weight we could consider the ratio of branching agent to molecular weight terminator.

In summary, this work describes the polymerization of branched polycarbonate with bisphenol A and trihydroxyphenyl co-monomers in batch reactors. The polymerization was based upon phosgenation, followed by condensation with triethylamine as a catalyst. The relative kinetic studies of branched polycarbonate system show that in polycondensation stage the reaction rates are faster than the corresponding linear polycarbonate. Branched polycarbonate was predominantly formed cyclic oligomers due to trihydroxyphenyl co-monomer. M_v (viscosity molecular weight)s of branched polycarbonate were obtained non-linear dependence on PTBP concentrations. The branching agent appeared to competitively and concurrently function as both molecular terminator and branching factors in polymerization.

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The Effect of Bases on the Reaction of (S)-Naproxen Chloride with Nucleophiles without Racemization

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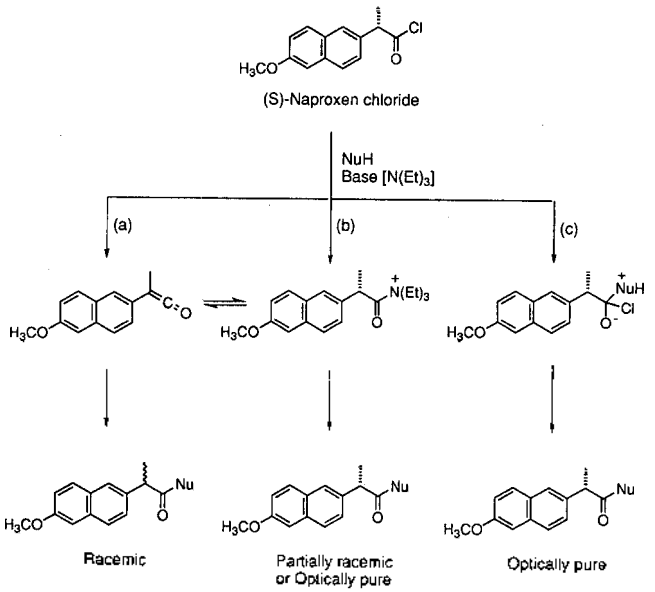
Two enantiomers of racemic drugs often show different pharmacological activities in living systems.[1] Consequently, individual enantiomers of chiral drugs should be studied for their own pharmacological properties during the process of marketing or developing chiral drugs according to the guidelines recently issued by the drug regulatory bodies around the world.[2] In this instance, the techniques of assaying the enantiomeric purity of chiral drugs are essential. For this purpose, various techniques are available.[3] However, liquid chromatographic separation of enantiomers on chiral stationary phases (CSPs) have been known the most convenient and accurate means in assaying the enantiomeric purity of chiral drugs.[4]

α-Arylpropionic acids such as naproxen are well known non-steroidal anti-inflammatory profen drugs. The two enantiomers of these chiral drugs have been known to show different metabolic pathway and different pharmacological activity.[5] Consequently, much attention has been given to the liquid chromatographic analytical resolution of α-arylpropionic acid enantiomers.[6,7] The resolution of profen drugs on Pirkle-type CSPs has been performed with their π-acidic or π-basic aromatic amide derivatives in order to utilize the π-π donor acceptor interaction between the profen derivatives and the CSPs.[6] Derivatization of racemic profen drugs has been usually done by treating α-arylpropionic acid chlorides with a π-acidic or a π-basic aromatic amino compound in the presence of a base such as triethylamine or without a base.[6] However, in some cases, the derivatization has experienced severe problem of racemization, which deteriorates the usefulness of the liquid chromatographic CSPs in determining the enantiomeric purity of optically active profen drugs. For example, the reaction of (S)-naproxen chloride with 3,5-dinitroaniline in the presence of triethylamine was found to afford partially racemized 3,5-dinitroanilide derivative of naproxen.[8] In order to overcome the racemization problem, in this study, we systematically

investigate the reaction of (S)-naproxen chloride with nucleophiles in the presence of various bases and report the optimum derivatization process without racemization.

(S)-Naproxen chloride has also been used as a chiral derivatizing agent in the determination of enantiomeric composition of chiral amines in biological fluides.[9] For (S)-naproxen chloride to be useful as a chiral derivatizing agent, no racemization during the reaction between (S)-naproxen chloride and chiral amines is essential. In this instance, this study concerning the optimum derivatization process without racemization would be also very valuable to the further utilization of (S)-naproxen chloride as a chiral derivatizing agent.

