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Racemization and hydrolysis of (*S*)-naproxen 2,2,2-trifluoroethyl ester in non-polar solvents by strong neutral bases: implication for ion-pair kinetic basicity and hydrolysis

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epoc ABSTRACT: By using strong neutral bases as catalyst, a detailed investigation of the racemization of (*S*)-naproxen 2,2,2-trifluoroethyl ester was conducted in the non-polar solvents isooctane, cyclohexane and *n*-hexane. The second-order interconversion constant k^*_{int} as representing the ion-pair kinetic basicity in isooctane was first estimated and correlated with the equilibrium ion-pair basicity pK_{ip} in tetrahydrofuran, giving slopes of 0.768 and 0.689 for non-phosphazene and phosphazene bases, respectively, in the Brønsted correlations. The result was further compared with that for (*S*)-naproxen 2,2,2-trifluoroethyl thioester, showing about a 1–2 orders of magnitude enhancement of k^*_{int} for the corresponding thio-containing analogue. A smaller influence of non-polar solvents (i.e. isooctane, *n*-hexane and cyclohexane) on k^*_{int} was found. Kinetic analysis of the racemization and hydrolysis of (*S*)-naproxen 2,2,2-trifluoroethyl ester in isooctane and *n*-hexane containing 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene and water suggests nucleophilic hydrolysis by the base, where the breakdown of tetrahedral intermediates I_{R1} and I_{S1} is the rate-limiting step and the hydrolysis constant k_{hy} is in proportion to the product of base and ion-pair concentrations.
Additional material for this paper is available in Wiley Interscience

KEYWORDS: racemization; hydrolysis; (*S*)-naproxen 2,2,2-trifluoroethyl ester; strong neutral bases; ion-pair basicity

INTRODUCTION

Base-catalyzed racemization has been employed for compounds with a stereogenic center bearing an acidic proton adjacent to an electron-withdrawing group, such as a ketone or ester, via an enolate intermediate. Various types of chiral α-substituted carboxyl acids, e.g. α-(hetero) arylcarboxyl acids, α-aryloxypropionic acids, α-alkylcarboxyl acids, α-halocarboxyl acids and α-amino acids, as valuable pharmaceuticals, agrochemicals, nutrients and intermediates for organic synthesis have been prepared via kinetic resolution processes. However, only special carboxyl acid derivatives of Ketorolac esters, hydantoins, substituted oxazol-5(4*H*)-ones, substituted thiazolin-5-ones and α-substituted propionic thioesters possessing relatively high α-proton acidity have been employed in dynamic kinetic resolution using enzymatic methods.[1,2] Recently, lipase-catalyzed resolutions of α-arylpropionic esters were demonstrated in organic solvents containing neutral organic bases, but the results were disappointing owing to the lower racemization rate of the remaining (*R*)-ester compared with the enzymatic rate of fast-reacting (*S*)-ester.[3] In order to explore more efficient racemization catalysts for racemic esters containing a chiral acid moiety in a non-polar solvent, isooctane containing (*S*)-naproxen 2,2,2-trifluoroethyl ester and strong neutral bases was first selected as a model system for estimating the second-order interconversion constant. It was then applied as a representation of the ion-pair kinetic basicity of the base and compared with that for the corresponding thio-containing analogue.[4]

When enzymatic biotransformations take place in non-polar solvents, certain water retention in the enzyme aggregate and dissolution in the solvent are needed to maintain the enzyme in a catalytically active conformation. It is then imperative to have non-enzymatic hydrolysis catalyzed by the base in the dynamic kinetic resolution of esters, thioesters or amides by employing enzymatic methods. This may have profound effects on decreasing the enantiomeric excess for the desired product. Therefore, isooctane, *n*-hexane and cyclohexane containing (*S*)-naproxen 2,2,2-trifluoroethyl ester, water and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) were designed as model systems for studying the kinetics

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of racemization and hydrolysis, where effects of ion-pair formation between MTBD and water on the amine and ion-pair concentrations were considered in deriving the rate equations.

