Time dependent efficiency of optical resolution of aminooxiranes with *O,O'*-dibenzoyl-(*R,R*)-tartaric acid

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Dedicated to Professor Sándor Antus on his 60th birthday
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Abstract
Crystallization time dependent efficiencies of optical resolutions of two aminooxirane derivatives have been investigated. Time-scaled experiments demonstrated that efficient chiral discrimination of aminooxirane enantiomers by the resolving agent develops in slow, diffusion controlled exchange of the enantiomers between the solution and the precipitated salt of an enantiomeric mixture and the resolving agent. Comparison of the determined absolute configurations of the resolved aminooxiranes showed that quasi enantiomers of the structurally similar two model compounds crystallized with the same resolving agent from ethyl acetate.

Keywords: Optical resolution, chiral amino oxiranes, chiral discrimination, diastereoisomeric salt formation

Introduction

Optical resolution via diastereoisomeric salt formation is known as a thermodynamically controlled process.[1] It means that the enantiomeric excess found in the crystallized salt has been determined by the solubility and dissociation constants of the two diastereoisomeric salts and the initial concentrations of the racemate and the resolving agent.[2]

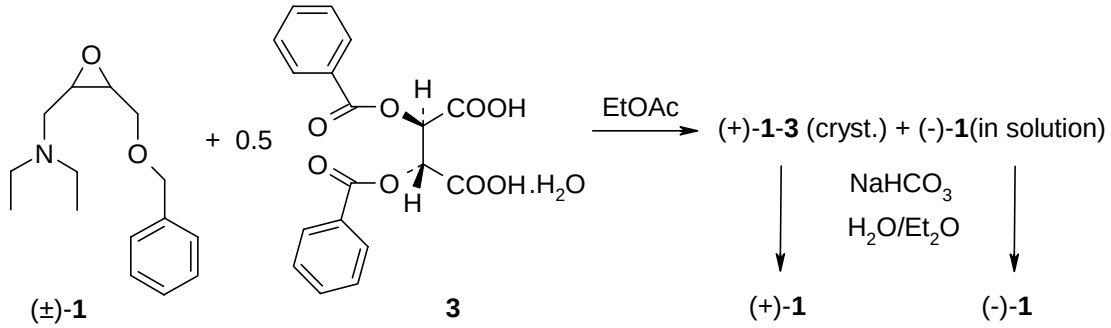
There are two classical methods to increase the enantiomeric excess of a diastereoisomeric salt: (a) recrystallization of the salt or (b) repeated resolution of the non racemic enantiomeric

mixture liberated from the crystalline salt of the first resolution.[3] We have applied the second method for preparation of optically active *cis*-2-benzyloxymethyl-3-diethylaminomethyloxirane (**1**) and *cis*-2-benzyloxymethyl-3-piperidinomethyloxirane (**2**) using O,O'-dibenzoyl-(*R,R*)-tartaric acid monohydrate (**3**) because of the sensitivity of the oxirane ring to elevated temperature used during recrystallization.[4] However, two repeated resolutions were necessarry to get (-)-**2** in 89 % ee and the yield of (+)-**1** (99 % ee) dropped to 38 % during the same procedure. Repeated resolutions and workup procedures are tedious, therefore further systematic investigation of the two resolution processes has been carried out in our laboratory.

