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# CHROMATOGRAPHIC RESOLUTION

## XI*. CONTROLLED CHIRAL RECOGNITION OF CELLULOSE TRIPHENYLCARBAMATE DERIVATIVES SUPPORTED ON SILICA GEL

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SUMMARY

Cellulose triphenylcarbamate and eighteen mono- or disubstituted derivatives were adsorbed on silica gel and their chiral recognition abilities as stationary phases for high-performance liquid chromatography were investigated. The inductive effect of the substituents greatly influenced the optical resolution ability when they were at the 3- or 4-position. 2-Substituted derivatives showed a low degree of resolution. Among nine 4-substituted phenylcarbamates, the 4-methyl, 4-ethyl, 4-chloro, or 4-trifluoromethyl derivative showed the most efficient chiral recognition for racemic compounds. Dimethylphenyl- and dichlorophenylcarbamates substituted at the 3,4- or 3,5-positions showed better chiral recognition for most enantiomers than the monosubstituted derivatives. Most stationary phases possessed high durability and many racemic compounds were resolved on these phenylcarbamates.

## INTRODUCTION

Recently, liquid chromatographic separation of enantiomers has attracted great attention and several useful chiral stationary phases have been reported[1–4]. Cellulose is one of the most accessible optically active macromolecules. Hesse and Hagel[5,6] found that the microcrystalline cellulose triacetate prepared by heterogeneous acetylation of native cellulose shows an interesting ability of chiral recognition when used as a stationary phase for liquid chromatography. Since then various racemic compounds, particularly aromatic compounds, have been resolved on microcrystalline cellulose triacetate[7–18]. When this cellulose triacetate was supported on silica gel from a solution, it also gave a useful stationary phase for high-performance liquid chromatography (HPLC), and its chiral recognition ability was completely different from that of microcrystalline cellulose triacetate[19,20]. More recently, we also reported briefly that phenylcarbamates of various polysaccharides, such as cellulose, amylose, xylan, chitosan, curdlan, dextran, and inulin, exhibited unique resolution ability as

* For Part X, see ref. 25.

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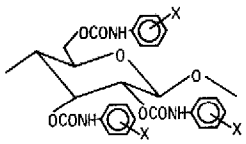
stationary phases for HPLC[21]. Among these phenylcarbamates, cellulose triphenylcarbamate separated the widest range of racemic compounds, and gave a practically useful HPLC column.



X=

| | |
|---|---|
| 1:4-$CH_3O$ | 10:3-Cl |
| 2:4-$CH_3$ | 11:2-Cl |
| 3:4-$CH_3CH_2$ | 12:3,4-$Cl_2$ |
| 4: H | 13:3,5-$Cl_2$ |
| 5:4-F | 14:2,6-$Cl_2$ |
| 6:4-Cl | 15:3-$CH_3$ |
| 7:4-Br | 16:2-$CH_3$ |
| 8:4-$CF_3$ | 17:3,4-$(CH_3)_2$ |
| 9:4-$NO_2$ | 18:3,5-$(CH_3)_2$ |
| | 19:2,6-$(CH_3)_2$ |

In the present study, we synthesized nineteen cellulose triphenylcarbamate derivatives (compounds 1–19) in order to correlate their optical resolution abilities with the characteristics of the substituents on the phenyl rings. We also attempted to control the chiral recognition of the phenylcarbamates as stationary phases for HPLC.

## EXPERIMENTAL

### *Cellulose triphenylcarbamate derivatives*

Cellulose triphenylcarbamate derivatives, except for compounds 16 and 19, were prepared by the reaction of microcrystalline cellulose (Avicel, Merck) with an excess of corresponding isocyanates in pyridine at *ca.* 100°C, and isolated as the methanol-insoluble fraction; yields were 60–100%. Derivatives 16 and 19 could not be prepared by this method, but were obtained by the reaction of cellulose dissolved in N,N-dimethylacetamide lithium chloride with corresponding isocyanates in the presence of pyridine at 80°C. Elemental analyses (Table I) showed that hydroxy groups of cellulose reacted almost quantitatively to form urethane bonds. Reasonable IR and NMR spectra were obtained with all the derivatives. The gel permeation chromatogram of compound 4 showed a peak at $\bar{M}_n = 1.08 \cdot 10^5$, $\bar{M}_w/\bar{M}_n = 4.46$ (where $\bar{M}_n$ is the number-average molecular weight and $\bar{M}_w$ the weight-average molecular weight).

### *Preparation of stationary phase*

Macroporous silica gel (Merck, LiChrospher SI 4000) was treated with 3-aminopropyltriethoxysilane in benzene at 80°C (analysis: C = 0.23; H = 0.07; N = 0.09%). A cellulose triphenylcarbamate derivative (0.75 g) was dissolved in 10 ml of tetrahydrofuran (THF). Because compounds 9 and 12 were insoluble in THF, they were dissolved in N,N-dimethylacetamide. The solution (*ca.* 5 ml) was added to the above silanized macroporous silica gel (3 g), and wetted silica gel was dried under

vacuum. This coating process was repeated with the remaining carbamate solution. The packing materials thus obtained were packed in a stainless-steel column (250 × 4.6 mm I.D.) at 300 kg/cm² by a slurry method. The plate numbers of these columns were 3000–6000 for benzene with hexane–2-propanol (90:10, 0.5 ml/min) as eluent at 25°C. The dead time ($t_0$) of the column was estimated to be 6.0 min with 1,3,5-tri-*tert.*-butylbenzene as a non-retained compound[12].

