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Temperature Selective Diastereo-Recognition (TSD): Enantiomeric Ibuprofen via Environmentally Benign Selective Crystallization

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Abstract:

Selective crystallization of ibuprofen/lysinate from 1 mol of (*R*,*S*)-(racemic) ibuprofen and ≤0.5 mol of (*S*)-lysine in aqueous ethanol affords either (*S*)-(+)-ibuprofen/(*S*)-lysinate or (*R*)-ibuprofen/(*S*)-lysinate (in preponderance) depending on the crystallization conditions. The previously unreported temperature selective diastereo-recognition (TSD) provides simple and efficient means to prepare either enantiomer of ibuprofen from (*R*,*S*)-ibuprofen utilizing the same commercially available inexpensive resolving agent, (*S*)-lysine. The unwanted enantiomeric ibuprofen could be recovered from the mother liquor and racemized by a simple, relatively waste-free thermal process. This racemization method when utilized in conjunction with the selective crystallization technology provides a simple, efficient, and eco-friendly means to prepare (*S*)-(+)-ibuprofen lysinate in an overall essentially quantitative yield. This technology also incorporates the fundamental principle of atom economy (via direct production of the preferred pharmaceutical salt of (*S*)-lysine).

Introduction

(*R*,*S*)-Ibuprofen belongs to a class of nonsteroidal anti-inflammatory agents that has remained an area of intense study.[1] (*S*)-(+)-Ibuprofen is the pharmacologically active component of (*R*,*S*)-ibuprofen. The (*R*)-(−) isomer is either inactive or weakly active in vitro although the difference in activity is markedly decreased in vivo due to metabolic inversion of the (*R*)-(−) to the active (*S*)-(+) enantiomer.[2] On the other hand, (*R*)-(−)-ibuprofen, the therapeutically inactive isomer, is expected to give less gastrointestinal side effects than the racemate but still retains its anti-inflammatory activity via metabolic inversion to the active (*S*)-(+) isomer. Also the (*R*) enantiomer can be potentially toxic due to its storage in fatty tissue as the glycerol ester, whose long-term effects are unknown.[3] To realize enhanced specificity and to avert an undesirable load on metabolism, (*S*)-(+)-ibuprofen in the form of its lysinate salt has been introduced as an alternative by Merck.[4] Asymmetric synthesis of (*S*)-(+)-ibuprofen via an elegant chiral protonation of aryl ketenes (Merck), asymmetric hydrogenation of vinyl arenes mediated by chiral catalysts, as well as chiral auxiliary has been reported.[5] Ibis developed an enzymatic resolution of the methyl ester.[6] In light of such continuing interest in the area of (*S*)-(+)-ibuprofen coupled with the recent demand for the enantiomerically pure drug in chemotherapy, an efficient preferential resolution of racemic (*R*,*S*)-ibuprofen is highly desirable. Although already demonstrated, the existing methods for resolving (*R*,*S*)-ibuprofen via fractional crystallization of diastereomeric salts with chiral amines (e.g., α-methybenzylamine, (*S*)-lysine) suffers from the following disadvantages: (a) Classical resolution is always accompanied by the production of at least 1 mol of salt (waste) with a maximum theoretical yield of only 50% (based on the chiral auxiliary). (b) Although synthetic resolving agents (e.g., α-methybenzylamine) are available in both enantiomeric forms, naturally occurring agents (e.g., (*S*)-lysine) are often only available in one enantiomeric form, thereby limiting the scope of such diastereomeric separations.[2a,7] (c) And, the success of resolution methods depends on an efficient

(1) (a) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron*. **1986**, *42*, 4095. (b) Sonwane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. J. *Tetrahedron: Asymmetry*. **1992**, *3* (2), 163.

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(4) (a) Tung, H. H.; Waterson, S.; Reynolds, S.; Paul, E. *AIChE Symp. Ser.* **1991**, *87* (84), 64. (b) Tung, H. H. U.S. Patent 4,994,604, 1991.

(5) (a) Ohta, T.; Takaya, M.; Kitamura, K.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174. (b) Chan, A. S. C. 199th American Chemical Society Meeting, Boston, April, 1990. (c) Alessandra, A.; Amoroso, R.; Bettoni, G.; De Filippis, B.; Giampietro, L.; Marco; Triccak, M. L. *Tetrahedron Lett.* **2002**, *43* (24), 4325. (d) Fan, Q. H.; Deng, G.-J.; Chen, X.-M.; Xie, W.-C.; Jiang, D.-Z.; Liu, D. S.; Chan, A. C. S. *J. Mol. Cat A: Chem.* **2000**, *159* (1), 37. (e) Chen, A.; Ren, Li.; Crudden, C. M. *J. Org. Chem*. **1999**, *64* (26), 9704. (f) Larsen, R. D.; Corely, E. G.; Davis, P.; Reider, P.; Grabowski, E. J. J. *J. Am. Chem. Soc*. **1989**, *111*, 7650. (g) Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Liu, T. J.; Corley, E. G.; Reider, P. J. *Synlett* **1994**, (3), 1999 and references sited therein.

