

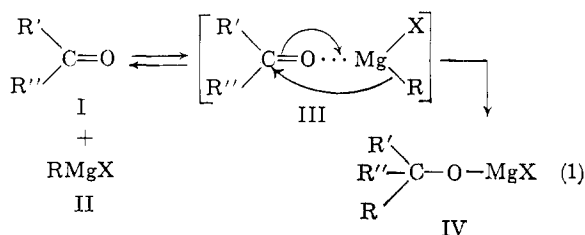
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF.]

Relative Rates of Grignard Addition and Reduction Reactions¹⁻³BY JOHN MILLER,^{2,4} GEORGE GREGORIOU² AND HARRY S. MOSHER

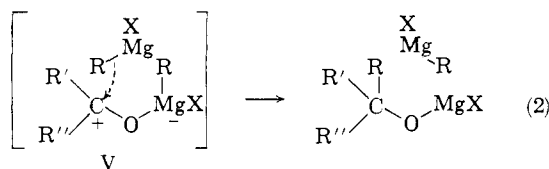
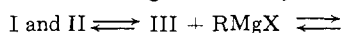
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The relative rates of addition and reduction were studied in a flow system using the reaction between 3-methyl-2-butanone and the Grignard reagent from 2-bromopropane and in the reaction between 2,4-dimethyl-3-pentanone and the Grignard reagent from bromoethane. In the latter reaction, the relationship between the product distribution and the ratio of the concentrations of the reactants indicated that the reaction was proceeding with consecutive, second-order kinetics. This was taken as evidence that either the Grignard reagent from bromoethane was composed of entities formally related to a dimer of ethylmagnesium bromide or that such entities were more reactive toward 2,4-dimethyl-3-pentanone than any other species of Grignard reagent present in solution.

Two proposals for the mechanism of the normal *addition reaction* have received serious consideration in the literature. The first of these proposals, advanced by Meisenheimer,⁵ conceived of the addition reaction as occurring by rearrangement of a Werner complex between the Grignard reagent and the ketone, by a mechanism which would now be considered a "four-centered" process. The



second of these proposals, advanced by Swain,⁶ conceived of the addition reaction as occurring as the result of an attack by a second Grignard entity upon a complex between the ketone and the Grignard reagent. The nature of the attack by a second Grignard entity was pictured^{6b} as in V.



The Meisenheimer mechanism (eq. 1), as written, requires that the addition reaction be second-order over-all whereas the mechanism of eq. 2, as written, requires that the addition reaction be second-order in Grignard reagent and third-order over-all.⁷

(1) This research was supported in part by a grant from the National Science Foundation.

(2) Based on theses submitted to Stanford University by (a) John A. Miller in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1960; and (b) George Gregoriou in partial fulfillment of the requirements for the M.S. degree, 1953.

(3) Presented in part before the Boston Meeting of the American Chemical Society, April, 1959.

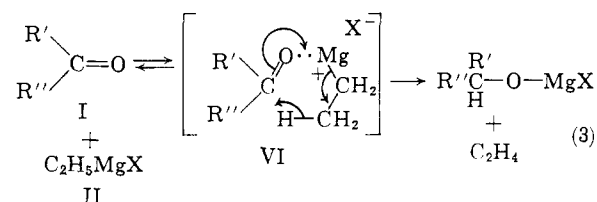
(4) Eastman Kodak Co. Fellowship holder, 1959-1960.

(5) See M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954.

(6) (a) C. G. Swain, *J. Am. Chem. Soc.*, **69**, 2306 (1947); (b) C. G. Swain and H. B. Boyles, *ibid.*, **73**, 870 (1951); (c) C. G. Swain and L. Kent, *ibid.*, **72**, 518 (1950).

(7) Gardner Swain in a personal communication has stated that he has not thought during the last ten years that reaction scheme 2 implied third-order kinetics. The third-order kinetics implicit in eq. 2

Evidence has been accumulated in these laboratories⁸ and elsewhere^{6,9} in support of the mechanism for the Grignard *reduction reaction* originally proposed by Whitmore: namely, rearrangement of a Werner complex between a ketone and a Grignard reagent *via* a six-centered transition state VI.



