Journal of Fluorine Chemistry 131 (2010) 545–548

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Attempts to explain the self-disproportionation observed in the partial sublimation of enantiomerically enriched carboxylic acids

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ARTICLE INFO

Article history:
Received 4 November 2009
Received in revised form 9 December 2009
Accepted 10 December 2009
Available online 16 December 2009

Keywords:
Self-disproportionation of enantiomers
Carboxylic acid
Sublimation
Kinetic versus thermodynamic

ABSTRACT

The partial sublimation of two carboxylic acids, the mandelic acid and ibuprofen has been studied. Many (*RS*) + (*S*) samples with various enantiomeric excesses (*ee*) have been slowly and partially sublimed at a low temperature and the sublimates have been condensed before analysis. About 1% of the starting material was sublimed in each experiment. The results are reproducible showing that the sublimation is under control. The *ee* of sublimates are comparable to the *ee* of the eutectic but also to those obtained by mixing the sublimates of two apparatuses used to sublime separately the racemate and the enantiomer. Thus, the sublimations of both carboxylic acids could be controlled by the saturated vapor pressure of the components ((*RS*) and (*S*)) or, as usually proposed, by the formation of a gas phase with a eutectic composition. In the case of mandelic acid, a definitive answer has been given by the partial sublimation of (*S*) + (*R*) solid mixtures where sublimates with a eutectic composition have been obtained and without any indication of the sublimation of a "kinetic conglomerate". This study paves the way for future investigations on the slow and partial sublimation of enantioenriched compounds to determine how this latter occurs.

1. Introduction

In 1959, Pracejus observed that fractional sublimation of some enantioenriched phenylalanine derivatives provides sublimates of increased enantiomeric purity [1]. Seven years later, Kwart and Hoster studied the sublimation of α-ethylbenzylphenyl sulfide and observed similar enantiomeric enrichments of partial sublimates [2]. In 1977, Garin et al. performed a quite complete study on three carboxylic acids, the mandelic, camphoric and bicyclo-[3.1.0]-hex-2-en-6-endo-carboxylic acids [3]. For the first time, increases and decreases of the *ee* of the sublimate in fractional sublimations were observed depending of the starting material. Garin has proposed that a sublimate with a eutectic composition preferentially sublimes. The composition of the eutectic of these carboxylic acids was determined by the melting point-composition diagram. However, most of the *ee* of the sublimed fractions were quite far from a eutectic composition.

In the book "Enantiomers, Racemates and Resolution" Jacques et al. [4] gave a way to predict the composition of the gaseous phase obtained by sublimation of enantioenriched compounds:

- "For racemic compound with enantiomeric purity less than that of the eutectic in the sublimation phase diagram, the part of the mixture which first sublimates has a greater enantiomeric purity than that of the substance taken; the non-sublimed residue is enriched in racemate.
- In the inverse case when racemic compound whose enantiomeric purity is greater than that of the eutectic, that which first sublimes is less pure than the initial mixture, while the enantiomeric purity of the residue rises and tends toward the pure enantiomer"

It was added "the initial sublimate possesses the composition of the *vapor eutectic*". As before for Garin et al. [3], Jacques et al. [4] considered that the usual "sublimation and condensation" follows the same rules that those deduced from the analysis of the gas phase at the equilibrium.

More recently, Cooks et al. in a non-standard experimental procedure observed huge enrichments of the *ee* of partial sublimates in the sublimation of D + L serine (up to 98% *ee* starting from a 3% *ee* sample) [5]. Under standard conditions Feringa and co-workers [6] studied the sublimation of samples of DL + L

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doi:10.1016/j.jfluchem.2009.12.008

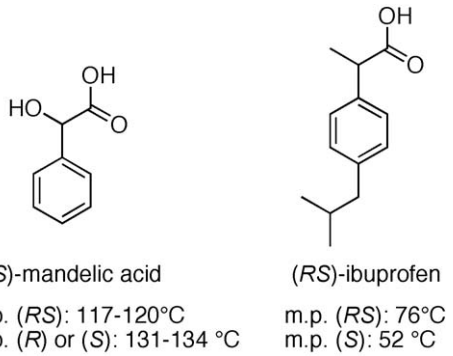
enantioenriched leucine (2–10%) and reported huge enrichments (up to 89%) of the *ee* of partial sublimates in about one half of the experiments. Using other experimental conditions (and particularly previously dissolved mixtures before drying, grinding and sublimation) or other amino acids, more modest enrichments were observed.

