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Epimerization of Acyclic Diastereomers. 2.[1] Bis(alkylphenylcarbinyl) Ether

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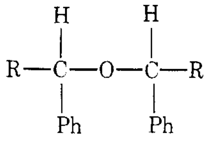
The epimerization of cyclic compounds has been extensively investigated[2-11] and it has been shown that the thermodynamic stabilities of cyclic diastereomers differed considerably in several cases.[2-5,10,11] On the other hand, thermodynamic stabilities of acyclic diastereomers do not differ by much in general.[12,13] However, in one case, i.e., 2,4-dichloropentane, a large energy difference between two diastereomers has been reported by Billups et al.[14,15] and calculated by MacMahon et al., assuming Lennard–Jones type interactions between nonbonded atoms.[16,17] In the preceding paper,[1] we reported the notable stability of the *dl* isomer compared to the meso isomer in bis(α-phenylethyl) ether and suggested that this stability of the *dl* isomer could not be explained entirely by steric factors (nonbonded interactions).

In the present report the even greater preference of the *dl* isomers of bis(alkylphenylcarbinyl) ether compared to the meso isomers is shown and the source of this preference of *dl* isomers is described.

Results and Discussion

Epimerization of three compounds (Ia, Ib, and Ic) catalyzed by boron trifluoride etherate in carbon tetrachloride or nitrobenzene was carried out.



$$\mathrm{R{-}\overset{\displaystyle H}{\underset{\displaystyle Ph}{C}}{-}O{-}\overset{\displaystyle H}{\underset{\displaystyle Ph}{C}}{-}R}$$

Ia, R = Et
b, R = *n*-Bu
c, R = cyclohexyl

As reported before,[1] an epimerization of bis(alkylphenylcarbinyl) ether is accompanied by an elimination reaction. The results of epimerization of Ia in carbon tetrachloride or nitrobenzene are shown in Figures 1 and 2. One might suppose that the meso isomer would be preferentially destroyed and that epimerization of the ether would not take place. To clarify this point, a reaction of Ia consisting of 3.5% *dl* and 96.5% meso isomers in carbon tetrachloride was carried out and the result is shown in Figure 3. This figure indicates that epimerization of the ether takes place in carbon tetrachloride giving an ether consisting of 100% *dl* isomer at prolonged time. The results of epimerization reactions of Ia, Ib, and Ic in carbon tetrachloride and nitrobenzene are summarized in Table I. The epimerization reaction of Ib was also started with equal concentrations of the *dl* and meso isomers, and a large excess of the meso isomer. A separation of isomers of Ic was unsuccessful. Each run was allowed to continue until the composition of the ether was constant. In the determination of the ether composition after epimerization of Ic in nitrobenzene by means of NMR (see Experimental Section), the signals of the methine proton doublet of the meso isomer overlapped with those of unknown by-products, making the isomeric composition uncertain. Since the reactions of Ia, Ib, and Ic in carbon tetrachloride were slow, boron trifluoride etherate was used in higher concentration than in nitrobenzene.

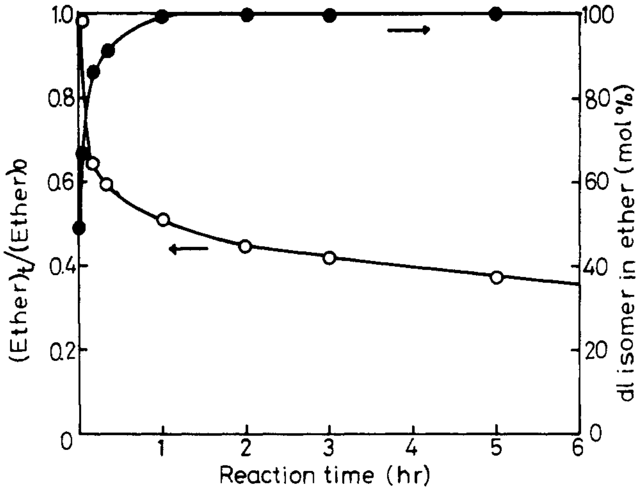


Figure 1. Epimerization and elimination of bis(ethylphenylcarbinyl) ether in carbon tetrachloride at 25 °C. Ether consisting of equal moles of *dl* and meso isomer was used. Ether, 0.05 mol/L; BF_3OEt_2, 0.04 mol/L. ○, decrease of ether; ●, mol % of *dl* isomer in ether.