*Measurement*

A JASCO TRIROTAR-II chromatograph equipped with a UV (JASCO UVIDIC-100-III) and polarimetric (JASCO DIP-181C) detectors was used. Optical rotation was followed in a flow cell (50 × 2 mm I.D.) at full lamp (mercury) intensity without filters. Resolution was carried out with a hexane–2-propanol (90:10) mixture at a flow-rate of 0.5 ml/min at 25°C unless otherwise stated. The $^1$H NMR spectrum was measured with a JEOL-MH-100 (100 MHz) spectrometer. Gel permeation chromatographic (GPC) analysis was carried out with two Shodex A-80M GPC columns connected in series, with THF as eluent. A calibration curve was obtained with standard polystyrene. IR spectra were taken on a JASCO IR-810 spectrophotometer in nujol.

## RESULTS AND DISCUSSION

*Resolution on 4-substituted derivatives*

The resolution of racemic 1-(9-anthryl)-2,2,2-trifluoroethanol (20) on cellulose tris-(4-tolylcarbamate) (2) is shown in Fig. 1. The enantiomers were eluted at $t_1$ and $t_2$ and completely separated. 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 1.54 and 2.34, respectively. The separation factor, $\alpha = k'_2/k'_1$, and the resolution factor, $R_s = 2(t_2 - t_1)/(W_1 + W_2)$; were found to be 1.52 and 3.83, respectively.

Table II shows the results of optical resolution for racemates 20, *trans*-2,3-diphenyloxirane (21), Tröger base (22), cobalt(III) tris(acetylacetonate) (23), *trans*-cyclopropanedicarboxylic acid dianilide (24), 2,2′-dihydroxy-6,6′-dimethylbiphenyl (25), 1,2,2,2-tetraphenylethanol (26), benzoin (27), 2-phenylcyclohexanone (28) and

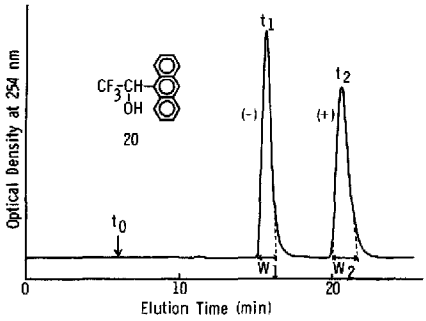



Fig. 1. Chromatographic resolution of 1-(9-anthryl)-2,2,2-trifluoroethanol (20) on a cellulose tris-(4-tolylcarbamate) (2) column. (Column, 250 × 4.6 mm I.D.; eluent, hexane–2-propanol (90:10, 0.5 ml/min); temperature, 25°C; $t_0$, 6 min).

TABLE I

ANALYTICAL DATA FOR CELLULOSE TRIPHENYLCARBAMATE DERIVATIVES

| Compound | Elemental analysis* | | | | $[\alpha]_D^{25}$ | Compound | Elemental analysis* | | | | $[\alpha]_D^{25}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | C (%) | H (%) | N (%) | Halogen (%) | | | C (%) | H (%) | N (%) | Halogen (%) | |
| 1 | 57.50 | 4.99 | 6.53 | | | 11 | 52.66 | 3.48 | 7.18 | 16.85 | |
| | (59.11 | 5.13 | 6.89) | | | | (52.07 | 3.56 | 6.75 | 17.08) | |
| 2 | 63.68 | 5.48 | 7.43 | | −87.2** | 12 | 44.39 | 2.66 | 5.86 | 28.46 | −41.1** |
| | (64.16 | 5.56 | 7.48) | | | | (44.66 | 2.64 | 5.79 | 29.29) | −4.8*** |
| 3 | 64.89 | 6.07 | 6.79 | | | 13 | 44.34 | 2.66 | 5.79 | 28.74 | −6.3** |
| | (65.66 | 6.18 | 6.96) | | | | (44.66 | 2.64 | 5.79 | 29.29) | |
| 4 | 61.23 | 4.72 | 7.92 | | −98.2** | 14 | 43.86 | 2.63 | 5.59 | 28.54 | −13.2** |
| | (62.42 | 4.85 | 8.09) | | −54.1*** | | (44.66 | 2.64 | 5.79 | 29.29) | |
| | | | | | −100§ | | | | | | |
| 5 | 55.39 | 3.73 | 7.01 | | | 15 | 63.88 | 5.52 | 7.51 | | |
| | (56.55 | 3.87 | 7.33) | | | | (64.16 | 5.56 | 7.48) | | |
| 6 | 51.75 | 3.60 | 6.67 | 16.64 | −67.2** | 16 | 64.31 | 5.49 | 7.56 | | |
| | (52.07 | 3.56 | 6.75 | 17.08) | | | (64.16 | 5.56 | 7.48) | | |
| 7 | 42.31 | 2.84 | 5.58 | 31.47 | | 17 | 64.81 | 6.05 | 6.88 | | −76.9** |
| | (42.89 | 2.93 | 5.54 | 31.71) | | | (65.66 | 6.18 | 6.96) | | |
| 8 | 49.72 | 3.05 | 5.88 | | | 18 | 64.14 | 6.06 | 6.80 | | −45.4** |
| | (49.80 | 3.06 | 5.81) | | | | (65.66 | 6.18 | 6.96) | | |
| 9 | 49.91 | 4.12 | 11.84 | | | 19 | 65.90 | 6.23 | 6.82 | | −6.9** |
| | (49.55 | 3.38 | 12.84) | | | | (65.66 | 6.18 | 6.96) | | |
| 10 | 51.67 | 3.54 | 6.76 | 17.13 | −52.0** | | | | | | |
| | (52.07 | 3.56 | 6.75 | 17.08) | | | | | | | |

* Calculated values of elemental analyses are shown in parentheses.

