[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Mechanism of Addition of Lithium Reagents to Ketones

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There are no reported kinetic studies of the mechanism of addition of lithium reagents to ketones. The reaction is homogeneous but very fast. Two techniques were used in this study to follow the reaction: (1) a flow method and (2) competition experiments.

The Flow Method.—Figure 1 illustrates the apparatus employed. Streams of Michler ketone (4,4′-bis-dimethylaminobenzophenone) in toluene solution and phenyllithium in ether solution were caused to "cross-fire" at each other under methanol. Reaction could take place in a disc-shaped volume element located between the two jets and radiating out into the solution for a short distance.. Beyond this the reaction was "quenched" by destruction of unreacted phenyllithium by methanol. In successive experiments the type of mixing and time of reaction were effectively held constant, since reactant volumes, applied pressure, solvents and temperature were never varied. Only the (dilute) concentration of the reactants in the solvents was changed from one run to another. Therefore the quantity of reaction product formed was proportional to the integrated rate of reaction in a given run over the period of contact (about 0.016 sec.). Table I gives data on this quantity as a function of the concentration of both reactants.

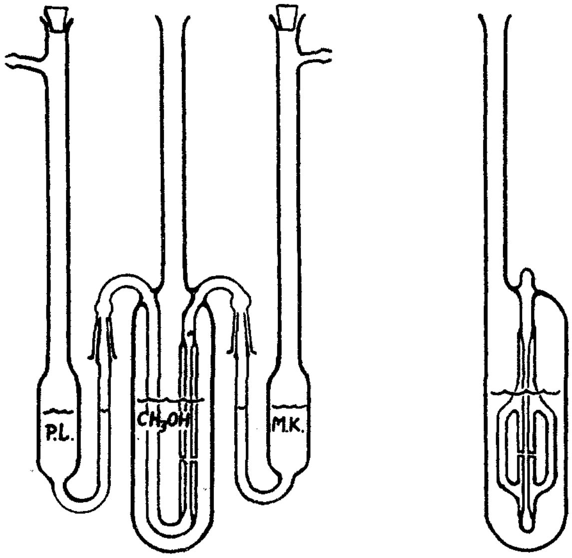

Fig. 1.—Flow apparatus used in studying the reaction between phenyllithium (P. L.) and Michler ketone (M. K.).

TABLE I

YIELD OF PRODUCT FORMED IN THE FLOW METHOD WITH DIFFERENT CONCENTRATIONS OF REACTANTS

Molarity before mixing of Phenyllithium	Molarity before mixing of Michler ketone	Micromoles of dye
0.0013	0.0028	0.22
.0062	.0028	0.77
.011	.0028	1.27
.015	.0028	1.31
.027	.0028	1.80
.11	.0028	3.06
.0008	.0385	0.69
.0026	.0385	2.04
.0087	.0385	3.40

The second order nature of the reaction is demonstrated by the equality of dependence on the concentration of phenyllithium and concentration of Michler ketone. For example, the dye yield with 0.0026 *M* phenyllithium and 0.0385 *M* Michler ketone is within 10% the same as that interpolated for 0.0028 *M* Michler ketone and 0.0385 *M* phenyllithium. Decreasing or increasing the concentration of either reactant by the same ratio has the same effect on dye yield.

The best conversion of reactants to dye under any conditions was about 11%. Therefore, it is reasonable to consider that 11% of the reactants were *mixed* before quenching and had the *opportunity* to react, while the rest of the reactants were never physically intermingled sufficiently to make reaction possible. The fraction of the maximum 11% reaction that occurred then depended on the rate of reaction and this in turn on the concentration of the reactants. By plotting the data for 0.0028 *M* Michler ketone on semi-logarithmic graph paper, representing 11% or 0.11 (10 cc.) (2.8×10^{-6} mole cc.$^{-1}$) = 3.1×10^{-6} mole as complete reaction, one obtains a straight line with an average deviation of points within ±3%, in accord with this hypothesis.

There cannot be any serious amount of complexing of phenyllithium with the two dimethylamino groups of Michler ketone, since good second order kinetics are observed.

One run was done with 0.0028 *M* ketone using isopropyllithium in place of phenyllithium. The rate was only one-third of that with phenyllithium.

