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Calculation of the efficiency of purification by crystallization of ideal multicomponent stereoisomeric mixtures

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Abstract

A method for evaluating the maximum theoretical recovery of pure component from a stereoisomeric mixture by crystallization is discussed. The approach is based on the approximation of ideal behaviour as exemplified by the Schroeder–van Laar equation for conglomerates, and the Prigogine–Defay equation for racemic compounds. These equations are used to calculate the n-dimensional eutectic. It is shown that the n-dimensional eutectic is more soluble than the $(n-1)$-dimensional eutectic. A calculation is performed which removes only the n-dimensional eutectic from the sample and calculation of recovery through this discrete purification step is possible. After this, a system of $n-1$ components is obtained. The calculation may be repeated until only one component remains. The overall recovery of pure isomer is the product of the recoveries at each discrete purification step. The procedure is well suited to computer algorithm and a summary listing is presented. A series of example calculations are included for reference purposes. The methodology is intended to be useful in guiding efforts to improve process economics.

1. Introduction

Chemical transformations to a greater or lesser extent result in a mixture of products, and purification of the desired component is often achieved by crystallization. Purification by crystallization relies on preferential solution of a portion of the sample containing the unwanted components, along with an amount of the desired component. The amount of desired component lost during this process is of particular interest in the industrial context.[1]

For maximal recovery it is necessary to dissolve no more of the sample than corresponds to the eutectic composition. Knowledge of the composition of the eutectic therefore provides the basis of estimating the maximum recovery of pure component from the mixture by crystallization.

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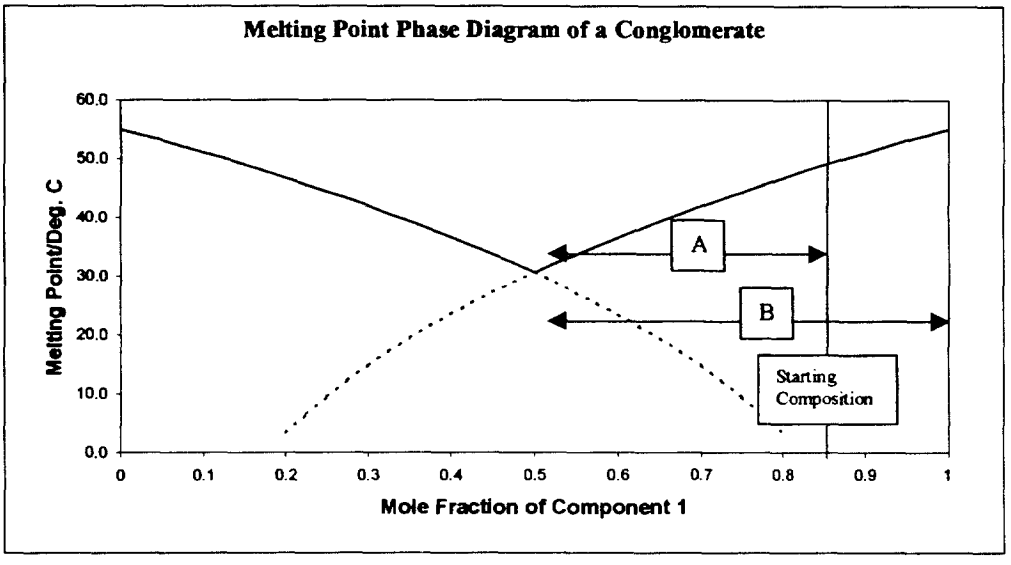

Fig. 1.

It is common to determine the eutectic and hence predict the maximum recovery for enantioenriched mixtures.[2] The method involves:

(i) determination of the melting point phase diagram of the enantiomers;
(ii) the assumption that the solubility of a mixture is inversely proportional to the melting point of that mixture; and
(iii) the assumption that differential solubility of the enantiomers is invariant in the choice of solvent.[3]

Sample composition and composition of the eutectic may be used to calculate the maximum recovery of pure component (R_{max}) from Eq. 1 assuming equilibrium crystallization and ideal behaviour.

$$R_{max} = \frac{(x_c - x_{eu})}{(1 - x_{eu})} \quad (1)$$

For example, consider an enantioenriched conglomerate with an initial composition (x_c) of 85% and a eutectic composition (x_{eu}) of 50%. Eq. 1 gives R_{max} at 70%. This calculation is often expressed graphically on the melting point phase diagram, where component 1 is the component in excess, as distance A/B (Fig. 1). Notice that Eq. 1 predicts that recovery of pure enantiomer is impossible then $x_c = x_{eu}$. Fortunately, since a conglomerate is a mechanical mixture of enantiomeric crystals, resolution by entrainment or triage is possible.[4]

With reference to point (iii) above; it is not surprising that enantiomers have identical solubilities (in any given solvent) since, in the absence of a chiral environment, they have identical melting points, heats of fusion and dipole moments. Hence there is no basis for differential solvation of the enantiomers and calculation of maximum recovery is invariant in the choice of solvent.

