Grignard Reagents.
Compositions and Mechanisms of Reaction

By E. C. Ashby
SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY,
ATLANTA, GEORGIA, 30332, U.S.A.

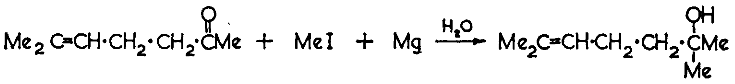
1 Introduction

Without doubt one of the most fascinating and fundamental problems in organic chemistry today concerns the composition of Grignard reagents in ether as solvent. A different, but closely related, problem involves the mechanism or mechanisms by which these Grignard reagents react with organic functional compounds, such as ketones, nitriles, etc. The solution to the second problem can only be forthcoming when the solution to the first problem is in hand. The importance and basic nature of these problems are well recognised, yet there has been no full scale assault for any length of time by anyone to bring about a complete solution. Many workers have become interested in the composition problem from time to time, but efforts have been somewhat sporadic and no real progress has appeared until recently.

In retrospect, it appears almost inconceivable that such a fundamental problem could have remained in so confused a state for so long, while much more seemingly complex problems were being solved every day. For example, the structures and absolute configurations of cholesterol and chlorophyll are known and yet organic chemists do not know the composition in solution of a class of compounds that bears the simple empirical formula RMgX. Part of the problem seems to be that it takes an organic chemist to recognise the importance of this problem, a physical chemist to make the type of measurements which could be informative in what has become a complex physical-chemical problem, and an organometallic chemist with the background and experience to handle studies involving such sensitive organometallic compounds. Each person, having faced the Grignard problem, soon recognises his weakness in at least one of the above areas, and is discouraged to make more than a token contribution in what has turned out to be a very elusive and complex problem. Another problem seems to have been that many of the contributions that have been made were a result of preconceived notions and hence the conclusions were not always justified by the results. As a result, workers entering this area become quickly confused because of so many conflicting conclusions presented by so many different contributors. Only if one studies the approximately 300 contributions in this area over and over again until all the conflicting facts are well recognised can one then decide what to believe and what might be poor work that should be repeated. If one is not hopelessly discouraged by such a large mass of data which does not appear to prove much of anything, then one can begin to try to decide first just what is the problem and secondly what is the best thing to do to solve it.

2 Composition of Grignard Compounds

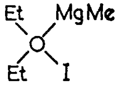
A. Early History.—In order to appreciate this problem fully one should go back to the very beginning of this story—the year 1900. Grignard, then a graduate student, was working in the laboratory of Professor Barbier at the University of Lyon in France. His problem was to optimise conditions for what is known today as the Barbier reaction. The specific system involved is shown in (1).



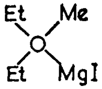
$$Me_2C{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{\overset{O}{\|}}{C}Me + MeI + Mg \xrightarrow{H_2O} Me_2C{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}\underset{Me}{\overset{OH}{C}}Me \quad (1)$$

Grignard thought the intermediate in this reaction to be RMgX and thus concluded that yields might be improved by preparing this compound first and then adding it to the ketone. He found that alkyl halides do react readily with magnesium in ether as solvent and that the resulting reaction mixture reacts with aldehydes and ketones in higher yields than when the Barbier procedure is used to produce the corresponding addition product.[1] Grignard represented the composition of the reaction product of an alkyl halide and magnesium in ether as RMgX and represented the reaction of this reagent with ketones as a simple addition reaction. For Grignard's great discovery and subsequent development of this finding, he was awarded the Nobel prize in Chemistry in 1912.

The first serious suggestion since Grignard's initial one concerning the composition of Grignard compounds in ether solution was made by Baeyer and Villiger.[2] These workers suggested representing Grignard compounds in ether solution as an onium compound. The structure suggested for methylmagnesium iodide is shown in (I).



(I)



(II)

This suggestion was followed by a similar one from Grignard[3] depicting the onium compound differently as (II).

Although Standnikov[4] appeared to have evidence to support Grignard's suggestion, it was later proved by both Gorskij[5], and Chelintzev and Pavlov[6] that the evidence presented was not unequivocal. Shortly thereafter Thorp and

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[1] V. Grignard, *Compt. rend.*, 1900, **130**, 1322.
[2] A. Baeyer and V. Villiger, *Ber.*, 1902, **35**, 1201.
[3] V. Grignard, *Compt. rend.*, 1903, **136**, 1260.
[4] G. L. Standnikov, *J. Russ. Phys.-Chem. Soc.*, 1911, **43**, 1235.
[5] A. I. Gorksij, *J. Russ. Phys.-Chem. Soc.*, 1912, **44**, 581.
[6] V. V. Chelintzev and B. V. Pavlov, *J. Russ. Phys.-Chem. Soc.*, 1913, **45**, 289.

Kamm[7] demonstrated conclusively that Grignard compounds could not be represented by the onium structure. They did this by demonstrating that the products of reactions (2) and (3) are not identical. While the onium com-

$$Et_2O + PhBr + Mg \xrightarrow{H_2O} C_6H_6\ (60\%) \tag{2}$$

$$EtOPh + EtBr + Mg \xrightarrow{H_2O} C_2H_6\ (99{\cdot}7\%) \tag{3}$$

position was being debated, Abegg[8] in 1905 suggested a polar composition for the Grignard reagent ($R^-[MgX]^+$) and even suggested the possibility of an equilibrium (4) to describe the system.

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \tag{4}$$

Jolibois[9] in 1912 was the first to suggest what is referred to as the unsymmetrical dimeric structure ($R_2Mg{\cdot}MgX_2$) to represent Grignard compounds in ether solution. This suggestion was based on the facts that (1) Grignard compounds in ether were believed to be dimeric, (2) Et_2Mg and MgI_2 in ether had the same physical properties as a solution prepared from C_2H_5I and Mg, and (3) electrolysis of EtMgI under certain conditions deposited magnesium at the cathode without evolution of gas. In rebuttal, Grignard[10] suggested that the observations of Jolibois could just as easily be explained by a symmetrical dimeric $(RMgX)_2$ composition. Thus the controversy began concerning the description of Grignard compounds by the symmetrical or unsymmetrical dimeric structure.[11]

Although Grignard[10] and Terentiev[12] reported dimeric association for methylmagnesium iodide, Meisenheimer and Schlichenmaier[13] later showed that over a wide concentration range the molecular association of this compound varies with the concentration. This information was partly the reason for a sudden surge of interest in explaining the composition of Grignard compounds by what is known today as the Schlenk equilibrium. Schlenk and Schlenk[14] found that essentially all of the halogen as MgX_2 could be removed from certain Grignard compounds in ether solutions by the addition of dioxan. Based on this information and the new association data, they suggested the equilibria (5) and (6) to explain the composition of Grignard reagents.

