Notes

Liquid Chromatographic Separations of the Enantiomers of Cyclic Amines

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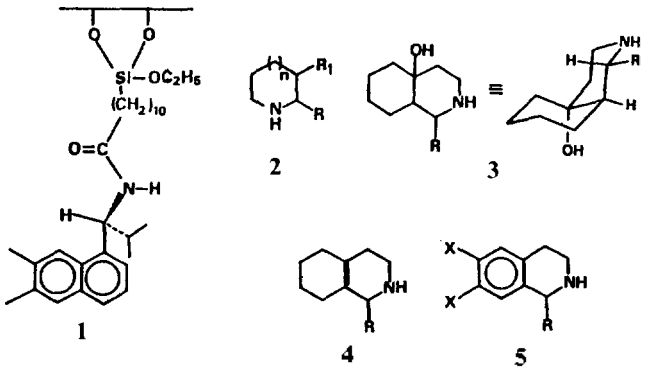
Optically active cyclic amines have been widely employed as important chiral building blocks or intermediates for the synthesis of biologically active natural products[1] and, in consequence, optically active cyclic amines have been subjected to asymmetric synthesis.[2] However, the methods which allow the simple and accurate assessment of enantiomeric composition of chiral cyclic amines synthesized asymmetrically are limited. Recently, a liquid chromatographic chiral stationary phase (CSP) derived from N-3, 5-dinitrobenzoylphenylglycine was successfully employed for the determination of enantiomeric composition of cyclic amines.[2a,3] Very recent brochure issued by the Daicel Chemical Industries, Ltd. also describes the liquid chromatographic resolution of a chiral aromatic cyclic amine such as DL-laudanosine.[4] However, CSP **1** which has been widely used for the separation of various racemates[5] has not been employed for the enantioseparation of chiral cyclic amines.

In this study, we want to extend the use of CSP **1** to the separation of the enantiomers of chiral cyclic amines **2-5**. Previously, racemic primary amines and racemic alcohols have been resolved on CSP **1** as their derivatives obtained from the reaction with 3, 5-dinitrobenzoyl chloride or with 3, 5-dinitrophenyl isocyanate.[6] The magnitude of the separation factor for the N-3, 5-dinitrobenzamides from primary amines was found to be typically larger on CSP **1** than those for the corresponding 3, 5-dinitrophenyl ureas. However 3, 5-dinitrophenyl carbamates of racemic alcohols were found to confer greater separability on CSP **1** than 3, 5-dinitrobenzoates.



To utilize the previous studies, cyclic amines **2-5** which were prepared by the known procedures[7] were converted into their 3, 5-dinitrobenzoyl derivatives or 3, 5-dinitrophenyl ureides *via* the reaction with 3, 5-dinitrobenzoyl chloride or 3, 5-dinitrophenyl isocyanate. All of these derivatives have a strong π-acidic site and, in consequence, are expected to be resolvable on CSP **1** which contains a stong π-basic site.

Table 1 summarises the data pertinent to the separation of the enantiomers of 3, 5-dinitrobenzoyl derivatives (DNBC derivatives) and 3, 5-dinitrophenyl ureides (DNPI derivatives) of cyclic amines **2-5** on CSP **1** and Figure 1 depicts the typical chromatograms. It should be noted that cyclic amines

Table 1. Resolution of Cyclic Amines as their Derivatives on CSP 1[a]