It is perhaps less obvious, but nonetheless a reasonable approximation, that the eutectics of other stereoisomeric systems may not be significantly affected by the choice of solvent. On further consideration, given that stereoisomers have the same functional groups and connecting framework differing only in their arrangement in space, discrimination of the stereoisomers by solvent may well be minimal. Indeed, the melting point phase diagram has been used to estimate the maximum recovery of resolution by diastereoisomer crystallization.[3,5]

It is known that the melting point phase diagram of a conglomerate may be characterized by the

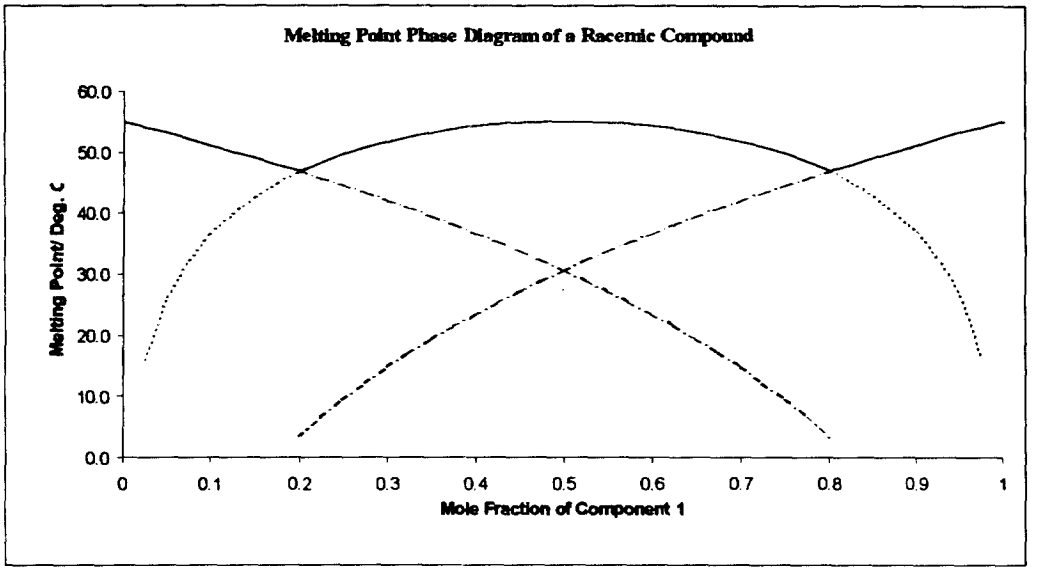

Fig. 2.

Schroeder–van Laar equation (Eq. 2). This, in its simplified form, relates the mole fraction (x) of the component to melting point (T), where T_P is the melting point and ΔH_{fP} is the heat of fusion of the pure isomer, and R is the gas constant.

$$\ln(x) = \frac{\Delta H_{fP}}{R}\left[\frac{1}{T_P} - \frac{1}{T}\right] \tag{2}$$

The practical benefit is that evaluation of a variety of diastereomer mediated resolutions may be approached by preparation of an array of p and n salts followed by differential scanning calorimetry (DSC) analysis and solution of the Schroeder–van Laar equations.

A deviation from conglomerate behaviour is commonly seen when enantiomeric systems are considered. Approximately 90% belong to a category known as racemic compounds. Here a form crystallizes with a 1:1 mixture of enantiomers in the unit cell. This racemic compound will have a defined melting point and heat of fusion which generally differs from that of the enantiomerically pure crystal. The behaviour of the racemic compound is described by the Prigogine–Defay equation (Eq. 3), where the terms ΔH_{fR} and T_R relate to the heat of fusion and the melting point of the racemic compound.

$$\ln[4x(1-x)] = \frac{2\Delta H_{fR}}{R}\left[\frac{1}{T_R} - \frac{1}{T}\right] \tag{3}$$

The melting point phase diagram of a racemic compound is described by the superposition of the Schroeder–van Laar equation and the Prigogine–Defay equation (Fig. 2).[6] Calculation of R_{max} follows from Eq. 1 when $x_c > x_{eu}$. However when $x_c < x_{eu}$, crystallization of racemate occurs and enrichment takes place in the mother liquors up to a composition x_{eu}. In the case where $x_c = x_{eu}$, no enrichment by crystallization is possible.

