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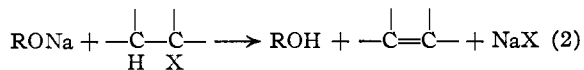
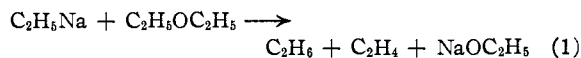
The Stereochemistry of an Elimination Reaction Effected by Butyllithium¹

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RECEIVED FEBRUARY 5, 1953

In order to determine the preferred stereochemical course for an elimination reaction caused by an organometallic compound, the reaction of butyllithium with the *cis* and *trans* isomers of methyl 2-phenylcyclohexyl ether was investigated. The *trans* ether (*trans* phenyl and methoxyl) was found to be converted to 1-phenylcyclohexene more rapidly than the *cis* isomer, demonstrating that in this case *cis* elimination occurs more rapidly than *trans* elimination. This fact differentiates the butyllithium reaction from the normal base catalyzed E2 reactions, where *trans* elimination is the preferred course.

In 1910 Schorigin observed that ethyl ether was decomposed by ethylsodium to give ethylene, ethane and sodium ethoxide² (equation 1). Since that time a number of other aliphatic ethers have been reported to react with organoalkali metal compounds in an analogous manner.³ These ether cleavages bear a formal similarity to the elimination reactions which occur when metal hydroxides and alkoxides react with alkyl halides, quaternary nitrogen salts, and similar compounds (equation 2).



In order to obtain information on the extent of this similarity we have investigated the stereochemistry of one of the ether cleavage reactions. Such data for these ether reactions have not been available, in contrast to the extensive literature which has been developed on the stereochemical course of the elimination reactions brought about by the alkoxide and hydroxide bases.

For this work the reaction of butyllithium with the *cis* and *trans* isomers of methyl 2-phenylcyclohexyl ether was selected. This ether appeared particularly well suited since a hydrogen β to the methoxyl group is activated by a phenyl group. As a result the elimination reaction should be favored and it should be possible to use conditions such that side reactions would not be troublesome.⁴

The stereoisomeric ethers, obtained by the action of sodium hydride and methyl iodide on the corresponding 2-phenylcyclohexanols, were mixed with butyllithium in both a pentane and a 50% pentane-ether solvent. With both solvents it was qualitatively apparent from the relatively rapid development of turbidity in the reaction containing the *trans* ether (*trans* phenyl and methoxyl groups) that this ether reacted much more rapidly than did the *cis* isomer. This observation was confirmed by

the analysis of the products of the reaction. Whereas the *cis* ether was recovered unchanged from the reaction in pentane, a 16% yield of 1-phenylcyclohexene was obtained from the *trans* ether reaction. With the mixed solvents the same relative order of reactivity was found, but the extent of reaction was considerably greater. In this case the *cis* ether yielded 8% and the *trans* ether 61% of phenylcyclohexene.

The characterization of the olefin as 1-phenylcyclohexene was based on refractive index data and on the fact that δ -benzoylvaleric acid was obtained from a permanganate oxidation of the product. Furthermore, it was found that methyl cyclohexyl ether and butyllithium did not react under the conditions employed for the phenyl-substituted ethers. This must mean that the hydrogen atom activated by the phenyl group is involved in the elimination reaction. The removal of this hydrogen atom would lead to the formation of 1- rather than 3-phenylcyclohexene.

Several experiments related to these elimination reactions were carried out. In one case the products from the reaction of butyllithium and the *cis* ether were treated with carbon dioxide before decomposition with water. As no acid or ketone other than valeric acid and dibutyl ketone was isolated, it was concluded that metalation of the aromatic ring in the phenylcyclohexyl methyl ether had not been a factor in the reaction. In another pair of experiments small amounts of triethylamine were added to the reaction solutions to see if this substance, which is a stronger base than ether, might affect the course of the reaction. Essentially the same results were obtained as in its absence, however, for the *cis* ether reacted to the extent of 11.5% and the *trans* ether, 61%. Methylithium was found to react with the stereoisomeric ethers much more slowly than butyllithium. No olefinic material was obtained from a methylithium *cis* ether reaction mixture which had been refluxed for seven days, and only about an 8% yield of olefin was obtained from a similar reaction of the *trans* ether.