(6) Mutsaers, J. H. G. M.; Kooreman, H. J. *Recl. Trav. Chim. Pays-Bas*. **1991**, *110*, 185.

(7) (a) Manimaran, T. U.S. Patent 5,015,764, 1991. (b) Chikusa, Y.; Fujimoto, T.; Ikunaka, M.; Inoue, T.; Kamiyama, S.; Maruo, K.; Matsumoto, J.; Matsuyama, K.; Moriwaki, M.; Nohira, H.; Saijo, S.; Yamanishi, M.; Yoshida, K. *Org. Process Res. Dev.* **2002**. *6*, 291. (c) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 251, 1981. (d) The cost of naturally occurring (*S*)-lysine is $2/kg, whereas the enantiomeric (*R*)-lysine (which is required for the production of (*R*)-(−)-ibuprofen via traditional classical resolution) costs $8000/kg. (e) The Anastas, P. T.; Warner, J. C. Twelve Principles of Green Chemistry. *Green Chemistry Theory and Practice*; Oxford University Press: New York, 1998.

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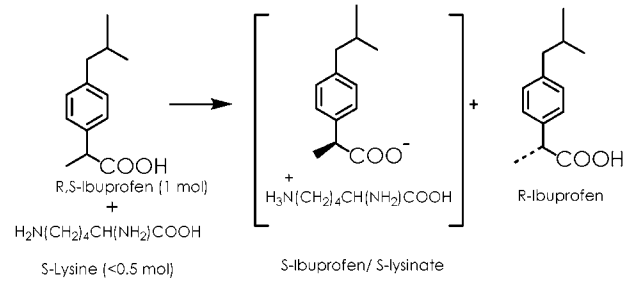
racemization and recycling of the unwanted (*R*)-isomer. Existing technologies to racemize ibuprofen are often nontrivial and waste producing. Examples include the following:[8] (a) Conversion of the acid functionality to the thioester, base-catalyzed racemization of the corresponding thioester, followed by hydrolysis to regenerate the acid and thiol is effective but cumbersome. (b) Refluxing in octane/Et_3N for 18 h followed by acidification generates salt waste. (c) Refluxing in concentrated HCl for 72 h requires expensive chloride-tolerant equipment (e.g., glass-lined) and generates acid waste. (d) Refluxing in excess 2-propanol/excess NaOH for 16 h followed by acidification is waste producing. (e) Refluxing in isopropyl acetate in the presence of acetic anhydride (0.1 mol) and sodium acetate (0.1 mol) generates salt/organic waste. (f) Heating ibuprofen acid chloride with sodium ibuprofenate requires expensive chloride-tolerant equipment (e.g., glass-lined) and generates salt waste. (g) Refluxing (*S*)-(+)-ibuprofen in acetic anhydride and pyridine is waste producing.

This report describes a selective crystallization of ibuprofen/lysinate from one mole of (*R*,*S*)-ibuprofen and ≤0.5 mol of (*S*)-lysine. An unprecedented temperature selective diastereo-recognition (TSD) leads to the preparation of either enantiomer of ibuprofen (as well as the preferred lysinate salt) utilizing the inexpensive, naturally occurring, and readily available (*S*)-lysine[7c] as the chiral resolving agent and appropriate choice of resolution conditions. In addition, we also report a convenient, waste-free, thermal racemization of (*S*)-(+)-ibuprofen that does not require any external reagent, catalyst, and/or solvent, thus rendering alternate racemization technologies less attractive. This racemization method, when utilized in conjunction with the selective crystallization technology, provides an efficient and environmentally benign technology to prepare (*S*)-(+)-ibuprofen lysinate in an overall yield which is nearly quantitative.[7e]

Results and Discussions

Selective Crystallization Studies of Ibuprofen Lysinate. Classical resolution of (*R*,*S*)-ibuprofen via conventional techniques utilizing equimolar quantities of (*R*,*S*)-ibuprofen and (*S*)-lysine (as the resolving agent) in aqueous ethanol afforded the diastereomeric (*S*)-(+)-ibuprofen/(*S*)-lysinate salt in >99% optical purity after two crystallizations. Conceptually, we envisaged the possibility of selective crystallization of (*S*)-(+)-ibuprofen/(*S*)-lysinate utilizing only 0.5 mol of (*S*)-lysine per 1 mol of (*R*,*S*)-ibuprofen in the crystallization medium, provided a significant differential rate of crystal growth exists between the two diastereomeric salts,[7b] thereby promoting the crystallization of only one diastereomer with the mother liquor being enriched in the other enantiomer as shown in Scheme 1. Crystallization studies were conducted by adding an aqueous solution of (*S*)-lysine to an ethanolic solution of (*R*,*S*)-ibuprofen, followed by seeding. The diastereomeric excesses (de) of the crystals (sampled at 1 h intervals) were monitored by chiral HPLC analysis. Initial