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \tag{5}$$

$$R_2Mg + MgX_2 \rightleftharpoons R_2Mg{\cdot}MgX_2 \tag{6}$$

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[7] L. Thorp and O. Kamm, *J. Amer. Chem. Soc.*, 1914, **36**, 1022.

[8] R. Abegg, *Ber.*, 1905, **38**, 4112.

[9] P. Jolibois, *Compt. rend.*, 1912, **155**, 353.

[10] T. Zerevitinov, *Ber.*, 1908, **41**, 2244.

[11] M. S. Kharasch and Otto Reinmuth, 'Grignard Reactions of Nonmetallic Substances', Prentice-Hall, Inc., New York, 1954, p. 103.

[12] A. Terentiev, *Z. anorg. Chem.*, 1926, **156**, 73.

[13] J. Meisenheimer and W. Schlichenmaier, *Ber.*, 1928, **61**, *B*, 720.

[14] W. Schlenk and W. Schlenk, jun., *Ber.*, 1929, **62**, *B*, 920.

Assuming that the equilibrium composition of (5) could be determined by the precipitation of the MgX_2 from the mixture by dioxan, Schlenk[15] used this method to determine equilibrium values for several Grignard compounds. Further determinations of equilibrium compositions by the same method were reported by several other workers.[16,17] A few years later in 1937 Noller and White[18] cast doubt on the validity of this method to determine equilibrium compositions by showing that the amount of MgX_2 precipitated as the bis-dioxan complex is a function of time. In 1950 Kullman[19] confirmed the original findings of Noller and White that the amount of MgX_2 precipitated was a function of time and thus, if an equilibrium did exist, it was being shifted. For example, Kullman showed that on treating ethylmagnesium bromide with dioxan, 55, 70, or 93% of the total $MgBr_2$ was precipitated depending on the mode of addition and the length of time the mixture was stirred.

An argument was presented by Aston and Bernhard[20] in an attempt to show that methylmagnesium iodide in dibutyl ether contains no dimethylmagnesium. Their evidence was based on the difference in relative rates and heats of reaction of solutions of methylmagnesium iodide and dimethylmagnesium with acetone and ethyl acetate. Further support included a comparison of the pyrophoric nature of a solution of methylmagnesium iodide and dimethylmagnesium. Clearly this conclusion was based on the lack of interaction between $(CH_3)_2Mg$ and MgI_2 or else the comparisons were not valid. Dialkylmagnesium compounds are now known to react rapidly with magnesium halide so that one cannot validly compare these compounds on the bases cited.

Because of the limited solubility of $MgCl_2$ in diethyl ether (*ca.* 1×10^{-3}M) a lack of precipitation of $MgCl_2$ from alkylmagnesium chlorides was cited as an indication of the Schlenk equilibrium (5) lying predominantly to the left.[21] Once again these conclusions are of questionable validity on the basis that it is now known that alkylmagnesium chlorides are dimeric even at low concentration, thus lack of precipitation of $MgCl_2$ is inconclusive. Many other reports could be cited, attempting to prove that there is or is not a Schlenk equilibrium or that the Schlenk equilibrium (5) lies to the right or left. They fall in the category of the above cited cases, namely, the conclusions are not valid either on the basis of information known at the time or more recently. In order to simplify further discussion, only those contributions which were once thought to be very important will be considered.

B. Ionic Nature.—There exists considerable evidence concerning the electrolytic nature of Grignard compounds in ether solution. Jolibois[9] was the first to report

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[15] W. Schlenk, *Ber.*, 1931, **64**, *B*, 734.
[16] A. C. Cope, *J. Amer. Chem. Soc.*, 1934, **56**, 1578; C. R. Noller and F. B. Hilmer, *ibid.*, 1932, **54**, 2503.
[17] P. D. Bartlett and C. M. Berry, *J. Amer. Chem. Soc.*, 1934, **56**, 2683.
[18] C. R. Noller and W. R. White, *J. Amer. Chem. Soc.*, 1937, **59**, 1354.
[19] R. Kullman, *Compt. rend.*, 1950, **231**, 866.
[20] J. G. Aston and S. A. Bernhard, *Nature*, 1950, **165**, 485.
[21] C. R. Noller and D. C. Raney, *J. Amer. Chem. Soc.*, 1940, **62**, 1749.

that Grignard compounds in ether are electrically conducting. This fact has been confirmed by several other research groups[22] and a great deal of information has been acquired through such experimentation. Both Evans and Pearson,[23] and Zeil,[24] from conductance measurements, have pictured the ionisation of Grignard compounds in ether solution as producing large, mobile, highly associated anions and small relatively immobile, ether co-ordinated cations. Décombe and Duval[25] had suggested earlier from much less information that phenylmagnesium bromide be represented by the ionic composition represented by (III). These workers suggested that if the composition below is correct, the

$$Mg^{++}[Ph_2MgBr_2(Et_2O)_2]^{2-} \qquad \text{(III)}$$

anionic magnesium should be replaceable by a less reactive metal such as zinc. Reaction of methyl iodide and magnesium–zinc alloy in diethyl ether produced what was thought to be $Mg^{++}[Me_2ZnI_2(Et_2O)_2]^{2-}$. Elemental analyses were consistent with the above formula; however, more important were the observations that (1) hydrolysis of the product produced methane, zinc iodide, and magnesium hydroxide and (2) electrolysis produced magnesium at the cathode and zinc at the anode. Although not conclusive, the evidence is consistent with the suggestion, and an earlier one by Evans and Lee,[26] that the products of electrolysis of ethylmagnesium bromide can be represented by equation (7).

$$Et_2Mg{\cdot}MgBr_2 \rightleftharpoons Mg^{++} + [Et_2MgBr_2]^{2-} \qquad (7)$$

Since the initial flurry of conductance and electrolysis experiments in the 1930's, little has been done along these lines. Dessy and Jones[27] confirmed the most important finding initially reported by Evans and Lee that in the electrolysis of n-butylmagnesium bromide, magnesium-containing species migrate to both the anode and the cathode. Although the number of possible ionic species described by all the contributors in this area are numerous, it appears that the most prevalent simple species in solution are RMg^+ and $RMgX_2^-$.

The work of Evans and Lee which shows an increase in conductivity with concentration, at concentrations greater than 0·5 M, indicates that the system is past the conductivity minimum. Thus it appears that in the higher concentration ranges studied (→0·5 M), one is dealing with ion-pair formation. Applying the Harned and Owen symbolism to this system: (1) RMg^+ and X^- would be single ions, (2) RMgX would be an ion pair, (3) $RMgX_2^-$ and $(RMg)_2X^+$ would be ion triplets, (4) $(RMgX)_2$ would be a quadruple ion and so on. RMgX and $(RMgX)_2$ should have zero conductance and hence could be in large concentration. The concentration of the ionic species (1 and 3) cannot be very great

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[22] J. M. Nelson and W. V. Evans, *J. Amer. Chem. Soc.*, 1917, **39**, 82; F. Kondyrew, *Ber.*, 1925, **58**, *B*, 459; L. W. Gaddum and H. E. French, *J. Amer. Chem. Soc.*, 1927, **49**, 1295.

