[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

THE CLEAVAGE OF SOME ETHERS BY ORGANOLITHIUM COMPOUNDS

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It has been recognized (1–3) for some time that organolithium compounds react with ethers, resulting in cleavage of the ether linkage and destruction of the organolithium compound, probably in essential accordance with a reaction such as the following:

$$\mathrm{RLi} + \mathrm{R'{-}O{-}R'} \rightarrow \mathrm{R'OLi} + \mathrm{R{-}R'}[\text{and } \mathrm{R(-H)} \text{ or } \mathrm{C_nH_{2n}}] \qquad (1g)$$

A very interesting secondary reaction has been described recently by Bartlett and co-workers (1g). The rate of these cleavage reactions is dependent upon the nature of the RLi compound, the nature of the ether, and the temperature. It is common practice to use ethyl ether, and occasionally other ethers, as solvents in organolithium chemistry. As a consequence, uncertainties often arise because of the unknown extent to which the RLi compounds are decomposed by the solvent. The present investigation was undertaken as a study (2, 3) of the rates of cleavage of a number of ethers by some representative organolithium compounds.

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EXPERIMENTAL

Ethers. The aliphatic ethers and the dioxane used in the experiments were commercial products which were first distilled and then dried over sodium wire. The N-methylmorpholine was dried over solid potassium hydroxide and distilled. The low-boiling petroleum ether used throughout the work was unsaturate-free and boiled over the range 28–38°.

Organolithium compounds. Methyllithium and the aryllithium compounds were prepared in ethyl ether in the usual manner (4). Ethyl-, *n*-propyl-, *n*-butyl-, *n*-amyl-, dodecyl-, *sec*-butyl-, *tert*-butyl-, isopropyl-, and cyclohexyl-lithium were prepared in low-boiling petroleum ether (5). The various ethers, in large excess, were then added to these petroleum ether solutions of the RLi compounds.

Analysis. The rate studies were carried out by periodically removing aliquots from the reaction mixtures and determining the RLi content. Two methods are available for the quantitative determination of alkyllithium compounds. The benzyl chloride method (6), which is usually preferable, involves the removal of two aliquots from the mixture. To one is added an excess of benzyl chloride which reacts with the RLi present but not with any ROLi or lithium oxide under the analytical conditions. Both aliquots are then hydrolyzed and titrated with acid. The difference in the two titration values indicates the quantity of RLi which was present.

The method of Ziegler and co-workers (2) also involves the removal of two aliquots from the reaction mixture. To one is added butyl bromide followed by dibenzylmercury, which combination reacts only with the RLi present. The two aliquots are then hydrolyzed and titrated with acid, and again the difference in the titration values indicates the quantity of RLi which was present.

In order to compare the two methods, a solution of *n*-butyllithium in ethyl ether was

