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Useful Chiral Stationary Phases for HPLC. Amylose Tris(3,5-dimethylphenylcarbamate) and Tris(3,5-dichlorophenylcarbamate) Supported on Silica Gel1)

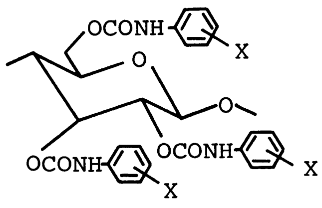
Yoshio OKAMOTO,* Ryo ABURATANI, Tohru FUKUMOTO, and Koichi HATADA
Department of Chemistry, Faculty of Engineering Science,
Osaka University, Toyonaka, Osaka 560

Amylose tris(3,5-dimethylphenylcarbamate) (ADMPC) and tris(3,5-dichlorophenylcarbamate) (ADCPC) were supported on macroporous silica gel to use as chiral stationary phases for HPLC. ADMPC showed higher optical resolving power for some enantiomeric pairs than cellulose tris(3,5-dimethylphenylcarbamate), and gave a practically useful chiral HPLC column. ADCPC resolved a few racemic drugs efficiently.

We reported that phenylcarbamates of various polysaccharides, cellulose (**1a**), amylose (**2a**), chitosan, xylan, curdlan, and inulin, showed characteristic chiral recognition ability as stationary phases for HPLC when supported on silica gel.2) Among these carbamates, cellulose derivative appeared to cover the optical resolution of a wide variety of racemic compounds. More recently, we also found that the substituents placed on the phenyl groups of **1a** influenced remarkably the chiral recognition ability and either 3,5-dimethylphenylcarbamate (**1b**) or 3,5-dichlorophenylcarbamate (**1c**) exhibited higher resolving power for many racemic compounds.3)

In the present study, we synthesized amylose tris(3,5-dimethylphenylcarbamate) (**2b**) and tris(3,5-dichlorophenylcarbamate) (**2c**), and used them as chiral stationary phases (CSP) upon adsorption over silica gel. These two, particularly **2b**, offered a practically useful chiral column with a high enantiomer-separability.

Amylose (Nakarai Chemicals, M.W. 16000) was allowed to react with an excess of 3,5-disubstituted phenylisocyanate in pyridine at 100 °C for 24 h. The reaction

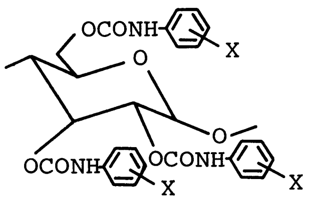


X =

1a: H

1b: 3,5-$(CH_3)_2$

1c: 3,5-Cl_2



X =

2a: H

2b: 3,5-$(CH_3)_2$

2c: 3,5-Cl_2

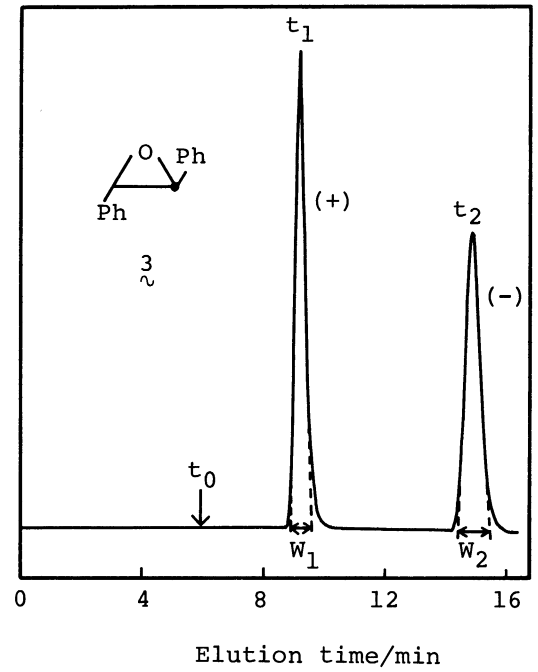


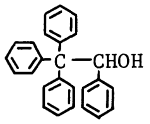
Fig. 1. Optical resolution of trans-2,3-diphenyloxirane (**3**) on an amylose tris(3,5-dimethylphenylcarbamate) (**2b**) column.

