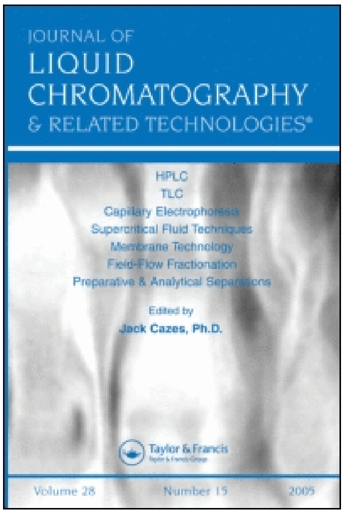

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Chiral Stationary Phases for HPLC: Cellulose Tris(3,5-dimethylphenylcarbamate) and Tris(3,5-dichlorophenylcarbamate) Chemically Bonded to Silica Gel*

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CHIRAL STATIONARY PHASES FOR HPLC: CELLULOSE TRIS(3,5-DIMETHYLPHENYLCARBAMATE) AND TRIS(3,5-DICHLOROPHENYLCARBAMATE) CHEMICALLY BONDED TO SILICA GEL*

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ABSTRACT

Cellulose was bonded chemically to 3-aminopropyl silica gel with diisocyanates and then allowed to react with a large excess of 3,5-dimethylphenyl- or 3,5-dichlorophenylisocyanate. Optical resolving power of these chiral stationary phases was compared with that of the cellulose triphenylcarbamate derivatives coated on silica gel.

INTRODUCTION

We recently demonstrated that 20 cellulose triphenylcarbamate (CTPC) derivatives which possess various

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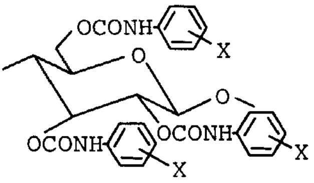
* Chromatographic Resolution XV, for part XIV, see Y. Okamoto, R. Aburatani, and K. Hatada, J. Chromatogr., in press.



X =

$4\text{-}CH_3O$, $4\text{-}CH_3$, $4\text{-}CH_3CH_2$, H, 4-F, 4-Cl,
4-Br, $4\text{-}CF_3$, $4\text{-}NO_2$, 4-Ph-N=N, 3-Cl,
2-Cl, $3,4\text{-}Cl_2$, $3,5\text{-}Cl_2$, $2,6\text{-}Cl_2$, $3\text{-}CH_3$,
$2\text{-}CH_3$, $3,4\text{-}(CH_3)_2$, $3,5\text{-}(CH_3)_2$, $2,6\text{-}(CH_3)_2$

substituents on phenyl groups exhibit characteristic optical resolving power as chiral stationary phases (CSP) for HPLC when they are coated on macroporous silica gel.1-3) The inductive effect of the substituents greatly influenced the chiral recognition of the CTPC derivatives, and either cellulose tris(3,5-dimethylphenylcarbamate) (CTPC-3,5-Me_2) or tris(3,5-dichlorophenylcarbamate) (CTPC-3,5-Cl_2) was found to show higher chiral recognition ability than mono-substituted CTPC's. These two CSP's have been used to resolve a variety of racemic compounds.2,4-6) The CTPC-3,5-Me_2 phase possesses a high durability as far as hexane containing 0-30% of 2-propanol is employed as eluent, whereas the CTPC-3,5-Cl_2 phase can not be used stably under the conditions with hexane containing greater than 10% 2-propanol because of its high solubility.

Thus, the latter CSP is not suitable for the separation of compounds well-retained on the CSP.