Since this mechanism for the reduction reaction, as written, requires that the reduction reaction be first-order in Grignard and first-order in ketone or second-order over-all, the assumption of the validity of this reduction mechanism would provide a means of substantiating one of these two mechanisms proposed for the addition reaction in any reaction where both addition and reduction products were produced concurrently. If the second-order Meisenheimer mechanism for addition (eq. 1) and the second-order Whitmore mechanism for reduction (eq. 3) were both correct, the ratio of the yields of addition and reduction products would be independent of the reactant concentrations in any reaction where both addition and reduction products were obtained whether the ketone or the Grignard reagent was in excess and whether the Grignard reagent was monomeric or associated. But if reduction and addition were reactions of different order, then the ratio of the yields of addition product to reduction product would be dependent upon the concentration of the Grignard reagent and ketone in these same reactions.

as written depends upon a free non-associated Grignard reagent. As will be shown, this assumption, at least for the Grignard reagent from ethyl bromide, under the conditions employed, is not valid. However, since the existence of association on the part of the Grignard reagent cannot be assumed *a priori*, it is necessary to allow this as a real possibility if only to prove it false. The crucial point of the Swain mechanism, "reaction of the Grignard-ketone complex with a second mole of Grignard reagent," in theory can be assumed to take place with a free monomeric Grignard entity or with dimeric or polymeric Grignard reagent within the ketone complex itself. These possibilities and how they fit the present experimental results will be considered in the Discussion section.

(8) E. P. Burrows, F. J. Welch and H. S. Mosher, *ibid.*, **82**, 880 (1960).

(9) G. E. Dunn and J. Warkentin, *Can. J. Chem.*, **34**, 75 (1956); E. T. McBee, O. R. Pierce and J. F. Higgins, *J. Am. Chem. Soc.*, **74**, 1736 (1952).

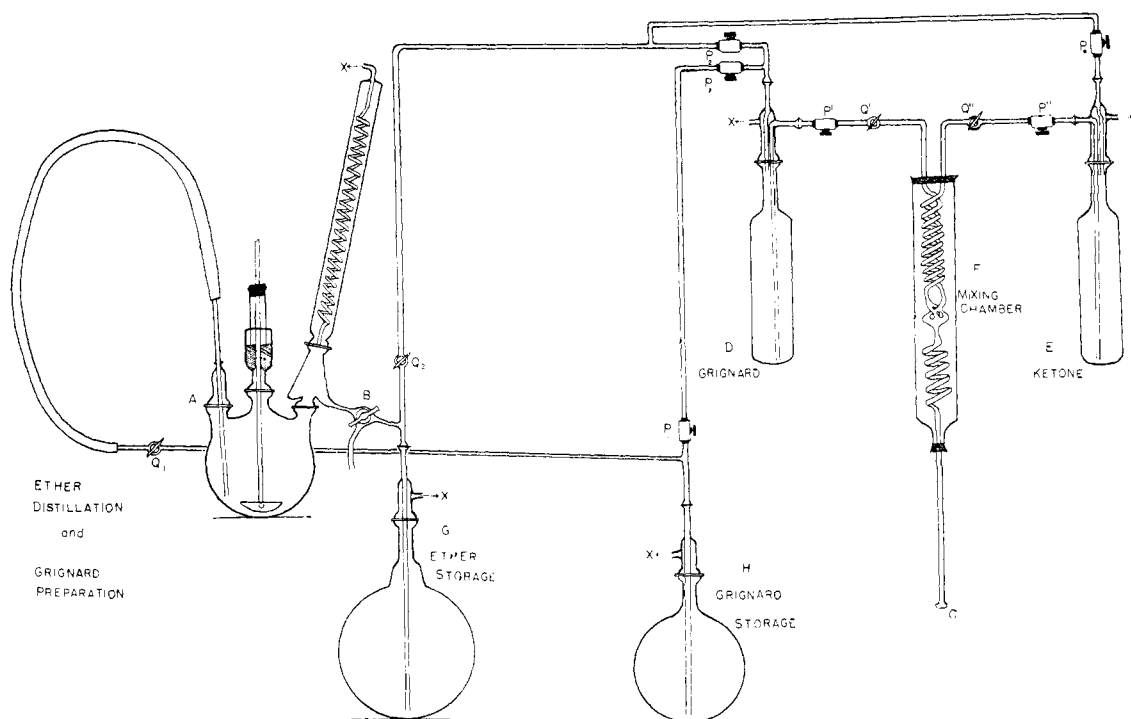


Fig. 1.—A, Probe for transfer of Grignard reagent through unplasticized polyethylene tubing; B, three-way stopcock to change from ether reflux to ether distillation; C, connection to interchangeable product receiver (not shown) which is protected from the atmosphere; D and E, demountable calibrated mixing flasks for reactant solutions which have a side arm (not shown) closed with a gum rubber ampule seal for removal of samples for analysis; F, water-jacketed mixing chamber with cooling coils; G and H, ether and Grignard storage flasks; P, Teflon needle valves; Q, non-lubricated Teflon-plug stopcocks; X, entry *via* two-way stopcock either to a higher pressure nitrogen manifold or to a lower pressure nitrogen exhaust manifold which is protected by a Gilman trap.