2. Calculation of a multicomponent eutectic

When a system is composed of more than two components the situation is a little more complicated. If all the components of the system behave as conglomerates, one may use the Schroeder–van Laar equation to determine the eutectic composition.[7]

$$\sum_{i=1}^{n} x_i = 1 \text{ when } T = T_{\text{eu}} \tag{4}$$

$$x_i = \exp\left(\frac{\Delta H_i}{\mathrm{R}}\left[\frac{1}{T_i} - \frac{1}{T}\right]\right) \tag{5}$$

The mole fraction (x_i) of a component is related to temperature (T) through the Schroeder–van Laar equation, where ΔH_i is the heat of fusion of component i, T_i is the melting point of pure component i, R is the gas constant and T_{eu} is the melting point of the eutectic.

When the system under consideration has a component which behaves as a racemic compound, it is appropriate to substitute the specified term in Eq. 4 with the standard quadratic solution of the Prigogine–Defay equation for the range $x_i \leq 0.5$ (Eq. 6).

$$x_i = \frac{-4 + \sqrt{16 - 16\exp\left(\frac{2\Delta H_i}{\mathrm{R}}\left[\frac{1}{T_i} - \frac{1}{T}\right]\right)}}{-8} \tag{6}$$

In order to calculate the maximum recovery of a pure component from an initial mixture it is necessary to consider:

(i) the initial composition; and

(ii) the steps by which purification takes place.

The latter point bears some discussion. Consider the eutectic of a three component system (Eq. 7) compared with the binary eutectic (Eq. 8). By inspection of the Schroeder–van Laar equation (Eq. 2) it is apparent that T will necessarily be lower that T_i in order to make the exponent negative (the region of interest is $1>x_i>0$). It is also clear when comparing the three component system (Eq. 7) with the corresponding two component system (Eq. 8) that $T_a<T_b$ (Eq. 9). Notice that ΔH_i and T_i (i=1, 2) have the same value in Eqs. 7 and 8 since they relate to the same compounds.

$$\exp\left(\frac{\Delta H_1}{\mathrm{R}}\left[\frac{1}{T_1} - \frac{1}{T_\mathrm{a}}\right]\right) + \exp\left(\frac{\Delta H_2}{\mathrm{R}}\left[\frac{1}{T_2} - \frac{1}{T_\mathrm{a}}\right]\right) + \exp\left(\frac{\Delta H_3}{\mathrm{R}}\left[\frac{1}{T_3} - \frac{1}{T_\mathrm{a}}\right]\right) = 1 \tag{7}$$

$$\exp\left(\frac{\Delta H_1}{\mathrm{R}}\left[\frac{1}{T_1} - \frac{1}{T_\mathrm{b}}\right]\right) + \exp\left(\frac{\Delta H_2}{\mathrm{R}}\left[\frac{1}{T_2} - \frac{1}{T_\mathrm{b}}\right]\right) = 1 \tag{8}$$

$$T_\mathrm{a} < T_\mathrm{b} \tag{9}$$

It has been established that the melting point of the ternary eutectic will be lower than the binary eutectic. It is assumed that the melting point of the mixture is related to the volume of solvent necessary to achieve solution.[2] Hence the lower the melting point, the less solvent required. It follows that the ternary eutectic will be more soluble than the corresponding binary eutectic. The same arguments may be applied to an n component system versus the $n-1$ component system. Hence, for the purposes of calculation, purification may be thought of as progressing in discrete steps.

Returning to the ternary system for illustration, the first step in purification corresponds to removal of the tertiary eutectic. After this a binary system remains. Removal of the binary eutectic leaves pure

Table 1
Calculation of recovery based on starting composition; example 1

MPt (T_i)/°C:	40.9°C	49°C	56.9°C
Heat of Fusion/kJ.mol^{-1}:	20.9618	27.6144	32.1750
Starting Composition :	90.00%	9.00%	1.00%
Eutectic Mpt: 16 °C, Composition:	50.11%	30.84%	19.05%
Composition After Ternary Eutectic Removal:	92.21%	7.79%	

Table 2
Calculation of recovery based on starting composition; example 2

MPt (T_i)/°C:	40.9°C	49°C	56.9°C
Heat of Fusion/kJ.mol^{-1}:	20.9618	27.6144	32.1750
Starting Composition :	50.00%	10.00%	40.00%
Eutectic Mpt: 16 °C, Composition:	50.11%	30.84%	19.05%
Composition After Ternary Eutectic Removal:	49.95%		50.05%

component. The overall recovery of pure component is the *product* of the recoveries from the two discrete purification steps.

Turning now to the issue of starting composition. This has a direct bearing on the maximum recovery of pure component. Unlike the composition of the various eutectics (n, $n-1$,..., 2), the starting composition is a variable and is a function of the chemistry practiced.

