Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl19

Mechanistic Study of Chiral Discrimination on Crystalline Polysaccharide Derivatives

Yoshio Okamoto [a] & Eiji Yashima [a]
[a] Department of Applied Chemistry, School of Engineering, Nagoya University, Chikusa-ku, Nagoya, 464-01, Japan
Version of record first published: 04 Oct 2006.

To cite this article: Yoshio Okamoto & Eiji Yashima (1996): Mechanistic Study of Chiral Discrimination on Crystalline Polysaccharide Derivatives, Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals, 276:1-2, 7-12

To link to this article: http://dx.doi.org/10.1080/10587259608039353

Mol. Cryst. Liq. Cryst., 1996, Vol. 276, pp. 7–12
Reprints available directly from the publisher
Photocopying permitted by license only

MECHANISTIC STUDY OF CHIRAL DISCRIMINATION ON CRYSTALLINE POLYSACCHARIDE DERIVATIVES

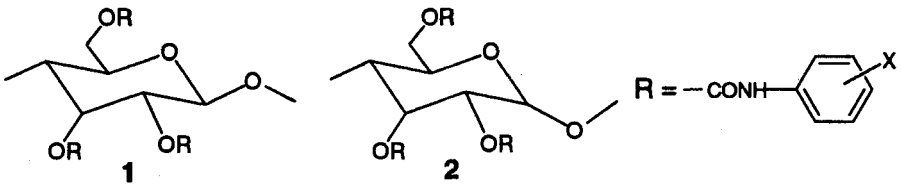
YOSHIO OKAMOTO* AND EIJI YASHIMA
Department of Applied Chemistry, School of Engineering,
Nagoya University, Chikusa-ku, Nagoya 464-01, Japan

Abstract Chiral discrimination mechanism on crystalline phenylcarbamate derivatives of cellulose, which are among the most useful chiral stationary phases for high-performance liquid chromatography, was investigated by means of chromatographic, spectroscopic, and computational methods.

INTRODUCTION

Recently, preparation and analysis of optically active compounds have become very important in many fields dealing with, for instance drugs, agrochemicals, natural products, and ferroelectric liquid crystals. Chromatographic enantioseparation, particularly resolution by high-performance liquid chromatography (HPLC), has advanced considerably in the past ten years and has been used for a practical method not only for determining optical purity but also for obtaining optical isomers. Therefore, many chiral stationary phases (CSPs) for HPLC have been developed.[1,2]

Crystalline polysaccharide derivatives are among the most widely used CSPs.[3,4] Especially, trisphenylcarbamate derivatives of cellulose (**1**) and amylose (**2**) have been deeply investigated with regard to the enantioseparation and the mechanism of chiral discrimination. Here, we report the mechanistic study on the resolution by crystalline phenylcarbamate derivatives of cellulose.



RESULTS AND DISCUSSION

Cellulose trisphenylcarbamate derivatives are readily prepared by the reaction of microcrystalline cellulose (Avicel, Merck) with substituted phenyl isocyanates, and show

a very high resolving power to a wide range of racemates having various functional groups when coated on macroporous silica gel (Daiso gel; 7 μm, pore size 100 nm). The chiral recognition abilities of a series of cellulose phenylcarbamate derivatives have extensively been evaluated.[3,5] Among them, cellulose tris(3,5-dimethylphenylcarbamate) (**1**: X = 3,5-$(CH_3)_2$, CTDMPC) shows particularly interesting and efficient resolving ability.

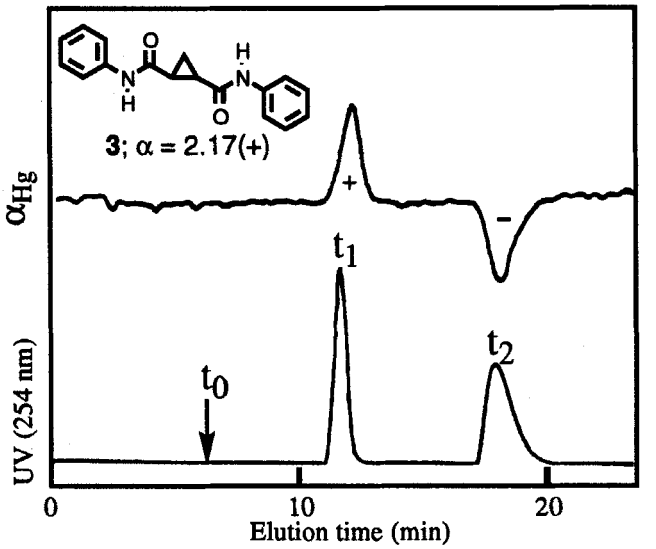


FIGURE 1 Resolution of (±)-**3** on CTDMPC (**1**; X = 3,5-$(CH_3)_2$) monitored with UV and polarimetric detectors. Eluent, hexane-2-propanol (90 / 10); flow rate, 0.5 ml / min.

