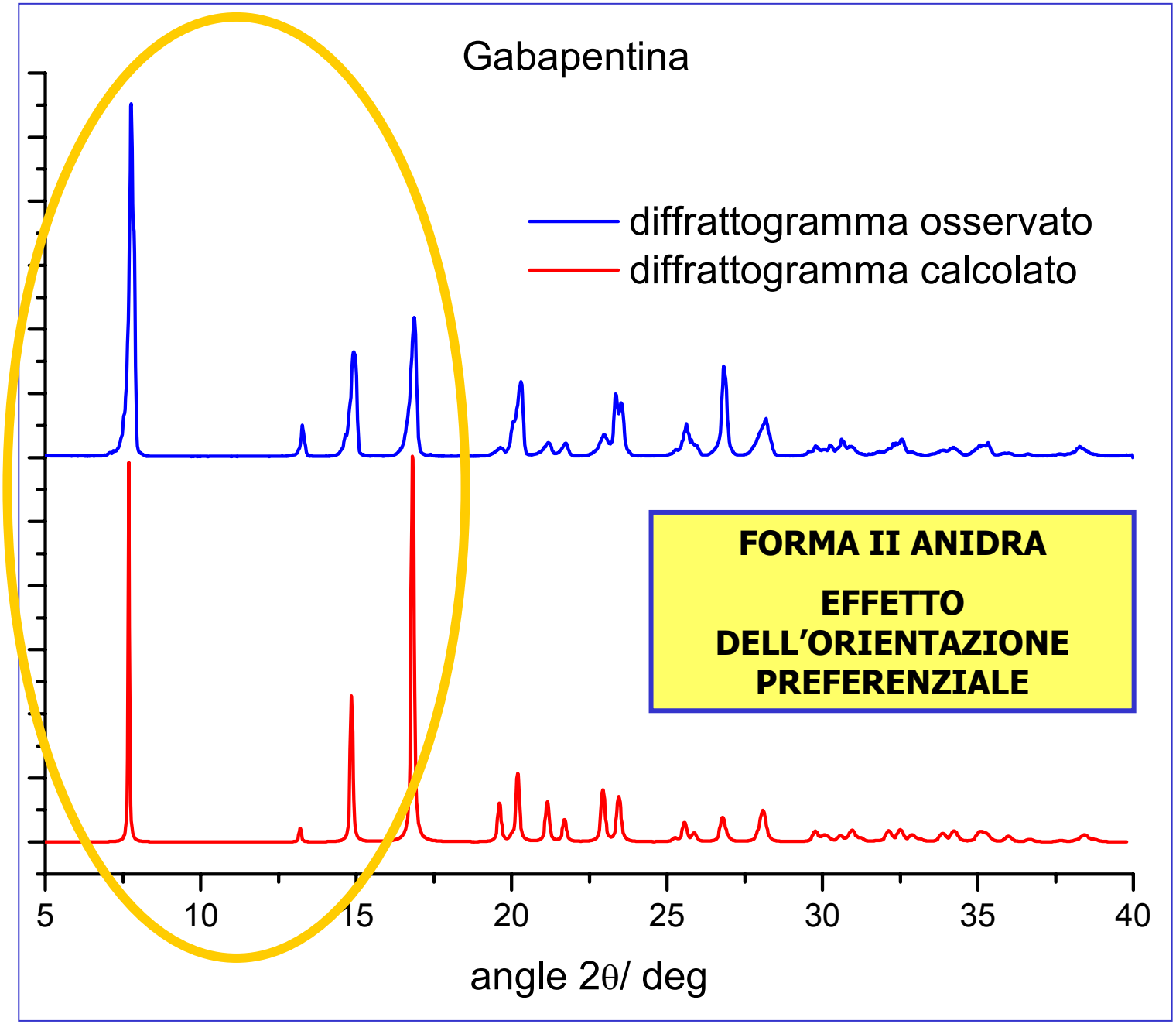
a= 5.8842(12) Å b= 6.9155(14) Å c = 22.414(5) Å

