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Chiral separation by enantioselective inclusion complexation-organic solvent nanofiltration

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1. Introduction

Enantioselective inclusion complexation (EIC) is a promising technique for chiral resolutions which, since it is not restricted to proton transfer interactions, can in principle be used to resolve compounds with almost any functional group. However, an outstanding difficulty with EIC is the separation of enantiomer from the enantioenriched solid complex, typically performed by distillation. This limits EIC to enantiomers with appreciable volatility, and even for these it would be difficult to operate at large-scale due to high temperature distillation, with concomitant problematic heat transfer and vacuum conditions. Here we report for the first time a novel enantioseparation process which combines the highly enantioselective nature of inclusion complexation with the subsequent separation of enantiomers from a chiral host using solvent decomplexation and organic solvent nanofiltration (OSN).

In our proposed process (Fig. 1), a racemate is added to a chiral host suspended in a resolution solvent. The S-enantiomer enantioselectively co-crystallizes with the chiral host while the R-enantiomer remains in the liquid (Step A). Nanofiltration of the resulting resolution suspension elutes the R-enantiomer (Step B), retaining the solid chiral host and the solid chiral host-S-enantiomer complex. A decomplexation solvent is then added to dissolve and dissociate the complex into S-enantiomer and host (Step C). This solution is then nanofiltered to elute the S-enantiomer, while the soluble host is retained by the membrane (Step D). The dissolved host is then returned as a suspension in resolution solvent to the next cycle of resolution. This is achieved by exchanging the decomplexation solvent for the resolution solvent via diafiltration (Step E). Since chiral hosts are used in stoichiometric quantities, their recovery and multiple reuse is a further key advantage of separation by OSN.

2. Results and discussion

To demonstrate this process, we used a chiral host with a large M_w to resolve a racemic of a smaller racemic alcohol. Starmem™ 122 (Starmem™ is a trademark of W. R. Grace & Co., US) with a nominal molecular weight cutoff

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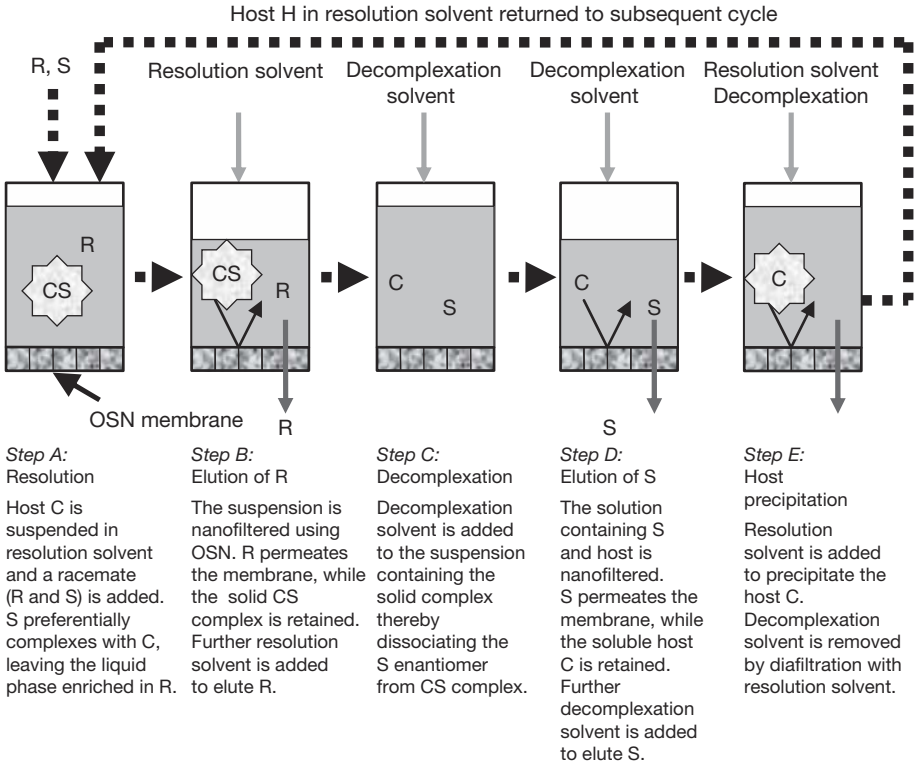

Fig. 1. Process schematic of enantioselective inclusion complexation-solvent decomplexation-organic solvent nanofiltration.

(MWCO) of 220 g mol^{-1} was used for OSN. The alcohol was highly permeable in the OSN membrane, and had zero rejection in both resolution and decomplexation solvents. The chiral host was retained efficiently by the OSN membrane (>99% rejection in both solvents). The molecular recognition of the S alcohol enantiomer by the chiral host employed was investigated by resolving the X-ray crystal structure of the complex formed.

We show in independent experiments that it is possible to run the resolution in the presence of 0–20 vol% decomplexation solvent without sacrificing the enantiomeric excess (ee), and so is not required to revert to pure resolution solvent at the end of each cycle (Step E in Fig. 1). Similarly, the complete dissociation of complex into free enantiomers and host happens for solvent mixtures enriched above 60 vol% in decomplexation solvent. Therefore, from the process point of view, it is not necessary to use either pure resolution solvent (Step A), or pure decomplexation solvent (Step D in Fig. 1), avoiding extensive diafiltration.

The feasibility of the process was tested throughout two resolution-filtration cycles. Each filtration step was carried out in several successive batches in a dead-end nanofiltration cell. Elution profile of resolution-filtration process and ee of the permeate stream in each filtration are shown in Fig. 1 and ee and yields for the combined streams are resumed in Table 1.

3. Conclusions

A novel enantioseparation process using the combination of EIC and OSN has been

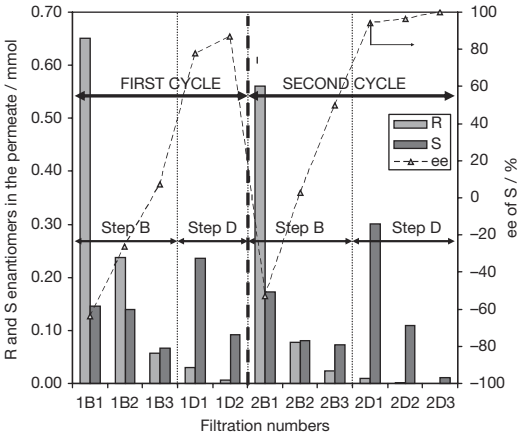

Fig. 2. Elution profile of resolution-filtration process and ee of the permeate stream in each filtration (indicated in Fig. 1) in two cycles. Step B is the elution of R and Step D is the elution of S. Positive ee indicates S-rich permeate. Negative ee indicates R-rich permeate.

demonstrated, showing for the first time that the use of solvent decomplexation with OSN allows enantiomer recycling of the chiral host. The strength of this process is the direct use of chiral host (without derivatization or immobilization), relatively high operating concentrations, and ambient temperature processing. We regard the method presented here as having potential as an alternative technique for preparative-scale chiral separations, which could extend the scope of EIC from lab to pilot and industrial scale.

Table 1
ee and the yield of permeates

Combined streams		1st Cycle (%)	2nd Cycle (%)
Step B	ee (of R)	–46	–34
	Yield (of R)	89	80
Step D	ee (of S)	80	95
	Yield (of S)	31	51