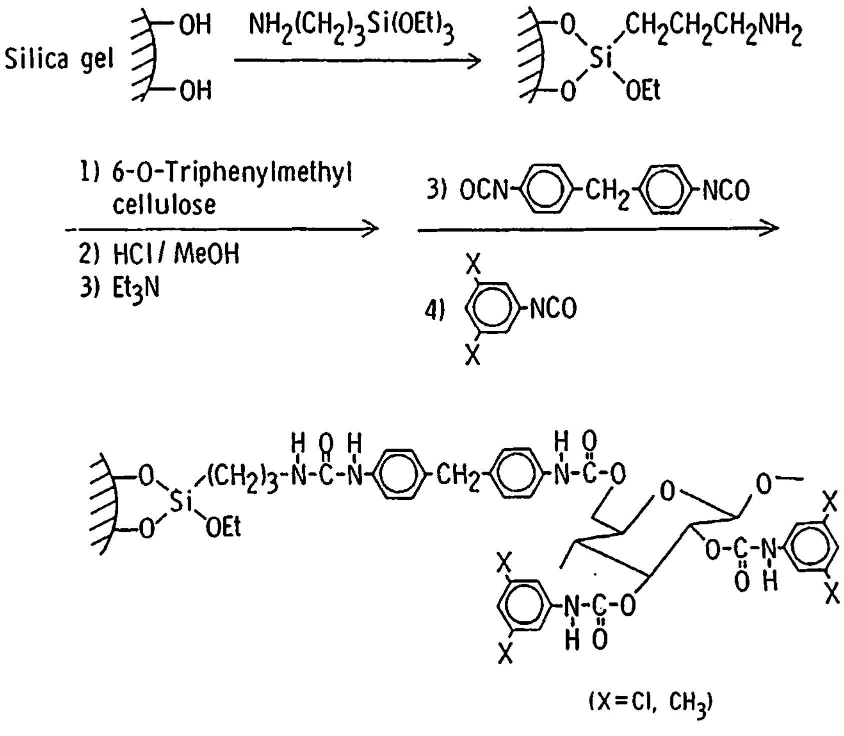
This defect of the CTPC-3,5-Cl_2 phase prompted us to prepare more durable CSP's which can be applied regardless of eluents. In this paper, we describe the preparation and chiral recognition of the CTPC-3,5-Me_2 and CTPC-3,5-Cl_2 chemically bonded to macroporous 3-aminopropyl silica gel.

EXPERIMENTAL

Preparation of CSP: The CSP was prepared according to scheme I. Macroporous silica gel (Merck, LiChrospher SI-1000, particle size 10 μm, pore size 100 nm) was treated with 3-aminopropyltriethoxysilane in benzene. Anal. C, 0.53 %; H, 0.10 %.

Trityl cellulose,7) which had been prepared by the reaction of cellulose (Merck, Avicel) and a large excess of trityl chloride in N,N-dimethylaceatamide-LiCl at 100 °C, was dissolved in chloroform and was adsorbed on the 3-aminopropyl silica gel in the same way as described previously.2) Then the trityl cellulose on silica gel was treated with methanol containing small amount of hydrochloric acid to split off the trityl group at room temperature. The content of cellulose on silica gel was estimated by elemental analysis.

The cellulose on 3-aminopropyl silica gel (3.3 g), was dispersed in a mixture of dry toluene (10 ml), 4,4'-diphenylmethane diisocyanate (30-230 mg) and pyridine (2 ml), and heated at 90-110 °C. After about 3 hr, an excess of 3,5-dimethyl- or 3,5-dichlorophenylisocyanate was added to the reaction mixture and allowed to react at 90-110 °C for 24 hr. The CSP thus



SCHEME 1

Preparation of CSP

obtained was collected by filtration and washed with tetrahydrofuran (THF) to exclude free CTPC derivatives. The content of the CTPC derivatives bonded to silica gel was estimated by elemental analysis and also from the amounts of THF-soluble CTPC derivatives recovered.

Optical resolution: The CSP was packed in a stainless steel tube (250 x 4.6 (id) mm) at 300 Kg/cm^2 by a slurry method.