[23] W. V. Evans and R. Pearson, *J. Amer. Chem. Soc.*, 1942, **64**, 2865.

[24] W. Zeil, *Z. Elektrochem.*, 1952, **56**, 789.

[25] J. Décombe and C. Duval, *Compt. rend.*, 1938, **206**, 1024.

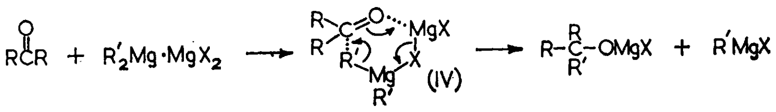
[26] W. V. Evans and F. H. Lee, *J. Amer. Chem. Soc.*, 1933, **55**, 1474.

[27] R. E. Dessy and R. M. Jones, *J. Org. Chem.*, 1959, **24**, 1685.

owing to the low conductances reported for Grignard compounds in ether solution.[27] Since high ionic mobilities would be expected in a medium of low viscosity such as diethyl ether, high conductances would be expected if dissociation into ions were extensive. Therefore ionic species of the type suggested are probably present only to a small extent in solution. Although these species may not be important in describing the composition of Grignard compounds owing to their low concentration, they could be important in describing the mechanism of Grignard reactions since reaction rate is not only a function of concentration, but of reactivity of the various species in solution.

C. Recent Work.—From the late 1930's to the late 1950's little was done to relieve the confusion concerning the nature of the composition of Grignard compounds in diethyl ether. Some workers used the RMgX formulation to represent Grignard compounds, some used the $R_2Mg{\cdot}MgX_2$ formulation, some gave up the solution to the problem as hopeless. It was not until 1957 that Dessy and his co-workers[28] presented the first convincing evidence permitting a clear-cut choice between the RMgX and $R_2Mg{\cdot}MgX_2$ formulations. These workers found no exchange between $^{28}MgBr_2$ and Et_2Mg and presented evidence that an equimolar mixture of $MgBr_2$ and Et_2Mg has the same characteristics as the Grignard reagent prepared from ethyl bromide and magnesium. Thus it was concluded (1) that alkyl exchange does not take place in ether solution, (2) the RMgX species does not exist in solution and therefore Grignard compounds are best represented by the structure first suggested by Jolibois, namely $R_2Mg{\cdot}MgX_2$.

Owing to the work of Dessy and his co-workers, the representation of Grignard compounds by the $R_2Mg{\cdot}MgX_2$ formulation was widely accepted. Thus Mosher,[29] Becker,[30] and their co-workers and others postulated that the reaction of Grignard compounds with ketones involves a six-centre transition state (IV) in which the Grignard compound is represented by the unsymmetrical dimer.



Although there has been much difficulty in rationalising all of the kinetic data in terms of reaction order and reaction mechanism with respect to an attacking dimeric species, certainly the mechanism presented was the most logical at the time and well accepted.

In spite of all the experiments to determine the nature of Grignard compounds in ether solution, none appeared significant beside the isotopic labelling experiments. Several additional contributions by Dessy[31] and his co-workers after 1957 only served to support the equivalency of a mixture of diethylmagnesium–

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[28] R. E. Dessy, G. S. Handler, J. H. Wotiz, and C. A. Hollingsworth, *J. Amer. Chem. Soc.* 1957, **79**, 3476.

[29] J. Miller, H. S. Mosher, G. Grigorian, *J. Amer. Chem. Soc.*, 1961, **83**, 3966.

[30] W. M. Bikales and E. I. Becker, *Canad. J. Chem.*, 1962, **41**, 1329.

[31] R. E. Dessy, *J. Org. Chem.*, 1960, **25**, 2260.

magnesium bromide and the Grignard compound prepared from ethyl bromide and magnesium. Attempts by J. D. Roberts and his co-workers[32,33,34] to verify the conclusions of Dessy and his co-workers by examination by nuclear magnetic resonance (n.m.r.) of Grignard solutions and mixtures of R_2Mg and MgX_2 were not fruitful. However, Kirrmann, Hamelin, and Hayes,[35] by crystallisation studies involving several Grignard compounds, showed that the crystalline fractions always contained more MgX_2 than R_2Mg. Unable to isolate RMgX, they concluded that the Grignard composition is expressed best by a mixture of R_2Mg and MgX_2 and associated forms.

D. $R_2Mg{\cdot}MgX_2$ Composition Questioned.—The composition of Grignard compounds represented by the unsymmetrical dimer $R_2Mg{\cdot}MgX_2$, although accepted for several years, was first questioned by Ashby in 1961 and again in 1963 on the basis of evidence establishing the existence of RMgX species in tetrahydrofuran solution.[36,37,38] It was shown that in tetrahydrofuran alkyl exchange in Grignard compounds does take place and that the species RMgX does indeed exist in solution. These conclusions were based on three observations. (1) Grignard compounds are monomeric in tetrahydrofuran over a wide concentration range, (2) crystallisation of Grignard compounds produced the compounds of stoicheiometry RMg_2X_3 and MgR_2 in essentially quantitative yield, and (3) in tetrahydrofuran $EtMg_2Cl_3$ is soluble and its molecular association was determined to be 0·62. (Molecular association = observed molecular weight $\div$ formula weight = *i*.) Since the specific conductance of ethylmagnesium chloride in tetrahydrofuran was shown to be very small, the association factor 0·62 indicates extensive dissociation of $EtMg_2Cl_3$ into two species in tetrahydrofuran according to (8). Thus the presence of EtMgCl, Et_2Mg, and $MgCl_2$

$$EtMg_2Cl_3 \longrightarrow EtMgCl + MgCl_2 \qquad (8)$$

in tetrahydrofuran was demonstrated, leading to the conclusion that ethylmagnesium chloride in tetrahydrofuran is best described by the formulations first reported by Schlenk,[15] namely (9). The concentration of RMgX was

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \qquad (9)$$

suggested to be significant on the basis that $MgCl_2$ is soluble in tetrahydrofuran

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[32] M. S. Silver, P. R. Shafer, J. Eric Nordlander, C. Ruchardt, and John D. Roberts, *J. Amer. Chem. Soc.*, 1960, **82**, 2646.

[33] G. M. Whitesides, F. Kaplan, K. Nagarajan, and John D. Roberts, *Proc. Nat. Acad. Sci.*, 1962, **48**, No. 7, 1112.