We therefore undertook a careful study of the dependence of the ratio of addition to reduction upon concentrations in order to determine whether or not the same kinetic description applied to both of these reactions.

Results

In this paper are reported the results from the study of the reaction between 3-methyl-2-butanone and the Grignard reagent from 2-bromopropane and the reaction between 2,4-dimethyl-3-pentanone and the Grignard reagent from bromoethane. The reactions were carried out under a positive nitrogen pressure in a closed, all-glass system with Teflon stopcocks, by bringing the reactants together in an efficient Venturi-type mixing device (Fig. 1). After hydrolysis with water, filtration and concentration of the filtrate by distillation of the solvent ether through an efficient column, the product mixtures were analyzed by gas chromatography.

The results from the reaction between 3-methyl-2-butanone and the Grignard reagent from 2-bromopropane are summarized in Table I. According to these data, the ratio of addition product to reduction product was approximately constant, within experimental error, at the selected ratio of about two equivalents of Grignard reagent to one of ketone. These results were not very precise and this reaction was not studied at widely differing concentration ratios because enolization and condensation were the major modes of reaction

and the analytical method was not capable of yielding significant results with the small relative concentrations of addition and reduction products observed.

The results from the reaction between 2,4-dimethyl-3-pentanone and the Grignard reagent from bromoethane are summarized in Table II. Since this reaction yielded only small amounts of enolization product and no condensation product, the results were more meaningful than the previous example studied. According to these results the ratio of addition to reduction was invariant with concentration and ratio of reactants *as long as the ketone was in sufficient excess*, but when the Grignard reagent was in excess the ratio of addition to reduction was a function only of the *ratio* of the reactions and not of their absolute concentrations. Thus although the same kinetic description does apply to both the addition and reduction reactions when ketone is in excess, the same kinetic description does not apply when Grignard is in excess.

Discussion

Assuming the correctness of the Whitmore mechanism for reduction (eq. 3) then the second-order Meisenheimer mechanism (eq. 1) is not capable of providing a rationalization for these experimental data since this mechanism would predict that the ratio of addition to reduction would be invariant with concentration change (which it was) and invariant with change in Grignard-ketone

TABLE I
YIELDS OF ADDITION AND REDUCTION PRODUCTS AND RATIO OF ADDITION TO REDUCTION IN THE REACTION OF 3-METHYL-2-BUTANONE WITH THE GRIGNARD REAGENT FROM 2-BROMOPROPANE

Grignard concn., ^a moles/ liter	Ratio of Grignard concn. to ketone concn. ^b	Yield, %		Ratio of addn. to redn.	Material bal- ance, ^c %
		Addition	Reduction		
0.18	2.2	6	19	3.1	85
.21	2.1	7	13	1.9	100
.50	2.0	5	9	1.8	88
.42	2.0	7	16	2.3	100
.16	2.0	8	19	2.4	100
.054	2.0	4	8	2.0	100
.048	2.0	3	6	2.0	100
.21	1.9	8	15	1.8	100
.35	1.8	6	18	3.0	58
.07	1.6	11	23	2.1	95

^a Concentration of the Grignard reagent based on the molecular formula RMgBr. ^b Ratio of the initial concentrations of the reactant solutions. In all cases, equal volumes of reactant solutions were mixed. ^c Percentage of limiting reagent (ketone) accounted for by the product analysis.

TABLE II
PRODUCT DISTRIBUTION AND RATIO OF ADDITION TO REDUCTION IN THE REACTION BETWEEN 2,4-DIMETHYL-3-PENTANONE AND THE GRIGNARD REAGENT FROM ETHYL BROMIDE

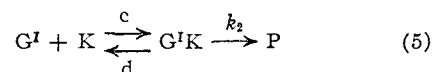
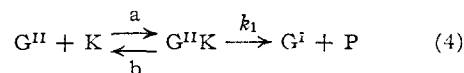
Ketone concn., mole/l.	Ratio of Grignard concn. ^a to ketone concn.	Yield, % ^b			Ratio of addn. to redn.
		Enoliza- tion	Reduc- tion	Addi- tion	
0.010	8	2	17	81	4.8
.031	4.2	3	22	75	3.3
.022	4.0	3	22	75	3.3
.046	2.1	3	29	67	2.3
.065	2.1	3	31	66	2.1
.13	2.1	4	32	64	2.0
.050	2.0	4	30	67	2.2
.15	1.9	4	31	65	2.1
.058	1.8	3	31	64	2.0
.098	0.71	16 ^c	34	50	1.5
.14	.56	16 ^c	35	49	1.5
.14	.50	16 ^c	36	48	1.3
.20	.50	16 ^c	33	51	1.6
.32	.50	16 ^c	34	50	1.5
.078	.41	16 ^c	37	47	1.3
.040	.35	16 ^c	32	52	1.6
.35	.32	16 ^c	35	49	1.4
.38	.28	16 ^c	37	47	1.3
.044	.27	16 ^c	32	52	1.6

