Resolution of Diastereomers

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Structural Aspects of Nucleation Inhibitors for Diastereomeric Resolutions and the Relationship to Dutch Resolution**

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The resolution of enantiomers[1a,b] by Dutch Resolution[2] involves the use of an equimolar mixture of two or three structurally similar and homochiral[3] resolving agents. Two major factors contribute to the success of the method. First, the structurally similar resolving agents often form a non-stoichiometric solid solution of crystals.[4,5] Second, one of the resolving agents can act as a nucleation inhibitor and retains the more soluble diastereomeric salt in solution longer.[6a,b] This kinetic effect effectively increases the solubility of the more soluble diastereomer. For example, if one starts with a solution of diastereomeric salts of composition S and an eutectic composition E^0, the phase rule requires that the solids have composition A^0 (Figure 1). If a nucleation inhibitor moves the (kinetically determined) eutectic composition to E^a, the solid composition changes from nearly racemic A^0 (in the example shown in Figure 1) to enantiopure A^a. Only a few percent of the additive can lead to profound effects.[6a,b]

One should not expect the design of nucleation inhibitors to be an easy task. Resolutions may be affected by many factors.[1a] The effects of additives in crystallization processes can be profound.[7] The separation of conglomerates by use of either a pure enantiomer (entrainment)[1a] or "tailor-made" additives has been well studied.[8–10] The number of candidates can be limited if only compounds with some structural resemblance to the resolving agent or racemate are investigated. The observation of Barton and Kirby that the resolution of narwedine is aided by traces of optically pure and structurally analogous galanthanine was seminal.[11a]

Our test system consisted of (*S*)-mandelic acid (MA) as the resolving agent and (±)-3-methoxyphenylethyl amine (3MeOPEA) as the racemate (Scheme 1). The ternary phase diagram is shown in Figure 2, and the crystal structures of the diastereomeric salts are given in the Supporting Information. Under the conditions used (see the Supporting Information), with the resolving agent but without an additive, the first salts

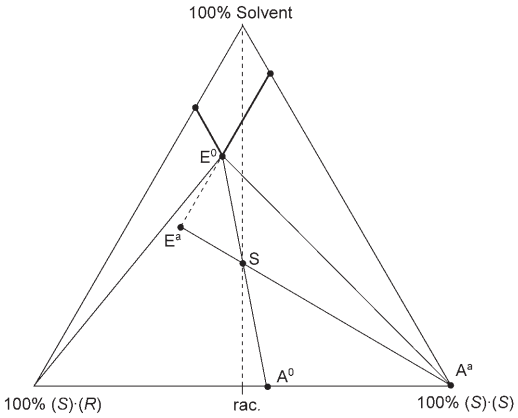
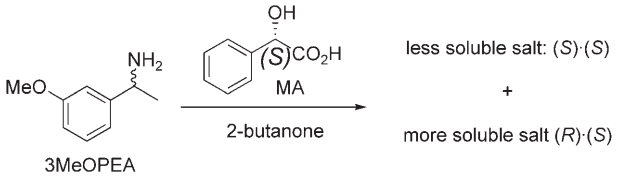


Figure 1. Ternary phase diagram for ideally behaving diastereomers and the effects of nucleation inhibition thereon.



Scheme 1. Resolution of (±)-3MeOPEA with (*S*)-MA.

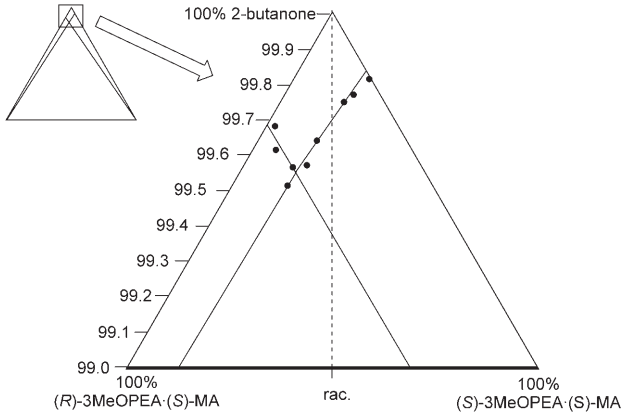


Figure 2. Phase diagram for mixtures of (*S*)-MA and (±)-3MeOPEA in 2-butanone at 20 °C; the scale is in wt%.

