Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 869–872
Tetrahedron Letters

A measure of the solid-solution extent useful for crystallisation resolution studies

Raymond McCague*

McCague Scientific Consulting, 77 The Footpath, Coton, Cambridge CB23 7PX, UK

Received 19 October 2006; revised 14 November 2006; accepted 22 November 2006
Available online 19 December 2006

Abstract—The ratio of partition coefficients of molecular components between crystal and liquor phases gives a measure of the solid-solution extent, termed *D*. This measure is considered useful to compare the results of resolution experiments and to make predictions of the crystal composition obtained under different starting compositions and crystal yields. The calculations show that a small extent of solid solution (e.g., 0.1%) can have a noticeable effect, and that the maximum efficiency of a resolution in certain cases is determined by the solid-solution extent rather than by the eutectic composition with the opposite isomer.

Crystallisation methods are highly important industrially for resolution and purification.[1] Yet their effectiveness is often limited because the crystals obtained retain some of the unwanted component(s). This may be the result of solid-solution formation whereby the crystalline lattice can partially accommodate molecules of impurity in place of those of the required compound. This scenario is particularly commonplace in resolutions of stereoisomers where structural similarity allows easy molecule substitution in the crystal lattice, and especially in classical resolution, where a racemate is resolved via formation of diastereoisomeric salts with a chiral acid or base resolving agent.[2]

In screening for a crystallisation method, it is valuable to have a measure of solid-solution extent in order to compare results, and thereafter to predict the outcome of performing a separation with a different starting composition. Figure 1 depicts the composition distribution between a crystalline and liquid phase according to the mole fractions *X*, of two molecular components A and B (subscripts), where A is the desired compound, and B the impurity. These components will partition between the crystal and liquor phases (superscripts C and L) according to partition coefficients p_A and p_B. It is apparent that if there is no solid solution then B will be entirely in the liquid phase and $p_B = 0$, whilst if the crystal phase cannot distinguish the components at all, then $p_B = p_A$. Consequently, a measure of the solid-solution extent, herein termed *D*,[3] in the range of 0–1 (or 0–100%) is given by Eq. 1[4]

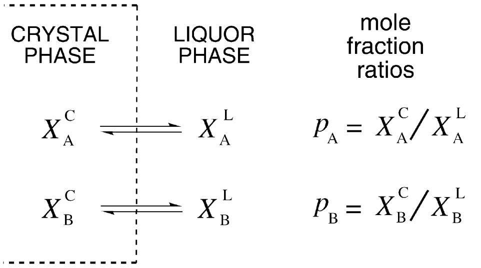

Figure 1. Distribution of mole fractions of two compounds A and B between a solid-solution crystal phase and a liquor phase.

$$D = \frac{p_B}{p_A} = \frac{X_B^C}{X_B^L} \cdot \frac{X_A^L}{X_A^C} \tag{1}$$

Given that the mole fractions in each phase must add to unity, the equation can be transformed to give the mole fraction of unwanted component in the crystals (X_B^C) compared to that in the associated liquors (X_B^L) of a crystallisation experiment at a different composition, that is, Eq. 2.[5] This is useful for predicting the outcome, once a value for the coefficient *D* has been established:

$$X_B^C = \frac{D \cdot X_B^L}{1 - X_B^L \cdot (1 - D)} \tag{2}$$

---

* Tel.: +44 1954 211122; fax: +44 1954 211616; e-mail: rmccague@mcc-sci.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.131

The treatment can be applied in principle to any crystallisation separation or purification, for example, to remove a process related impurity, but for resolution of enantiomers the composition is conventionally expressed as the enantiomeric excess, or in the case of classical resolution studies, as the diastereoisomeric excess (de) of the salts. Then, the corresponding relationships to obtain or use the coefficient D are given, respectively, by Eqs. 3 and 4. So for example, at $D = 10\%$, crystals of 81.8% de will be derived from liquors of racemic composition ($\mathrm{de}^{\mathrm{L}} = 0$). In using Eq. 3, de^{C} must always be entered as positive, and in both, de^{L} should be entered as negative if the liquors are enriched in the opposite isomer to the crystals:

$$D = \frac{(1 + \mathrm{de}^{\mathrm{L}}) \cdot (1 - \mathrm{de}^{\mathrm{C}})}{(1 + \mathrm{de}^{\mathrm{C}}) \cdot (1 - \mathrm{de}^{\mathrm{L}})} \tag{3}$$

$$\mathrm{de}^{\mathrm{C}} = \frac{2 - (1 - \mathrm{de}^{\mathrm{L}}) \cdot (1 + D)}{2 - (1 - \mathrm{de}^{\mathrm{L}}) \cdot (1 - D)} \tag{4}$$

The usefulness of the measure is dependent upon the value of D remaining essentially constant across the range of compositions of interest. In this regard, comparison may be made with the experimental data reported for diastereoisomers of (R)-α-methylbenzylammonium mandelate.[6] This is a worthy example because the solid-solution extends across the full range of compositions. Table 1 shows that with three crystal compositions de^{C}, the corresponding calculated values of liquor composition de^{L} when $D = 12\%$ lie very close to the experimentally reported values.

In a resolution process starting from the racemate, the composition of the liquors will become increasingly enriched in the unwanted isomer as the desired isomer crystallises, and in turn this will affect the crystal composition. If the approximations are made that (i) the solid-solution extent value D remains constant through the range of compositions of the resolution and (ii) that sufficient time is given for the crystal composition to equilibrate with that of the liquors, then Eq. 5 can be derived[7] incorporating the crystal yield R. At selected values of D, the crystal and liquor compositions are thereby charted according to Figure 2.[8] For example, it is seen that a diastereoisomeric salt showing $D = 10\%$ would, at a 50% yield, give crystals and liquors of 52% de. It is also apparent that even a very small extent of solid solution will have a noticeable effect on the resolution; thus at $D = 0.1\%$ and 50% yield the crystals obtained are somewhat below stereopurity at 94% de:

$$\mathrm{de}^{\mathrm{C}} = \frac{Q - \sqrt{Q^2 - 4R \cdot (1 - R)}}{2R} \quad \text{where } Q = \frac{1 + D}{1 - D} \tag{5}$$

Table 1. Comparison with experimental data[6] for (R)-α-methylbenzylammonium (S)- or (R)-mandelate (in water at 10 °C)

de^{C} (%)	de^{L} experimental (%)	de^{L} calculated (%)
78	0	−2
−14	−86	−84
−40	−90	−90

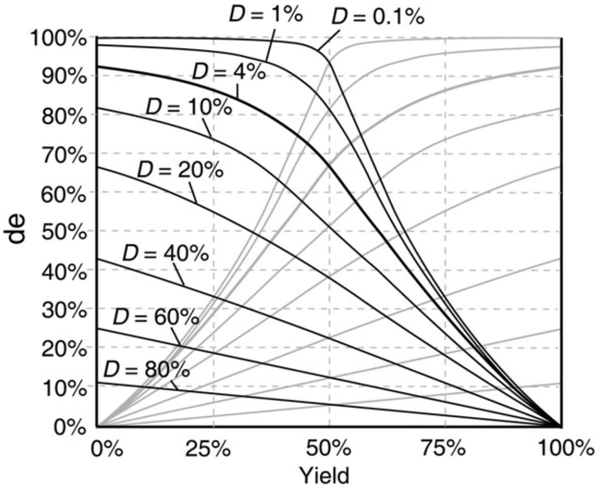

Figure 2. Calculated variation of de with yield for various extents of solid-solution formation of a diastereoisomeric salt starting from racemic (de = 0%) composition; black curves labelled with D-value are crystal de; matching grey curves are liquor de.

The treatment may be extended to the scenario of starting with a non-racemic composition; this is relevant to recrystallising the salt obtained from an initial resolution. Figure 3 plots the relationship of de against crystal yield for different starting compositions (de^0) in the case of a diastereoisomeric salt with a solid-solution extent of $D = 4\%$.[9,10] Here for example, 80% de salt obtained from an initial resolution (in 38% yield) would recrystallise up to 96% de in 75% yield.