EXPERIMENTAL

Materials. Optically pure (*S*)-naproxen [(*S*)-2-(6-methoxy-2-naphthyl)propionic acid] was obtained from Sigma. The strong neutral bases trioctylamine (TOA), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), MTBD, *tert*-butyliminotris-(dimethylamino)phosphorane (P1), *tert*-butyliminotris (pyrrolidino)phosphorane (P1-tris) and 1-*tert*-butyl-4, 4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)phosphoranylidenamino]-2λ^5,4λ^5-catenadi(phosphazene) (P4) were purchased from Aldrich and Fluka. Other chemicals of analytical grade were commercially available and employed without further purification. Anhydrous isooctane, cyclohexane and *n*-hexane were prepared by adding molecular sieve (Type 3A, J. T. Baker) to the solvent for more than 3 days.

Analysis. The racemization and hydrolysis of (*S*)-naproxen 2,2,2-trifluoroethyl ester in the organic solvent were monitored by HPLC using a chiral column of (*S*,*S*)-WHELK-01 from Regis capable of separating the internal standard 2-nitrotoluene, (*R*)- and (*S*)-naproxen, (*R*)- and (*S*)-ester with retention times of 4.5, 12.2, 21.5, 7.2 and 8.9 min, respectively. The mobile phase was a mixture of *n*-hexane–propan-2-ol–acetic acid (80:20:0.5, v/v/v) at a flow-rate of 1.0 ml min^{-1}. UV detection at 270 nm was used for quantification at a column temperature of 25 °C.

Synthesis of (S)-naproxen 2,2,2-trifluoroethyl ester.[5] Following a standard procedure, the acid chloride of (*S*)-naproxen was prepared by refluxing 20 ml of benzene containing 3.45 g of the acid and 3.20 g of thionyl chloride for 1.5 h. The resultant solution was evaporated to dryness under vacuum, 30 ml of benzene containing 2.70 g of 2,2,2-trifluoroethanol and 1.19 g of pyridine were added and the mixture was refluxed for 4 h. After cooling the reaction solution, an aqueous solution (50 ml) containing 6 mM sodium carbonate and deionized water (100 ml) were successively employed four times and twice, respectively, to extract the excess alcohol and remaining (*S*)-naproxen. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under vacuum. After purification by silica gel chromatography with the mobile phase *n*-hexane–ethyl acetate (2:1, v/v) and concentration by vacuum, the desired (*S*)-naproxen 2,2,2-trifluoroethyl ester was obtained as a white powder and confirmed by HPLC using authentic products from lipase-catalyzed esterification of (*R*,*S*)-naproxen with 2,2,2-trifluoroethanol in isooctane. ^{1}H NMR spectra were also recorded at 400 MHz on a Bruker spectrometer in deuteriochloroform solutions with tetramethylsilane as an internal standard. Chemical shifts in ppm from tetramethylsilane were as follows: δ1.61 (3H, t), 3.92 (3H, s), 3.95–4.00 (1H, q), 4.36–4.57 (2H, m), 7.12–7.17 (2H, q), 7.37–7.41 (1H, q), 7.67–7.73 (3H, m).

Racemization of (S)-naproxen 2,2,2-trifluoroethyl ester. To 10 ml of anhydrous isooctane were added 1 mM (*S*)-naproxen 2,2,2-trifluoroethyl ester and various bases of different concentration with stirring at 45 °C. Samples were removed and injected into the above HPLC system at different time intervals for analysis. From the time-course variations of the enantiomeric excess for the ester {i.e. $ee_S = [(A_S) - (A_R)]/[(A_S) + (A_R)]$ where (A_S) and (A_R) are the concentrations of (*S*)- and (*R*)-naproxen 2,2,2-trifluoroethyl ester, respectively}, the first-order interchange constant k_{int} at each base concentration and hence the second-order interchange constant k^*_{int} for the base were estimated. Similar experiments with MTBD as the base in anhydrous *n*-hexane and cyclohexane were carried out.