[34] G. M. Whitesides, F. Kaplan, and John D. Roberts, *J. Amer. Chem. Soc.*, 1963, **85**, 2167.

[35] A. Kirrmann, R. Hamelin, and S. Hayes, *Bull. Soc. Chim. France*, 1963, 1395.

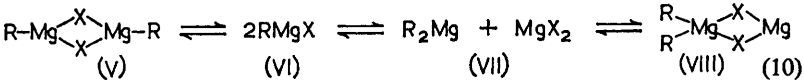
[36] Discussion of paper presented by R. E. Dessy, Organometallic Symposium, Vancouver, British Columbia, 1961.

[37] Panel discussion concerning Grignard Compound Composition, H. S. Mosher, E. I. Becker, A. Frey, and E. C. Ashby, 1st International Organometallic Symposium, Cincinnati, Ohio, 1963.

[38] E. C. Ashby and W. E. Becker. *J. Amer. Chem. Soc.*, 1963, **85**, 118.

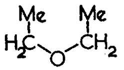
only up to 0·5M, whereas a 2·0M solution of ethylmagnesium chloride in tetrahydrofuran deposited no precipitate after 3 months.

It was also reported[33] that a study of the molecular association of ethylmagnesium chloride in diethyl ether over a concentration range indicated associated species in solution. This fact complicated the simple equilibrium suggested for Grignard compounds in tetrahydrofuran, in that, in diethyl ether solution, dimeric species would have to be included.

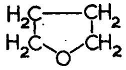


(10)

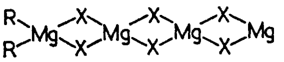
The equilibrium (10) was suggested on the grounds that the difference between tetrahydrofuran and diethyl ether is one of degree rather than of kind and one would only expect to find a difference in the association reflected by the difference in basicity of the two solvents. The structures for diethyl ether (IX) and tetrahydrofuran (X) are drawn only to focus attention on the structural similarity of the two compounds. Isolation of RMg_2X_3 compounds from diethyl ether solution was also reported, but these compounds would not redissolve in diethyl ether and therefore their molecular association could not be studied. For this reason the possibility of these compounds being represented by structure (XI) does exist, although structure (XII) would appear more reasonable.



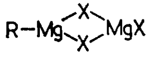
(IX)



(X)



(XI)



(XII)

Although the existence of RMgX species had been demonstrated in tetrahydrofuran, it was not until later that evidence became available to indicate that such was also the case in diethyl ether. Almost simultaneously, two laboratories[37,39,40] reported that ethylmagnesium bromide in diethyl ether is monomeric at low concentration (<0·1M). Vreugdenhill and Blomberg[39] with unusual care determined the molecular association of ethylmagnesium bromide, diethylmagnesium, magnesium bromide, and a mixture of diethylmagnesium and magnesium bromide as 1·00 ± 0·02, 1·00 ± 0·02, 1·13 ± 0·04 and 1·05—1·06 respectively. They concluded from these measurements that at low concentrations there esists no equilibrium of the type represented by (11). The results of

$$Et_2Mg + MgBr_2 \rightleftharpoons Et_2Mg{\cdot}MgBr_2 \qquad (11)$$

Ashby and Smith[37,40] showed clearly that in diethyl ether organomagnesium bromides and iodides are monomeric at low concentrations (*ca.* 0·05M) and associate only at higher concentrations whereas organomagnesium chlorides are associated even at low concentration.

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[39] A. D. Vreugdenhill and C. Blomberg, *Rec. Trav. chim.*, 1963, **82**, 453.

[40] E. C. Ashby and W. B. Smith, *J. Amer. Chem. Soc.*, 1964, **86**, 4363.

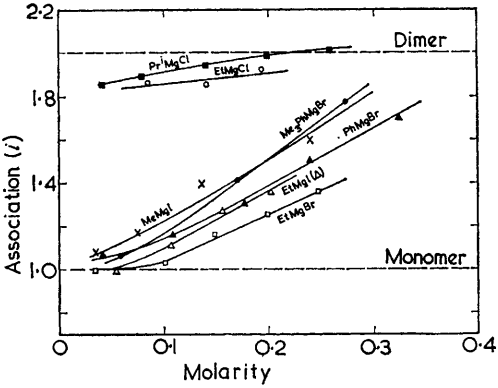
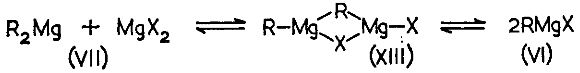


Fig. 1 *Association of Grignard compounds in diethyl ether.*

The difference between chlorides and bromides–iodides can be explained easily in terms of inductive and steric effects. These results establish without question that in diethyl ether the composition $R_2Mg{\cdot}MgX_2$ is not adequate to describe Grignard compounds. Since Grignard compounds are normally employed in solution between 0·1 and 0·5M concentration, it appears that one must consider reaction of both monomeric and associated species at these concentrations. The conclusion drawn from this work was that the composition of Grignard compounds in diethyl ether should be represented by a monomer–dimer equilibrium (2 M $\rightleftharpoons$ D) and more specifically could be expressed by the equilibria (10) although no concrete evidence for the existence of the RMgX species was presented.

The reaction between R_2Mg and MgX_2 to form 2RMgX was suggested[40] to proceed *via* a mixed alkyl–halogen bridge intermediate (XIII) as in (12). This is



(12)

not unreasonable since alkyl-bridged compounds are well known in the chemistry of related aluminium compounds. The species (XIII) would not be expected to have more than a transitory existence since dimeric structures containing halogen atoms in both bridging positions should be thermodynamically favoured.

E. Consequence of Association Data.—The knowledge of how the degree of association of Grignard compounds in diethyl ether depends on concentration has turned out to be very important. This information has been used[40] to overcome evidence that was thought to argue against the presence of RMgX species in diethyl ether solution. For example, Evans and Maher,[41] on the basis of n.m.r. studies of Me_2Mg and 'MeMgI' in ether, suggested that the complex $Me_2Mg{\cdot}MgI_2$, a dimeric species, is stable in highly dilute solution. (The quota-

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[41] D. F. Evans and J. P. Maher, *J. Chem. Soc.*, 1962, 5125.

tion marks, as in 'RMgX', are used not to indicate the RMgX species, but merely the Grignard compounds formed from RX and Mg.) The molecular weight studies (Figure 1), however, indicate that 'MeMgI' is essentially monomeric at the concentration of the measurements (0·06M). Since, according to Evans and Maher, Me_2Mg and MgI_2 interact, the product of this interaction must be MeMgI. The τ-values reported by Evans and Maher for dimethylmagnesium in diethyl ether show an appreciable concentration-dependence, whereas the concentration-dependence for methylmagnesium iodide is very small over a considerable concentration range. These authors attributed this difference to the dissociation of polymeric dimethylmagnesium species on dilution. This appears unlikely since diethylmagnesium is monomeric at this concentration.[39] It appears that these data support the conclusion that 'MeMgI' does not contain an appreciable amount of Me_2Mg rather than the opposite conclusion drawn by the authors.