For this purpose, the relationship of crystal de to yield is given more generally by Eq. 6.[11] By substituting enantiomeric excesses (ee) for the de values, the equation also applies to purification by recrystallisation of *enantiomerically* enriched material obtained from cracking of

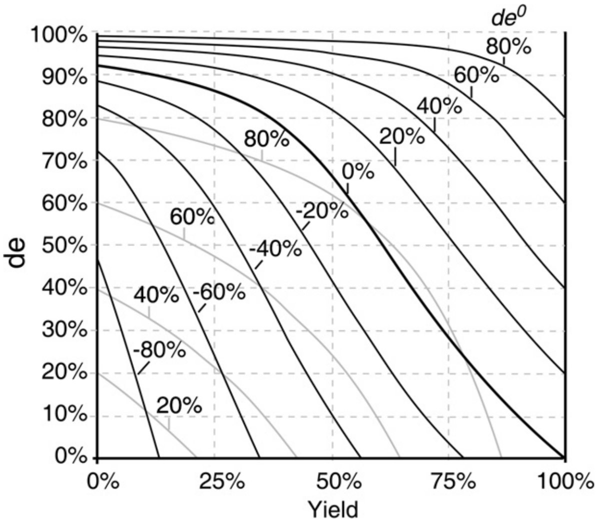

Figure 3. Calculated variation of de with yield for various starting compositions (de^0) of a diastereoisomeric salt at a solid-solution extent $D = 4\%$; black curves are crystal de; grey curves are liquor de. Data are shown only for resultant de values in favour of the less-soluble isomer.[10]

the salt, or obtained by other means, such as from asymmetric synthesis:

$$\mathrm{de}^{\mathrm{C}} = \frac{Q + \mathrm{de}^0 - \sqrt{(Q + \mathrm{de}^0)^2 - 4R \cdot (1 - R + Q \cdot \mathrm{de}^0)}}{2R} \tag{6}$$

The efficiency of a classical resolution, starting with a racemate, is given by Fogassy's parameter, $S = 2 \cdot R \cdot \mathrm{de}^{\mathrm{C}}$.[12] By Eq. 5 above, for a single-crystal-phase solid solution, the maximum value of this parameter ($S_{\max}$) is reached when the yield $R = 50\%$ and is given by Eq. 7. As a transposition of the value of D, this $S_{\max}$ value may be termed D'. The mapping of D to D' is displayed in Figure 4 but this is shown only for values of D up to 20% because a higher solid-solution extent is unlikely to give a workable resolution. The steep rise in the curve at a low D-value (<1%) further shows the sensitivity of the resolution efficiency to a small extent of solid-solution formation:

$$D' = S_{\max} = \mathrm{de}^{\mathrm{C}} = \frac{1 + D - 2\sqrt{D}}{1 - D} \quad \text{at } R = 0.5 \tag{7}$$

Just as D is the ratio of partition coefficients between the crystals and liquors, so it is in principle the ratio of the solubilities of the end-member compositions (of entirely A or B) of the solid-solution crystal form.[13] This approximation enables phase-diagrams to be simulated once a value of D is established. For the earlier mentioned literature example of α-methylbenzylammonium mandelate,[6] solubilities of the salts were 34 and 230 g/kg, which would imply $D = 15\%$, reasonably close to the value of $D = 12\%$ used to match the crystal versus liquor de data. In the case where the solid-solution extent is small, the solubility of the end-member composition of entirely impurity B will be high, and it is likely to be of virtual existence only. In that event, crystallisation from a mixture containing a high proportion of B will usually deposit in addition, another crystal form, essentially comprising of molecule B. This is revealed as two solubility (liquidus) lines on the ternary phase diagram, which intersect at a eutectic composition of maximum solubility. Such a ternary phase diagram is computed according to Figure 5. The measurement of the solid-solution extent according to the coefficient D then applies only for compositions in which a single-crystal form deposits, that is before the eutectic is reached. In purification of an enantiomer (as opposed to a diastereoisomer), the measurement likewise applies provided the composition is such that only the single-enantiomer crystal form deposits, that is not together with its enantiomeric crystal form or a racemic-compound crystal form.

