Calculation of the Efficiency of Optical Resolutions on the Basis of the Binary Phase Diagram for the Diastereoisomeric Salts

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In resolutions based on the solubility difference between pairs of diastereoisomeric salts, the maximum efficiency (parameter *S*) can be calculated from a knowledge of the eutecic composition of the binary *T–x* diagram. We demonstrate that an approximate binary phase diagram can be determined from the DSC melting curve of a single diastereoisomeric salt mixture, namely the global 1:1 mixture of diastereoisomeric salts isolated from a resolution without separation. Data estimated with the reported method are compared to the experimental results of seven resolutions. The method has proved to be efficient for diastereoisomeric salt systems forming crystalline conglomerates. Comparison of calculated *S* values obtained from a single racemic substrate with different resolving agents facilitates selection of the best resolving agent in the set.

Since Pasteur, the commonest method of splitting a racemic substance into its optically active components has been optical resolution *via* diastereoisomeric salt formation.[1] The main problems with optical resolution are the selection of the resolving agent and the solvent and, in connection with these choices, the prediction of the efficiency of the separation† and the configuration† of the enantiomers obtained. To date only a few attempts have been reported[2] on the approaches to this problem of optical resolution and only the 'trial and error' method is having an extended application.

Results and Discussion

After selection of the resolving agent the optimization of the resolution can be carried out by constructing the ternary (solubility) phase diagrams. In this way the optimal conditions (concentration, temperature) for the equilibrium process can be determined.[3,4] On comparison of the results for different diastereoisomeric salt systems, the best resolving agent can be chosen. In general, an efficient enantiomer separation can be expected in those cases in which both the diastereoisomeric salts crystallize separately and the product is a physical mixture of the crystals. In the following this mixture will be referred to as a conglomerate (of the diastereoisomeric salts, Fig. 1) and the efficiency of the resolution is determined by the position of the so-called eutectic composition in the diagram, as is evident from the following considerations. When starting an optical resolution, both of the diastereoisomeric salts are present in an equivalent amount ($q_{FR} = q_{\neg R} = q$[mole]) in the reaction mixture. Provided that crystallization takes place under equilibrium conditions, the less soluble component of the system precipitates first (its quantity is represented by n_{FR}[mole]). The crystallization should be continued until the solution (mother liquor) attains the eutectic composition; at this point the molar fraction of the less soluble component (x_e) in the mixture of the diastereoisomeric salts in solution is given by $x_e = (q - n_{FR})/\{(q - n_{FR}) + n_{\neg R}\}$. The procedure has to be terminated at this point. Hence the precipitate contains both diastereoisomeric salts. If the procedure is stopped when the eutectic is reached, then the quantity of the less soluble salt ($r = q - n_{FR}$) in the solution and its amount—provided that in equilibrium the more soluble salt remains completely in solution (*i.e.* $n_{\neg R} = q$)—can be expressed from the material balance, eqn. (1), followed by the quantity of the precipitated salt, eqn. (2).

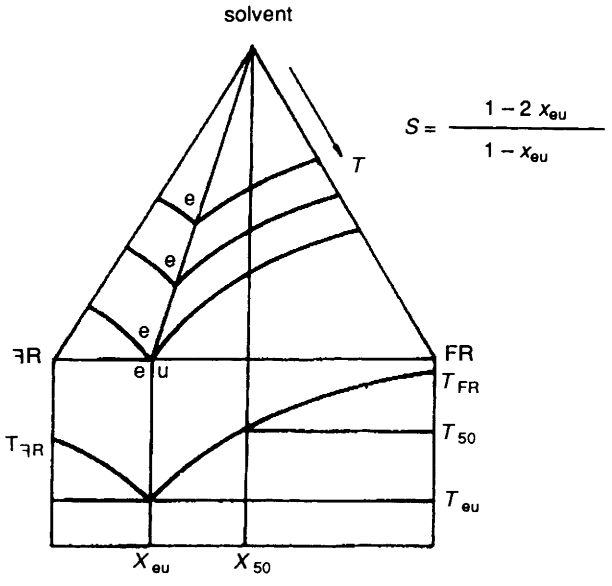

Fig. 1 A schematic representation of the relationship between the ternary and binary phase diagrams for conglomerate-forming diastereoisomers. On increasing the temperature the isotherms in the ternary phase diagrams are shifted downward.