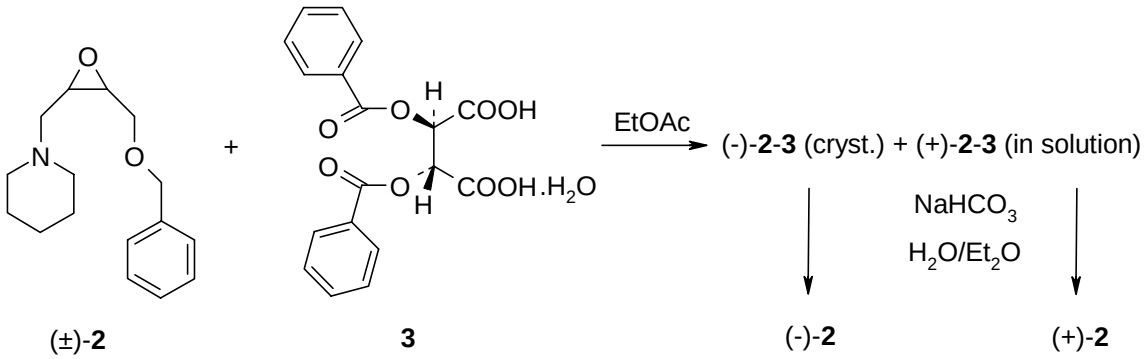
Results and Discussion

Dilution of the reaction mixture or addition of seeding crystals of salts made from optically pure (+)-**1** + **3** and from (-)-**2** + **3**, separately, did not result in higher optical purities of enantiomers in the crystallised diastereoisomeric salts if the crystals were filtered off from the reaction mixture after an hour stirring. However, in time-scale experiments we observed a gradual increase in the enantiomeric excess of (+)-**1** and (-)-**2** in the filtered salts, respectively.

It is important to mention that the racemate/resolving agent molar ratios were different in the two procedures: half an equivalent amount of **3** for (±)-**1** and an equivalent amount of **3** for (±)-(**2**) were used without any achiral acid additive (Schemes 1 and 2).



Scheme 1



Scheme 2

Despite the different molar ratios, the material balances (observed during recovering of (+)-**1** and (-)-**2** from the diastereoisomeric salts) demonstrated that unsolvated, hemitartrate type salts crystallized in both cases independently of the crystallization time. The results of the experiments are summarized in Table 1 and Table 2 for the two resolutions, respectively. Parallel experiments gave similar results.

Table 1. Time-scaled resolutions of ´(±)-**1** with half an equivalent amount of DBTA (**3**)

Crystallization time (hour)	Yield of crystallized diastereoisomeric salt (%)	Optical purity[a] (%)	Efficiency of resolution[b] (S)
1	57	87	0.50
2	46	86	0.40
16	64	84	0.53
72	55	<98	0.54
144	47	<98	0.46
2 x 16[c]	38	<98	0.37

[a] Determined from the measured $[\alpha]_D$ value of the recovered (+)-**1** enantiomer and the $[\alpha]_D$ value of the pure enantiomer.[4]
[b] S=yield x optical purity, according to the literature definition:[5] yield = [molar amount of **1** in the crystalline salt]/[half of the molar amount of **1** in the racemate].
[c] Overall yield and final optical purity after two repeated resolutions carried out with 16 hours crystallization time.

Table 2. Time-scaled resolutions of ´(±)-**2** with an equivalent amount of DBTA (**3**)

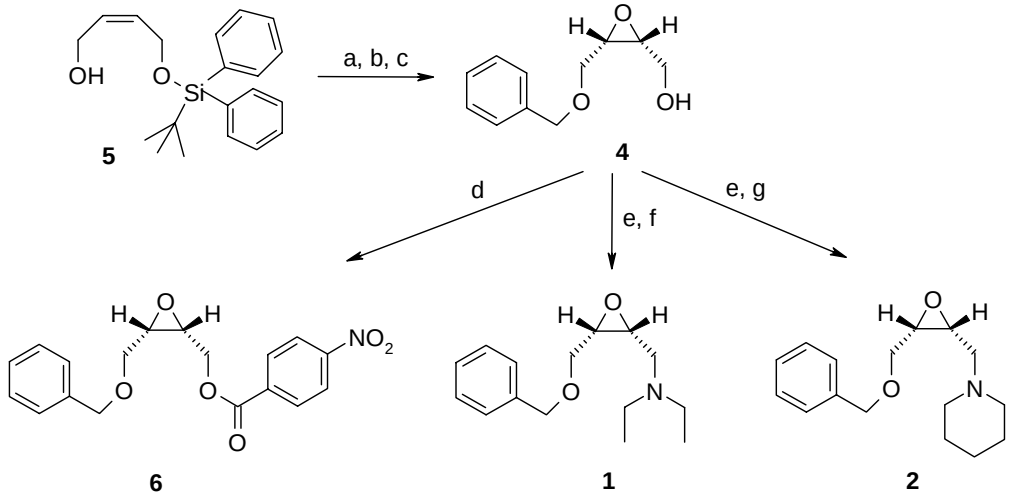
Crystallization time (hour)	Yield of crystallized diastereoisomeric salt (%)	Optical purity[a] (%)	Efficiency of resolution[b] (S)
1	88	71	0.63
3	87	68	0.59
16	93	74	0.69
48	85	92	0.78
144	95	96	0.91
2 x 16[c]	95	89	0.85