Chromatographic resolution was performed on a JASCO TRIROTAR-II chromatograph equipped with UV (JASCO UVIDEC-100-III) and polarimetric (JASCO DIP-181C) detectors. Optical rotation was monitored in a flow cell (50 x 2 (id) mm) at full lamp (mercury) intensity without filters. A hexane-2-propanol (90:10) mixture was used as eluent at a flow rate of 0.5 ml/min. The dead time (t_0) of the column was estimated with 1,3,5-tri-tert-butylbenzene as a non-retained compound.8)

RESULT AND DISCUSSION

Preparation of CSP: Some typical results on the preparation of the CTPC-bonded silica gel are listed in Table 1. The data indicate that the cellulose regenerated from trityl cellulose was quantitatively fixed on 3-aminopropyl silica gel by using 4,4'-diphenylmethane diisocyanate corresponding to 12.8% of the hydroxy groups of the cellulose. About 70% of the cellulose was also bonded to the silica gel even with 3-5% of the diisocyanate. Elemental analyses and IR spectra of the CSP indicate that almost all hydroxy groups of the cellulose were converted to urethane groups by the reaction with an excess of 3,5-dimethylphenyl- or 3,5-dichlorophenylisocyanate. We also examined dichlorodiphenylsilanized silica gel in place of 3-aminopropyl silica gel. However, in this case, only a small quantity of the cellulose was fixed on the silica gel probably through cross-linkage between cellulose

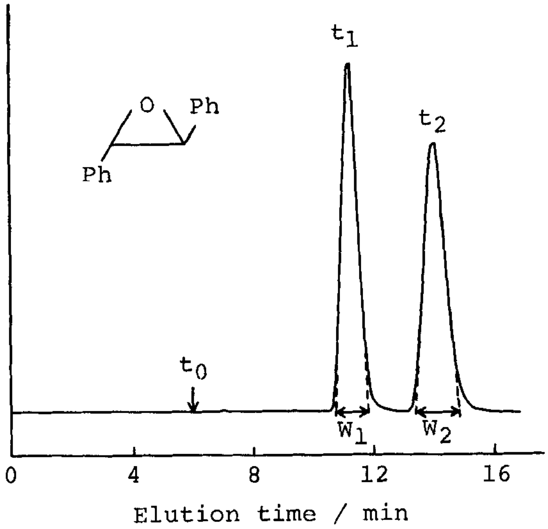


FIGURE 1. Resolution of trans-2,3-diphenyloxirane on CTPC-3,5-Cl_2-bonded(3%) phase. (column 250 x 4.6 (id)mm, eluent hexane-2-propanol (90:10), 0.5 ml/min, 25 °C)

TABLE 1

Preparation of CTPC-3,5-Cl_2-Bonded Phase

Cellulose / Silica gel (g/g)	Diisocyanate[a]	Elemental analyses C %	Elemental analyses Cl %	CTPC-3,5-Cl_2 / Silica gel (g/g)	Bonded CTPC-3,5-Cl_2 (%)
0.068	12.8 %	10.9	4.9	0.20	100
0.073	5.0 %	8.1	4.1	0.14	65
0.12	3.0 %	12.8	7.4	0.26	73
0.10[b]	3.0 %	2.3	——	0.02	5

[a] Based on hydroxy group of cellulose.

[b] Silica gel treated with dichlorodiphenylsilane was used.

chains. This suggests that the fixation of the cellulose is mainly attributable to the bond formation between the amino group of 3-aminopropylsilanized silica gel and the hydroxy group of the cellulose by the diisocyanate.

CTPC-3,5-Me_2 was also chemically bonded to similar extents to 3-aminopropyl silica gel under the same reaction conditions.

OPTICAL RESOLUTION ON CTPC-3,5-Cl_2 PHASE

Figure 1 shows the chromatogram of the resolution of racemic trans-2,3-diphenyloxirane on a CTPC-3,5-Cl_2 (3%)* column. The enantiomers were eluted at t_1 and t_2 and the capacity factors (k_1' and k_2'), which are estimated as $(t_1-t_0)/t_0$ and $(t_2-t_0)/t_0$, were determined to be 0.86 and 1.32, respectively. The separation factor, $\alpha = k_2'/k_1'$ and the resolution factor, $Rs = 2(t_2-t_1)/(W_1+W_2)$, were found to be 1.54 and 2.22, respectively.