Previously, the reaction of an acid chloride containing an α-hydrogen with an alcohol nucleophile in the presence of triethylamine was reported to afford ester *via* the two competing pathways, an elimination-addition process involving a ketene intermediate and a substitution process involving an acyl quaternary ammonium intermediate, the two intermediates of which are interconvertible.[10] In addition, the reaction between acid chlorides and nucleophiles was reported to undergo *via* a tetrahedral addition intermediate.[11] Based on those previous studies, the reaction of (S)-naproxen chloride with a nucleophile in the presence of a base such as triethylamine is presumed to proceed to afford (S)-naproxen derivatives as shown in Scheme 1. From the three possible pathways shown in Scheme 1, the racemization during the reaction of (S)-naproxen chloride with a nucleophile in the presence of a base such as trietylamine is supposed to be originated from the formation of an achiral ketene intermediate by eliminating hydrogen chloride from the acid chloride containing an α-hydrogen. Consequently the racemization during the derivatization of (S)-naproxen chloride is expected to be minimized by selecting an appropriate base which does not promote the formation of an achiral ketene intermediate.



Scheme 1. (a) Elimination-addition process involving an achiral ketene intermediate. (b) Substitution process involving an acyl ammonium intermediate. (c) Direct substitution (addition-elimination) process involving a tetrahedral addition intermediate.

In order to find out the most pertinent base in the reaction of (S)-naproxen chloride with various nucleophiles without racemization, as a first step, the effect of various bases on the racemization during the reaction of (S)-naproxen chloride with 3,5-dinitroaniline as a nucleophile in methylene chloride at room temperature are investigated and the results are summarized in Table 1. As shown in Table 1, the enantiomeric excess [ee(%)] of the 3,5-dinitroanilide derivative obtained from the reaction of (S)-naproxen chloride with 3,5-dinitroaniline or the degree of racemization [rac(%)] is strongly dependent on the base used. Especially the use of a strong base such as TED (1,4-diazabicyclo[2.2.2]octane) or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) afforded almost completely racemized 3,5-dinitroanilide derivative of naproxen (entry b and c). The use of triethylamine afforded partially racemized 3,5-dinitroanilide derivative of naproxen (entry d). When a weak base such as pyridine or 2,6-lutidine was used, however, no racemization was observed (entry e and f). From these results it is assumed that the elimination-addition process (process a in Scheme 1) is predominant when a strong base is used while the substitution process (process b in Scheme 1) in which an acyl quaternary ammonium intermediate is not convertible to a ketene intermediate or the direct substitution process (process c in Scheme 1) is predominant when a weak base is used. When trietylamine was used as a base, it is supposed that both of the two processes (processes a and b in Scheme 1) are competing. The chemical yield of each derivatization reaction was only moderate as shown in Table 1. However, the use of propylene oxide, which has been used as a scavenger for hydrogen chloride,[12] is very interesting in that the chemical yield of the reaction is almost quantitative and no racemization is observed as shown in Table 1 (entry g). When propylene oxide is used as a base, the reaction is assumed to proceed *via* the direct substitution process (process c in Scheme 1) and consequently no racemization is observed.

The usefulness of propylene oxide in the reaction of (S)-naproxen chloride with other nucleophiles was also tested and the results are summarized in Table 2. As shown in

Table 1. The effect of bases on the chemical yield and the racemization of the reaction of (S)-naproxen chloride with 3,5-dinitroaniline[a]

entry	base	yield(%)[b]	ee(%)[c]	rac(%)[d]
a	no base	45	94	3
b	TED	38	0	100
c	DBU	18	4	96
d	triethylamine	53	22	77
e	pyridine	59	97	0
f	2,6-lutidine	82	97	0
g	propylene oxide	97	97	0

[a] See the experimental part for the reaction conditions. [b] Isolated yield. [c] Enantiomeric excess of the 3,5-dinitroanilide derivative obtained from the reaction of (S)-naproxen chloride with 3,5-dinitroaniline in the presence of the indicated base. [d] Degree of racemization calculated based on the enantiomeric excess of the 3,5-dinitroanilide derivatives and the optical purity (97% ee) of (S)-naproxen used in this study. rac(%)=100-[ee(%)/97]$\times$100.