In order to establish the proportion of the sample to be removed, it is necessary to consider the starting composition and the composition of the eutectic at each discrete purification step. The following worked example illustrates a method of calculating the composition of a sample after removal of the ternary eutectic. The approach generalizes to n-dimensions and is well suited to computer algorithm.

	Component 1	Component 2	Component 3	$\sum x$
❖ Melting point of pure isomer (Ti)/°C	40.9	49	56.9	N/a
❖ Heat of fusion of pure isomer (ΔH_i)/kJ.mol^{-1}	20.9618	27.6144	32.1749	N/a
❖ Initial composition (x_i)	0.5	0.1	0.4	1.00
❖ Calculated ternary eutectic (x_{eui}) assuming conglomerate behaviour	0.501	0.308	0.190	1.00
❖ Determine x_{eui}/x_i. Note which component offers the largest ratio. In this case Component 2 with 3.080	1.002	3.080	0.475	N/a
❖ Scale the initial composition by the largest value x_{eui}/x_i. The sample and the eutectic are now on the same scale, hence the eutectic may be subtracted directly	1.540	0.308	1.232	3.08
❖ Calculated ternary eutectic (x_{eui})	0.501	0.308	0.190	1.00
❖ Composition after subtraction of the ternary eutectic	1.039	0.000	1.042	2.08
❖ Scale the binary mixture to add up to 1 for clarity	0.50		0.50	1.00

The recovery of binary mixture after removal of the ternary eutectic may be calculated from the sum of the components after subtraction of the eutectic compared with the sum of components prior to subtraction, 2.08÷3.08=67.5% of binary mixture of 1:1 composition.

The starting composition has an important effect on the profile of the purification process. This is illustrated in the following tables where partial purification of the same components is evaluated with different starting compositions (Tables 1 and 2).

With the foregoing ideas in hand, the generalized problem may be viewed in five parts:

(i) determination of the composition of the n-dimensional eutectic using the Schroeder–van Laar or Prigogine–Defay equation as appropriate;
(ii) calculation of the portion of the sample which corresponds to the n-dimensional eutectic;
(iii) removal of a portion of the sample corresponding to the n-dimensional eutectic composition thereby reducing the dimensionality of the system and obtaining a new composition;
(iv) calculation of recovery after removal of the eutectic; and
(v) repetition of the procedure for the mixture of composition obtained at step (iii).

This type of problem is readily solved by computer. Appendix A gives a summary of the core operations necessary to solve a general n-dimensional problem.

3. Example calculations

3.1. Comparison with literature multidimensional eutectic calculations

A computer program based on the summary listing in Appendix A was developed. Previous multidimensional eutectic calculations on nematic liquid crystals were compared with the results of the calculations using the literature melting points and heats of fusion (Table 3). The overall results of the calculations agree closely.

3.2. Enantioenriched binary racemic compound

The normal method of analysis of these systems involves finding the roots of the Prigogine–Defay equation by determination of the melting point and heat of fusion of the racemate, and observing the melting point of a partially enriched sample. The latter corresponds to T_{eu}, since the eutectic will begin to melt first.[2]

As seen from Fig. 2, the melting point phase diagram is composed of the superposition of the Schroeder–van Laar curves derived from the pure enantiomers, and the Prigogine–Defay quadratic for the racemic compound. Therefore T_{eu} may be found where the curves intersect. The hypothetical data used to plot Fig. 2 is presented in Tables 4 and 5.

The calculated roots x_{eu_1} and x_{eu_2} in Table 4 have been found using the standard solution to a quadratic equation using ΔH_R, T_R and T_{eu}. With a starting composition of 90% the maximum recovery of pure enantiomer (as calculated by Eq. 1) is 50%.

The data associated with pure enantiomer utilized in Fig. 2 may be found in Table 5. The data listed in Table 6 are the calculated temperatures from the Prigogine–Defay equation or the Schroeder–van Laar equation on the basis of the T_R, ΔH_R, and T_1, ΔH_1, T_2, ΔH_2 from Tables 4 and 5 respectively. Note that the roots are located where the temperatures are identical and the compositions sum to unity (underlined on Table 6).

The actual implementation of the summary listing presented in Appendix A provides the following results (Table 7) based on the T_i, ΔH_i data in Tables 4 and 5.

Clearly the results from the algorithm accord with the calculated eutectic and maximum recovery from the standard calculational methodology.

3.3. Estimation of maximum recovery from an ideal four component mixture

Consider a chemical transformation whereby an enantioenriched product (A) has been obtained at 81% isomeric purity. The product has two chiral centres and contamination with all three stereoisomeric side products has been noted (Fig. 3).

