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Optical Resolution of Alcohols as Carbamates by HPLC on Cellulose Tris(phenylcarbamate) Derivatives[1)]

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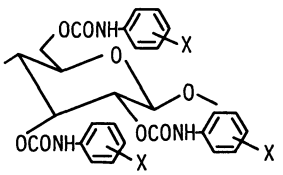
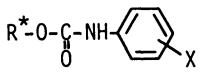
The optical resolutions of various alcohols as phenylcarbamates were examined by HPLC on chiral stationary phases derived from sixteen cellulose tris(phenylcarbamate) derivatives. The optical resolving power of chiral stationary phases was greatly influenced by substituents on the phenyl groups of the cellulose derivatives. Also, cellulose tris(3,5-dimethylphenylcarbamate) could very efficiently resolve many racemic phenylcarbamates, including the carbamates of 2-butanol, 3-buten-2-ol, and 1-phenylethanol. Racemic phenylcarbamates having electron-donating substituents on the phenyl group were better resolved than those having electron-withdrawing substituents. The benzoates of most alcohlos were not resolved as efficiently as the carbamates.

Optical resolution by chiral high-performance liquid chromatogaphy (HPLC) has been attracting much attention as a procedure for obtaining optical isomers and determining their purity; many chiral stationary phases (CSP) have been reported over the past several years.[2)] We recently reported that phenylcarbamate derivatives of polysaccharides,[3)] particularly cellulose,[4–10)] show characteristic optical resolving abilities to a variety of enantiomers. The optical resolving power of nineteen cellulose tris(phenylcarbamate) (CTPC) derivatives depended greatly on the inductive effect of substituents on the phenyl group and either 3,5-dimethyl or 3,5-dichloro derivatives (CTPC-3,5-Me_2 or -3,5-Cl_2) showed the best resolution to many of the racemic compounds examined.[4)] CTPC-3,5-Me_2, which has the most electron-donating substituent, seemed to effectively resolve polar compounds that could interact with the carbonyl group of the urethane bond of the carbamate. However, CTPC-3,5-Cl_2 seemed to possess a higher resolving power for compounds that can be adsorbed on the NH group of the urethane bond.

The optical resolution of alcohols is laborious and usually they are resolved as diastereomeric salts of acid phthalates. A direct resolution of alcohols by chiral HPLC has been attained only for several aromatic alcohols.[4,11,12)] However, many alcohols, including aliphatic alcohols, have been successfully resolved by chiral HPLC as proper derivatives, such as esters[12,13)] or urethanes.[14,15)] Racemic 3,5-dinitrophenylcarbamates of racemic alcohols have been utilized for effective chiral discrimination through a π–π interaction.[14,15)] In this work, in order to attain an efficient resolution of alcohols by HPLC, the urethanes of various racemic alcohols were prepared by reactions with twelve substituted phenyl isocyanates; they were subjected to optical resolution on 16 CTPC derivatives **1—16**.



X=



X=

1: 4-CH_3O	**9**: 4-NO_2	3,4-$(CH_3)_2$, 3,5-$(CH_3)_2$,
2: 4-C_2H_5	**10**: 3-CH_3	2,6-$(CH_3)_2$, 4-CH_3, 3-CH_3,
3: 4-CH_3	**11**: 3,5-$(CH_3)_2$	2-CH_3, H, 4-F, 4-Cl,
4: H	**12**: 3,4-$(CH_3)_2$	4-Br, 3,5-Cl_2, 4-NO_2
5: 4-F	**13**: 2,6-$(CH_3)_2$	
6: 4-Cl	**14**: 3-Cl	
7: 4-Br	**15**: 3,5-Cl_2	
8: 4-CF_3	**16**: 2,6-Cl_2	

Experimental

Materials. Details on the preparation of CSPs were described previously.[4)] CTPC derivatives (25wt% of silica gel) were adsorbed on macroporous silica gel (diameter 10 μm, pour size 400 nm), and used as CSPs. Racemic alcohols were allowed to react with substituted phenyl isocyanates in the presence of a small amount of pyridine to give racemic carbamates. The carbamates were purified by either distillation or recrystallization.