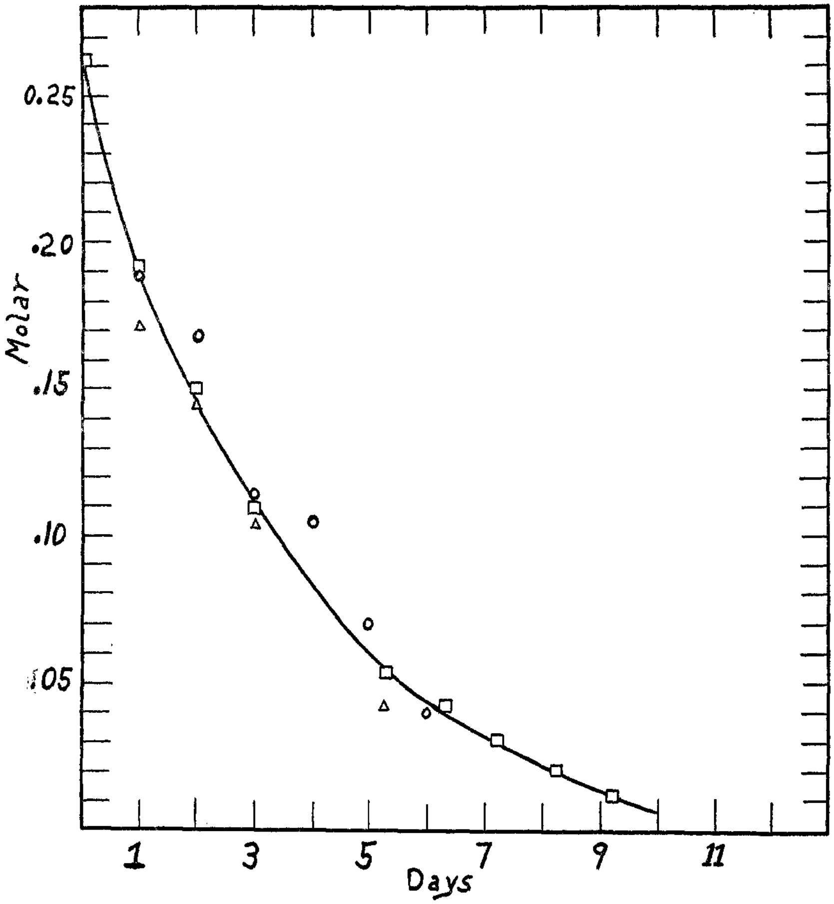

Fig. 1. Cleavage of Ether at 25°. □ Benzyl chloride method; △ Ziegler method; ○ Benzyl chloride method in 50% petroleum ether (Negative Color Test I on the 11th day).

allowed to stand at room temperature, and aliquots were periodically removed and analyzed by both methods. The results of this experiment are shown in Fig. 1. The Ziegler method gave slightly lower values; however, the difference is not significant.

That the presence of petroleum ether has no effect upon the rate of cleavage of ether by *n*-butyllithium was fixed conclusively by allowing a 50% ether-petroleum ether solution of *n*-butyllithium to stand at room temperature and periodically determining the RLi concentration by the benzyl chloride method. The results of this experiment are given in Fig. 1 in comparison with the rate of cleavage in ethyl ether alone.

In the analysis of methyllithium the benzyl chloride method failed, but the Ziegler method was satisfactory. Neither method gave satisfactory results with the arylalkyllithium compounds, triphenylmethyllithium and phenylethynyllithium. These RLi solutions were analyzed by removing aliquots and carbonating them with solid carbon dioxide. The resulting carboxylic acids were then isolated and weighed.

Ethyl ether. Since ethyl ether is the most common and widely used of the ethers, its behavior toward the RLi compounds has been most extensively examined. ROLi was established as one among the several products of the cleavage of ether by *n*-butyllithium. This was done by allowing *n*-butyllithium to react with ethyl ether until Color Test I (7) was

