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Elucidation of the mechanism of chiral selectivity in diastereomeric salt formation using organic solvent nanofiltration

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Organic solvent nanofiltration (OSN) was used to investigate the mechanism of chiral selectivity in diastereomeric salt formation of α-phenylethylamine with D-tartaric acid and di-*p*-toluoyl-D-tartaric acid as resolving agents; results indicate that for these systems chiral selectivity occurs only upon crystallisation and chiral interactions in solution were negligible.

Although the principle of chiral resolution *via* diastereomeric salt formation has been well studied,[1] the kinetics and thermodynamics of the process have remained relatively unexplored. In particular, it has not yet been determined whether the enantioselection occurs in solution, upon crystallization, or both.[2] The aim of this work was therefore to determine whether a resolving agent can selectively bind to one of the enantiomers of a racemic mixture in solution.

Nanofiltration is a relatively new membrane process with a nominal molecular weight cut-off (MWCO)[3] ranging from 200 to 1000 Da. Recently, nanofiltration membranes capable of performing separations in organic solvents have become available.[4] These OSN membranes have been found to be effective for performing molecular scale separations, such as for the recycling of homogeneous catalysts.[5] We have used OSN membranes to test whether chiral selectivity occurs in solution (Fig. 1), by filtering a racemic mixture (*R*-**1**, *S*-**1**) mixed with a resolving agent (C) at concentrations too dilute for crystallisation (*i.e.* below saturation). The membrane was chosen to have an MWCO such that *R*-**1** and *S*-**1** can permeate, whilst enantiomer–resolving agent diastereomeric salts [(*R*-**1**)·C and (*S*-**1**)·C] are retained. C will either permeate or be retained by the membrane depending on its molecular weight (MW) relative to the MWCO of the membrane. After filtration, the amount of enantioselective binding which occurred in solution was inferred by measuring the enantiomeric enrichment of the unbound enantiomers in the permeate (Fig. 1).

The system studied was racemic α-phenylethylamine (α-PEA) **1**, with chiral diacids di-*p*-toluoyl-D-tartaric acid (DTTA) **2** and D-tartaric acid (TA) **3** as the resolving agents. The complexation reactions between α-PEA and diacids are described in Scheme 1, illustrating that two types of soluble salt can form: (A) an acidic salt, when only one mole of α-PEA binds with one mole of the diacid (leaving one of the acid hydrogens in the diacid free), and (B) a neutral salt, where two moles of α-PEA bind with one mole of diacid.

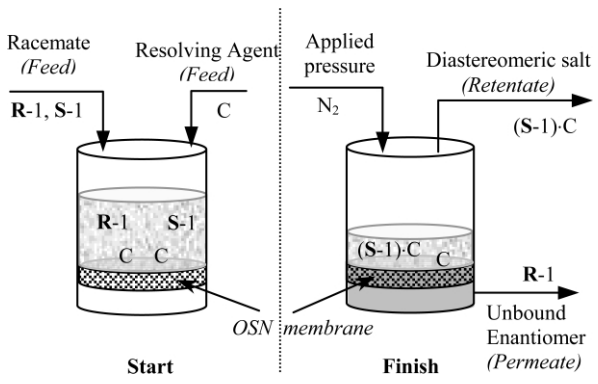


Fig. 1 Schematic of the batch OSN of a solution containing a racemate (*R*-**1**, *S*-**1**) and resolving agent (C). This illustrates the case where there is (i) 100% retention of C and of (*S*-**1**)·C soluble salts, (ii) 100% enantioselectivity of C for the *S*-**1** enantiomer, and (iii) excess C is added.

Dead-end nanofiltration experiments[6] were performed at room temperature using STARMEM™ 122 membranes.[7] Solutions for filtration were prepared by adding α-PEA (MW: 122 g mol^{-1}) to a solution of either TA (MW: 151 g mol^{-1}) or DTTA (MW: 386 g mol^{-1}) in methanol until the final α-PEA concentration was 0.1 mol L^{-1}. The concentrations of TA and DTTA were varied from 0 to 1 molar equivalents of α-PEA. After α-PEA addition, solutions were stirred for 24 h and then filtered.[7] Concentrations of α-PEA in the permeate and retentate were measured using normal phase HPLC.[8]

