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Gas chromatographic separation of deuterated and optical isomers of di-2-butyl ethers

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Abstract

By connecting a DB-5 column in series with a Cyclodex-B column, nine of ten isomers of a mixture of di-2-butyl ether-d_0, di-2-butyl ether-d_5 and di-2-butyl ether-d_{10} produced during the dehydration of a 1:1 mixture of 2-butanol-d_0 and 2-butanol-d_5 using an Al_2O_3 catalyst, were separated and identified. The (*R*,*S*) and (*S*,*R*) isomers of di-2-butyl ether-d_5 could not be separated due to the similarity of their interactions toward the DB-5 and Cyclodex-B columns.

1. Introduction

Gas chromatographic methods permit pairs of isotopic molecules to be separated completely and determined quantitatively [1–5]. The introduction of highly efficient capillary GC columns in recent years permits this analysis to be accomplished in just a few minutes [6,7]. The heavier species (deuterated) always elutes first. This phenomenon is an inverse isotope effect to which intermolecular Van der Waals forces make the major contribution [1–8].

The separation of the components of an enantiomeric pair has also been accomplished by chromatographic methods [9–14]. The separation of chiral compounds by GC is an important and growing application area and has the potential to replace most classical methods of optical purity determination, such as optical rotation measurements and diastereomeric separations [14].

The separation of a pair of isotopic molecules or the separation of a pair of enantiomeric molecules is usually difficult, but either can be accomplished by the proper selection of the column and the GC separation conditions. However, when the separation of pairs of isotopic *and* enantiomeric molecules is desired, especially when the enantiomeric molecules are deuterated to different degrees, the separation of the mixture becomes more difficult and more challenging. This problem may be rare today, but it does occur in mechanistic studies, and interest in this will increase in the future.

We report here the results where nine of the ten isomers of a mixture of di-2-butyl ether-d_0, di-2-butyl ether-d_5 and di-2-butyl ether-d_{10} were separated, identified and quantitatively determined by connecting a DB-5 column in series with an optically active Cyclodex-B column.

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2. Experimental

The DB-5 column, purchased from J & W Scientific, was a 60 m × 0.32 mm fused-silica column (0.25 μm film thickness). The liquid phase was 5% phenyl- and 95% dimethylsilicone. The Cyclodex-B column, also purchased from J & W Scientific, is a 30 m × 0.32 mm column (0.25 μm). The liquid phase was β-cyclodextrin. The columns were connected in series using a capillary connector (Supelco), in such a way that the compounds were separated first on the DB-5 column and then on the Cyclodex-B column. A Hewlett-Packard 5890 Series II gas chromatograph, interfaced with an HP5971A mass-selective detector, and operated under the control of a Vectra 05/165 computer using HPG1034B software, was used for identification. A Hewlett-Packard 5880 gas chromatograph equipped with a flame ionization detector was used for quantitative analysis. Helium was used as the carrier gas.

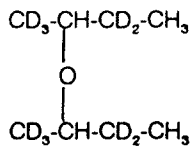
Retention volumes have been corrected using the retention time of methane to determine the dead volume. The mixture of di-2-butyl ethers was obtained from a reaction of a 1:1 mixture of (±)-butanol-d_5 and (±)-2-butanol-d_0 with Al_2O_3 at 230°C.

3. Results and discussion

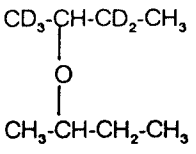
In a study of the mechanism of dehydration of 2-butanol on Al_2O_3, an intermolecular competition technique has been utilized to determine the deuterium isotope effect for the rate of conversion of the alcohol and for the formation of butenes. For this purpose, a 1:1 mixture of 2-butanol-d_0 and 2-butanol-d_5 (C^2H_3–CHOH–C^2H_2–CH_3) was used as the feed. The liquid products were collected at timed intervals and were analyzed. Six peaks were always observed in the gas chromatogram when using only the DB-5 column (Fig. 1a). To determine the identity of the compounds responsible for these peaks, an experiment using only 2-butanol-d_0 as the reactant was conducted. In this case, only two peaks with about equal areas were observed (Fig. 1b). The compounds responsible for these peaks were separated and collected using liquid chromatographic techniques. These two compounds were identified from ^1H NMR, ^{13}C NMR, two-dimensional NMR and GC–MS data to be di-2-butyl ethers.