Racemization and hydrolysis of (S)-naproxen 2,2,2-trifluoroethyl ester. The racemization and hydrolysis of 1 mM (*S*)-naproxen 2,2,2-trifluoroethyl ester in isooctane, *n*-hexane and cyclohexane containing different water contents and MTBD were carried out. From the time-course variations of (*R*)- and (*S*)-naproxen 2,2,2-trifluoroethyl ester concentrations and hence ee_S, one could first estimate the hydrolysis constant k_{hy} and k_{int}, and then the equilibrium constant K_{eq} for the ion-pair formation between MTBD and water and the kinetic constants for hydrolysis.

RESULTS AND DISCUSSION

Racemization of (*S*)-naproxen ester in isooctane

The mechanism for the racemization of (*S*)-naproxen 2,2,2-trifluoroethyl ester involves α-proton abstraction by the base to give a planar enolate. In most cases, the α-proton abstraction is the rate-limiting step and the mechanism can be expressed as follows:[6]

$$A_s \underset{k_{int}}{\overset{k_{int}}{\rightleftharpoons}} A_R \qquad (1)$$

where A_R and A_S represent (*R*)- and (*S*)-naproxen 2,2,2-trifluoroethyl ester, respectively. Therefore, the first-order interconversion constant k_{int} can be estimated from the time-course data for ee_S coupled with the theoretical equation $\ln(ee_S/ee_{S0}) = -2tk_{int}$, where ee_{S0} and t are the initial ee_S and time, respectively.

Figure 1 demonstrates typical time-course variations of $\ln(ee_S/ee_{S0})$ at various DBU concentrations in isooctane at 45 °C, from which k_{int} was determined and is presents

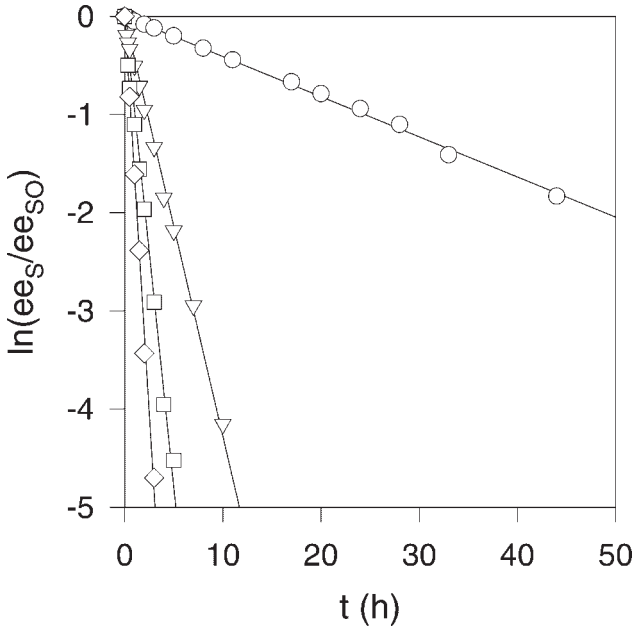


Figure 1. Time-course variations of $\ln(ee_S/ee_{S0})$ in isooctane at 45 °C for 1 mM (*S*)-naproxen 2,2,2-trifluoroethyl ester and DBU concentrations of (○) 1, (▽) 10, (□) 20 and (◇) 30 mM

