Notes

Enhancement of Optical Activity by Fractional Sublimation. An Alternative to Fractional Crystallization and a Warning

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Fractional crystallization is most often used to separate an enantiomorph from its racemate after partial resolution. We inadvertently discovered that it is possible to effect such separation for bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxylic acid (1) via fractional sublimation. To our knowledge, the only other report of the separation of an enantiomorph from its racemate by sublimation was the accidental discovery by Kwart and Hoster for α-ethylbenzylphenyl sulfide.[1] We wish to dramatize the fact that the original report did not involve a unique example, to encourage the use of this technique, and to dramatize *the possibility of fractionation which may result from partial sublimation of optically active samples.*

Results and Discussion

As a representative example, 100 mg of 1 ($[\alpha]^{23}$D −310°, 73% optical purity[2]) was placed in a glass tube at reduced pressure (10 mm) and inserted into a temperature gradient oven (ca. 54 to 38 °C distributed over a 40-cm length). After 26 h, the solid material was distributed along the walls of the tube. The tube was cut to separate samples. The distribution by weight and rotation is shown in Table I. We recovered 93% of the original sample which can account for 92% of the original activity, strongly suggesting that neither rearrangement or new product formation had occurred.

We have also resorted to partial sublimation in a standard apparatus to obtain highly enriched optically active material. Starting with an 8.0-g sample of 1 of 40% optical purity ($[\alpha]^{23}$D +170°), we observed that the first 1.85 g of material to sublime had an optical purity of 64% ($[\alpha]^{23}$D +270°). Partial sublimation of this material gave 0.50 g of 1 of 85% optical purity ($[\alpha]^{23}$D +360°). As reported in the case of α-ethylbenzylphenyl sulfide, it is necessary for the sample of 1 to be in the crystalline state for separation of the enantiomorph and racemate to occur. Infrared and ^{1}H NMR analyses of samples were used to demonstrate that neither rearrangement or new product formation had occurred. Thus, we must conclude that the enantiomer preferentially sublimed from its mixture with the racemate.

The enantiomer has a lower melting point than the racemate (72–73 and 89–90.5 °C, respectively). Since fusion temperature and volatility are both related to the intercrystalline forces, when dealing with enantiomeric mixtures *the modification with the lowest melting point should exhibit the greater volatility and should sublime preferentially.* This interpretation is in accord with the data reported for α-ethylbenzylphenyl sulfide and for 1.

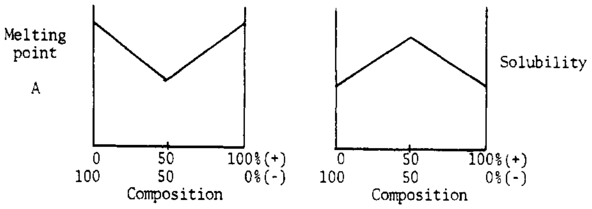
Typical melting point vs. composition curves and solubility vs. composition curves are shown in Figure 1 for racemic mixtures, racemic compounds, and racemic solid solutions (curves A, B, and C, respectively).[3] These solubility vs. composition curves can be used to predict the results of fractional crystallization. Curve A predicts that the less soluble enantiomorph can be obtained by crystallization leaving the racemic modification in solution. Curve B predicts that *either* the racemic modification *or* the enantiomorph can be obtained by crystallization depending upon the initial composition of the mixture with the eutectic modification being most soluble. Mixtures exhibiting curve C behavior cannot be separated by fractional crystallization.

We have attempted to use melting point vs. composition curves to predict the results of fractional sublimation of mixtures of optical antipodes. To do this, we sought readily available optically active compounds with high optical rotations that exhibited large differences in melting point between enantiomeric and racemic modifications. We chose mandelic acid (2), whose melting point vs. composition curve (Figure 2) had recently been determined by DTA.[4] This is a type B curve with eutectic composition at ca. 75% mole fraction. One obvious feature of this curve is that *the eutectic composition*

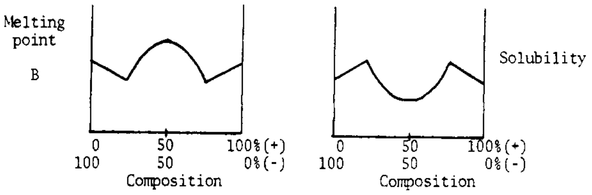
Table I. Fractional Sublimation of Bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxylic Acid (Condition 1)

Sample	Wt mg	$[\alpha]^{23}$D (95% EtOH)
Stg mat.	100	−310
Fraction 1 (28–39 cm)[a]	14.2	−373
Fraction 2 (11–27 cm)	18.6	−361
Fraction 3 (5–10 cm)	28.2	−310
Fraction 4 (0–5 cm)	32.1	−239
	93.1[b]	

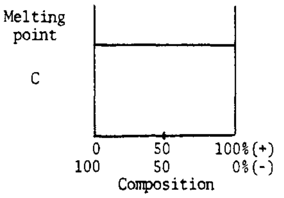
[a] Distances refer to the position of the sample along the length of the tube having migrated from point zero. [b] Material balance: 93% recovery.