The formation of 1-phenylcyclohexene from *trans*-methyl 2-phenylcyclohexyl ether involves the removal of a hydrogen and a methoxyl group which bear a *cis* relationship to each other. *cis*-Elimination, therefore, proceeds faster than *trans*-elimination in this ether cleavage. By contrast, in the elimination reactions caused by alkoxide and hydroxide bases *trans* substituents are removed much more readily than *cis* substituents from stereoisomers.

(1) Presented at the meeting of the American Chemical Society, Atlantic City, New Jersey, Sept. 14-19, 1952.

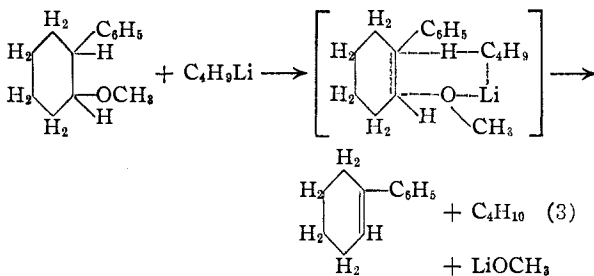
(2) P. Schorigin, *Ber.*, **43**, 1931 (1910).

(3) (a) R. L. Letsinger, A. W. Schnizer and E. Bobko, *THIS JOURNAL*, **73**, 5708 (1951); (b) D. H. Gould, K. H. Schaaf and W. L. Ruigh, *ibid.*, **73**, 1263 (1951); (c) K. Ziegler and N. G. Gellert, *Ann.*, **567**, 185 (1950); (d) A. Luttringhaus, G. Wagner-v. Saaf, E. Sucker and G. Borth, *ibid.*, **557**, 46 (1945); (e) G. Wittig and L. Lohman, *ibid.*, **550**, 260 (1942); (f) W. Hückel and H. Bretschneider, *J. prakt. Chem.*, **151**, 61 (1938).

(4) Ethers may react with organometallic compounds in a number of ways. In addition to decomposition in the Schorigin sense, they may undergo a rearrangement or form complex products by a sequence of reactions involving substitution and displacement reactions.^{3c,d,e}

meric compounds.⁵ Frequently the rates of the reactions will differ by a factor of 7000 to 24000.⁶ It is therefore apparent that the mechanism of this elimination reaction effected by butyllithium must be different from that operative in the E2 reactions of the conventional basic reagents.

Ziegler^{3c} has suggested that the initial and rate determining step in ether cleavages of this type is the removal of a proton from the α -carbon atom by the organometallic reagent. While an α -elimination cannot be excluded as a possibility here, it seems preferable, since *trans*-methyl 2-phenylcyclohexyl ether reacts with butyllithium much more rapidly than does methyl cyclohexyl ether, to consider this reaction in terms of the more conventional β -elimination process. This formulation adequately accounts for the facts and requires fewer assumptions than one involving an α -attack. A possible path for the reaction is illustrated in equation 3. The cyclic transition state resembles the ones postulated for pyrolytic elimination reactions, where *cis* elimination also is found to occur more readily than *trans* elimination.⁷



Experimental

cis- and *trans*-2-Phenylcyclohexanol.—A mixture of 61.1 g. (0.35 mole) of 2-phenylcyclohexanone⁸ (m.p. 57.5–58.5°) and 25 g. of Raney nickel catalyst in 250 cc. of absolute ethanol was heated at 55° with hydrogen (73 atmospheres) for five hours. After filtration and distillation a solid product was obtained which after two recrystallizations from pentane weighed 28.8 g. (47%); m.p. 39–41°; m.p. of the phenylurethan 128–129°. The reported constants for *cis*-2-phenylcyclohexanol are: m.p. 42–43°,⁷ m.p. of the phenylurethan 127.5–128°.⁸

The *trans* isomer was prepared by the method of Alexander and Mudrak.⁷ It melted at 55.5–56.5° and the phenylurethan melted at 136.5–138° (reported values, 56–57.5° and 136–137°, respectively).

cis- and *trans*-Methyl 2-Phenylcyclohexyl Ether.—Attempts to alkylate the isomeric alcohols with methyl iodide