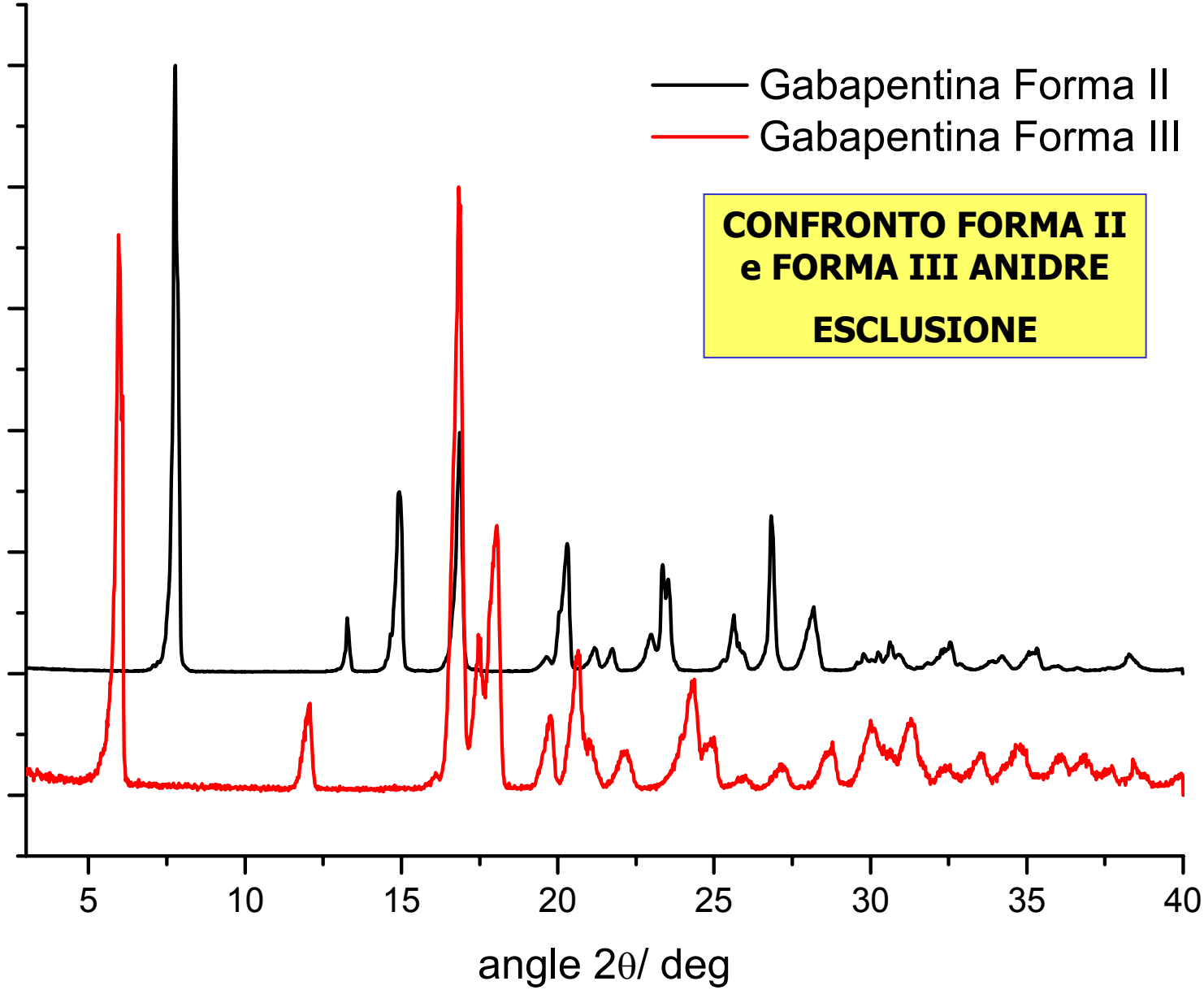
ß = 90.01(3)°

V= 912.1(3) $Å^3$ Z= 4



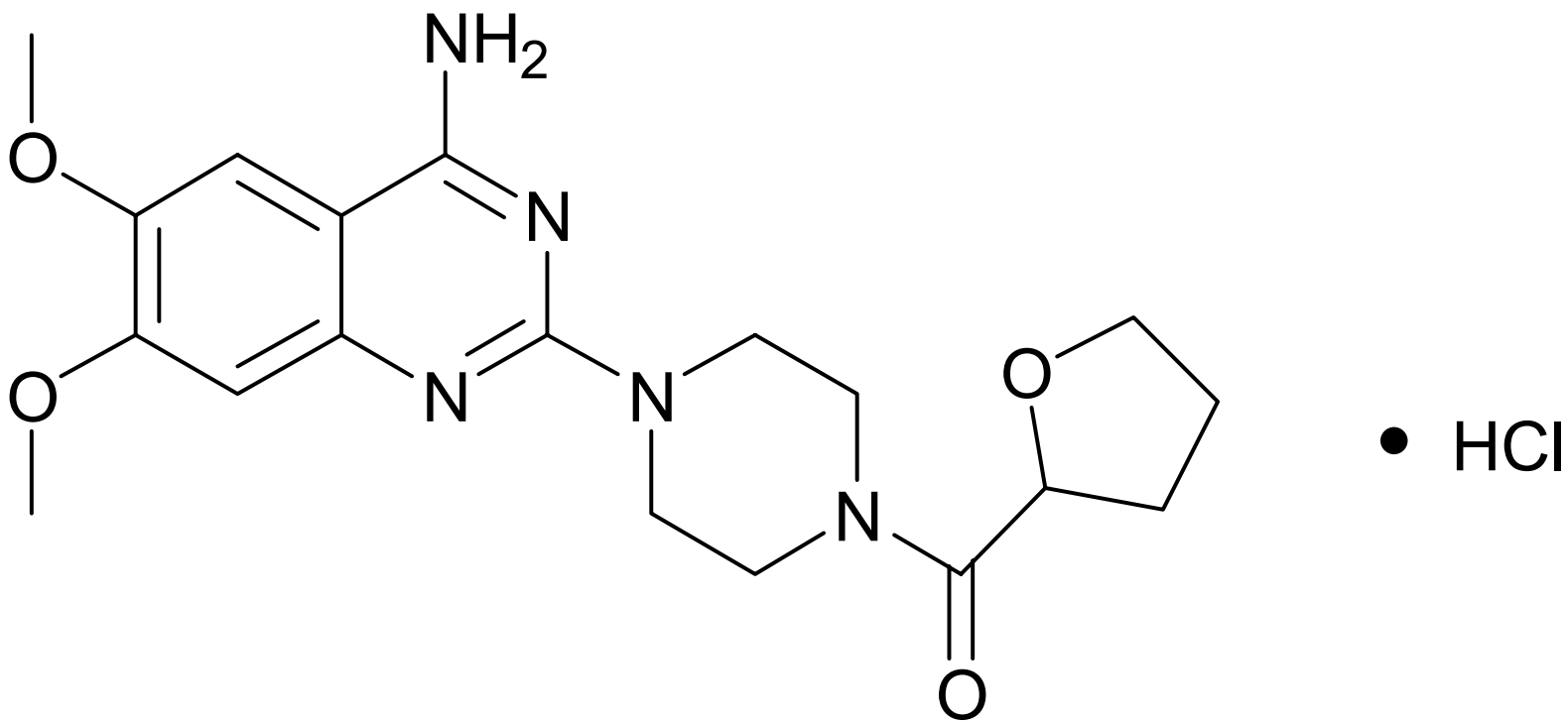

Gabapentina
FORMA II ANIDRA
Diffrattogramma calcolato
sulla base della struttura
ottenuta dalla diffrazione
di raggi X da cristallo singolo
Intensità (unità arbitrarie)
20
10
10
20
30
40
2θ /deg