** In 1,4-dioxane.

*** In N,N-dimethylacetamide.

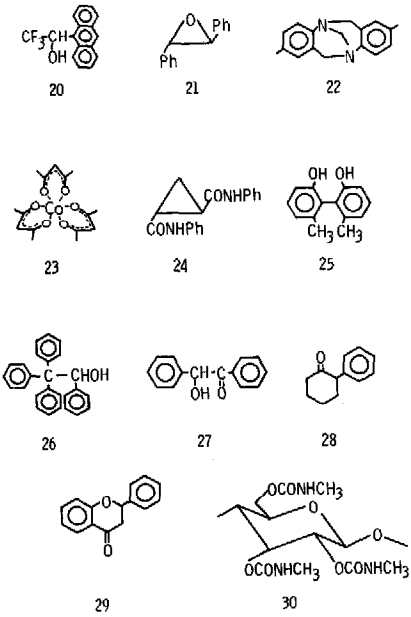
§ In chloroform.

TABLE II

RESOLUTION OF ENANTIOMERS (COMPOUNDS 20–29) AND ELUTION TIMES OF ACETONE ($T_a$) AND THE FIRST-ELUTING ISOMER OF COMPOUND 20 ($T_b$) ON CELLULOSE 4-SUBSTITUTED TRIPHENYLCARBAMATE DERIVATIVES 1–9

$R_s$ = Resolution.

| *Column with compound* | *20* | | | *21* | | | *22* | | |
|---|---|---|---|---|---|---|---|---|---|
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 1 | 1.79 (−) | 1.35 | 0.57 | 0.56 (+) | 1.34 | 0.77 | 1.09 (+) | *ca.* 1 | |
| 2 | 1.54 (−) | 1.52 | 3.83 | 0.51 (+) | 1.55 | 2.39 | 0.75 (+) | 1.48 | 2.61 |
| 3 | 1.13 (−) | 1.57 | 2.15 | 0.47 (+) | 1.55 | 2.00 | 0.74 (+) | 1.11 | 0.58 |
| 4 | 1.56 (−) | 1.45 | 1.38 | 0.67 (+) | 1.46 | 2.00 | 1.12 (+) | 1.37 | 1.73 |
| 5 | 0.73 (−) | 1.26 | 1.20 | 0.52 (+) | 1.38 | 1.60 | 1.00 (+) | 1.14 | 0.76 |
| 6 | 0.48 (−) | 1.29 | 1.05 | 0.38 (+) | 1.68 | 2.30 | 0.89 (+) | 1.16 | 0.83 |
| 7 | 0.61 (−) | 1.29 | 1.14 | 0.51 (+) | 1.70 | 2.65 | 1.24 (+) | 1.19 | 1.15 |
| 8 | 0.39 (−) | 1.30 | 0.91 | 0.41 (+) | 1.61 | 2.46 | 0.75 (+) | 1.23 | 1.32 |
| 9 | 0.53 (+) | *ca.* 1 | | 0.60 (+) | 1.33 | 0.45 | 0.45 (−) | *ca.* 1 | |
| | *23* | | | *24* | | | *25* | | |
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 1 | 0.95 (+) | *ca.* 1 | | 2.41 | 1.00 | | 1.39 (−) | 1.15 | |
| 2 | 0.90 (+) | 1.75 | 3.39 | 1.83 (−) | 1.35 | 1.79 | 2.48 (−) | 1.30 | 0.86 |
| 3 | 0.50 (+) | 1.76 | 2.67 | 1.48 (−) | 2.12 | 4.47 | 1.45 (−) | 1.33 | 1.90 |
| 4 | 2.57 (+) | 1.24 | 0.75 | 2.08 (−) | 1.45 | 1.27 | 2.37 (−) | 1.65 | 2.56 |
| 5 | 2.33 (+) | 1.53 | 2.24 | 2.69 (−) | *ca.* 1 | | 1.85 (−) | 1.17 | 0.66 |
| 6 | 3.16 (+) | 1.46 | 2.81 | 1.45 (−) | 1.44 | 1.29 | 0.90 (−) | 1.20 | 0.84 |
| 7 | 2.37 (+) | 1.79 | 3.89 | 1.96 (−) | 1.17 | 0.55 | 1.62 (−) | 1.21 | 0.76 |
| 8 | 1.75 (+) | 2.06 | 6.22 | 1.29 (−) | 1.22 | 1.07 | 1.56 (−) | 2.04 | 1.40 |
| 9 | 0.25 (+) | *ca.* 1 | | 0.67 (+) | *ca.* 1 | | 1.10 (+) | *ca.* 1 | |
| | *26* | | | *27* | | | *28* | | |
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 1 | 1.52 | 1.00 | | 0.48 (+) | *ca.* 1 | | 1.31 (−) | 1.13 | |
| 2 | 1.33 (+) | 1.37 | 2.46 | 3.00 (−) | 1.12 | 1.13 | 1.14 (−) | 1.20 | 1.41 |
| 3 | 1.00 (+) | 1.59 | 2.88 | 2.40 (−) | 1.14 | 1.41 | 0.95 (−) | 1.19 | 1.09 |
| 4 | 2.58 (+) | 1.22 | 0.77 | 5.28 (+) | *ca.* 1 | | 1.88 (−) | 1.17 | 0.98 |
| 5 | 0.97 (+) | 1.64 | 2.27 | 4.26 (−) | 1.14 | 1.36 | 1.74 (−) | 1.12 | 0.90 |
| 6 | 0.81 (+) | 1.95 | 3.34 | 4.00 (−) | 1.20 | 2.00 | 1.63 (−) | 1.16 | 1.31 |
| 7 | 1.10 (+) | 1.95 | 3.05 | 4.82 (−) | 1.13 | 1.33 | 1.98 (−) | 1.17 | 1.08 |
| 8 | 0.38 (+) | 1.48 | 1.61 | 4.17 (−) | 1.10 | 1.06 | 1.94 (−) | 1.18 | 1.70 |
| 9 | 0.13 | 1.00 | | 6.92 | 1.00 | | 2.53 (−) | *ca.* 1 | |
| | *29* | | | *$T_a$ (min)* | *$T_b$ (min)* | | | | |
| | $k'_1$ | $\alpha$ | $R_s$ | | | | | | |
| 1 | 2.23 (+) | *ca.* 1 | | 10.0 | 16.7 | | | | |
| 2 | 1.57 (+) | 1.16 | 1.48 | 10.1 | 15.2 | | | | |
| 3 | 1.26 (−) | 1.22 | 1.67 | 9.4 | 12.8 | | | | |
| 4 | 2.22 (+) | 1.10 | 0.68 | 10.9 | 15.4 | | | | |
| 5 | 1.89 (+) | 1.13 | 1.08 | 12.3 | 10.4 | | | | |
| 6 | 1.85 (+) | 1.12 | 1.11 | 11.3 | 8.9 | | | | |
| 7 | 2.39 (+) | 1.13 | 0.86 | 11.2 | 9.7 | | | | |
| 8 | 1.45 (+) | 1.14 | 1.24 | 16.8 | 8.3 | | | | |
| 9 | 3.00 | 1.00 | | 13.8 | 9.2 | | | | |