^a Ratio of initial concentration of reactants. Grignard reagent concentration based on molecular formula of RMgBr. ^b Yield based on limiting reagent; equal volumes of reactant solutions mixed. Data have been corrected for presence of a small impurity of 3-hexanone in the 2,4-dimethyl-3-pentanone. ^c See ref 21.

(which it was not). Neither can the results be rationalized by an addition process which is second-order in Grignard reagent alone, *i.e.*, a process which proceeds according to eq. 2 as written with unassociated Grignard reagent since this mechanism would require that the ratio of addition to reduction would decrease with dilution at any ketone-Grignard ratio. But the attack of a second Grignard entity upon a Grignard-ketone complex need not be third order if the Grignard reagent were associated and the second

Grignard entity was part of the association complex. The present data are compatible with a mechanism for addition and reduction which involves consecutive reactions in each step of which all of the independent reactions (addition, reduction and enolization) have the same kinetic description. We shall now consider the consequences of an associated Grignard reagent upon the addition and reduction reactions.

If the assumptions are made that the Whitmore reduction mechanism is correct and that reaction between 2,4-dimethyl-3-pentanone and the Grignard reagent from bromoethane proceeds by consecutive steps, then it must be concluded that the Grignard reagent (or at least the most reactive form thereof) is present in solution in an associated state in order to rationalize the present data. Studies of the physical properties of Grignard reagent solutions have produced direct evidence in support of a dimeric Grignard reagent¹⁰ in the concentration ranges here employed. If it is assumed that the reactive form of the Grignard reagent is a dimer in the case at hand and that the addition and reduction reactions are second-order, then we may write the generalized reaction scheme



where G^{II} is a Grignard reagent with the molecular formula $R_2Mg_2X_2$, K is a ketone, G^I is a Grignard reagent with the molecular formula $RMgX$, formed uniquely by reaction 4 and is probably still coordinated to the magnesium alcoholate product P as represented in eq. 12 and 13. The cumulative rate constant for the first step reactions is k_1 , and k_2 is the cumulative rate constant for the second step reactions. For this reaction sequence, it can be shown that if the complexing reactions are rapid and reversible and that if a steady state exists for the complex concentrations, then

$$\frac{(G_0^{II}) - x}{G_0^{II}} = \left[1 + \frac{\theta y}{G_0^{II} - x} \right]^{-1/\theta} \quad (6)$$

where G^{II} is the initial concentration of the Grignard reagent (as a dimer), x is the amount of dimeric Grignard reagent consumed after a given time interval, y is the concentration of the intermediate Grignard reagent (G^I)¹¹ and θ is a rate constant parameter defined by

(10) (a) A. P. Terentiev, *Z. anorg. allgem. Chem.*, **156**, 73 (1926); (b) W. Slough and A. R. Ubbelohde, *J. Chem. Soc.*, 108 (1955); (c) R. E. Dessy, G. S. Handler, J. H. Wotiz and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 3476 (1957); (d) R. E. Dessy and G. S. Handler, *ibid.*, **80**, 5824 (1958); (e) R. E. Dessy and R. M. Jones, *J. Org. Chem.*, **24**, 1685 (1959); (f) S. J. Storer and E. I. Becker, Abstracts of Papers presented at 138th Meeting of the Am. Chem. Soc., New York, N. Y., Sept., 1960, p. 80-P.