[a] Determined from the measured $[\alpha]_D$ value of the recovered (-)-**2** enantiomer and the $[\alpha]_D$ value of the pure enantiomer.[4]
[b] S=yield x optical purity, according to the literature definition:[5] yield = [molar amount of **2** in the crystalline salt]/[half of the molar amount of **2** in the racemate].
[c] Overall yield and final optical purity after two repeated resolutions carried out with 16 hours crystallization time.

It is clear from the data that the previously applied 16 hours crystallization time at 25 °C was insufficient for completion of enantiomer exchange between the solid and liquid phases of the reaction mixture. There is no regular tendency in the change of yields during resolutions of **1** and a small increase in the yield could be observed during the resolutions of **2**. Comparison of the resolution efficiencies (S)[5] of the 144 hours resolutions and those of repeated resolutions (last lines in Table 1 and 2, respectively) shows that long crystallization times resulted in higher efficiencies in both cases. Prolonged crystallization time is also advantageous from a practical point of view since repeated salt and mother liquor workup procedures can be avoided. Consequently, waste of materials can be reduced and much less polluted water and organic solvents result.

Such a kinetic effect in resolution processes is quite rare in the literature. One example has been published by our institution[6] but in that case salt formation at 50 °C and/or application of half an equivalent of hydrochloric acid together with half an equivalent of resolving agent eliminated the kinetic effect. In the present cases, those tricks did not help because of the sensitivity of the model compounds (**1** and **2)**. Thus, the simplest way to get (+)-**1** or (-)-**2** in high optical purity and good yield is to work with prolonged crystallization time according to our observations.

Attempts to prepare single crystals from the diastereoisomeric salts or from other derivatives have failed. Therefore absolute configurations of (+)-**1** and (-)-**2** have been determined using a chemical correlation method. (*2S,3R*)-2-Benzyloxymethyl-3-hydroxymethyloxirane (**4**) can be prepared from *cis*-4-benzyloxy-2-butene-1-ol[7] or from *cis*-4-(*tert*-butyldiphenyl)silyloxy-2-butene-1-ol[8] (**5**) by Sharpless-epoxidation. We used the latter procedure as outlined in Scheme 3.



Scheme 3. a: Sharpless-epoxidation;[7, 8] b: NaH, DMF then BnCl[10]; c: TBAF, THF[8], d: PNBCl, TEA, CH_2Cl_2;[9] e: PTSCl, pyridine;[10] f: diethylamine, DMF[10]; g: piperidine, DMF.[10]

The configuration of **4** was confirmed by comparison of the direction of optical rotation of its 4-nitrobenzoate **6** with authentic literature data.[9] Then, optically active (*2S,3R*)-**1** and (*2S,3R*)-**2** were prepared from compound (*2S,3R*)-**4** via consecutive tosylation and amination reactions.[10]

On the basis of the optical rotations of these samples, the absolute configuration of (+)-**1** is *2S,3R*, and that of (-)-**2** is *2R,3S*.

Conclusions

The experimental results can be rationalised if two consecutive steps of crystallization are taken into consideration. At first, kinetic control governs crystallization of the hemitartrate type enantiomeric mixture containing salts in both investigated cases. Then, a slow diffusion controlled change of (-)-**1** content of the solid salt to (+)-**1** from the solution (and (+)-**2** to (-)-**2**) provides the optically pure diastereoisomeric salts in several days. In other words, development of chiral discrimination between enantiomers of **1** or **2** in the presence of **3** is a slow, thermodynamically controlled process that works via exchange of the corresponding enantiomers between the solution and the crystalized, enantiomeric mixture containing diastereoisomeric salt.

Comparison of the results of repeated resolutions and the long crystallization time resolutions shows the significant advantage of the latter method and sheds light again upon the importance of crystallization time during resolution via diastereoisomeric salt formation.