In Table 2 are summarized the results of the resolution of five racemic compounds on the CTPC-3,5-Cl_2 phases which were prepared with different amounts

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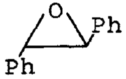
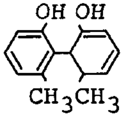
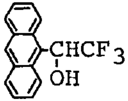
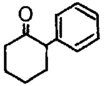
* The number 3% represents the amount of diisocyanate used for the bond formation between cellulose and 3-aminopropyl silica gel.

TABLE 2

Resolution of Five Racemates on CTPC-3,5-Cl_2-Bonded Phases

Racemate	12.8 %[a]			5 %[a]			3 %[a]			coated type[b]
	k_1'	α	Rs	k_1'	α	Rs	k_1'	α	Rs	α
	0.49(+)	1.34	1.11	0.37(+)	1.54	1.71	0.86(+)	1.54	2.22	1.84(+)
	1.14(-)	1.22		1.13(-)	1.31	1.33	2.23(-)	1.20	0.78	1.11(+)
	0.46(-)	1.14		0.32(-)	1.27		0.52(-)	1.38		1.38(-)
	2.25(-)	1.16	0.87	1.90(-)	1.23	1.60	4.47(-)	1.24	1.66	1.26(-)
Co(acac)$_3$	5.48(+)	1.16		3.61(+)	1.18	0.53	3.61(+)	1.40	0.93	1.82(+)

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[a] Amount of the diisocyanate used for the preparation of the CSP.

[b] Data reported in ref. 2.

of the diisocyanate. The table also contains the data on the resolution with the CTPC-3,5-Cl_2-coated silica gel reported previously.[2)] Chiral recognition of the bonded-type CSP decreased as the chemical bond between the cellulose and silica gel increased, and the use of greater than 10% diisocyanate was not preferable. For many enantiomers besides those in Table 2, the CTPC-3,5-Cl_2-bonded phase showed lower resolving power than the coated phase, although a few compounds were better resolved on the latter. Fixation of cellulose on silica gel must prevent the CTPC-3,5-Cl_2 from forming an ordered structure on the surface of the silica gel. We have shown that most CTPC derivatives can form liquid crystal phases and this character is essential for the derivatives to exhibit high chiral recognition. Such an ordered arrangement of CTPC-3,5-Cl_2 molecules seems impossible for the CTPC-3,5-Cl_2 chemically bonded to silica gel. This may be the reason for lower chiral recognition of the bonded phase than the coated phase.

The bonded phase was quite stable under the typical chromatographic conditions with hexane-2-propanol (90:10), while the coated phase gradually lost the CTPC-3,5-Cl_2 on silica gel because of its high solubility.

In order to change the conformation and orientation of the CTPC-3,5-Cl_2, the chemically bonded phase was heated in a packed column filled with xylene at 65 ^{o}C and 130 ^{o}C. However, no change of separation factors was observed for the compounds listed in Table 2. The CTPC-3,5-Cl_2 bonded on the silica gel seems to take the most stable structure immediately after the preparation of the phase.

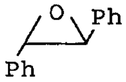
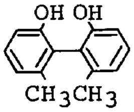
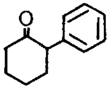
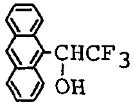
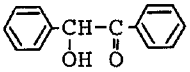
OPTICAL RESOLUTION ON CTPC-3,5-Me_2 PHASE

Table 3 shows the results of optical resolution of five racemic compounds on the CTPC-3,5-Me_2-bonded phases which were prepared with 3% and 5% of the diisocyanate to the hydroxy group of the cellulose. The data obtained on CTPC-3,5-Me_2 coated phase are also shown for comparison. The optical resolving power of the bonded phase was low in comparison with that of the coated phase except for the resolution of 2,2'-dihydroxy-6,6'-dimethylbiphenyl. The lower extent of chemical bonding between cellulose and silica gel seems to afford a better CSP.

