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G. W. Tindall^a

^a Research Laboratories Eastman Chemicals Division, Eastman Kodak Company, Kingsport, Tennessee

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BONDED CYCLODEXTRIN STATIONARY PHASE COLUMNS FOR THE SEPARATION OF CIS/TRANS CYCLOHEXANE DERIVATIVES

G. W. Tindall
*Research Laboratories
Eastman Chemicals Division
Eastman Kodak Company
Kingsport, Tennessee 37662*

ABSTRACT

Cyclohexane derivatives are important in the manufacture of monomers for the preparation of polyester polymers. The separation of cis/trans isomers of these derivatives has been investigated by using a bonded cyclodextrin column. This stationary phase offers excellent selectivity for the separation of these compounds. Although the efficiency of this column with the cyclohexane derivatives is less than the efficiency with nitroanilines, its excellent selectivity enabled adequate separation of the isomers of all but one of the compounds studied. A strategy for enhancing the efficiency and selectivity of this stationary phase is presented.

INTRODUCTION

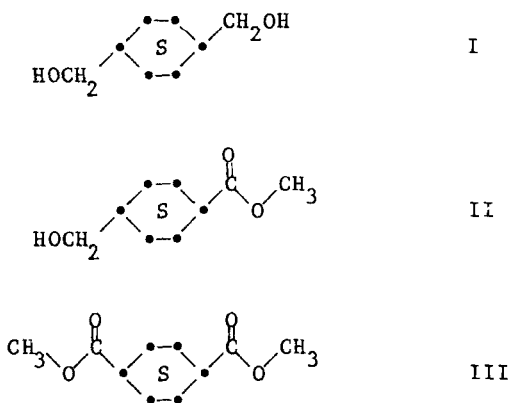
The utility of cyclodextrins for the separation of isomers has been known for some time.(1-5) Initially, cyclodextrins were added to the mobile phase to effect separation. Fujimura (6) first reported the preparation of a chemically bonded cyclodextrin-silica stationary phase that could be used with the convenience of conventional columns. The shortcomings of this

bonding chemistry limited the acceptance of this stationary phase. Armstrong (7) developed the first robust, high efficiency, bonded cyclodextrin stationary phase. The commercial preparation of this material has enabled the liquid chromatography community to conveniently explore its uses.

Difunctional acid and alcohol derivatives of cyclohexane are used in the preparation of polyester polymers. The *cis/trans* ratio of these monomers has important effects on the physical properties of the polymer; hence, the *cis/trans* ratio of raw materials must be known. In the analysis of competitive polymers, and in the investigation of production problems, the *cis/trans* ratio of monomers hydrolysed from the polymer must be determined to fully characterize the polymer composition.

The three cyclohexane derived monomers commonly used in the preparation of polymers are shown in Table 1. The separation and determination of *cis/trans* isomers of I and II are easily achieved by using gas chromatography, and this method is the one of choice. However, we have never achieved more than a partial separation of III on any gas chromatography or reverse phase liquid chromatography column. In the work reported here, we have investigated the use of liquid chromatography on bonded cyclodextrin-silica columns for the separation of *cis/trans* isomers of cyclohexane derivatives.

TABLE 1
Monomers for Polyester Preparation



EXPERIMENTAL

Standard solutions were prepared by dissolving 0.1 g of each cyclohexane derivative in 10 ml of methanol or acetonitrile, depending on the eluent used. The identity of the standard, in particular whether it was cis or trans, was determined by nuclear magnetic resonance. All separations were done isocratically, by using premixed solvents deaerated with helium. Injections were made with a Perkin-Elmer Model 600 autosampler with a 10- μ l loop. A Waters Model 510 pump and a Model 410 refractive index detector were used. The column was a 250- x 4.6-mm Cyclobond I β -cyclodextrin column manufactured by Astec, Whippany, N.J. The column delivered about 7000 plates under the test conditions specified by the manufacturer. Flow rates of 1 ml/min were used. Unless noted, the separations were done at 25°C.

For the purpose of this work, k' was determined by using the equation

$$k' = \frac{t - t^*}{t^*}$$

where t is the retention time of the compound and t^* is the time of the first baseline disturbance. Because most compounds are at least somewhat included by cyclodextrin, t^* has no rigorous theoretical significance, but it does provide an internally consistent means of summarizing data.

RESULTS AND DISCUSSION


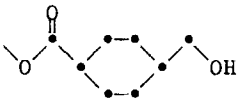
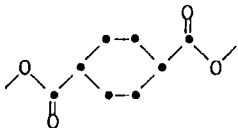

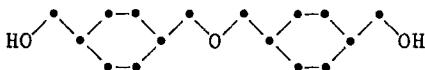


The k' 's for the cyclohexane derivatives investigated are tabulated in Table 2. A typical chromatogram is shown in Figure 1. Separations adequate for quantitation were achieved for all but the cis/trans pair of compound II. Noteworthy is the excellent separation for the cis/trans mixture of compound III. All separations were much poorer when acetonitrile was used as the solvent rather than methanol. By comparison, a separation sufficient to enable quantitation of the cis/trans ratio was only achieved for the ether and monomethyl derivatives when a DuPont 25-cm Zorbax C18 reverse phase column was used with acetonitrile-water as an eluent. With a Zorbax C8 column, no useful separations were achieved.