Compound type		R	R_1	X	n	DNBC Deriv.		DNPI Deriv.	
						α[b]	k_1'[c]	α[b]	k_1'[c]
1	2	Me	H		0	1.09	4.31	1.09	15.87
2	2	Octyl	H		0	1.24	1.01	1.28	6.20
3	2	Octyl	H		1	1.00	0.81	1.19	6.45
4	2	H	Octyl		1	1.00	0.91	1.06	6.73
5	3	Me				1.10	6.00	1.00	9.24
6	3	C_6H_5				1.00	4.93	1.08	11.81
7	3	p-MeO-Benzyl				1.35	5.27	1.81	6.87
8	4	p-MeO-Benzyl				1.19	1.53	2.03	3.20
9	5	Me		H		1.05	2.17	1.28	7.01
10	5	Benzyl		H		1.08	1.67	1.75	4.47
11	5	Me		MeO		1.00	9.73	1.14	20.93
12	5	C_6H_5		MeO		1.05	5.00	1.18	18.75
13	5	Benzyl		MeO		1.08	6.73	1.50	12.55

[a]The chromatography was performed with Waters Model 510 pump, Waters Model U6k Liquid chromatographic Injector, Waters Model 441 Absorbance Detector and Waters Model 740 Data Module Recorder. All Data were obtained by using 10% isopropyl alcohol in hexane(DNBC Deriv.) and 20% isopropyl alcohol in hexane(DNPI Deriva.) as a mobile phase with flow rate of 2 ml/min. at 254 nm UV. [b]Separation factor. [c]Capacity factor for the first eluted enantiomer.

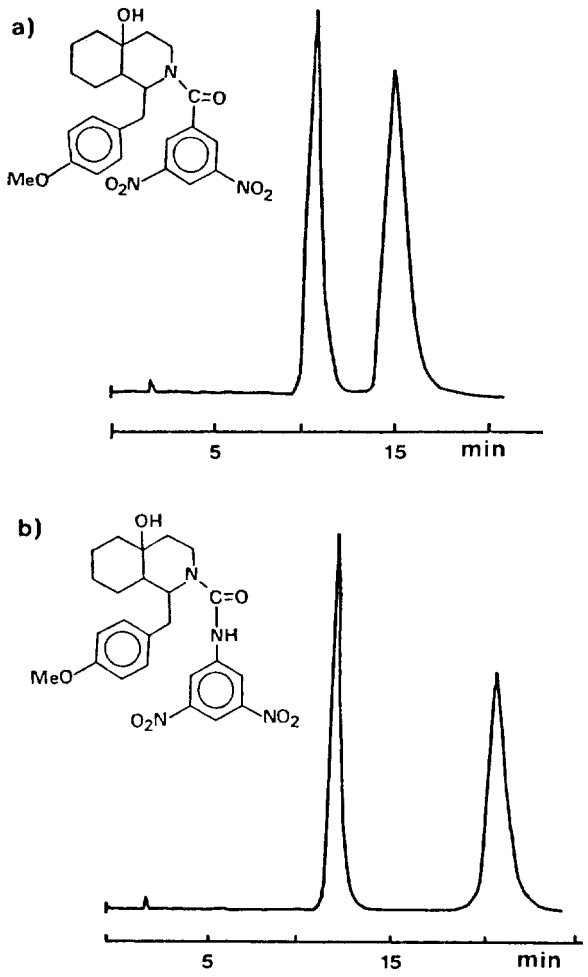


Figure 1. Liquid chromatographic resolution of (a) 3, 5-dinitrobenzoyl derivative and (b) 3, 5-dinitrophenyl ureide of 1-(p-methoxybenzyl)-10-hydroxydecahydroisoquinoline(entry 7 in Table 1) on CSP **1**. For HPLC conditions, see footnote to Table 1.

3 have three chiral centers and, in consequence, total of eight stereoisomers are theoretically possible. However, only two enantiomers have been known to be produced from the known synthetic procedure.[7b] The CD spectra shown in Figure 2 demonstrates the inverse optical activity of the two enantiomers which were obtained from the preparative resolution of 3, 5-dinitrophenyl ureide of cyclic amine **4** on an analytical column (250×4.6 mm I. D.) packed with CSP **1**.