Chromatographic Analyses. CSPs were packed in a stainless-steel tube (25 cm×0.46(id) cm) by a slurry method. Chromatographic analyses were carried out on a JASCO TRIROTAR-II chromatograph equipped with UV (JASCO UVIDEC-100-III) and polarimetric (JASCO DIP-181C) detectors. The optical resolution was monitored in a flow cell (50 mm×2(id) mm) at full lamp (mercury) intensity without a filter. Optical resolution was performed with a hexane-2-propanol mixture at a flow rate of 0.5 or 1.0 ml min^{-1} at 25 °C. Dead time (t_0) of the chromatograph system was estimated with 1,3,5-tri-*t*-butylbenzene as a non-retained compounds.[16)]

Results and Discussion

2-Butanol was completely resolved into enantiomers as phenylcarbamate on cellulose tris(4-ethylphenylcarbamate) (**2**) as shown in Fig. 1. Capacity

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factors (k_1' and k_2') for the first- and second-eluting isomers, which were estimated as $(t_1-t_0)/t_0$ and $(t_2-t_0)/t_0$, were obtained as 0.88 and 1.61, respectively, and separation factor ($\alpha=k_2'/k_1'$), which represents the chiral recognition ability of CSP, was determined to be 1.83. The resolution factor (R_s), which stands for the efficiency of a column, can be estimated by $2(t_2-t_1)/(W_1+W_2)$, where W_1 and W_2 are bandwidths of the peaks. Here, R_s was 3.84. Such an effective optical resolution of simple aliphatic alcohol derivatives by HPLC does not seem to have been reported before.[4,11-15]

Phenylcarbamates of 2-butanol and 1-phenylethanol were subjected to resolution on CTPC derivative columns (Table 1). Chiral recognition abilities of CSPs depended greatly on the substituents of CTPCs. Among nine para-substituted CTPCs **1**—**9**, methyl and ethyl derivatives exhibited better resolving powers for both racemic carbamates, suggesting that an electron-donating group would be preferable to an electron-withdrawing group. However, a more electron-donating substituent, methoxyl, was not better than alkyl. This may be attributed to the adsorption of the solute on the methoxyl group.[4] Since the methoxyl group is far from a chiral glucose

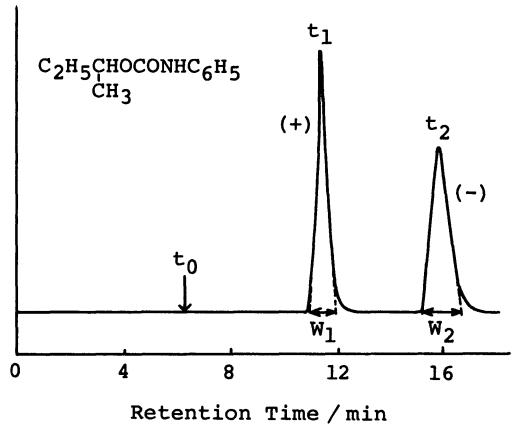


Fig. 1. Resolution of *s*-butyl phenylcarbamate on cellulose tris(4-ethylphenylcarbamate) (hexane-2-propanol(90:10), 0.5 ml min^{-1}, 25 °C).

Table 2. Resolution of *s*-Butyl Phenylcarbamate (*s*-$C_4H_9OCONHC_6H_4X$) on Cellulose Tris(phenylcarbamate) (**4**) and Tris(3,5-dimethylphenylcarbamate) (**11**)