A typical chromatogram of the resolution of *trans*-cyclopropanedicarboxylic acid dianilide (**3**) on CTDMPC monitored by UV and polarimetric detectors is shown in Figure 1. The enantiomers eluted at retention times of t_1 and t_2 showing complete separation. Separation factor α [= $(t_2 - t_0) / (t_1 - t_0)$], where t_0 is the elution time for a non-retained compound, in this case 1,3,5-tri-*tert.*-butylbenzene, was estimated to be 2.17. The results of the enantioseparation of ten racemates, **3**, Tröger base (**4**), 1-(9-anthryl)-2,2,2-trifluoroethanol (**5**), *trans*-stilbene oxide (**6**), 2,2'-dihydroxy-6,6'-dimethyl-1,1'-biphenyl (**7**), 1,2,2,2-tetraphenylethanol (**8**), flavanone (**9**), 2-phenylcyclohexanone (**10**), and benzoin (**11**) on CTDMPC are given in Figure 2 using separation factor (α). CTDMPC can resolve a variety of enantiomers including aromatic hydrocarbons, amines, carboxylic acid,[6] alcohols, amino acid derivatives,[7] and many drugs[8] including β-adrenergic blocking agents (β-blockers).[9]

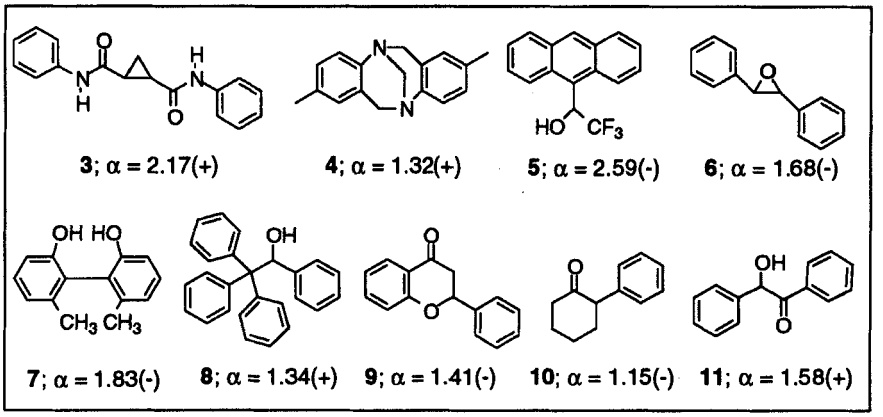


FIGURE 2 Resolution results of racemates (**3** - **11**) on CTDMPC (**1**).
Eluent, hexane-2-propanol (90 / 10); flow rate, 0.5 ml /min.
The sign of optical rotation of the first-eluted enantiomer is shown in parentheses.

Most of cellulose trisphenylcarbamate derivatives form a lyotropic liquid crystalline phase in a highly concentrated solution[5,10] and show a high crystallinity under a polarizing microscope when they are cast from a solution. This indicates that the carbamates coated on silica gel from a solution also have an ordered structure where the phenylcarbamate groups may be regularly arranged along the polymer chain. A few cellulose phenylcarbamate derivatives and alkylcarbamates do not form such a liquid crystalline phase and show low chiral resolving ability. This means that a regular higher-order structure seems to be essential for efficient chiral recognition as CSPs. For **1** (X=H, CTPC), a left-handed 3/2 helical conformation has been proposed on the basis of X-ray analysis.[11,12]

Figure 3 (a) shows a stable structure of CTPC obtained by molecular mechanics calculation based on the X-ray analysis. CTPC possesses a left-handed three-fold (3/2) helix and glucose residues are regularly arranged along the helical axis. A chiral helical groove with polar carbamate residues exists along the polymer chain. The polar carbamate groups, probably the most important adsorbing sites for chiral discrimination, are favorably located inside and hydrophobic aromatic groups are placed outside the polymer chain so that polar enantiomers may insert to the groove and interact with the carbamate residues *via* hydrogen bonding formation with the NH and C=O groups as illustrated in Figure 3 (b) and the dipole-dipole interaction on C=O.[3,5] This interaction may play an important role for the efficient chiral discrimination.

The regular conformation is probably maintained even in solution.[13] Hence, NMR study in solution will give useful information on the chiral discrimination mechanism of the derivatives. However, most derivatives including CTPC and CTDMPC are soluble

only in polar solvents such as THF and pyridine where no chiral discrimination of enantiomers is detected by NMR due to strong interaction of the solvents with the derivatives. Recently, we found that several phenylcarbamate derivatives having 4-trimethylsilyl group (**12**)[14] or 5-fluoro-2-methyl group (**13**)[15] on the phenyl groups are soluble in chloroform and exhibit chiral discrimination for a variety of enantiomers in NMR as well as in HPLC.