Determination of the absolute configurations of **1** and **2** led us to conclude that the less soluble salts contain the quasi enantiomers of **1** and **2**; that is (*2S,3R*)-(+)-**1**-**3** and (*2R,3S*)-(-)-**2**-**3** salts crystallized from the same solvent despite the structural similarity of the two model compounds.

Experimental Section

General Procedures. Commercial chemicals were purchased from Merck or Fluka AG and were used without any further purifiation. Solvents were freshly distilled. Optical rotations were determined on a Perkin Elmer 241 polarimeter. The ^{1}H NMR spectra were recorded at 250 MHz on a Bruker AC-250 spectrometer. Chemical shifts (δ in ppm) are given from internal tetramethylsilane (0.00 ppm).

Compounds (±)-**1** and (±)-**2** were synthesized according to the literature protocol.[10] The racemic and the optically active forms of **1** and **2** are oils at ambient temperature,[4, 10] spectroscopic data are identical with those published in the literature.[4, 10]

***cis*-1-Benzyloxy-4-diethylamino-2,3-epoxybutane** (**1**) δ_H ($CDCl_3$): 7.36-7.28 (Ph, 5H, m), 4.64 ($C\underline{H}_aH_bPh$, 1H, d, *J* = 11.6 Hz), 4.53 ($CH_a\underline{H}_bPh$, 1H, d, *J* = 11.6 Hz), 3.71 ($C\underline{H}_aH_bO$, 1H, dd, *J* = 4.2, 11.2 Hz), 3.54 ($CH_a\underline{H}_bO$, 1H, dd, *J* = 6.4, 11.2 Hz), 3.18 (oxirane C<u>H</u>, 2H, m), 2.81-2.38 ($NC\underline{H}_2$, 4H, m), 1.03 (<u>Me</u>, 6H, t, *J* = 6.8 Hz).

***cis*-1-Benzyloxy-4-piperidino-2,3-epoxybutane** (**2**) δ_H ($CDCl_3$): 7.36-7.26 (Ph, 5H, m), 4.65 ($C\underline{H}_aH_bPh$, 1H, d, *J* = 11.8 Hz), 4.52 ($CH_a\underline{H}_bPh$, 1H, d, *J* = 11.8), 3.70 ($C\underline{H}_aH_bO$, 1H, dd, *J* = 4.1, 11.2), 3.54 ($CH_a\underline{H}_bO$, 1H, dd, *J* = 6.4, 11.2), 3.19 (oxirane C<u>H</u>, 2H, m), 2.66 ($C\underline{H}_aH_bN$, 1H, dd, *J*

= 3.3, 13.3), 2.42 (C$\underline{H}_2$N, 4H, m), 2.29 (CH$_a\underline{H}_b$N, 1H, dd, *J* = 6.6, 13.3), 1.60 (C$\underline{H}_2$, 4H, m), 1.44 (C$\underline{H}_2$, 2H, m).

Time-scaled resolution experiments

Resolution of (±)-1. *O,O'*-Dibenzoyl-(*R,R*)-tartaric acid monohydrate (1.57 g, 4.16 mmol) was added into an ethyl acetate (100 ml) solution of (±)-**1** (2.08 g, 8.33 mmol) and the mixture was stirred at 25 °C for a time given in Table 1. The precipitate was filtered off, washed with cold ethyl acetate (3 x 5 ml) and dried to get (+)-**1**-*O,O'*-dibenzoyl-(*R,R*)-tartrate (yields are given in Table 1). A suspension of (+)-**1**-*O,O'*-dibenzoyl-(*R,R*)-tartrate (about 1.6g) in diethyl ether (30 ml) was stirred with a saturated aqueous solution of sodium hydrogen carbonate (30 ml). The aqueous phase was extracted with diethyl ether (20 ml). The collected organic phases were washed with brine (20 ml) then dried and concentrated in vacuo to afford (+)-**1** as an oil (optical purities are given in Table 1). Chemical purities of (+)-**1** samples were checked by ^{1}H-NMR, the spectra were identical with the spectrum of the racemate. Optical purities were determined by measuring the optical rotation of (+)-**1** samples; the maximum value of specific rotation is known from the literature[4]: $[\alpha]_{D\ max.}$= +6.6 (c:0.7, chloroform). For controlling material and optical balance, the filtrate from the salt formation was concentrated in vacuo and worked up according to the above described protocol.