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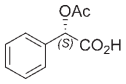
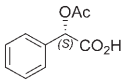
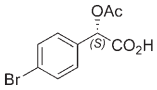
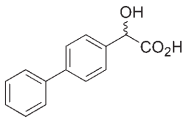
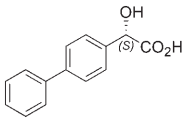
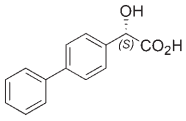
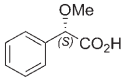
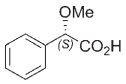
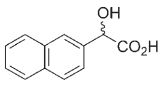
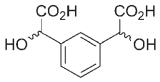
formed with only 10% *de* (Table 1, entry 1). Various additives structurally related to MA were tested. The most effective are shown in Table 1, entries 2a, 4a,b, and 5a. The diastereomeric excess (*de*) of the first salts increases to nearly 100% although the yields decrease. The additive used for entry 4a (Table 1) is racemic. From the comparison of entries 2a and 2b, and entries 5a and 5b (Table 1) it is clear that the enantiomer that has the same chiral sense as the resolving agent (entry 4b) is responsible for the inhibition. The additives could not be detected by HPLC in the precipitated salts (sensitivity limit: <0.1%) except in the case of entry 4a (Table 1), in which 1% incorporation was observed.[12] The stereochemical correlations resemble the "rule of reversal" postulated by Lahav[8] and others.[13] We also note the strong inhibitory action of a bifunctional compound (entry 7, Table 1, mixture of diastereomers).

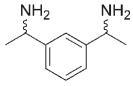
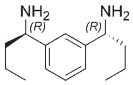
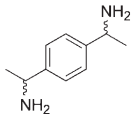
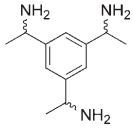
Table 1: Resolutions of (±)-3MeOPEA with MA and nucleation inhibitors resembling mandelic acid.

Entry	Additive[a]	(*R*)-(*S*)-MA	Yield [%][b]	*de* [%][c]	S-factor[d]
1	none	*S*	72	10	0.14
2a		*S*	42	97	0.81
2b		*R*	70	12	0.17
3		*S*	31	99	0.62
4a		*S*	36	95	0.68
4b		*S*	42	95	0.80
4c		*R*	68	15	0.20
5a		*S*	40	96	0.77
5b		*R*	63	11	0.15
6		*S*	26	94	0.48
7		*R*	16	93	0.30

[a] In these experiments, 6 mol% of additive (based on the carboxylic acid function) was used relative to enantiopure MA; the ratio of total acid to total amine was 1:1. [b] All experiments were performed in duplicate. [c] The *ee* values determined by HPLC on a chiral stationary phase are identical to *de* values. [d] Resolution efficiency:[21] S-factor = yield *de* 2.

Nucleation inhibition should also apply to the racemate to be resolved. We had previously observed that certain bifunctional amines effectively blocked the activity of 1-phenylethyl amine as a resolving agent.[6b] Some of these compounds have been investigated as inhibitors in the resolution of (±)-3MeOPEA by (*S*)-MA. Results with the best inhibitors are shown in Table 2. The additives tested in entries 2, 4, and 5 (Table 2) are racemic and a mixture of diastereomers, whereas that of entry 3 is enantiomerically pure.[14] This inhibitor (see entries 3a and 3b, Table 2) is equally effective in a resolution following the Marckwald principle (reciprocal resolution).[15] We have no ready explanation for this.

Table 2: Resolutions of (±)-3MeOPEA with (*S*)-MA and nucleation inhibitors resembling the racemate.

