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Separation of the Stereoisomers of Di-*s*-butyl Ether

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d-Di-*s*-butyl ether was prepared by the reaction of *d*-*s*-butyl-alcoholate and optically inactive di-*s*-butyl sulfate, followed by displacement chromatography. With the same chromatographic technique, *meso*- and *rac*-di-*s*-butyl ether were separated from the commercial di-*s*-butyl ether.

The synthetic method and some physical properties of di-*s*-butyl ether have been already studied by Drake,[1] Senderens,[2,3] and Katsuno,[4] and further data on the physical properties[5] have been reported recently. These reports, however, have been concerned with a mixture of *meso*- and *rac*-isomers of di-*s*-butyl ether, optically pure di-*s*-butyl ether has never been successfully synthesized.

Although many methods of separating stereo- and optically active isomers have been established, the separation of di-*s*-butyl ether has been considered to be difficult. The separation of the optically pure di-*s*-butyl ether by means of partial crystallization, for example, seemed to be troublesome, because of its low melting point (−104——145°C), the separation method using an addition compound was also difficult because of the low reactivity of the ethers to other reagents. Meanwhile, the synthesis of optically pure di-*s*-butyl ether was troublesome as well. The commonly-used Williamson synthesis method was unsuitable for the synthesis of *s*-alkyl ethers because of the low yield, another method, the condensation of alcohol with an acid catalyst, could not be applied because racemization took place during the etherification.

For this paper, *d*-di-*s*-butyl ether was prepared by the reaction of d-*s*-butyl alcoholate and di-*s*-butyl sulfate,[6] followed by displacement chromatography. With the same chromatographic technique, *meso*- and *rac*-*s*-butyl ether were then separated from the commercial di-*s*-butyl ether.

Purified sodium *d*-*s*-butyl alcoholate[7,8] and optically inactive di-*s*-butyl sulfate[4] were reacted to form a mixture of *d*-di-*s*-butyl ether and *meso*-di-*s*-butyl ether in a 34% yield:

$$d\text{-}C_4H_9ONa + (C_4H_9)_2SO_4 \rightarrow d\text{-}(C_4H_9)_2O + meso\text{-}(C_4H_9)_2O + NaSO_4C_4H_9$$

It seems plausible that the configuration of the asymmetric carbon of sodium *d*-*s*-butyl alcoholate is preserved in this reaction[9] and that the racemization of sodium *d*-*s*-butyl alcoholate does not take place in a neutral-alkaline medium.[10]

The mixture of *d*-di-*s*-butyl ether and *meso*-di-*s*-butyl ether thus prepared was separated by displacement chromatography. It was found that displacement column chromatography with alcohol displacer made it possible to separate two stereoisomers from a mixture of them, silica gel powder (100—200 mesh) was the best adsorber, but alumina gel and other substances would also be suitable. The mixture of stereoisomers was first adsorbed to silica gel, and then gradually displaced with isopropyl alcohol over a 5 hr period. The effluents were divided at every 1/10 volume of the charged di-*s*-butyl ether and analyzed by gas chromatography. It is very interesting that a gas chromatogram taken under ordinary analytical conditions (90°C) showed only one peak, but at a lower temperature (50°C) two peaks appeared (A and B in Fig. 1). A linear relationship was found between the concentration of component A and the optical rotation of each fraction (Fig. 2). The facts to be observed in Fig. 2 indicate that component A, in which the earlier fraction of the effluent is rich, is *d*-di-*s*-butyl ether, while component B is *meso*-di-*s*-butyl ether. The specific rotation of pure *d*-di-*s*-butyl ether was estimated to be $[\alpha]_D^{20}$ +45.0° from the relationship shown in Fig. 2. It will be shown that *d*-di-*s*-alkyl ethers containing two asymmetric carbons[11] can be obtained by this combination of the reaction