$$r = q\frac{x_e}{1 - x_e} \qquad (1)$$

$$(q - r) = q\cdot\frac{1 - 2x_e}{1 - x_e} \qquad (2)$$

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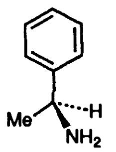
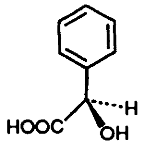
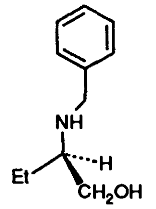
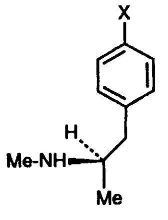
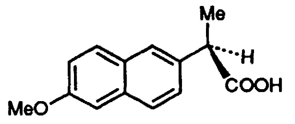
† The efficiency ($0 < S < 1$) of the optical resolution has been defined as the multiplication of the optical purity ($0 < \mathrm{OP} < 1$) by the yield ($0 < Y < 1$) of the precipitated salt: $S = \mathrm{OP} \times Y$, in E. Fogassy, A. Lopata, F. Faigl, F. Darvas, M. Ács and L. Töke, *Tetrahedron Lett.*, 1980, **21**, 647.

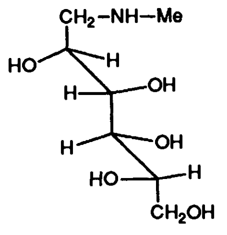

(*S*)-1

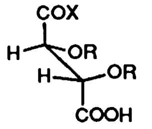

(*R*)-2

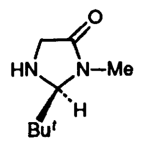

(*R*)-3

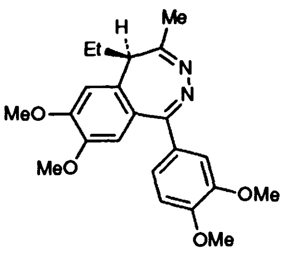

(*R*)-4 (X = H)
(*R*)-5 (X = F)

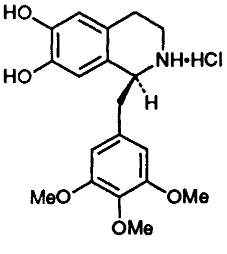

(*R*)-6

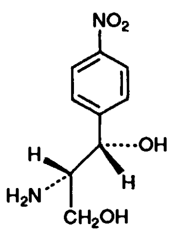

(*R*)-7

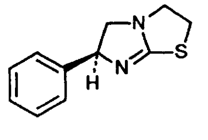

(2*R*, 3*R*)-8 (R = H, X = OH)
(2*R*, 3*R*)-9 (R = PhCO, X = OH)
(2*R*, 3*R*)-11 (R = PhCO, X = NMe₂)

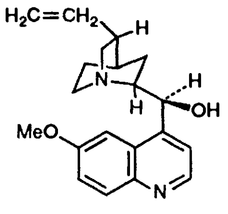

(*S*)-10


(*R*)-12


(*S*)-13


(1*S*, 2*S*)-15


(*S*)-14


cinchonidine 16

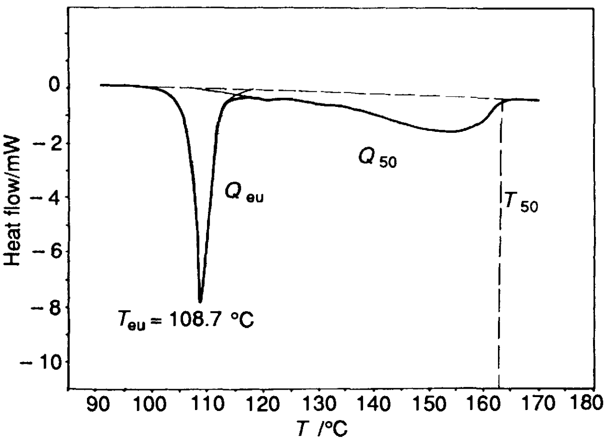


Fig. 2 Melting curve for the 1:1 mixture of (*RS*)- and (*RR*)-α-phenylethylammonium mandelates. The first peak represents the melting of the eutectic, the second belongs to the remaining solid. Q_i is calculated from the time integral of the corresponding peak and related to one mole of the substance.

