# Racemization of (*S*)-Profen Thioesters by Strong Neutral Bases in Nonpolar Organic Solvents: Implication for Ion-Pair Kinetic Basicity

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The racemization of (*S*)-profen 2,2,2-trifluoroethyl thioesters in isooctane with trioctylamine as base was carried out, in which the Hammett equation $\log(k^*_{int}) = 3.584\sigma - 3.745$ was successfully applied to describe the electron-withdrawing effect of the substituents to the α-phenyl moiety of the thioesters. A combination of neutral strong organic bases with different nonpolar solvents was employed to determine the second-order interconversion constants for the racemization of (*S*)-naproxen 2,2,2-trifluoroethyl thioester, in which solvent hydrophobicity was found to have less effect on the racemization. Implication for ion-pair kinetic basicity scale for the neutral strong bases in isooctane was further discussed.

## Introduction

Recently, enzyme-catalyzed resolution of racemic compounds has become a valuable method for obtaining optically pure pharmaceutical, agricultural, and other specialty chemicals.[1] On the basis of the racemic starting substrate, the standard kinetic resolution process has a disadvantage of maximum 50% yield in obtaining the desired enantiomer. This limitation has been overcome by employing the dynamic kinetic resolution process in which the standard kinetic resolution is coupled with continuous in situ racemization of the undesired substrate.[2] Therefore, it is possible to give theoretical 100% yield of the desired product. Although such a process has industrial practicality, only fairly specific examples were reported.[2,3] One may attribute to in general the harsh racemization condition of high temperature in polar organic solvents to deactivate the enzyme.[4] Therefore, continuous studies on finding milder racemization conditions that simultaneously maintain the enzyme active and stereoselective are needed.

As an important class of nonsteroidal antiinflammatory drugs, 2-arylpropionic acids (i.e. profens) have their pharmacological activity mainly on the (*S*)-enantiomer.[5] Various kinetic resolution and asymmetric synthesis processes have been proposed to produce the desired (*S*)-profens.[6] Recently, a dynamic kinetic resolution process with lipase and trioctylamine as catalysts in isooctane has been developed to obtain a high yield and optical purity of (*S*)-naproxen or (*S*)-suprofen from their thioesters.[7] Since the racemization step plays an important role in the resolution process, a 34-fold enhancement of the racemization rate of (*S*)-suprofen thioester was further noticed when comparing with that of (*S*)-naproxen thioester. This implies that comparing with the 6-methoxyl-2-naphthyl substitute for the later, the *para*-2-thenoyl moiety of the former was more favorable on the racemization of thioesters. Thus, to broaden the resolution strategy to the production of other (*S*)-profens, the electron-withdrawing effect of the α-aryl substitute on the racemization of (*S*)-profen thioesters in isooctane was first studied (Scheme 1).[8] A drawback of relative lower racemization rate of the remaining (*R*)-thioester compared with the enzymatic rate of the fast-reacting (*S*)-thioester was also observed.[7] To explore more efficient racemization catalysts, several strong neutral organic bases were screened for (*S*)-naproxen thioester in nonpolar organic solvents. The second-order interconversion constants obtained were further interpreted as an implication of the ion-pair kinetic basicity of the base in nonpolar organic solvents and were compared with the equilibrium ion-pair basicity.

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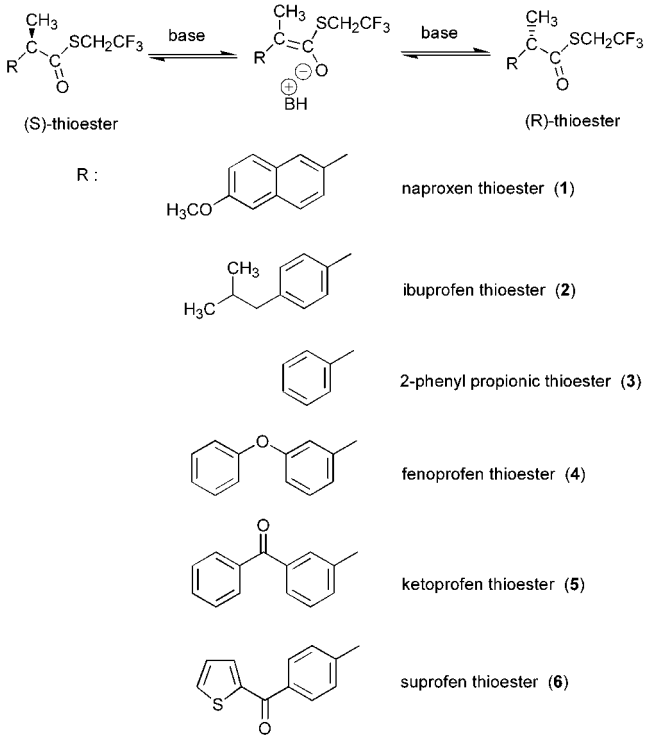
**Scheme 1**