Scheme 1



studies using 0.5 mol of (*S*)-lysine per 1 mol of (*R*,*S*)-ibuprofen and seeding provided (*S*)-(+)-ibuprofen/(*S*)-lysinate with modest de's, up to 30%. Significant enhancement of the diastereomeric purity of the product was achieved by carrying out the crystallization under kinetic conditions (0−5 °C) with seeding using pure (*S*)-(+)-ibuprofen/(*S*)-lysinate crystals. The crystallization was optimized by manipulating the four key independent variables: (*R*,*S*)-ibuprofen:lysine ratio; ethanol:(*R*,*S*)-ibuprofen ratio; temperature; and ethanol:water ratio. The optimized crystallization afforded our best results, a 95:5 diastereomer ratio (90% de) with an 80% isolated yield of the product. The optimum conditions were: (a) (*R*,*S*)-ibuprofen:lysine 2.5 mole:1mole; (b) 3.4 mL ethanol/1 g of (*R*,*S*)-ibuprofen; (c) ethanol:water 95:5 (v/v); and (d) 0 °C for 4 h.[9a]

The product of the first crystallization can be recrystallized (see experimental below) once from aqueous ethanol (90 wt %) to afford (*S*)-(+)-ibuprofen/(*S*)-lysinate monohydrate in 99% de.[9b] Maintaining the water content to at least the 10 wt % level or higher in the aqueous ethanol during the recrystallization is imperative for obtaining the pharmacologically desired monohydrate form in a reproducible manner.

The combined mother liquor and the wash liquor from the first crystallization (enriched in (*R*)-(−)-ibuprofen) was evaporated and partitioned between hexane and aqueous HCl. The hexane phase was evaporated to provide a residue of lysine-free ibuprofen that underwent >99% racemization on heating at 235 °C for 4 h.

Further investigation revealed the following facts that were crucial to the success of the selective crystallization technology.

Seeding. The crystals of (*S*)-(+)-ibuprofen/(*S*)-lysinate obtained by this method did not carry any water of crystallization. From an experimental standpoint, it is important that the crystallization process be seeded with the same anhydrous form of crystals that is desired. Seeding with the monohydrate form of the diastereomeric salt was shown to inhibit the crystallization.[10] The initial anhydrous seed crystals were independently prepared by crystallization of (*S*)-(+)-ibuprofen/(*S*)-lysinate from aqueous ethanol (97 wt %).

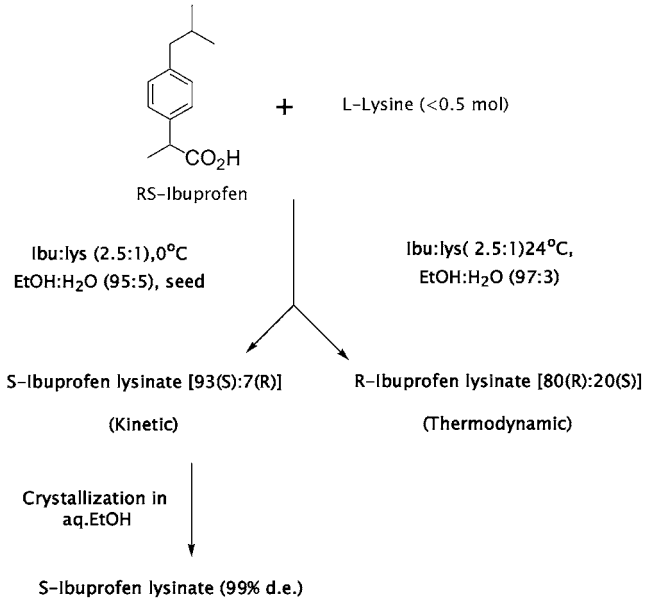
Crystallization Conditions (Time and Temperature). Particularly noteworthy and remarkable is the fact that a

(8) (a) Chen, C. Y.; Chang, S. Y.; Lin, S. A.; Wen, H. I.; Cheng, Y. C.; Tsai, S. W. *J. Org. Chem*. **2002**, *67* (10), 3323. (b) Manimaran, T. U.S. Patent 5,015,764, 1991. (c) Larsen, R. D. U.S. Patent 4,946,997, 1990. (d) Ruchardt, C.; Gartner, H.; Salz, Ulrich. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 162.

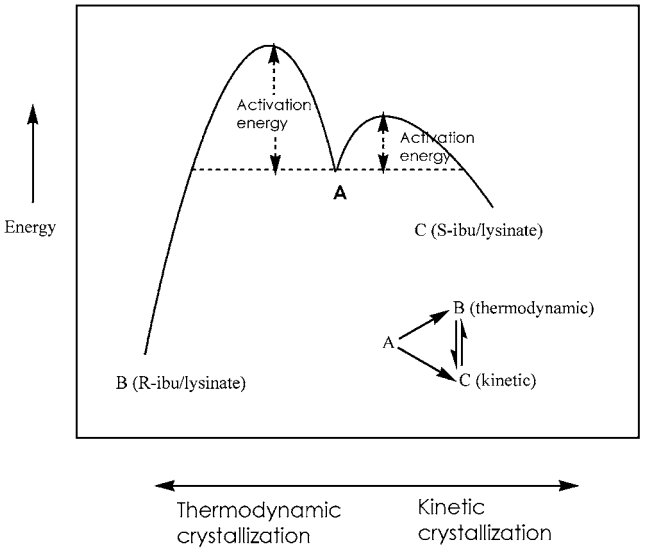
(9) (a) D-optimal design with a quadratic model was utilized for the optimization studies. (b) Monohydrate is the form desired by Merck.