(11) Complete derivation of this equation can be found in ref. 2a, pp. 101-103. Note that eq. 4 and 5 assume that enolization, reduction and addition, as first-step processes, all lead to the same specific form of intermediate Grignard reagent monomer (G^I) and that only complexes between Grignard reagent entities and ketone are effective in reaction. It is doubtful whether both of these conditions are realized in all cases, but the close correspondence between experimental data and the model presented in eq. 4 and 5 obviates any need of a discussion of those cases for which these assumptions may not be valid.

$$\theta = 1 - \frac{ck_2(b + k_1)}{ak_1(d + k_2)} \quad (7)$$

Although it is impossible to separate the variables in eq. 6, this equation may be used indirectly to confirm the existence of consecutive second-order kinetics in the reaction between 2,4-dimethyl-3-pentanone and the Grignard reagent from bromoethane. Table II shows that the product distribution in this reaction was constant in the region where ketone was in excess and that the product distribution apparently approached a limiting value in the region where Grignard reagent was in great excess. If the reaction was proceeding in two steps, then the limiting product distribution when Grignard reagent G^{II} was in large excess was the product distribution for the first step of the reaction (eq. 4) because the relatively small concentration of intermediate Grignard reagent G^I would not have been able to compete effectively with the abundance of unreacted dimeric Grignard reagent.¹² According to Table I, the limiting product distribution with excess Grignard reagent was 82% addition, 17% reduction and 1% enolization.

The product distribution in the second stage of the reaction (eq. 5) may be calculated from a combination of the first-stage product distribution and the product distribution when ketone is in large excess. This latter product distribution represents an equal contribution toward the total product distribution by each of the two steps of the reaction because all the Grignard reagent was completely consumed. Using the limiting product distribution in the region where Grignard is in excess and the product distribution when ketone was in excess (50% addition, 34% reduction and 16% enolization), the product distribution for the second step of the reaction (eq. 5) may be calculated as 18% addition, 51% reduction and 31% enolization.

The quantities x and y needed in eq. 6 may be calculated from these product distributions and from the data in Table II. Since x is the amount of dimeric Grignard reagent consumed (eq. 6), it is also the amount of ketone consumed in this same process. If w is the amount of ketone consumed in the second-step process (eq. 5), then

$$x + w = K \quad (8)$$

where K is the total amount of ketone consumed. The quantity y in eq. 6 is the difference between the amount of G^I produced and the amount consumed in the second-stage process, *i.e.*

$$y = x - w \quad (9)$$

If F is the observed percentage addition at any reactant concentration ratio where Grignard reagent is in excess, then

(12) The assumption here made is that during the course of the reaction the equilibrium $2G^I \rightleftharpoons G^{II}$ has no appreciable effect on the concentration of G^I . In other terms: the dimerization of the monomeric Grignard reagent, which is produced by the first stage reaction, is not fast compared to the addition and reduction reactions of the monomeric Grignard reagent consumed in the second stage of the reaction. In the present experiments where the rate of mixing of the reactant is in the order of 0.15 second this must be essentially so; otherwise the data could not be rationalized on the basis of consecutive bimolecular kinetics. However in the usual technique for the preparative Grignard reaction where carbonyl compound is added slowly to the Grignard reagent, this assumption may not hold

$$0.82 + 0.18w = FK \quad (10)$$

because the first and second stages of the reaction yielded 82 and 18% addition, respectively. Finally, by defining the initial concentration of the Grignard reagent (as a dimer) to be NK , eq. 8-10 may be combined to give

$$\frac{(G_0^{II}) - x}{(G_0^{II})} = \frac{(0.64N - F + 0.18)}{(0.64N)} \quad (11)$$

and

$$y/(G_0^{II}) - x = \frac{2F - 1}{0.64N - F + 0.18} \quad (12)$$

The left-hand side of eq. 6 may be calculated from the experimental data by the use of eq. 11. The right-hand side of eq. 6 may be calculated from the experimental data by the use of eq. 12 after a determination of the value of θ . From trial solutions of eq. 6 using the experimental data and eq. 11 and 12, the best value of θ was found to be $\theta = 0.5$. Using eq. 6, 11 and 12, this value of θ and the experimental data from Table II, the "observed" value $[(G_0^{II}) - x]/(G_0^{II})$ taken from eq. 11 was compared with the "calculated" value of this same quantity as obtained from eq. 6 and 12. The results of this comparison are shown in Table III.

TABLE III

OBSERVED AND CALCULATED VALUES OF $[(G_0^{II}) - x]/(G_0^{II})$ AT SEVERAL VALUES OF N

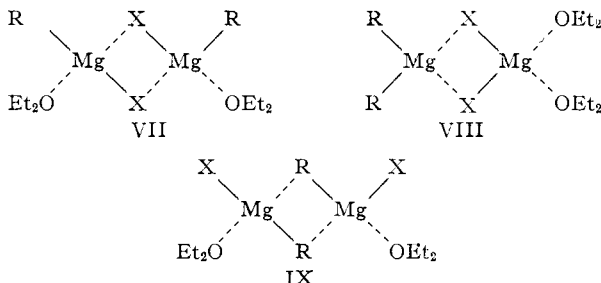
N	F	$y/[(G_0^{II}) - x]$	$[(G_0^{II}) - x]/(G_0^{II})$ Obsd.	$[(G_0^{II}) - x]/(G_0^{II})$ Calcd.
0.60	0.55	10	0.026	0.028
0.75	.60	3.3	.125	.154
1.00	.66	2.0	.250	.250
2.00	.75	0.705	.555	.550
3.00	.80	.461	.678	.662
4.00	.81	.321	.752	.747