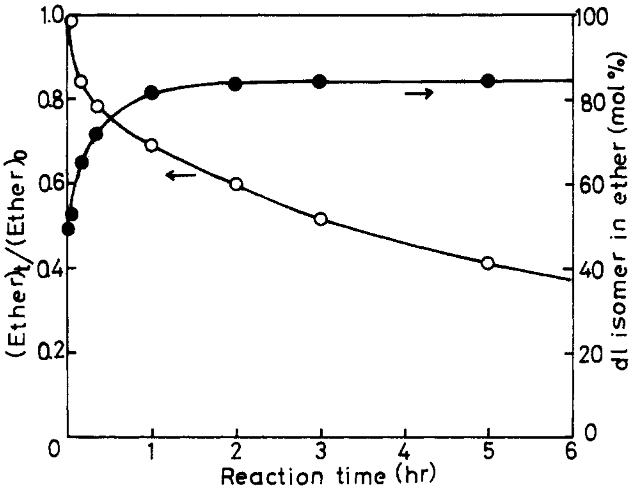


Figure 2. Epimerization and elimination of bis(ethylphenylcarbinyl) ether in nitrobenzene at 25 °C. Ether consisting of equal moles of *dl* and meso isomer was used. Ether, 0.05 mol/L; BF_3OEt_2, 0.01 mol/L. ○, decrease of ether; ●, mol % of *dl* isomer in ether.

Steady-state values of ether composition shown in Table I do not depend on the composition of starting ether and do not change even after prolonged reaction time. These results indicate that destruction of both isomers (*dl* and meso isomers) and epimerization of isomers took place. Since the rate of the epimerization reaction is faster than that of the destruction, the reaction of the ether with boron trifluoride etherate should give the steady-state composition of ether. Although, strictly speaking, the product compositions in Table I are not equilibrated but kinetically controlled, these values would indicate thermodynamic stabilities of these isomers. Generally speaking, the difference in thermodynamic stabilities between two isomers is even greater in the less polar solvent than in the polar solvent. Therefore, although the destruction of ether in carbon tetrachloride seriously competes

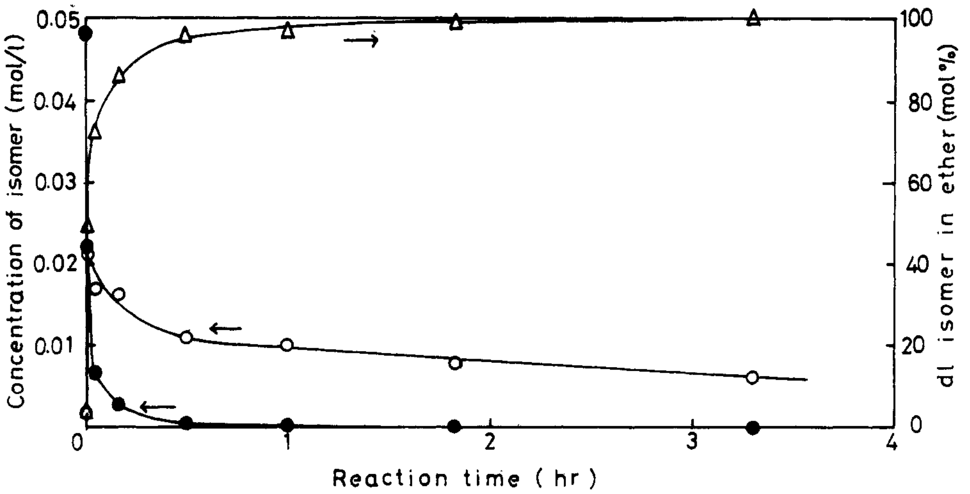


Figure 3. Epimerization and elimination of bis(ethylphenylcarbinyl) ether consisting of 3.5% *dl* and 96.5% meso isomer in carbon tetrachloride at 25 °C. Ether, 0.05 mol/L; BF_3OEt_2, 0.06 mol/L. ○, concentration of *dl* isomer; ●, concentration of meso isomer. △, mol % of *dl* isomer in ether.

Table I. Composition of Ether Obtained by Epimerization of Bis(alkylphenylcarbinyl) Ether at 25 °C