X	**4**[a]			**11**[b]		
	k_1'	α	R_s	k_1'	α	R_s
3,4-$(CH_3)_2$	4.17	1.54	2.63	3.05	2.84	8.74
3,5-$(CH_3)_2$	2.71	1.45	2.35	2.14	2.50	7.53
2,6-$(CH_3)_2$	3.13	1.05		1.99	1.0	
4-CH_3	3.85	1.33	2.49	1.63	2.67	7.98
2-CH_3	3.39	1.43	2.96	2.15	3.01	9.24
3-CH_3	2.61	1.08	0.70	2.09[c]	1.32	2.60
H	3.72	1.34	1.81	1.85	2.78	8.57
4-F	3.01	1.11	1.17	0.67	1.42	2.10
4-Cl	2.81	1.10	0.86	0.63	1.22	1.11
4-Br	3.03	1.09	0.88	2.45[c]	1.19	1.49
3,5-Cl_2	1.65	1.11	0.78	0.54	1.19	0.88
4-NO_2	13.75	1.05		1.00	1.00	

a) Eluent: hexane-2-propanol (98:2), 0.5 ml min^{-1}, 25 °C. b) Eluent: hexane-2-propanol (90:10), 1.0 ml min^{-1}, 25 °C. c) Eluent: hexane-2-propanol (98:2), 1.0 ml min^{-1}, 25 °C.

Table 1. Resolution of *s*-Butyl and 1-Phenylethyl Phenylcarbamates on CTPC Derivative Columns[a]

No.	CTPC's substituent	Hammett σ value	$C_2H_5(CH_3)CHOCONHC_6H_5$[b]			$C_6H_5(CH_3)CHOCONHC_6H_5$[c]		
			k_1'	α	R_s	k_1'	α	R_s
1	4-CH_3O	−0.27	0.76	1.22	0.57	1.96	1.94	2.28
2	4-C_2H_5	−0.15	0.88	1.83	3.84	1.38	4.35	10.43
3	4-CH_3	−0.17	1.00	1.46	2.06	2.02	2.90	7.67
4	H	0	1.00	1.29	1.47	2.16	2.09	4.48
5	4-F	0.06	0.84	1.20	0.90	1.91	1.48	2.43
6	4-Cl	0.23	0.67	1.0		1.63	1.0	
7	4-Br	0.23	0.80	1.18	1.09	1.88	1.20	1.17
8	4-CF_3	0.54	1.00	1.0		1.56[d]	1.24	1.85
9	4-NO_2	0.78	0.88	1.0		2.35	1.0	
10	3-CH_3	−0.07	0.52	1.29	1.00	0.80	1.95	2.70
11	3,5-$(CH_3)_2$		1.83	2.79	10.02	2.34[e]	4.52	12.41
12	3,4-$(CH_3)_2$		0.91	1.92	3.36	1.58	3.18	7.65
13	2,6-$(CH_3)_2$		0.93	1.0		1.87	1.0	
14	3-Cl	0.37	0.73	1.15	0.67	1.59	1.27	1.79
15	3,5-Cl_2		0.88	1.16	0.77	1.28	1.73	3.80
16	2,6-Cl_2		0.97	1.0		2.52	1.0	

a) Eluent: hexane-2-propanol (90:10), 0.5 ml min^{-1}, 25 °C. b) (*S*)-(+)-Isomer eluted first. c) (*S*)-(−)-Isomer eluted first. d) (*R*)-(+)-Isomer eluted first. e) 1.0 ml min^{-1}.

unit, such an adsorption must lower the optical resolving power of CSP. To attain an effective chiral recognition, solutes must be adsorbed on the urethane bond of CSP.

Dimethyl-substituted derivatives **11** and **12**, particularly the former, possessed a better resolving power over monosubstituted derivatives. However, 2,6-dimethyl-substituted derivative **13** showed no chiral recognition, as observed in the previous work.[4] 2,6-Dichloro derivative **16** also exhibited no resolving power. In almost all cases, (±)-1-phenylethyl phenylcarbamate was better resolved than (±)-*s*-butyl phenylcarbamate and both (*S*) isomers were eluted first. Reversed elution order of enantiomers was observed only in the resolution of (±)-1-phenylethyl phenylcarbamate on **8**. The reason for this is not clear.

s-Butyl phenylcarbamates (*s*-$C_4H_9OCONHC_6H_4X$) having various substituents were resolved on **4** and **11** (Table 2). The latter column always showed better resolving power than the former, and good resolution was attained on racemic unsubstituted phenylcarbamate (X=H) and methyl-substituted phenylcarbamates except for 2,6-dimethyl and 3-methyl derivatives. In all runs, (+)-isomers were eluted first. These results suggest that simple unsubstituted phenylcabamates of racemic alcohols may be one of the most suitable carbamates for resolution. Electron-withdrawing substituents were not suitable.