Table 3
Comparison with literature calculations

Mixture Name	Melting Point/ °C	ΔH_f kJ.mol^{-1}	Lit.[8] x_{eu}	Calculated x_{eu}
HRL-2N52	75.4	26.2094	0.093	0.093
	62.8	29.4751	0.102	0.102
	39.5	32.7408	0.189	0.189
	68.6	22.9855	0.147	0.146
	54.9	25.9163	0.168	0.168
	81.0	31.4847	0.049	0.049
	67.2	34.2899	0.060	0.060
	50.7	25.6651	0.193	0.193
HRL-25N4	75.4	26.2094	0.079	0.079
	62.8	29.4751	0.085	0.085
	40.9	23.1949	0.256	0.256
	68.6	22.9855	0.127	0.127
	54.9	25.9163	0.143	0.143
	63.8	22.0226	0.155	0.155
	74.1	29.9775	0.057	0.057
	65.0	27.0886	0.098	0.097
HRL-26N3	75.4	26.2094	0.033	0.043
	40.9	23.1949	0.147	0.148
	51.8	25.6232	0.086	0.087
	54.9	25.9163	0.065	0.077
	38.4	15.9517	0.280	0.282
	30.6	23.9066	0.220	0.190
	40.1	21.5620	0.169	0.173
HRL-26N4	75.4	26.2094	0.108	0.108
	62.8	29.4751	0.120	0.120
	54.9	25.9163	0.194	0.194
	81.0	31.4847	0.058	0.058
	67.2	34.2899	0.073	0.073
	50.7	25.6651	0.223	0.223
	48.1	27.1305	0.222	0.222
HRL-246N1	75.4	26.2094	0.087	0.090
	62.8	29.4751	0.094	0.097
	54.9	25.9163	0.157	0.161
	30.6	23.9066	0.390	0.374
	44.4	21.8970	0.272	0.279

Table 4
Eutectic calculation for racemic compound in Fig. 2

Heat of Fusion of Racemate (ΔHr):	23.419 kJ.mol^{-1}
Melting Point of Racemate (T_R):	55.0 °C
Beginning Melting of Partially Resolved Mixture (T_w):	46.69 °C
Prigogine-Defay Solution x_{eu1} =	0.200
Prigogine Defay Solution x_{eu2} =	0.800
Starting Composition (x_c):	90.0%
Maximum Physical Recovery of Pure Enantiomer:	50.0%

Table 5
Pure components data for Fig. 2

T_1	55.0°C
ΔH_1	23.419 kJ/mol
T_2	55.0°C
ΔH_2	23.419 kJ/mol

Table 6
Temperature versus composition using data from Tables 4 and 5

Mole Fraction	Temperature Given by Schroeder-van Laar or Prigogine-Defay Equations		
	SVL1	SVL2	PD
0.00	55.000		
0.05	53.053	-29.829	26.081
0.10	51.025	-14.352	36.584
0.15	48.908	-4.349	42.626
0.20	46.693	3.230	46.693
0.25	44.368	9.410	49.596
0.30	41.920	14.669	51.704
0.35	39.332	19.270	53.209
0.40	36.585	23.377	54.222
0.45	33.652	27.096	54.808
0.50	30.503	30.503	55.000
0.55	27.096	33.652	54.808
0.60	23.377	36.585	54.222
0.65	19.270	39.332	53.209
0.70	14.669	41.920	51.704
0.75	9.410	44.368	49.596
0.80	3.230	46.693	46.693
0.85	-4.349	48.908	42.626
0.90	-14.352	51.025	36.584
0.95	-29.829	53.053	26.081
1.00		55.000	

SVL = Schroeder-van Laar equation used
PD = Prigogine-Defay equation used

Table 7
Alternative method of calculating eutectic and recovery

R_{max}	Equation:	SVL	PD
	T_i/°C:	55.0	55.0
	ΔH_i:	23.419	23.419
	Starting Composition :	90.00%	10.00%
	Eutectic Mpt: 46.7 °C. Composition:	80.00%	20.00%
50.00%	Composition After Eutectic Removal:	100.00%	0.00%

SVL = Schroeder-van Laar equation used
PD = Prigogine-Defay equation used

Using the methodology outlined above it is possible to calculate the maximum yield of pure component from the mixture by DSC analysis. Note that use has been made of the Prigogine–Defay equation for the enantiomeric pairs A/B and C/D. It is statistically likely that the enantiomeric systems behave as racemic compounds since 90% of racemates belong to this classification. Additionally it is assumed that the diastereomeric relationships are characterized by conglomerate behaviour.

