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Optical Purification of Profen Drugs

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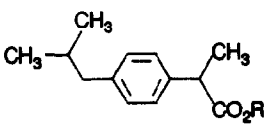
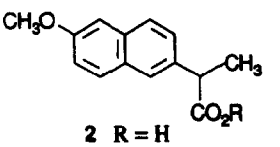
Abstract: *Ibuprofen (1) and naproxen (2) are optically purified by crystallization of their sodium salts (3 and 4) from optically enriched mixtures. Treatment of an acetone solution of 76% ee 1 with NaOH afforded 100% ee 3. Calculated melting point phase diagrams of compounds 1-4 are presented.*

Profens are a structural class of nonsteroidal antiinflammatory drugs consisting of propionic acids bearing variously-substituted aromatic groups at the 2-positions. 2-(4-Isobutylphenyl)propionic acid (ibuprofen, 1) and 2-(6-methoxy-2-naphthyl)propionic acid (naproxen, 2) are the best known members of the class.



1 R = H
3 R = Na



2 R = H
4 R = Na

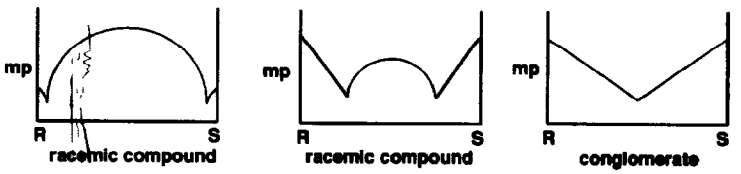
Profens contain a stereogenic center α to the aromatic ring. Naproxen (2) is the only profen currently sold in enantiomerically pure form. Ibuprofen (1) and other profens, such as ketoprofen and flurbiprofen, are sold as racemates. The development of optically pure forms of existing drugs undertaken by several companies in the 1980s led to extensive investigation of methods for the production of chiral profens. Described in the literature are diastereomeric salt resolutions, chemical and enzymatic kinetic resolutions, asymmetric syntheses using chiral auxiliaries, and asymmetric syntheses using chiral catalysts.[1]

Diastereomeric salt resolution, a classic method of racemate separation, has been widely applied to profens. Profen salts of many chiral amines are separable by crystallization, including those of lysine[2] and α-methylbenzylamine[3] with 1 and those of N-ethyl-D-glucamine[4], cinchonidine[5], and dehydroabietylamine[6] with 2. The efficiencies of these resolutions vary. For example, one crystallization of the 2/cinchonidine salt from methanol gave 2 in 86% enantiomeric excess (ee)[5], while one crystallization of the 2/N-ethyl-D-glucamine salt from isopropanol gave 2 in only 42% ee.[4]

Another method of resolving a racemic mixture, preferential crystallization (also called resolution by entrainment)[7], is possible if the compound exists as a conglomerate rather than a racemic compound.[8] To understand this purification method, the melting point phase diagrams (MPPDs) of the various materials must

be considered. Figure 1 shows generalized MPPDs. The eutectic (low-melting) composition of a conglomerate is the racemic composition; the eutectic composition of a racemic compound is *not* the racemic composition. Only 10-20% of mixtures of enantiomers exist as conglomerates. A useful concept is that conglomerates represent one end of a continuum of melting point behavior, varying in the composition of the eutectic. Recrystallization of a certain composition typically yields a solid whose composition is uphill on the phase diagram curve compared to the starting composition (uphill concept). This is consistent with preferential crystallization of conglomerates. Also, for a racemic compound, the eutectic composition may not be passed by crystallization under thermodynamic conditions.

Figure 1. Generalized Melting Point Phase Diagrams



The preferential crystallization method is not applicable to resolution of **1** and **2** because they are racemic compounds rather than conglomerates, as is evident from examination of their MPPDs (the MPPD of **1** is published[9]). One strategy previously employed for resolution of **2** was to search for derivatives that exist as conglomerates. Methyl and ethyl esters of **2** were found to be conglomerates, and therefore racemic mixtures of these are resolvable by preferential crystallization.[10]

During a similar investigation related to **1**, we discovered that the sodium salt of **1** (**3**) is a derivative whose solid properties allow easy optical purification. However, this derivative does not exist as a conglomerate. The infrared spectra of racemic and S-**3** are very similar, but do exhibit some differences as expected of a racemic compound. The most convincing evidence that **3** is a racemic compound rather than a conglomerate was our inability to obtain optically purified material by seed-induced crystallization of racemic material (preferential crystallization).

Optical purification did occur using non-racemic (optically enriched) mixtures. The starting material in this study was **1**, typically containing from 85-90% S isomer (70-80% ee). Such mixtures were generated by crystallization of the **1**/α-methylbenzylamine salt[3] followed by acidification and recovery of **1**, but could in principle come from asymmetric synthesis as well. Recrystallization of a 70% ee mixture of **1** from hexane afforded a racemic crystal crop. However, treatment of the 70% ee mixture of **1** with one-half an equivalent of NaOH in acetone afforded solid **3** which, after acidification, gave **1** containing >99% S isomer. The chemical yield in the latter process was nearly quantitative based on NaOH.