The resolution of phenylcarbamates of various aliphatic alcohols, including an allyl alcohol, were examined on columns packed with **4** and **11** (Fig. 2 and Table 3). All alcohols having a hydroxy group on the asymmetric carbon were sufficiently resolved as carbamates particularly on **11**, probably eluting (*S*)-(+)-isomers first. However, the carbamates of alcohols carrying a methylene group between hydroxy group and asymmetric carbon were not resolved as efficiently as the above alcohols. It can be expected that chiral discrimination will become more difficult as the distance between the urethane group and asymmetric center of racemic carbamates increases, since the urethane group must be adsorbed on CTPCs.

Table 4 shows the comparison data of the resolution of phenylcarbamates and benzoates of racemic alcohols on an **11** column. Most alcohols were better

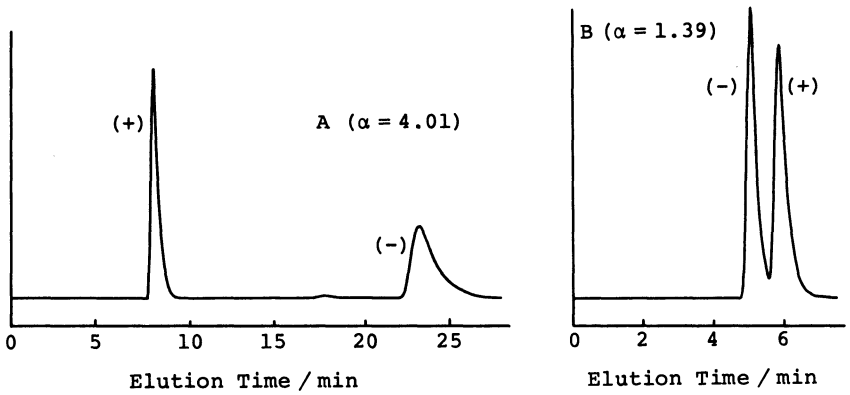


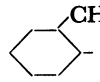
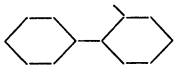
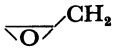
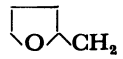
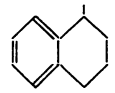
Fig. 2. Resolution of phenylcarbamates of 3-buten-2-ol (A) and 3-octanol (B) on cellulose tris(3,5-dimethylphenylcarbamate) (hexane–2-propanol(90:10), 1.0 ml min^{-1}, 25 °C).

Table 3. Resolution of Aliphatic Alcohols as Phenylcarbamate ($ROCONHC_6H_5$) on Cellulose Tris(phenylcarbamate) (**4**) and Tris(3,5-dimethylphenylcarbamate) (**11**)

R	**4**[a]			**11**[b]		
	k_1'	α	R_s	k_1'	α	R_s
$CH(CH_3)C_2H_5$	3.72(+)	1.34	1.81	1.85(+)	2.78	8.57
$CH(CH_3)C_3H_7$	2.93(+)	1.43	2.64	1.47(+)	3.26	7.80
$CH(CH_3)C_6H_{13}$	1.94(+)	1.47	2.81	1.19(+)	3.90	9.57
$CH(CH_3)CH{=}CH_2$	4.90(+)	1.59	3.32	1.68(+)	4.01	8.61
$CH(CH_3)CH(CH_3)_2$	2.52(+)	1.41	2.21	0.84(+)	3.16	5.85
$CH(C_2H_5)C_5H_{11}$	1.54(−)	1.08	0.30	0.67(−)	1.39	1.42
$CH_2CH(CH_3)C_2H_5$	5.33(+)	1.05		4.00[c]	1.00	
$CH_2CH(CH_3)C_3H_7$	5.27	1.00		6.42	1·00	
$CH_2CH(CH_3)C_6H_5$	3.13(−)[b]	1.11	0.39	9.42(+)	1.06	