The most common method for determining conglomerate or racemic compound behaviour is by comparison of the solid phase infrared (IR) spectra of the enantiomerically pure compound and the racemate. Since the conglomerate is a mechanical mixture of enantiomeric crystals, the IR spectra will be identical within the variation of sample preparation, whereas the racemic compound will most

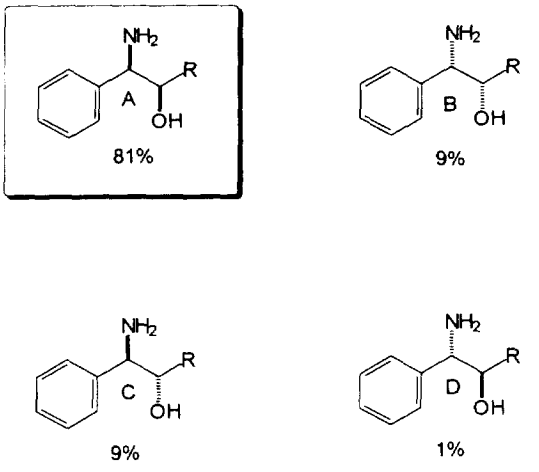

Fig. 3.

Table 8
Multicomponent eutectic/recovery calculation involving racemic compound and conglomerate behaviour

Recoveries	Component :	A	B†	C	D†
	Equation:	SVL	PD	SVL	PD
	MPt (T_i)/ °C:	117.6	128.9	144	128
	Heat of Fusion (ΔH_i):	31.6000	28.7000	29.7738	28.6314
	Starting Composition :	81.0%	9.0%	9.0%	1.0%
	Eutectic Mpt: 95.7 °C, Composition:	56.05%	5.63%	32.43%	5.89%
83.02%	Composition After Eutectic Removal:	86.10%	9.69%	4.21%	0.00%
	Eutectic Mpt: 97.8 °C, Composition:	59.42%	6.31%	34.27%	0.00%
87.73%	Composition After Eutectic Removal:	89.84%	10.16%	0.00%	0.00%
	Eutectic Mpt: 111.9 °C, Composition:	86.49%	13.51%	0.00%	0.00%
24.78%	Composition After Eutectic Removal:	100.00%	0.00%	0.00%	0.00%

† Note that the minor component of the enantiomeric pair specifies the use of the Prigogine Defay equation (*cf.* the example calculation in Table 7) and that T_B, ΔH_B, T_D, ΔH_D data are obtained from the respective racemates and generally differ from the data associated with the enantiomers
SVL = Schroeder-van Laar equation used
PD = Prigogine-Defay equation used

Cumulative Recovery = 18.05%

likely display observable differences. Additionally, conglomerate behaviour may be anticipated when the racemate melts 25–30°C lower than the enantiomerically pure compound.

The results of the calculation based on melting point and heat of fusion data are presented in Table 8.

The product of the recoveries, from each discrete purification step, gives an overall maximum theoretical recovery of 18.05%. This would no doubt make the economics of purification by crystallization wholly unacceptable.

The calculation has been repeated assuming that the enantiomers behave as conglomerates (Table 9) where it may be seen that a significant increase in the maximum recovery is predicted.

Fortunately, with the functionality described in Fig. 3 there are options for modifying the physical properties of the system in order to maximize recovery of desired isomer A. These fall into two obvious categories: (i) formation of salts with an achiral acid, and (ii) formation of salts with a homochiral acid (covalent derivatives are not considered here though are equally applicable). The former is advantageous due to the array of inexpensive organic and inorganic acids available. However, the approach suffers from limitations associated with enantiomeric relationships displaying symmetry in the eutectic, or racemic

Table 9
Multicomponent eutectic/recovery calculation assuming conglomerate behaviour

Recoveries	Component:	A	B	C	D
	Equation:	SVL	SVL	SVL	SVL
	MPt (T_i)/ °C:	117.6	117.6	144	144
	Heat of Fusion (ΔH_i):	31.6000	31.6000	29.7738	29.7738
	Starting Composition :	81%	9%	9%	1%
	Eutectic Mpt: 75.9 °C, Composition:	31.28%	31.28%	18.72%	18.72%
94.66%	Composition After Eutectic Removal:	83.81%	7.74%	8.45%	0.00%
	Eutectic Mpt: 82.8 °C, Composition:	38.59%	38.59%	22.82%	0.00%
79.94%	Composition After Eutectic Removal:	95.16%	0.00%	4.84%	0.00%
	Eutectic Mpt: 100.2 °C, Composition:	63.51%	0.00%	36.49%	0.00%
86.72%	Composition After Eutectic Removal:	100.00%	0.00%	0.00%	0.00%

SVL = Schroeder-van Laar equation used.
Note also that T_B, ΔH_B, T_D, ΔH_D are associated with the enantiomers (*cf.* Table 8)

Cumulative Recovery = 65.62%

Table 10
Multicomponent eutectic/recovery calculation of a hypothetical achiral salt assuming conglomerate behaviour