(10) External seeding is not an absolute necessity for the crystallization. Thus, a crystallization mixture left at 0 °C in the refrigerator for 48 h showed slow crystal growth of (*S*)-(+)-ibuprofen/lysinate without external seeding.

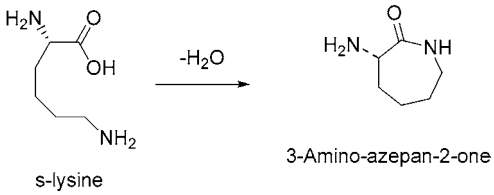
Scheme 2



Scheme 3



Scheme 4



complete reversal of diastereoselectivity was observed when the crystallization was conducted at 22 °C for 24 h under otherwise identical conditions, thereby producing the (*R*)-(−)-ibuprofen/(*S*)-lysinate in 80:20 diastereomer ratio (60% de). The same diastereo-reversal was also observed when the heterogeneous crystallization mixture obtained after 4 h at 0 °C (where the isolated crystals were diastereomerically enriched in (*S*)-(+)-ibuprofen/(*S*)-lysinate) was allowed to stir at ambient temperature for an additional 24 h, as depicted in Scheme 2. Selective precipitation of the (*R*)-(−)-ibuprofen/(*S*)-lysinate also gives rise to an interesting possibility where the mother liquor is enriched with the (*S*)-(+)-ibuprofen (as the free acid and not as the lysinate salt) and direct recovery of (*S*)-(+)-ibuprofen from the mother liquor is a distinct and lucrative probability.

The ability to produce either diastereomer utilizing the same chiral auxiliary ((*S*)-lysine) is previously unreported.[7c] These results can be explained by assuming that under a given set of conditions the crystallization process is undergoing two competing pathways to produce either diastereomer. Scheme 3 depicts a free-energy profile for such a crystallization process in which (*R*)-(−)-ibuprofen/(*S*)-lysinate (B) is the thermodynamic sink but (*S*)-(+)-ibuprofen/(*S*)-lysinate (C) is formed faster due to lower E_{act}. If the crystallization is reversible (which is usually the case when the mother liquor is not supersaturated with the solute) and the process is terminated well before the equilibrium has been established (0 °C, 4−6 h.), the crystallization will be kinetically controlled producing the (*S*)-salt. However, if the crystallization is permitted to approach equilibrium (22 °C 24 h), the process will be thermodynamically controlled, producing the (*R*)-salt.[11] Therefore, when (*S*)-(+)-ibuprofen/(*S*)-lysinate is the desired product, maintaining kinetic conditions throughout the whole process is crucial. A crystallization mixture which is preferentially enriched with the (*R*)-(−)-ibuprofen/(*S*)-lysinate crystals can be reworked by the following process: (a) redissolving the whole mixture (60 °C) in the mother liquor and (b) recrystallizing under kinetic conditions (0°, 4−6 h) to produce the kinetically preferred (*S*)-salt.

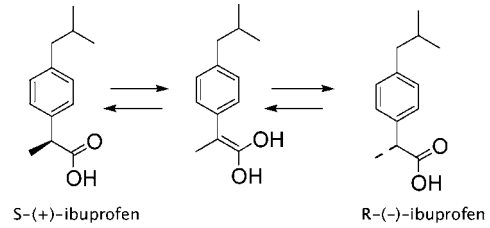
Conceivably, the mechanism for the conversion from the *S*−*S* diastereomeric salt to the corresponding *R*−*S* diastereomeric salt does not necessarily exclude a temperature-dependent equilibrium pathway. Further investigation indicated that this was not the case. A crystallization mixture which had achieved equilibrium conditions at 22 °C (80:20 *R*:*S* ratio) after 24 h, was cooled to 0 °C and kept at 0 °C for 12 h. No change in the diastereomeric ratio of the isolated crystals was observed. The above explanation is hypothetical at this juncture, and further detailed kinetic/mechanistic studies are needed.