In a feature article, Blackmond and Klussmann [7] attempted to give an explanation to these recent observations on the basis of the analysis of Jacques et al. [4] and their own determination of the eutectic composition of these amino acids performed in water solutions saturated with the racemate and the enantiomer. In the same article, the authors recalled that the eutectic composition in a solvent can move dramatically in function of the nature of the solvent and the presence of impurities. This statement has also been reported by Hayashi et al. [8].

Very recently, the first example of the obtaining of an enantiomerically pure residue after a partial sublimation of a (*RS*) + (*S*) enantioenriched (trifluoromethyl)lactic acid has been reported by Soloshonok et al. [9] and commented by Cintas [10]. It is interesting to note that in the last articles [5,6,9] the authors did not propose an explanation of the results based on the sublimation of a gaseous phase with the composition of the vapor eutectic. As recalled in a footnote of one of these articles [9], various explanations have been reported in the literature to explain the *ee* of sublimates: "the eutectic composition is predicted to preferentially sublime regardless of the initial composition" [4], "sublimation process for both the racemate and the enantiomer was found to be enthalpy driven." [11] "the modification with the lowest melting point should exhibit the greater volatility and should sublime preferentially" [3,4]. That evidences the difficulties to explain many results.

We have investigated studies on leucine and then extended them to alanine and proline [12]. Starting from DL + L samples of leucine with a *ee* of 10–90% we observed enrichments or depletions leading to a sublimate (1% of the starting material) with a *ee* around 50%. Quite similar results were obtained with alanine and proline or starting from previously solubilized mixtures. The sublimation of D + L mixtures of enantioenriched leucine gave a new light to this study. Independently of the starting *ee* (10–70%), we observed a *ee* of the first sublimate of 8–13%. We attributed these last results to the sublimation of a "kinetic conglomerate" [7,13] a mixture of enantiopur crystals able to form a racemate but subliming as a conglomerate. However, what controls this partial sublimation leading in all cases to a sublimate with a low *ee*? We proposed for these experiments a control by the vapor pressures of D- and L-leucine which are identical. In this case the question is why DL and L crystals of leucine are not able to sublime independently? The explanation given in the literature is based on interactions in the gas phase between monomeric D and L enantiomers [4,14]. However, the hypothesis of a sublimate with the composition of the *vapor eutectic* ignores the kinetics to reach the equilibrium, and the "kinetic conglomerates" concept represents one kind of sublimations without a eutectic composition of the gaseous phase.

On the other hand, we cannot conclude that this equilibrium was undoubtedly reached with mixtures of DL and L amino acid since using two sublimation apparatuses, one containing DL crystals and the other one L crystals of one of the three amino acids, the *ee* of both sublimates (about 5 mg for each) mixed together was again around 50%. Thus nothing proves that the sublimation–condensation via some organization between monomeric D and L enantiomers in the gas phase is the sole way to explain the results. We have proposed a control of the sublimation–condensation based on the vapor pressures of dimeric compounds (D_2, L_2 or DL) that should be equal for the racemate and enantiomer for each of the three studied amino acids. Kinetic reasons can also be proposed [12]. Nevertheless, this work on amino acids cannot be *a priori* generalized to the sublimation of any enantioenriched chiral compound. We here report an extension of this study to two chiral carboxylic acids, mandelic acid and ibuprofen, to reinforce or limit the scope of our conclusions.



Scheme 1.

2. Partial sublimation of enantioenriched carboxylic acids

Carboxylic acids are well-known to be more or less partially under a dimeric form in the gas phase, especially at low temperature [15]. The choice of the two acids was determined, for mandelic acid as a reinvestigation of the work of Garin and, for Ibuprofen because very different vapor pressures between the enantiomer and the racemate have been reported for this compound (Scheme 1) [16].