An optically active GC column (Cyclodex-B) was used to identify the two isomers of the ether formed from 2-butanol-d_0. The earlier eluting peak in Fig. 1b using the DB-5 column was split into two peaks (Fig. 2) by the optically active column Cyclodex-B. This result indicates that the first peak eluting from the DB-5 column corresponds to the (*R*,*R*) and (*S*,*S*) isomers. A known mixture of di-2-butyl ether was used to identify the peaks from the Cyclodex-B experiment. The results indicate that the first peak eluting from Cyclodex-B column corresponds to the (*R*,*R*) isomer, the second to the (*S*,*S*) isomer and the third to the (*R*,*S*) isomer.

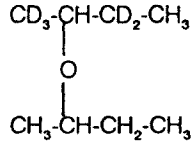
When a reaction involves the conversion of a 1:1 mixture of (±)-2-butanol-d_0 and (±)-2-butanol-d_5, ten isomers of di-2-butyl ether are expected, and they are (D = deuterium):



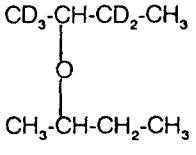
1. (R,R)-d_{10}
2. (S,S)-d_{10}
3. (R,S)-d_{10}



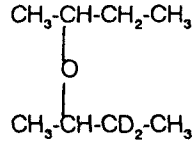
4. (R,R)-d_5
5. (S,S)-d_5



6. (R,S)-d_5



7. (S,R)-d_5



8. (R,R)-d_0
9. (S,S)-d_0
10. (R,S)-d_0

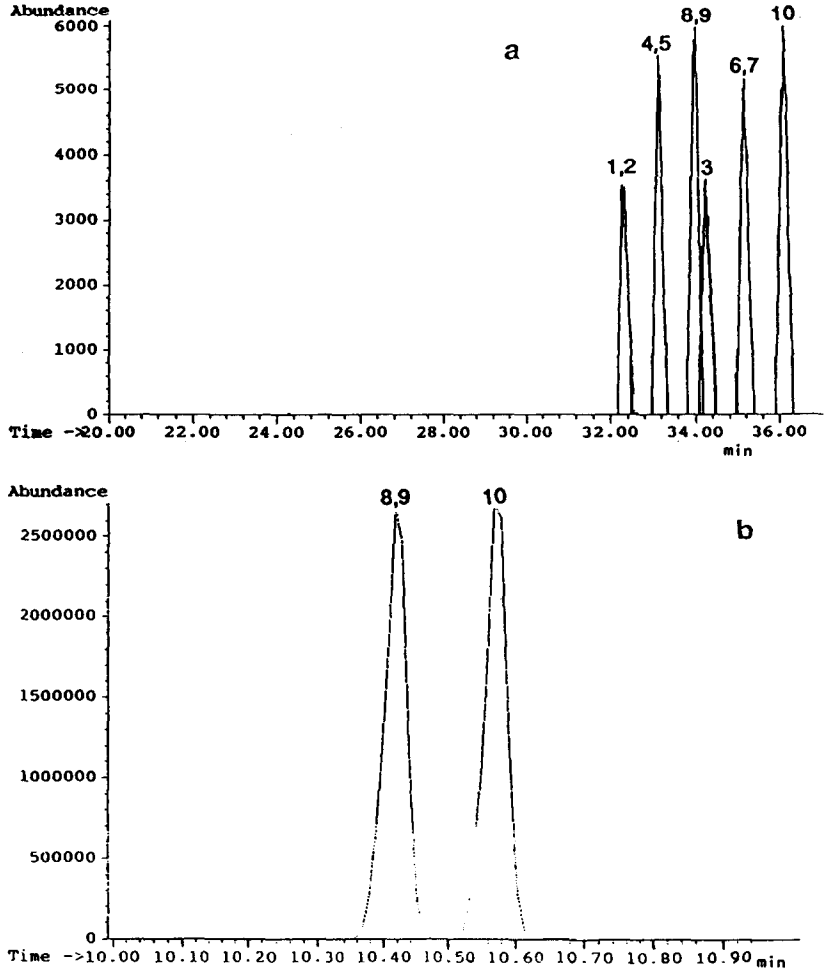


Fig. 1. Gas chromatograms using a DB-5 column to separate the ethers formed during the dehydration of 2-butanol: (a) 1:1 mixture of 2-butanol-d_0 and 2-butanol-d_5 as the feed, column temperature 15°C; (b) 2-butanol-d_0 as the feed, column temperature 45°C. See text for compound identities.

Complete separation of these ten isomers is not possible using the DB-5 column or the Cyclodex-B column alone. Using the DB-5 column, only six peaks were obtained as shown in Fig. 1a. The first peak on this chromatogram was identified as a mixture of 1 and 2; the second peak corresponds to a mixture of 4 and 5; the third peak corresponds to a mixture of 8 and 9; the fourth corresponds to isomer 3; the fifth corresponds to a mixture of 6 and 7 and the last one is due to compound 10. Using only the Cyclodex-B column, the deuterium-containing compounds cannot be separated from the undeuterated compounds.

