

Crystallization, Characterization and Crystal Structure of Host-Guest Inclusion Complexes. Potential Application for Enantiomeric Resolution.

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Owing to the different biological activities exhibited by the two enantiomers of a chiral compound, the preparative resolution (i.e., separation) of racemic mixtures is a major topic in the field of physical chemistry applied to pharmaceutical systems. Among other crystallization techniques (formation of diastereomeric salts, preferential crystallization, etc.), the formation of crystalline supramolecular complexes formed between a enantiopure host and a guest introduced as a racemic mixture is an alternative method which is not yet widely applied, probably because several conditions should be simultaneously fulfilled: (i) sufficient quantities of the chiral host should be available, (ii) the solid state supramolecular complexes should be easy to collect from the mother liquor, (iii) the specific interactions between the host and the two guest enantiomers should induce different physical properties (e.g. solubilities) of the diastereomeric compounds and (iv) the release of the guest and the host should be easy to perform.

Several of these criteria are satisfied in the case of β -cyclodextrin (β -CD) since the latter and some of its derivatives are already used in the pharmaceutical industry [1]. Nevertheless, it has been postulated that the poor ability of native β -CD to separate racemic mixtures by means of crystallization procedures was a consequence of its conformational rigidity [2]. We have therefore selected as chiral macrocyclic host the 2,3,6-trimethylated derivative of β -CD (TRIMEB), which exhibits a larger molecular flexibility because of its inability to form intramolecular H-bonds, and we have investigated the possible enantiomeric resolution of *p*-halogenated derivatives of phenylethanol (*p*-X-PE) via the formation of host-guest supramolecular complexes in aqueous medium.

Our preliminary results have shown that chiral discrimination occurs during simple crystallization experiments, leading to an enantioenrichment of the guest compounds. However, the obtained enantiomeric excesses appeared to be highly sensitive to the chemical nature of the halogenated substituent, and to kinetic parameters [3]. In the case of *p*-Br-PE, a procedure involving successive recrystallizations allowed to isolate the two diastereomeric compounds and to characterize them by XRPD, thermal analysis and solubility measurements. Furthermore, crystal growth investigations performed from a quasi-racemic solution induced the successive formation of two families of single crystals, from which the two crystal structures could be determined. The analysis of structural data and the comparison with previously published data allows to envisage an extension of our procedures to other supramolecular systems.

1. A.R. Hedges, *Chem. Rev.* **98** (1998), 2035-2044.

2. K. Harata, *Chem. Rev.* **98** (1998), 1803-1827.

3. A. Grandeury, S. Tisse, G. Gouhier, V. Agasse, S. Petit, G. Coquerel, *Chem. Eng. Technol.* **26** (2003), 3, in press.