Gabapentina
diffrattogramma osservato
diffrattogramma calcolato
FORMA II ANIDRA
EFFETTO DELL'ORIENTAZIONE PREFERENZIALE
5
10
15
20
25
30
35
40
angle 2θ/ deg


Gabapentina Forma II
Gabapentina Forma III
CONFRONTO FORMA II
e FORMA III ANIDRE
ESCLUSIONE
5
10
15
20
25
30
35
40
angle 2θ/ deg

TERAZOSIN HCL

Developed by Abbott for treatment of hypertension and PBH and marketed as dihydrate as HYTRIN since 1987 (patent *4,026,894*)



United States Patent *4,026,894*

Winn , et al. **May 31, 1977**

Abstract Described are antihypertensive agents selected from the class consisting of 2[4(tetrahydro-2-furoyl)-piperazino]-4-amino-6,7-dimethoxyquinazoline and 2-[4(tetrahydropyran-2-carbonyl)-piperazinyl]-4-amino-6,7-dimethoxyquinazo line, and pharmaceutically acceptable acid addition salts thereof. The compounds are highly water soluble and can be administered in time release form as well as parenterally, including intravenously.

Abbott Laboratories (North Chicago, IL)

United States Patent 5,504,207

Mannino , et al. **April 2, 1996**

Abstract A process for the preparation of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-tetrahydrofuroyl)piperazine hydrochloride (terazosin hydrochloride dihydrate comprises the steps of reacting 4-amino-2-chloro-6,7-dimethoxy-quinazoline with N-(2-tetrahydrofuroyl)piperazine in an anhydrous polar organic solvent in the absence of an added acid scavenger to produce anhydrous 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-tetrahydrofuroyl)piperazine hydrochloride **(Form IV)** and thereafter converting the product of that step to 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-tetrahydrofuroyl)-piperazine hydrochloride dihydrate.

Assignee:

Abbott Laboratories (Abbott Park, IL)

After elapsing of the 4,026,894, Geneva and others entered the market of TERAZOSIN with an anhydrous form (form I) not covered by the subsequent 5,504,207 patent

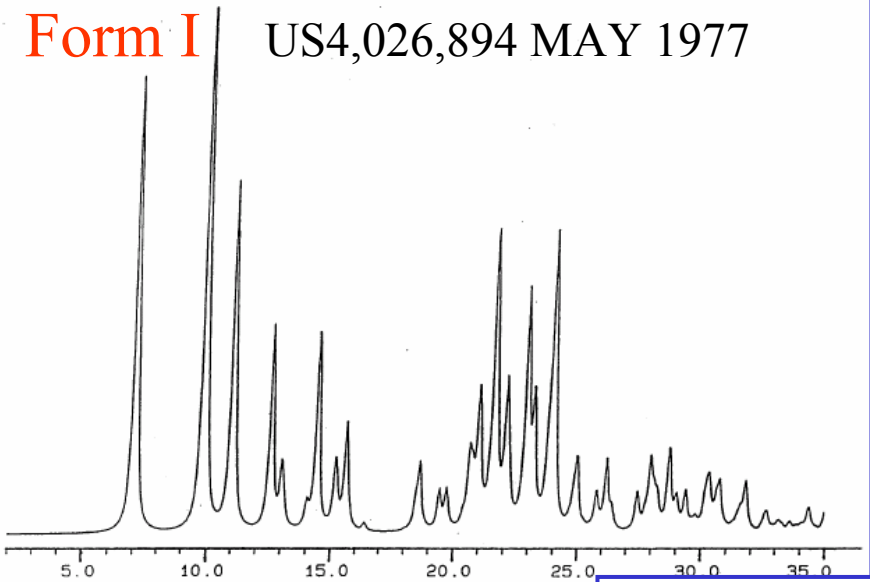
Abbott suited Geneva and others saying that <u>form I was instead form IV</u> covered by the 5,504,207

Abbott lost the trial because Geneva could demonstrate that form IV was on sale in US BEFORE the ‘207 patent was issued!