According to Table III, the observed values for $[(G_0^{II}) - x]/(G_0^{II})$ are very close to the calculated values for this quantity. Trial solutions show that the discrepancies between the observed and calculated values represent no more than a 1% error in the determinations for percentage addition, an error which is well within the assumed experimental error of 3%. This analysis of our data is equally valid for several specific forms of the reagent $R_2Mg_2X_2$ either free or associated and these experiments cannot indicate the state of association of the $R_2Mg_2X_2$ entities. However, the simple assumption of an associated Grignard reagent of molecular formula $(RMgX)_n$ without the assumption of dimer entities is not capable of rationalizing our experimental results. On this basis it seems reasonable to assume that the reaction between 2,4-dimethyl-3-pentanone and the Grignard reagent from bromoethane was proceeding with consecutive, second-order kinetics. The existence of consecutive, second-order kinetics in turn indicates either that the Grignard reagent prepared from bromoethane was a dimer in solution or that the dimeric form of this Grignard reagent was much more reactive toward 2,4-dimethyl-3-pentanone than any other form which might have been present.

It is of special interest that Storfer and Becker^{10f} recently have proposed consecutive second-order kinetics to explain results obtained in a study of

Grignard reactions on nitriles and that a similar proposal has been made by Hamelin.¹³

Based on the assumption of a dimeric Grignard reagent ($R_2Mg_2X_2$), which is accommodated by our present studies and strongly supported by physical measurements,^{10a} the magnesium isotope studies of Dessy, *et al.*,^{10c,d,e} and the kinetic study of Aston and Bernhard,¹⁴ several structures, of which VII and VIII are examples, may be written for the reagent. These two are bonded through a halogen bridge. Other structures involving ether bridges



have not been considered likely in view of the relative complexing abilities of halogens and ether, and structures such as IX, bridged through the R group by some unspecified fashion,^{10b} have not been considered for lack of evidence. The kinetic evidence in the present study cannot distinguish between these alternatives. The Meisenheimer mechanism for addition and the Whitmore mechanism for reduction only require that a reactive alkyl group be attached to a magnesium atom which is capable of complexing with a carbonyl oxygen. Each of these structures satisfies this requirement. The simple second-order kinetics predicted by eq. 1 and 3, in which a monomeric Grignard reagent is considered, can be rewritten equally as well with the dimeric forms of the Grignard reagent such as VII, VIII and IX, but under this circumstance¹² the kinetics will become consecutive second order as actually observed. The present evidence is clearly incompatible with a monomeric Grignard reagent operating as indicated by eq. 1 and 3.

Although the present evidence cannot permit a choice between VII, VIII and IX, the findings of Dessy, *et al.*,^{10c,d,e} clearly indicate that there exist two distinct non-equilibrated types of magnesium in a Grignard solution. Only formula VIII fulfills this condition and the speculations concerning the mechanism for Grignard addition and reduction reactions on carbonyl compounds will be based upon this structure.¹⁵

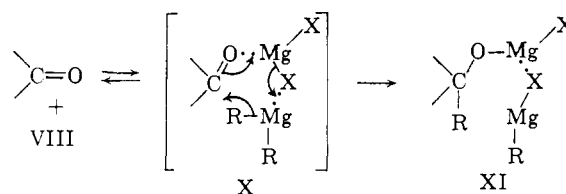
One may speculate that the first-stage addition reaction takes place by an attack of VIII on the ketone as shown in X.¹⁶

(13) R. Hamelin, Theses, Faculte des Science de l'Universite de Paris, February, 1961, p. 31.

(14) J. G. Aston and S. A. Bernhard, *Nature*, **165**, 485 (1950).

(15) Our present data might be explained by assuming a dialkylmagnesium uncomplexed with magnesium halide as the reactive species in a Grignard solution. The considerable differences observed in preliminary experiments between R_2Mg and $RMgX$ in parallel studies indicate, however, that this cannot be the case.