a) Eluent: hexane–2-propanol (98:2), 0.5 ml min^{-1}, 25 °C. b) Eluent: hexane–2-propanol (90:10), 1.0 ml min^{-1}, 25 °C. c) Eluent: hexane–2-propanol (80:20), 1.0 ml min^{-1}, 25 °C.

Table 4. Resolution of Racemic Alcohols as Phenylcarbamates ($ROCONHC_6H_5$) and Benzoates ($ROCOC_6H_5$) on Cellulose Tris(3,5-dimethylphenylcarbamate)[a]

R	Phenylcarbamate				Benzoate			
	Eluent[b]	k_1'	α	R_s	Eluent[c]	k_1'	α	R_s
$CH(CH_3)C_2H_5$	B	1.85(+)	2.78	8.57	A	0.33	1.00	
$CH(CH_3)C_3H_7$	B	1.47(+)	3.26	7.80	A	0.31	1.00	
$CH(CH_3)C_6H_{13}$	B	1.19(+)	3.90	9.57	A	0.23	1.00	
$CH(CH_3)C_6H_5$	B	2.34(−)	4.52	12.41	A	0.74(−)	1.18	1.20
	A	3.60(+)	1.82	5.87	A	0.33	1.00	
	A	2.20(+)	2.06	5.95	A	0.24	1.00	
	C	2.43(−)	1.17	0.89	A	3.86(+)	1.18	1.70
	C	4.32(+)	1.76	4.08	A	2.14	1.00	
	B	3.51(−)	1.05		A	0.74(+)	1.08	0.45
$CH(CH_3)C_2H_5$	B	0.54(+)[d]	1.19	0.88	A	0.17[e]	1.00	

a) Eluent: A, hexane-2-propanol(98:2) B: hexane-2-propanol (90:10) C: hexane-2-propanol(80:20). b) 1.0 ml min^{-1}. c) 0.5 ml min^{-1}. d) As 3,5-dichlorophenylcarbamate. e) As 3,5-dichlorobenzoate.

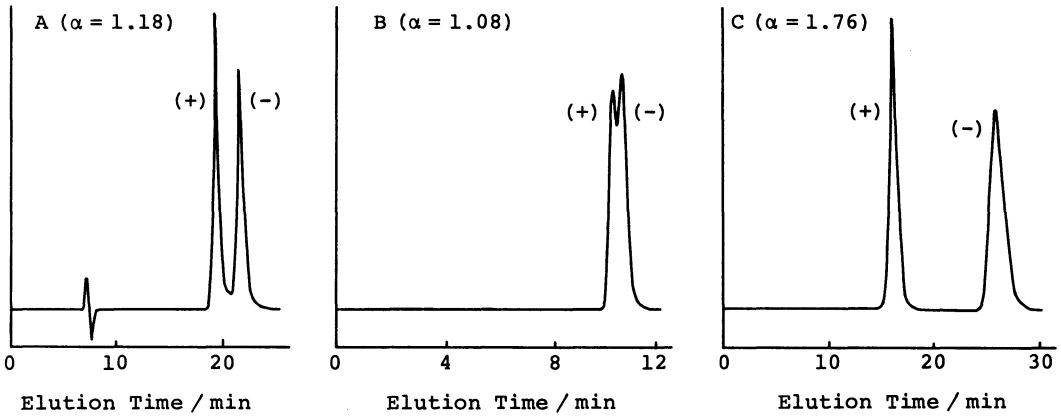


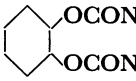
Fig. 3. Resolution of benzoates of glycidol (A) and 1,2,3,4-tetrahydro-1-naphthol (B), and carbamate of tetrahydrofurfuryl alcohol (C) on cellulose tris(3,5-dimethylphenylcarbamate) (A, B: hexane-2-propanol(98:2), 0.5 ml min^{-1}, 25 °C, C: hexane-2-propanol(80:20), 1.0 ml min^{-1}, 25 °C).