(5) The only reported base-catalyzed E2 reaction for which *cis* substituents are removed faster than *trans* under comparable conditions is that described recently by Cristol and Hause, *THIS JOURNAL*, **74**, 2193 (1952). This reaction involved a bridged molecule, 11,12-dichloro-9,10-dihydro-9,10-ethanoanthracene, which possesses unusual geometrical restraints. The reversal of the relative rates of reaction of the *cis* and *trans* isomers was attributed to the fact that the molecule was incapable of forming a planar four centered transition state at the reaction site. As restraints of this type are absent in methyl 2-phenylcyclohexyl ether, one would expect the rate of *trans* elimination to exceed that of *cis* elimination if the reaction proceeded by the usual mechanism for base catalyzed E2 reactions.

(6) S. J. Cristol, *THIS JOURNAL*, **69**, 338 (1947); S. J. Cristol, H. L. Hause and J. S. Meek, *ibid.*, **73**, 674 (1951).

(7) (a) W. Hüchel, W. Tappe and G. Legutke, *Ann.*, **543**, 191 (1940); (b) E. R. Alexander and A. Mudrak, *THIS JOURNAL*, **72**, 1810, 3194 (1950); (c) D. H. R. Barton and co-workers, *J. Chem. Soc.*, 2174, 2459 (1949); 1048 (1951); 453 (1952).

(8) This ketone was prepared by the method of M. S. Newman and M. D. Farman, *THIS JOURNAL*, **66**, 1550 (1944). In our hands this procedure was more satisfactory than that of C. C. Price and J. V. Karabinos, *ibid.*, **62**, 1159 (1940).

and silver oxide by the method of Mislow⁹ were unsuccessful. The sodium hydride–methyl iodide method employed by Burwell and co-workers¹⁰ for the preparation of optically active methyl *s*-butyl ether was found to be satisfactory.

A mixture of 8.81 g. (0.05 mole) of *cis*-2-phenylcyclohexanol, 2.39 g. (0.10 mole) of sodium hydride and 50 cc. of dry benzene was heated under an atmosphere of hydrogen. A reaction commenced (vigorous evolution of gas) when the temperature reached 50°. The temperature was gradually raised to 70° and kept at this point for four more hours. The sodium salt of the alcohol precipitated and formed a gray amorphous mass at the bottom of the flask. To this cooled reaction mixture, 40.55 g. (0.29 mole) of methyl iodide was added. Heating was recommenced and the temperature was maintained at 63° for 19 hours, with occasional shaking. The reaction mixture, gray initially, turned white as the reaction progressed due to the precipitation of sodium iodide. Excess sodium hydride was decomposed by the dropwise addition of water. After separation of the organic material, benzene and excess methyl iodide were removed by evaporation at reduced pressure. Distillation of the residue yielded 8.04 g. (85%) of a colorless liquid, b.p. 123–125° (10 mm.), n_D^{20} 1.5218.

Anal. (by J. Sorenson). Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.46; H, 9.93.

The *trans* ether was prepared by the same procedure used for the *cis* isomer. A vigorous evolution of gas took place when *trans*-2-phenylcyclohexanol and sodium hydride were heated in benzene; however, the sodium alcoholate did not precipitate as in the case of the *cis* compound. When methyl iodide was added to the solution a white precipitate formed almost immediately. Workup of the reaction mixture yielded 8.14 g. (86%) of the *trans* ether, b.p. 125–126° (10 mm.), n_D^{20} 1.5208.

Anal. (by J. Sorenson). Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.35; H, 9.59.

Reaction of Methyl 2-Phenylcyclohexyl Ether with Butyllithium in Pentane.—Butyllithium was prepared in a pentane solution from lithium raspings and *n*-butyl bromide, and the solution was filtered through a sintered glass filter in order to remove the lithium residues and the insoluble lithium bromide. One hundred cubic centimeter portions (containing 0.077 mole of butyllithium) of this solution were siphoned into each of two 200-cc. flasks, one of which contained 5.22 g. (0.027 mole) of *cis*-methyl 2-phenylcyclohexyl ether, and the other, an equal quantity of the *trans* ether. A nitrogen atmosphere was used in this and in all subsequent reactions which employed butyllithium. After the reaction mixtures had stood at 26° for 30 minutes with no sign of reaction, they were both heated to reflux. The one containing the *trans* isomer became turbid within three hours, and by the time the mixture was decomposed with water (21 hours total reaction time) a white precipitate had settled out from the orange solution. Aside from a slight discoloration, the solution containing the *cis* ether appeared the same after 20 hours of refluxing as it did at the beginning of the reaction. After decantation onto ice, separation of the organic material, and removal of solvent, the products from each reaction were obtained by distillation.