Other studies by Evans and Maher in diethyl ether showed that the proton resonance spectra of 'EtMgBr' closely resembles that of Et_2Mg for the concentration range 0·040—0·296M (with respect to the ethyl group). They interpreted this as indicating the absence of a significant amount of EtMgBr and supporting the representation of Grignard compounds in solution as $R_2Mg{\cdot}MgX_2$. However, the molecular weight studies indicate that at the highest concentration studied (0·296M), about 64% of the 'EtMgBr' exists as dimeric species, either (V) or (VIII), or both; n.m.r. was therefore unable to distinguish between Et_2Mg and structures (V) or (VIII). Since each of these structures contains Mg bonded to both carbon and halogen, it follows that n.m.r. could not be expected to distinguish between Et_2Mg and EtMgBr.

It was later shown[40] that in tetrahydrofuran, 'EtMgCl' and Et_2Mg exhibit essentially identical n.m.r. spectra, yet in tetrahydrofuran the RMgX species is present in solution. Apparently n.m.r. is unable to distinguish between Et_2Mg and EtMgCl in tetrahydrofuran or diethyl ether solution. Recently, Fraenkel and his co-workers[42] reported little if any difference between the n.m.r. spectra of 'MeMgI' and MeLi. Once again this points out the inability of n.m.r. in certain cases to differentiate between two different chemical species.

As a second example, Dessy[31] reported dielectric constants for 0·139M-$MgBr_2$ in Et_2O to which was added varying amounts of Et_2Mg. The plot of dielectric constant against the ratio $Et_2Mg/MgBr_2$ showed a distinct break at the 1:1 ratio, indicating compound formation. The dielectric constant for the 1:1 mixture was identical with that measured for 'EtMgBr' at the equivalent concentration, indicating that the mixture and the 'EtMgBr' contained the same species. According to Figure 1, the *i*-value for 'EtMgBr' (at 0·278M) is 1·43, so that about 60 wt. % of the 'EtMgBr' is present as monomer. Since this monomeric 'EtMgBr' is a compound rather than a mixture of Et_2Mg and $MgBr_2$, it must consist predominantly of the species EtMgBr.

The existence of the species EtMgBr in dilute ether solution is also indicated

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[42] G. Fraenkel, D. Adams, and J. Williams, *Tetrahedron Letters*, 1963, 767.

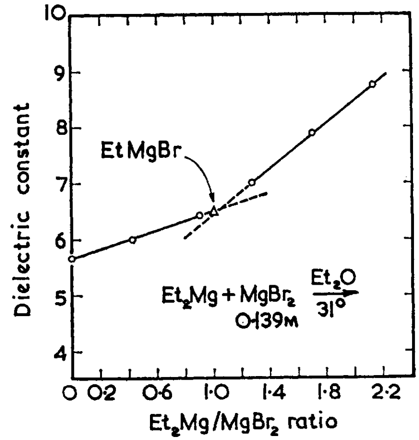

Fig. 2 *Dielectric constant as a function of the ratio* $Et_2Mg/MgBr_2$

by the data of Vreugdenhill and Blomberg[39] who reported the association factors listed earlier at concentrations of 10^{-3}—10^{-2}M. A possible interpretation of their results follows. If the 'EtMgBr' had consisted of $Et_2Mg + MgBr_2$, it should have had an *i*-value of 1·06 [calculated from the *i*-values for Et_2Mg and $MgBr_2$] as was actually found for the mixture. The *i*-value of 1·00 determined for 'EtMgBr' did not change within 72 hr., indicating that the monomeric Grignard compound must have consisted of EtMgBr and that the latter had no measurable tendency to disproportionate to $Et_2Mg + \frac{1}{2}MgBr_2$. The *i*-value of 1·05—1·06 for $Et_2Mg + MgBr_2$ indicates that very little reaction took place. Perhaps this reaction is quite slow, particularly at these low concentrations, unless a suitable catalyst is present. The argument based on the data of Vreugdenhill and Blomberg is not strong and is only valid if the small association differences reported by these authors is real.

The possible existence of the symmetrical dimeric structure (V) for 'EtMgBr' was argued[40] by comparison of the association phenomena for 'mesityl magnesium bromide'. 'Mesitylmagnesium bromide' in diethyl ether solution showed at least as much association as EtMgBr' (Figure 1) in the same medium. If the dimeric species in diethyl ether solution exists as the unsymmetrical dimer, it seems that 'mesitylmagnesium bromide' should be more dissociated than 'EtMgBr' over a wide concentration range because of its greater steric requirement. Since 'mesitylmagnesium bromide' shows a slightly higher degree of association over the same concentration range as 'EtMgBr', it was suggested that the dimer formed would be predominantly the symmetrical one which could only originate from monomeric RMgX species.

Stucky and Rundle recently[43] found by *X*-ray studies that phenylmagnesium bromide is composed of units containing the phenyl group, a bromine atom,

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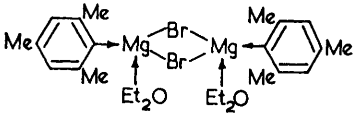
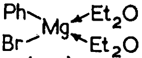
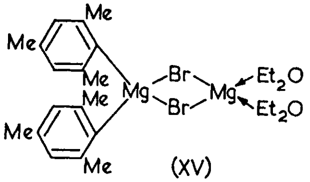
[43] G. D. Stucky and R. E. Rundle, *J. Amer. Chem. Soc.*, 1963, **85**, 1002.



(XIV)



(XVI)



(XV)

and two diethyl ether molecules bonded tetrahedrally to a single magnesium atom (XVI). Although the structure of phenylmagnesium bromide in the solid state cannot be extrapolated to solution without causing some concern, this work did add to the evidence supporting the existence of RMgX species in diethyl solution of Grignard compounds.

As another example, Dessy and his co-workers[28,44] described experiments in which equimolar amounts of $MgBr_2$ (labelled with radioactive magnesium) and Et_2Mg were dissolved in diethyl ether to give a solution 1·0M in Mg. In all the experiments in which ^{25}Mg was used as the tracer, complete exchange occurred between Et_2Mg and $^{25}MgBr_2$. Evidently the Et_2Mg and $^{25}MgBr_2$ reacted according to the Schlenk equilibrium to form EtMgBr + $Et^{25}MgBr$. On the other hand, when ^{28}Mg was used as the tracer, only 6—10% exchange was reported to occur even after contact times as long as 36 hr. This difference in behaviour of ^{25}Mg and ^{28}Mg was attributed to impurities in the ^{25}Mg which was concluded to have catalysed the exchange. The possibility that some trace impurity in the ^{28}Mg may have inhibited exchange was not considered.