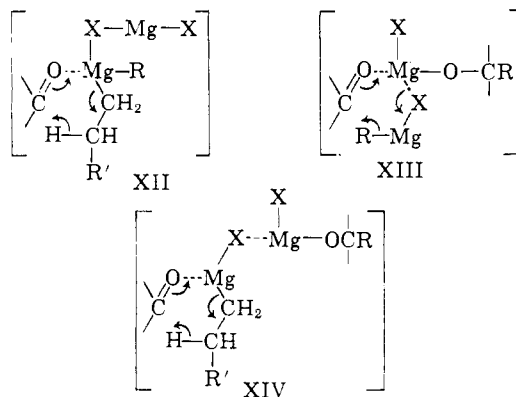
(16) In all subsequent formulas it will be assumed that the coordination number of four for magnesium at every stage will be made up by ether molecules which, however, for simplicity of representation, will not be shown.



This differs from eq. 2 only in defining more precisely, in terms of structure VIII for the Grignard reagent, the manner of attack of the second Grignard entity upon the carbonyl compound. If one of the halogen bridges in X becomes disrupted as the result of coordination with a carbonyl oxygen, the resulting complex will allow the alkyl group attached to the magnesium atom which is *not* complexed with the carbonyl oxygen to participate in a concerted mechanism for addition.

If the complex between ketone and VIII is with the other magnesium atom as shown in XII, then the β -hydrogen of the R group can assume a position for reduction of the carbonyl compound by hydrogen transfer. Thus the complex (in either structure X or XII) can account for addition or reduction by a six-centered concerted mechanism. As long as the Grignard reagent is in sufficient excess, the ratio of addition to reduction should be a property of the complex and thus independent of concentration as actually observed.

The second stage reaction (eq. 5) which is required by our findings when ketone is in excess requires the further reaction of XI with ketone to give both addition and reduction products. If this complexes with a ketone in this second-stage reaction to give a conformation which is set up for the transition state represented in XIII, then it will lead to further addition. But if the complex



in the second-stage reaction is between the carbonyl oxygen and the magnesium carrying the R group, then instead of XIII there will be formed XIV which is set up for the second-stage reduction reaction. The ratio of addition to reduction in the first stage (as represented by X and XII) will not be the same as the ratio for addition to reduction in the second stage as represented by XIII and XIV.

In the second stage of the reaction of the Grignard reagent with 2,4-dimethyl-3-pentanone it is calculated that there was only 18% addition. Because of this relatively small amount of addition,

the establishment of second-order kinetics for the second stage of the reaction is based primarily on reduction and enolization which constitute 82% of the reaction. It is therefore quite possible that the analytical technique was not sensitive to addition reaction taking place by kinetics other than second-order and thus the second-order nature of the second-stage addition reaction cannot be considered rigorously established.

This mechanism, represented by XI and XIII for addition and XII and XIV for reduction, is useful in rationalizing the results of Shine¹⁷ who found that in the reaction of a given ketone with a series of Grignard reagents differing only in halogen, the amount of addition was directly dependent upon the size of the halogen atom. Since the halogen atom is directly involved in the transition states for addition (XI and XIII) the size of the halogen would have an effect upon the closeness of approach of the adding alkyl group to the carbonyl carbon and hence would have an effect upon the stability of the transition state.

Further tests of these ideas are being carried out by a similar study using the dialkylmagnesium reagents.

Experimental

Materials.—The alkyl halides used in the Grignard reagent preparations were freshly distilled through an efficient column and checked for homogeneity by gas chromatography. The magnesium was either Baker and Adamson magnesium turnings or magnesium turnings from triply sublimed magnesium of high purity¹⁸; these two grades of magnesium were used interchangeably and gave the same results.

The 3-methyl-2-butanone was commercial material which had been distilled through an efficient column and the homogeneity of the product fraction was verified by gas chromatography. The 2,4-dimethyl-3-pentanone was prepared by oxidation of 3,4-dimethyl-3-pentanol with chromium trioxide in acetic acid.¹⁹ The crude product was isolated by steam distillation after the reaction mixture had been neutralized with sodium hydroxide. Although the fractionated 2,4-dimethyl-3-pentanone obtained from the crude product was apparently homogeneous by gas chromatography, a consistent spurious product from the reaction with the Grignard reagent from bromoethane gave evidence of an impurity. Subsequent experiments showed that the 2,4-dimethyl-3-pentanone contained *ca.* 5% 3-hexanone which evidently arose from a 3-hexanol impurity in the 2,4-dimethyl-3-pentanol. Although the 3-hexanone reacted with Grignard reagents much faster than did the 2,4-dimethyl-3-pentanone, the presence of this impurity had no effect on the distribution of the products from the reaction between 2,4-dimethyl-3-pentanone and the Grignard reagent from bromoethane.²⁰ Both ketones were stored over alumina after distillation.