If the crystallization can be stopped on reaching the eutectic composition, then optically pure compound (OP = 1 for the FR salt) is obtained. In this case the efficiency (*S*) of the resolution is equal to the yield [$Y = (q - r)/q$] of the precipitated salt, eqn. (3).

$$S = \mathrm{OP}\cdot Y = Y = \left\{q\cdot\frac{1-2x_e}{1-x_e}\right\}/q = \frac{1-2x_e}{1-x_e} \qquad (3)$$

The use of solubility diagrams in evaluating the resolution procedures is not widespread since both pure diastereoisomeric salts are required in quite large amounts (this is a *circulus viciosus* since the pure diastereoisomeric salts can only be prepared after a successful resolution).

When constructing the ternary phase diagram for the diastereoisomeric α-phenylethylammonium hydratropates, Leclercq and Jacques found that the eutectic composition (x_e) depends only a little on the temperature and is nearly identical to the eutectic composition (x_{eu}) of the binary (melting point–composition) diagram.[4] Generalization of this observation involves a temperature-independent interaction between the components of the diastereoisomeric salts, *i.e.* the solubility ratio is regarded as being nearly constant. In an unspecified case, increasing temperature increases the solubility as well. The isotherms are shifted towards the base of the triangle (FR–ꟻR) and gradually less solvent is required for complete dissolution. When the temperature reaches the melting point of the solid eutectic, no solvent is required for dissolution. Now the ternary phase diagram overlaps the binary phase diagram, *e.g.* the computable maximum efficiency does not depend on the actual solubility relation, but exclusively on the location of the eutectic point (*i.e.* $x_e = x_{eu}$; Fig. 2). The cases listed in Table 1 reveal that there is fairly good agreement between the experimental and calculated efficiency. As a clear consequence of the above consideration, the construction of the binary phase diagram enables us to predict the expected separability of a given diastereoisomeric salt pair. The liquidus curve of a binary phase diagram for conglomerates is calculated on the basis of the simplified Schroeder–van Laar equation (4)[5] using the thermal data recorded by DSC (differential scanning calorimetry).

$$\ln x = \frac{\Delta H_i}{R}\left(\frac{1}{T_i} - \frac{1}{T}\right) \qquad (4)$$

In eqn. (4), x is the molar fraction, ΔH_i the enthalpy of fusion of the pure, individual diastereoisomers, T_i the melting point of the diastereoisomers, T the melting point, *i.e.* end of the fusion of a mixture with a molar fraction of x, R the ideal gas constant,

Table 1 Comparison of the thermoanalytical data obtained from DSC measurements for the pure diastereoisomeric salts and their 1:1 mixtures[a]

Compound		M.p./K			Heat of fusion/ −kJ mol^{-1}					S^{ref}	
ꟻF	R	T_{FR}	$T_{ꟻR}$	T_{eu}	ΔH_{FR}	$\Delta H_{ꟻR}$	Q_{FR}	Q_{eu}	x_{eu}	direct resolution	reciprocal resolution
1	**8**										
Meas.		**464**	**460**	444	**33.1**	**28.5**	78.2	18.5	0.34	0.52[7]	
Calc.		467	457	**443**	46.9	15.0	—	—	**0.10**	**0.90**	
2	**1**										
Meas.		**450**	**382**	381	**48.9**	**30.3**	15.7	19.1	0.09	0.86[8]	
Calc.		449	386	**382**	53.5	31.1	—	—	**0.10**	**0.90**	
2	**3**										
Meas.		**381**	**357**	342	**32.1**	**28.8**	9.8	23.0	0.32	0.45[9]	
Calc.		378	355	**341**	35.6	29.9	—	—	**0.31**	**0.52**	
2	**10**										
Meas.		**391**	**352**	349	**51.5**	**30.6**	23.9	16.8	0.15	0.82[13]	0.82[14]
Calc.		390	349	**346**	55.3	26.9	—	—	**0.12**	**0.88**	0.85
4	**8**										
Meas.		**437**	**387**	382	**50.0**	**35.9**	19.6	23.4	0.13	0.85[11]	0.85
Calc.		438	385	**381**	46.7	41.2	—	—	**0.14**	**0.84**	**0.70**
5	**8**										
Meas.		**426**	**393**	358	**35.0**	**58.9**	41.7	47.8	0.47	0.10[12]	
Calc.		423	392	**355**	39.5	61.3	—	—	**0.45**	**0.11**	
6	**7**										
Meas.		**431**	**398**	393	**61.6**	**30.4**	37.2	29.8	0.24	0.65[10]	
Calc.		434	399	**395**	65.2	31.9	—	—	**0.24**	**0.65**	