## Experimental Section

**Chemicals.** (*S*)-Naproxen ((*S*)-2-(6-methoxyl-2-naphthyl)-propionic acid), (*R*,*S*)-fenoprofen ((*R*,*S*)-2-(3-phenoylphenyl)-propionic acid) calcium salt, and phenyl dichlorophosphate were purchased. Lipase MY (triacylglycerol ester hydrolases, EC 3.1.1.3) from *Candida rugosa* (30 units/mg of solid) was provided by Meito Sangyo (Tokyo, Japan) and immobilized on polypropylene powders.[9] Other chemicals of analytical grade that were commercially available are as follows: (*S*)-ibuprofen ((*S*)-4-isobutyl-2-methylphenylacetic acid); (*S*)-ketoprofen ((*S*)-2-(3-benzoylphenyl)propionic acid); (*S*)-2-phenylpropionic acid; (*R*,*S*)-flurbiprofen (2-fluoro-2-methyl-4-biphenylacetic acid); 2,2,2-trifluoroethanethiol; isooctane; sodium chloride; thionyl chloride; triethylamine (TEA); trioctylamine (TOC); chloroform; 1,2-dimethoxyethane; anhydrous pyridine; 1,8-diazabicyclo[5,4,0]undec-7-ene(1,5-5) (DBU); 1,4-diazabicyclo[2,2,2]-octane (DABCO); diethylaminomethyl-polystyrene (DEAM-PS).

**Analysis.** The racemization of (*S*)-profen 2,2,2-trifluoroethyl thioester in organic solvents was monitored by HPLC using a chiral column capable of separating the internal standard, (*R*)- and (*S*)-profen thioesters. In general, the mobile phase was pure *n*-hexane or a mixture of *n*-hexane−2-propanol−acetic acid. UV detection at 270 nm was for quantification at the column temperature of 25 °C. Details were given in the Supporting Information section.

**Synthesis of (*S*)- or (*R*,*S*)-Profen Thioesters.** To 25 mL of ice-cooled dry 1,2-dimethoxyethane was added 2 mmol of (*S*)- or (*R*,*S*)-profen, 1.15 mL of anhydrous pyridine, 1.07 mL of phenyl dichlorophosphate, and 8.6 mmol of 2,2,2-trifluoroethanethiol and reacted at room temperature for 16 h with stirring. The resulting solution was added to 20 mL of ice-cooled NaOH solution (1 M), and then 25 mL of chloroform was added with stirring for 30 min for the extraction of the product. The organic layer was separated and successively washed twice with 50 mL of 1 M NaOH solution and twice with 50 mL of saturated NaCl solution, dried over $MgSO_4$ for 24 h, filtered, and concentrated in a vacuum. The resulting oil was purified by silica gel liquid chromatography and concentrated in a vacuum. The desired thioesters were confirmed from the retention time in HPLC. $^1$H NMR spectra were also recorded at 200 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. Details were given in the Supporting Information section.

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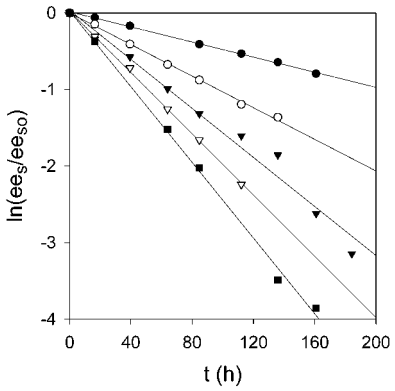


**Figure 1.** Time-course variations of $\ln(ee_S/ee_{SO})$ in isooctane for 3 mM (*S*)-ibuprofen thioester at 45 °C at TOC concentration of (●) 25 mM, (○) 50 mM, (▼) 75 mM, (▽) 100 mM, and (■) 125 mM.

To 15 mL of isooctane were added 3 mM (*R*,*S*)-fenoprofen thioester and 60 mg/mL of the immobilized lipase. Enantioselective hydrolysis was carried out at 45 °C. The resultant solution was filtrated, and the products of (*R*)- and (*S*)-fenoprofen were extracted by adding 15 mL of aqueous solution containing NaOH (pH 10). Then, the organic phase was removed, dried over $MgSO_4$, filtered, and concentrated in a vacuum, giving a mixture of (*R*)- and (*S*)-fenoprofen thioesters of known $ee_S$ value defined as the enantiomeric excess for the enantiomers.