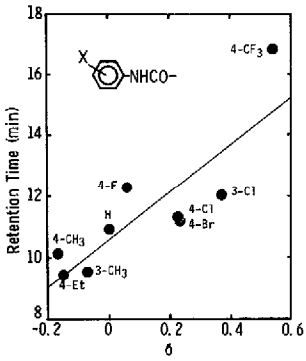

20 21 22 23 24 25 26 27 28 29 30

flavanone (29), and retention times ($T_a$ and $T_b$) for acetone and the first eluting isomer of compound 20 on 4-substituted derivative columns. The electron-withdrawing power of the substituents increases in the order from 1 to 9 on the basis of the Hammett's $\sigma$ values.

The resolution factors depended greatly on the 4-substituents. Columns with compounds 2–8 resolved all the above compounds effectively except for a few cases, but columns with compounds 1 and 9, which possess the most electron-donating and electron-withdrawing substituents, respectively, showed very poor chiral recognition and could resolve only a few compounds. The reason for this low chiral recognition ability will be explained later. Although a simple correlation was not observed between the $\alpha$ values and the nature of the substituents, the best chiral recognition was mostly attained with the carbamates having either electron-donating (2 and 3) or electron-withdrawing (6, 7, and 8) groups. The unsubstituted carbamate 4 was not the best stationary phase for any of the compounds listed in Table II.

The retention times of acetone on these columns increased roughly as the electron-withdrawing power of the substituents increased, and they are plotted against the Hammett's $\sigma$ values in Fig. 2. The $^1$H NMR spectra of the NH proton of cellulose triphenylcarbamate derivatives 2 and 4–8 in [$^2H_6$]acetone are shown in Fig. 3. The spectra indicate that the NH resonances shift downfield as the electron-withdrawing power of the substituents on the phenyl group increases. This observation may be ascribed to the fact that the acidity of the NH proton increases with an increase of the electron-withdrawing power of the substituents. Probably, acetone is adsorbed on the stationary phase via hydrogen-bonding with the NH proton, and this interaction must be stronger when the proton is more acidic.