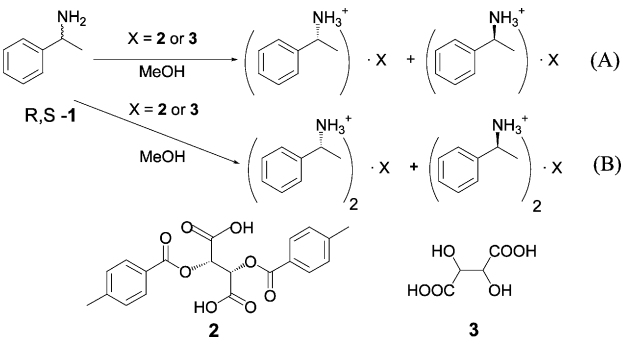
In each experiment, the results from the filtrations were used to both determine whether an acid or neutral soluble salt had formed and to determine the enantioselectivity of the salt formation. To enable this, each OSN separation was characterised by two main parameters: enantiomeric excess (%) and the retention by the membrane (%). Enantiomeric excess (ee), as a percentage, is defined as:

$$\text{ee} = (\text{mole fraction}_{\text{major enantiomer}} - \text{mole fraction}_{\text{minor enantiomer}}) * 100\% \quad (1)$$

The retention of species *i* (R_i) is defined as the amount of one enantiomer (bound and free) in the retentate per amount of this enantiomer in the feed, calculated as a percentage:[9]

$$R_i = \frac{C_{i\text{R}} V_{\text{R}}}{C_{i\text{F}} V_{\text{F}}} * 100\% \quad (2)$$

Filtration of α-PEA as the sole solute gave a retention of 48%, showing that α-PEA could pass freely through the membrane (for a non chiral selective, fully permeable membrane when V_R/V_F = 0.5, R_i = 50%).[9] Based on MW, TA was expected to pass through the membrane, whilst DTTA was retained. After α-PEA was mixed with these diacids and nanofiltered, its experimental and theoretical retention increased (Fig. 2).[10] The retention of α-PEA further increased with a greater molar equivalent of either of the diacids, indicating that α-PEA–diacid soluble salts were forming. Moreover, the experimental retention follows the 'theo(neut)' line in Fig. 2 (*i.e.* at 0.5 mol equivalent of TA and DTTA the experimental retention approaches 100%). This suggests that neutral soluble salts were formed for both the TA and DTTA systems. Salt formation therefore follows the Scheme 1(B) mechanism.



Scheme 1 Complexation of **1** using X as the resolving agent (X = **2** or **3**), illustrating the cases of (A) acidic and (B) neutral salt formation.

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Tables 1 and 2 show that this salt formation is not enantioselective however. The ee in the permeate was negligible (within experimental error)[11] for all the different concentrations of TA and DTTA added to α-PEA. In terms of the binding mechanism in the retentate (Fig. 3), this means that the binding constants of each enantiomer are approximately equal ($K_S \approx K_R$). Therefore, both unbound enantiomers pass through the membrane in equal amounts resulting in negligible enantiomeric enrichment in the permeate.

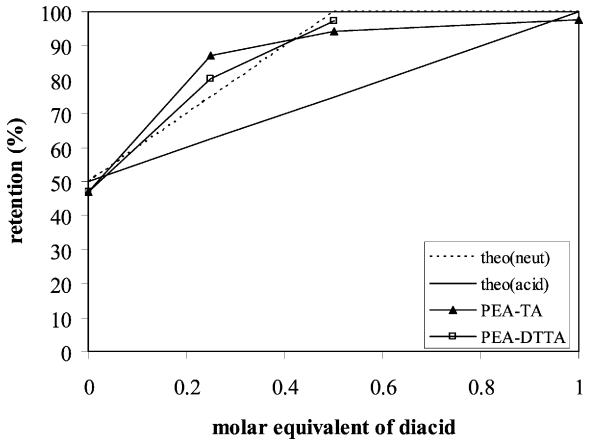

Fig. 2 Theoretical and experimental retention of α-PEA with diacids (TA and DTTA). The 'theo(neut)' and 'theo(acid)' lines respectively illustrate the theoretical retention calculated for an acidic or neutral α-PEA–diacid soluble salt.[10]

Table 1 Data for α-PEA–TA filtration (with no crystallisation)