Purity of the Ingredients. Purity of the ingredients plays an important role in the success of the crystallization. For example, the cycloamide, 3-amino-azepan-2-one, a common impurity resulting from intramolecular dehydration of lysine, (Scheme 4) tends to hinder the crystallization and produce pasty, hard-to-filter material with poor de's (c.a. 50%). Presumably, the free $-NH_2$ group of the cycloamide is capable of forming a different pair of diastereomeric salts with (*R*,*S*)-ibuprofen, thereby complicating the selective crystallization.[12] Residual hydrocarbons (e.g., cyclohexane

(11) (a) Klumpp. *Reactivity in Organic Chemistry*; Wiley: New York, 1982; pp 36−89. (b) Even at 0 °C, the reversal of diastereomer in the crystallization to produce the thermodynamically favored (*R*)-(−)-ibuprofen/(*S*)-lysinate was observed by carrying out the crystallization over a longer period of time. Thus, conducting the crystallization at 0 °C over an 18 h period under otherwise identical conditions produced the diastereomeric (*R*)-salt in 33% diastereomeric excess although the same crystallization when sampled after 4, 5, and 6 h showed the normal 93:7 (*S* over *R*) selectivity.

(12) Significant cycloamide was detected in samples of lysine, which has been kept on the shelf for an extended period of time.

Scheme 5



and hexane) introduced as trace (1% based on ethanol) impurities also produced slow-filtering, poor quality (60% de or less) material. No crystallization was observed in the presence of heptane. Particularly noteworthy is the fact that absolute ethanol obtained from two different sources (Spectrum and Midwest) showed significant variability in their performance. Reason for this is not entirely clear, but it may be linked to the fact that hydrocarbon-mediated azeotropic drying is often utilized to produce absolute ethanol.[13]

Choice of Solvent to Wash the Product Cake. Since the preferential crystallization involves separation of (*S*)-(+)-ibuprofen/(*S*)-lysinate salt from the enantiomeric *R*-(−)-ibuprofen, the major impurity in the product cake is the (*R*)-(−)-ibuprofen (in free acid form and not as the lysinate salt). An optimum result (86−90% de) was obtained when the product cake was washed with cold (0 °C), dry ethanol which solubilizes the *R*-(−)-ibuprofen and not the salt. Increasing the water content in the cake-wash solvent (e.g., 90:10 ethanol:H_2O) decreased the diastereomeric purity of the product by preferentially solubilizing the (*S*)-salt over (*R*)-(−)-ibuprofen.

Racemization Studies of Enantiomeric Ibuprofen. Racemization of a carboxylic acid with a chiral center at the α-position via the corresponding ketene formed by the treatment of acid chloride with a base (e.g., triethylamine) was reported as early as 1919.[14] We envisaged the possibility of an efficient, waste-free racemization of ibuprofen by (a) enolization of enantiomeric ibuprofen at an elevated temperature, followed by (b) enantiorandom reprotonation of the enol moiety to produce racemic ibuprofen. This surmise was confirmed by experiment (Scheme 5).

Racemization of (*S*)-(+)-ibuprofen was achieved by heating molten (*S*)-(+)-ibuprofen at 235 °C under an inert atmosphere for 4 h after which time complete racemization (1:1 *S*:*R*) was confirmed by chiral HPLC analysis. The optimum temperature range for conducting the racemization was 230−235 °C, which enabled the racemization to be complete within a reasonable time period (4−5 h) without any significant decomposition (<2% by LC area percent) of ibuprofen. Although these experiments were performed in the batch mode, in a commercial process, these conditions can be easily translated to a continuous process in a commercial plug flow reactor.

(13) Selective crystallization performed under established conditions using absolute ethanol obtained from "Spectrum" afforded product with the expected diastereomeric ratio (93:7, *S*:*R*), whereas absolute ethanol obtained from "Midwest Grain" afforded product with a lower diastereomeric ratio (80:20, *S*:*R*). Traces of hydrocarbon have been detected by GC analysis of the "Midwest Grain" ethanol.

(14) McKenzie, A.; Christie, E. W. *J. Chem. Soc.* 1070, **1934**. (b) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; American Chemical Society: Washington, DC, **1980**.