The association studies in diethyl ether solution have shed light on the validity of much of the work reported in the 1930's concerning the determination of equilibrium constants for the Schlenk equilibrium. Noller and Raney[21] and others[16,17] attempted to determine equilibrium compositions of Grignard compounds by shaking Grignard solutions with excess of $MgCl_2$ in order to precipitate any $MgCl_2$ present in what other workers described as super-saturated solutions. The equilibrium composition of n-butylmagnesium chloride at concentrations ranging from 0·4 to 1·8M shows that in spite of the low solubility of $MgCl_2$–ether complex in ether, only 3—10% of the halogen originally present precipitated as magnesium chloride. Precipitation with dioxan indicates that at least 88% of the halogen should be present as $MgCl_2$ in solution. These workers concluded either that precipitation with dioxan does not give a correct picture of the composition of Grignard solutions and the reagent is almost entirely in the form RMgX, or that the solubility of $MgCl_2$ is increased from essentially zero to the extent of approximately one mole per mole of R_2Mg.

Of course the solubility of $MgCl_2$ *can* be increased from essentially zero to one mole of $MgCl_2$ per mole of R_2Mg. This, however, does not necessarily mean conversion into RMgX, but could represent association to $R_2Mg{\cdot}MgX_2$. It appears that $MgCl_2$ is held in solution by both of the equilibria suggested by Schlenk.

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[44] R. E. Dessy and G. S. Handler, *J. Amer. Chem. Soc.*, 1958, **80**, 5824.

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \quad (13)$$

$$R_2Mg{\cdot}MgX_2 \rightleftharpoons R_2Mg + MgX_2 \quad (14)$$

The lack of acceptance of (14) was based on the fact that both the dioxan precipitation method and the $MgCl_2$ supersaturation method produced equilibrium values independent of Grignard concentration. Since it is now clear that alkylmagnesium chlorides (those studied) are associated even at low concentration, it does not appear that these conclusions are valid or that compositions of Grignard compounds can be determined by precipitation of $MgCl_2$ incurred by addition of dioxan or by adding an excess of $MgCl_2$. Since equilibria are involved, this approach can only be valid if it is possible to freeze the equilibria and prevent RMgX from producing more R_2Mg and MgX_2 with time as the MgX_2 is recovered as a precipitate.

Although the arguments presented by Ashby and Smith[37,40] were somewhat revolutionary in 1964, they are not nearly so revealing now, since Dessy and his co-workers[45] have repeated the exchange experiments they initially reported in 1957. In their most recent publication these workers report statistical exchange in the system $^{28}MgBr_2$ and Et_2Mg with two out of the three grades of magnesium used. Exchange took place with the purest forms of magnesium used (triply sublimed and Grignard grade turnings) whereas no exchange was observed with the most impure sample (Dow atomised shot). Soon thereafter Cowan, Hsu, and Roberts[46] reported statistical exchange in the system $^{25}MgBr_2$ and Et_2Mg. There now appears no doubt that there is exchange in Grignard solutions and that RMgX is an intermediate in this exchange, even if not present in appreciable concentration. Thus it appears that the equilibria represented by (10) is a reasonable representation of Grignard compounds in diethyl ether solution.

It is entirely possible that small traces of some metal impurity (in p.p.m.) in the several grades of magnesium used for the exchange experiments could have catalysed or inhibited the exchange of R_2Mg and MgX_2. It is also possible, as suggested by Vreugdenhill,[47] that the exchange is catalysed by oxygen and therefore the extent to which oxygen was excluded in the experiments becomes very important. Thus one must be cautious in generalising the exchange phenomena. The conclusions are, however, that exchange has been observed on mixing R_2Mg and MgX_2 under the best possible conditions obtainable. Although it may be possible in the future to obtain non-exchange results with ultrapure magnesium in a completely oxygen-free atmosphere, the point remains that under the normal conditions of Grignard formation alkyl exchange takes place and RMgX species in some concentration are present.

Even though the position for the monomer–dimer equilibrium is known, it would be of more importance to know the concentration of RMgX with respect

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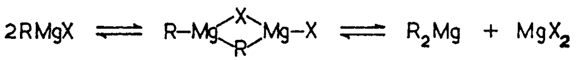
[45] R. E. Dessy, S. Green, and R. M. Salinger, *Tetrahedron Letters*, 1964, 1369.

[46] D. O. Cowan, J. Hsu, and J. D. Roberts, *J. Org. Chem.*, 1964, **29**, 3688.

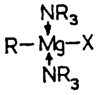
[47] A. D. Vreugendhill, opinion expressed at the 3rd International Organometallic Symposium, Madison, Wisconsin, September 1965.

to $R_2Mg + MgX_2$. The best way of course to establish equilibrium constants would be to observe the concentration of the undisturbed species in solution by n.m.r. or infrared analysis. Unfortunately attempts by Roberts[32] and Fraenkel[42] and their colleagues to do this by n.m.r. analysis were not successful. Attempts by Salinger and Mosher[48] to detect RMgX species in diethyl ether solution by high-resolution infrared analysis also were not successful. However, Mosher and his co-workers were able to detect the RMgX species in tetrahydrofuran solution, reaffirming the existence of a Schlenk equilibrium (9) established earlier.[38] Mosher and his co-workers assigned an equilibrium constant $K = 4$ for ethylmagnesium bromide in tetrahydrofuran, indicating statistical distribution.

F. Evidence for RMgX Composition.—The first direct observation of RMgX species in diethyl ether other than as an intermediate was provided recently.[49] The same report also claimed that RMgX is the initial species formed when an alkyl halide and magnesium react. It was argued that the difference between the composition of Grignard compounds in tetrahydrofuran (9) and diethyl ether (10) is explained by the difference in basicity of the two solvents. Ebullioscopic measurements show a monomer–dimer equilibrium in diethyl ether, but only monomer, present in tetrahydrofuran. Thus tetrahydrofuran co-ordinates with magnesium more strongly than diethyl ether, and a stable halogen-bridge compound is not formed. The exchange of alkyl groups in either tetrahydrofuran or diethyl ether can be explained by an intermediate mixed alkyl–halogen bridge structure of the type suggested earlier.[40] Grignard compounds co-ordinated to a more basic solvent than diethyl ether or tetrahydrofuran might not form such intermediates if the magnesium orbitals are strongly bonded to the basic solvent. Thus disproportionation might be prevented and the initial species formed by reaction of RX and Mg could be isolated.