Table 2. Comparison of the reactions of (S)-naproxen chloride with various nucleophiles in the presence of propylene oxide or trimethylamine and the reactions of (S)-naproxen with various nucleophiles in the presence of a coupling agent, EEDQ or DCC[a]

entry	NuH[d]	propylene oxide[b]			triethylamine[b]			EEDQ[c]			DCC[c]		
		yield[e]	ee[f]	rac[g]	yield[e]	ee[f]	rac[g]	yield[e]	ee[f]	rac[g]	yield[e]	ee[f]	rac[g]
a	3,5-dinitroaniline	97	97	0	53	22	77	trace	97	0	trace	89	8
b	m-nitroaniline	98	97	0	83	82	15	52	97	0	30	94	3
c	aniline	100	97	0	100	94	3	98	97	0	90	95	2
d	3,5-dimethylaniline	100	97	0	100	97	0	100	97	0	93	95	2
e	propylamine	100	97	0	100	97	0	64	97	0	45	97	0
f	diethylamine	100	97	0	100	97	0	73	97	0	53	97	0
g	methyl alcohol	100	97	0	96	80	18	46	97	0	40	97	0

[a] See the experimental part for the reaction conditions. [b] Base used in the reaction of (S)-naproxen chloride with nucleophiles. [c] Coupling reagent used in the reaction of (S)-naproxen with nucleophiles. [d] Nucleophile. [e] Isolated yield. [f] Enantiomeric excess of the derivative obtained from the reaction of (S)-naproxen chloride or (S)-naproxen with nucleophiles. [g] Degree of racemization calculated from the ee (%) value of (S)-naproxen derivatives based on the optical purity (97% ee) of (S)-naproxen used in this study. rac(%)=100-[ee(%)/97]×100.

Table 2, the reaction of (S)-naproxen chloride with various nucleophiles in the presence of propylene oxide is very excellent in that each reaction proceeds completely without racemization. The same reaction of (S)-naproxen chloride with various nucleophiles was also performed in the presence of triethylamine and the results are compared with those obtained from the reaction of (S)-naproxen chloride with various nucleophiles in the presence of propylene oxide in Table 2. When nucleophiles are strong enough (entry d, e, f in Table 2), the use of triethylamine in the reaction of (S)-naproxen chloride with nucleophiles is very effective as evidenced by the chemical yield and the degree of racemization. When a strong nucleophile such as 3,5-dimethylaniline, propylamine or diethylamine is used, it is supposed that a nucleophile attacks the electron deficient carbonyl carbon center before triethylamine attacks the α-hydrogen to afford achiral ketene intermediate and consequently, the direct substitution process (process c in Scheme 1) is expected to be predominant over the elimination-addition process which leads to racemization. However, the reaction of (S)-naproxen chloride with weak nucleophiles (for example, entry a, b, g in Table 2) in the presence of triethylamine proceeds with partial racemization, indicating that the process involving achiral ketene intermediate formed from the HCl elimination by triethylamine is involved in the reaction to some extent.

The utility of propylene oxide in the reaction of (S)-naproxen chloride with nucleophiles was also compared with the direct derivatization of (S)-naproxen with nucleophiles in the presence of a coupling agent such as EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) or DCC (1,3-dicyclohexylcarbodiimide) in Table 2. As shown in Table 2, the use of EEDQ as a coupling agent for the derivatization of (S)-naproxen with some nucleophiles is very excellent in that no racemization was absorbed. However, the chemical yield is not so satisfactory except for the reaction with aniline and with 3,5-dimethylaniline. The use of DCC as a coupling agent for the derivatization of (S)-naproxen with some nucleophiles is also not satisfactory in terms of chemical yield and the degree of racemization.

In conclusion, in this study, we demonstrated that the reaction of (S)-naproxen chloride with various nucleophiles proceeds almost completely without racemization when propylene oxide is used as a scavenger for hydrogen chloride. The method utilized in this study for the reaction (S)-naproxen chloride with nucleophiles in the presence of propylene oxide is, therefore, expected to be widely applicable in the derivatization of optically active α-arylpropionic acids without racemization in good yield. In addition, the method is expected to extend the utility of (S)-naproxen chloride as a chiral derivatizing agent in the determination of enantiomeric composition of chiral amines or alcohols.

