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RESOLUTION OF ENANTIOMERS BY HPLC ON CELLULOSE TRANS- AND CIS-TRIS(4-PHENYLAZOPHENYLCARBAMATE)[1)]

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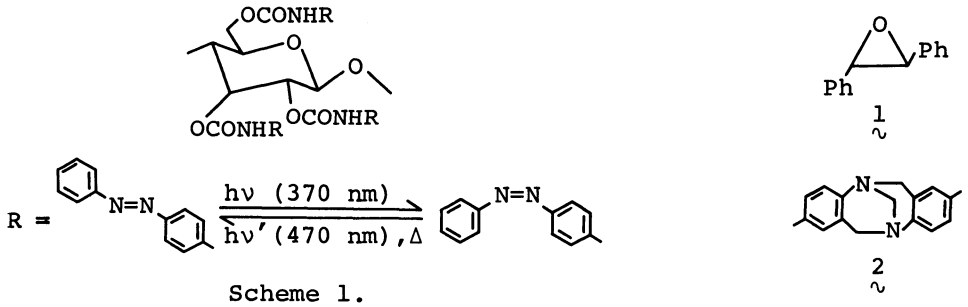
Cellulose tris(4-phenylazophenylcarbamate) (CPAPC) having azobenzene pendant groups was adsorbed on silica gel to use as a chiral stationary phase for HPLC. Pure trans-CPAPC resolved many racemic compounds, whereas 70% cis-CPAPC showed very poor resolving power.

Optical resolution of enantiomers by liquid chromatography has been greatly developed in past ten years and several practically useful chiral stationary phases have been reported.[2)] We reported recently that polysaccharide derivatives, especially cellulose triphenylcarbamate, coated on macroporous silica gel showed a high ability of resolution as a stationary phase for high-performance liquid chromatography (HPLC).[3)] On the other hand, photoresponsible azobenzene group has often been incorporated in polymers as well as in small molecules in order to change their conformations and functions by irradiation of light.[4)] This has been successfully applied in liquid chromatography.[5)] In the present study, we prepared cellulose tris(4-phenylazophenylcarbamate) (CPAPC) having azobenzene pendant groups as a photoresponsible polymer (Scheme 1), and investigated the change of the chiral recognition as a stationary phase for HPLC induced by trans-cis isomerization of azo groups. The trans isomer showed efficient resolution of enantiomers while the cis isomer showed almost no separation. This may be the first example of resolution of enantiomers by HPLC in which light is the trigger for changing chiral recognition of stationary phase.



Scheme 1.

CPAPC was prepared by the reaction of excess of 4-phenylazophenyl isocyanate with cellulose (Avicel, Merck) in pyridine. Elemental analysis,[6] ^{1}H-NMR, and IR spectra indicated that hydroxy groups of cellulose were almost quantitatively converted into urethane bonds. Photoirradiation of CPAPC was carried out with a 300-W high-pressure mercury lamp and the wavelength was selected with Toshiba cutoff filters. Chiral stationary phase for HPLC was prepared in the same manner as described previously using macroporous silica gel (Merck, LiChrospher SI-4000).[7] CPAPC (0.75 g) was coated on the silica gel (3.00 g).

Azobenzene is known to be isomerized from the trans to the cis form by irradiation with ultraviolet light (≈320 nm). As illustrated in Scheme 1, azobenzene pendant groups of CPAPC were isomerized from the trans to the cis form with light of 370 nm, and the cis isomer was photochemically (470 nm) or thermally converted into the trans isomer. Specific rotation $[\alpha]_D^{25}$ of trans-CPAPC in THF was +94° and that of 90% cis-CPAPC was -41°. Figure 1 shows the changes of the absorption and circular dichroism (CD) spectra during the course of isomerization. The change of absorption spectra was similar to that observed for a model compound, methyl 4-phenylazophenylcarbamate ($C_6H_5N{=}NC_6H_4NHCOOCH_3$), which showed absorption maxima at 355 nm for the trans form and at 444 nm for the cis form. The absorption band at 348 nm in Fig. 1 is ascribable to the π-π^* transition of the trans form of the pendant azobenzene residue and the band at 444 nm to the n-π^* transition of the cis form. The change was completely reversible, indicating that no degradation occurred during the trans-cis isomerization of pendant azobenzene residues. CD spectra changed remarkably upon the isomerization. The trans isomer showed an intense peak at 365 nm, while the cis isomer gave almost no peaks in this region. The CD intensity at 365 nm steeply decreased with an increase of the cis content. The intense peak at 365 nm may be due to the trans-azobenzene units arranged regularly.