[a] ꟻF: racemate; R: resolving agent; Q: heat quantity absorbed during the melting/kJ mol^{-1}; x_{eu}: eutectic composition for FR and ꟻR diastereoisomeric salts; meas., measured; calc., calculated. **Bold characters**: measured m.p.s and heats of fusion of the pure diastereoisomeric salts; T_{eu}: x_{eu} and S calculated by the Schroeder–van Laar equation (4) by using the above experimental m.p. and ΔH_f data. Plain characters: measurements performed on the 1:1 mixtures of the diastereoisomeric salts. With the aid of the data, eqn. (11) and Fig. 3 provide the composition of the eutectic (x_{eu}) and eqns. (9) and (14), the estimated characteristics of the pure diastereoisomeric salts.

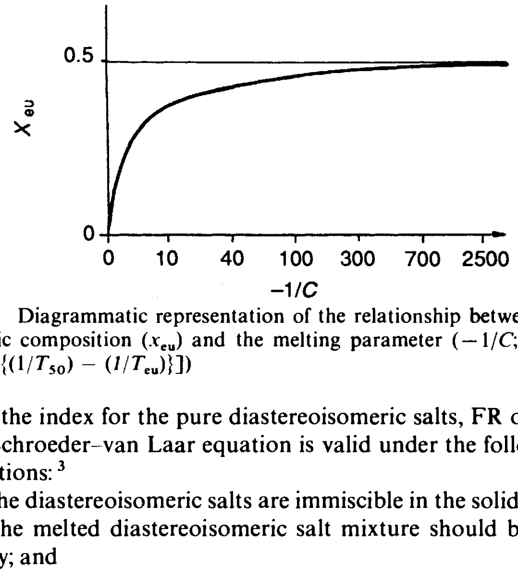


Fig. 3 Diagrammatic representation of the relationship between the eutectic composition (x_{eu}) and the melting parameter ($-1/C$; [$C = Q_{FR}/R\{(1/T_{50}) - (1/T_{eu})\}$])

and i the index for the pure diastereoisomeric salts, FR or ꟻR. The Schroeder–van Laar equation is valid under the following conditions:[3]

1. the diastereoisomeric salts are immiscible in the solid state;
2. the melted diastereoisomeric salt mixture should behave ideally; and
3. the heat of fusion should not depend on the temperature.

Using this method the binary phase diagram can be easily constructed, however, a few milligrams of both of the pure diastereoisomeric salts are still needed. When newly-synthesized racemic substances are to be resolved, then no pure diastereoisomeric salt pairs are available. The question arises: is there any possibility of constructing the binary phase diagram, *i.e.*, can the method be used for rapid selection of the optimum resolving agent in those cases in which only the racemic starting material is available?

Application of the Schroeder–van Laar equation for calculating the diagram illustrates that along one branch of the melting point diagram the same constants (ΔH_i and T_i) are employed over the whole concentration range, *i.e.*, the same equation should be valid for any point on the curve. The eutectic composition is produced by the intersection of the two curves. Being aware of the concentrations and of the melting temperature of two randomly selected points the diagram can be constructed.