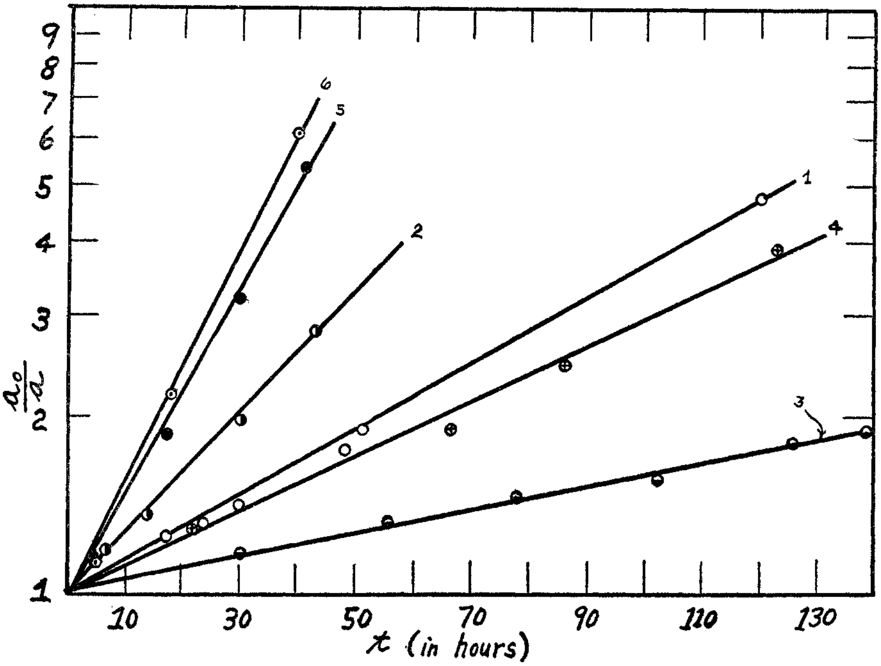

FIG. 2. CLEAVAGE OF ETHER BY ALKYLLITHIUM COMPOUNDS AT 25°. 1. Ethyllithium; 2. *n*-Propyllithium; 3. *n*-Butyllithium; 4. *n*-Amyllithium; 5. Dodecyllithium; 6. Isobutyllithium.

negative, showing that all of the RLi compound had been consumed. Water was then added, and from the mixture ethyl alcohol was isolated and identified as the 3,5-dinitrobenzoate.

The rates at which a series of six alkyllithium compounds reacted with ethyl ether were determined at 25° and at 35°. (At the higher temperature phenylethynyllithium was substituted for isobutyllithium.) Ether solutions of the organolithium compounds were prepared and titrated for their RLi content (6). Then, periodically, aliquots of each solution were removed and the RLi concentration again was determined. An examination of the data revealed that all six of the reactions were of the first order, and, therefore, they could be expressed by the equation[1]

$$K = \frac{2.303}{t} \log \frac{a_0}{a}$$

where K is the rate constant, a_0 is the initial concentration of the organolithium compound, and a is the concentration at time t. In Fig. 2 a_0/a on a log scale is plotted against t for the reactions conducted at 25°, and in Fig. 3 the same relationships are plotted for the reactions conducted at 35°. The slopes of the curves, $K/2.303$, indicate the rates of the various reactions. It is seen in Figures 2 and 3 that the order of decreasing rate of cleavage of ethyl ether by this series of organolithium compounds is: isobutyl > dodecyl > *n*-propyl > ethyl > *n*-amyl > *n*-butyl ≫ phenylethynyl.

The marked influence of temperature on the rate of cleavage of ether by the alkyllithium compounds may be seen by a comparison of the slopes of the curves in Figures 2 and 3. For example, the half-life period[2] of *n*-butyllithium in ethyl ether at 25° is 153 hours, but

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[1] Ether was always present in large excess so that its concentration remained constant for all practical purposes.

[2] The equation, $t_{\frac{1}{2}} = \frac{0.693}{K}$, was used to calculate the half-life periods.