From the reaction of the *cis* ether with butyllithium was recovered 3.78 g. of unreacted ether (b.p. 128–132° at 13 mm., n_D^{20} 1.5215; it gave a negative test for unsaturation with bromine in carbon tetrachloride and with neutral permanganate). The material unaccounted for probably represents losses in manipulation rather than losses from some reaction.

The products from the *trans* ether reaction yielded a 1.92-g. portion, b.p. 121–123° (10 mm.), n_D^{20} 1.5307; and a 2.01-g. portion, b.p. 123–127° (10 mm.), n_D^{20} 1.5292. A quantitative microhydrogenation of the latter portion showed unsaturation which corresponded to a composition of 17.4% phenylcyclohexene and 82.6% methyl phenylcyclohexyl ether. The yield was also estimated by interpolation from the refractive indices, assuming that the product consisted only of 1-phenylcyclohexene (n_D^{20} 1.5670)⁷ and the *trans* ether (n_D^{20} 1.5208).² These calculations indicated a yield of 1-phenylcyclohexene of 15.2%. The refractive index of 3-phenylcyclohexene is 1.5440,¹¹ so if appreciable quantities

(9) K. Mislow, *ibid.*, **73**, 4043 (1951).

(10) R. L. Burwell, L. M. Elkin and L. G. Maury, *ibid.*, **73**, 2428 (1951).

(11) A. Berlande, *Compt. rend.*, **213**, 437 (1951).

of this substance had been present, the value of the yield determined from the refractive indices would have differed markedly from that obtained from the hydrogenation data.

Reactions of *cis*- and *trans*-Methyl 2-Phenylcyclohexyl Ethers with *n*-Butyllithium in Pentane-Ether Solution. (1).—To a solution (which has been filtered through a sintered glass filter to remove lithium bromide) of *n*-butyllithium (0.21 mole) in 125 cc. of pentane, an equal volume of ether was added. One hundred cubic centimeters of the resulting solution (0.083 mole of *n*-butyllithium) was siphoned into each of two 200-cc. flasks, one of which contained 5.05 g. of *trans*-methyl 2-phenylcyclohexyl ether, the other an equal amount of the isomeric *cis* ether. Both reaction mixtures were then refluxed for 21 hours. The solution which originally contained the *trans*-methyl 2-phenylcyclohexyl ether became turbid within 20 minutes whereas the other solution became turbid only after 3.5 hours. The amount of precipitate present at the end of 21 hours was much greater in the former than in the latter mixture. After decanting the reaction mixtures onto ice, the products were isolated as before.

From the reaction of the *cis* ether with *n*-butyllithium, 3.88 g. of colorless liquid, b.p. 131–132° (16–17 mm.), n_D^{20} 1.5255, was obtained. A sample of this product (2.6931 g.) was microhydrogenated using 0.0229 g. of platinum oxide as catalyst. After four hours, 42 cc. (at 743.7 mm. and 22.0°) of hydrogen had been absorbed. From the foregoing data the yield of 1-phenylcyclohexene was calculated to be 8.3%. By interpolation of refractive indices as described in the previous experiment the yield of olefin was found to be 7.8%.

From the reaction of the *trans* ether with *n*-butyllithium, 3.40 g. of a colorless liquid, b.p. 131–135° (18–20 mm.), n_D^{20} 1.5546, was obtained. A sample of this product (0.8945 g.) was added to 0.0390 g. of platinum oxide and microhydrogenated. After five hours, 140 cc. (at 751 mm. and 26°) of hydrogen had been absorbed. The yield of 1-phenylcyclohexene was the same (61%) when calculated from the hydrogenation data as when calculated from the refractive indices of the isolated product, olefin and *trans* ether.