Recoveries	Component:	A	B	C	D
	Equation:	SVL	SVL	SVL	SVL
	MPt (T_i)/ °C:	275	275	207	207
	Heat of Fusion (ΔH_i):	39.1272	39.1272	34.2720	34.2720
	Starting Composition :	81%	9%	9%	1%
	Eutectic Mpt: 160.4 °C, Composition:	10.31%	10.31%	39.69%	39.69%
97.48%	Composition After Eutectic Removal:	82.83%	8.97%	8.21%	0.00%
	Eutectic Mpt: 183.5 °C, Composition:	17.88%	17.88%	64.25%	0.00%
87.23%	Composition After Eutectic Removal:	92.34%	7.66%	0.00%	0.00%
	Eutectic Mpt: 234.1 °C, Composition:	50.00%	50.00%	0.00%	0.00%
84.68%	Composition After Eutectic Removal:	100.00%	0.00%	0.00%	0.00%

SVL = Schroeder-van Laar equation used

Cumulative Recovery = 72.0%

compound behaviour. Use of a homochiral acid does not suffer from these limitations since all four derivatives will now be related diastereomerically and the possibility exists to find a system where all unwanted isomers are the major components of the eutectic. This may be readily understood by the somewhat extreme assumption that the derivative of component A has a melting point in excess of 100°C and the unwanted diastereomers are liquids at room temperature. One anticipates separation of the unwanted components by solvent wash would be effective with minimal loss of component A.

The following example calculation assumes that an achiral salt (such as a hydrochloride) has been formed (Table 10). The enantiomeric components behave as conglomerates and as before one assumes conglomerate behaviour for the diastereomeric relationships. A significant improvement in maximum recovery is predicted at 72.0%. This is a consequence of the lower melting point of the C/D diastereomers (the converse situation was described in Table 9). The desired component along with the enantiomer B consequently forms the minor components of the eutectic.

For completeness, calculation assuming a homochiral salt formation is presented in Table 11. Here it is assumed that a system has been found where the desired component forms the higher melting diastereomer which maximizes recovery on crystallization. Again conglomerate behaviour has been assumed and the Schroeder–van Laar equation employed. The calculation implies that nearly all of the component A may be accessed via crystallization with less than 0.5% lost to the mother liquors. However,

Table 11
Multicomponent eutectic/recovery calculation of a hypothetical chiral salt assuming conglomerate behaviour

Recoveries	Component:	A	B	C	D
	Equation:	SVL	SVL	SVL	SVL
	MPt (T_i)/ °C:	250	95	120	131
	Heat of Fusion (ΔH_i):	37.3422	26.2752	28.0602	28.8456
	Starting Composition :	81%	9%	9%	1%
	Eutectic Mpt: 68.3 °C, Composition:	1.03%	51.08%	27.23%	20.65%
95.16%	Composition After Eutectic Removal:	85.07%	6.86%	8.07%	0.00%
	Eutectic Mpt: 76.8 °C, Composition:	1.42%	63.96%	34.62%	0.00%
89.28%	Composition After Eutectic Removal:	95.12%	0.00%	4.88%	0.00%
	Eutectic Mpt: 117.5 °C, Composition:	5.42%	0.00%	94.58%	0.00%
94.84%	Composition After Eutectic Removal:	100.00%	0.00%	0.00%	0.00%

SVL = Schroeder-van Laar equation used

Cumulative Recovery = 80.57%

it would be prudent to consider the additional cost of the homochiral acid compared with the increased yield over and above the system described in Table 10.

3.4. *Deviations from the ideal approximation*

Initially it was stated that the system of interest may be described by the Schroeder–van Laar equation. This implies that the components crystallize with a unit cell composed of the pure component and form a completely miscible system in the solid state. The simplified Schroeder–van Laar equation neglects specific heat capacity terms.[3] Additionally, use of the Schroeder–van Laar equation in the manner described implies that the heat of fusion of the components is invariant over the temperature range of interest.

A common deviation of conglomerate behaviour in enantiomeric systems relates to an additional compound known as the racemic compound. Fortunately, it is straightforward to determine if the system in hand corresponds to this category and calculation incorporating racemic compound behaviour is easily accommodated by use of the Prigogine–Defay equation. However, it may be the case that other addition compounds form part of the system,[9] in which case deviations from the simple model discussed above will be noted.

In the case of enantiomeric systems, a third category of crystalline system is described as the pseudoracemate or solid solution. This situation is rare but is particularly prevalent among molecules forming plastic crystals leading to rotationally disordered lattice structures made up of spheroidal molecules.