The chiral recognition of the CTPC-3,5-Me_2-bonded phase remarkably shifted by heat treatment. The column filled with xylene was heated for 1 hr at 45, 65, 100, and 130 ^{o}C, and optical resolving power after heat treatment was investigated at 25 ^{o}C (Figure 2). Separation factors for the racemic compounds increased as the temperature of heat treatment rose except for the

TABLE 3

Resolution of Five Racemates on CTPC-3,5-Me_2-Bonded Phases

Racemate	5 %[a]			3 %[a]			coated type[b]
	k_1'	α	Rs	k_1'	α	Rs	α
	0.44(-)	~ 1		0.74(-)	1.18		1.68(-)
	1.00(-)	3.24	6.12	1.86(-)	4.02	6.09	1.83(-)
	0.76(-)	1.20	1.28	1.27(-)	1.26	1.30	1.15(-)
	1.10(-)	1.82	3.69	1.91(-)	2.03	2.95	2.59(-)
	1.76(+)	1.17	1.44	2.97(+)	1.24	1.31	1.58(+)

[a] Amount of the diisocyanate used for the preparation of CSP.

[b] Data reported in ref. 2.

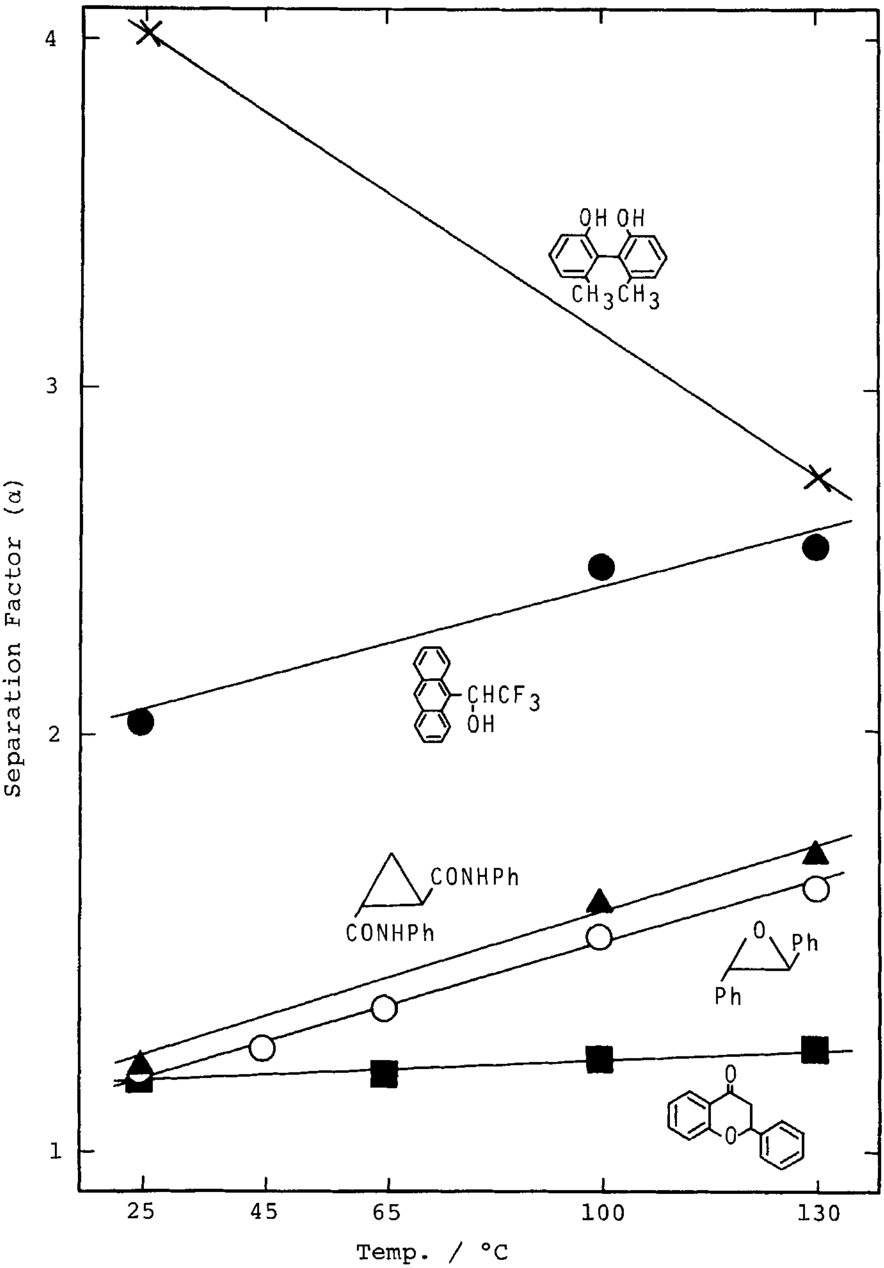
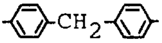
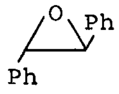
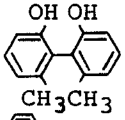
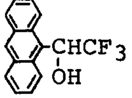
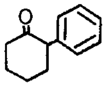
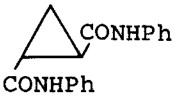