Competition Experiments.—The relative reactivities of different lithium reagents and of different aromatic ketones was determined by competition experiments. A limited amount of 0.100 *M* Michler ketone in benzene solution was added to a solution of two organolithium compounds, one aliphatic and one aromatic. The solution of lithium reagents was swirled by hand as the ketone was added. No precipitates were formed. The product derived from the aromatic

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lithium reagent could be dehydrated to a stable colored dye (malachite green in the case of phenyllithium) and quantitatively determined colorimetrically without interference from the colorless product from the aliphatic lithium reagent. By assuming that the rest of the ketone reacted quantitatively with the aliphatic lithium reagent, the per cent. of the aliphatic derivative could be obtained by difference. Similarly, to determine the relative reactivity of different ketones toward phenyllithium, Michler ketone, which gave malachite green, was successively paired with the other ketones, which gave colorless products.

Competition experiments run with equimolar ratios of all three reactants indicate that the relative reactivities are *p*-tolyllithium > phenyllithium > ethyllithium > isopropyllithium; and 4,4'-dichlorobenzophenone > benzophenone > Michler ketone (see Tables II and III). There is a remarkable similarity to Gilman's data[1] on the relative reactivity of Grignard reagents toward benzonitrile, where also *p*-tolyl > phenyl > ethyl > isopropyl (*cf.* Tables II and IV).

TABLE II

ADDITION OF LITHIUM REAGENTS TO MICHLER KETONE

Lithium reagent	Relative rate
p-Tolyl	1.3
Phenyl	1.00
Ethyl	0.33
Isopropyl	0.10

TABLE III

ADDITION OF PHENYLLITHIUM TO KETONES

Ketone	Relative rate
4,4'-Dichlorobenzophenone	1.4
Benzophenone	1.00
Michler ketone	0.9

TABLE IV

ADDITION OF GRIGNARD REAGENTS TO NITRILES[1]

Grignard reagent	Relative rate
p-Tolyl	3.1
Phenyl	1.00
Ethyl	0.37
Isopropyl	0.08

Discussion

We shall consider briefly eight mechanisms in the light of the above experimental facts. Let L represent the lithium reagent; K, the ketone; C, a complex between them; and P, the product.

(1) $L + K \xrightarrow{\text{slow}} P$

(2) $L \xrightarrow{\text{slow}} Li^{\oplus} + R{:}^{\ominus} \xrightarrow[\text{fast}]{K} P$

(3) $L + K \xrightarrow{\text{slow}} C \xrightarrow{\text{fast}} P$

(4) $L + K \xrightarrow{\text{fast}} C \xrightarrow{\text{slow}} P$ or $C \xrightarrow[\text{slow}]{K} P$

(5) $L + K \underset{\text{very fast}}{\overset{\text{fast}}{\rightleftarrows}} C \xrightarrow[\text{slow}]{} P$

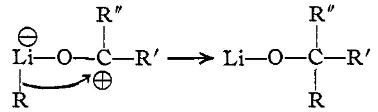
(6) $L + K \underset{\text{very fast}}{\overset{\text{fast}}{\rightleftarrows}} C \xrightarrow[\text{slow}]{L} P + L$

(7) $L + K \underset{\text{very fast}}{\overset{\text{fast}}{\rightleftarrows}} C \xrightarrow[\text{slow}]{K} P + K$

(8) $L + 2K \underset{\text{very fast}}{\overset{\text{fast}}{\rightleftarrows}} C' \xrightarrow{\text{slow}} P + K$

Second order kinetics are inconsistent with mechanisms 2, 4, 6, 7 and 8. The relative reactivity of different ketones eliminates mechanism 3, since the least nucleophilic (poorest complex-forming) ketones react most rapidly. The relative reactivity of different lithium reagents eliminates mechanism 1, since the aliphatic lithium reagents are more ionic and normally more reactive than the aromatic ones (only aliphatic organolithium reagents cleave ethers and metalate benzenes readily), but here we have the reverse order.