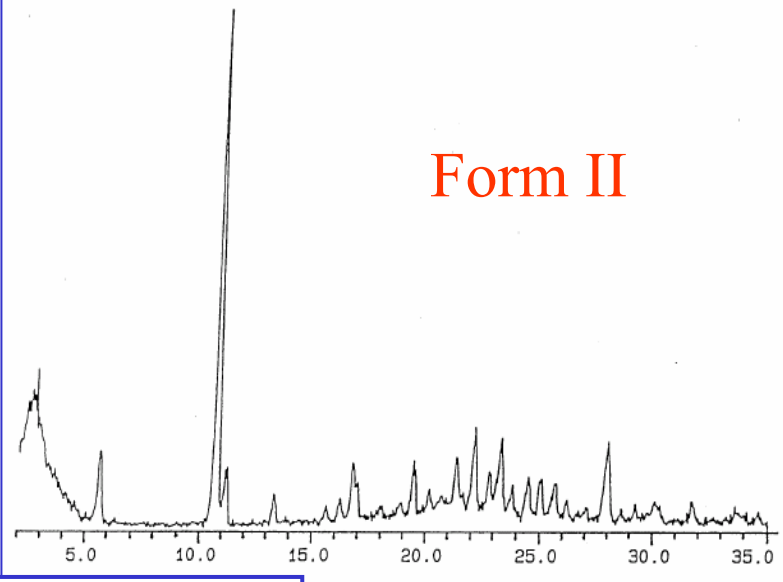
TERAZOSIN HCL

Form I

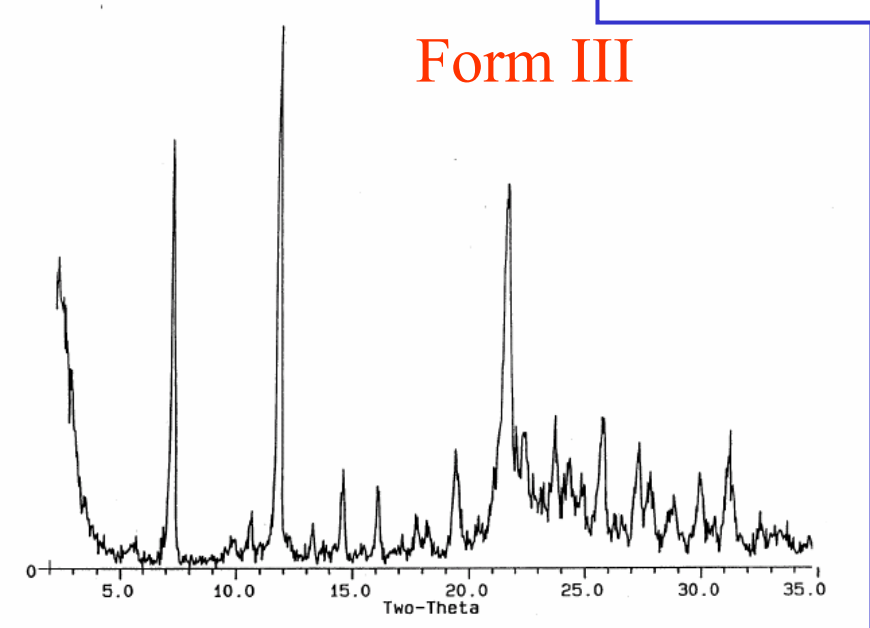
US4,026,894 MAY 1977



Form II

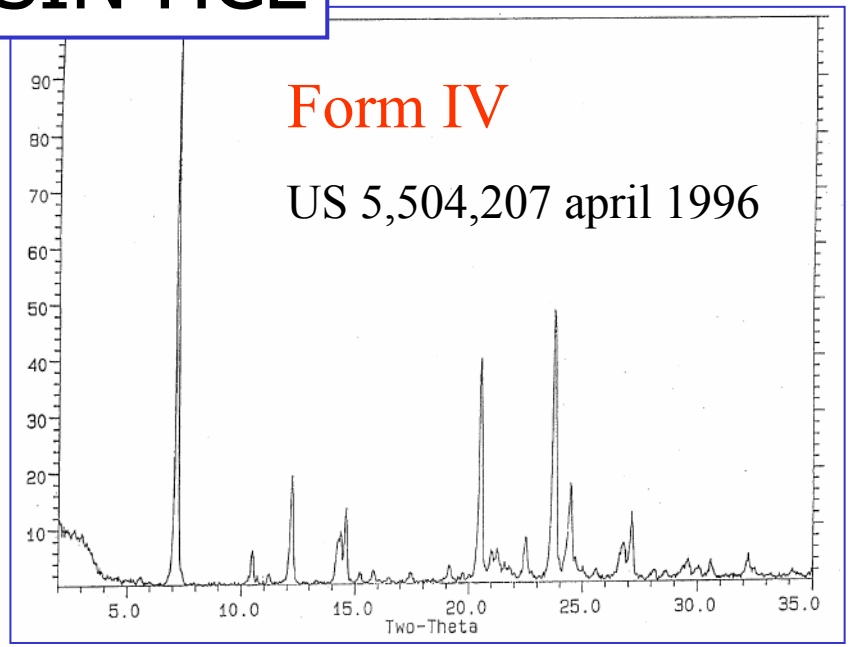


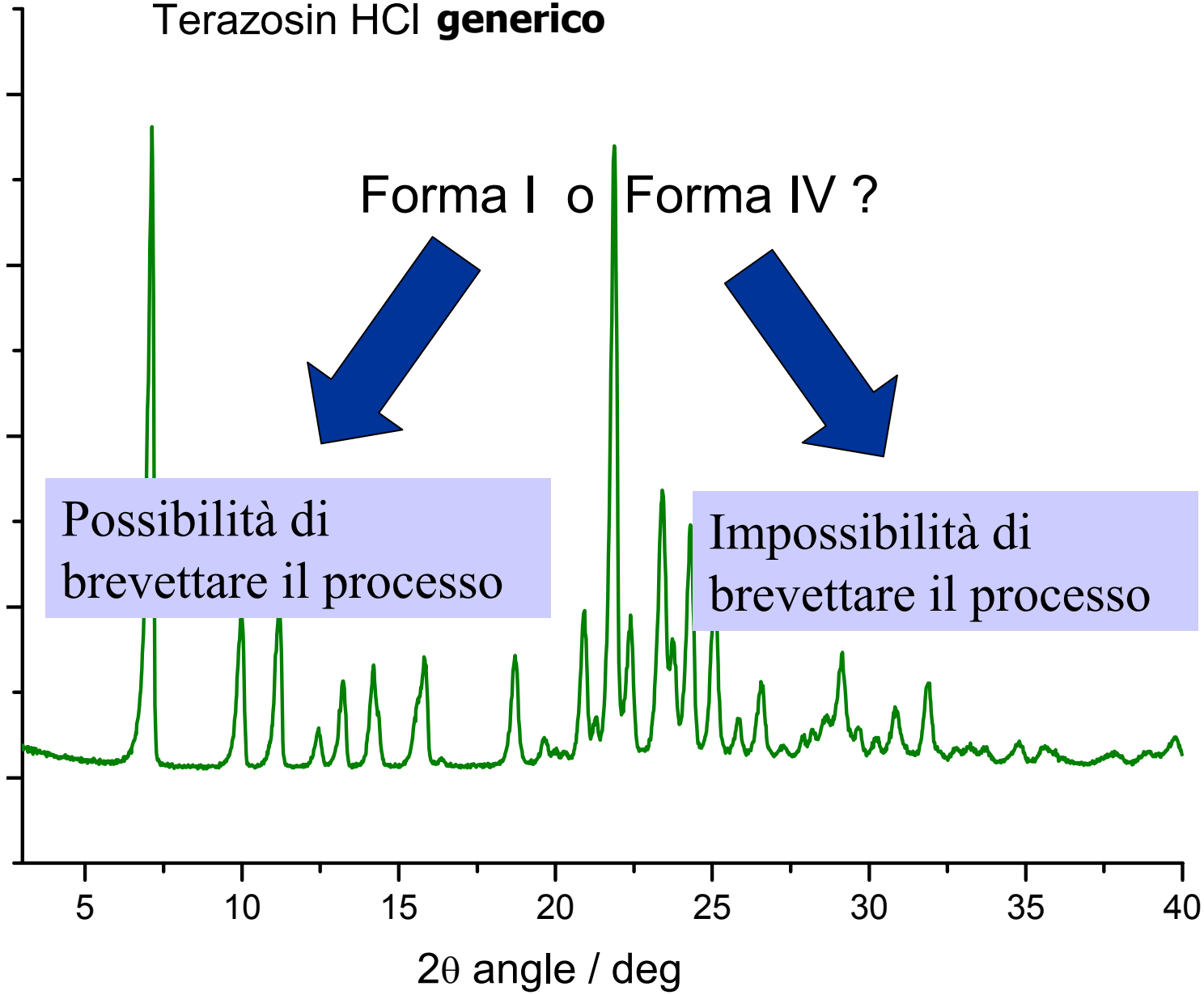
Form III



Form IV

US 5,504,207 april 1996