**Racemization of (*S*)-Profen Thioesters.** All solvents were dried over the molecular sieves for 24 h before the experiment. To 15 mL of isooctane was added 3 mM (*S*)-profen thioester (or a mixture of (*R*)- and (*S*)-fenoprofen thioesters of known initial $ee_S$ value, i.e., $ee_{SO}$), and TOC of concentrations varied from 17 to 150 mM. The resultant solution was stirred with a magnetic stirrer at 45 °C. Samples were removed and injected onto HPLC at different time intervals for analysis. From the time-course variations of $ee_S$, the interconversion constants for the racemization were estimated from the experimental data coupled with the theoretical equation. The racemization of (*S*)-naproxen thioester was further carried out except that a different combination of solvents (i.e. isooctane, cyclohexane, or *n*-hexane) and organic bases (i.e. DABCO, DBU, DEAM-PS, or TEA) was employed.

## Results and Discussion

**Racemization of (*R*)- or (*S*)-Profen Thioesters in Isooctane.** As shown in Scheme 1, the mechanism for the racemization of (*R*)- or (*S*)-profen thioester may involve the α-proton abstraction by base to give a planar enolate. In most cases, the α-proton abstraction was found to be the controlling step for the racemization of α-carbon acids in organic solvents.[8] This implies that a pseudo-steady-state assumption for the intermediate might simplify Scheme 1 as follows:

$$(S)\text{-profen thioester} \underset{k_{int}}{\overset{k_{int}}{\rightleftharpoons}} (R)\text{-profen thioester} \quad (1)$$

Therefore, the interconversion constant $k_{int}$ can be fitted from the experimental data coupled with the theoretical equation $\ln(ee_S/ee_{SO}) = -2tk_{int}$ with $t$ as time.[8c]

Figure 1 illustrates typical time-course variations of $\ln(ee_S/ee_{SO})$ with TOC concentrations in isooctane at 45 °C for (*S*)-ibuprofen 2,2,2-trifluoroethyl thioester. At any

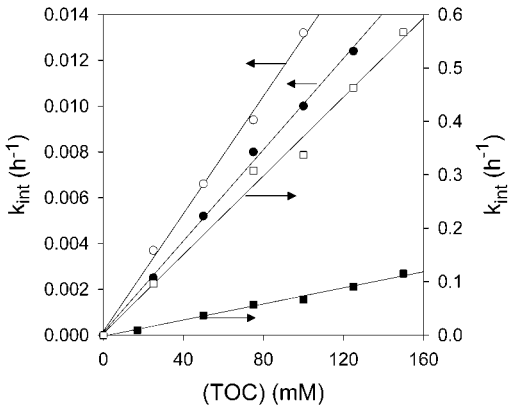


**Figure 2.** Variations of interconversion constant with TOC concentration for (○) (*S*)-2-phenylpropionic thioester, (●) (*S*)-ibuprofen thioester, (□) (*S*)-ketoprofen thioester, and (■) (*S*)-fenoprofen thioester.

**Table 1. Effect of Hammett Substituent Constant of the Substituent in the α-Phenyl Moiety of (*S*)-Profen Thioesters on the Second-Order Interconversion Constant (with Unit of $h^{-1}$ $mM^{-1}$) in Isooctane at 45 °C**

| param | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| $\sigma^a$ | 0.039[b] | −0.12 | 0 | 0.25 | 0.34 | 0.43[c] |
| $10^4 k^*_{int}$ | 2.48[d] | 1.03 | 1.28 | 7.53 | 36.9 | 86.0[e] |

[a] Hammett substituent constants $\sigma$ from ref 10. [b] The $\sigma$ value was calculated from the Hammett equation $\log(k^*_{int}) = 3.584\sigma - 3.745$. [c] The $\sigma$ value of the *para*-(2-thenoyl) substitute in suprofen thioester was regarded as that of the *para*-(benzoyl) substitute. [d] Reference 7a. [e] Reference 7b.

specific time, increasing the TOC concentration results in the decrease of $\ln(ee_S/ee_{SO})$ and hence the greater racemization. A linear relationship for each TOC concentration was illustrated in which the interconversion constant was estimated and represented in Figure 2, from which the second-order interconversion constant $k^*_{int} = 1.03 \times 10^{-4}$ $h^{-1}$ $mM^{-1}$ as the slope of the line was determined. Similar results as shown in Figure 1 for the racemization of other (*R*)- or (*S*)-profen thioesters were obtained (data not shown), with which the interconversion constants varied with the TOC concentration were also represented in Figure 2 and the second-order interconversion constants were determined.