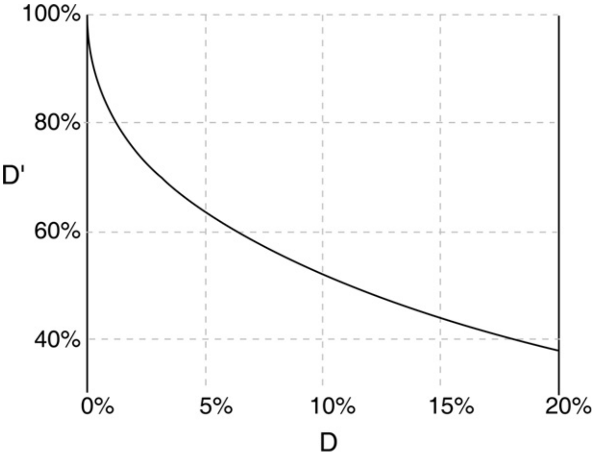

Figure 4. Calculated variation of the maximum resolution efficiency D' for a solid-solution extent D.

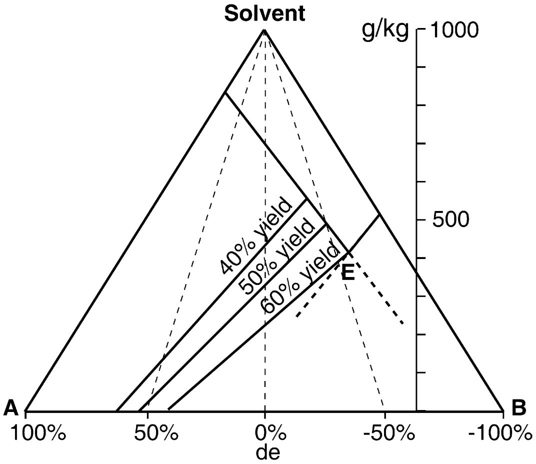

Figure 5. Calculated ternary phase diagram of a pair of diastereoisomeric solid solutions each of $D = 10\%$ having pure-diastereoisomer solubilities of 160 and 480 g/kg. E marks the eutectic composition at the intersection of the solubility lines. Tie lines are given corresponding to starting at 1:1 isomers ($\mathrm{de}^0 = 0\%$) at crystal yields of 40%, 50% and 60%.

In the scenario of a classical resolution with no solid solution (for either diastereoisomer), where there are two crystal forms (of A and B), a eutectic composition exists, and if equilibrium is reached, then the maximum resolution efficiency is attained when the yield of crystallisation is such that the liquors first reach this eutectic composition. This yield will be less than 50%. However, with a solid solution, the eutectic is not reached until a higher crystal yield. This is evident from Figure 5, which represents a situation of diastereoisomeric salts with solid-solution extents of $D = 10\%$, where tie lines have been added to represent the composition distribution at crystal yields of 40%, 50% and 60%. Of these, only the 60% yield situation reaches liquors of eutectic composition, yet the maximum resolution efficiency in this case will have been arrived at 50% yield, due to the effect of the solid solution. Consequently, it is evident that the maximum performance of a resolution may be dictated either by the composition of the eutectic (if that is reached at <50% yield) or by the extent of solid solution otherwise.

Whilst, giving a measure of solid-solution extent, the value of D, readily calculated from the crystal and liquor compositions, should be useful generally as a measure of the relative distribution of two chemical components (especially isomers) between phases, regardless of the reason for the distribution. For instance, it may measure insufficiency of crystal purity caused by such phenomena as crystal defects, mother liquor inclusion, or contamination by other crystal forms. The value of D may be measured to compare results of experiments, or be used to predict the outcome of new experiments. Likewise, its transposed value D' is useful as a measure of the extent of divergence of composition between the phases, reaching 100% when that divergence is complete. The D' value should thus be a useful complementary measure of resolution efficiency alongside the Fogassy parameter, S. The treatment should also be useful as an additional component to mathematical models of crystallisation equilibria[14,15] in order that they may accommodate sub-standard crystal stereopurity. With regard to the variable thermodynamics of solid solutions, the value of D might be found to be not quite constant with change of composition; the deviation could then be useful to give information on the particular thermodynamic nature of the solid-solution concerned.[16]

Supplementary data

Derivations of the various equations used in this Letter are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.131.