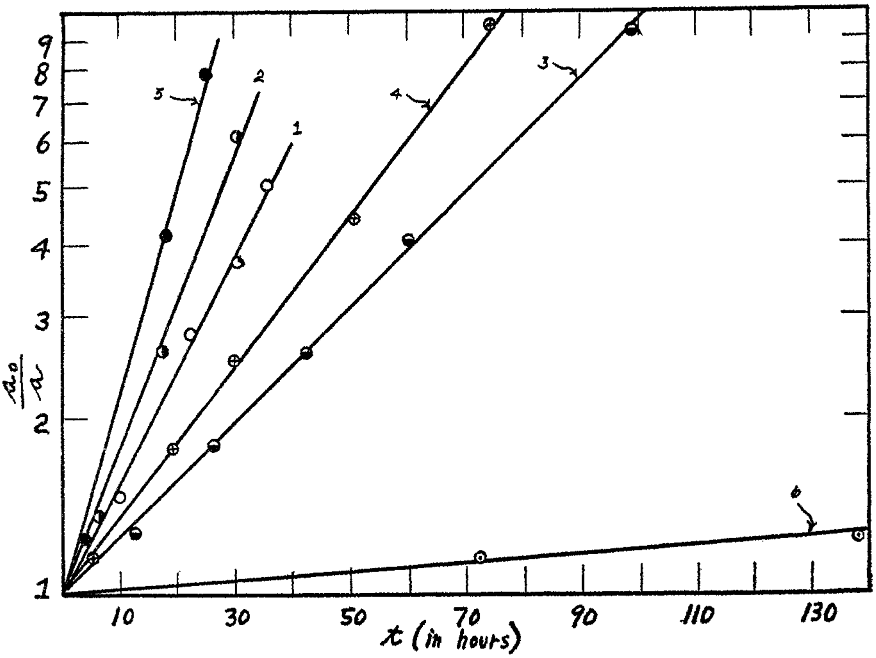

FIG. 3. CLEAVAGE OF ETHER BY ALKYLLITHIUM AND ARYLALKYLLITHIUM COMPOUNDS at 35°. 1. Ethyllithium; 2. *n*-Propyllithium; 3. *n*-Butyllithium; 4. *n*-Amyllithium; 5. Dodecyllithium; 6. Phenylethynyllithium.

at 35° it is only 31 hours. Ethyllithium in ethyl ether has a half-life period of about 54 hours at 25° and 17 hours at 35°.

At temperatures somewhere above 35°, the ether cleavages become complicated by secondary reactions (1g). One of these side reactions is the thermal decomposition of the RLi compounds. *sec*-Butyllithium (0.486 *molar*) in petroleum ether when heated at 90° was completely decomposed in 8 to 10 hours, and *n*-butyllithium (0.446 *molar*) in petroleum ether under the same conditions was decomposed to the extent of about 24% in 47 hours. One of the decomposition products may have been lithium hydride. Thomson and Stevens (8) found that when ethyllithium was heated in ligroin at 120° large quantities of lithium hydride were formed.

Unlike the other alkyllithium compounds, methyllithium (5b, 9) reacts extremely slowly with ether.[3] With respect to ether cleavage it is one of the most stable organolithium compounds known. Only a slight reaction was observed upon refluxing a 0.606 *molar* ether solution of methyllithium for 12 days. A 0.54 *molar* ether solution of methyllithium was sealed in a glass tube under nitrogen, and after 1 year at room temperature the concentration had dropped to 0.14 *molar*.

Secondary and tertiary alkyllithium compounds react unusually rapidly with ether (1g). When ether was added to petroleum ether solutions of isopropyl-, cyclohexyl-, *sec*-butyl-, and *tert*-butyl-lithium, a yellow color developed, and heat was evolved so that the solutions began to reflux. In each case within 30 minutes one-half or more of the organolithium compound was decomposed. Because of the rapid reactions and the difficulty in controlling the temperature, no satisfactory rate studies were made with ethyl ether.

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[3] The relatively high stability of methyllithium in ether solution suggests its use in the Zerewitinoff analysis. In this connection, it is interesting to note that many —OLi compounds are more soluble in ether than are the corresponding —OMgX compounds. See reference 5b.