In order to separate these ten isomers completely, a DB-5 column has been connected in series to a Cyclodex-B column. It was anticipated that the deuterated compounds would be separated from the undeuterated ones, and that the optically active isomers would be separated from the *meso* isomers by the DB-5 column, and then the optical active isomers would be separated into the (*S*,*S*) and (*R*,*R*) isomers on the Cyclodex-B columns. The early experiments showed that the situation was not so simple. In isothermal runs, whether at a low temperature (12°C) or at a high temperature (45°C), poor separations were obtained. The results from

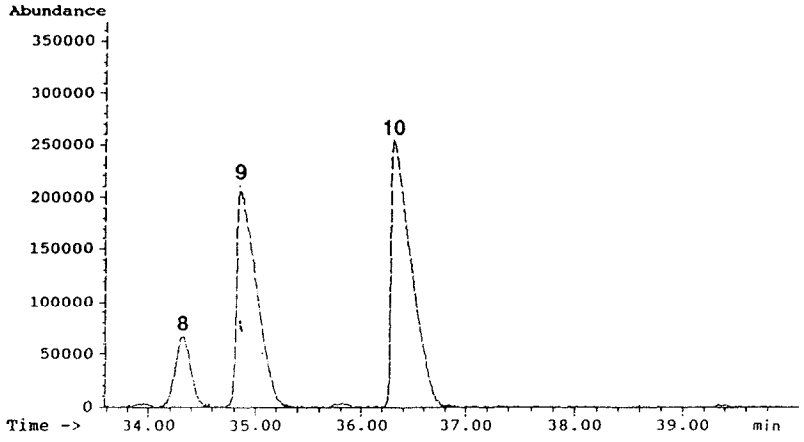


Fig. 2. GC separation of di-2-butyl ether on Cyclodex-B column. Column temperature: 25°C. See text for compound identities.

these experiments indicated that just simply connecting the two columns did not result in a chromatogram (or total ion chromatogram) that initially had the six compounds separated by the DB-5 column, which in turn were separated into the optical isomers on the Cyclodex-B column, to produce the expected ten peaks.

The obvious overlap was due to the good enantiomeric separation on the Cyclodex-B column. It is well known [3–7] that the isotopic separation is temperature dependent, and the lower the column temperature, the better the separation. To obtain the most favorable operating temperature, the separation factor has been measured from 15 to 55°C on the DB-5 column. As indicated in Fig. 3, the best separation factors are observed around 15°C and the inverse isotope effect of di-2-butyl ether-d_{10} is larger than that of di-2-butyl ether-d_5. The difference in enthalpy of the pairs of isotopic molecules related to the chromatographic process on DB-5 column are calculated according to Eq. 1 (Table 1)

Table 1
Difference in enthalpy for the pairs of isotopic molecules related to the chromatographic process on the DB-5 column

Pairs of isotopic molecules	$\Delta H_H - \Delta H_D$ (J)
Di-2-butyl ether-d_0/-d_{10} (*R,R*; *S,S*)	−247.7
Di-2-butyl ether-d_0/-d_5 (*R,R*; *S,S*)	−118.8
Di-2-butyl ether-d_0/-d_{10} (*R,S*)	−386.3
Di-2-butyl ether-d_0/-d_5 (*R,S*)	−116.7

$$\log (V_R)_H/(V_R)_D = -(\Delta H_H - \Delta H_D)/2.3RT + c \quad (1)$$

where $(V_R)_H$ and $(V_R)_D$ are the retention volumes of hydrogen-containing compound and deuterated compound, respectively, and c is a constant. The optical active and *meso* isomers of di-2-butyl ether-d_5 have the same response toward the temperature (Table 1); however, the *meso* isomer of di-2-butyl ether-d_{10} is more sensitive to temperature than the optically active isomer of di-2-butyl ether-d_{10}. It is also known [14] that the enantioselectivity of a chiral pair,

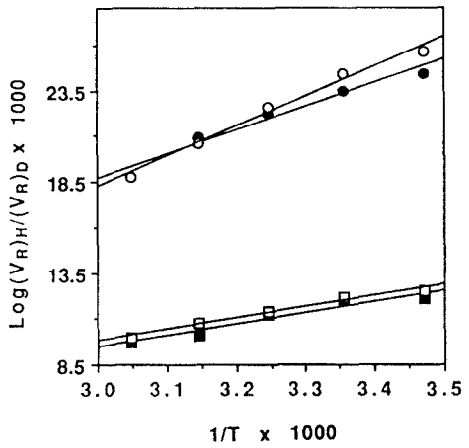


Fig. 3. Plot of the logarithms of the retention volumes versus $1/T$. ○ = Di-2-butyl ether-d_0/-d_{10} (*R,S*); ● = Di-2-butyl ether-d_0/-d_{10} (*R,R*; *S,S*); □ = Di-2-butyl ether-d_0/-d_5 (*R, S*); ■ = Di-2-butyl ether-d_0/-d_5 (*R,R*; *S,S*).