The ether used in the Grignard reagent preparations was Mallinckrodt anhydrous diethyl ether which was transferred from the container by a nitrogen pressure siphon.

(17) H. J. Shine, *J. Chem. Soc.*, 8 (1951).

(18) We wish to thank the Dow Chemical Co. for this magnesium which was reported in parts per million to have: Al, 1; Cu, < 1; Fe, < 4; Ni, < 4; Pb, < 10; Si, < 10; Sn, < 10; Zn, < 100; Ba, < 1; Ca, < 18; K, < 5; Na, < 6; Sr, < 1.

(19) C. C. Price and J. V. Karabinos, *J. Am. Chem. Soc.*, **62**, 1159 (1940).

(20) The data shown in Table II have been corrected for the presence of the 3-hexanone in the 2,4-dimethyl-3-pentanone by neglecting the 3-ethyl-3-hexanol product which was actually obtained.

The ether for the dilution of Grignard reagents and ketones was Mallinckrodt anhydrous diethyl ether which had been distilled under nitrogen from Grignard reagent and stored under nitrogen. The nitrogen was Matheson Co. high purity oil-pumped nitrogen and was used directly from the tank without further purification.

The Grignard reagents were prepared, transferred, stored and used within 40 hours, in an all-glass apparatus with Teflon stopcocks under an atmosphere of nitrogen in the apparatus shown in Fig. 1. They were prepared to a nominal concentration of 0.75 *N*. For use in a reaction, they were transferred within the system to a calibrated vessel and diluted with purified ether. The concentrations of the solutions thus obtained were determined by withdrawing an aliquot with a syringe, adding standard hydrochloric acid solution and then titrating to the phenolphthalein end-point with a standard solution of sodium hydroxide.²¹ The ketone reactant solutions were prepared by pipetting a known volume of ketone under nitrogen into a calibrated vessel and diluting with purified ether.

After the reactant solutions were thoroughly mixed, they were forced through an efficient mixing device²² and collected in a receiving flask protected from the atmosphere. The mixing chamber was water-jacketed with cooling coils above and below and the reactions were carried out at the ambient water temperature of 21–23°. Since the Grignard preparation flask, the Grignard storage flask, the ether distillation and storage flasks, the reactant preparation vessels, the mixing device and the product receiving flasks were all part of the same system, it was possible to carry out all of the experimental operations in the absence of air.

After standing for 24 hours, the product mixtures were hydrolyzed by the addition of water.²³ The magnesium salts were removed by filtration and the filtrate then was concentrated by careful distillation of the ether through an efficient column (18 theoretical plates). The distillation residues then were subjected to gas chromatography and the analyses were effected by comparing the component areas with those obtained from reference solutions of similar, known composition.²⁴

(21) Although every effort was exerted to exclude air from the system, the experimental operations inevitably resulted in trace contamination of the Grignard reagent by basic magnesium salts other than Grignard reagent. The method used for the determination of the concentration of the Grignard reagent, therefore, would give analyses which were somewhat high to the extent that such basic salts were present. Since the amount of enolization with ketone in excess was determined by taking the differences between the amount of Grignard reagent employed and the amount actually consumed in the formation of addition and reduction products, the presence of basic magnesium salts in the Grignard reagent led to apparent yields of enolization product which were slightly high. A low yield of 16% enolization was obtained consistently, however, under the best conditions and it was felt justified to correct the experimental data where ketone was in excess with yields of enolization product larger than this value to this value of 16%. The data in Table II have been so corrected. It was demonstrated experimentally by collection of ethane from the reaction that the apparent high yields of enolization product with ketone in excess were not due to unreacted Grignard reagent.

(22) The mixing device had a Venturi-type mixing chamber of *ca.* 1 ml. volume. On the assumption that the reactant solutions were thoroughly mixed before exit from the mixing chamber, the normal mixing time was *ca.* 0.15 sec. In a rough determination, the half-life of the reaction between 3-methyl-2-butanone and the Grignard reagent from bromoethane was found to be *ca.* 0.8 sec. On the basis of an assumed longer half-life for the reaction of this Grignard reagent with 2,4-dimethyl-3-pentanone, because of increased hindrance at the carbonyl carbon, it appears safe to assume that this mixing device resulted in mixing times which were small compared to the half-lives of the reactions.

(23) B. F. Landrum and C. T. Lester, *J. Am. Chem. Soc.*, **76**, 5797 (1954).

(24) The reagents for the analytical reference solutions were either prepared by synthesis or were collected from the product mixtures by gas chromatography. Special attention was directed toward obtaining pure materials for use in the analytical reference solutions.