From the Table 1 and Figure 1, it is apparent that 3, 5-dinitrophenyl ureides of cyclic amines show greater enantioselectivity and longer retention than 3, 5-dinitrobenzoyl derivatives of cyclic amines on CSP **1** with only one exception (entry 5). Another resolution trend noted from the Table **1** is that, in general, cyclic amine derivatives which have a large substituent (R) at the chiral center are resolved on CSP **1** with greater enantioselectivity than those which have a small substituent at the chiral center.

The chiral recognition mechanism which is applicable in explaining the experimental observations mentioned above may be postulated by considering the conformational preferences of both CSP **1** and analytes. The conformation of CSP **1** has been presented previously,[5] but that of cyclic amine

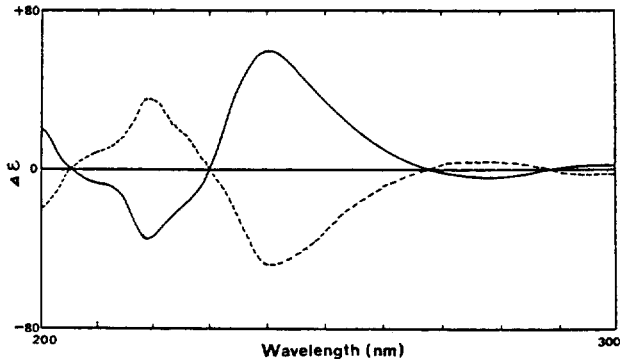


Figure 2. CD Spectra of the two enantiomers of 3, 5-dinitrophenyl ureide of cyclic amine 4(entry 8 in Table 1). (——) the first eluted enantiomer on CSP **1**. (------) the second eluted enantiomer on CSP **1**. CD Spectra were obtained by using JASCO Model J-600 CD/ORD Spectrophotometer. path length : 1 mm (quartz cell), solvent : 20% isopropyl alcohol in n-hexane.

derivatives is not known. In consequence, at the present stage, it is difficult to propose the chiral recognition mechanism operative on CSP **1**. However, longer retention and greater enantioselectivity of 3, 5-dinitrophenyl ureides of cyclic amines, compared to those of 3, 5-dinitrobenzoyl derivatives of cyclic amines may be rationalized by considering that 3, 5-dinitrophenyl ureides of cyclic amines undergo stronger interaction with CSP **1** than do 3, 5-dinitrobenzoyl derivatives of cyclic amines. The 3, 5-dinitrophenyl ureides of cyclic amines contain both of hydrogen bonding donor and acceptor site such as ureide carbonyl oxygen and ureide N-H hydrogen which are coplanar with the 3, 5-dinitrophenyl group and, in consequence, interact with CSP **1** through the π-π interaction and the two hydrogen bondings. However, the 3, 5-dinitrobenzoyl derivatives of cyclic amines interact with CSP **1** through the π-π interaction and the hydrogen bonding between the carbonyl oxygen of 3, 5-dinitrobenzoyl group of analytes and the N-H hydrogen of CSP **1**. In consequence, the interaction between the 3, 5-dinitrophenyl ureides of cyclic amines and CSP **1** is expected to be stronger than that between the 3, 5-dinitrobenzoyl derivatives of cyclic amines and CSP **1**. In conclusion, CSP **1** has been proved to be useful as a means for the rapid and accurate assessment of enantiomeric composition of cyclic amines as their derivatives.

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Oxidative Conversion of Organophosphonates to Carbonyl Compounds *via* α-Hydroxyorganophosphonates