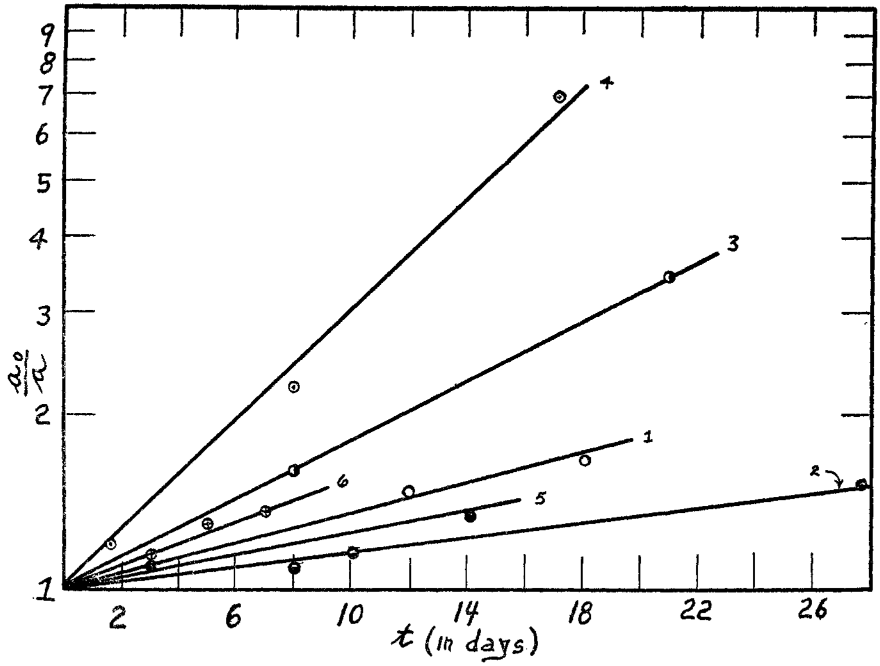

FIG. 4. CLEAVAGE OF ETHER BY ARYLLITHIUM AND ARYLALKYLLITHIUM COMPOUNDS AT 35°. 1. *p*-Dimethylaminophenyllithium; 2. *p*-Xenyllithium; 3. Phenyllithium; 4. α-Naphthyllithium; 5. β-Naphthyllithium; 6. Triphenylmethyllithium.

An examination of five representative aryllithium compounds showed that they react with ether at a much slower rate than do the alkyllithium types (with the exception of methyllithium). The rate at which triphenylmethyllithium cleaves ether was found to be comparable with that of the aryllithium compounds. The data from these experiments are given in Fig. 4 wherein the a_0/a values on a log scale are plotted against time *t*. A comparison of the slopes of the various curves shows that the order of decreasing rate of cleavage of ether by this series of organolithium compounds is: α-naphthyl > phenyl > triphenylmethyl > *p*-dimethylaminophenyl > β-naphthyl > *p*-xenyl. Müller and Töpel (10) have suggested that α-naphthyl- and *p*-xenyl-lithium are of no use for synthetic purposes because of their rapid decomposition by ether. This is not substantiated by the present findings. According to the data of Fig. 4 the half-life period of α-naphthyllithium with respect to ether cleavage is more than 6 days at 35°. *p*-Xenyllithium is among the organolithium compounds least reactive toward ether; the half-life period in this case is approximately 41 days at 35°.

Isopropyl, n-butyl, n-hexyl, and dodecyl ethers. It is significant that the various aliphatic ethers react with a given organolithium compound at distinctly different rates. The rates at which several representative ethers are cleaved by *n*-butyllithium were determined, and the results are given in Fig. 5. From the data of Fig. 5 and that of Fig. 2 for the rate of reaction of *n*-butyllithium with ethyl ether, the order of increasing stability of the ethers toward *n*-butyllithium is: dodecyl < ethyl < isopropyl < *n*-butyl < *n*-hexyl. In the series between *n*-hexyl and dodecyl there is probably an ether of minimum reactivity toward *n*-butyllithium.

sec-Butyl- and *tert*-butyl-lithium, which rapidly cleaved ethyl ether, reacted so much more slowly with *n*-butyl ether that it was possible to make satisfactory rate measurements in this solvent. The results of these rate studies are recorded in Fig. 5. A solution of *sec*-butyllithium, which had completely reacted with ethyl ether in 1 day, required 15 days