FIGURE 2. Effect of heat treatment of CTPC-3,5-Me_2-bonded phase (3%) on separation factor.

biphenyl derivative. The additional heat treatment at 130 °C did not bring about the change of the chiral recognition power of the CSP. The chiral recognition after the treatment at 130 °C was rather similar to that of the coated phase. This indicates that the conformation and/or orientation of chemically bonded CTPC-

TABLE 4

Influence of Diisocyanate (OCN-R-NCO) on Separation Factors (CTPC-3,5-Cl_2-Bonded Phase)[a]

Racemate	R of diisocyanate		
		-$(CH_2)_6$-	
	1.54 (+)	1.58 (+)	1.47 (+)
	1.20 (-)	1.13 (-)	1.09 (-)
	1.38 (-)	1.40 (-)	1.30 (-)
	1.24 (-)	1.25 (-)	1.34 (-)
	1.24 (+)	1.34 (+)	1.30 (+)

[a] Diisosyanates were used by 3 % based on hydroxy groups of cellulose.

$3,5$-Me_2 approaches to that of the coated CTPC-$3,5$-Me_2 by heating.

INFLUENCE OF DIISOCYANATE

The CSP's so far discussed were prepared by bonding cellulose on silica gel with 4,4'-diphenylmethane diisocyanate. Hexamethylene diisocyanate and p-phenylene diisocyanate were also employed in the same manner as 4,4'-diphenylmethane diisocyanate. The results of the preparation of CTPC-$3,5$-Cl_2 phases are summarized in Table 4. Three CSP's obtained with 3% diisocyanates to the hydroxy groups of cellulose exhibited almost similar optical resolving power. Chiral recognition due to the urethane bond formed by the diisocyanates seems negligible.

CONCLUSION

CTPC-$3,5$-Cl_2 and CTPC-$3,5$-Me_2 were well chemically bonded to 3-aminopropyl silica gel with diisocyanates. The optical resolving power of the phases was slightly low compared with that of the coated-type phases. The use of 3-5% of diisocyanate to the hydroxy group of cellulose seems to be most suitable. The chiral recognition power of the CTPC-$3,5$-Me_2 phase greatly changed by heat treatment of the phase and approached to that of the coated phase. The phase could be used with the eluents that dissolve the CTPC derivatives.

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