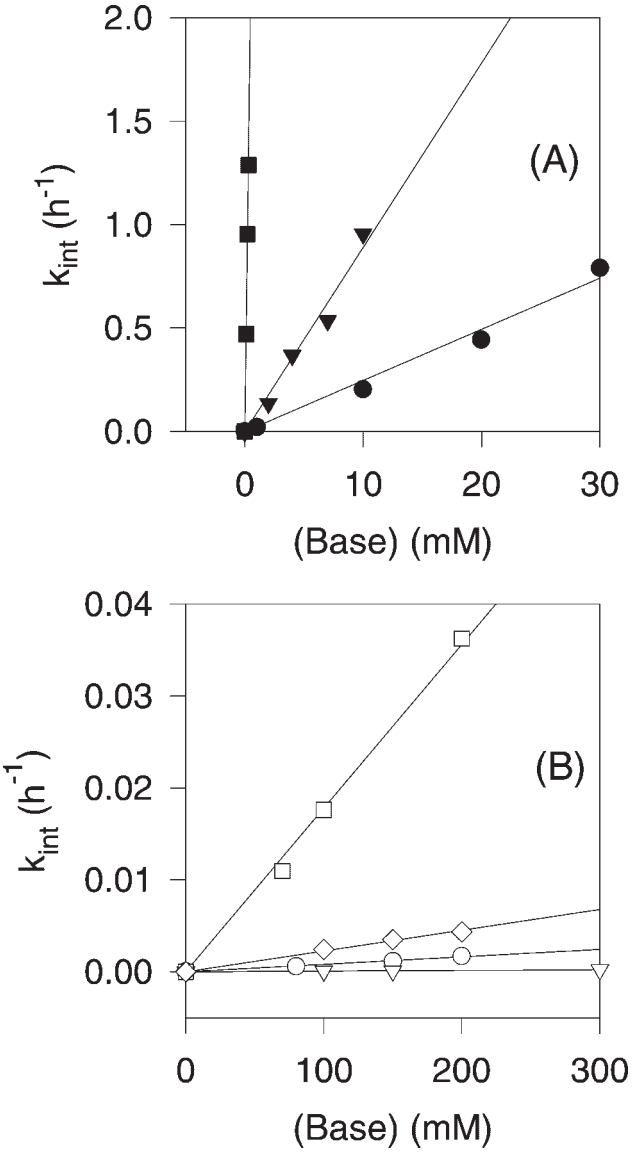


Figure 2. Variations of first-order interconversion constants with base concentrations in isooctane for various strong neutral bases: (A) (■) P4, (▼) MTBD and (●) DBU; (B) (□) P1-tris, (◇) P1, (○) DABCO and (▽) TOA

in Fig. 2(A) for illustration. As indicated by the linear dependence of k_{int} on DBU concentration, the second-order interconversion constant as the slope of the straight line, $k^*_{int} = 2.56 \times 10^{-2}\,h^{-1}\,mM^{-1}$, was further estimated. Similar results to those shown in Fig. 1 for other neutral bases were obtained (data not shown), from which the first-order interconversion constants varied with the base concentration as illustrated in Fig. 2(A) and (B), and hence the second-order interconversion constants were obtained as listed in Table 1.

In general, the stronger is the base in terms of the equilibrium acidity pK_A of the conjugated acid in acetonitrile (no available data in isooctane), the greater is the second-order interconversion constant in isooctane. About a five orders of magnitude enhancement of k^*_{int} is obtained when TOA is replaced by MTBD, or P1 by P4. Brønsted plots have been proposed to elucidate the nucleophilic and/or general base catalysis of the acyl group transfer reactions of esters and thioesters. Although the mechanism of based-catalyzed racemization is completely different from that of acyl transfer reaction, the Brønsted correlations can be employed to investigate the effect of the substrate and base on k^*_{int}. A good linear relationship,

Table 1. Effect of strong neutral bases on the second-order interconversion constants for the racemization of (*S*)-naproxen 2,2,2-trifluoroethyl ester and (*S*)-naproxen 2,2,2-trifluoroethyl thioester in isooctane at 45 °C

Parameter	TOA	DABCO	DBU	MTBD	P1	P1-tris	P4
pK_A[a]	18.04	18.29	24.33	25.44	26.88	28.40	42.70
pK_{ip}[b]	12.63	12.85	17.80	18.83	18.80	20.10	na[e]
k^*_{int}[c]	$7.467^{(-7)}$	$8.315^{(-6)}$	$2.470^{(-2)}$	$8.902^{(-2)}$	$2.262^{(-5)}$	$1.781^{(-4)}$	$4.459^{(0)}$
k^*_{int}[d]	$2.48^{(-4)}$	$4.00^{(-3)}$	$2.20^{(0)}$	nd[f]	nd	nd	nd

[a] In acetonitrile.[7]
[b] pK_{ip} for TOA, DABCO or MTBD estimated from $pK_A = 1.195pK_{ip} + 2.94$ ($R^2 = 0.97$) for non-phosphazene bases in tetrahydrofuran.[8]
[c] Units $h^{-1}\,mM^{-1}$ for (*S*)-naproxen 2,2,2-trifluoroethyl ester. Values in parentheses are exponents, e.g. $(-7) = \times 10^{-7}$.
[d] Units as $h^{-1}\,mM^{-1}$ for (*S*)-naproxen 2,2,2-trifluoroethyl thioester from Ref. 4. Values in parentheses are exponents (see footnote c).
[e] na, Not available.
[f] nd, Not done.