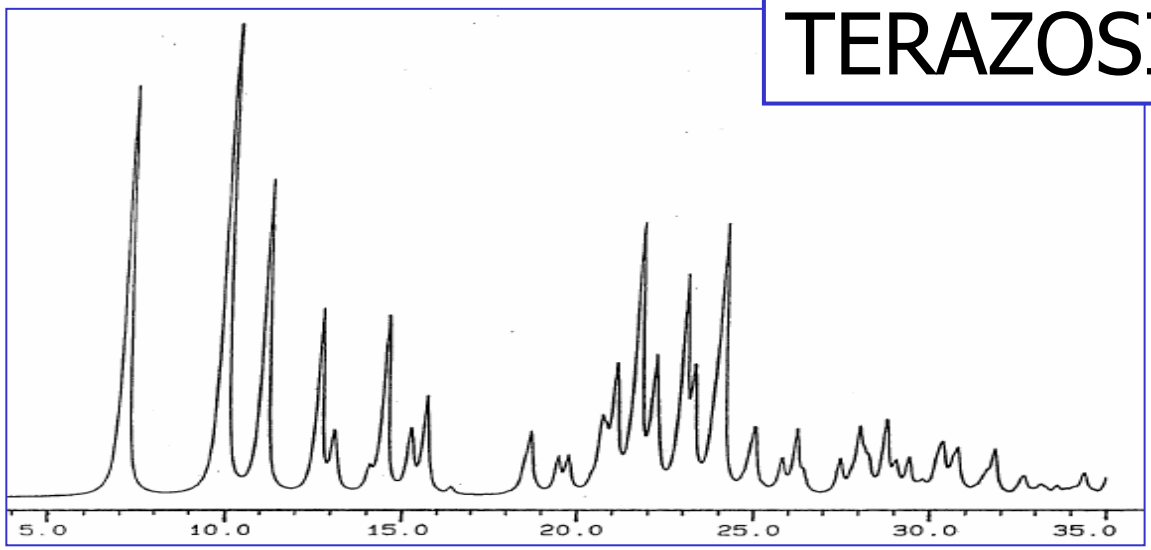


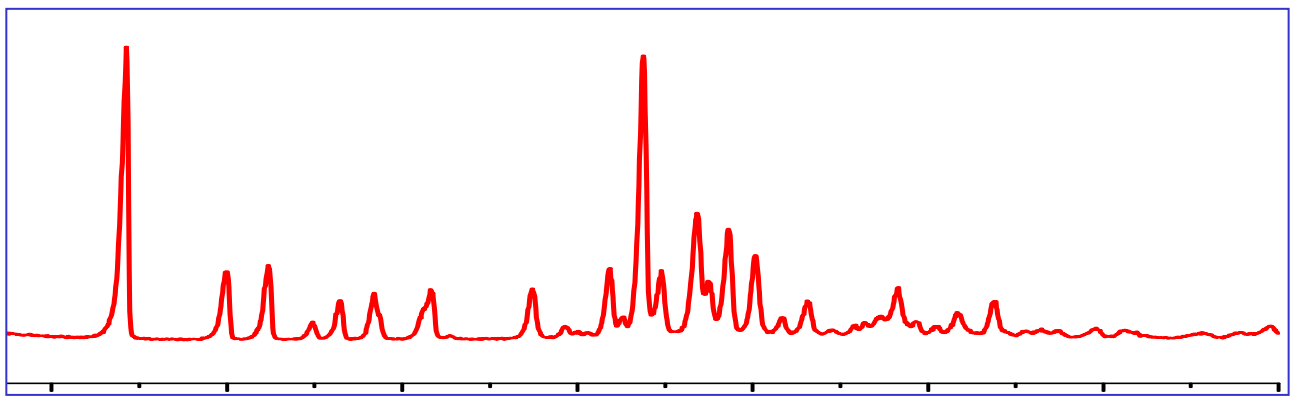

Terazosin HCl **generico**
Forma I o Forma IV ?
Possibilità di brevettare il processo
Impossibilità di brevettare il processo
5
10
15
20
25
30
35
40
2θ angle / deg