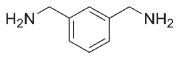
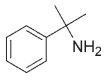
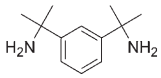
Entry	Additive[a]	Yield [%][b]	*de* [%][c]	S-factor[d]
1	none	72	10	0.14
2		32	96	0.61
3a		32	97	0.62
3b	–[e]	31	96	0.60
4		35	89	0.63
5		27	95	0.51

[a] In these experiments, 6 mol% amine of additive was used relative to (±)-3MeOPEA; the ratio of total acid to total amine was 1:1. [b] All experiments were performed in duplicate. [c] The *ee* values determined by HPLC on a chiral stationary phase are identical to *de* values. [d] S-factor = yield *de* 2. [e] (*R*)-MA was used for the resolution.

A remarkable observation is that an achiral bisamine can be an extremely effective nucleation inhibitor. In entry 4 of Table 3 the results with 1,3-bis(2-amino-2-propyl)benzene (1,3-BAPB) are given. Both the bifunctionality and the bulk seem to be necessary for nucleation inhibition, as may be concluded from entries 2 and 3 (Table 3).

A larger scale resolution with 1,3-BAPB as the additive was examined. Starting from 40 g of the (±)-3MeOPEA/(*S*)-MA salt, a resolution in 2-butanone with 0.5% and 1.0% of the 1,3-BAPB/$[(S)\text{-MA}]_2$ salt as an additive was performed and compared to the results of resolution without an additive (isolated salt 10% *de*). From the results the kinetic time frame in which the additive is effective can be derived (Figure 3). When 0.5% 1,3-BAPB was used, the first sample of isolated solid after 1 h had >90% *de*. However, a second sample removed after another hour had only 10% *de* in the collected solids, and this percentage remained constant over time. Analysis by HPLC established that after 1 h the additive 1,3-

Table 3: Resolutions of (±)-3MeOPEA with (*S*)-MA and nucleation inhibitors resembling 1,3-BAPB.

Entry	Additive[a]	Yield [%][b]	*de* [%][c]	S-factor[d]
1	none	72	10	0.14
2		59	13	0.16
3		69	14	0.20
4[e]		43	95	0.82

[a] In these experiments, 6% equiv wt amine of additive was used relative to (±)-3MeOPEA; the ratio of total acid to total amine was 1:1. [b] All experiments were performed in duplicate. [c] The *ee* values determined by HPLC on a chiral stationary phase are identical to *de* values. [d] S-factor = yield *de* 2 [e] The isolated solids contained 2% additive.

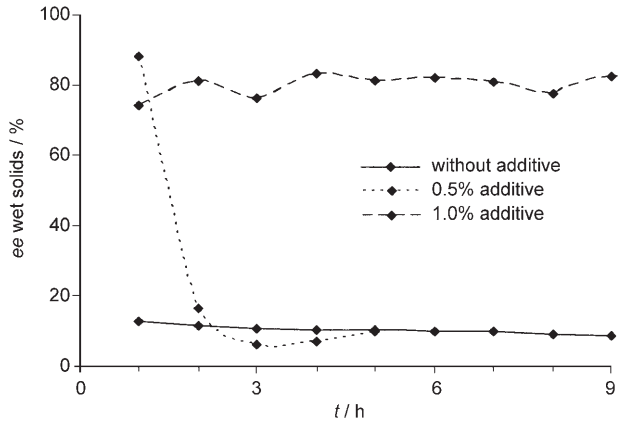


Figure 3. Composition of the solids without washing; after washing (line ◆) the composition is 96% *de* in accord with Table 3, entry 3.

BAPB was for the major part incorporated in the precipitated less soluble salt. The resulting low concentration of additive in the mother liquor made the system unstable and in the next hour the more soluble salt also precipitated with incorporation of the rest of the additive. However, when 1.0% 1,3-BAPB was used, the more soluble diastereomeric salt remained dissolved for at least 5 days.[16] Analysis by HPLC established that only 0.38% of the additive was still present in the mother liquor, the rest was incorporated in the precipitated less soluble salts. The solids were collected, washed, and dried to give (*S*)-3MeOPEA/(*S*)-MA in 43% yield and 96% *de* (S-factor = 0.83). Apparently at least 0.5% additive is consumed during crystallization.[17] The mother liquor shows more enrichment: 79% *de* with additive versus 53% *de* without additive (see Figure 1). This finding is very useful if also the other enantiomer is required.[18]

