



# LARGE SUPRAMOLECULAR ASSEMBLIES AND INCLUSION COMPOUNDS

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## General scope

The content and scope of the supramolecular field has undergone large changes during the last 10 years. The original target aimed mainly at inclusion compounds involving recognition and association steps. This area comprises crystalline hydrates and other clathrates, as well as individual "supermolecules" already existing in solution such as cyclodextrins, calixarenes, or crown ethers.

Soon it appeared that a fruitful new research direction in *supramolecular chemistry* arises by studying and using non-covalent forces (hydrogen bonds, Van der Waals forces,  $\pi$ -interactions, coordination bonds) issued from every molecule at well defined directions. Thus pre-designed **molecular recognition** involving many molecules occurs and leads to a **molecular assembly** with **specific architecture and properties**.

A further step consists of "*imprinting information*" into molecular components (by creating chemical functions with pre-designed geometry) so that upon mixing of the components a supermolecular entity is spontaneously generated by molecular recognition and by **self-assembly processes**. This new concept allowed further developments in the inclusion area.

The elaboration of "multiple recognition algorithms" concurrently employed (for instance,  $\pi$ - and hydrogen bonds) has recently reached a high degree of sophistication in the sequence:

### *Individual molecules - supermolecule - supramolecular array - crystal or conglomerate*

It is remarkable that novel *large assemblies* comprise synthetic entities with molecular weights as high as 15000, as well as hybrid supramolecular assemblies of synthetic molecules with DNA.

Clearly the supramolecular discipline heavily relies on 3D structural information at "both ends": in the process of designing a new compound, and in the process of characterization of the final product. In this general description, crystallographers immediately recognize most of their motivations and their views on the very essence of a crystal, of a complex molecule, of a molecular assembly. Crystallization itself is a prototype of a self-assembly process, and some crystallographers have further focused on "the crystal as a supermolecule".

It is worth noticing that the role of crystallography is widely recognized, and it is now of general use that the displayed chemical formulas are computer outputs of crystal structure determination. In particular, crystal engineering,

boosted by current achievements in the supramolecular area, is now rapidly developing.

Prediction of crystal structures has always been a subject of tantalising work. A turning point is being reached by current structure investigations of crystals involving supramolecular features or assemblies originating from molecular and supramolecular recognition. The concept of building blocks and synthons endowed with directional linking functions undergoes vigorous new developments. Several novel crystalline supramolecular families are based on the synergy between different types of non-covalent bonds.

The supramolecular discipline provides fruitful interface to other disciplines, such as biology, materials sciences, supramolecular polymers (in particular dendrimers), and recently with supramolecular physics.

Thus, crystallography is a necessary, quasi-indispensable part in any supramolecular area:

- As fundamental source of information in the initial process of conception and design (retro-synthetic methods, synthons), often retrieved from data banks (Cambridge databank of organic and organometallic compounds [1], Protein structure database [2], Polymer structure database [3]).
- For the creation and optimization of new classes of crystalline compounds and solid state synthesis with specific properties.
- As a tool for structural characterization.

The supramolecular field is rapidly expanding through studying highly sophisticated supramolecular compounds and exploring new systems. Twenty-one communications presented at the microsposium "Large Supramolecular Assemblies and Inclusion Compounds" organized during the ECM-18 reflect well the variety of the motivations and topics outlined above and show the following trends in concurrent research.

## Natural or semi-natural compounds

Higher cyclodextrins homologues, larger than cyclodextrins, show quite unusual conformations based upon reversal of the usual mutual orientation of consecutive glucose rings. The isolation and crystallisation of cyclodextrins with 9, 10, 14, 16 and 26 rings is a remarkable achievement. It provides a wealth of information on the difficult question of saccharide conformation whose variability causes problems in crystal structure determination of glycoproteins and other important biological structures. A new model for V-amylose proposed by Gessler



et al [4] is a nice example of further implications of a crystallographic structure determination.

An almost total chiral separation from a racemic mixture of a pheromone has been achieved based on the chiral cavity of a trimethylated cyclodextrin. It should be emphasized that here chiral discrimination and separation only involves van der Waals forces or very weak polar interactions, and this sheds new light on the importance of appropriate supramolecular crystalline compounds synthesized for a specific purpose [5].

The crystal structures of several salts of bile acids allowed identifying structure models to represent micellar aggregates in aqueous solutions. These aggregates play a crucial role in the biliary stone formation and dissolution [6].