$\log k^*_{int} = 0.639pK_A - 17.2$ ($R^2 = 0.98$), was estimated for TOA, DABCO, DBU and MTBD. For the extremely hindered phosphazene bases P1, P1-tris and P4, the correlation became $\log k^*_{int} = 0.324pK_A - 13.2$ ($R^2 = 0.99$). The different slopes and intercepts in the Brønsted correlations for phosphazene and non-phosphazene bases implies that aside from different hindrance effects of strong neutral bases in abstracting the α-proton, the contact ion-pair formation in isooctane, but not free ions in polar solvents such as acetonitrile, might affect the ion-pair formation of enolate intermediate with the base and hence the k^*_{int} value during racemization. Therefore, when the equilibrium ion-pair basicity in tetrahydrofuran (Table 1) is regarded as that in isooctane,[8] the correlations become $\log k^*_{int} = 0.768pK_{ip} - 15.4$ ($R^2 = 0.96$) for TOA, DABCO, DBU and MTBD and $\log k^*_{int} = 0.689pK_{ip} - 17.6$ for P1 and P1-tris (no data available pK_{ip} for P4), respectively. The similar slopes of 0.768 and 0.689 imply that an increase of one unit in pK_{ip} yields a similar enhancement for k^*_{int}, regardless of whether a tertiary amine, amidine, guanidine or phosphazene base is used. Moreover, the lower value of -17.6 in comparison with -15.4 for non-phosphazene bases reflects the extremely hindered nature of phosphazene bases, giving about a two orders of magnitude lower k^*_{int} at the same pK_{ip} value. Obtaining more data using other neutral bases as the racemization catalyst and/or enantiomers as the substrate in isooctane to test the validity of the above Brønsted correlations awaits further studies.

Several scales of the equilibrium acidity in non-polar solvents such as tetrahydrofuran and heptane have been reported.[9] The difficulty in measuring the ion-pair dissociation constant has impeded further development of the equilibrium ion-pair acidity scale.[10] Similarly, only recently was the equilibrium ion-pair basicity scale anchored to the pK_A value of 12.5 for triethylamine in tetrahydrofuran.[8] Isotope exchange of the α-proton in non-polar solvents by base reagents might be employed to measure the kinetic basicity of the base. However, unless the exchange rate is much greater than the internal-returning rate of the intermediate, the observed rate will not reflect the kinetic basicity. With a careful selection of chiral compounds, racemization of the enantiomer in principle can overcome the limitation of the internal-returning effect and be employed to construct the kinetic basicity scale for strong neutral bases in non-polar organic solvents.

The racemization of (*S*)-naproxen 2,2,2-trifluoroethyl thioester in isooctane at 45 °C by using TOA, DABCO and DBU as the base was carried out to estimate k^*_{int} values (Table 1).[4] In general, more than a one order of magnitude enhancement of k^*_{int} for (*S*)-naproxen 2,2,2-trifluoroethyl thioester is found, which indicates that the 2,2,2-trifluoroethanethiol moiety plays an important role in increasing the α-proton acidity during racemization.[1b] A Brønsted correlation of $\log(k^*_{int})_{thioester} = 0.659pK_{ip} - 11.37$ ($R^2 = 0.94$) is obtained, where the slope is similar to the value of 0.768 for (*S*)-naproxen 2,2,2-trifluoroethyl ester.