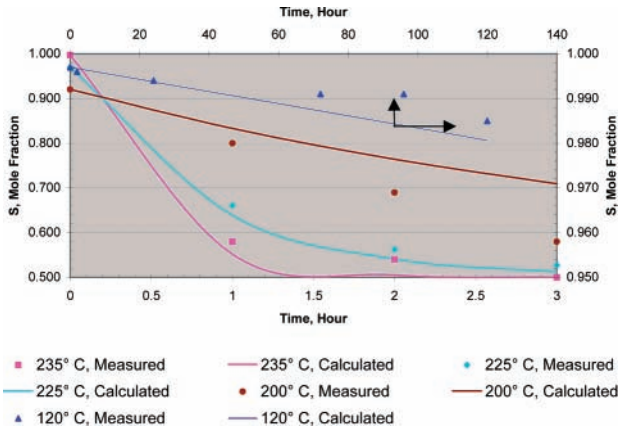


Figure 1. **Racemization of Ibuprofen.**

Table 1. **Racemization kinetics of (*S*)-(−)-ibuprofen**

S_o	*S* measured	time (h)	temp (K)	*x*[a] (cal/mol)	*y*[a] (h^{-1})	*k* '(h^{-1})	*S* calculated
0.997	0.996	2	393	0.001 29	−7.5939	0.000 14	0.997
0.997	0.994	24	393	0.001 29	−8.9782	0.000 14	0.994
0.997	0.991	72	393	0.001 29	−9.3806	0.000 14	0.987
0.997	0.991	96	393	0.001 29	−9.6683	0.000 14	0.984
0.997	0.985	120	393	0.001 29	−9.1921	0.000 14	0.981
0.92	0.8	1	473	0.001 07	−1.7824	0.116 09	0.833
0.92	0.69	2	473	0.001 07	−1.6179	0.116 09	0.764
0.92	0.58	3	473	0.001 07	−1.2860	0.116 09	0.709
0.97	0.661	1	498	0.001 01	−0.6243	0.609 99	0.639
0.97	0.562	2	498	0.001 01	−0.6804	0.609 99	0.541
0.97	0.527	3	498	0.001 01	−0.7420	0.609 99	0.512
0.997	0.580	1	508	0.000 99	−0.0907	1.131 55	0.552
0.997	0.540	2	508	0.000 99	−0.4622	1.131 55	0.505
0.997	0.500	3	508	0.000 99	-	1.131 55	0.501

[a] $x = (1/RT)$, $y = \ln[(1/2t)\ln((2S_o - 1)/(2S - 1))]$. E_a(calculated) = 30.95 K cal/mole; Arrhenius frequency factor = 2.6×10^{13} hr^{-1}.

A. Kinetic Studies. The kinetics of the racemization process were measured by conducting a series of thermal racemization experiments at different temperatures. Batch temperatures throughout the experiments were maintained constant with the aid of a digital Therm-O-Watch, and the enantiomeric excesses as a function of time were monitored by chiral HPLC analysis. The degree of racemization of (*S*)-ibuprofen as a function of time at different temperatures is depicted in Figure 1, and the data are given in Table 1. In Figure 1, the range of rates is so great that secondary axes are used to present data for the lowest temperature, 120 °C; that is, the scales for 120 °C data are along the top and right side of the figure.

Calculation of the above values for *S* (mol fraction of (*S*)-(+)-ibuprofen) follows a standard kinetic development. It is assumed that the kinetics are first order in both enantiomers and that the rate constants for both the forward and reverse reactions are the same. The rate equation for the change in (*S*)-(+) concentration is then

$$\frac{d[S]}{dt} = -k([S] - [R]) \qquad (1)$$

where [*S*] is the concentration of (*S*)-(+)-ibuprofen and [*R*] is the concentration of (*R*)-(−)-ibuprofen. If the substitution

is made to replace concentration, [*S*], with mole fraction, *S*, eq 1 becomes

$$\frac{dS}{dt} = -k(S - R) = -k(S - (1 - S)) \quad (2)$$

Separating variables and integrating gives

$$\int_{S=S_o}^{S} \frac{dS}{1 - 2S} = -\int_{t=0}^{t} k\, dt \quad (3)$$

Substituting $(^1/_2)\ d(2S) = dS$ and integrating gives

$$-\frac{1}{2}\ln\left(\frac{2S - 1}{2S_o - 1}\right) = kt \quad (4)$$

Substituting the Arrhenius equation [in which *R* is the gas constant, (not the concentration of the *R* enantiomer) and F is a pre-exponential Arrhenius frequency factor]

$$k = F \exp\left(\frac{-E_a}{RT}\right) \quad (5)$$

into the above eq 4, transposing, and taking the log of both sides give

$$\ln\left(\frac{1}{2t}\ln\left(\frac{2S_o - 1}{2S - 1}\right)\right) = -E_a\frac{1}{RT} + \ln F \quad (6)$$

which is in the form $y = mx + b$, since E_a and ln *F* are constants and *t*, *T*, and *S* are variables with experimentally known values.

Excel's linear curve fit was used to solve for E_a and *F*. The result is given in Table 1, where $\ln(^1/_2 t \ln(2S_o - {}^1/_2 S - 1))$ is *y* and $(1/RT)$ is *x*. The calculated E_a is 30.95 K cal/mol, and the Arrhenius frequency factor is $2.6 \times 10^{13}\ h^{-1}$. These constants describe the rate over the entire range of the experiments, a range of nearly 4 orders of magnitude.