The cis/trans elution order was not always the same for the pairs of compounds investigated. For example, trans elutes before cis for compound I, for compound II, cis and trans coelute, and for compound III, cis elutes before trans. By reversed phase liquid chromatography and by gas chromatography,

TABLE 2

Retention Data for *cis/trans* Pairs of Cyclohexane Derivatives

60/40 methanol/water, 25°C

| | <u>trans</u> | <u>cis</u> |
|---|--------------|------------|
|  | 0.77 | 0.91 |
|  | 1.20 | 1.20 |
|  | 1.61 | 1.19 |
|  | 1.85 | 2.72 |
|  | 3.12 | 3.65 |
|  | 1.27 | 1.60 |
|  | 1.47 | 1.97 |

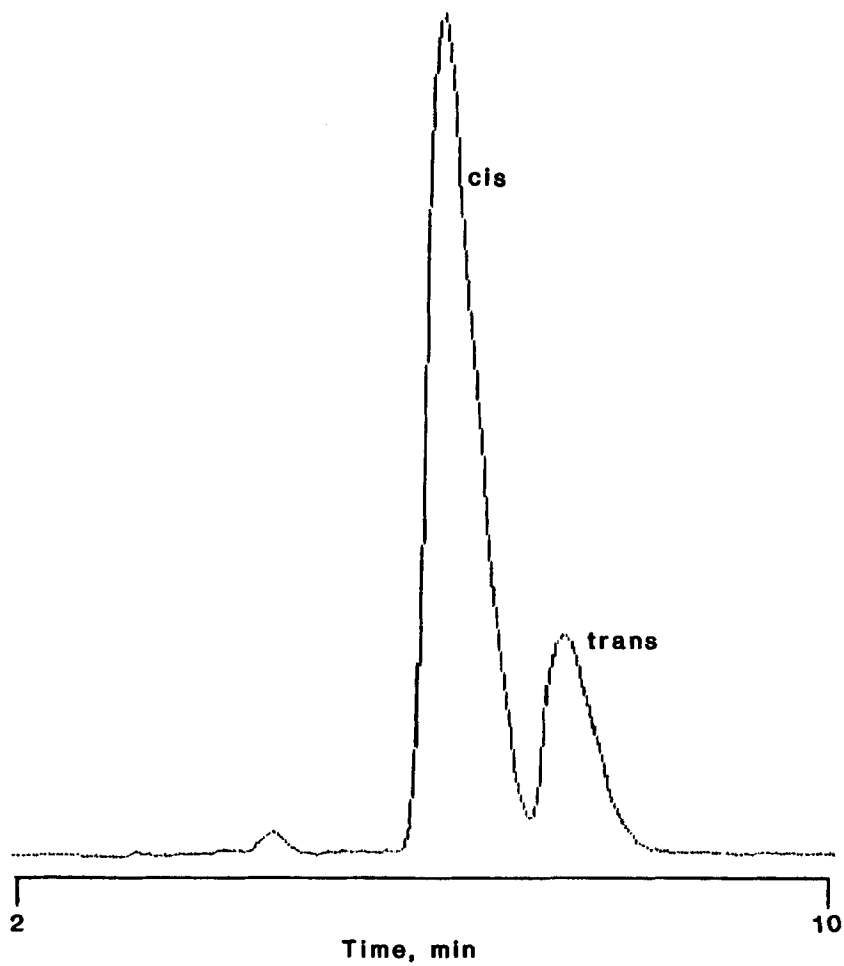


FIGURE 1. Chromatogram of compound III separation.
60/40 methanol/water 25⁰C.

these elution orders are reversed in the cases where there is enough separation to determine an elution order. It has been previously reported that cyclodextrin columns yield unique elution orders.(8) A rationale for some elution orders has recently been provided by the computer modeling work of Armstrong.(9)

The efficiency measured for nitroanilines was much greater than the efficiency for the cyclohexane derivatives. With an eluent of 60/40 methanol/water, plate counts estimated from measurements of peak retention time and half width were about 1000 plates per column. About 7000 plates/column were measured when nitroaniline was used. The peak asymmetry factors for each class of compounds were in the same range. These plate counts were not significantly affected by flow rates in the range of 0.5 to 1 ml/min. The addition of 0.1 M ammonium acetate or 1% triethylamine acetate did not significantly improve efficiency.

