Journal of Chromatography, 202 (1980) 478–482
Elsevier Scientific Publishing Company, Amsterdam — Printed in The Netherlands

CHROM. 13,297

Note

Crown ether-catalyzed synthesis of diastereoisomeric esters

Enantiomeric purity of mandelic acid via high-performance liquid chromatographic analysis of its diastereoisomeric 2-octyl esters

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(Received August 27th, 1980)

Carboxylic acids are often converted to their derivatives before chromatographic analysis. With enantiomeric acids, the use of an optically pure alcohol in the esterification process produces diastereoisomeric esters which can be resolved on the basis of differences in physical properties[1]. The standard syntheses for these diastereoisomers employ thionyl chloride or acid catalysts, either of which often cause unwanted side reactions, especially if the reactants are polyfunctional molecules. Thus, a rapid, quantitative, stereospecific method that can be carried out under mild conditions is needed for diastereoisomeric ester synthesis.

In 1975, Durst *et al.*[2] reported the crown ether-catalyzed esterification of fatty acids. The reaction conditions were mild; the reaction, quantitative; and the product could be analyzed directly by high-performance liquid chromatography (HPLC). Davis has reported the esterification of a wide variety of carboxylic acids and phenols by pentafluorobenzyl bromide with the crown ether, 18-crown-6, and potassium carbonate as catalysts[3]. Lam and Grushka[4] have also reported the application of crown ether-catalyzed esterifications to the analysis of fatty acids. Although none of these studies has involved the synthesis of diastereoisomeric esters through the use of enantiomeric acids and optically pure bromides, there is evidence that such a reaction would proceed with complete inversion at the reactant site; there would be no racemization of the optically active bromide and, consequently, no stereochemical problems would be raised[5,6].

We have, therefore, investigated the enantiomeric purity of mandelic acid in our laboratory by means of the esterification reaction with *l*-2-bromooctane in the presence of the crown ether catalyst, 18-crown-6, with subsequent HPLC separation of the esters. The procedure is direct, quantitative, and rapid, and proceeds under mild conditions. Our results indicate that this approach is an accurate and convenient probe of enantiomeric purity.

The use of crown ethers and optically pure bromides for the synthesis of diastereoisomeric esters may lead to the development of assays for enantiomeric purity of other compounds having acidic functional groups.

EXPERIMENTAL

Apparatus

HPLC separation of the esters was performed with a Spectra-Physics Model 8000 liquid chromatograph equipped with an SP 8000 data system, a Spectra-Physics Model 8310 UV–visible detector set at 254 nm, and a temperature-controlled column compartment. A stainless-steel DuPont-packed Zorbax Sil column, 5–6 μm particle size (25 cm × 6.2 mm I.D.) was used for both the preparative and analytical experiments. ^{1}H Nuclear magnetic resonance (NMR) spectra (C^2HCl_3) were measured on a 60 MHz NMR Model R12B spectrometer (Perkin-Elmer, Norwalk, CT, U.S.A.). Optical rotations were determined with a Model 241 MC polarimeter (Perkin-Elmer).

Materials

18-Crown-6, *d*-2-octanol, *d*-mandelic acid, *l*-mandelic acid, and *dl*-mandelic acid were purchased from Aldrich (Milwaukee, WI, U.S.A.). All HPLC organic solvents used were Burdick & Jackson Labs. (Muskegon, MI, U.S.A.) UV quality, distilled-in-glass. The remaining chemicals and solvents were reagent grade and used as purchased.

Synthesis of l-2-bromooctane

d-2-Octanol was reacted with PBr_3 at −5°C to give the desired bromide in a 62% yield[7]. Boiling point at 7 atm and specific rotation for *l*-2-bromooctane are: b.p.$_7$ = 68°C; $[\alpha]_D^{25} = -32.3°$ (neat).

General esterification procedure

The esters were prepared according to the general procedure described by Durst *et al.*[2]. An amount of 10 mmol of acid was dissolved in methanol and titrated to a phenolphthalein end point with a 10% solution of potassium hydroxide in methanol. The methanol was evaporated at reduced pressure and the resulting solid was redissolved in a solution of 20 mmol of bromide, 1 mmol of crown ether (18-crown-6), and 5.3 ml of acetonitrile. The solution was refluxed overnight at 80°C. A white precipitate slowly formed during the course of the reaction.

The mixture was cooled and filtered. Evaporation of the acetonitrile left a yellow oil, which was redissolved in toluene and filtered through a column containing 10 g of silica gel. Evaporation of the toluene yielded a pale yellow to colorless oil, which was redissolved in methylene chloride to make a 10% (v/v) solution. (Since some unreacted bromide was present in the oil, the concentration of the ester in solution was <10%. The unreacted bromide did not interfere with the HPLC analysis.)

Chromatographic conditions

The mobile phase was methylene chloride–hexane (9:1). A flow-rate of 2 ml/min and a column temperature of 40°C were maintained throughout the analysis.

Enantiomeric purity

In an enantiomeric mixture where % (w/w) of optical isomer A > % (w/w) of optical isomer B, % enantiomeric purity = 100 × (weight of A − weight of B)/(weight of A + B).