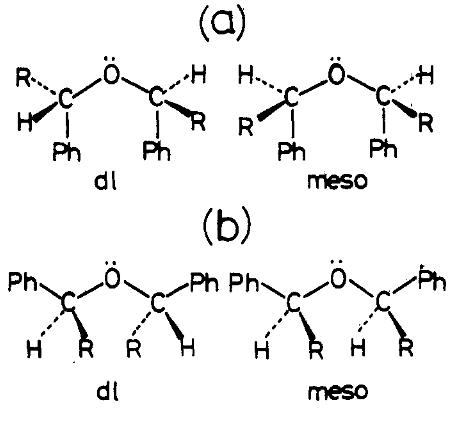
Reaction conditions: $(\mathrm{R{-}\overset{Ph}{\underset{H}{C}}{-}})_2\mathrm{O}$							Products, mol %			
		mol %					In CCl_4		In $C_6H_5NO_2$	
Registry no.	R	*dl*	meso	Concn, mol/L	$[BF_3OEt_2]$, mol/L	Time, h	*dl*	meso	*dl*	meso
	CH_3[a]						89.0	11.0	68.1	31.9
61462-92-8 (*dl*)	C_2H_5	50	50	0.05	0.04	3	100	0		
61446-47-7 (meso)		3.5	96.5	0.05	0.06	3.3	100.	0		
		50	50	0.05	0.01	3			84.5	15.5
		3.5	96.5	0.05	0.01	3 (days)			84.7	15.3
61446-48-8 (*dl*)	n-C_4H_9	50	50	0.05	0.06	0.5	100	0		
61446-49-9 (meso)		14.4	85.6	0.05	0.08	1	100	0		
		50	50	0.05	0.01	2			87.8	12.2
		14.4	85.6	0.05	0.01	4 (days)			87.5	12.5
61446-50-2 (*dl*)	C_6H_{11}	50	50	0.04	0.02	24	100	0		
61446-51-3 (meso)										

[a] From the preceding paper.[1]

with the epimerization reaction (see Figure 3), a comparison of the steady-state values in carbon tetrachloride with those in nitrobenzene would afford the conclusion that the results (100% *dl* and 0% meso) can be attributed to the difference in thermodynamic stabilities between the two isomers. Such a result appears to be a first example of an overwhelming preference of one isomer compared to the other isomer in an acyclic diastereomer.

Data in Table I indicate that as the size of the alkyl group increases so does the relative concentration of the *dl* isomer compared to the meso isomer. If the source of the energy difference is steric as described in the literature,[12,16] the isomers of Ic, having two similarly sized alkyl groups (cyclohexyl and phenyl) on an asymmetric carbon, should have similar thermodynamic stabilities while for bis(α-phenylethyl) ether they should not have similar thermodynamic stabilities. In the preceding paper,[1] it was reported that a change from phenyl to n-hexyl caused a remarkable difference in the results. These facts would suggest that the presence of two phenyl groups in a molecule caused a special effect on thermodynamic stabilities of the isomers. This special effect would favor conformer a or b (Scheme I). Both conformers well explain an increase of the preference of the *dl* isomer compared to the meso isomer on changing from a small alkyl group to a bulkier one. If two phenyl groups attract each other through space, conformer a should be favored. The thermodynamic preference of cis or gauche conformers in some 1,2-disubstituted ethylenes or 1,2-disubstituted ethanes, respectively, has been explained by a conjugative destabilization which is transmitted through bonds.[18] If a conjugative destabilization is transmitted through bonds in an ether, the syn conformer such as

Scheme I



a or b should be favored. Since UV absorption spectra of these ethers well coincide with those of corresponding alcohols, a direct through-space interaction between two phenyl groups in ether presumably does not operate. On the basis of the information presently available a possible explanation for *dl* preference is that a conjugative destabilization which has been suggested by Bingham favors conformation a or b.

Experimental Section

Preparation of Ethers. Bis(ethylphenylcarbinyl) ether was obtained as follows. A mixture of water, concentrated sulfuric acid, and ethylphenylcarbinol (obtained by the reaction of benzaldehyde with ethylmagnesium iodide[19]) in the ratio of 2:3:15 by volume was stirred for 2 h at room temperature and was washed with water several times and then distilled under reduced pressure. Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.71. Found: C, 85.22; H, 8.36.

The preparation procedure for bis(*n*-butylphenylcarbinyl) ether was similar to that for Ia using *n*-butylmagnesium chloride instead of ethylmagnesium iodide.[20] Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.76. Found: C, 85.24; H, 9.66.

Bis(cyclohexylphenylcarbinyl) ether was obtained as follows. A mixture of water, concentrated sulfuric acid, and cyclohexylphenylcarbinol (obtained by the reaction of benzaldehyde with cyclohexylmagnesium chloride) in the ratio 2:3:15 by volume was stirred for 30 min at 40 °C and was dissolved in diethyl ether. The solution was washed with water prior to the ether being removed under reduced pressure. Anal. Calcd for $C_{26}H_{34}O$: C, 86.13; H, 9.45. Found: C, 85.88; H, 9.33.

General Procedure of Epimerization. The procedure of epimerization was described in the preceding paper.[1] The composition of starting ethers used is listed in Table I. Separation and analyses of isomers were carried out by GLC using a 4.5-m ethylene glycol adipate polyester, 20% on Chromosorb W, column at 180 °C (for Ia) or at 200 °C (for Ib). In these analyses the isomers which had shorter retention time were assigned the *dl* configuration as described in the preceding paper.[1] Since the two isomers of Ic did not sufficiently separate in GLC, these were analyzed by NMR, in which the isomer with the methine protons signal at higher field was assigned the *dl* configuration as described in the preceding paper.[1]

Registry No.—Ethylphenylcarbinol, 93-54-9; *n*-butylphenylcarbinol, 583-03-9; cyclohexylphenylcarbinol, 945-49-3.