The NH resonance shifted greatly when [$^2H_5$]pyridine was added (Fig. 4). As the concentration of [$^2H_5$]pyridine increased, the NH peaks moved downfield, and



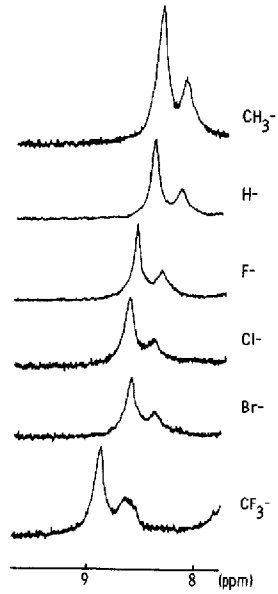



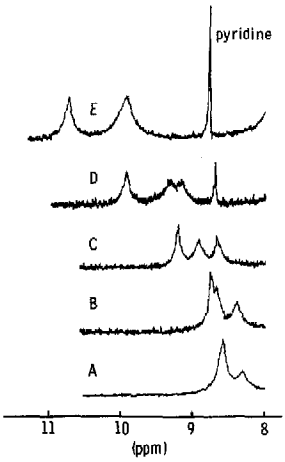

Fig. 2. Plots of retention time of acetone on the columns of cellulose triphenylcarbamate derivatives against the Hammett's $\sigma$ values. Et = Ethyl.

Fig. 3. $^1$H NMR spectra of NH protons of cellulose 4-substituted triphenylcarbamate derivatives ([$^2H_6$]acetone, 50°C, TMS).

three peaks, which were assigned to three carbamate NH protons of a glucose unit, were clearly observed in the presence of 9% [$^2H_5$]pyridine. This indicates that the three carbamate groups possess different adsorbing powers.

On the other hand, the retention times of the first-eluting isomer of compound 20 on the carbamate columns with compounds 1–9 decreased roughly as the electron-withdrawing power of the substituent increased (Table II and Fig. 5). A similar pattern was observed for the second-eluting isomer of compound 20. The electron density of the carbonyl oxygen of the carbamates is expected to increase with a decrease of the Hammett's $\sigma$ values of the substituents. Thus compound 20 is expected to be adsorbed more strongly via hydrogen-bonding to the carbonyl oxygen of the carbamates with electron-donating substituents than those with electron-withdrawing substituents.

Retention times of benzene and monosubstituted benzenes were measured on a column with compound 4 in order to reveal the adsorbing powers of substituted phenyl groups of the carbamates. The results are summarized in Table III. Very similar retention times were observed for benzene, toluene, ethylbenzene, and halogenated benzenes, suggesting that alkyl and halogen substituents do not interact with solutes when they are present on the stationary phases. However, anisole and nitrobenzene, particularly the latter, showed longer retention times. This indicates that methoxy and nitro groups can interact with compound 4. Therefore, if a stationary phase has a methoxy or nitro group, polar solutes should be adsorbed on these groups. Because these substituents on compounds 1 and 9 are far from a chiral



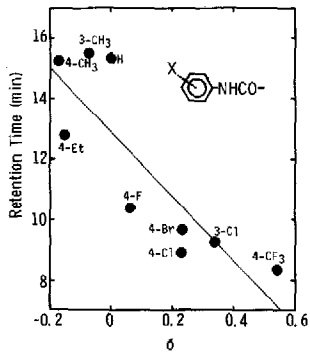




Fig. 4. $^1$H NMR spectra of NH protons of cellulose triphenylcarbamate (4) in [$^2H_6$]acetone–[$^2H_5$]pyridine. Content of [$^2H_6$]acetone: A = 100%; B = 98%; C = 91%; D = 71%; E = 0% (50°C, TMS).

Fig. 5. Plots of retention time of the first-eluting isomer of compound 20 on the columns of cellulose triphenylcarbamate derivatives against the Hammett's $\sigma$ values.

glucose unit, the interaction on the groups should lower the chiral recognition ability of the stationary phases.

From these results, the main chiral adsorbing sites are considered to be the polar carbamate groups (Fig. 6). The groups can interact with a solute via hydrogen-bonding with NH and C=O groups and the dipole–dipole interaction on C=O. The adsorbing powers of these sites may be strongly influenced by the nature of the substituents on the phenyl group. The $\pi$–$\pi$ interaction of phenyl groups on the stationary phases with aromatic groups of solutes may be less important than the above polar interaction. Of course, the function of phenyl groups can not be ignored because cellulose trimethylcarbamate (30) showed very low chiral recognition ($\alpha$ = 1 for compounds 21 and 27, and $\alpha$ = 1.19 for compound 24). Phenyl groups may have

TABLE III

RETENTION TIMES OF BENZENE AND MONOSUBSTITUTED BENZENE ON A CELLULOSE TRIPHENYLCARBAMATE (4) COLUMN

Eluent, hexane–2-propanol (80:20).

| *Substituent* | *Retention time (min)* |
|---|---|
| H | 6.85 |
| $CH_3$ | 6.70 |
| Br | 7.00 |
| Cl | 6.29 |
| F | 6.90 |
| $OCH_3$ | 7.56 |
| $NO_2$ | 10.43 |

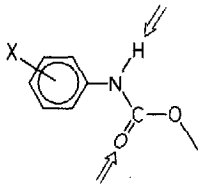


Fig. 6. Sites for hydrogen-bonding on substituted phenylcarbamates.