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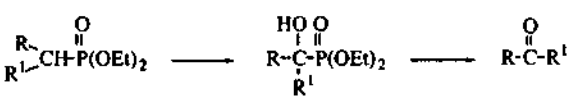
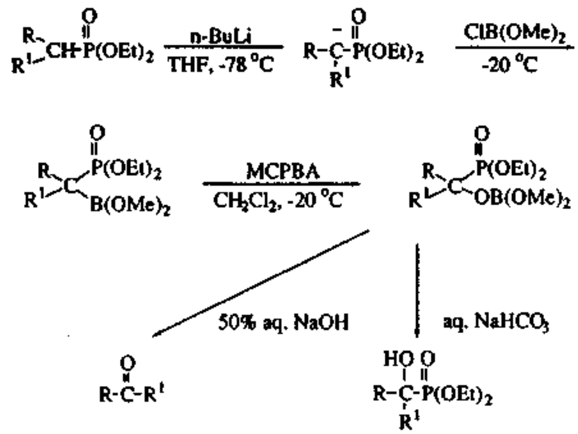
In connection with our ongoing research, an efficient method for conversion of organophosphonates into aldehydes or ketones is needed. In this regard, organophosphonates can be regarded as acyl anion equivalents. An α-anion of organophosphonates, which is more nucleophilic than phosphorus yields, is known to react with a variety of electrophiles.[1] Conversion to the ketones may be accomplished by anion formation followed by oxidation with various reagents. They may include molecular oxygen,[2] MoOPH,[3] bis (trimethylsilyl) peroxide,[4] and halodimethylborate / m-chloroperoxybenzoic acid(MCPBA).[5]



In order to test the effectiveness of these reagents, an α-anion of an organophosphonate ($R=n\text{-}C_8H_{17}$, $R^1=CH_3$), which was generated by treatment with n-buthyllithium in tetrahydrofuran at −78℃, was reacted with molecular oxygen, MoOPH, and chlorodimethylborate / MCPBA,[6,7] respectively and the resulting α-hydroxyorganophosphonate was treated with 50% aqueous sodium hydroxide to produce 2-decanone. Oxidation with MoOPH gave 2-decanone in 66% yield along with the recovery of 16% of the starting material, whereas the reaction with molecular oxygen afforded the desired product in 76% yield.[8] The reaction with chlorodimethylborate / MCPBA gave the best result, yielding 80% of 2-decanone. Also, it is noteworty that α-hydroxyorganophosphonates can be isolated by quenching the reaction mixture with aqueous sodium bicarbonate. When α-anion of diethyl benzylphosphonate with fluorodimethylborate and NaOH / H_2O_2 or MCPBA, diethyl α-hydroxybenzylphosphonate was obtained in 34% and 66% yield, respectively. However, chlorodimethylborate / MCPBA procedure gave diethyl α-hydroxybenzylphosphonate in 78% yield. Therefore, remaining reactions were carried out with chlorodimethylborate / MCPBA, as shown in Scheme 1.



Scheme 1.

Table 1. Oxidation of Organophosphonates Using $ClB(OMe)_2$ / MCPBA

$RR^1CH\text{-}P(O)(OEt)_2$	$R\text{-}C(OH)(R^1)\text{-}P(O)(OEt)_2$, %[a]	$R\text{-}C(O)\text{-}R^1$, %[b]
Ph, H > CH-P(O)(OEt)$_2$	78	62
Ph, C_2H_5 > CH-P(O)(OEt)$_2$	70	70
$n\text{-}C_8H_{17}$, H > CH-P(O)(OEt)$_2$	78	50(28)[c]
$n\text{-}C_8H_{17}$, CH_3 > CH-P(O)(OEt)$_2$	83	80
$PhO(CH_2)_4$, CH_3 > CH-P(O)(OEt)$_2$	90	74
$PhCH(CH_3)$, CH_3 > CH-P(O)(OEt)$_2$	92	64

[a]Isolated yields using Method A. [b]Isolated yields using Method B. [c]The number in parenthesis indicates the yield of the aldol product ($n\text{-}C_7H_{15}\text{-}C(CHO)=CH\text{-}C_8H_{17}$).

Table 1 summarizes some experimental results and illustrates the efficiency and the scope of the present method. Several structurally different α-hydroxyphosphonates were isolated in high yields by quenching with aqueous sodium bicarbonate. In the direct conversion of organophosphonates