Table 2. Effect of non-polar solvents on water content saturated, $(H_2O)_{sat}$, equilibrium constant for ion-pair formation between MTBD and water, K_{eq}, and second-order interconversion constants, k^*_{int}, for racemization of (*S*)-naproxen 2,2,2-trifluoroethyl ester with MTBD at 45 °C

	Isooctane	*n*-hexane	Cyclohexane
$(H_2O)_{sat}$ (mM)[a]	16.2	15.0	16.8
K_{eq} (mM^{-1})[b]	0.16 (0.98)	0.62 (0.98)	0.30 (0.99)
$k^*_{int} \times 10^2$ ($h^{-1}\,mM^{-1}$)[b]	8.90 (0.96)	7.66 (0.98)	6.57 (0.99)

[a] Estimated from Table 2 in Ref. 13.
[b] Values in parentheses are error estimates (R^2).

Inspection on the lipase-catalyzed rate for the fast-reacting (*S*)-2,2,2-trifluoroethyl ester in isooctane and the racemization rate calculated by using the k^*_{int} values (Table 1) indicates that MTBD and other stronger neutral bases are good candidates for developing related dynamic kinetic resolution processes.[3b] Although an order of magnitude difference in the $\log P$ value (where P is the partition coefficient of solvent between octanol and water) between isooctane and *n*-hexane (or cyclohexane) has been reported,[11] very similar values of k^*_{int} using MTBD as the base are given in Table 2. In contrast, almost the same dielectric constant of 2.02 for the solvent is found. Therefore, more experiments to check the possible correlation between k^*_{int} and the dielectric constant of the solvent are required.

Racemization and hydrolysis of (*S*)-naproxen ester

When (*S*)-naproxen 2,2,2-trifluoroethyl ester is employed as the model compound in non-polar solvents containing water and strong neutral bases, ion-pair formation between the base and water and hydrolysis and racemization of (*R*)- and (*S*)-naproxen 2,2,2-trifluoroethyl ester may occur simultaneously.

Let us assume rapid ion-pair formation between the base and water as follows (see Supplementary Material):

$$B + H_2O \overset{K_{eq}}{\rightleftharpoons} B^* \tag{2}$$

One may express the base concentration (B) in terms of the initial base concentration $(B)_0$, initial water concentration $(H_2O)_0$ and equilibrium constant K_{eq} as

$$(B) = 0.5\Big[(B)_0 - (H_2O)_0 - K_{eq}^{-1} + \{[(B)_0 + (H_2O)_0 + K_{eq}^{-1}]^2 - 4(B)_0(H_2O)_0\}^{0.5}\Big] \tag{3}$$

Three mechanisms, i.e. stepwise, dissociative and concerted, have been employed to describe the acyl group

transfer reactions of esters.[12a] The switchover from one mechanism to another depends on the nature of the leaving group and nucleophile. A stepwise mechanism has been proposed for base-catalyzed ester hydrolysis in aqueous solution or a polar organic solvent.[12b–e] Depending on the substituent of the acyl moiety, the leaving ability of the alcoholic group and the structure of the base, the stepwise mechanism via the formation of a tetrahedral intermediate is furthermore classified into two kinds, i.e. nucleophilic catalysis and general base catalysis. It is well known that usually esters possessing a good leaving group, such as 4-nitrophenyl or 2,4-dinitrophenyl, are subject to nucleophilic catalysis.[12d] Since the 2,2,2-trifluoroethyl moiety is a good leaving group, MTBD-catalyzed nucleophilic catalysis is proposed for the hydrolysis of (*R*)- and (*S*)-naproxen 2,2,2-trifluoroethyl ester in this work.

As illustrated in Scheme 1, the hydrolysis reaction of A_R and A_S passes through the first tetrahedral intermediates I_{R1} and I_{S1}, and then the second ones intermediates I_{R2} and I_{S2} to the products P_R and P_S. Unlike the nucleophilic hydrolysis of esters in polar solvents such that alkyl oxide anions could leave, the requirement of contact ion-pair between MTBD and the alcohol product in non-polar solvents suggested that the reaction rate from I_{R1} to I_{R2} (or I_{S1} to I_{S2}) was proportional to $k_2(B^*)$.