1) N. L. Drake and F. P. Veitch, *J. Am. Chem. Soc.*, **57**, 2623 (1935).
2) J. B. Senderens, *Compt. rend.*, **181**, 698 (1925).
3) J. B. Senderens, *ibid.*, **179**, 1015 (1924).
4) T. Suwa, S. Katsuno and K. Oshida, *Kogyo Kagaku Zasshi (J. Chem. Soc. Japan, Ind. Chem. Sect.)*, **47**, 632 (1944).
5) M. Iriuchijima and Y. Komatsu, *Sekiyu Gakkaishi (J. Japan Petrol. Inst.)*, **7**, 797 (1964).
6) E. M. Marks, D. Lipkin and B. Bettman, *J. Am. Chem. Soc.*, **59**, 946 (1937).
7) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).
8) R. H. Pickard and J. Kenyon, *ibid.*, **103**, 1923 (1913).
9) T. Lauder and S. H. Green, *Nature*, **157**, 767 (1946).
10) Jr. R. L. Burwell, *J. Am. Chem. Soc.*, **64**, 1025 (1942).
11) Unpublished paper.

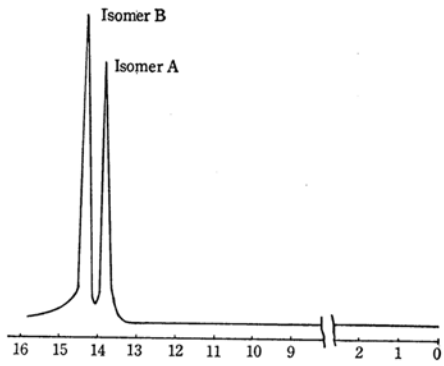

Fig. 1. Gas chromatogram of di-*s*-butyl ether.

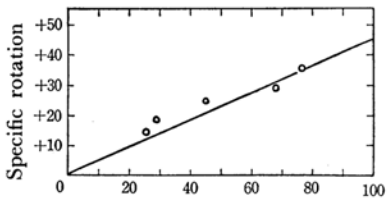

Fig. 2. The relationship between % of the component A and specific rotation.

and the displacement-chromatographic separation method.

Similarly, commercial di-*s*-butyl ether was displaced by isopropyl alcohol, after which effluents were collected, their optical rotation measured, and analyzed by low-temperature gas chromatography. None of the fractions thus obtained showed any optical rotation, but gas chromatogram showed that the earlier fraction contained much component A (Table 1). Comparing this finding with the results of the *d*-di-*s*-butyl ether synthesis, the earlier effluent fraction obtained from commercial pure di-*s*-butyl ether is, undoubtedly *rac*-, while the latter one is *meso*-di-*s*-butyl ether. This method may be applied to the preparation of *meso*- and *rac*-ether from commercial pure di-*s*-alkyl ether.

TABLE 1. THE SILICA GEL CHROMATOGRAPHIC SEPARATION OF COMMERCIAL DI-*S*-BUTYL ETHER

Fraction No.*1 of silica gel chromatography	Composition*2		Specific rotation $[\alpha]_D^{20°}$
	Conmponent A %	Component B %	
1	79.1	20.9	0.0
2	58.2	41.8	0.0
3	54.7	45.3	0.0
4	45.6	54.4	0.0
5	46.9	53.1	0.0
6	48.2	51.8	0.0
7	40.3	59.7	0.0
8	40.4	59.6	0.0
9	36.5	63.5	0.0
10	12.9	87.1	0.0
Commercial di-*s*-butyl ether*3	45.3	54.7	0.0

*1 No. 1 shows the first fraction and No. 10, the final fraction. All fractions were collected with equal volume.

*2 Component A shows the isomer A in Fig. 1 and component B, the isomer B in Fig. 1.

*3 It is a remarkable result that the gas chromatographic area % of component A and B of commercial di-*s*-butyl ether is not equal.

Although there have been several examples of the application of the development chromatographic technique to the separation of stereoisomers of solid esters,[12,13] the displacement chromatographic method has never been applied.

Two isomers are, however, more adequately separated by the displacement chromatographic method than by the development chromatographic method, and no fraction collected from the former is contaminated with any diluent.