Summary

We have demonstrated a simple, unprecedented, efficient, and environmentally friendly temperature selective diastereorecognition (TSD) to convert (*R*,*S*)-ibuprofen to either enantiomer utilizing the same commercially available inexpensive resolving agent, (*S*)-lysine.[15] The process obviates the shortcomings associated with both classical resolution (involving expensive synthetic resolving agents) and enzyme technology. The process also produces the enantiomeric ibuprofen directly as the preferred lysinate salt, which is desirable for human consumption thereby avoiding the obligatory separation of ibuprofen from a chiral auxiliary (atom economy).[7e] Diastereomeric enrichment of (*S*)-(+)-ibuprofen lysinate to a 99% level via a single recrystallization also demonstrates the superiority of lysine as a resolving agent for ibuprofen. This TSD when utilized in conjunction with the waste-free thermal racemization of enantiomeric ibuprofen provides an efficient and environmentally friendly process to prepare (*S*)-(+)-ibuprofen lysinate in an overall essentially quantitative yield. Several resolving agents obtained in nature are available only as a single enantiomer. As long as the diastereomers are not formed by covalent bonding, such equilibration between diasteroemeric and enantiomeric species will exist, and if the conditions permit, it will lead to selective crystallization. The TSD technology introduces a new possibility in the preparation of either separate enantiomer utilizing the same chiral resolving agent. Application of this methodology to a host of α-arylpropionic acids (profens) is under investigation. As chemical resolution technology continues to play a dominant role despite increasing competition from the enzymatic methods, the potential offered by such selective crystallization technology especially in the TSD of other α-arylpropionic acids should not be overlooked.[16]

Experimental Section

Materials and Methods. Reactions were carried out under an atmosphere of nitrogen and were stirred magnetically unless otherwise noted. All solvents were reagent grade. ^{1}H NMR spectra were recorded on a Varian UNITY-400 spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Analytical high performance liquid chromatography (HPLC) was carried out by using a Beckman 110B pump with a model 421-A gradient controller and a Hitachi L 4000 variable wavelength detector. The chiral assay was carried out with an Altex model 110A pump and a Hitachi L 4000 variable wavelength detector.

Preparation of Seed Crystals of (*S*)-(+)-Ibuprofen/(*S*)-Lysinate for the Selective Crystallization. A solution of (*S*)-(+)-ibuprofen (5.26 g, 0.025 mol) dissolved in 25 mL of absolute ethanol was added to an aqueous solution of (*S*)-lysine (3.75 g, 0.025 mol) in 4.2 mL of water with stirring. The resulting solution was filtered through a sintered glass funnel to remove any insoluble material. To this clear solution was added absolute ethanol (57.5 mL) with stirring over 5 min at 22 °C. The turbid solution was stirred for 30 min, and then an additional 40 mL of ethanol was added to this mixture over a period of 10 min with stirring. The resulting suspension was cooled to 0 °C and stirred for an additional 4 h. The crystals were filtered, washed with ice-cold (2 °C) ethanol (10 mL), and dried under house vacuum overnight to produce 7.4 g (84% yield) of (*S*)-(+)-ibuprofen/(*S*)-lysinate. The product contained 0.2% water as determined by a Karl Fischer titration. [Ethanol < 100 ppm by GC.]

Selective Crystallization of (*S*)-(+)-Ibuprofen/(*S*)-Lysinate. Racemic (*R*,*S*)-ibuprofen (41.25 g, 0.2 mol) was dissolved in absolute ethanol (140 mL). The solution was cooled to 0 °C and (*S*)-lysine (11.7 g, 0.08 mol dissolved in 7 mL water) was added to this solution while the solution temperature was maintained 0 °C. The solution was seeded with (*S*)-(+)-ibuprofen/(*S*)-lysinate (100 mg). The resulting mixture was stirred at 0 °C for 4 h. The crystallization was monitored by filtering a small sample through a disposable centrifugal Teflon membrane microfilter. The crystals were analyzed by chiral HPLC analysis for (*S*)- and (*R*)-ibuprofen content, and the mother liquor was analyzed by achiral HPLC for total contained ibuprofen. The crystals were filtered,

(15) (*S*)-Lysine hydrochloride (feed grade, 98.5% chemical purity, 100% optical purity) is available from Archer Daniel Midland Co. in bulk quantities at a price of $2 per kg.

(16) Bhattacharya, A. U.S. Patent 5,332,834, 1994; U.S. Patent 5,380,867, 1994; U.S. Patent 5,399,707, 1994.

washed with ice-cold (0 °C) ethanol (40 mL), and dried under house vacuum overnight to give 22.6 g (80% yield based on (*S*)-lysine) of (*S*)-(+)-ibuprofen/(*S*)-lysinate salt in 90% diastereomeric purity as evidenced by chiral HPLC. The mother liquor was concentrated in a rotary evaporator to produce an amber oil which was partitioned between hexane (200 mL) and water (50 mL containing 0.1 g of HCl) to remove the residual lysine. Removal of hexane in a rotary evaporator produced (*R*)-enriched ibuprofen (approximately 75:25, *R*:*S*) which was first racemized by heating at 230 °C for 4 h under a nitrogen atmosphere and was then distilled at about 220 °C, under vacuum (10 mM Hg), to produce substantially pure racemized ibuprofen (26 g, 96% recovery) that was recycled to the selective crystallization stream.

Analysis. A. Chiral HPLC Analysis. Column: CHIRAL-HSA (astec) 100 × 4.0 mm^2. Mobile phase: 5 mM octaonic acid and 10% 2-propanol in 0.1 M phosphate buffer (pH = 7). Flow: 0.9 mL/min. Wavelength: 236 nm. Detector: Hitachi L 4000, AUFS 0.02. Retention times: (*S*)-(+)-ibuprofen, 7.93 min; (*R*)-(−)-ibuprofen, 12.92 min.