Under the conditions of the resolution 1,3-BAPB is probably doubly protonated. The C_2 conformation with the ammonium groups located on opposite faces of the molecule is chiral. Both steric factors and charge repulsion could favor this conformation. Unfortunately an attempt to test this idea with 1,4-BAPB/[(*S*)-MA]$_2$ salt (structure not shown), which cannot have such a chiral conformation, was foiled by the total insolubility of this material.

A search for inhibitors to improve resolutions may lead to success if homochiral structural analogues of either resolving agent or racemate are examined, although in many cases racemic additives may safely be tested. Along this line, bifunctional analogues of resolving agent or racemate may be particularly effective, and bifunctional achiral materials with a structural resemblance to either racemate or resolving agent may also be active. It has been noted that the use of slightly contaminated racemates or resolving agents as a result of a previous reaction step might improve the subsequent resolution, because of the structural resemblance to the racemate or the resolving agent.[20] A general point is that there is a better chance of optimizing a resolution that has a significant diastereomeric excess at the eutectic point and little tendency to form end solid solutions. Determination of eutectic compositions is time well spent.

Experimental Section

General procedure for the resolution of (±)-3MeOPEA with (*R*)- or (*S*)-MA.: A 2.5-mL aliquot of a 0.13 M stock solution of (±)-3MeOPEA in 2-butanone was pipetted into a Kimble reactor tube equipped with a magnetic stirrer (⌀2 cm). Subsequently, a 2.5-mL aliquot of a 0.13 M stock solution of (*R*)- or (*S*)-MA in 2-butanone was added to the tube and spontaneous crystallization occurred within a couple of minutes. In a typical experiment, 6% of either 3MeOPEA or MA was replaced by an equal amount of additive in such a manner that the ratio of the total amount of amine relative to the total amount of acid was maintained at 1:1 and the total volume was 5 mL. In this manner, direct comparison to the experiment without an additive (entry 1, Table 1) can be made. Further details are given in the Supporting Information.

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Keywords: chiral resolution · crystal growth · Dutch resolution · nucleation inhibitors · phase diagrams

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[11] a) D. H. R. Barton, G. W. Kirby, *J. Chem. Soc.* **1962**, 804; b) see also: K. R. Wilson, R. E. Pincock, *J. Am. Chem. Soc.* **1975**, *97*, 1474.
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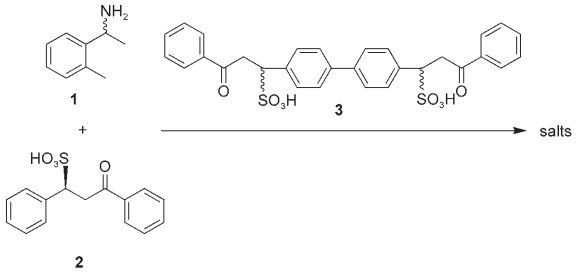
[14] J. Dalmolen, M. van der Sluis, J. W. Nieuwenhuijzen, A. Meetsma, B. de Lange, B. Kaptein, R. M. Kellogg, Q. B. Broxterman, *Eur. J. Org. Chem.* **2004**, 1544.
[15] See reference [1a], p. 306.
[16] Similar observations in other systems have been made: J. S. C. Loh, W. J. P. van Enckevort, E. Vlieg, C. Gervais, R. F. P. Grimbergen, B. Kaptein, *Cryst. Growth Des.* **2006**, *6*, 861.
[17] In resolutions with 1% additive some of the additive is initially incorporated into the salt, but over a period of hours it slowly returns into solution.
[18] Bifunctional inhibitors work in other resolutions. Sulfonic acid **2** (absolute configuration not established) and derivatives thereof are good resolving agents.[19] The resolution efficiency for racemate **1** is improved from S = 0.14 without the bifunctional additive **3** to S = 0.38 with 3% of additive **3**.



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