$$2RMgX \rightleftharpoons R{-}Mg\overset{X}{\underset{R}{\diamond}}Mg{-}X \rightleftharpoons R_2Mg + MgX_2 \qquad (15)$$



$$R{-}\overset{\overset{NR_3}{\downarrow}}{\underset{\underset{NR_3}{\uparrow}}{Mg}}{-}X$$

(XVII)

In order to test this hypothesis ethylmagnesium bromide was prepared from ethyl bromide and Mg in triethylamine. The reaction product (XVIII) was fractionally crystallised into seven fractions. Each fraction had a Mg:Br:N ratio of 1·0:1·0:1·0 within experimental error. (Although C_2H_5MgBr crystallises

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[48] R. M. Salinger and H. S. Mosher, *J. Amer. Chem. Soc.*, 1964, **86**, 1782.
[49] E. C. Ashby, *J. Amer. Chem. Soc.*, 1965, **87**, 2509.

from triethylamine as the bis-solvate, the monosolvate is isolated on drying under high vacuum.) Molecular association measurements of the crystallised fractions in triethylamine at 35° showed the presence of only monomeric species over a wide concentration range. Because of the highly insoluble nature of $MgBr_2$ in triethylamine and the soluble nature of Et_2Mg, precipitation of $MgBr_2$ from solution would have occurred if an unassociated mixture of these two products were present. These data prove that the reaction product is a single species and not a mixture. The product, $EtMgBr{\cdot}NEt_3$, did not disproportionate in boiling triethylamine during 24 hr., nor was it formed by redistribution of Et_2Mg and $MgBr_2$ in triethylamine. Thus the indication is that EtMgBr is the initial product formed by the reaction of EtBr and Mg, and in triethylamine solution the composition can be represented by this single structure.

Similarly, the existence of RMgX in diethyl ether solution was established. When a diethyl ether solution of ethylmagnesium bromide, prepared from EtBr and Mg in diethyl ether, was added slowly to a large, rapidly stirred volume of triethylamine, $EtMgBr{\cdot}NEt_3$ was isolated in over 90% yield by fractional crystallisation. In the Schlenk equilibrium (16) magnesium bromide is the

$$2EtMgBr \rightleftharpoons Et_2Mg + MgBr_2 \qquad (16)$$

strongest Lewis acid and diethylmagnesium is the weakest. It is not reasonable that triethylamine would solvate only the species of intermediate acidity (RMgX). The fact that no $MgBr_2{\cdot}Et_3N$ was isolated, although it is the most insoluble of the possible products, leads to the conclusion that the rate of solvation is greater than the rate of equilibration and therefore in diethyl ether solution ethylmagnesium bromide consists mainly, if not entirely, of RMgX species (as monomer or dimer).

Since RMgX is the only product isolated in triethylamine when RX and Mg are allowed to react, it must be the initial and only magnesium compound formed in the reaction. If any other magnesium compounds such as R_2Mg or MgX_2 had been formed, they would have been solvated and protected from redistribution. Diethyl ether and tetrahydrofuran, being more weakly basic solvents than triethylamine, are not sufficiently strong complexing agents to prevent the disproportionation of the initially formed RMgX and therefore, in these solvents, redistribution takes place.

The position of the equilibria (10) in diethyl ether was further verified by Smith and Becker[50] in a more exact and convincing way than previously reported.[47] They reported that 0·1M solutions of diethyl magnesium and magnesium bromide reacted instantaneously in 1:1 molar ratio on mixing to evolve 3·6 kcal/mole of heat. Since only monomeric species are involved at this concentration and heats of dilution were found to be negligible this evolution of heat was attributed to the formation of EtMgBr. Figure 3 represents the heat evolved on addition of $MgBr_2$ to one mol. of Et_2Mg.

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[50] M. B. Smith and W. E. Becker, *Tetrahedron Letters*, 1965, 3843.

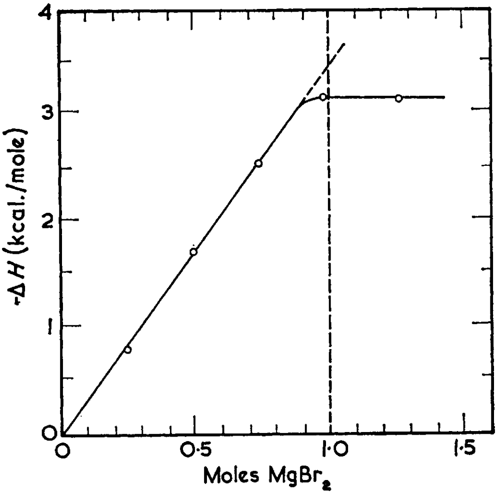

Fig. 3 *Heat of reaction as a function of the ratio* $Et_2Mg/MgBr_2$

Equilibrium constants for Grignard compounds

$$R_2Mg + MgX_2 \rightleftharpoons 2RMgX$$

Grignard compound	K (in Et_2O)[50]	K (in THF)[51]
EtMgBr	480	4
EtMgI	630	
PhMgBr	55	
PhMgI	15	

The equilibrium constants shown in the Table were obtained by measuring the heat evolved when the R_2Mg compound was added to the MgX_2 and *vice versa*. The curves of ΔH plotted against $MgBr_2/Et_2Mg$ or $Et_2Mg/MgBr_2$ were superimposable. These results indicate that in diethyl ether solution the equilibrium $R_2Mg + MgX_2 \rightleftharpoons 2RMgX$ lies predominantly to the right. The results are in agreement with the earlier work involving quenching experiments in triethylamine.[48]

Similar thermochemical experiments were conducted by Smith and Becker[51] in tetrahydrofuran. In this solvent the instantaneous reaction of R_2Mg with MgX_2 occurs with *absorption* of heat. The position of the equilibrium $R_2Mg + MgX_2 \rightleftharpoons 2RMgX$ is not nearly as far to the right as it is in diethyl ether. The equilibrium constants (Table) do not differ greatly from the value $K = 4$ which corresponds to statistical distribution, in agreement with the earlier work of Salinger and Mosher[48]. In the case of the system Et_2Mg—$MgCl_2$, the curve of ΔH against MgX_2/R_2Mg is different from the curve of ΔH against R_2Mg/MgX_2. This was shown to indicate the existence of appreciable quantities of the species $EtMg_2Cl_3$ in tetrahydrofuran solution. This result is

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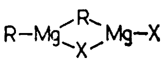
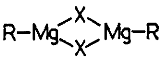
[51] M. B. Smith and W. E. Becker, *Tetrahedron*, 1966, **22**, 3027; 1967, **23**, in press.

consistent with the work of Ashby and Becker[35] who obtained crystals of the compound $EtMg_2Cl_3$ by fractional crystallisation of the corresponding Grignard reagent from tetrahydrofuran solution.