Experimental

^{1}H NMR spectra were taken on a Varian Gemini 200 spectrometer (200 MHz). IR spectra were recorded on a Mattson Polaris FT-IR spectrometer. Enantiomeric excess (ee) of the derivatives of (S)-naproxen (the ee data in Table 1 and 2) were determined by HPLC analysis on a commercial chiral column derived from (S)-N-(3,5-dinitrobenzoyl)leucine.[13]

(S)-Naproxen, (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid, was purchased from Aldrich Chemical Co. Optical purity of (S)-naproxen from Aldrich Chemical Co. was found to be 97% ee by HPLC analysis on a commercial chiral column, Whelk-O1 (Regis, Morton grove, IL., U.S.A.).[7b,c] The degree of racemization (% racemization) during the derivatization of (S)-naproxen was determined based on the optical purity (97% ee) of the commercial (S)-naproxen.

One example of the detailed derivatization process of (S)-naproxen is as following. (S)-Naproxen (0.2 g, 0.87 mmole) and freshly distilled thionyl chloride (0.3 mL, 4.3 mmole) were dissolved in 20 mL of benzene and then the mixture was heated to reflux for 2 hr under an argon atmosphere. After cooling to room temperature, the mixture was evaporated to dryness using a rotary evaporator. The residue was dissolved in 20 mL of dry methylene chloride and then a mixture of 3,5-dinitroaniline (0.16 g, 0.87 mmole) and propylene oxide (1.0 mmole, 1.2 eq.) diluted in 10 mL dry methylene chloride was added slowly with stirring. The reaction mixture was stirred at room temperature under an argon atmosphere for 12 hr and then washed successively with 60 mL of saturated $NaHCO_3$ solution, 50 mL of 6 N HCl solution and brine. The organic solution was dried over anhydrous $MgSO_4$, filtered and then evaporated. The residue

was purified by flash chromatography on silica gel (ethyl acetate/hexane/methylene chloride : 1/3/1, v/v/v) to afford 3,5-dinitroanilide of (S)-naproxen. The spectroscopic (^{1}H NMR and IR) and melting point data of this compound were consistent with those reported previously.[8]

All other derivatization reactions of (S)-naproxen were performed via the same procedure as described above for 3, 5-dinitroanilide of (S)-naproxen except for the use of 2 N HCl solution instead of 6 N HCl solution to wash the reaction mixture.

Derivatization of (S)-naproxen with various nucleophiles in the presence of a coupling agent such as EEDQ or DCC was performed as following. (S)-Naproxen (0.20 g, 0.87 mmole) and EEDQ (0.26 g, 1.05 mmole, 1.2 eq.) or DCC (0. 22 g, 1.06 mmole, 1.2 eq.) dissolved in 20 mL of methylene chloride was stirred for 20 min at room temperature and then a nucleophile (1.0 eq.) was added. The whole mixture was stirred at room temperature for 12 hr and then washed successively with 60 mL of saturated $NaHCO_3$ solution, 50 mL of 2 N HCl solution and brine. The organic solution was dried over anhydrous $MgSO_4$, filtered and then evaporated. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane/methylene chloride : 1/3/1, v/v/v) to afford a derivative of (S)-naproxen.

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Asymmetrically Substituted Calix[5]arene Derivatives

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Calixarenes are macrocyclic compounds available in a variety of ring sizes and are of interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures.[1-3] One of the main features of naturally occurring host molecules is their capacity for enantioselective recognition. Various attempts have therefore been made to obtain chiral host molecules based on calixarenes. The most simple method to convert calixarene into chiral derivatives is the introduction of chiral substituent at the lower[4,5] or upper[3,6] rim of calixarene skeleton. More interest has been focused on the possibility of synthesizing "inherently" chiral calixarenes, which are built up of nonchiral subunits and consequently owe their chirality to the fact that the calixarene molecule is not planar and several procedures for the inherently chiral calix[4]arene were reported.[7-20] However only one article was published by Böhmer and Pappalardo[21] for the preparation of chiral *p-t*-butylcalix[5]arene. They treated *p-t*-butylcalix[5]arene with suitable oligoethylene glycol ditosylate in the presence of CaF_2 to produce 1,2- or 1,3-isomer of calix[5]crownether, which was desymmetrized by O-alkylation of one of the two adjacent hydroxy groups to afford asymmetrically substituted calix[5]arenes. Recently we reported the facile preparation of calix[5]arene which have different substituents at the upper