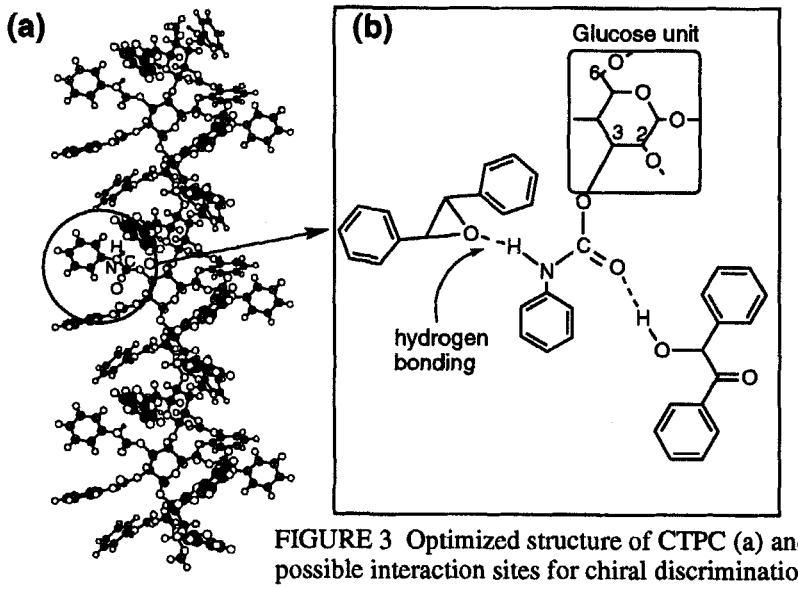
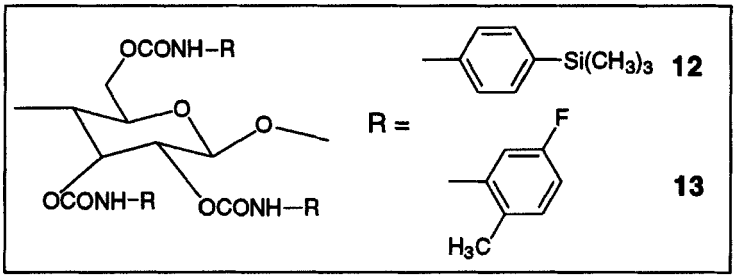


FIGURE 3 Optimized structure of CTPC (a) and possible interaction sites for chiral discrimination (b).

Figure 4 shows the 500 MHz ^{1}H NMR spectra of (±)-*trans*-stilbene oxide (**6**) in the presence and absence of **12**. The methine proton of **6** was enantiomerically separated into two singlet peaks in the presence of **12**.[14] This indicates that **12** can discriminate the enantiomers even in solution. From the measurement of enantiomerically pure (+)- and (-)-**6**, it was found that only the methine proton of (-)-**6** shifted downfield, whereas that of (+)-**6** scarcely shifted. In the chromatographic enantioseparation of (±)-**6** on the CSP **12**, (+)-isomer eluted first followed by (-)-isomer and complete baseline separation was observed, indicating that (-)-**6** adsorbs more strongly on **12**. This stronger interaction should be related with the downfield shift of (-)-**6** observed in NMR.

As described above, the most important adsorbing site for chiral discrimination on phenylcarbamate derivatives appears to be the polar carbamate residue, which can interact with enantiomers *via* hydrogen bonding formation (Figure 3 (b)). In the case of **6**, the cyclic ether oxygen may interact with the NH proton of the carbamate residue. Therefore, addition of hydrogen bond acceptor such as acetone resulted in no splitting of the methine proton.[14] The ^{1}H NMR signals of other enantiomers of Tröger base (**4**),

benzoin (**11**), and several *sec*-alcohols such as 2-butanol and 2-octanol were enantiomerically separated into two sets of peaks in the presence of **12** in $CDCl_3$.



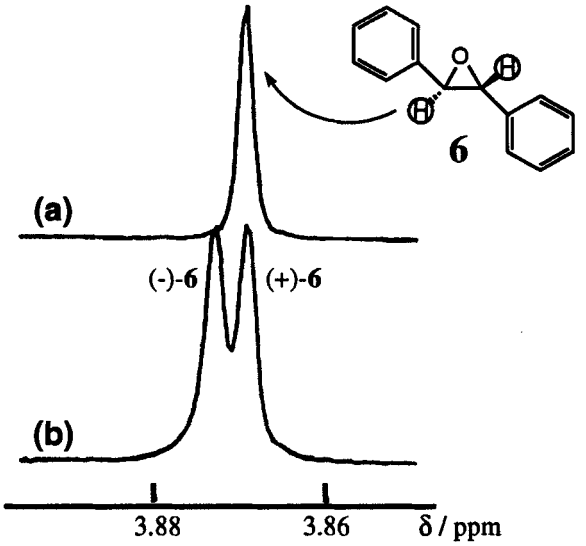
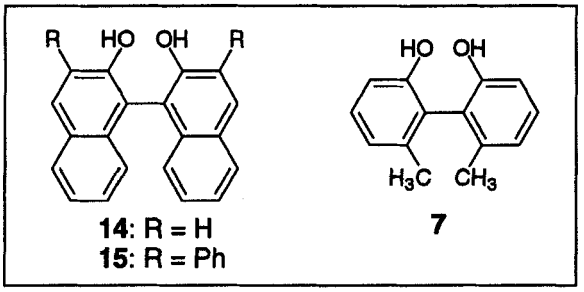