The partial sublimation of enantioenriched samples of (*RS*)- + (*S*)-mandelic acid was performed at 40 °C, a temperature allowing to sublime about 1% (≈5–10 mg) of the starting mixture after 16 h in vacuo (0.1 mbar). The curve represented in Fig. 1 and the data given in Table 1 (entries 1–8) have been obtained starting from various samples with different *ee*. The error bar on each data has been estimated to ±5%. The curve is quite similar to the ones previously obtained for amino acids [12] and gave a plateau around 42 ± 5% *ee*. Previously solubilized samples gave similar results (Table 1, entries 9,10). The eutectic composition for the solid of mandelic acid has been determined at 50% [3], and 40% *ee* [4]. Thus the preferential sublimation of sublimates with a eutectic composition could give a simple

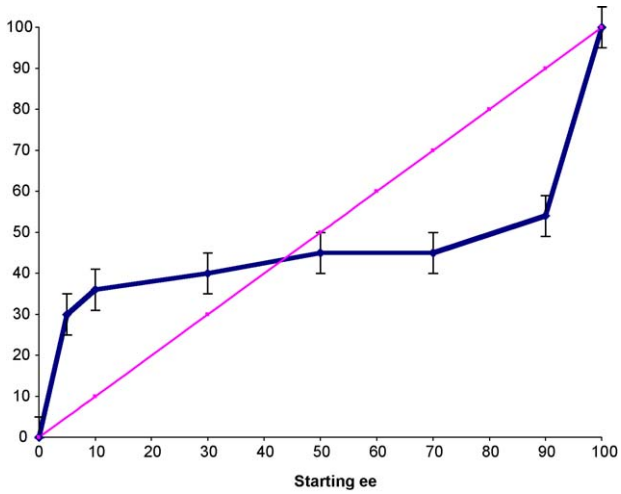


Fig. 1. *ee* of the sublimate versus *ee* of the starting material of mandelic acid (◆: measured *ee*, ■: linear effect) (temperature of sublimation: 40 °C, 0.5–1% of the starting material was sublimed, error bars: ±5%).

Table 1
Partial sublimation[a] of enantioenriched samples of (*S*)-mandelic acid.

Entry	Starting *ee* (%)	*ee* sublimed (%)	
1[b]	0	0	Grinded
2[b]	5	30	
3[b]	10	36	
4[b]	30	40	
5[b]	50	45	
6[b]	70	45	
7[b]	90	54	
8[b]	100	100	
9[c]	30	41	Previously solubilized
10[c]	70	49	
11[d]	50	49	2 sublimation apparatuses

[a] 0.5–1% of the starting material.
[b] 1–8: standard conditions.
[c] 9–10: previously solubilized samples before drying, grinding and sublimation.
[d] Two apparatuses.

explanation to these results. However, we then performed a sublimation using two sublimation apparatuses, one containing 1 g of (*RS*)-mandelic acid and the second one 1 g of (*S*)-mandelic acid. A 49% *ee* was observed for the sublimate obtained by the mixing of both sublimates. Once again, a preliminary organization of the gas phase up to a eutectic composition is not proved by the results we obtained using one sublimation apparatus since similar results are observed without any possible interaction between (*RS*)- and (*S*)-mandelic acid.

We then moved to ibuprofen, a carboxylic acid used in pharmacology for anti-inflammatory properties. It is interesting to observe that the ratio between the (*S*)- and (*RS*)-ibuprofen vapor pressure is increasing with the decrease of the temperature to move from 2.27 at 45 °C to 2.5 at 40 °C [16]. A eutectic composition for the solid of 90% *ee* has been reported [17]. We found that a temperature of 35 °C for the oil bath allowed to sublime about 0.5–1% (≈5-10 mg) of the starting solid mixture in 16 h with a pressure of 0.1 mbar. The results obtained using one sublimation apparatus and various enantioenriched (*RS*) + (*S*) samples are reported in Fig. 2 and Table 2 (entries 1–9). For this compound, the curve dramatically moved up to a plateau around 85% for the *ee* of the sublimate. This approach could be very efficient to isolate 85% *ee* samples starting from material with a low initial *ee* at a preparative level. Similar results were obtained starting from previously solubilized samples (Table 2, entries 10–11) but a very different result was obtained with a melted sample (Table 2, entry 12). However, after grinding, this latter led to a

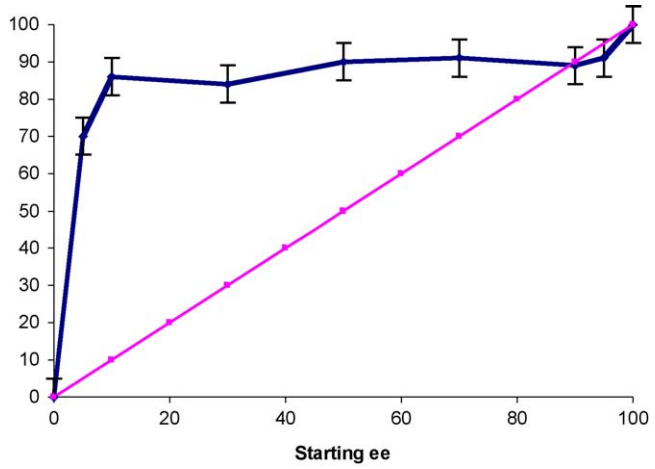


Fig. 2. *ee* of the sublimate versus *ee* of the starting material of ibuprofen (◆: measured *ee*, ■: linear effect) (temperature of sublimation: 35 °C, 0.5–1% of the starting material was sublimed, error bars: ±5%).