TABLE IV

RESOLUTION OF ENANTIOMERS (COMPOUNDS 20–29) AND ELUTION TIME OF ACETONE ($T_a$) ON CELLULOSE CHLORO-SUBSTITUTED TRIPHENYLCARBAMATE DERIVATIVES (6 AND 10–14)

| *Column with compound* | *20* | | | *21* | | | *22* | | |
|---|---|---|---|---|---|---|---|---|---|
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 6 | 0.48 (−) | 1.29 | 1.05 | 0.38 (+) | 1.68 | 2.30 | 0.89 (+) | 1.16 | 0.83 |
| 10 | 0.54 (−) | 1.41 | 1.37 | 0.51 (+) | 1.88 | 3.30 | 1.06 (+) | 1.30 | 1.70 |
| 11 | 1.64 | 1.00 | | 0.73 (+) | 1.23 | 0.51 | 0.86 (+) | *ca.* 1 | |
| 12 | 0.33 (−) | 1.21 | | 0.38 (+) | 1.93 | 2.86 | 0.79 (+) | 1.47 | 1.69 |
| 13 | 0.28 (−) | 1.38 | 0.87 | 0.56 (+) | 1.84 | 4.20 | 0.87 (+) | 1.65 | 3.89 |
| 14 | 1.98 | 1.00 | | 0.56 (+) | 1.28 | 0.74 | 1.08 (+) | *ca.* 1 | |
| | *23* | | | *24* | | | *25* | | |
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 6 | 2.16 (+) | 1.46 | 2.81 | 1.45 (−) | 1.44 | 1.29 | 0.90 (−) | 1.20 | 0.84 |
| 10 | 2.00 (+) | 1.41 | 2.10 | 1.07 (−) | 1.37 | 1.04 | 1.11 (−) | 1.56 | 2.34 |
| 11 | 0.25 | 1.00 | | 0.76 | 1.00 | | 2.45 (+) | 1.56 | 0.58 |
| 12 | 1.21 (+) | 1.63 | 2.08 | 0.81 (+) | 1.15 | | 1.34 (−) | *ca.* 1 | |
| 13 | 0.76 (+) | 1.82 | 4.06 | 0.59 (+) | 1.41 | 1.47 | 1.62 (+) | 1.11 | 0.75 |
| 14 | 0.39 (+) | *ca.* 1 | | 0.57 | 1.00 | | 1.98 (−) | *ca.* 1 | |
| | *26* | | | *27* | | | *28* | | |
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 6 | 0.81 (+) | 1.95 | 3.34 | 4.00 (−) | 1.20 | 2.00 | 1.63 (−) | 1.16 | 1.31 |
| 10 | 0.85 (+) | 1.54 | 2.02 | 4.54 (−) | 1.40 | 3.33 | 2.09 (−) | 1.22 | 1.54 |
| 11 | 0.56 (+) | *ca.* 1 | | 4.44 (−) | *ca.* 1 | | 1.53 (−) | *ca.* 1 | |
| 12 | 0.48 | 1.00 | | 3.24 (−) | 1.10 | 0.63 | 1.92 (−) | 1.31 | |
| 13 | 0.40 (+) | 1.29 | 0.84 | 3.08 (−) | 1.21 | 1.91 | 2.65 (−) | 1.26 | 1.95 |
| 14 | 0.17 (+) | *ca.* 1 | | 6.37 (−) | *ca.* 1 | | 1.15 (−) | *ca.* 1 | |
| | *29* | | | *$T_a$ (min)* | | | | | |
| | $k'_1$ | $\alpha$ | $R_s$ | | | | | | |
| 6 | 1.85 (+) | 1.12 | 1.11 | 11.3 | | | | | |
| 10 | 2.00 (−) | 1.09 | 0.84 | 12.0 | | | | | |
| 11 | 2.51 (+) | *ca.* 1 | | 9.8 | | | | | |
| 12 | 1.29 (+) | 1.04 | | 13.7 | | | | | |
| 13 | 1.55 (−) | 1.20 | 1.48 | 15.0 | | | | | |
| 14 | 2.69 | 1.00 | | 11.6 | | | | | |

important roles for the cellulose triphenylcarbamates to hold a sterically regular structure, which is probably very important for efficient chiral recognition.

The structure of compound 4 in solution and in the solid state has been studied in detail[22,23]. The experimental data show that compound 4 is a stiff rod-like molecule. This has been ascribed to the hydrogen-bonding between adjacent carbamate groups, which function to fix glucose units. It forms a liquid crystal phase[24]. Most of the cellulose triphenylcarbamate derivatives used in this work also formed a liquid crystal phase in tetrahydrofuran and showed very high crystallinity under a polarizing microscope when they were cast from a solution. This means that the carbamates coated on silica gel from a solution also have an ordered structure in which phenylcarbamate groups are arranged regularly. Methylcarbamate 30 did not show crystallinity under a polarizing microscope when cast from a solution.

*Chloro-substituted phenylcarbamates*

The influence of the position and number of chloro-substituents on the phenyl group of cellulose triphenylcarbamate was investigated. Table IV summarizes the resolution of racemates 20–29 on six chloro-substituted phenylcarbamate columns. Chiral recognition of the stationary phases depended greatly on the position and number of chloro-substituents. The derivatives substituted at the 3- or 4-position, particularly derivatives 10 and 13, showed good chiral recognition, and 2-substituted derivatives 11 and 14 showed a broad single peak for many compounds. The low efficiency of the latter two stationary phases seems to be due to the disordered structure of the carbamates. 2,6-Disubstituted carbamates 14 did not give a liquid crystal phase in THF and showed no crystallinity when cast from a THF solution. The IR spectra of compounds 11 and 14 were rather different from those of compounds 4 and 6 (Fig. 7) and showed relatively a strong NH peak at 3410 $cm^{-1}$ which is assigned to free NH. The hydrogen-bonding between adjacent carbamate unit residues may be disturbed by the steric hindrance of a 2- or 6-substituent, which may induce disorder in the chain structure of the cellulose triphenylcarbamate derivatives. This disorder probably yields many different kinds of chiral adsorbing sites, which should cause peak broadening of the enantiomers. Disorder may also arise from twisting of