Then the next question arises: how can we get two independent points with known concentration located on the same branch of the binary phase diagram? The answer is supplied by the well-known melting behaviour of the two-component systems. In any nearly ideal case, two peaks characterize the melting profile of the system (Fig. 2). The first is connected with the melting of the eutectic composition, thus giving the melting point (T_{eu}) for the eutectic, and the second represents the melting of the diastereomeric salt in excess (T_{mixt}). The isolated peak areas are directly proportional to the heat necessary to melt the eutectic (Q_{eu}) and the excess of the higher melting diastereoisomeric salt (Q_{FR}).

At this point we can conclusively answer the initial question: by employing a 1:1 mixture of the diastereoisomeric salts (prepared directly by mixing the racemate and the 'would-be' resolving agent in solution, then evaporating the solvent) the binary phase diagram can be constructed as follows: $x = 0.50$ and $T_{mixt} = T_{50}$. Then in the Schroeder–van Laar equation the eutectic composition (x_{eu}), the enthalpy of fusion (ΔH_{FR}) and the melting point (T_{FR}) are unknown. The equation can be applied to the eutectic point and the 1:1 composition, eqns. (5a) and (5b).

$$\ln x_{eu} = \frac{\Delta H_{FR}}{R} \cdot \left(\frac{1}{T_{FR}} - \frac{1}{T_{eu}}\right) \tag{5a}$$

$$\ln 0.5 = \frac{\Delta H_{FR}}{R} \cdot \left(\frac{1}{T_{FR}} - \frac{1}{T_{50}}\right) \tag{5b}$$

Rearranging $\Delta H_{FR}/RT_{FR}$ and equating the two expressions we obtain eqn. (6).

$$\ln 0.5 + \frac{\Delta H_{FR}}{RT_{50}} = \ln x_{eu} + \frac{\Delta H_{FR}}{RT_{eu}} \tag{6}$$

Rearranging eqn. (6) one obtains eqn. (7), *i.e.* the molar heat

$$\ln 2x_{eu} = \frac{\Delta H_{FR}}{R}\cdot\left(\frac{1}{T_{50}} - \frac{1}{T_{eu}}\right) \tag{7}$$

(Q_{FR}) required to melt the residue of the diastereoisomeric salt of higher melting point is proportional to the quantity of the diastereoisomer in question (n_{FR}) melted during the second step, eqn. (8).

$$Q_{FR} = n_{FR}\Delta H_{FR} \tag{8}$$

Starting from 1 mol of the 1:1 ratio of the two diastereoisomeric salts (FR + ꟻR) the quantity n_{FR} can be expressed in terms of molar fractions of the eutectic mixture: $n_{FR} = (1 - 2x_{eu})/(2 - 2x_{eu})$. Then the enthalpy of fusion is expressed as eqn. (9), and can be substituted into eqn. (7) to give eqn. (10).

$$\Delta H_{FR} = Q_{FR}/n_{FR} = Q_{FR}\cdot\frac{2 - 2x_{eu}}{1 - 2x_{eu}} \tag{9}$$

$$\ln 2x_{eu} = \frac{Q_{FR}}{R}\cdot\frac{2 - 2x_{eu}}{1 - 2x_{eu}}\cdot\left(\frac{1}{T_{50}} - \frac{1}{T_{eu}}\right) \tag{10}$$

Rearrangement of the eqn. (10) gives eqn. (11).

$$\frac{1 - 2x_{eu}}{2 - 2x_{eu}}\cdot\ln 2x_{eu} = \frac{Q_{FR}}{R}\cdot\left(\frac{1}{T_{50}} - \frac{1}{T_{eu}}\right) = C \tag{11}$$

For various eutectic compositions a series of possible C values can be computed. For easier handling, a diagrammatic representation is advisable (Fig. 3), then having determined the melting points and the heat of fusion (Q_{FR}), the eutectic composition (x_{eu}) can be obtained from the diagram.