FIGURE 4 500 MHz ^1H NMR spectra of (±)-**6** in the absence (a) and presence (b) of **12** in $CDCl_3$ (1.0 ml) at 22 °C (TMS).



The phenylcarbamate derivative (**13**) also showed chiral discrimination for some racemates in $CDCl_3$, especially, enantiomers of 2,2'-dihydroxy-1,1'-binaphthyl (**14**) and its derivative (**15**) and 2,2'-dihydroxy-6,6'-dimethyl-1,1'-biphenyl (**7**) were

distinctly discriminated by **13** in ^1H and ^{13}C NMR as well as in HPLC. The interaction between **14** and **13** was extensively investigated at a molecular level by using 2D-NOESY technique.[16]

The computer simulation may be a useful and effective approach for not only elucidating the chiral recognition mechanism on other $CDCl_3$-insoluble phenylcarbamate derivatives of polysaccharides, but also for predicting the elution order of enantiomers. The force-field calculation of interaction energies between cellulose trisphenylcarbamate (CTPC) and **6** or *trans*-1,2-diphenylcyclopropane (**16**) was carried out using QUANTA / CHARMm and MOLECULAR INTERACTION programs (Molecular Simulations Incorp.) to gain insight into the chiral discrimination mechanism of phenylcarbamate derivatives.[17] In chromatographic enantioseparation, **6** was completely resolved (α = 1.46) on CTPC and (+)-isomer eluted first followed by (-)-isomer, but **16** was not separated ($\alpha = \sim 1$). The results of calculation of interaction energies between CTPC and the enantiomers suggested that (-)-(S,S)-**6** may more closely interact with CTPC than (+)-(R,R)-**6**, and significantly different interaction energy was not observed for the enantiomers of **16**. These calculations agreed well with the observed chromatographic resolution on CTPC.[17] Computational studies will be useful and appreciable to the fields in chiral discrimination.

REFERENCES

1. Y. Okamoto, Chemtech, 176 (1987).
2. W. H. Pirkle and T. C. Pochapsky, Chem. Rev., 89, 347 (1989).
3. Y. Okamoto and Y. Kaida, J. Chromatogr. A, 666, 403 (1994).
4. Y. Okamoto, Y. Kaida, R. Aburatani, and K. Hatada, in Chiral Separations by Liquid Chromatography, edited by S. Ahuja (ACS Symposium Series 471, 1990), Chap. 5.
5. Y. Okamoto, M. Kawashima, and K. Hatada, J. Chromatogr., 363, 173 (1986).
6. Y. Okamoto, R. Aburatani, Y. Kaida, and K. Hatada, Chem. Lett., 1125 (1988).
7. Y. Okamoto, Y. Kaida, R. Aburatani, and K. Hatada, J. Chromatogr., 477, 367 (1989).
8. Y. Okamoto, R. Aburatani, K. Hatano, and K. Hatada, J. Liq. Chromatogr., 11, 2147 (1988).
9. Y. Okamoto, M. Kawashima, R. Aburatani, K. Hatada, T. Nishiyama, and M. Masuda, Chem. Lett., 1237 (1986).
10. U. Vogt and P. Zugenmaier, Makromol. Chem. Rapid Commun., 4, 759 (1983).
11. H. Steinmeier and P. Zugenmaier, Carbohydrate Research, 164, 97 (1987).
12. U. Vogt and P. Zugenmaier, Ber. Bunsenges. Phys. Chem., 89, 1217 (1985).
13. J. Danhelka, M. Netopilik, and M. Bohdanecky, J. Polym. Sci. Part B. Polym. Phys., 25, 1801 (1987).
14. E. Yashima, M. Yamada, and Y. Okamoto, Chem. Lett., 579 (1994).
15. E. Yashima, C. Yamamoto, and Y. Okamoto, Polym. J., 27, 858 (1995).
16. E. Yashima, C. Yamamoto, and Y. Okamoto, munuscript in preparation.
17. E. Yashima, M. Yamada, Y. Kaida, and Y. Okamoto, J. Chromatogr. A, 694, 347 (1995).