Table 2
Sublimation[a] of enantioenriched samples of (*S*)-ibuprofen.

Entry	Starting *ee* (%)	*ee* sublimed (%)	
1[b]	0	0	Grinded
2[b]	5	70	
3[b]	10	86	
4[b]	30	84	
5[b]	50	90	
6[b]	70	91	
7[b]	90	89	
8[b]	95	91	
9[b]	100	100	
10[c]	30	81	Previously solubilized
11[c]	70	87	
12[d]	30	36	Melted
13[e]	17	73	2 sublimation apparatuses
14[e]	83	84	

[a] 0.5–1% of the starting material.
[b] 1–9: standard conditions.
[c] 10–11: previously solubilized samples before drying, grinding and sublimation.
[d] 12: melted sample.
[e] 13–14: independent sublimation of (*RS*)- and (*S*)-ibuprofen.

sublimate with a 80% ee. This last result is consistent with the observation of Kwart and Hoster [2] and indicates, once again, that the structure of the starting solid mixture determines the *ee* of the first sublimate. Although all the results except this one can be explained by the preferential sublimation of a vapor eutectic, similar data were still obtained for the *ee* of the mixed sublimates coming from two sublimation apparatuses, one containing (*RS*)-ibuprofen and the other one (*S*)-ibuprofen (Table 2, entries 13,14).

3. Analysis of the results

The sublimation of mixtures of (*RS*) + (*S*) mandelic acid and ibuprofen gave results comparable to the ones we obtained with leucine, proline and alanine [12]: the curves are similar and the use of previously solubilized samples or the sublimation with two apparatuses did not change the *ee* of the partial sublimate. Here also in the first and second part of the curve, the (*S*)-enantiomer in the sublimates is respectively more and less abundant than in the starting mixture.

The sublimation followed by condensation, performed under standard conditions, is considered as quite far from the equilibrium. By the reproducibility of our experiments and the obtaining of almost identical *ee* for the sublimate starting from samples with various *ee*, we can easily demonstrate that the sublimation is controlled and does not give random results.

On one hand, in the hypothesis of the sublimation of a sample with a eutectic composition, we cannot prove in the experiments reported above the formation of a eutectic mixture in the gas phase before the condensation. On the other hand, if we have the sublimation of a "kinetic conglomerate" ((*RS*) and (*S*)) we cannot explain the lack of organization in the gas phase and can just propose, for example, dimeric structures in the gas phase or kinetic reasons. In the last part of this article, we will try to support and to invalidate at least one of these hypotheses.

The formation of a mixture with a eutectic composition in the gas phase at the equilibrium has been proposed many times in the literature [3,4,7,14] but recent results [5,6,12] show that this explanation cannot be a general rule. Several points cannot be explained by that: the sublimation of a "kinetic conglomerate" already observed in the literature for several compounds [5,7,12], the obtaining of different results depending on the nature of the starting mixture of solids and the identical *ee* using one or two independent sublimation apparatuses. The usual assertion of a

Table 3
Sublimation[a] of grinded (*S*)+(*R*) mixtures of mandelic acid.

Entry	Starting *ee* (%)	*ee* sublimed (%)
1	20 (S)	38 (S)
2	50 (S)	41 (S)
3	80 (S)	50 (S)
4	90 (S)	49 (S)
5	80 (R)	44 (R)

[a] 0.5–1% of the starting material.

sublimate with the composition of the vapor eutectic more easily formed starting from (*RS*) + (*S*) (or (*R*)) than from (*S*) + (*R*) is also doubtful [10].