resolved as phenylcarbamates than benzoates. The benzoates of glycidol and 1,2,3,4-tetrahydro-1-naphthol were exceptionally better resolved than the carbamates (Fig. 3). The carbamate of tetrahydrofurfuryl alcohol was much better resolved than the benzoate (Fig. 3). Although glycidol and tetrahydrofurfuryl alcohol possess a methylene group between asymmetric center and hydroxyl group, these were resolved as phenylcarbamates. Adsorption on ether groups may contribute effective chiral discrimination.

Several 1,2- and 1,3-diols were also separated into enantiomers as phenylcarbamates (Table 5). The separation of diastereomers and the resolution of enantiomers were attained on 2,4-pentanediol.

One of possible space-filling structure (CPK) of CTPC is shown in Fig. 4. The carbamate and phenyl groups are aligned without any difficulty so that hydrogen bonds are formed between 2-3 carbamate groups and 2-6 carbamate groups.[17] These hydrogen bonds must contribute to the fixation of the adjacent glucose units which may lead to the formation of a liquid crystal phase.[18] The regularly arranged -NHCOO- groups of CTPC must be the most attractive adsorbing sites. Since the racemic esters were not well resolved, the hydrogen bonding and dipole interactions between the urethane bond of CTPC and the ester group of the solutes do not seem to strong enough to attain effective chiral discrimina-

Table 5. Resolution of Diols as Phenylcarbamates on Cellulose Tris(3,5-dimethylphenylcarbamate)[a]

Racemate	k_1'	α	R_s
$CH_3CHOCONHC_6H_5$ $CH_2OCONHC_6H_5$	4.24(−)	1.90	3.42
$CH_3CHOCONHC_6H_5$ CH_2 $CH_3CHOCONHC_6H_5$	0.52(+)[b]	8.76	2.94
$CH_3CH_2CH_2CHOCONHC_6H_5$ $CH_3CH_2CHOCONHC_6H_5$	2.01(+)[c]	1.25	0.89
	0.71(−)	1.31	0.97

a) Eluent: hexane-2-propanol (80:20), 0.5 ml min^{-1}, 25 °C. b) Capacity factor of meso-isomer was 1.92. c) Only one enantiomeric pair was found.

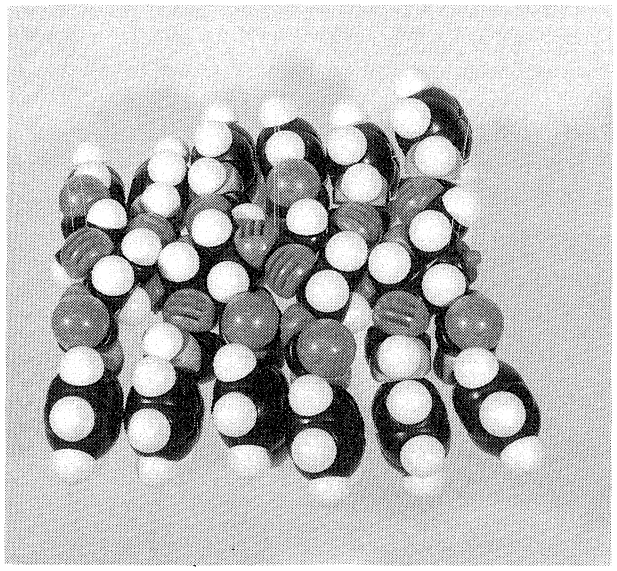


Fig. 4. CPK model of cellulose tris(phenylcarbamate).

tion. A stronger interaction between the two urethane groups of CTPC and solutes may be responsible for the effective chiral discrimination of the racemic carbamates.

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