α-PEA (M)	TA (molar equiv.)	Enantiomeric excess of *S*, ee[11] (%)
0.10	0.25	1.1
0.10	0.50	4.2
0.10	1.0	5.9

Table 2 Data for α-PEA–DTTA filtration (with no crystallisation)

α-PEA (M)	DTTA (molar equiv.)	Enantiomeric excess of *R*, ee (%)
0.46	0	0.7
0.46	0.25	0.5
0.46	0.50	0.9

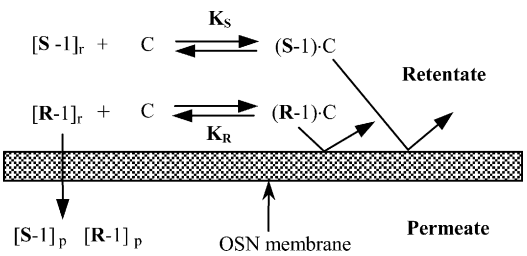

Fig. 3 Schematic diagram of the permeation of enantiomers *R*-**1** and *S*-**1**. Resolving agent (C) and diastereomeric salts are retained by the membrane. Subscripts: r = retentate, p = permeate.

To determine whether enantioselective separation can be achieved, an α-PEA–TA crystallisation was also performed.[12] The *R* enantiomer ee in resulting crystals was 70.8%. This confirms that enantioselective enrichment occurs upon crystallisation for this system. Other authors have also demonstrated this.[1] Cumulatively, these results therefore indicate that the complexation prior to diastereomeric salt formation was nonselective in solution, *i.e.* there is negligible preferential binding of the resolving agent to the enantiomers in solution. Enantioselective resolution of α-PEA with either TA or DTTA can therefore only be achieved by crystallisation.

Notes and references

1 D. Kozma (ed.), *CRC Handbook of Optical Resolution via Diastereomeric Salt Formation*, CRC Press, Boca Raton, 2002; J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Wiley and Sons, New York, 1981; E. L. Eliel, S. H. Wilen and M. P. Doyle, *Basic Organic Stereochemistry*, John Wiley & Sons Inc., New York, 2001.

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3 Molecular weight cut-off is defined by the molecular weight for which 90% rejection of the solute is achieved by the membrane.

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6 Experiments were conducted in a stainless steel, SEPA ST (Osmonics, USA) dead-end nanofiltration cell with an effective membrane area of 14 cm². The driving force for the filtration was pressure applied with nitrogen gas. A new membrane disc was used at each pressure to avoid problems of polymer memory. All filtrations were run so that at the end the filtration half of the feed volume had permeated. All filtrations were repeated at least once. All chemicals used were of AnalR grade.

7 STARMEM™ is a trademark of W.R. Grace, Columbia, MD, USA. Membranes were obtained from Membrane Extraction Technology Ltd, UK, www.membrane-extraction-technology.com. STARMEM™ 122 membranes have a nominal MWCO of 220 Da.

8 A Chiralcel OD-H column (Chiral Technologies, France) was run isocratically with mobile phase at a flow rate of 0.5 mL min^{-1}. The mobile phase was hexane/IPA (90/10) with 0.1% ethanolamine modifier. Solvents from all samples were evaporated and the contents then redissolved in mobile phase prior to analysis.

9 Notation: R_i = retention of species *i*; C_{iR} = concentration of species *i* in the retentate; C_{iF} = concentration of species *i* in the feed; V_R = volume of retentate; V_F = volume of feed.

10 Theoretical retention is calculated assuming 100% retention of diastereomeric salts. For example, consider 1 mol of racemic base in feed and 0.25 mol of diacid. If neutral salt forms, then 0.5 mol of one enantiomer will react with 0.25 mol of diacid leaving 0.5 mol of base to partition equally in permeate and retentate (*i.e.* 0.25 mol). The retention is then calculated using Equation 2.

11 α-PEA–TA salts formed in permeate samples as TA passed through the membrane. A small amount of the α-PEA was enantioselectively liberated from these salts during sample work-up prior to HPLC analysis, giving an increase of 2–5% in the ee.

12 Crystallisation method was based on: A. Ault, *Org. Synth.*, 1969, **49**, 93. The crystals were then redissolved using methanol and analysed by HPLC to determine the ee.