By employing steady-state assumptions for the intermediates I_{R1}, I_{R2}, I_{S1} and I_{S2} in Scheme 1, the hydrolysis constant for the (*R*)- and (*S*)-ester can be derived as follows (see Supplementary Material):

$$k_{hy} = k_1(B)(B^*)/[(B^*) + k_{-1}(k_{-2} + k_3)/k_2k_3] \qquad (4)$$

In comparison with P_R and P_S, the intermediates I_{S2} and I_{R2} are not stable and will rapidly transform into the product (i.e. $k_3 \gg k_{-2}$). Moreover, if the 2,2,2-trifluoroethyl moiety departs from I_{R1} and I_{S1} to I_{R2} and I_{S2} much faster than the base to the substrates A_R and A_S [i.e. $k_2(B^*) \gg k_{-1}$], the formation of I_{R1} and I_{S1} is the rate-limiting step, giving $k_{hy} = k_1(B)$ from Eqn (4). On the other hand, if the expulsion of the base proceeds much faster than that of the leaving group, the breakdown of I_{R1} and I_{S1} to I_{R2} and I_{S2} is rate limiting [i.e. $k_{-1} \gg k_2(B^*)$], giving $k_{hy} = k_1k_2(B)(B^*)/k_{-1}$.

When the hydrolysis and racemization for both ester substrates are considered at the initial stage, the balance equations for both enantiomers were solved (see Supplementary Material) and rearranged as

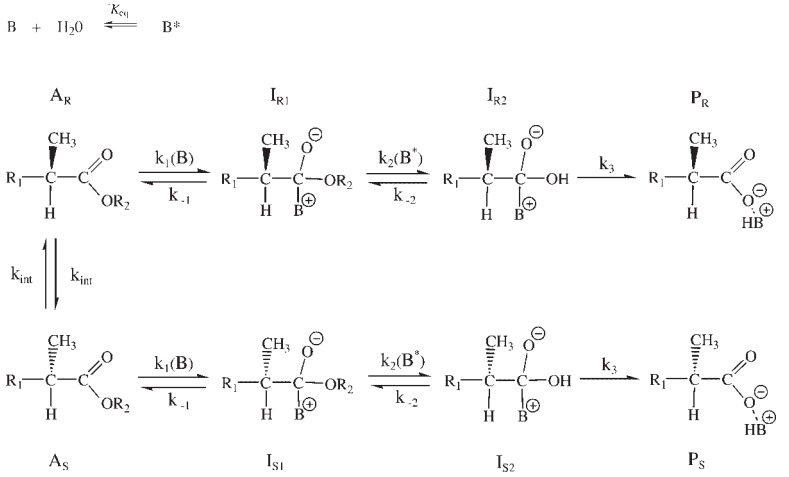
$$\ln(ee_S/ee_{S0}) = -2tk_{int} \qquad (5)$$

$$\ln\{[(A_R) + (A_S)]/[(A_R)_0 + (A_S)_0]\} = -k_{hy}t \qquad (6)$$

Therefore, the first-order interconversion constants at various combinations of $(B)_0$ and $(H_2O)_0$ can be determined from the time-course data of ee_S coupled with Eqn (5). One can further estimate K_{eq} from the relationship $k_{int} = k^*_{int}(B)$ coupled with Eqn (3), where k^*_{int} has been determined in anhydrous solvents. Similarly, from the time-course data for $(A_R) + (A_S)$ coupled with Eqn (6), the hydrolysis constants are estimated at various combinations of $(B)_0$ and $(H_2O)_0$, and then the kinetic constants in Eqn (4) by using Eqn (3) and the relationship $(B^*) = [(B)_0 - (B)]$.

Similar data (not shown) to those illustrated Fig. 1 at various combinations of initial concentrations of MTBD and water in *n*-hexane, cyclohexane and isooctane were obtained, and k_{int} values determined. Good linear relationships between k_{int} and (B) are illustrated in Fig. 3 for all solvents. The equilibrium constants were then estimated and are presented in Table 2. Unlike the saturated water concentration and k^*_{int}, the inert solvent has a slight influence on the K_{eq} value and hence the base and ion-pair concentrations for a given combination of $(B)_0$ and $(H_2O)_0$.