(A) Melting point and solubility diagrams of racemic mixtures.



(B) Melting point and solubility diagrams of racemic compounds.
(The compound may melt at a lower point than the pure enantiomers, see Figure 2)



(C) Melting point diagram of racemic solid solution.

Figure 1. Melting point and solubility diagrams (only liquidus curves are shown).

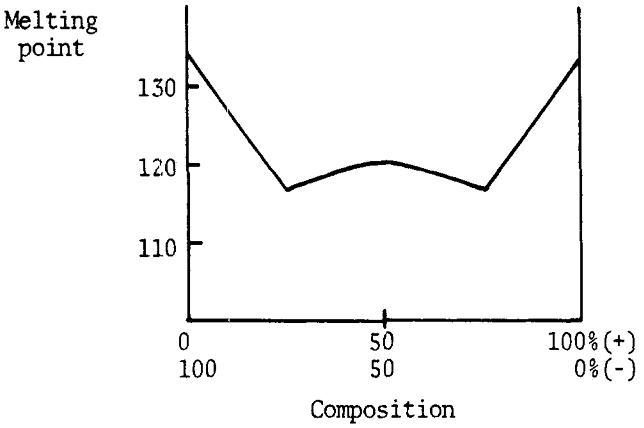


Figure 2. Melting point–composition diagram of mandelic acid.[4]

Table II. Fractional Sublimation of DL- and L-Mandelic Acid (Condition 2)

Sample	Wt, g	$[\alpha]^{23}{}_{365}$	Enantiomeric[5] purity	Mole fraction L
Stg mat.	0.2021	+118	20.7	60.3
Fraction 1	0.0437	+212	37.2	68.6
Fraction 2	0.0261	+179	31.5	65.7
Fraction 3	0.0333	+144	25.2	62.6
Fraction 4	0.0328	+91	16.0	58.0
Fraction 5	0.0641	+27	4.7	52.3
	0.2000[a]			

[a] Material balance = 99% recovery.

Table III. Fractional Sublimation of DL- and L-Mandelic Acid (Condition 2)

Sample	Wt, g	$[\alpha]^{23}{}_{365}$	Enantiomeric[5] purity	Mole fraction L
Stg mat.	0.1635	+344	60.2	80.1
Fraction 1	0.0537	+300	52.5	76.3
Fraction 2	0.0539	+354	62.0	81.0
Fraction 3	0.0315	+366	64.1	82.1
Fraction 4	0.0164	+424	74.3	87.1
	0.1555[a]			

[a] Material balance = 95% recovery.

Table IV. Fractional Sublimation of D- and L-Mandelic Acid (Condition 1)

Sample	Wt, g	$[\alpha]^{23}{}_{365}$	Enantiomeric[5] purity	Mole fraction L
Stg mat.	0.1091	+332	58.1	79.1
Fraction 1 (ca. 17 in.)[a]	0.0333	+253	44.3	72.2
Fraction 2 (ca. 11 in.)	0.0113	+339	59.4	79.7
Fraction 3 (ca. 8 in.)	0.0440	+453	79.3	89.7

[a] Distances refer to the position of the sample along the length of the tube having migrated from point zero.

Table V. Fractional Sublimation of D- and L-Mandelic Acid (Condition 1)

Sample	Wt, g	$[\alpha]^{23}{}_{365}$	Enantiomeric[5] purity	Mole fraction D
Stg mat.	0.1014	−6.8	1.20	50.6
Fraction 1 (ca. 17 in.)[a]	0.0060	−113	19.8	59.9
Fraction 2 (ca. 11 in.)	0.0045	0.0	0.0	50.0
Fraction 3 (ca. 8 in.)	0.0671	0.0	0.0	50.0
Fraction 4 (ca. 5 in.)	0.0165	0.0	0.0	50.0
	0.0941[b]			

[a] Distances refer to the position of the sample along the length of the tube having migrated from point zero. [b] Material balance = 93% recovery.

Table VI. Fractional Sublimation of *dl*- and *d*-Camphoric Acid

Sample	1.2100 g	$\xrightarrow{1}$ 0.2600 g	$\xrightarrow{2}$ 0.0094 g
$[\alpha]^{23}{}_{365}$	59		96
Enantiomeric[5] purity	41		67
Mole fraction *d*	71		83

is predicted to preferentially sublime regardless of the initial composition unless it is pure racemate or pure enantiomer.