Similarly, other metal salts of **1** are useful derivatives in this purification scheme. Treating **1** of 76%

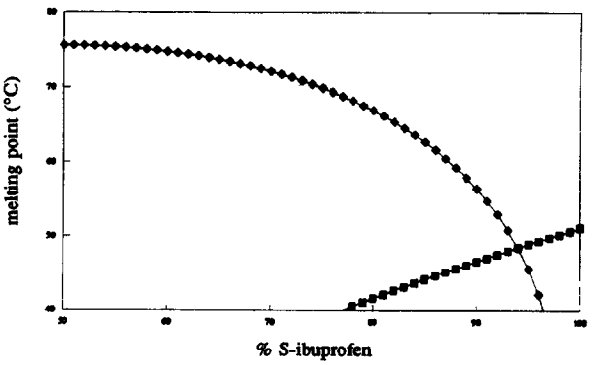
ee with CsOH, LiOH, or $ZnCl_2$ gave precipitated salts of 99% ee, 96% ee, and 96% ee, respectively.

This procedure was also used to optically purify enriched 2. Commercially available S-2 was partially racemized by heating with triethylamine, giving 2 containing 89% S isomer and 11% R isomer (78% ee). Treatment of this with one-half an equivalent of NaOH in acetone gave the sodium salt of 2 (4) as a solid. Acidification afforded 2 containing 94% S isomer (88% ee).

A process of this type has been reported for optical purification of aryloxypropionic acids.[11] For example, the n-propylamine salt of R-2-phenoxypropionic acid was used to upgrade the acid purity from 75% ee to >99% ee.[11a]

As stated earlier, 1 is a racemic compound. The eutectic composition for 1 is somewhere around 90%S/10%R (or 90%R/10%S). Dwivedi *et al* reported the eutectic at 82%S, but extrapolated part of the diagram to arrive at that figure.[9] We constructed the MPPD of 1 by differential scanning calorimetric (DSC) analyses (for melting points) of varying mixtures, followed by chiral high pressure liquid chromatographic analyses (for compositions) of the actual DSC samples. The eutectic was found at 89%S/11%R (or 89%R/11%S). We also calculated the MPPD by applying the Schröder-Van Laar equations to melting points and enthalpies of fusion determined by DSC (Figure 2 shows one half of the symmetrical MPPD). The intersection of the line calculated for the racemate with the line calculated for one enantiomer gives the calculated eutectic, which for 1 is 94%S/6%R (or 94%R/6%S). The calculated and experimental eutectics match reasonably well.

Figure 2. Calculated Melting Point Phase Diagram for Ibuprofen (1)

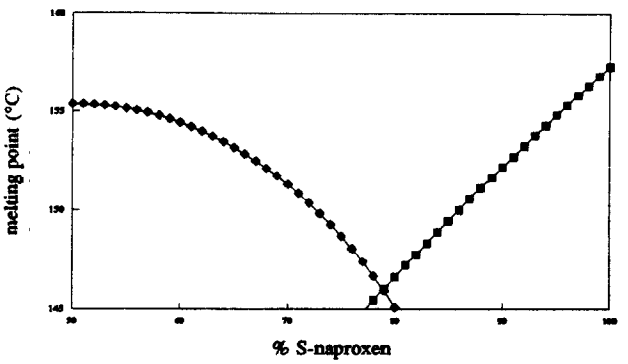


Similarly the calculated MPPD for 2 (Figure 3) indicates the eutectic is about 79%S/21%R (or 79%R/21%S). These MPPDs, particularly that of 1, are close to the non-conglomerate end of the continuum (Figure 1, left MPPD). It is important to remember when using such calculations that the Schröder-Van Laar equations assume ideal behavior.

Based on the uphill concept, 1 must be at least about 90% enantiomerically pure, and 2 at least about 80% enantiomerically pure, before crystallization will result in further optical purification. In practice, we find

that crystallization of 1 of >95% enantiomeric purity affords only marginal (0.5-1%) optical purification. This

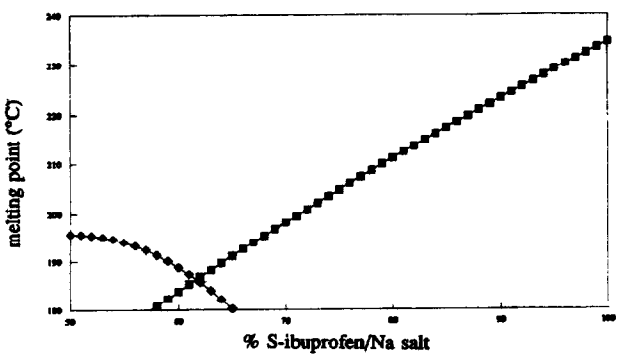
Figure 3. Calculated Melting Point Phase Diagram for Naproxen (2)



can be rationalized by noting that, for 1, the slope of the MPPD line between the eutectic composition and the pure enantiomer is very small. There is almost no "uphill" in this region.