B. Achiral HPLC Analysis. 1. For (*R*,*S*)-Ibuprofen. Column: ALTECH Hypersil ODS (C_{18}), 25 cm × 4.6 mm. Mobile phase: 40% H_2O (0.1% H_3PO_4), 60% Acetonitrile. Flow: 1.2 mL/min. Wavelength: 236 nm. Detector: Hitachi L 4000, AUFS 0.02. Retention times: ibuprofen, 7.3 min.

2. For Lysine. Column: ALTECH Hypersil ODS (C_{18}) 25 cm × 4.6 m. Solvent: 100% H_2O (0.1% H_3PO_4). Flow: 0.6 mL/ min. Detector: Hitachi L 4000, AUFS 0.02. Wavelength: 200 nm. Retention time: lysine, 5.42 min.

Recrystallization to Produce Diastereomerically Pure (*S*)-(+)-Ibuprofen/(*S*)-Lysinate. (*S*)-(+)-Ibuprofen/(*S*)-lysinate (2 g, 90% diastereomeric purity) was dissolved in a mixture of ethanol (12 mL) and water (1.2 mL) at 60 °C. The mixture was slowly cooled from 60 °C to 0 °C over a period of 2 h and then stirred at 0 °C for an additional 2 h. The crystals were collected by filtration, washed with cold (0 °C) ethanol (6 mL), and dried under vacuum overnight to give 1.72 g (90% yield of the available (*S*)-salt) of the (*S*)-(+)-ibuprofen/(*S*)-lysinate in >99% diastereomeric purity. (The 30 °C/hour gradient during the cooling process is important in obtaining the required diastereomeric purity. Thus, when the crystallization mixture was cooled at a faster rate (ca. 10 min), the diastereomeric purity of the product was only 97%.)

Selective Crystallization of (*R*)-(−)-Ibuprofen/(*S*)-Lysinate. Racemic (*R*,*S*)-ibuprofen (20.6 g, 0.1 mol) was dissolved in absolute ethanol (107 mL). The solution was cooled to 12 °C. (*S*)-Lysine (5.84 g, 0.04 mol dissolved in 6.6 mL of water) was added to this solution while maintaining 12 °C temperature and then was followed by an additional 107 mL of ethanol over a period of 1 h again maintaining the 12 °C temperature. The reaction mixture was stirred at 22 °C for 48 h. The crystals were collected by filtration, washed with ethanol (40 mL), and dried under house vacuum overnight to give 9.9 g (70% yield based on (*S*)-lysine) of (*R*)-(−)-ibuprofen/(*S*)-lysinate salt in 60% diastereomeric purity as evidenced by chiral HPLC. The salt was recrystallized from 65.3 mL of ethanol/water (10:1 v:v) as described above to produce 7.1 g (90% yield of the available (*R*)-salt) of the (*R*)-(−)-ibuprofen/(*S*)-lysinate in >99% diastereomeric purity.

Preparation of (*S*)-(+)-Ibuprofen from (*S*)-(+)-Ibuprofen/(*S*)-Lysinate. (*S*)-(+)-Ibuprofen/(*S*)-lysinate, 35.2 g (99% de), was dissolved in 300 mL of water at 22 °C. The solution was adjusted to pH = 1 by the addition of concentrated aq HCl. The mixture was stirred for 1 h at 22 °C. The heterogeneous mixture was filtered, and the crystals were washed with water (60 mL). The crystals were dried at 50 °C under house vacuum to give 20.6 g of (*S*)-(+)-ibuprofen (100% yield) of 99% enantiomeric purity as evidenced by chiral HPLC. Mp 52−53 °C (lit[7b] 52−53 °C for 99% pure (*S*)-isomer). ^{1}H NMR δ ($CDCl_3$) 7.21 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 3.70 (q, J = 7.2 Hz, 1H), 2.44 (d, J = 6.8 Hz, 2H), 1.95−1.75 (m, 1H), 1.49 (d, J = 7.2 Hz, 3H), 0.89 (d, J = 7.2 Hz, 6H).

Preparation of (*R*)-(−)-Ibuprofen from (*R*)-(−)-Ibuprofen/(*S*)-Lysinate. (*R*)-(−)-Ibuprofen/(*S*)-lysinate, 35.2 g (99% de), was subjected to the same acidification process as described above to give 20.6 g of (*R*)-(−)-ibuprofen (100% yield) in 99% enantiomeric purity as evidenced by chiral HPLC.

Racemization of (*S*)-(+)-Ibuprofen. (*S*)-(+)-Ibuprofen (10 g, >99% ee) was held at 230 °C for 4 h at the end of which time complete racemization of (*S*)-(+)-ibuprofen was observed as evidenced by chiral HPLC. Upon cooling to room temperature, the racemic (*R*,*S*)-ibuprofen crystallized on standing. HPLC analysis of the product showed no significant (<1%) decomposition.

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