products were precipitated in methanol. Elemental analysis, IR, and NMR data indicated that hydroxy groups of amylose were almost completely converted to the corresponding carbamate groups. The obtained carbamates **2b** and **2c** were dissolved in N,N-dimethylacetamide and N,N-dimethylacetamide-tetrahydrofuran (1:5), respectively, and adsorbed on macroporous silica gel (particle size 10 μm, pore size 400 nm) which has been treated with 3-aminopropyltriethoxysilane in advance in the same manner as reported previously.[2,3] The weight ratio of the carbamate to the silica gel was 0.75/3.0. The packing materials were packed in a stainless steel tube (25 cm x 0.46 (i.d.) cm) by a slurry method. The **2a** column used here was the same as previously reported.[2]

Chromatographic analysis was performed on a JASCO TRIROTAR-II equipped with UV (UVIDEC 100-V) and polarimetric (DIP-181C, Hg) detectors at 25 $^{\circ}C$, a hexane-2-propanol (90:10) mixture being used as an eluent at a flow rate of 0.5 ml min^{-1}. Dead time (t_0) was estimated with 1,3,5-tri-t-butylbenzene.[4]

Figure 1 shows the chromatogram of the resolution of trans-2,3-diphenyloxirane (**3**) on a **2b** column. The oxirane was sufficiently resolved eluting (+)- and (-)-isomers at t_1 and t_2, respectively. Capacity factors, k_1' (= $(t_1-t_0)/t_0$) and k_2' (= $(t_2-t_0)/t_0$), which represent the strength of the interaction of the stationary phase and enantiomers, were 0.42 and 1.28, respectively. Optical resolving power of the CSP can be evaluated from separation factor α (k_2'/k_1' = 3.04), and efficiency of the column from resolution factor Rs ($2(t_2-t_1)/(W_1+W_2)$ = 6.67).

The results of optical resolution of ten racemic compounds **3**-**12** on **2a**-**c** are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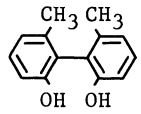
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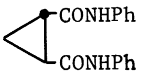
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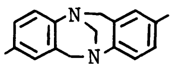
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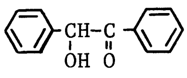
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Co(acac)$_3$

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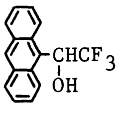
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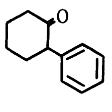
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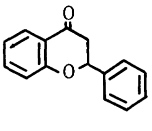
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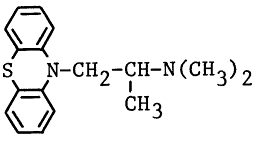
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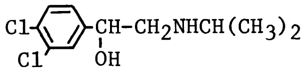
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Table 1. Optical resolution on amylose tris(phenylcarbamate) derivatives a)

Racemic	2a			2b			2c		
compd	k_1'	α	Rs	k_1'	α	Rs	k_1'	α	Rs
3	0.39(+)	1.46	1.29	0.42(+)	3.04	6.67	0.50(+)	1.32	1.69
4	1.42(+)	1.86	3.11	2.65(+)	1.98	5.48	0.88(+)	2.25	6.05
5	1.15(-)	1.53	1.74	2.46(-)	2.11	6.38	1.10(+)	≃ 1	
6	1.83(+)	1.52	1.70	3.25(+)	2.01	3.59	0.59(-)	1.11	
7	0.77(+)	1.28	1.10	0.53(+)	1.58	2.30	0.84(+)	1.34	2.27
8	3.72(+)	≃ 1		3.14(-)	1.21	2.07	6.08(+)	≃ 1	
9	1.80(-)	1.28	0.87	0.25(-)	≃ 1		0.63(+)	≃ 1	
10	0.61	1.00		1.30(+)	1.15	0.75	0.37	1.00	
11	1.19(-)	≃ 1		0.61(-)	≃ 1		1.26(-)	≃ 1	
12	2.21(+)	1.51	2.72	0.93(+)	1.12	0.77	1.62(+)	1.10	1.02

a) The sign in parentheses represents optical rotation of the first-eluted isomer.