TERAZOSIN HCL

Forma I

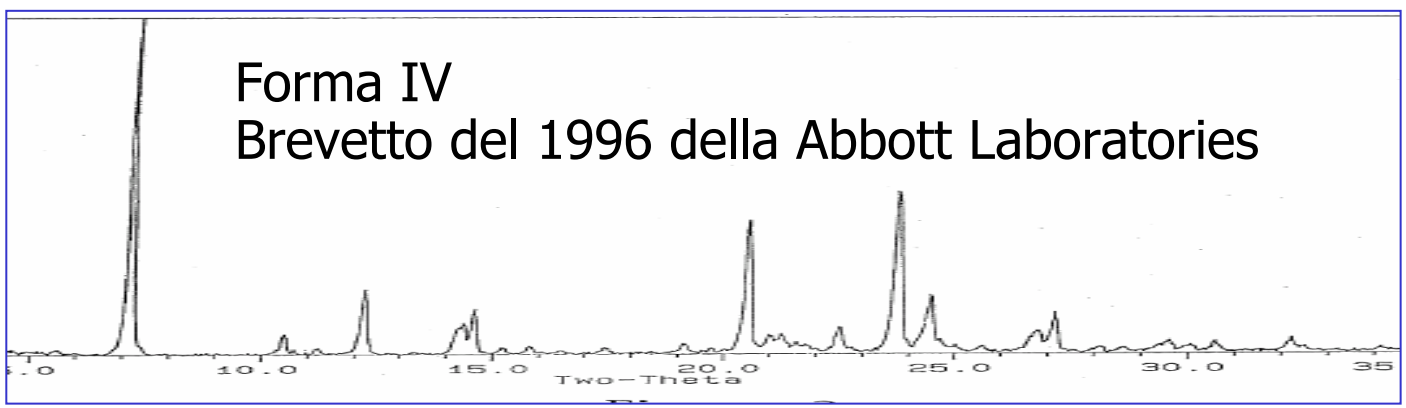
Brevetto del 1977



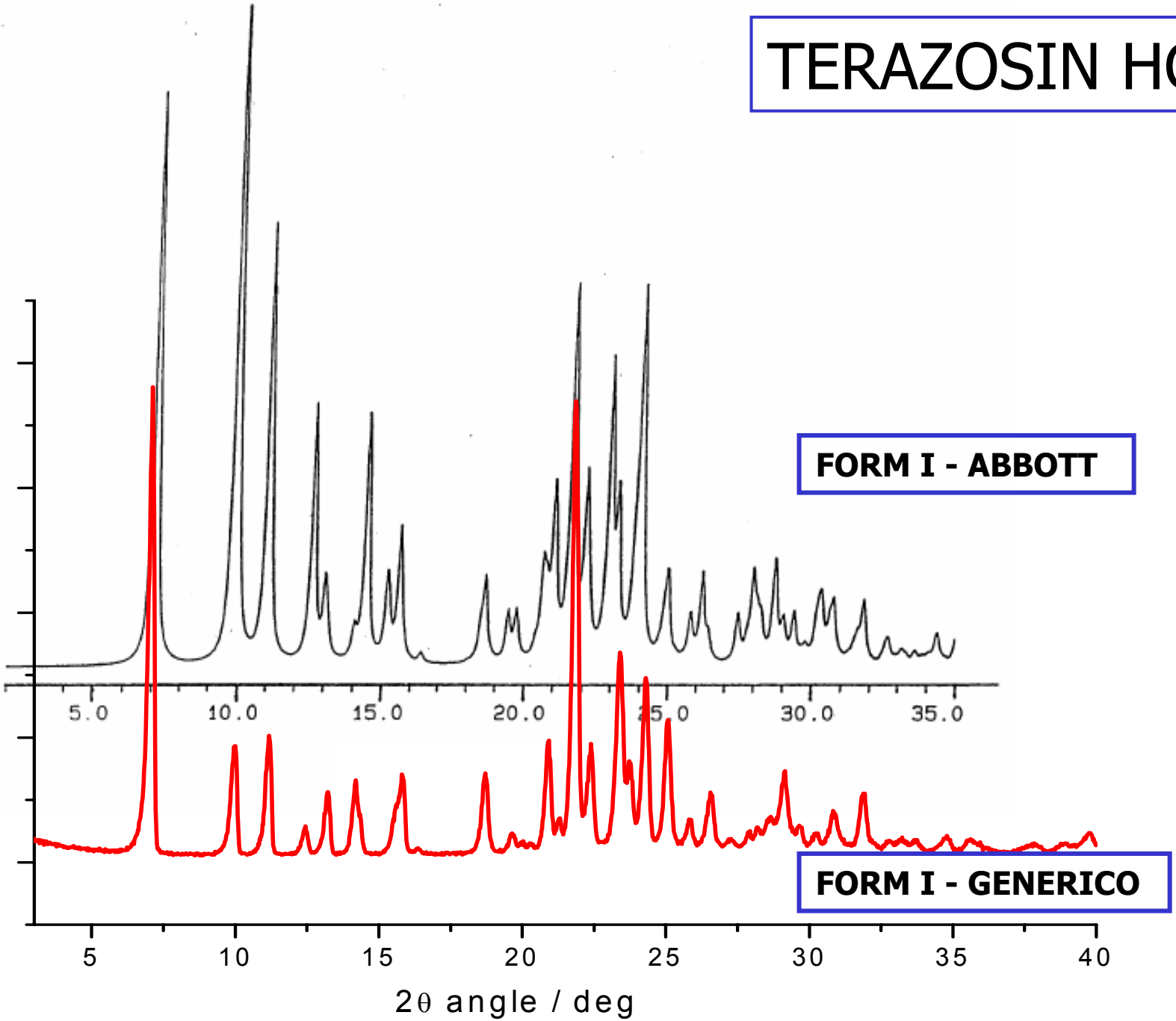


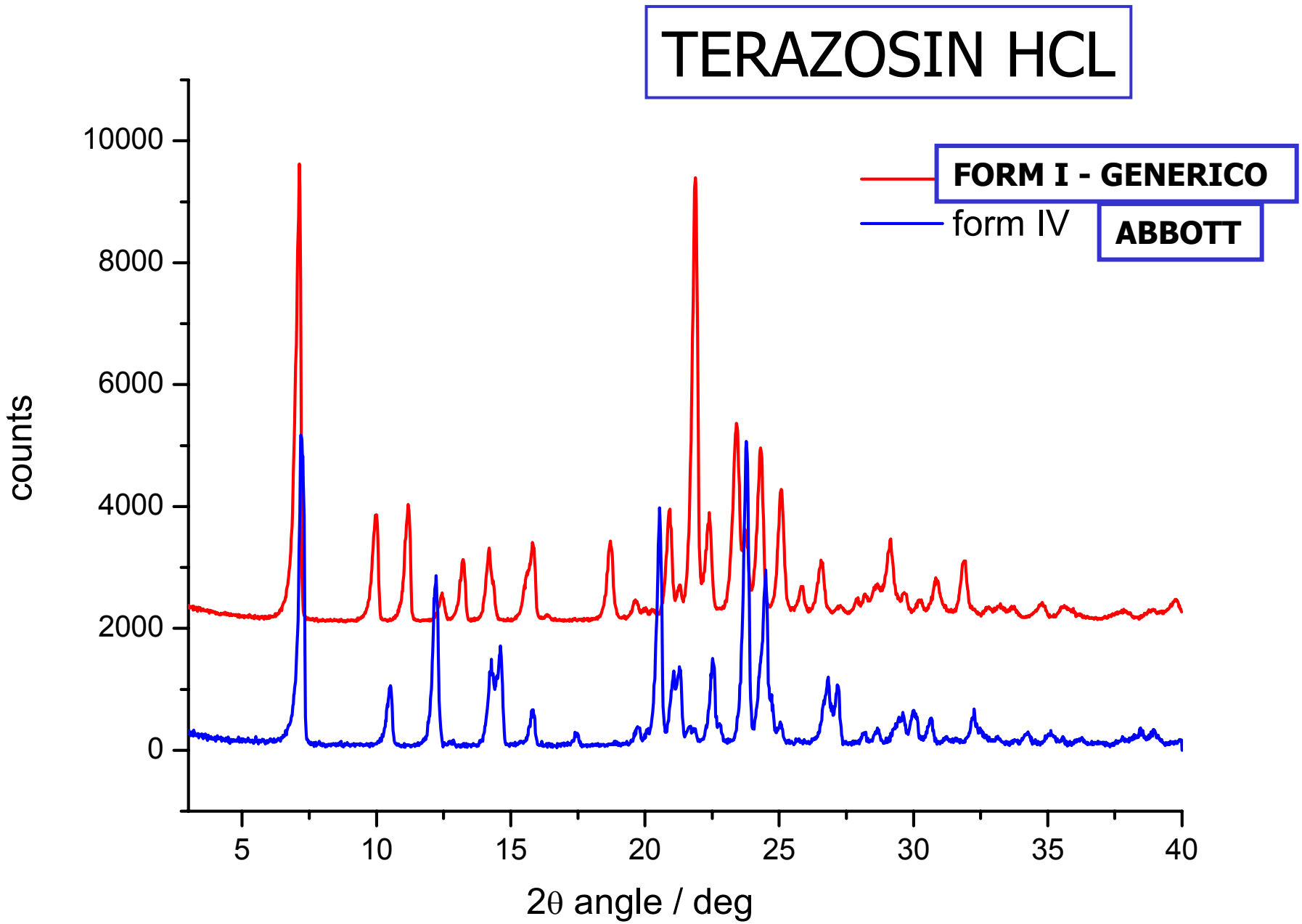
Forma IV

Brevetto del 1996 della Abbott Laboratories



TERAZOSIN HCL




TERAZOSIN HCL
FORM I - GENERICO
form IV
ABBOTT
counts
10000
8000
6000
4000
2000
0
5
10
15
20
25
30
35
40
2θ angle / deg

US005859245A

United States Patent [19]

Cannata et al.

[11] Patent Number: 5,859,245

[45] Date of Patent: Jan. 12, 1999

[54] **PROCESS FOR THE PRODUCTION OF THE FORM I OF THE ANHYDROUS TERAZOSIN MONOHYDROCHLORIDE**

[75] Inventors: **Vincenzo Cannata**, Borgo Nuovo di Pontecchio Marconi; **Tiziano Ferrario**, Ceriano Laghetto; **Barbara Galbiati**, Milan, all of Italy