Results Using Mandelic Acid. We prepared mixtures of varying composition using D-, L-, and DL-mandelic acid. The mixtures were subjected to fractional sublimation both in the temperature gradient apparatus described above (condition 1) and in a standard sublimation apparatus via continual interruption of the sublimation followed by collection of sublimate samples (condition 2). Our results are in agreement with our predictions based on the melting point vs. composition curves. When we started with a 60.3% mole fraction composition (which is between eutectic and racemic compositions), the initial sublimate approached eutectic composition (higher optical rotation, see Table II). Successive fractions approached racemic composition (lower optical rotation). Alternatively, in two experiments when we started with a mole fraction composition which was between eutectic and enantiomeric compositions (80.1 and 79.1%) the initial sublimate approached eutectic composition (lower optical rotation, see Tables III and IV), with successive fractions approaching enantiomeric composition (higher optical rotation). Note that in Table II, the 99% of recovered starting material can account for 98% of the initial optical activity; in Table III, the 95% of recovered starting material can account for 95% of the initial optical activity. Thus, it is obvious that racemization cannot account for these results in the absence of rearrangement or new product formation. As further proof that neither rearrangement nor new product formation is occurring, we obtained rotations at three wavelengths (546, 436, 365 nm) for several samples. The ratios of rotations at different wavelengths for these samples were consistent within 1%.

It is often extremely difficult to obtain material of high optical purity when working with small amounts of material of low optical purity. To test the utility of fractional sublimation, we prepared a sample of 101 mg of mandelic acid of 1.2% enantiomeric purity[5] (50.6% mole fraction D). The excess enantiomer (as the eutectic) sublimed preferentially, allowing us to concentrate the active material quickly and cleanly (see Table V). The isolated 6-mg sample contained virtually all of the excess enantiomer initially present in the 101-mg sample. Attempts to perform this separation via fractional crystallization would have resulted in the initial crystallization of the racemate, the active material remaining in the crystallizing solvent until final concentration.

We attempted to use fractional sublimation in similar fashion with camphoric acid, whose melting point vs. composition curve has been reported[7] (type B curve with eutectic composition at ca. 93.5% mole fraction). Results were not as satisfactory although the trend followed the predictions of the model. We made an attempt to determine the eutectic point by two simple sublimations starting with 1.2 g of sample which was 71% mole fraction *d*. Our results, shown in Table VI, fall short of the reported value. The first 9.4 mg of material from the second sublimation was 83% mole fraction *d*.

Conclusions

Fractionation can occur during the sublimation of optically active compounds and such fractionation may be predictable on the basis of melting point vs. composition curves. In the absence of such curves, when dealing with racemic compounds (as opposed to racemic mixtures and racemic solid solutions), it has been shown previously that it is possible to determine the relative position of the starting composition with respect to the eutectic point.[8] For the enhancement of optical activity, fractional sublimation provides an alternative to fractional crystallization for suitable compounds. This may be especially useful when working with material of very low optical purity. There are advantages and disadvantages inherent in a choice between fractional crystallization and fractional sublimation. This choice must be made on the basis of the properties of the individual compounds under investigation and has been discussed elsewhere.[1]

One of the authors (D.L.G.) would appreciate receiving correspondence from other researchers who may have experienced similar results.

Experimental Section

Rotations of 1 were taken using a Rudolph Model 80 polarimeter. All other rotations were taken on a Perkin-Elmer Model 141 automatic recording polarimeter. All rotations have an accuracy of 1% or better.

The preparation of optically active 1 has been reported.[9] All other compounds were purchased and sublimed prior to use: D(−)-mandelic acid and DL-camphoric acid (Sigma Chemical Co.), *d*-camphoric acid (Eastman), and L(+)-mandelic acid (Aldrich). The solid samples were carefully ground and mixed in a ball mill apparatus. Heating bath and oven temperatures were kept at least 10 °C below the melting point of the most volatile modification. Sublimations in the temperature gradient oven (condition 1) were allowed to proceed for 1–4 days; those in a standard sublimation apparatus (condition 2) typically were interrupted after 2–4 h to obtain fractions. Optical rotations were determined on ca. 1–2% solutions in 95% ethanol.[10] Enantiomeric purity is based upon the rotations obtained for pure isomers.

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Registry No.—Bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxylic acid, 61117-21-3; DL-mandelic acid, 611-72-3; L-mandelic acid, 17199-29-0; D-mandelic acid, 611-71-2; *dl*-camphoric acid, 560-05-4; *d*-camphoric acid, 124-83-4.