RESULTS AND DISCUSSION

The esterification of racemic mandelic acid with *l*-2-bromooctane proceeds smoothly, and a better than 90% yield of the desired esters can be recovered via preparative HPLC. The HPLC analysis of the product produced a chromatogram (Fig. 1) with two prominent peaks, present in a 50:50 ratio with a separation factor, $\alpha = 1.27$, and a resolution value (R_s) of 1.01. A separate esterification of *l*-mandelic acid with *l*-2-bromooctane produced a product having a chromatogram with a single prominent peak and a retention volume corresponding to those of compound A in Fig. 1, while the separate esterification of *d*-mandelic acid with the same bromide produced a product having a chromatogram with a single prominent peak corresponding to that of compound B. The latter chromatogram also contained a peak corresponding to that of compound A; this peak was less than 2% of the total area. Since a similar peak did not appear in the chromatogram produced by the ester of *l*-mandelic acid, it was assumed that the peak was due to an impurity in the starting material and was not a result of the esterification procedure.

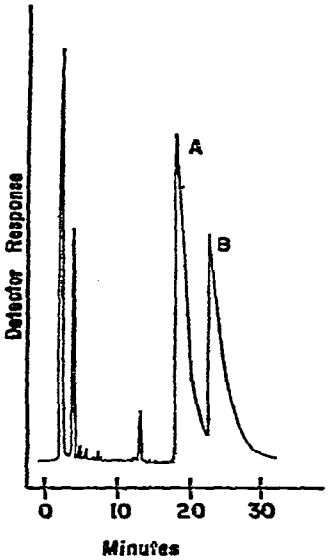

Fig. 1. Chromatogram of the mixture of diastereoisomeric esters (A and B) prepared from racemic mandelic acid and *l*-2-bromooctane. A = 2-octyl ester of *l*-mandelic acid; B = 2-octyl ester of *d*-mandelic acid.

After compounds A and B were isolated by preparative HPLC, they were identified as the 2-octyl esters of mandelic acid by NMR and infrared spectroscopy.

The relative percentages of compounds A and B in the diastereoisomeric ester mixture were determined by a comparison of the integrated areas of their respective UV responses at 254 nm. This method is valid since the chromophores in both compounds are identical. A plot of percent ester A found in the diastereoisomeric ester mixture *versus* the known percent of enantiomeric purity of *l*-mandelic acid samples is shown in Fig. 2. The samples were prepared by mixing the appropriate weights of

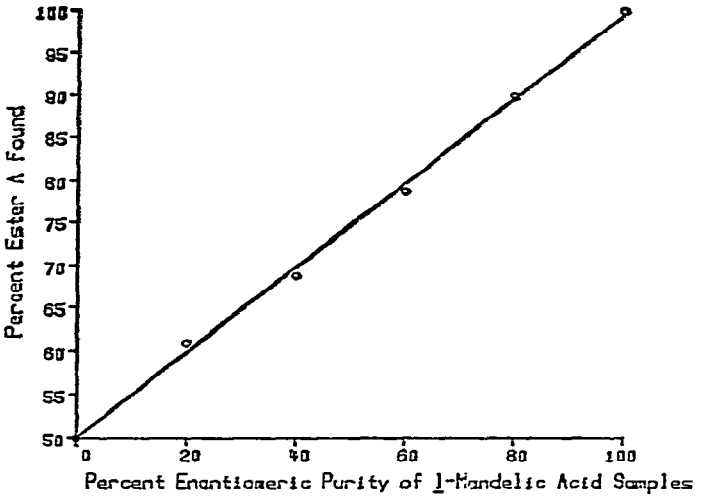

Fig. 2. The relationship between known percent enantiomeric purity of *l*-mandelic acid samples prepared and the percent ester A found after esterification.

pure *d*- and *l*-acids. The plot is linear over the range studied and demonstrates that the percent ester found is directly related to the enantiomeric purity of the sample.

The reproducibility of this method is demonstrated in Table I; four aliquots were taken from the same enantiomeric mixture (60%, w/w, *l*-mandelic acid); each portion was esterified, the diastereoisomeric esters produced were separated by HPLC, and the enantiomeric purity (%) was calculated from the percent ester A found.

TABLE I

ENANTIOMERIC PURITY OF SEVERAL *l*-MANDELIC ACID SAMPLES VIA THE HPLC ANALYSIS OF THEIR 2-OCTYL ESTERS

Samples contain 60% (w/w) *l*-mandelic acid and are 20% enantiomerically pure.

Sample	*Ester A (%)*	*Enantiomeric purity (%)*
1	61.2	22.4
2	61.5	23.0
3	61.7	23.4
4	61.3	22.6
Mean ± S.D.	61.4 ± 0.2	22.8 ± 0.4

The HPLC analysis of the product of the crown ether-catalyzed esterification of mandelic acid with *l*-2-bromooctane is a direct, accurate, and relatively rapid probe of enantiomeric purity. The application of this method to other compounds containing acidic functional groups is currently underway in our laboratory.

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