Mechanism 5 is the only one in this group which is consistent with all the experimental facts. Many other mechanisms besides the other seven can be eliminated, and mechanism 5 seems to be to a remarkable degree a unique solution among what might have been considered *a priori* as probable mechanisms for this reaction. That the lithium reagent can coördinate with the carbonyl oxygen is reasonable in view of the tight complexes which it forms with diethyl ether, as observed in the experimental section. The order of reactivity of different lithium reagents is characteristically that of ionic, or Wagner–Meerwein type, rearrangements. The rearrangement may be pictured as



$$\overset{\ominus}{\underset{R}{Li}}-O-\overset{R''}{C}{}^{\oplus}-R' \longrightarrow Li-O-\underset{R}{\overset{R''}{C}}-R'$$

This route no. 5 is the same mechanism that was found necessary earlier to explain the data on addition of Grignard reagents to nitriles.[2] However, it cannot be the mechanism of reaction of Grignard reagents with ketones for reasons which have been discussed.[2]

Experimental

Reagents.—Phenyllithium was prepared in the usual way in ether solution under nitrogen from 39 g. (0.25 mole) of bromobenzene, b. p. 154–156°, and 4.3 g. (0.62 mole) of lithium metal. A 0.85 *M* solution was obtained. *p*-Tolyllithium (0.20 *M*) was prepared similarly. Ethyllithium (0.52 *M*) was prepared from ethyl bromide, b. p. 38–39°, in pentane solution. Isopropyllithium (1.4 *M*) was prepared from isopropyl chloride, b. p. 35°, in pentane solution.[3] The solutions of lithium reagents were allowed to settle, then siphoned out under nitrogen pressure

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[1] Gilman, St. John, St. John and Lichtenwalter, *Rec. trav. chim.*, **55**, 577 (1936).

[2] Swain, THIS JOURNAL, **69**, 2306 (1947).

[3] We are indebted to Marguerite S. Swain for the isopropyllithium. For general method of preparation, see Gilman, Langham and Moore, *ibid.*, **62**, 2327 (1940).

through a filtering pad of glass wool into screw-capped bottles. The bottles were stored at 4° in a desiccator containing potassium hydroxide pellets and a nitrogen atmosphere. Frequent analyses showed negligible decomposition of these concentrated solutions of the reagents even after several months' storage, although the isopropyllithium became slightly pyrophoric.

Michler ketone, m. p. 174–176°, was prepared by crystallizing Eastman Kodak Co. white label material from 95% ethanol, drying at 25° under 15 mm. pressure over potassium hydroxide, and recrystallizing from benzene. Standard solutions in dry toluene (0.0028 and 0.0385 *M*) or in benzene (0.100 *M*) were used. These had to be protected from atmospheric moisture, since the latter imparts a strong yellow color to the ketone which it does not have when pure and dry. Benzophenone was recrystallized from ligroin, 4,4′-dichlorobenzophenone twice from 3:1 95% ethanol–acetone.

Benzene, ether and pentane were reagent quality, stored over sodium wire. High purity nitrogen (0.001% oxygen), dried over potassium hydroxide pellets and finally anhydrone or drierite, was used in all operations.

The Flow Method and the Determination of Kinetic Order.—Figure 1 shows the apparatus employed. The tubes were 8 mm. diameter × 2 mm. bore Pyrex capillary with their ends ground off square on a grinding wheel and facing each other with a 0.5 mm. spacing between. The apparatus was swept with oxygen-free nitrogen, 10 cc. of reactant solution was pipetted into each reservoir, and 75 cc. of methanol was added to the center bulb. The contents of the reservoirs were blown over together by suddenly applying a standard pressure (2.73 lb. per sq. in.) from a large reservoir through a short section of 1.0 mm. capillary to the interconnected reservoirs. The time of flow before exhaustion of the ether solution was 1.4 sec. At this point about 1 cc. of the toluene solution of the ketone was left in the other reservoir. The reaction zone was estimated by using aqueous phenolphthalein and dilute sodium hydroxide, respectively, in the two reservoirs and a large excess of acid as a quenching medium. A sharply defined red disc extending 8 mm. either side of the capillary tubes was formed. The volume is therefore $\pi(1.2)^2(0.05) = 0.23$ cc. Assuming the same reaction zone in the reaction between Michler ketone and phenyllithium, the reaction time, admittedly rough but probably within a factor of five, is 1.4 (0.23)/2 = 0.016 sec. The rate constant may be approximated, probably only within a factor of five due to this uncertainty about the reaction time, by noting that 50% of the maximum reaction with 0.0028 *M* Michler ketone occurs when we have 0.019 *M* phenyllithium. Hence

$$k_2 \cong \frac{2.303}{(0.016)(.0014)(5.8)} \log \frac{6.3}{(6.8)(0.5)}$$

$$\cong 5 \times 10^{+3} \text{ liter mole}^{-1} \text{ sec.}^{-1} \text{ at } 25°$$

This would correspond to a half-life of 0.002 sec. with 0.1 *M* reactants at 25°.