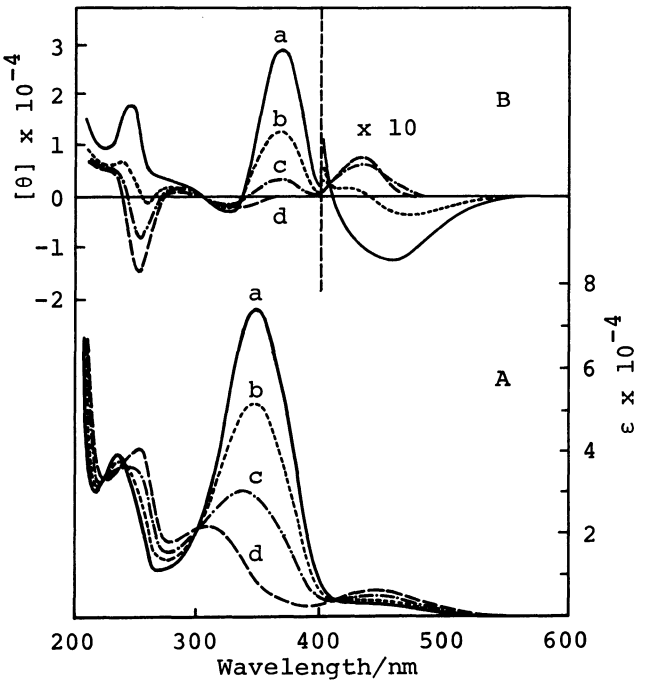


Fig. 1. Absorption (A) and CD (B) spectra in the trans-cis isomerization of CPAPC in THF.[8] (trans content: a, 100%; b, 70%; c, 40%; d,10%).

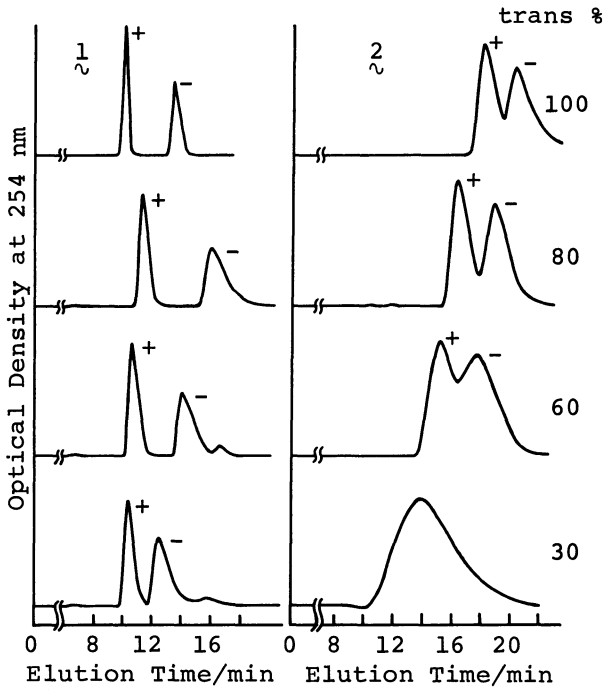


Fig. 2. Resolution of 1 and 2 on CPAPC columns. Eluent, hexane-2-propanol (90 : 10 vol); flow rate, 0.5 ml min^{-1}; temperature, 25 °C.