The enthalpy of fusion (ΔH_{FR}) can be calculated from the eutectic composition and eqn. (8), thus one branch of the binary phase diagram can be constructed. To compute the branch describing the melting point depression for the lower melting diastereoisomeric salt as a function of composition requires the enthalpy of fusion for this compound ($\Delta H_{\text{ꟻ}R}$). The enthalpy of fusion can also be calculated on the basis of the heat balance using the heat of fusion measured for the eutectic composition (Q_{eu}), eqn. (12).

$$\Delta H_{eu} = (1 - x_{eu})\,\Delta H_{\text{ꟻ}R} + \Delta H_{FR}x_{eu} \tag{12}$$

The enthalpy of fusion for the eutectic (ΔH_{eu}) is derived from the measured heat of fusion (Q_{eu}) and the amount of the eutectic (e), which can be calculated from the eutectic composition (x_{eu}) by means of the expression $1/e = 2(1 - x_{eu})$. Thus the enthalpy of fusion is given by eqn. (13).

$$\Delta H_{eu} = Q_{eu}/e = 2(1 - x_{eu})Q_{eu} \tag{13}$$

Equating eqns. (12) and (13) we obtain eqn. (14).

$$\Delta H_{\text{ꟻ}R} = 2Q_{eu} - \Delta H_{FR}\cdot\frac{x_{eu}}{1 - x_{eu}} \tag{14}$$

The melting point for this diastereoisomeric salt ($T_{\text{ꟻ}R}$) can be calculated with the aid of the Schroeder–van Laar equation written for the eutectic composition, but using $\Delta H_{\text{ꟻ}R}$. All the information required for the construction of the approximate binary phase diagram is then available by analysing the melting profile of a single diastereoisomeric salt mixture.

In order to obtain information about the reliability of the method we have investigated known resolution procedures. The measured and calculated eutectic compositions, melting points and enthalpies of fusion were compared (Table 1). In our approach—based on the assumption of nearly ideal systems—the solvent in the resolutions investigated may not be specified, *i.e.* in ideal cases the ratio of the two components in the eutectic composition is independent of the nature of the solvent.*

If both diastereoisomeric salt systems (FR/FЯ; FR/ꟻR) are ideal conglomerate forming, then an identical phase diagram characterizes the 'diastereoisomeric' mixture: FR/FЯ [which forms during the reciproal resolution procedure, *i.e.* when one enantiomer of the former racemate (F) becomes a resolving agent for the former resolving agent (ЯR)], and the calculated optimum value should be valid for the reciprocal procedure. This way we can select a new resolving agent with predicted efficiency for selected cases. However, the success of the predicted resolution confirms the conglomerate formation for these diastereoisomeric salt pairs. Table 1 lists the successful reciprocal resolution cases and the optical resolution of racemic tartaric acid (**8**) with the aid of (*R*)-methamphetamine† (**4**) serves as an illustrative example of the applicability of the method.

Compound (*R*)-**4** (1 mmol, 0.15 g) and racemic-**8** (1 mmol, 0.15 g) were each dissolved in aq. ethanol (1.1 cm^3) and the solutions combined. The solvent was evaporated to dryness under reduced pressure. The DSC curve of the residue was measured. The obtained data are as follows: T_{eu} = 381 K, T_{50} = 417 K; Q_{eu} = 23.4 kJ mol^{-1}; Q_{FR} = 19.6 kJ mol^{-1}. Substituting these data into eqn. (11) yields a value of 0.533 for C. The corresponding eutectic composition x_{eu} is 0.13. The expected maximum optical yield (S) from eqn. (3) is 0.85. This value is worth testing in practice (see the results of the Experimental section).

As we have already pointed out the method is applicable only for conglomerates. For its applicability, DSC peaks should be separable, *i.e.* a large overlap between the peaks is not allowed. In the case of 1:1 molecular compound and solid solution formation, the DSC trace consists of one single peak. In these cases the efficiency of the resolution is generally poor or tends to zero. An additional problem may emerge if the system exhibits limited solubility or when only one of the diastereoisomers is crystalline. In those cases only partial information can be gained. For some rough estimate of the expected efficiency of the selected resolving agent it can still be useful. When the mixture is amorphous, or decomposition takes place, the method loses its applicability. Similarly solvate inclusion, pseudopolymorphism and polymorphism also prohibit the application, although even in these cases successful resolutions might be accomplished. Out of the 13 cases listed (Tables 1 and 2) we have found two solid solutions, in two cases one of the isomers was amorphous and decomposition took place in the remaining three sytems (Table 2).