With 40/60 methanol/water as an eluent, the column efficiency became less than 200 plates per column. Under these conditions, the peaks for compound III were very broad and they tailed. As column temperature was increased from 25-70°C, the peaks for compound III sharpened and the retention time decreased. At 70°C, the efficiency had increased to 1500 plates per column. The resolution of the cis and trans isomers of III was better in 40/60 methanol/water above 55°C than in 60/40 methanol/water at 25°C.

From these data, it is not apparent why the efficiency of the column is much less for the cyclohexane derivatives than the nitroanilines. Because the peak asymmetry factors are the same for these compound classes, the low efficiency for cyclohexane derivatives probably is not the result of mixed modes of retention unique to this class of compounds. The results suggest slow inclusion/exclusion kinetics but, if this were the case, one would expect efficiency to be more sensitive to flow rate and temperature than was observed.

Lowering the methanol concentration of the eluent generally improves the selectivity of the cyclodextrin column. But for the compounds important in this work, lower concentrations of methanol resulted in less efficiency. As was noted for the cyclohexane derivatives, raising the column temperature improves the efficiency with a slight loss of selectivity. The strategy of lowering methanol concentration to increase selectivity and raising column temperature to maintain efficiency may be generally applicable to separations on cyclodextrin columns. This strategy is illustrated in Figure 2' for the separation of cis/trans isomers of decahydro-2,6-naphthalenedimethanol. Four

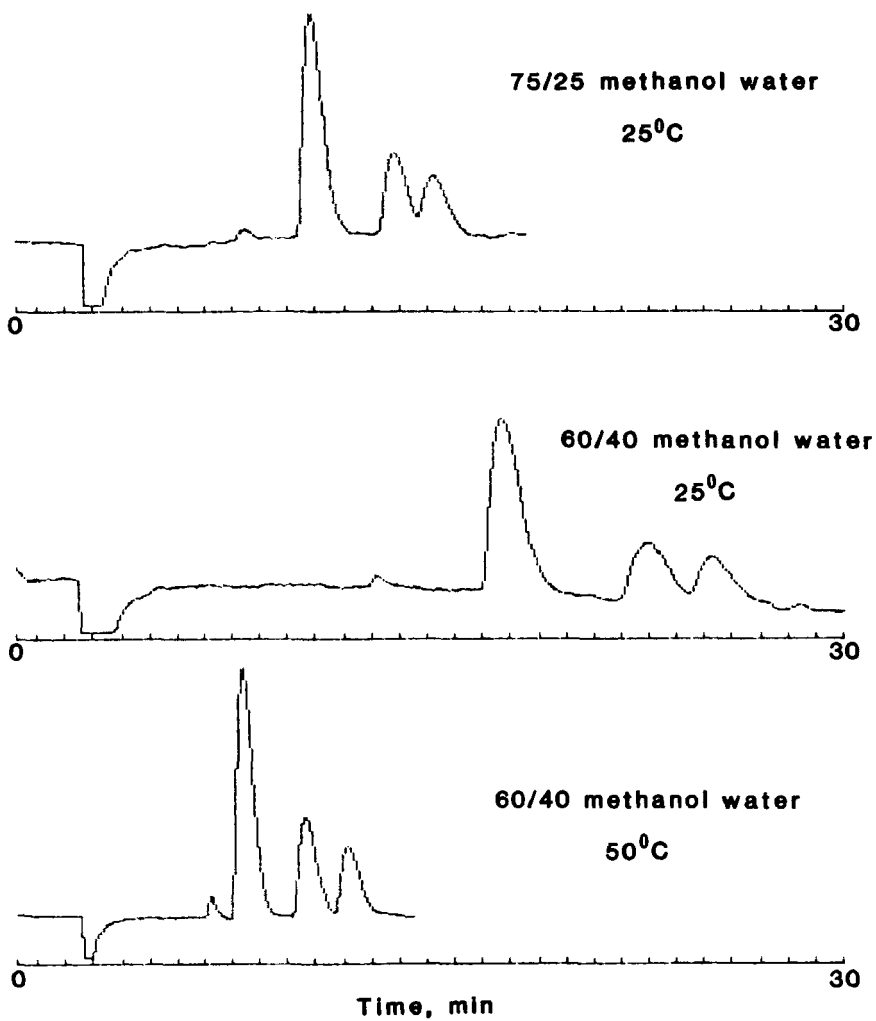


FIGURE 2. Separation of cis/trans isomers of decahydro-2,6-naphthalenedimethanol.

isomers are clearly separated. It is not known if more than four of the seven possible cis/trans isomers were present in this sample.

CONCLUSIONS

The bonded cyclodextrin-silica stationary phase offers excellent selectivity for the separation of cis/trans isomers of cyclohexane derivatives. Although the efficiency of this column for the cyclohexane derivatives is much less than for nitroanilines, its excellent selectivity enabled adequate separation of the cis/trans isomers of all but one of the compounds investigated.

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