summarized in Table 1. Optical resolving power of the stationary phases was varied greatly by the introduction of the substituents and most compounds were best resolved on the dimethyl derivative 2b. Tris(acetylacetonato)cobalt(III) (9) and flavanone (12) were best resolved on 2a and 1,2,2,2-tetraphenylethanol (4) on 2c. For the resolution of 3, 4, 2,2'-dimethyl-6,6'-dihydroxybiphenyl (5), and Tröger base (7), amylose derivative 2b exhibited better chiral recognition ability than the corresponding cellulose derivative 1b.3) As for the dichloro derivatives, cellulose derivative 1c was superior to amylose derivative 2c in the resolution of nine enantiomeric pairs except for 4 which was resolved more effectively by 2c than by any cellulose tris(phenylcarbamate) derivatives.3) Characteristic resolving power of 2c was also exerted in the resolution of a few racemic drugs including a neuroleptic promethazin (13) and a β-blocker dichloroisopretherenol (14) (Fig. 2). These drugs were not yet resolved on the derivatives of 1a.

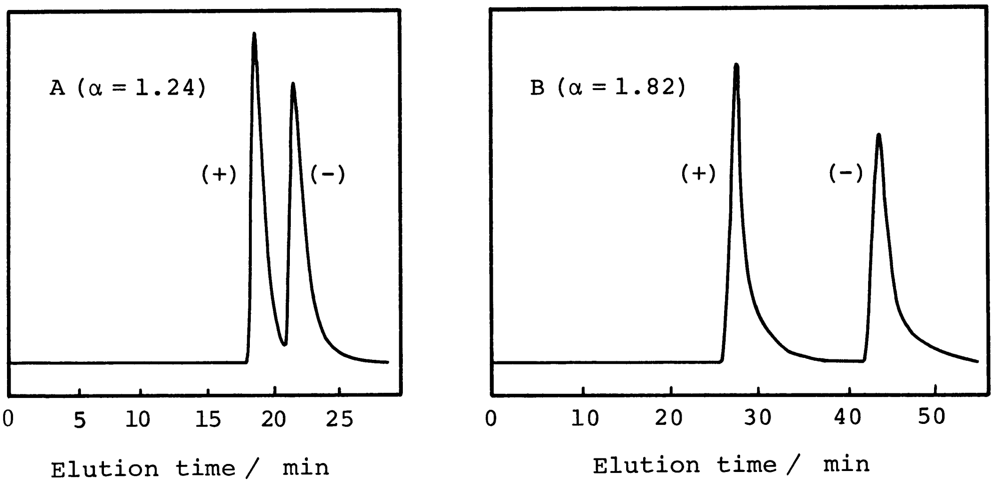

Fig. 2. Resolution of (A) racemic promethazin (**13**) and (B) dichloroisopretherenol (**14**) on amylose tris(3,5-dichlorophenylcarbamate) (**2c**). (Eluent : hexane-2-propanol (98:2))

A more readily available material, soluble starch (Merck), was also used in place of amylose. Usually starch contains 20-25% of linear component amylose and 75-80% of branched component amylopectin. Starch tris(3,5-dimethylphenylcarbamate) supported on silica gel exhibited similar but slightly lower chiral recognition compared with that of **2b**; for instance $k_1' = 0.36$, $\alpha = 2.28$, Rs = 3.94 for **3**, $k_1' = 0.50$, $\alpha = 1.46$, Rs = 1.67 for **7**.

The amylose columns possessed a good durability and did not change its ability under chromatographic conditions using hexane containing 0-30% of 2-propanol or ethanol as an eluent. The columns, particularly **2b** column, seem to be practically useful for resolving many racemic compounds some of which are difficult to resolve on the currently widely used **1a**-**c** columns.$^{5)}$

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