Experimental

DSC curves were recorded and integrated with a Dupont 1090B Thermal Analysis System and samples of 1–3 mg were run in hermetically-sealed aluminium pans with a heating rate of 5 K min^{-1}. The temperature range of thermal decomposition was determined by thermogravimetric measurements (carried out on the same system).

Optical Resolution of (2RS,3RS)-*Tartaric Acid.*—(R)-*Methamphetamine* (2R,3R)-*Tartrate.* Racemic tartaric acid (0.01 mol, 1.5 g) was dissolved in water (4.5 cm^3). To the clear

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* In their paper, A. D. van der Haest, H. Wynberg, F. J. J. Leusen and A. Bruggink, *Recl. Trav. Chim. Pays-Bas*, 1990, **109**, 523, revealed the practical solvent-independency of six optical resolutions of racemic ephedrine accomplished with different cyclic phosphoric acids.

† (*R*)-2-Methylamino-1-phenylpropane.

Table 2 Illustrative examples for the limits of applications[a]

Compound		Thermal data							
ꟻF	R	FR		ꟻR		Mixture			
		T/K	ΔH/kJ mol^{-1}	T/K	ΔH/kJ mol^{-1}	T/K	ΔH/kJ mol^{-1}	$S^{\text{ref.}}$	
12	**9**	390	38.4		(A)		(A)	0.57[15]	
15	**11**	423	(C)		(A)		(A)	0.77[16]	
14	**9**	422	(B)		(B)	415	(B)	0.90[17]	
13	**8**	506	(B)		(B)		(B)	0.79[18]	
2	**16**	453	35.8	451	37.4	452	40.3	0[19]	(D)
15	**2**	447	55.7	444	35.9	443	71.8	0[19]	(D)

[a] One of the diastereoisomeric salts is (A) amorphous or an oil, (B) decomposes before or during the melting, (C) crystallizes with solvate or (D) is a solid solution.

solution was added (R)-methamphetamine base (0.01 mol, 1.49 g). The warmed solution was allowed to cool to room temperature and was then seeded* with crystals of (R)-base (2R,3R)-tartrate·dihydrate. Precipitation commences immediately and is complete after the mixture has been stirred at room temperature for 1 h then 2 h at 5 °C. The crystalline mass was filtered off, washed with cold water and dried under water-free conditions (1.03 g, 70%) (Found: C, 56.1; H, 6.9; N, 4.6. Calc. for $C_{14}H_{21}NO_6$: C, 56.19; H, 7.02; N, 4.68%).

(2R,3R)-*Tartaric acid.* The precipitated diastereoisomeric salt was dissolved in the minimum amount of water, the pH was adjusted to 11, and the solution extracted three times with benzene (5 cm^3). The organic phase was washed and dried, and after evaporation of the solvent the resolving base was regenerated with a yield of 95% in unchanged optical purity.

The aqueous phase was concentrated to dryness and recrystallized from conc. HCl (1 cm^3 HCl g^{-1} of residue). The crystalline product was optically pure natural tartaric acid (0.56 g, 68%); $[\alpha]_D = 12.0$ (c 20 in H_2O); m.p. 172–173 °C {lit.,[6] $[\alpha]_D = 12.4$ (c 20 in H_2O); m.p. 170–172 °C}.

(2S,3S)-*Tartaric acid.* The pH of the mother liquor of the resolution was adjusted to 11, the resolving agent was eliminated as described above, and the whole procedure was repeated to yield unnatural tartaric acid (0.59 g, 79%); $[\alpha]_D = 11.7$ (c 20 in H_2O); m.p. 171–173 °C.

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* In order to eliminate the uncertainty caused by seeding the experiments were also performed without it. The same yield and optical purity can be achieved after 48 h stirring at room temperature. Thus the seeding only accelerates but not disorientates the precipitation of the expected diastereoisomeric salt. Although the seeding crystal contains two water molecules, upon drying both of them are eliminated. The thermoanalytical measurements were performed on the water-free species.

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