The entire resulting methanol solution was evaporated with 25 cc. of water on the hot-plate to a volume of 20 cc., then analyzed by making up to 50 cc. with methanol and taking aliquots for analysis as described below under analysis of aromatic lithium reagents.

While this analytical method gave good results in determining the micromoles of product formed with phenyllithium, the product with isopropyllithium gave a much more weakly colored dye which in addition faded too rapidly to be measured. Significant results could be obtained only by modifying the analytical technique. The sample in methanol boiled down to a volume of less than 5 cc. was added to the colorimeter tube and brought up to the 5-cc. mark with methanol. Glacial acetic acid was added to the 10-cc. mark, the tube was shaken, and immediately measured.

The point which gave 1.27 micromoles of dye is unique in that 10% pentane was added to the ether solution of phenyllithium used. This was to rule out the possibility of an effect of change of solvent on the rate in the isopropyllithium reaction. For the latter reaction 5 cc. of a solution of isopropyllithium in pentane was diluted to 100 cc. with ethyl ether and used at once in the rate measurement. The point for this reaction (0.030 *M* i-C_3H_7Li, 0.0028 *M* Michler ketone, 0.67 micromole of dye) corresponds to a threefold slower reaction than with phenyllithium.

Analysis of Aromatic Lithium Reagents.—The procedure involved pipetting a sample (usually 2.00 cc.) of the aromatic lithium reagent into approximately twice the theoretical amount of Michler ketone in dry toluene or benzene, converting the tertiary carbinol thus formed into the highly colored dye and measuring the dye with a Cenco Photolometer and a Corning no. 246 (2424) lighthouse red filter. To standardize the method a calibration curve was first prepared by adding 4 cc. of 0.1 *M* phenyllithium (excess) in ether to 2.00 cc. of 0.100 *M* Michler ketone in dry benzene in a flask that had been carefully dried and swept with nitrogen beforehand. After five minutes 50 cc. of methanol and 5 cc. of 10 *M* acetic acid–1.0 *M* sodium acetate buffer was added (which immediately gave a dark blue solution) and the solution was made up to 100.0 cc. with methanol. Aliquot portions of this solution were quantitatively diluted with a blank solution containing 0.5 *M* acetic acid, 0.05 *M* sodium acetate and 20% methanol (*p*H 3.6 with a glass electrode) until light blue solutions suitable for measurement were obtained. Matched cells (differing less than 0.5% at maximum reading) were used, one containing the solution and one the blank solution. Nine different dilutions of each of three independent preparations of carbinol were used to prepare the calibration curve. A similar calibration curve was prepared for *p*-tolyllithium. The analyses were carried out in the same manner as the calibrations, always in duplicate until analyses checking within 1% were obtained.

Analysis of Aliphatic Lithium Reagents.—A pipetted sample of the aliphatic lithium reagent in pentane was added to the 40-cc. reaction bulb of the gasometric apparatus, which had been previously dried and swept with dry nitrogen. The pentane was evaporated, finally heating to 80° at 15 mm. for one minute. The bulb was again filled with dry nitrogen, equilibrated with the gas buret, and 5 cc. of water was dropped slowly onto the solid lithium reagent. From the increase in volume (approx. 50 cc.) read on the gas buret and corrected for temperature (25°) and pressure (considered to be 760 mm. − 24 mm. vapor pressure of water = 736 mm.), the concentration of reagent in pentane was calculated. All determinations were made in duplicate and averaged; they generally checked within 3 cc.

Determination of the Stability of Aryl and Alkyl Lithium Reagents.—Before running competition experiments between an alkyl and an aryl lithium reagent, it was necessary to show that each reagent was stable in the presence of the other and that cleavage of ether by the alkyl reagent was negligibly slow. The quinoid dye forms of the alkyl derivatives of Michler ketone are very unstable. They show the usual intense blue-green color only for about 10 sec. after their formation under the usual conditions and then decolorize to a very light yellow-green. A mixture of 5 cc. of 0.0439 *M* phenyllithium and 2 cc. of 0.185 *M* ethyllithium analyzed as containing 5 cc. of 0.0436 *M* phenyllithium, showing no interference or interaction. A similar check was obtained in the analysis of *p*-tolyllithium in the presence of ethyllithium, and of phenyllithium in the presence of isopropyllithium.