The logarithm of the second-order interconversion constants varied with the Hammett substituent constants as further shown in Table 1.[11] A good linear correlation of $\log(k^*_{int}) = 3.584\sigma - 3.745$ with the correlation coefficient of 0.97 was determined without employing the data of (*S*)-naproxen thioester. The high coefficient in the Hammett equation points to great development of charge in the transition state of racemization in Scheme 1. By comparison of the second-order interconversion constant of (*S*)-suprofen thioester with that of (*S*)-ibuprofen thioester, an 85-fold enhancement of the racemization rate for the former at a given TOC concentration was obtained. Although the acyl group of the thioester plays the main role in stabilizing the intermediate, the α-aryl substituent has apparently contributed more inductive and resonance effects on increasing the acidity of the α-proton and, hence, the racemization. Therefore, a higher racemization rate must be associated with a higher $\sigma$ value of the substituent in the α-phenyl moiety of the thioesters. Indeed, the successful racemization of (*S*)-profen thioesters in the present reaction condition that is mild enough for carrying out enzyme-catalyzed resolution will broaden the previous dynamic kinetic process to the production of other (*S*)-profens in the future.

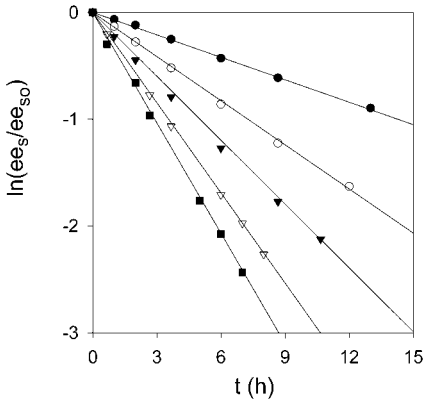


**Figure 3.** Time-course variation of $\ln(ee_S/ee_{SO})$ in *n*-hexane for (*S*)-ibuprofen thioetser at 45 °C at DABCO concentration of (●) 10 mM, (○) 20 mM, (▼) 30 mM, (▽) 40 mM, and (■) 50 mM.

Substitution of the second-order interconversion constant of (*S*)-naproxen thioester into the Hammett correlation yields the apparent $\sigma$ value as 0.039. By comparison of $\sigma = -0.27$ for the *para*-$OCH_3$ moiety in the α-phenyl substituent,[11] the α-naphthalene substituent has the effect of buffering the electron-donating strength of the *para*-$OCH_3$ moiety to increase the apparent $\sigma$ value from −0.27 to 0.039. Then, a further correlation between the second-order interconversion constant and the $\sigma$ value of the substituent in the α-naphthalene moiety of profen thioesters awaits further study.

**Racemization of (*S*)-Naproxen Thioester in Nonpolar Organic Solvents.** By employment of (*S*)-naproxen 2,2,2-trifluoroethyl thioester as the model compound, more experiments were carried out at the condition of different combinations of nonpolar solvents and neutral strong organic bases. Some results were represented in Figure 3 where *n*-hexane and DABCO were the solvent and base, respectively. Therefore, from the slope of the time-course $\ln(ee_S/ee_{SO})$ for each base concentration, the interconversion constant was determined. Some results of the interconversion constant varied with DABCO (or DBU) concentration in isooctane (cyclohexane or *n*-hexane) were further demonstrated in Figure 4, from which the second-order interconversion constant was found and represented in Table 2.

In general, the stronger is the base, the greater the second-order interconversion constant is found. About a 4-order-of-magnitude enhancement of $k^*_{int}$ was obtained when tertiary amines were replaced by DBU in isooctane or cyclohexane. Since isooctane, *n*-hexane, and cyclohexane are classified as inert solvents and have almost the same low dielectric constants, less difference of the second-order interconversion constants was observed for a specified base. This may be attributed to the formation of contact ion pairs, but not separated ion pairs or free ions, as shown in Scheme 1. Therefore, the solvent molecule has less effect on the stabilization of the