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An Improved Procedure for the Preparation of Bicyclo[2.2.2]octa-2,5,7-triene (Barrelene)

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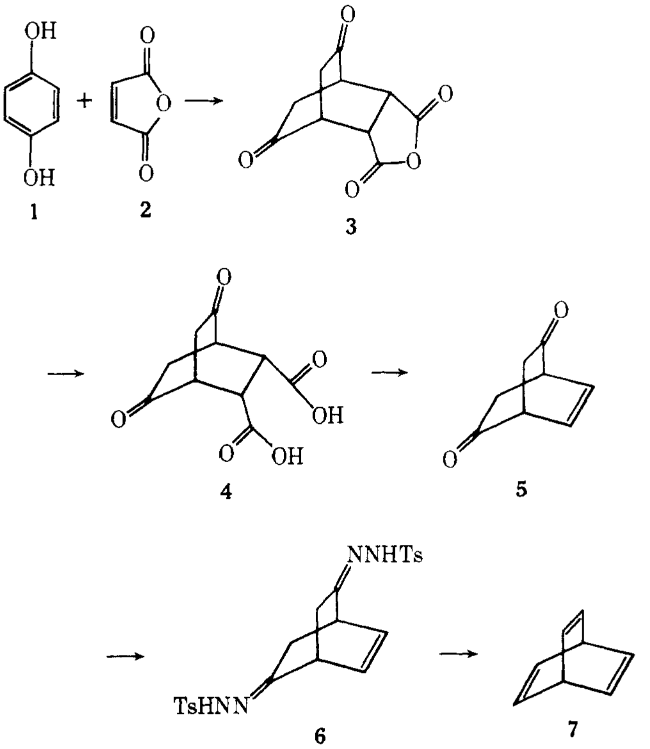
Barrelene (7) is a molecule of considerable theoretical and experimental interest.[1] However, each of the methods for its preparation [2–4] has its disadvantages. The recently published method of Dauben et al.[4] is undoubtedly the most efficient, but requires the rare and costly cyclooctatetraene as starting material.[5] The method of Taylor[3] is simple in that bicyclo[2.2.2]oct-2-ene is essentially halogenated and dehalogenated to give 7 together with bicyclo[2.2.2]octa-2,5-diene. Nevertheless, the manipulation is bothersome as the starting olefin has to be prepared in an autoclave and the products, which are only obtained in low yields, need to be separated by programmed gas–liquid chromatography. We report another method of preparation, which is short, easy to carry out, and makes use of cheap, readily available starting materials.

The key step, namely the construction of the bicyclo[2.2.2]-octane skeleton, is achieved readily, but in low yield, by simply melting together maleic anhydride (2) with hydroquinone (1) at 200 °C for 2 h.[6] From the mixture, the adduct (3) is isolated and immediately hydrolyzed to the corresponding acid (4) in an overall yield of 7%. Oxidative decarboxylation of 4 is crucial, as yields tend toward the low side.[7,8] However, heating 4 with lead tetraacetate in pyridine and dioxane under nitrogen for 10 min gives bicyclo[2.2.2]oct-2-ene-5,7-dione (5) in 42% yield. Subsequent conversion to the bistosylhydrazone 6 is straightforward (98% yield). Submission of 6 to methyllithium leads to barrelene (7) in 12% yield accompanied by benzene.[9,10] The latter probably arises by competitive fragmentation; in any event its presence will not interfere with any chemical reactions which might be done with 7 and it can be simply removed if needs be.



Experimental Section

5,7-Dioxobicyclo[2.2.2]octane-2,3-dicarboxylic Anhydride (3).[6] A mixture of hydroquinone (**1**, 607.0 g, 5.52 mol) and maleic anhydride (**2**, 1097.0 g, 11.2 mol) are heated in an atmosphere of carbon dioxide under strong reflux in a 2-L round-bottom three-neck flask for 2 h. The mixture, at about 70 °C, just above its solidification point, is carefully poured with stirring into ethyl ether (3.2 L) in a 5-L beaker and left overnight. The Diels-Alder adduct (**3**) is collected on a Buchner funnel and washed with cold ether. The beige crystals, 170.0 g, are used directly.

5,7-Dioxobicyclo[2.2.2]octane-2,3-dicarboxylic Acid (4). The crude anhydride (**3**, 170.0 g) is dissolved in water (1 L) and warmed to 80 °C with mechanical stirring for 2 h. Activated charcoal is added and heating continued for 15 min. Filtration over Celite followed by