Similar behavior to that in Fig. 1 (data not shown) for the time-course variations of $\ln\{[(A_R) + (A_S)]/[(A_R)_0 +$



Scheme 1

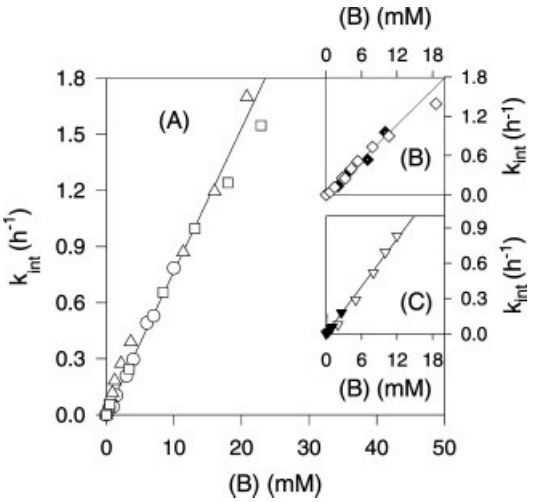


Figure 3. Variations of first-order interconversion constant with (B) using MTBD as the base: (A) in hexane containing (○) no water, (△) $(H_2O)_0 = 15.0$ mM and (□) $(H_2O)_0 = 7.5$ mM; (B) in isooctane containing (◇) no water and (◆) $(H_2O)_0 = 16.2$ mM; (C) in cyclohexane containing (▽) no water and (▼) $(H_2O)_0 = 16.8$ mM

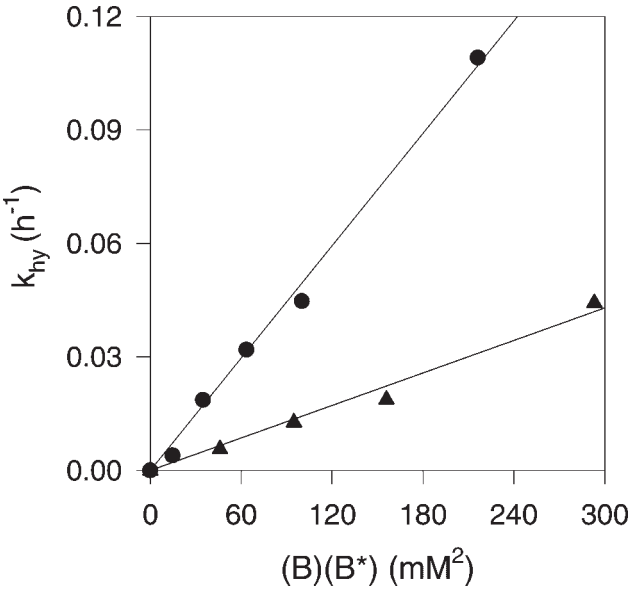


Figure 4. Variations of the hydrolysis constant with (B)(B*) using MTBD as the base in (●) isooctane containing $(H_2O)_0 = 16.2$ mM and (▲) hexane containing $(H_2O)_0 = 15.0$ mM

$(A_S)_0]\}$ in *n*-hexane and isooctane at various combinations of initial MTBD and water concentrations were obtained. Good linear relationships between k_{hy} and (B)(B*), but not (B), are illustrated in Fig. 4, from which slopes (i.e. k_1k_2/k_{-1}) of 4.95×10^{-4} and $1.46 \times 10^{-4}\,h^{-1}\,mM^{-2}$ for isooctane and *n*-hexane, respectively, are determined. No elucidations are made for the slightly higher slope and the hydrolysis rate in isooctane. More experiments to test the validity of the proposed hydrolysis mechanism await further studies, e.g. by employing esters containing an electron-withdrawing group on the acyl moiety or an alcoholic leaving group without electron-withdrawing groups in which the mechanism of nucleophilic hydrolysis may change.

Supplementary material

The equilibrium base and ion-pair concentrations, rate equations for the racemization and hydrolysis of (*R*)- and (*S*)-naproxen 2,2,2-trifluoroethyl ester in non-polar solvents were derived by considering the ion-pair formation between the base and water. This material is available in Wiley Interscience.

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