Table 2
GC data on the separation of di-2-butyl ether-d_0 on Cyclodex-B column

Temperature (°C)	$r_{S,S/R,R}$	$k_{S,S} - k_{R,R}$ (min)
15	1.02	1.23
25	1.03	0.93
35	1.02	0.46
45	1.02	0.24
55	1.02	0.13

Inlet pressure, 0.6 bar.

$r_{R/S}$, can be expressed in terms of the retention factors as shown in Eq. 2:

$$r_{R/S} = \frac{k_R}{k_S} \quad (2)$$

The value of $r_{R/S}$ is independent on the temperature; however, the value of $(k_R - k_S)$ is temperature dependent according to Eq. 3:

$$k = A \cdot \frac{RT_c}{P^0 r^0} \quad (3)$$

where A is the stationary phase contribution, T_c is the column temperature, R is the gas constant, P^0 is the vapor pressure of the compound and r^0 is the activity of the compound. The value of $(k_R - k_S)$ determines how good the separations are. As can be seen from Table 2, the (R,R) isomer of di-2-butyl ether eluted first from the Cyclodex-B column and the value of $r_{S,S/R,R}$ is around 1.02 over the temperature range of 15 to 55°C. However, the value of $(k_{S,S} - k_{R,R})$ changes from 0.13 min at 55°C to 1.23 min at 15°C.

Table 3
Relative amounts of each isomer of di-2-butyl ether-d_0, -d_5 and -d_{10}

Compound	Determined by GC (%)	Expected[a]
1	5.0	6.3
2	4.7	6.3
3	10.3	12.5
4	11.5	12.5
5	13.2	12.5
6, 7	25.1	25.0
8	8.3	6.3
9	8.3	6.3
10	13.7	12.5

[a] Assuming an SN_2 type mechanism for the formation of the ethers.

The above experiments suggest that if the temperature is adjusted so that the isotopic separation is at its maximum and the enantiomeric separation is kept to a minimum, a satisfactory separation may be possible. As expected, when the GC temperature program included holding the temperature at 12°C for 20 min, then increasing the temperature at a rate of 4°C/min to 45°C, a very good separation was obtained (Fig. 4). The identities of each component, verified by GC–MS, are also shown in Fig. 4.

Compounds 6 and 7 could not be separated. They are different compounds, but they have the same behavior on the DB-5 and Cyclodex-B columns.

The relative amounts of each isomer are given in Table 3. The data determined by GC using a

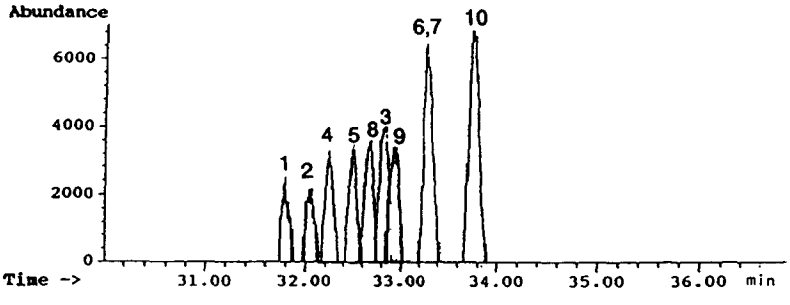


Fig. 4. GC separation of a mixture of di-2-butyl ether-d_0, -d_5 and -d_{10} on a DB-5 and Cyclodex-B column in series (12°C, hold 20 min, then 4°C/min to 45°C). See text for compound identities.

flame ionization detector are close to those expected if the ether formation follows a SN_2 type mechanism.

4. Conclusions

Deuterated enantiomeric isomers can be separated by a GC method that combines two columns, one of which is responsible for the separation of isotopic pairs and the other for the separation of the enantiomeric pairs. The separation of nine of the ten isomers of di-2-butyl ether-d_{10}, di-2-butyl ether-d_5 and di-2-butyl ether-d_0 provides an excellent example for the utility of this technique.

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