References and Notes

(1) H. Kwart and D. P. Hoster, *J. Org. Chem.*, **32**, 1867 (1967).

(2) Based on a determination of the activity of the pure enantiomorphs ($[\alpha]^{23}\text{D}$ 425°).

(3) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962.

(4) Y. Fujita, Y. Baba, A. Kagemoto, and R. Fujishiro, *Nippon Kagaku Kaishi*, 1563 (1972). The curve that appears in this publication is erroneously labeled "mole fraction". The numbers actually represent "enantiomeric purity".[5]

(5) Enantiomeric purity, which is equivalent to optical purity, is defined as $2F - 1$ where F = mole fraction of the predominant isomer.[6]

(6) M. Raban and K. Mislow, *Top. Stereochem.*, **2**, 199 (1967).

(7) J. D. M. Ross and I. C. Somerville, *J. Chem. Soc.*, 2770 (1926).

(8) Reference 6, p 227.

(9) D. L. Garin and D. J. Cooke, *J. Chem. Soc., Chem. Commun.*, 33 (1972). The fractional sublimation results do not alter the data or conclusions of our earlier study with this compound as reported in this reference.

(10) The report by Kwart and Hoster (ref 1) that observed molecular rotations of α-ethylbenzylphenyl sulfide varied significantly with concentration was later corrected: H. Kwart and D. P. Hoster, *J. Org. Chem.*, **34**, 3714 (1969).

Photochemical Addition of Sulfur Dioxide to Certain Arylcyclopropanes

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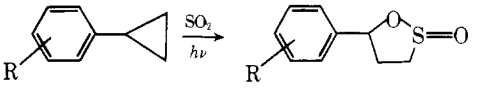
During some studies of the photochemical addition of halogens to arylcyclopropanes,[1] it was observed that if the solvent was sulfur dioxide, some of the cyclopropanes added sulfur dioxide in preference to halogen, and that the same reactions occurred in the absence of halogen. Although the phenomenon has not been investigated in detail, we report here a brief survey of its scope.

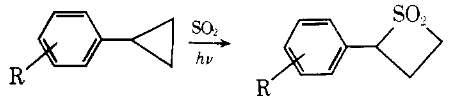
Sulfur dioxide has been found to add to cyclopropanes in two ways. The first, reaction 1, is to form sultine **1** as a mixture of geometric isomers.



(1)

1a, R = p-CN
b, R = p-CH_3CO
c, R = p-NO_2

The second, reaction 2, is to form sulfone **2**.

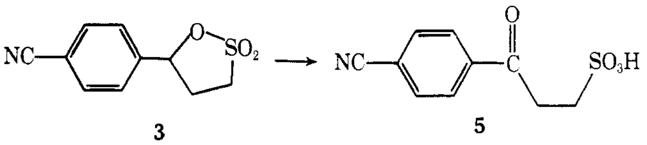


(2)

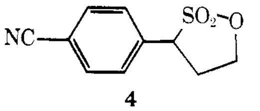
2a, R = p-NO_2
b, R = o-NO_2

Our best characterized example of reaction 1 is the formation of **1a** from *p*-cyanophenylcyclopropane. When *p*-cyanophenylcyclopropane was irradiated in sulfur dioxide solution with sun lamps for 25.5 h, there was a 36% conversion to **1a**, a white solid with mp 87–92 °C. The infrared spectrum showed a single strong band in the S=O region at 1120 cm^{-1} and the NMR spectrum showed two complex multiplets in the aliphatic region at 2.00–4.33 (2 H) and 4.10–5.28 ppm (3 H). These data suggested a mixture of the two geometric isomers of **1a**. To test this hypothesis, a peroxide oxidation to the sultone **3** was carried out. Compound **3** was a solid with mp 118.5–121.5 °C. It gave a correct analysis for addition of one oxygen atom and appropriate change in the infrared spectrum, the band at 1120 cm^{-1} having been replaced with a strong pair at 1345 and 1210–1170 cm^{-1}.

Sultone **3** was further oxidized with dimethyl sulfoxide to distinguish it from the isomer **4**, which would have formed if the original sultine **1a** had had the corresponding orientation of the sulfur-oxygen bond. Oxidation gave a product with a strong ketone carbonyl at 1690 cm^{-1}, as expected for **5**, and no bands at 2500–2900 or 1725 cm^{-1}, which would have been expected from the aldehydic product from **4**.



3 5



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p-Acetylphenylcyclopropane in sulfur dioxide was irradiated to give a viscous oil whose infrared and NMR spectra closely resembled those of **1a**, indicating that the isomeric mixture of sultines **1b** had formed.