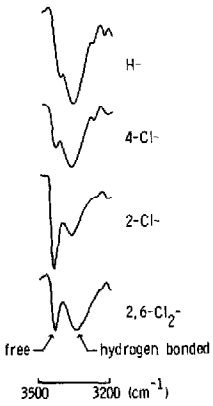



Fig. 7. IR spectra of NH of cellulose triphenylcarbamate derivatives, 4, 6, 11 and 14.

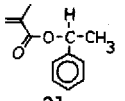
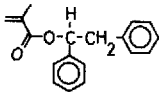
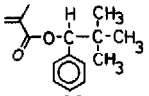
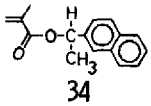
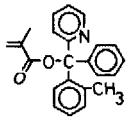
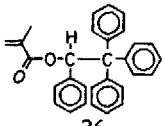
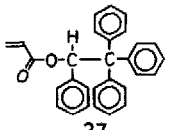
the phenyl group about the C–N bond. To keep a planar structure in $C_6H_5$–NH–CO may be difficult when there is a substituent at the 2- or 6-position.

Retention times of acetone on columns with disubstituted compounds 12 and 13 were longer than on columns with monosubstituted compounds, as expected from the results shown in Fig. 2. However, columns with compounds 14 and 11 showed relatively shorter retention times for acetone, probably owing to steric hindrance of the chlorine atoms at the 2- or 6-position.

TABLE V

RESOLUTION OF METHACRYLATES AND ACRYLATE (31–37) ON A CELLULOSE TRIS-(3,5-DICHLOROPHENYLCARBAMATE) (13) COLUMN

Eluent, hexane–2-propanol (98:2).

| *Ester* | $k'_1$ | $\alpha$ | $R_s$ |
|---|---|---|---|
|  31 | 0.70 (+) | 1.09 | |
|  32 | 0.74 (+) | 1.12 | 0.70 |
|  33 | 0.43 (−) | 1.14 | |
|  34 | 0.84 (+) | 1.36 | 2.48 |
|  35 | 2.69 (+) | 2.36 | 8.90 |
|  36 | 0.48 (+) | 4.23 | 9.70 |
|  37 | 0.68 (+) | 5.40 | 11.9 |

The elution order of enantiomers was not the same on all the columns. For example, the (−)-isomer of compound 24 was eluted first on columns with compounds 6 and 10, whereas the (+)-isomer was eluted first on columns with compounds 12 and 13; complete separation with reverse elution order was observed for compound 29 between the columns with compounds 6 and 13. These data also suggest that there were several factors that influence the chiral recognition of the stationary phases.

TABLE VI

RESOLUTION OF ENANTIOMERS (COMPOUNDS 20–29) AND ELUTION TIME OF ACETONE ($T_a$) ON CELLULOSE METHYL-SUBSTITUTED TRIPHENYLCARBAMATE DERIVATIVES 2 AND 15–19

| *Column with compound* | *20* | | | *21* | | | *22* | | |
|---|---|---|---|---|---|---|---|---|---|
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 2 | 1.54 (−) | 1.52 | 3.83 | 0.51 (+) | 1.55 | 2.39 | 0.75 (+) | 1.48 | 2.61 |
| 15 | 1.25 (−) | 1.56 | 2.33 | 0.54 (+) | 1.28 | 1.13 | 0.77 (+) | 1.45 | 1.65 |
| 16 | 1.92 (−) | 1.10 | | 0.61 (+) | 1.35 | 1.12 | 0.79 (+) | *ca.* 1 | |
| 17 | 1.76 (−) | 2.13 | 4.75 | 0.61 (+) | 1.13 | 0.59 | 0.87 (+) | 1.49 | 2.11 |
| 18 | 2.13 (−) | 2.59 | 6.40 | 0.74 (−) | 1.68 | 3.22 | 0.97 (+) | 1.32 | 1.92 |
| 19 | 1.97 (+) | 1.17 | 0.59 | 0.54 (−) | *ca.* 1 | | 0.60 (+) | *ca.* 1 | |
| | *23* | | | *24* | | | *25* | | |
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 2 | 0.90 (+) | 1.75 | 3.39 | 1.83 (−) | 1.35 | 1.79 | 2.48 (−) | 1.30 | 0.86 |
| 15 | 0.89 (+) | 1.29 | 0.97 | 1.43 (−) | *ca.* 1 | | 1.80 (−) | 2.63 | 5.06 |
| 16 | 1.01 (+) | *ca.* 1 | | 2.77 (−) | *ca.* 1 | | 2.93 (+) | *ca.* 1 | |
| 17 | 0.57 (+) | 1.32 | 1.05 | 1.27 (+) | 2.39 | 3.57 | 1.86 (−) | 1.87 | 2.62 |
| 18 | 0.42 (+) | *ca.* 1 | | 0.83 (+) | 3.17 | 6.17 | 2.36 (−) | 1.83 | 4.39 |
| 19 | 0.96 (−) | *ca.* 1 | | 1.97 (+) | 1.36 | 0.59 | 1.52 (−) | 1.34 | 0.90 |
| | *26* | | | *27* | | | *28* | | |
| | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ | $k'_1$ | $\alpha$ | $R_s$ |
| 2 | 1.33 (+) | 1.37 | 2.46 | 3.00 (−) | 1.12 | 1.13 | 1.14 (−) | 1.20 | 1.41 |
| 15 | 1.43 (+) | 1.45 | 1.72 | 3.02 (−) | *ca.* 1 | | 1.30 (−) | 1.17 | 0.93 |
| 16 | 1.83 (+) | *ca.* 1 | | 4.61 (+) | 1.10 | 0.71 | 1.58 (−) | *ca.* 1 | |
| 17 | 1.55 (+) | *ca.* 1 | | 2.77 (+) | 1.31 | 1.93 | 0.95 (−) | 1.20 | 0.81 |
| 18 | 1.37 (+) | 1.34 | 1.87 | 2.43 (+) | 1.58 | 4.38 | 1.17 (−) | 1.15 | 0.90 |
| 19 | 1.44 (−) | *ca.* 1 | | | | | 1.10 (+) | *ca.* 1 | |
| | *29* | | | *$T_a$ (min)* | | | | | |
| | $k'_1$ | $\alpha$ | $R_s$ | | | | | | |
| 2 | 1.57 (+) | 1.16 | 1.48 | 10.1 | | | | | |
| 15 | 1.61 (+) | 1.14 | 0.88 | 9.5 | | | | | |
| 16 | 2.39 (−) | *ca.* 1 | | 10.8 | | | | | |
| 17 | 1.53 (−) | 1.42 | 2.56 | 9.0 | | | | | |
| 18 | 1.47 (−) | 1.41 | 3.08 | 8.4 | | | | | |
| 19 | | | | 10.5 | | | | | |