On the other hand, the sodium salts of 1 and 2 exhibit MPPDs with eutectic compositions much closer to racemic compositions (Figure 1, middle MPPD). The calculated MPPD for 3 (Figure 4) yields a eutectic composition of 62%S/38%R (or 62%R/38%S); that for 4 (Figure 5) yields a eutectic composition of 66%S/34%R (or 66%R/34%S). Therefore crystallization of 3 which contains at least 62% of the S-isomer gives solid material of increased optical purity.

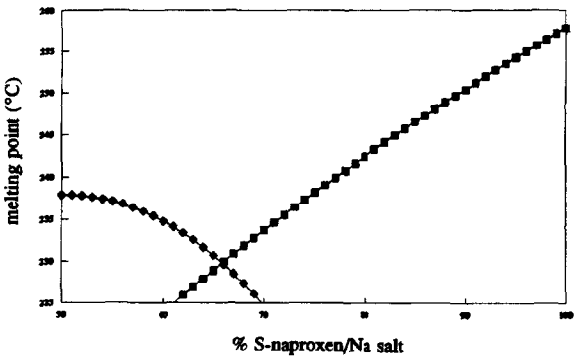
Figure 4. Calculated Melting Point Phase Diagram for Ibuprofen/Na Salt (3)



The practical advantages of the described optical purification method are significant. Primarily, fewer process steps are required. Ibuprofen (1)/α-methylbenzylamine salt of 78% ee requires three recrystallizations from ethanol to generate >98% ee material.[3b] By switching from the α-methylbenzylamine salt to the sodium

salt, the purity of 76% ee **1** can be upgraded to >98% ee in only one crystallization. The number and volume of recycle streams are decreased along with the number of steps. Also, chemical and handling losses of expensive chiral resolution agents are minimized by removing such reagents from the process as early as possible.

Figure 5. Calculated Melting Point Phase Diagram for Naproxen/Na Salt (4)



EXPERIMENTAL SECTION

General. Optical purities of ibuprofen (1) and naproxen (2) were determined on a Hewlett-Packard 1090 high-pressure liquid chromatograph (HPLC) equipped with a filter photometric detector and a chiral AGP 100-4 column from Advanced Separation Technologies. The eluent was 10% (V/V) isopropyl alcohol in water containing 0.01 M potassium dihydrogen phosphate and 0.005 M octanoic acid and adjusted to pH 7 with sodium hydroxide. Differential scanning calorimetric (DSC) data were measured on a TA Instruments 2100 Thermal Analysis System equipped with a 912 dual sample cell. Melting point phase diagrams were calculated based on the Schröder-Van Laar equations[8] using Lotus 1-2-3 Release 3.1 software.

Calculation of Melting Point Phase Diagrams. DSC data obtained:

Compound	Melting Point (°C)	Enthalpy of Fusion ($cal \cdot g^{-1}$)
racemic 1	75.47	29.65
S-1	51.10	22.90
racemic 2	155.38	33.52
S-2	157.28	32.52
racemic 3	195.72	11.22
S-3	234.61	20.33
racemic 4	237.91	24.99
S-4	257.82	31.36

The Schröder-Van Laar equations were rearranged and input into Lotus 1-2-3 in the following forms:

racemate: (-a/ln(%S/100)-b)-273; where a = ΔH_{fus}(cal·mole^{-1})/ R(1.9869 cal·mol^{-1}·K^{-1}), b = a/melting point(K)

enantiomer: (-c/ln(4*%S/100*(1-%S/100))-d))-273; where c = 2(ΔH_{fus}(cal·mole^{-1}))/R(1.9869 cal·mol^{-1}·K^{-1}), d = c/melting point(K)

Optical Purification of Ibuprofen (1). Ten g (48 mmol) of 1 containing 88%S isomer and 12% R isomer (76% ee) were dissolved in 100 mL of acetone. To this was added 1.0 g (25 mmol) of sodium hydroxide (pellets) and the resulting mixture was stirred until the sodium hydroxide dissolved. The acetone was allowed to evaporate and the solid residue was triturated with 100 mL of diethyl ether. Filtration afforded 5.4 g (95% yield) of the sodium salt of 1. Some of this was partitioned between diethyl ether and 10% HCl. Drying ($MgSO_4$) and concentration of the ether layer afforded 1, which contained 100% S isomer by HPLC.

Optical Purification of Naproxen (2). To a solution of 4.6 g (20 mmol) of naproxen (78% ee) in 50 mL of acetone was added 0.4 g (10 mmol) of sodium hydroxide. The heterogeneous mixture was stirred overnight at room temperature, then filtered to give 2.5 g (100% yield) of the sodium salt of 2. Acidification as described above gave 2 containing 97% S isomer (94% ee).

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