Further studies on complexation by  $\alpha$ -cyclodextrin concern aroma glycosides, where the aroma (menthol) is included in the cavity, while the glycoside moiety is involved in intermolecular hydrogen bonds [7].

A striking fact arising from the above crystallographic works is their relevance to models of more complex molecular associations (hydrated polymers, micels) or more general phenomena (hydrophobic chiral discrimination). These provide striking examples where the high precision of structure determination plays an increasingly important role in biological studies.

## Materials

Porphyrins, a chemical family originally known from biology, are interesting versatile materials where a suitable substitution is used to control the modes of supramolecular association of these metal binding molecules for various purposes (photosynthetic systems, nanoporous solids and others). Crystal structure design and determination combined with chemical synthesis provide here an important area of crystal engineering [8].

A new work has shown that hydrocarbon derivatives in a single urea inclusion can undergo continuous replacement by another hydrocarbon entering from one end of the crystal and pushing out the original guest at the other end. These spectacular experiments lead to enantiomeric discrimination and illustrate the paramount importance of precise supramolecular interactions in well-defined systems [9].

Some Mo-, V- and W- based polyoxometallates exhibit a variety of structures revealed by crystallographic studies in relation with numerous applications in catalysis, analytical chemistry and materials sciences [10].

## Ionophores and inclusion compounds

- Crystals of protonated calixarenes exhibit specific supramolecular assemblies greatly depending on the metal chloride anions [11].
- Larger anions such as azodibenzoate derivatives are selectively included in a specific cationic receptor both in solution and in the crystal state. This complexation is able to modify the cis-trans photoequilibrium of the guest [12].

- A phosphate calix-type host has a specific stereochemistry favorable to intra-cavity strong complexation of cationic species [13].
- Crystallographic studies have shown the possibility of creating an almost perfect fit of  $\text{Cs}^+$  into a crown ether cavity by appropriate choice of the counter-anion [14].

## Coordination supramolecular compounds

Newly discussed supramolecular compounds include the following topics:

- bis-macrocyclic Ni receptors have been synthesized and their ability to bind small organic guests has been investigated [15].
- A crystalline material from a solution of Ni complexes with oxime ligands proved to have a very complicated nonameric metallacrown complex structure [16].
- Conformational studies of several novel oxime ligands are an important step for their further use in coordination complexes [17].
- A crystallographic study has shown specific structures of binuclear Au and Ag complexes formed with ligands containing phosphor and nitrogen [18].

## General structural information on supramolecular assemblies

The analysis of various intermolecular forces (Br contacts, hydrogen bonds) has shown how a balance of these forces may control the polymorphism observed in a dihydroanthracene-based host [19]. Crystallographic studies of oxime carboxylic acid systems provide further data on supramolecular synthons [20].

## Methodologies useful for supramolecular assemblies

Upgrading and combining methodologies is presently the main theme of active research. Producing large supramolecular assemblies and obtaining structural information is so difficult, that a single technique is not sufficient. Various methods are used and combined such as *computer simulations*, *solid state NMR*, *electrospray mass spectroscopy*, *single-molecule force spectrometry*, *time resolved diffraction* and others.

*Crystallisation of supramolecular compounds* is still a major problem and a subject of active research, yet some spectacular achievements have been recorded. It is to be noted that crystal growth of biological macromolecules has reached a high level of performance and is the object of special meetings.

*Thermodynamic and kinetics data* are clearly important aspects for the formation and decomposition of supramolecular compounds. The determination of the pertinent data is often long and requires instrumentation with high precision. Special equipment has been developed to measure the kinetics of enclathration and desolvation. The activation energies have been evaluated and correlated with other data [5].



The *quick and precise data collection using synchrotron single crystal diffraction* is now an important facility, especially appreciable for supramolecular crystals which are often difficult to grow. The discussion session with the participation of Dr Kvik and W. Clegg [21] dealt with difficult problems at the limit of the today instrumentation.

Recent developments of direct methods have found successful applications in large supramolecular compounds and assemblies (e.g. group of G.M.Sheldrick) [4]. It is worth emphasizing that the supramolecular synthesis - by assembly or self-assembly of large number of molecular components - is likely to produce bigger and bigger supermolecules. Direct methods are clearly the most suitable, if not the only, method of crystal structure determination for 500 - 1000 atom assemblies.

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