Experimental

d-Di-*s*-butyl Ether. Ten grams of *d*-*s*-butyl alcohol, prepared by a modification of the method of Pickard and Kenyon[7] (bp 99.5°C, $[\alpha]_D^{20}$ +13.8°, (*c* 5.00, ethyl alcohol)) and 1.16 g of sodium slices were allowed to react until the sodium metal had been completely dissolved. The mixture was then cooled to 0°C, 10.0 g of pure di-*s*-butyl sulfate[4] was added, and the solution was allowed to stand overnight in an ice bath. After the solution had been allowed to react at 70°C for 7 hr, some water was added to the reaction mixture and it was distilled up to 100°C. The distillate was then separated into two phases. After the upper layer had been washed repeatedly with water until no *s*-butyl alcohol had been contained, it was dried with anhydrous sodium sulfate to give 3 g of a mixture of *d*-di-*s*-butyl ether and *meso*-di-*s*-butyl ether. The yield was 34% based on the charged alcohol. The mixture had $[\alpha]_D^{20}$ +18.0° (*c* 5.00, ethyl alcohol). It was then separated into *d*-di-*s*-butyl ether and *meso*-di-*s*-butyl ether by means of silica gel-displacement chromatography. The apparatus and procedure were as in JIS-2526. A glass column which had a separator section in the upper part (ϕ, 7 m/m: *l*, 200 m/m) and an analyzer section in the lower part (ϕ, 2.6 m/m: *l*, 1500 m/m) was used for the separation. As the adsorber 100--200 mesh silica gel powder was most suitable, but alumina gel powder could be used, too. The silica gel was taken from the analyzer section to fill half of the separator section of the column, a little indicator (Luxol Fast Red B and FIA Fluorescent Indicator) was added, and then the separator section was filled with silica gel. Three milliliters of the mixture were charged on the top of the column and covered with some more silica gel powder. After 20 m*l* of an isopropyl alcohol displacer

12) M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, **1942**, 611.
13) H. B. Hass, Thos de Uries and H. H. Jaffe, *J. Am. Chem. Soc.*, **65**, 1486 (1943).

had been poured on it, the column was connected to the line of the air compressor (0.4—0.5 kg/cm²). Ethers were developed downward in the analyzer section of the column by isopropyl alcohol over a 5 hr period. The first effluent (0.3 m*l*) (3.4%) was collected and analyzed by gas chromatography (stationary phase; squarane, 150-ft Golay column; temperature, 50°C). This fraction was 73.5% *d*-di-*s*-butyl ether and 26.5% *meso*-di-*s*-butyl ether, $[\alpha]_D^{20}$ +30.9° (*c* 5.00, ethyl alcohol), Fp −121°C, mp −111°C, d_4^{20} 0.7537, n_D^{20} 1.3945.

Found: C, 73.6; H, 13.6; O, 12.8%. Calcd for $C_8H_{18}O$; C, 73.8; H, 13.9; O, 12.2%.

***meso*-Di-*s*-butyl Ether.** 1) The last effluent in displacement chromatography (0.3 m*l*) (3.4%) was collected during the synthesis of *d*-di-*s*-butyl ether. *meso*-Di-*s*-butyl ether content: 87.2%; *d*-di-*s*-butyl ether: 12.8%. Fp −145°C, $[\alpha]_D^{20}$ +6.8°, d_4^{20} 0.7593, n_D^{20} 1.3924.

Found: C, 74.0; H, 14.0; O, 12.0%.

2) From 300 m*l* of commercial di-*s*-butyl ether, the last fraction (30 m*l*) (10%) was collected by means of displacement chromatography. It was then again separated by displacement chromatography, and the last fraction, (3 m*l*) (1%) of di-*s*-butyl ether, was collected. *meso*-Di-*s*-butyl ether content: 96.6%; *rac*-di-*s*-butyl ether: 3.4%. Fp −145°C, d_4^{20} 0.7709, n_D^{20} 1.3941.

Found: C, 73.3; H, 13.9; O, 12.8%.

***rac*-Di-*s*-butyl Ether.** 0.3 m*l* (10%) of the first effluent-fraction was collected from commercial di-*s*-butyl ether. The *rac*- and *meso*-di-*s*-butyl ether contents were 94.7 and 5.3% respectively. Fp −109°C, mp −96°C, d_4^{20} 0.7582, n_D^{20} 1.3917.

Found: C, 73.6; H, 13.7; O, 12.7%.

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