In a conglomerate, each enantiomer sublimes independently of the other one. The *ee* of the sublimate is 0%, the experiment being controlled by the vapor pressure of each enantiomer which are equal at the same temperature. In a "kinetic conglomerate", the enantiomers are able to form a racemate but this latter is not formed in the solid or gas phase, and each enantiomer sublimes independently of the other one. As in the case of a conglomerate, the control is performed by the vapor pressure of each enantiomer and the *ee* of the sublimate tends to 0% whatever the *ee* of the starting mixture.

On the other hand, it is difficult to accept for any compound the sublimation without interaction between the racemate and the pure enantiomer if mixtures of pure (*S*) and (*R*) enantiomers do not sublime as a "kinetic conglomerate". So we performed the sublimation of samples of (*S*) and (*R*) mandelic acid under standard conditions. The results reported in Table 3 unambiguously demonstrate the formation of a gas phase with a eutectic composition. Probably a similar composition is formed starting from (*RS*) and (*S*) crystals since similar results were obtained (Table 1). In this case, the identical *ee* obtained using one or two sublimation apparatus(es) appears as coincidental.

4. Conclusion

The slow sublimation–condensation at a low temperature of an enantioenriched compound can give conditions able to evaluate the eutectic composition or to show that something different occurs. The sublimation of a "kinetic conglomerate" or a previously melted sample is typical of such another behaviors. Kinetic reasons, the sublimation of dimeric, trimeric or oligomeric structures could be an explanation to the differences observed between a theoretical model based on the vaporization of monomeric structure at the equilibrium and the experimental results [5,12]. To identify the type of sublimation we have to perform for a chiral compound, the sublimation of

(i) several samples of mixtures of (*RS*) and (*S*) (or (*R*)) crystals with various *ee*,
(ii) several samples of mixtures of (*S*) and (*R*) crystals with various *ee* and
(iii) the independent sublimation using two sublimation apparatuses of (*RS*) and (*S*) (or (*R*)) crystals with various ratios.

When identical results are obtained in (i) and (ii), the sublimation probably occurs with a gas phase at the composition of the vapor eutectic. On the contrary, when (i) and (ii) give different results, the compound presents different physical properties. In this case, when (i) and (iii) give identical results, the hypothesis of a sublimation based on the ratio of the vapor pressures of the components can be proposed.

In this article, we showed that the case of mandelic acid is clearly unambiguous since in our experimental conditions, the vapor phase has the composition of the vapor eutectic independently of the nature of the starting mixture. This study confirms the hypothesis of Garin et al. [3] on this compound. Many other experiments on other compounds are currently under progress in the lab to complete these studies and to increase the number of examples.

5. Experimental

Materials. Standard sublimation apparatuses and both carboxylic acids were purchased from Aldrich.

Sublimation of mandelic acid or ibuprofen: general procedure. A mixture of 1 g of racemate and enantiomer were cautiously grinded in a mortar for about 10 min. The mixture was then cautiously introduced in the sublimation apparatus with a funnel to avoid deposition on the walls. The sublimation apparatus was connected to a vacuum pump and the gas phase was evacuated. The bottom of the apparatus (2 cm) was introduced in an oil bath (θ: 40 °C (mandelic acid), 35 °C (ibuprofen)). About 0.5% (5 mg) of the starting material was sublimed after 16 h under 0.1 mbar. The sublimate was collected from the cold finger by dissolution in acetone. The solvent was then removed *in vacuo* and the solid was dried *in vacuo* for 10 min at room temperature.

Derivatization of a carboxylic acid. A sample of all the starting mixtures and all the sublimates was derivatized to determine the *ee* by GC. The samples of the starting mixtures showed the lack of racemization or enantioenrichment in these conditions.

In a 10 mL flask were introduced about 15 mg of carboxylic acid solubilized in 2 mL of a 12% methanolic solution of boron trifluoride. The mixture was stirred for 2 h under reflux and then cooled at room temperature. 50 μL of the mixture was quenched with 1 mL of potassium carbonate (1N). Cyclohexane (1 mL) was added and the organic phase was then separated. The low boiling compounds were evaporated and ethyl ether was added to the residue for GC analysis on a CP-Cyclodex B capillary column.

Mixtures of (*S*)- and (*RS*)-ibuprofen or mandelic acid previously dissolved in acetone, recrystallized and then grinded gave comparable results after sublimation and derivatization (±3%).

Acknowledgments

The authors thank Prof. Vadim Soloshonok (Univ of Oklahoma, USA) and Martin Suhm (Univ. Göttingen, Germany) for helpful discussion. This work has been financially supported by the Centre National d'Etudes Spatiales (CNES).

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