Resolution of (±)-2. *O,O'*-Dibenzoyl-(*R,R*)-tartaric acid monohydrate (4.15 g, 11.02 mmol) was added into an ethyl acetate (70 ml) solution of (±)-**2** (2.88 g, 11.02 mmol) and the mixture was stirred for a time given in Table 2, at 25 °C. The precipitate was filtered off, washed with cold ethyl acetate (3 x 5 ml) and dried to get (-)-**2**-*O,O'*-dibenzoyl-(*R,R*)-tartrate (yields are given in Table 2). A suspension of (-)-**2**-*O,O'*-dibenzoyl-(*R,R*)-tartrate (about 3.5 g) in diethyl ether (30 ml) was stirred with a saturated aqueous solution of sodium hydrogen carbonate (45 ml). The aqueous phase was extracted with diethyl ether (20 ml). The collected organic phases were washed with brine (20 ml) then dried and concentrated in vacuo to yield (-)-**2** as an oil (optical purities are given in Table 2). Chemical purities of (-)-**2** samples were checked by ^{1}H-NMR; the spectra were identical with the spectrum of the racemate. Optical purities were determined by measuring the optical rotation of (-)-**2** samples; the maximum value of specific rotation is known from the literature[4]: $[\alpha]_{D\ max.}$= -15.6 (c:0.7, chloroform). For controlling material and optical balance, the filtrate from the salt formation was concentrated in vacuo and worked up according to the above described protocol.

Determination of absolute configurations of (+)-1 and (-)-2

(*2S,3R*)-2-Benzyloxymethyl-3-hydroxymethyloxirane ((*2S,3R*)-**4**)[7] was prepared from *cis*-butene-1,4-diol via Sharpless-epoxidation of 4-(*tert*-butyldiphenyl)silyloxy-2-butene-1-ol[7, 8] followed by standard benzylation[10] and desilylation protocols. Thus, (*2S,3R*)-2-benzyloxymethyl-3-(*tert*-butyldiphenyl)silyloxymethyloxirane (1.25 g, 2.8 mmol) was treated with tetrabutylammonium fluoride·3H$_2$O (TBAF, 1.06 g, 3.4 mmol) in tetrahydrofuran (15 ml) at room temperature for 12 h. The reaction mixture was extracted with diethyl ether/water, the organic extracts dried and concentrated in vacuo to yield (*2S,3R*)-**4** (0.45 g, 2.3 mmol, 83%) as

an oil. Spectroscopic data are identical with those published in the literature.[7, 10] δ_H ($CDCl_3$): 7.41-7.24 (Ph, 5H, m), 5.75 (=C<u>H,</u> 2H, m), 4.51 (C<u>H</u>$_2$Ph, 2H, s), 4.13 (C<u>H</u>$_2$OH, 2H, d, *J* = 5.6 Hz), 4.07 (C<u>H</u>$_2$OBn, 2H, d, *J* = 5.7 Hz), 2.36 (O<u>H,</u> 1H, bs).

The enantiomeric excess of (*2S,3R*)-**4** was established by transformation into the *p*-nitrobenzoate.[9] Optical rotation value of the prepared sample: $[\alpha]_D$= +20 (c: 0.5, chloroform), *ee:* 59 %. Literature value[9] for the optically pure compound: $[\alpha]_D$= +34, (c:0.5, chloroform).

Samples of (*2S,3R*)-**4** were transformed into the diethylamino ((*2S,3R*)-**1**) and the piperidino ((*2S,3R*)-**2**) derivatives, respectively, using known literature protocols.[4, 10] Both compounds were isolated from the reaction mixtures as oils.[4] Optical rotation value for (*2S,3R*)-**1**: $[\alpha]_D$= +3.8 (c: 0.8, chloroform, *ee:* 59 %), for (*2S,3R*)-**2**: $[\alpha]_D$= +9.1 (c: 0.8, chloroform, *ee:* 58 %).

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