[73] Assignee: **Alfa Chemicals Italiana S.r.l.**, Bergamo, Italy

[21] Appl. No.: **954,708**

[22] Filed: **Oct. 20, 1997**

[30] **Foreign Application Priority Data**

Nov. 29, 1996 [IT] Italy BO96A0611

[51] **Int. Cl.**^{6} **C07D 239/84**

[52] **U.S. Cl.** **544/291**; 544/284; 544/295

[58] **Field of Search** 544/284, 293, 544/291

[56] **References Cited**

U.S. PATENT DOCUMENTS

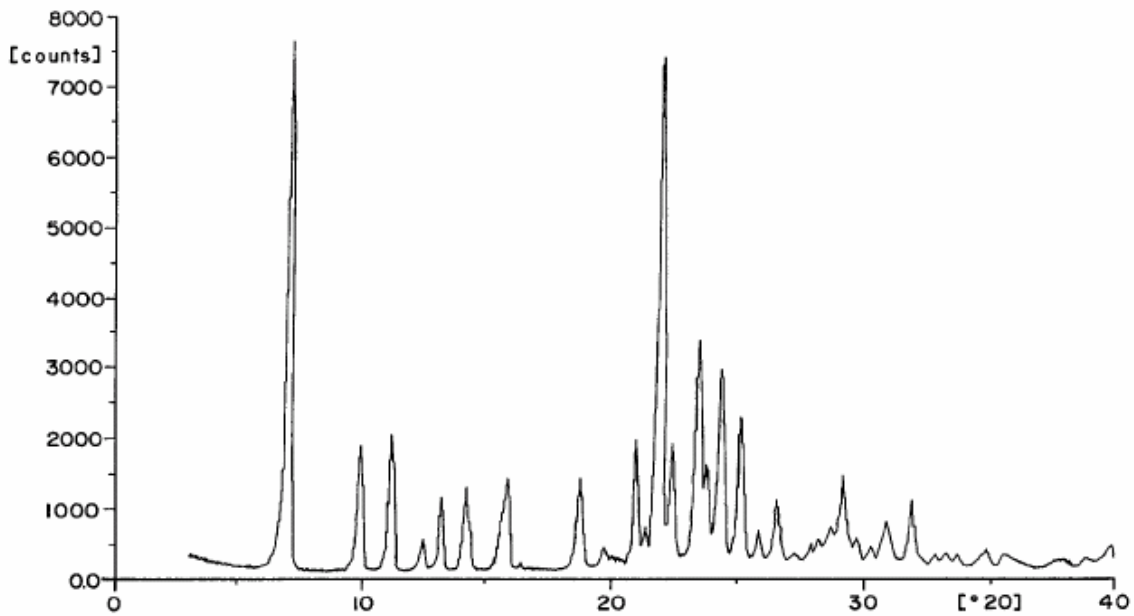
4,026,894	5/1977	Winn et al.	544/291
4,251,532	2/1981	Roteman	544/291
5,212,176	5/1993	Kyncl et al.	544/291
5,294,615	3/1994	Meyer et al.	544/291
5,412,095	5/1995	Morley et al.	544/291

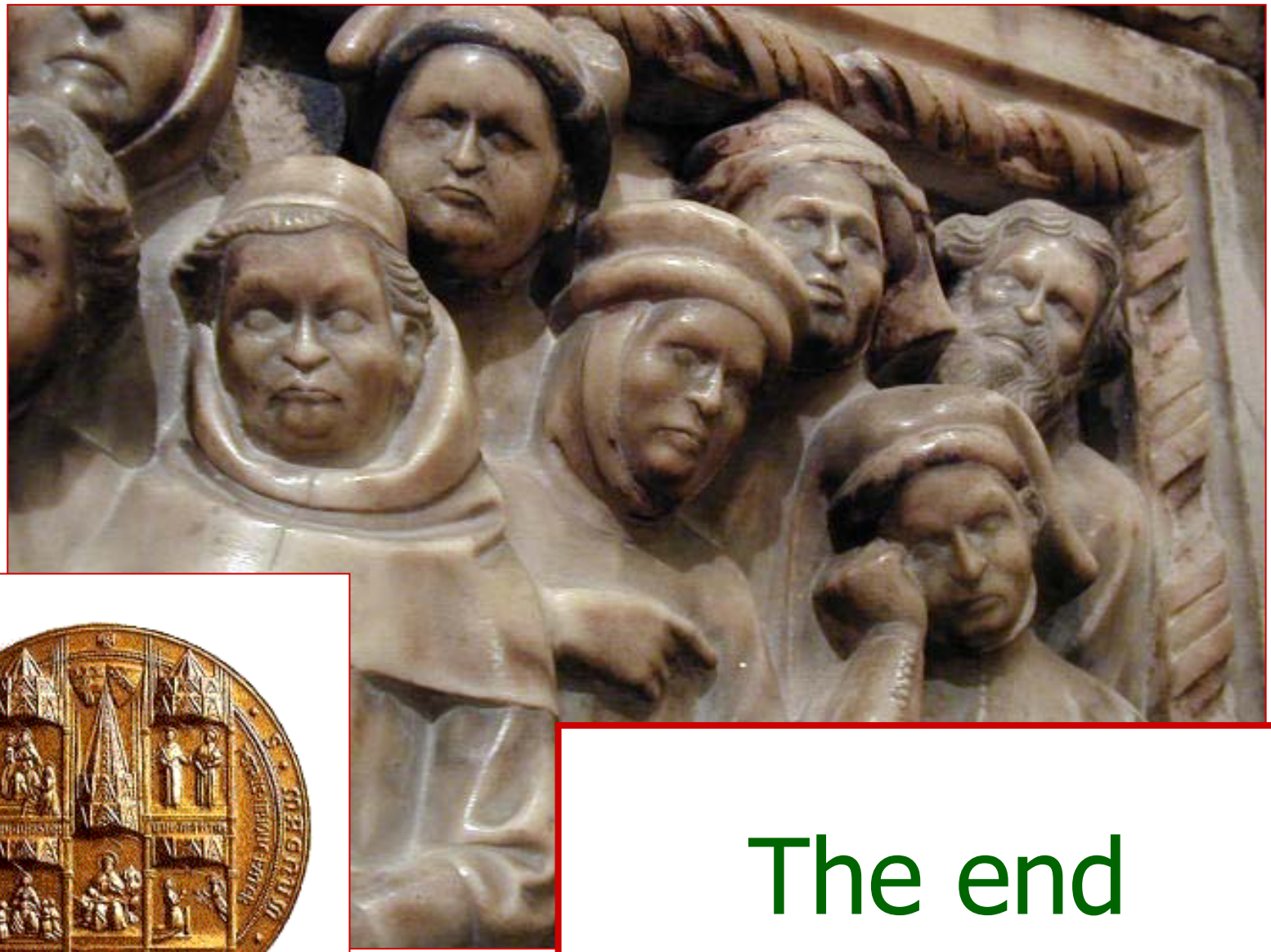
Primary Examiner—Yogendra N. Gupta
Attorney, Agent, or Firm—Bucknam and Archer

[57] **ABSTRACT**

The process for the production of form I of anhydrous terazosin monohydrochloride consists of heating terazosin suspended in a mixture made by methanol and a solvent selected from C_2 to C_6, straight or branched alcohols, esters of C_1–C_8 aliphatic carboxylic acids with straight or branched C_1 to C_8 alcohols, C_3 to C_8 aliphatic ketones, C_4 to C_8 straight branched or cyclic aliphatic ethers, aliphatic amides and aliphatic nitriles with a methanol solution of hydrochloric acid.

3 Claims, 3 Drawing Sheets





The end

Crystal Engineer ?