Among the chlorine-containing carbamates, compound 13 resolved many racemic compounds most efficiently. Table V shows the results of the resolution of racemic methacrylates and an acrylate (31–37). The column resolved several bulky esters completely. However, this column possesses a defect, in that compound 13 is exceptionally soluble in hexane containing *ca.* 20% 2-propanol. Therefore, the column is stable only when used with hexane containing less than 5% 2-propanol as eluent.

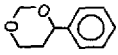
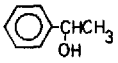
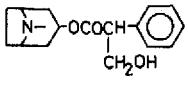
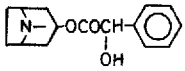
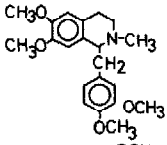
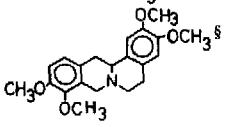
*Methyl-substituted phenylcarbamates*

Table VI shows the results of resolution on six cellulose methyl-substituted triphenylcarbamate columns. The retention time of acetone was shortened by introducing two methyl groups at the 3- or 4-position, and was shortest on compound 18. Again, the chiral recognition of the stationary phases depended greatly on the position and number of methyl groups. The column with 2,6-disubstituted 19 showed a very broad peak with most compounds, probably for the same reasons as for columns with compounds 11 and 14. The elution order of the enantiomers of compounds 21, 24, 27 and 29 on disubstituted carbamates 17 and 18 was opposite to that on mono-

TABLE VII

RACEMATES WELL RESOLVED ON A CELLULOSE TRIS(3,5-DIMETHYLPHENYLCARBAMATE) (18) COLUMN

Eluents: A = hexane–2-propanol (90:10); B = hexane–2-propanol (98:2); C = hexane–2-propanol–diethylamine (80:20:0.1).

| *Racemate* | *Eluent* | $k'_1$ | $\alpha$ | $R_s$ |
|---|---|---|---|---|
|  | A | 0.83 (−) | 1.88 | 3.98 |
|  * | B | 3.55 (+) | 1.33 | 2.41 |
|  ** | C | 0.72 (+) | 1.62 | 2.30 |
|  | C | 0.84 (+) | 3.13 | 5.78 |
|  *** | C | 1.17 (+) | 3.31 | 6.69 |
|  § | C | 4.50 (+) | 1.61 | 1.39 |

* Atropine
** Homatropine.
*** Laudanosine.
§ Tetrahydropalmatine.

substituted carbamates 2 and 15, and interestingly compound 18 was the best stationary phase for about half of the racemic compounds in Table VI. Besides the compounds shown in Table VI, compound 18 resolved many other racemic compounds; some of them are shown in Table VII. This column was quite stable even with hexane–2-propanol–diethylamine (80:20:0.1, v/v) as eluent.

## CONCLUSIONS

Chiral recognition of nineteen cellulose triphenylcarbamate derivatives supported on silica gel depended greatly on the position and number of substituents on the phenyl groups. Most racemic compounds shown in this paper were resolved most effectively with either 3,5-dichloro- or 3,5-dimethylphenylcarbamate. The derivatives with a substituent containing a heteroatom, such as a methoxy or nitro group, or a substituent at the 2-position showed low chiral recognition. These results were explained by taking account of the inductive effect of substituents, interaction of the heteroatom with a solute, or disordering of the structure of the carbamates induced by a substituent at the 2-position.

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