Benefits and Limitations of Crystal Structure Determinations for the Understanding of Host-Guest Supramolecular Complexation

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Supramolecular complexes of cyclomalto-oligosaccharides (cyclodextrins, CDs) have received in recent years much attention due to their significance for the understanding of non-covalent forces in their hydrophobic cavity (similar mechanisms as enzymes), as well as for their applications in farm-produce and pharmaceutical industries, particularly for drug encapsulation and for the modulation of the physical properties of the guests [1].

Cyclodexrins are enantiomerically pure compounds and their complexation with a racemic mixture of a chiral guest can lead to the formation of diastereomeric complexes, which should allow the separation of the guest enantiomers through crystallization procedures. Therefore, this method could be a valuable alternative for chiral resolutions, compared to usual processes such as the formation of diastereomeric salts or preferential crystallization.

Previous studies in this field using native cyclodextrins have revealed their poor ability to resolve racemic mixtures, probably due to their conformational rigidity caused by the intramolecular hydrogen bonding network. Nevertheless, CDs can be easily modified, and complete methylation of the hydroxyl functions lead to 2,3,6-trimethylated derivatives (TM-CD) which have been shown to exhibit an improved molecular flexibility [2].

With the aim to get insights into the molecular recognition mechanisms and to evaluate the capacity of these chiral macrocyclic compounds for the enantiomeric discrimination, we have investigated the crystallization behaviours of supramolecular complexes formed between TM-βCD and parahalogenated derivatives of phenylethanol (*p*X-PE). In these studies, we have tried to explain enantio-enrichments on the basis of structural data.

Our first results have revealed that the discrimination can be efficient, but is very sensitive to the nature of the halogenated guest and to kinetic parameters [3]. Therefore, structural studies were performed at different enantiomeric compositions and have highlighted that supramolecular recognition mechanisms could involve different pathways for this series. It has appeared that the most decisive factor was the solubility differences, connected or not to different inclusion geometries in the host cavity for each enantiomer [4]. Other important parameters involve metastable domains of solid solutions, nucleation rates, stoichiometry in the solid phases and an unexpected ability of crystal packings to include both selective and non selective supramolecular complexes. This unexpected diversity among supramolecular complexation behaviours can affect the resolution and induce some limitations.

Hence, crystal structure determinations appeared helpful in several cases for the understanding of the enantio-enrichment induced by crystallization procedures, but our investigations also revealed that the knowledge of physical properties of the diastereomeric supramolecular complexes are often required in order to rationalize the results of crystallization experiments.

References

1. Hedges, A.R. (1998) Chem. Rev. **98**, 2035-2044 ; Szentje, L., Szejtli, J. (2004) Trends Food Sci. Tech. **15**, 137-142.
2. Harata, K. (1998) Chem. Rev. **98**, 1803-1827.
3. Grandeury, A., Tisse, S., Gouhier, G., Agasse, V., Petit, S., Coquerel, G. (2003) Chem. Eng. Technol. **26**, 354-358.
4. Grandeury, A., Gouhier, G. Agasse, V., Petit, S., Coquerel, G. (2003) Tet.: Asym. **14** 2143-2152 ; Grandeury, A., Renou, L., Dufour, F., Gouhier, G., Petit, S., Coquerel, G. (2004) J. Therm. Anal. Cal., *in press*.