Building on the illustration in Fig. 3, consider the formation of salts with dibasic acids (e.g. tartaric acid or sulphuric acid). One may find that there is the preponderance for some of the components to form a monobasic salt, whereas others may form a dibasic salt. Other factors such as polymorphism and significant differential interaction of isomers with certain solvents will lead to deviations from the predicted behaviour. The latter may be anticipated where situations such as conformational constraints may allow intramolecular hydrogen bonding in only one stereoisomer.

In order to evaluate the benefits of the approach described, given the fact that deviations from ideal behaviour will occur, it is appropriate to clarify the intent of the approach. The methodology provides a quick method to calculate the efficiency of a purification by crystallization via readily accessible physical data, namely IR and DSC analysis. Where the chemical nature of the system permits, one may rapidly prepare a series of derivatives of the pure components and rank in order of yield of purification compared

with the cost of derivatization. One may then select a short list of systems where the ideal approximation indicates acceptable yield and undertake a further laboratory evaluation in order to optimize recovery of pure component. Deviations from the predicted behaviour may well be noted and one can expect the real system to fall short of the predicted ideal yield.

Will the method discard a system on the basis of the ideal approximation when the real system will perform significantly better? This may occur, but given the myriad of interactions in the real world, is it likely that synergy will provide the chemist with a significantly improved recovery of pure isomer? It is arguable that this is less likely than the real system falling short of the ideal prediction.

4. Conclusion

A simple method for evaluating the maximum recovery of pure compound from a mixture of stereoisomeric components has been described and comprises DSC analysis for the pure components or racemate as applicable. This relies on the assumption of ideal conglomerate or racemic compound behaviour, that the n-dimensional eutectic is more soluble than the $(n-1)$-dimensional eutectic and that the differential solubility of the stereoisomeric components is invariant in the choice of solvent. A comparison with previously published multicomponent eutectics as defined by the Schroeder–van Laar equation and results using the standard approach to solution of the Prigogine–Defay equation confirm the strategy described in the summary listing.

The results of a series of example calculations have been set out for explanatory purposes and as a mechanism for cross checking any actual program developed from the summary listing.

It is argued that a real system studied is more likely to fall short of the predicted ideal behaviour than the converse. It therefore seems reasonable that the approach may be used to prioritize laboratory study to optimize the crystallization process for yield and quality.

Appendix A. Summary listing

Read the starting composition to the array x_i (determine how many components there are and whether to use the Schroeder–van Laar equation or Prigogine–Defay equation for a specified component)
For i=1 **To** NoOfComponents (check to see which component has the highest melting point to define a convenient starting point for T)
Next i
Do
Initialize appropriate parameters, variables, arrays and constants
Do
For i=1 **To** NoOfComponents
IF conglomerate use $x_{\mathrm{eu}_i} = \exp\left(\frac{\Delta H_i}{\mathrm{R}}\left[\frac{1}{T_i} - \frac{1}{T}\right]\right)$
Or use ... $x_{\mathrm{eu}_i} = \frac{-4+\sqrt{16-16\exp\left(\frac{2\Delta H_i}{\mathrm{R}}\left[\frac{1}{T_i}-\frac{1}{T}\right]\right)}}{-8}$ for a racemic compound (note that additional code will be required to avoid errors from $\sqrt{-1}$)
Total up the components of the eutectic (SumOfX_{eu}s)
Next i

If SumOfX_{eu}s is equal to 1 **Then** Convergence=**True**
Else decrement T (Convergence=**False**)
End If
Loop Until Convergence
For i=1 **To** NoOfComponents
Which component has the maximum value calculated by x_{eu_i}/x_i? [Code will be necessary to avoid division by zero errors. Note also that a previous pass could remove more than one component in only one pass. This situation will occur when components are degenerate (e.g. enantiomers)]
On the basis of above set the array pointer LocationOfKeyComponent
Next i
Set up a scale factor by Factor=x_{eu}(LocationOfKeyComponent)/x(LocationOfKeyComponent)
For i=1 **To** NoOfComponents
Scale the composition according to x_i=Factor×x_i
TotalOfScaledXs=TotalOfScaledXs+x_i
Next i
For i=1 **To** NoOfComponents
Subtract the eutectic from the scaled mixture according to $x_i=x_i-x_{eu_i}$
SumAfterSubtraction=SumAfterSubtraction+x_i
Next i
Recovery=SumAfterSubtraction/TotalOfScaledXs
CumulativeRecovery=CumulativeRecovery×Recovery
Decrement NoOfComponents as appropriate — reduce the dimensionality
Write new composition by x_i/SumAfterSubtraction
[which for clarity is normalized to $\sum_{i=1}^{\text{NoOfComponents}} x_i = 1$
This new composition will be the starting point for the next cycle]
Write Recovery
If more than one component left **Then** Finished=**False**
Else Finished=True
Loop Until Finished (i.e. only one component left — purification achieved)
Write CumulativeRecovery
End

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