Figure 2 shows the chromatograms of resolution of trans-2,3-diphenyloxirane (**1**) and Tröger base (**2**) on CPAPC columns with various trans contents (100, 80, 60, 30%). The results for 100% trans column were evaluated with the column packed with pure trans isomer, and other data were obtained with the column of originally 30% trans content.[9] The 100% trans column completely resolved many racemic compounds such as atropine (k_1' = 3.43, α = 1.29),[10] pindolol (k_1' = 3.97, α = 1.29), flavanone (k_1' = 3.06, α = 1.15), and $Cr(acac)_3$ (k_1' = 3.22, α = 2.08) in addition to **1** and **2**, while the trans 30% column resolved only **1** into two peaks. Cellulose triphenylcarbamate has been postulated to take a rigid conformation by intramolecular hydrogen bond which aligns the substituents along the cellulose backbone,[11] and this rigid ordered structure may be responsible for its high ability of optical resolution. Such a structure seems to be possible only for the trans isomer and impossible for the cis isomer on the basis of the CPK molecular model. trans-CPAPC formed a liqud-crystalline phase in a concentrated THF solution whereas cis-CPAPC did not formed it under the same conditions. cis-CPAPC appears to exist in a disordered form, which probably possesses much more adsorbing sites with different chiral recognition than trans-CPAPC. This must

lower the resolving power of the stationary phase and will induce the broadening of the peaks. The 80% trans column showed better chiral recognition for **1** than the 100% trans column. Some specific adsorbing sites for **1** must exist on the 80% trans column. Most compounds were less retained on the column of low trans contents than the 100% trans column. Therefore, if reversible trans-cis isomerization of CPAPC on silica gel is possible, expeditious chromatographic resolution of enantiomers will be attained by isomerizing the trans form to the cis form after the elution of a less-retained isomer.

References

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2) For recent reviews, see G. Blaschke, Angew. Chem., Int. Ed. Engl., 19, 13, (1980); W. H. Pirkle and J. Finn, "Asymmetric Synthesis, Vol. 1, Analytical Method," ed by J. Morrison, Academic Press, New York (1983), p. 87; V. A. Davankov, A. A. Kurganov, and A. S. Bochkov, Adv. Chromatogr., 21, 71, (1983); Y. Okamoto, J. Synth. Org. Chem., 42, 995, (1984).
3) Y. Okamoto, M. Kawashima, and K. Hatada, J. Am. Chem. Soc., 106, 5357, (1984).
4) For example, M. Irie and H. Tanaka, Macromolecules, 16, 210 (1983) and references cited therein.
5) For review, K. Ishihara, Kobunshi, 35, 248 (1986).
6) Found: C, 64.28; H, 4.41; N, 15.05%. Calcd for $(C_{45}H_{37}N_9O_8)_n$: C, 64.97; H, 4.48; N, 15.16%. Degree of polymerization of Avicel was estimated to be 200 from GPC curve of cellulose triphenylcarbamate. GPC of CPAPC showed very broad peaks probably due to association in tetrahydrofuran.
7) The packing material thus obtained was packed in a stainless steel column (25 x 0.46 (i.d.) cm). Chromatography was accomplished on a JASCO TRIROTAR-II chromatograph equipped with a JASCO UVIDEC-III UV and DIP-181C polarimeter detectors.
8) Molar extinction coefficient ε and molar ellipticity $[\theta]$ were calculated on the basis of a glucose unit and trans contents were calculated from the absorbance around 350 nm, assuming that the absorbance of cis isomer at 350 nm is negligible.
9) trans-Content of CPAPC in an HPLC column gradually increased with time. Therefore, it was possible to obtain chromatographic data at 30, 60, and 80% trans contents with the same column. trans-Content of CPAPC was estimated from the absorption spectra of CPAPC recovered from the packing materials which was kept under the same conditions in an HPLC column.
10) k'_1: capacity factor for the first eluted isomer; α: separation factor.
11) H. Bittiger and G. Keilich, Biopolymer, 106, 539 (1959).

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