References and notes

1. Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Sturmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824.
2. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Krieger: Malabar, 1981, reprinted 1994; pp 104–131, 299–301.
3. The use of D herein for 'Distribution' should not be confused with its use as a diffusion coefficient in kinetics studies.
4. A simpler coefficient ($X_{\mathrm{B}}^{\mathrm{C}}/X_{\mathrm{B}}^{\mathrm{L}}$) has been used to measure the limit of miscibility in terminal solid solutions; this approaches equality to D as defined herein when at small $X_{\mathrm{B}}^{\mathrm{C}}$ values Beckmann, W.; Lorenz, H. *Chem. Eng. Technol.* **2006**, *29*, 226–232.
5. The equation may alternatively be expressed in terms of the desired isomer 'A' as

$$X_{\mathrm{A}}^{\mathrm{C}} = \frac{X_{\mathrm{A}}^{\mathrm{L}}}{X_{\mathrm{A}}^{\mathrm{L}} \cdot (1 - D) + D}.$$

6. Leclercq, M.; Jacques, J. *Bull. Soc. Chim. Fr.* **1975**, 2052–2056, The experimental figures used are measured from the ternary phase diagram therein.
7. See the Supplementary data for the derivation of equations.
8. All the calculations in this letter concerning yield assume that there is no interconversion between the diastereoisomers (via racemisation). Then, given the crystal de, the liquor de can be readily calculated from the yield according to

$$\mathrm{de}^{\mathrm{L}} = \frac{\mathrm{de}^{0} - R \cdot \mathrm{de}^{\mathrm{C}}}{1 - R}.$$

9. The opposite sign of de^{L} compared with de^{C} has been ignored in plotting Figure 2 but not Figure 3.
10. The complete diagram of Figure 3 will range from −100% to +100% de; however the diagram is semi-symmetric by a 180° rotation such that at a given yield the crystal de corresponds to that of minus the liquor de from minus the starting de.
11. The coefficient Q is as defined in Eq. 5, to which Eq. 6 reduces if $\mathrm{de}^0 = 0\%$.
12. Fogassy, E.; Lopata, A.; Faigl, F.; Darvas, F.; Acs, M.; Toke, A. L. *Tetrahedron Lett.* **1980**, *21*, 647–650.
13. By an alternative derivation of coefficient D, the propensity of the end-members A and B of the solid solution to crystallise is in the proportion $X_{\mathrm{A}}^{\mathrm{L}}$ to $D \cdot X_{\mathrm{B}}^{\mathrm{L}}$; then the proportion of compound B in the crystal is given by: $D \cdot X_{\mathrm{B}}^{\mathrm{L}}/(X_{\mathrm{A}}^{\mathrm{L}} + D \cdot X_{\mathrm{B}}^{\mathrm{L}})$, which is Eq. 2. At the solubility equilibrium, the propensity of A and B to crystallise will be equal so $X_{\mathrm{A}}^{\mathrm{L}} = D \cdot X_{\mathrm{B}}^{\mathrm{L}}$, which gives D as the ratio of solubilities.
14. Ferreira, F. C.; Ghazali, N. F.; Cocchini, U.; Livingston, A. G. *Tetrahedron: Asymmetry* **2006**, *17*, 1337–1348.
15. Smith, A. A.; McKay, B.; Damen, E. W. P.; Darphorn-Hooijschuur, S.; Ras, E.-J.; Verspui, G. *Org. Process Res. Dev.* **2006**, *10*, 1132–1143.
16. The thermodynamics of solid solutions involving various enthalpic and entropic contributions is complex and several different types of solid solution may be characterised. A treatment of solid-solution thermodynamics as applied in the field of mineralogy is given in Ganguly, J. *EMU Notes Mineral.* **2001**, *3*, Chapter 3, 37–69.