Gasometric determinations on mixtures were slightly in error apparently due to coördination of ether by phenyllithium or ethyllithium even at 100°; this ether was subsequently released when the water was added. However, there was no indication of decomposition of the aliphatic reagent under any of the conditions tried.

Determination of Relative Reactivities.—For competition experiments the following relation was used to determine the relative reactivities

$$\frac{k_B}{k_c} = \frac{\log (b/(b - x))}{\log (c/(c - a + x))} \qquad (1)$$

TABLE V

TYPICAL EXPERIMENTAL DATA FROM COMPETITION EXPERIMENTS

In this table, M. K. = Michler ketone, P. K. = benzophenone, C. K. = 4,4'-dichlorobenzophenone. The other symbols are those of equation (1).

Expt.	A	B	C	a	b	c	Total volume, cc.	x	k_B/k_c
4	M. K.	C_6H_5Li	C_2H_5Li	0.250	0.224	0.218	6.5	0.169	3.0 ± 0.2
5	M. K.	C_6H_5Li	C_2H_5Li	.200	3.79	4.10	27.0	.120	1.6 ± 0.4
7	M. K.	p-$CH_3C_6H_4Li$	C_2H_5Li	.424	0.423	0.424	9.1	.306	3.9 ± 0.2
8	M. K.	p-$CH_3C_6H_4Li$	C_2H_5Li	.450	.410	.525	14.5	.298	3.8 ± 0.3
9	M. K.	p-$CH_3C_6H_4Li$	C_2H_5Li	.200	2.00	2.00	25.1	.125	1.7 ± 0.6
18	M. K.	C_6H_5Li	i-C_3H_9Li	.640	0.621	0.640	11.2	.528	9.8 ± 3.0
14	M. K.	C_6H_5Li	i-C_3H_9Li	.500	1.45	1.40	12.0	.280	1.3 ± 0.4
11	M. K.	C_6H_5Li	i-C_3H_9Li	.200	5.75	4.90	12.0	.079	0.6 ± 0.2
19	C_6H_5Li	M. K.	P. K.	.406	0.500	0.500	12.0	.194	.89 ± 0.1
20	C_6H_5Li	M. K.	C. K.	.406	.500	.500	12.0	.168	.63 ± 0.1

where the reactions considered are

$$A + B \xrightarrow{k_B} D$$

$$A + C \xrightarrow{k_c} E$$

and where A is the component in limited quantity, initially a millimoles, b is the initial number of millimoles of B, c the initial millimoles of C, and x the final millimoles of D. Typical results are recorded in Table V. The k_B/k_c relative reactivity values were checked several times using different values of $a:b:c$ for each combination of reactants. The values are reproducible to about the precision indicated in the table. However, there is a distinct dependence on the ratio of reactants ($a:b:c$) used (*cf.* expts. 4 and 5, 8 and 9, 18 and 11). This dependence on the ratio of reactants is not due to a change in the ratio of ether, benzene or pentane, since these varied in a random manner, and the values in a continuous curve. The dependence is probably due to complexing by the aliphatic lithium reagents, especially by isopropyllithium, with the dimethylamino group, increasing the susceptibility of the carbonyl group to attack by any uncomplexed organolithium compounds left in the solution. Therefore only the data from Table V for 1:1:1 ratios, where complexing would be least important, were used for comparisons of relative rate. These and other data for 1:1:1 ratios are summarized in Tables II and III.

Summary

The reaction between phenyllithium and Michler ketone is homogeneous and second order with a rate constant of approximately $5 \times 10^{+3}$ liters mole^{-1} sec.$^{-1}$ at 25°. This corresponds to a half-life of 0.002 sec. with 0.1 M reactants at 25°. The order of relative reactivity of different reactants is p-tolyllithium > phenyllithium > ethyllithium > isopropyllithium; and 4,4'-dichlorobenzophenone > benzophenone > Michler ketone. Out of eight mechanisms considered, the only one consistent with these data involves rapid reversible formation of a low concentration of complex between the lithium of the lithium reagent and the oxygen of the ketone, followed by rate determining rearrangement of this complex. This is the same type of mechanism that was found earlier for the addition of Grignard reagents to nitriles.

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