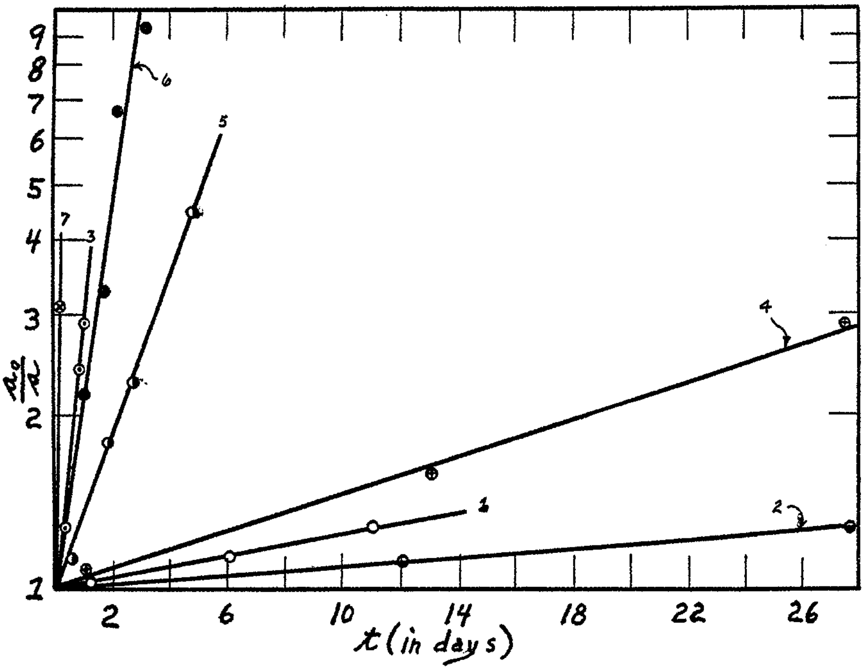

FIG. 5. CLEAVAGE OF ETHERS BY ORGANOLITHIUM COMPOUNDS AT 25°. 1. *n*-Butyllithium in *n*-butyl ether; 2. *n*-Butyllithium in *n*-hexyl ether; 3. *n*-Butyllithium in *n*-dodecyl ether; 4. *n*-Butyllithium in isopropyl ether; 5. *sec*-Butyllithium in *n*-butyl ether; 6. *sec*-Butyllithium in *n*-hexyl ether; 7. *tert*-Butyllithium in *n*-butyl ether.

to completely react with *n*-butyl ether. Likewise, a solution of *tert*-butyllithium, which reacted completely with ethyl ether in 30 minutes, required 36 hours to react completely with *n*-butyl ether. It is interesting to note that *n*-butyllithium cleaved *n*-butyl ether more rapidly than *n*-hexyl ether, whereas *sec*-butyllithium cleaved *n*-butyl ether less rapidly than *n*-hexyl ether.

Dioxane. When dioxane was added to a 0.6 *molar* petroleum ether solution of *n*-butyllithium, the mixture became warm, and all of the RLi compound was consumed (as indicated by a negative Color Test I) within 45 minutes. A similar experiment was carried out at 0°, and in this case the Color Test became negative within 1 hour.

Ethylene glycol dimethyl ether. A 0.5 *molar* petroleum ether solution of *n*-butyllithium was treated with two-thirds its volume of ethylene glycol dimethyl ether. The mixture became warm, a precipitate formed, and Color Test I was negative within 20 minutes.

N-Methylmorpholine. An equal volume of N-methylmorpholine was added to a 0.33 *molar* solution of *n*-butyllithium in petroleum ether. Color Test I was negative after 24 hours. A solution of 0.6 *mole* of N-methylmorpholine in 200 ml. of 0.25 *molar* phenyllithium in ethyl ether was refluxed for 5 days before Color Test I became negative.

Phenyl ether. To 100 ml. of a 0.21 *molar tert*-butyllithium solution in petroleum ether was added 0.027 mole of phenyl ether. The solution was refluxed for 24 hours and then carbonated with solid carbon dioxide. The only product isolated was *o*-phenoxybenzoic acid (14% yield). This indicates *ortho* metalation of the ether.

SUMMARY

1. The order of decreasing rate of cleavage of diethyl ether by a number of alkyl- and arylalkyl-lithium compounds was found to be: isobutyl > dodecyl > *n*-propyl- > ethyl > *n*-amyl > *n*-butyl ≫ phenylethynyl.

2. A 10°-increase in temperature from 25° to 35° significantly increases the rate of ether cleavage by organolithium compounds.

3. Somewhere above 35°, thermal decomposition of alkyllithium compounds becomes an important factor.

4. The order of decreasing ease of cleavage of diethyl ether by a number of aryl- and arylalkyl-lithium compounds was found to be: α-naphthyl > phenyl > triphenylmethyl > *p*-dimethylaminophenyl > β-naphthyl > *p*-xenyl.

5. The order of increasing stability of some ethers toward *n*-butyllithium was found to be di-*n*-dodecyl < diethyl < diisopropyl < di-*n*-butyl < di-*n*-hexyl.

6. Several other ethers were found to be cleaved by organolithium compounds. Diphenyl ether was metalated by *tert*-butyllithium to give *o*-phenoxybenzoic acid on carbonation followed by hydrolysis.

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