A 2.50-g. portion of the product from the *trans* ether was oxidized with a cold solution of potassium permanganate (4 g.). After standing at room temperature for 24 hours, the reaction mixture was filtered, acidified with concentrated hydrochloric acid, and filtered to separate the resulting precipitate. Recrystallization from water yielded 0.59 g. (25%) of a white crystalline solid; m.p. 74–75°, m.p. of the semicarbazone, 188–189°. The reported constants for δ -benzoylvaleric acid are: m.p. 75–76°, m.p. of the semicarbazone, 183–185°. ¹²

(2) (**Carbonation Experiment**).—The procedure described above for the reaction of the isomeric ethers with *n*-butyllithium was repeated for the *cis* ether to the point of hydrolysis of the reaction mixtures, in this case the mixture being siphoned onto Dry Ice. After all of the Dry Ice had disappeared, water was added, and the organic layer separated. The aqueous layer from the reaction of the *cis* ether (5.04 g. of the ether was used in the experiment) was acidified and extracted with ether. Distillation yielded 1.0 g.

of valeric acid (b.p. 72–75° at 6 mm., n_D^{20} 1.4102) but no higher boiling acids were found. If metalation of the aromatic ring of methyl phenylcyclohexyl ether had occurred, some of the corresponding acid should have been found at this point. The original organic layer yielded on distillation 0.7 g. of di-*n*-butyl ketone (b.p. 66–68° at 7 mm., n_D^{20} 1.4199), 1.0 g. of an intermediate fraction (b.p. 68–115°) and 3.8 g. of material (b.p. 116–119° at 7 mm.) which was largely recovered *cis* ether.

(3) (**Triethylamine Experiment**).—The procedure described under (1) was repeated with the exception that a molar amount of anhydrous triethylamine equivalent to the butyllithium reagent was added to the solution of the latter prior to the addition of the ethers. Observations made during the course of this reaction corresponded closely to those already described.

From the solution originally containing the *cis* ether (5.00 g.), 4.04 g. of a colorless liquid, b.p. 126–130° (9 mm.), n_D^{20} 1.5272, was isolated. The yield of 1-phenylcyclohexene calculated by interpolation of refractive indices was 11.5%.

From the solution originally containing the *trans* ether (5.00 g.), 3.20 g. of a colorless liquid, b.p. 124–128° (9 mm.), n_D^{20} 1.5574, was obtained. Calculated on the basis of refractive indices, the yield equaled 61%.

Reaction of Methyl 2-Phenylcyclohexyl Ether with Methylithium.—Each of the isomeric ethers (5 g.) was refluxed with a fourfold molar excess of methylithium in ether (150 cc.) for a period of one week. At the end of this period both reaction mixtures had the same appearance, a small amount of white precipitate suspended in a very pale greenish solution.

From the reaction of the *cis* isomer there was recovered 3.45 g. of unreacted methyl phenylcyclohexyl ether, b.p. 130–135° (10 mm.), n_D^{20} 1.5218, and no other product. This material gave a negative test for unsaturation with permanganate.

From the *trans* ether reaction was isolated 3.40 g. of liquid which boiled at 128–132° (8 mm.) and had an index of refraction of n_D^{20} 1.5247. As the refractive index was somewhat higher than that of the pure ether, and as the product gave a positive unsaturation test with permanganate a small amount of elimination must have occurred (estimated at 8%).

Reaction of Methyl Cyclohexyl Ether with *n*-Butyllithium.—Methyl cyclohexyl ether (b.p. 132–134°, n_D^{20} 1.4354) was prepared from the alcohol and methyl iodide with sodium hydride by the method used for the phenyl substituted isomers. A sample of this ether (10.64 g., 0.093 mole) was refluxed with 150 cc. of a lithium halide free ethyl ether-pentane (50% by volume) solution of *n*-butyllithium (0.112 mole) for 45 hours. Since no turbidity of precipitate formation was discernible in the reaction mixture, little, if any, reaction was presumed to have occurred. The solution did acquire a pale tan color. After hydrolysis with ice-water, separation of the organic material, and distillation, two liquid fractions were obtained: 0.5 g., 60–125°, 10.5 g., 125–133°. As neither fraction showed unsaturation, it was concluded that cyclohexene had not been formed. The higher boiling fraction consisted of methyl cyclohexyl ether contaminated with small amounts of octane (formed during the preparation of the *n*-butyllithium).

(12) C. C. Price and J. V. Karabinos, *THIS JOURNAL*, **62**, 1159 (1940).