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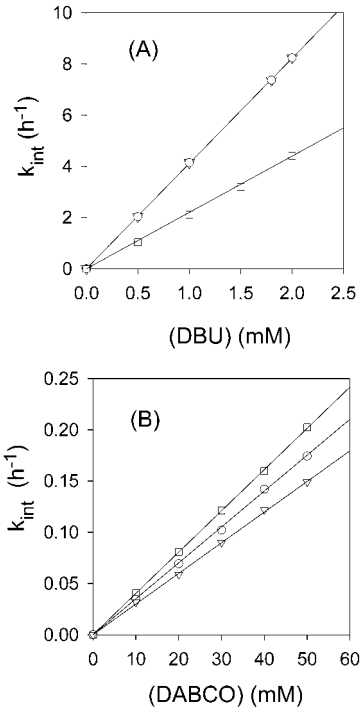


**Figure 4.** Variations of interconversion constant with (A) DBU concentrations and (B) DABCO concentration in (□) isooctane, (○) *n*-hexane, and (▽) cyclohexane.

**Table 2. Effect of Neutral Strong Bases on the Second-Order Interconversion Constants with Unit of $h^{-1}$ $mM^{-1}$ for the Racemization of (*S*)-Naproxen Thioester in Organic Solvents at 45 °C**

| base | isooctane ($\epsilon$ < 2.02)[b] | hexane ($\epsilon$ = 2.02) | cyclohexane ($\epsilon$ = 2.02) |
|---|---|---|---|
| DBU | 2.20 | 4.09 | 4.11 |
| DABCO | $4.00 \times 10^{-3}$ | $3.50 \times 10^{-3}$ | $3.00 \times 10^{-3}$ |
| TOC[a] | $2.48 \times 10^{-4}$ | | |
| DEAM-PS | $2.40 \times 10^{-4}$ | $1.8 \times 10^{-4}$ | |
| TEA | $3.00 \times 10^{-4}$ | | |

[a] Reference 7a. [b] Dielectric constant.

**Table 3. $pK_{Ip}$ of Ion-Pair Basicity of Strong Neutral Bases in THF at 25 °C[a]**

| | DBU | DABCO | TOC | DEAM-PS | TEA |
|---|---|---|---|---|---|
| $pK_{ip}$ | −3.78 | 0.80 | 3.40 | 2.11 | 2.11 |

[a] From ref 12; TOC and DEAM-PS were considered as $(C_4H_9)_3N$ and TEA, respectively.

intermediate. Yet, the order of $k^*_{int}$ of DABCO in all solvents is opposite to that of DBU, which implies that there still exists an unknown interaction between the solvent molecule and the ion pairs. Of course, the more efficient racemization base obtained in the present report still awaits further testing in the previous dynamic kinetic resolution processes.[7]

**Implication for Ion-Pair Kinetic Basicity.** The dissociation constant of the conjugated acid of a neutral strong organic base has been measured by the spectrophotometric method to express the equilibrium basicity in terms of a $pK_a$ value.[13,14] Although several scales for the equilibrium ion-pair acidity in inert solvents, such as benzene, tetrahydrofuran (THF), and heptane, have been reported,[14a] the difficulty in measuring the ion-pair dissociation constant has impeded further developments of the $pK_a$ acidity scale. The isotope exchange of proton in deuterium or tritrium medium by a base reagent has been proposed to measure the kinetic acidity of carbon acids.[15] Unless the exchange rate is much greater than the internal-returning rate of the intermediate, the observed rate does not reflect the base basicity. However with a careful selection of chiral compounds, racemization of the enantiomer in principle can overcome the limitation of internal-returning effect and can be employed to construct the kinetic basicity scale. For examples, Scheme 1 is written as follows:

$$\text{(}S\text{)-profen thioester} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} \text{(}R\text{)-profen thioester} \quad (2)$$

With the pseudo-steady-state assumption for the intermediate, the result of $k_1 = 2k_{int}$ is derived. Thus, both $k_1$ and $k_{int}$ may reflect the base strength in abstracting the α-proton of the thioetsers. A good linear correlation of $\log(k^*_{int}) = -2.0 - 0.60pK_{ip}$ ($R^2 = 0.97$) was found where the ion-pair $pK_{ip}$ values in THF are shown in Table 3. This really implies the nature of ion-pair formation in measuring the equilibrium or kinetic basicity in nonpolar organic solvents of low dielectric constants. More data for using neutral strong bases as the racemization catalysts in nonpolar organic solvents to test the good linearity between equilibrium and kinetic basicities await further study.

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**Supporting Information Available:** Experimental details about the purification and analytical conditions including $^1$H NMR spectra for profen thioesters. This material is available free of charge via the Internet at http://pubs.acs.org.

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