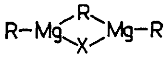
Recent n.m.r. studies by Roberts and his co-workers[52] and Fraenkel and his co-workers[53] on Grignard reagents in diethyl ether have established the ionic nature of the C–Mg bond and rapid inversion at the α-carbon atom. The n.m.r. work was not informative in establishing the nature of the associated species in solution or the magnitude of equilibrium constants for the Schlenk equilibrium. Evidence was presented in favour of a bimolecular mechanism to explain the alkyl transfer from one magnesium atom to another involving inversion at the α-carbon atom by means of a mixed alkyl–halogen bridge intermediate (XVIII). Thus some evidence is now available to verify alkyl transfer in the Grignard system by a mixed-bridge intermediate suggested earlier[40] strictly on an intuitive basis.



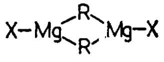
(XVIII)



(XIX)



(XX)



(XXI)

In 1965 Hashimoto and his co-workers[54] reported results which appeared to confuse the evolving picture of Grignard compound composition in solution. They reported that EtMgBr in diethyl ether is associated in solution past the dimer state ($i = 2{\cdot}4$ at 1·0M) and then decreases in association below the dimer stage with an increase in concentration ($i = 1{\cdot}6$ at 2·0M). They also report that EtMgBr in tetrahydrofuran is associated at low concentration ($i = 1{\cdot}6$ at 0·1M) and then decreases in association to a monomer only at high concentration ($i = 1{\cdot}0$ at 1·2M). It does not seem reasonable that association phenomena should decrease with an increase in concentration and indeed this does not appear to be the case.

A recent report by Ashby and Walker[55] sustantiates earlier data and conclusions[40] concerning association of Grignard compounds in both diethyl ether and tetrahydrofuran. They were attempting to establish the exact nature of the associated magnesium species in solution. For example, if 2 molecules of the RMgX species associate to a dimer in solution, the resulting structure can be represented by (XIX), (XX), or (XXI). Although structure (XIX) should be the most stable, there exists no evidence anywhere to substantiate such a choice. Likewise, association of the R_2Mg and MgX_2 species can be described by means of a double halogen-bridge, a double alkyl-bridge, or a mixed alkylhalogen-bridge species. Since RMgX is the predominant species in diethyl ether, only the association of this species will be considered here.

The data (Figure 4) show quite clearly that association of magnesium through the halogen in $MgBr_2$ and MgI_2 ($MgCl_2$ is insoluble in diethyl ether) is much

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[52] G. M. Whitesides and J. D. Roberts, *J. Amer. Chem. Soc.*, 1965, **87**, 4878.
[53] G. Fraenkel and D. T. Dix, *J. Amer. Chem. Soc.*, 1966, **88**, 979.
[54] H. Hashimoto, T. Nakano, and H. Okada, *J. Org. Chem.*, 1965, **30**, 1234.
[55] E. C. Ashby and F. Walker, *J. Organometallic Chem.*, 1967, **7**, P17.

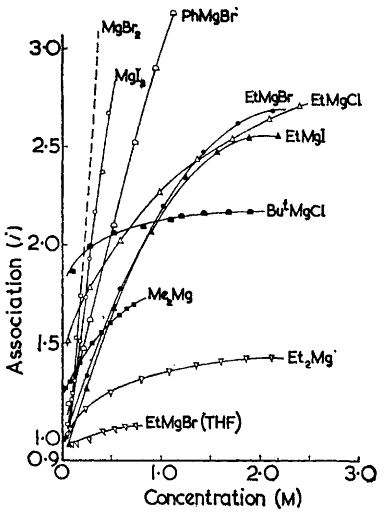
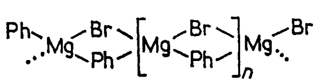


Fig. 4 *Association of Grignard species at high concentrations.*

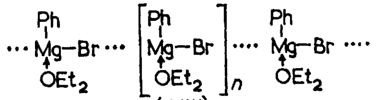
stronger than through the alkyl group as in Et_2Mg or Me_2Mg. Since methyl and ethyl are optimum bridging groups, and dimethylmagnesium and diethylmagnesium are only weakly associated in diethyl ether, it appears that association of the Grignard compounds is predominantly through the halogen. The association of all of the compounds studied can be explained purely on inductive grounds, *i.e.*, association is proportional to the positive character of the magnesium atom.

The association of some Grignard compounds past the dimer stage points out the need to consider the possibility that different Grignard compounds are associated differently. For example, it appears that PhMgBr is linearly associated whereas the ethyl Grignard compounds appear to be either linearly associated (curvature due to deviation from ideality at high concentration) or are trimeric. On the other hand, the association of t-butylmagnesium chloride appears to level off at the dimer stage.

The representation of associated molecules of PhMgBr does not appear to be tenable on the basis of structure (XIX) since association of this type would predict gross curvature of the association line at $i = 2$ owing to the change in the nature of the bonding which must take place at this point. Structures (XXII) and (XXIII) are compatible with the type of association exhibited by PhMgBr. Since solid magnesium halides and Grignard compounds hold one molecule of the



(XXII)



$$\cdots\underset{\overset{\uparrow}{OEt_2}}{\overset{Ph}{Mg}}-Br\cdots\left[\underset{\overset{\uparrow}{OEt_2}}{\overset{Ph}{Mg}}-Br\right]_n\cdots\underset{\overset{\uparrow}{OEt_2}}{\overset{Ph}{Mg}}-Br\cdots$$

(XXIII)

ether tightly per magnesium atom, structure (XXIII) is preferred. The *X*-ray data reported by Stucky and Rundle[43] would also favour structure (XXIII).

In contrast to the report of Hashimoto, Nakano, and Okada,[54] these results confirm an earlier report[38] that ethylmagnesium bromide is monomeric in tetrahydrofuran showing only a low degree of association at high concentration. The anomalies exhibited in the data of Hashimoto *et al.* could be due to any of several problems which make measurements on such sensitive systems very difficult.

G. Grignard Reagents prepared in Hydrocarbon Diluent.—Some investigations into the preparation of Grignard compounds in hydrocarbon solvent have been reported by Bryce-Smith and his co-workers,[56] who reported that aryl and alkyl primary chlorides, bromides, and iodides react with magnesium in hydrocarbon solvents at elevated temperature ($>100°$c). The solvents employed were deca- or tetra-hydronapthalene and paraffin oil while the choice of optimum reaction temperature was a compromise of many factors, such as sufficient reaction rate, Wurtz-type coupling, Friedel–Crafts-type alkylation of aromatic solvents, etc. The products of these reactions are white, amorphous, non-volatile solids. The solubility of these products is quite small in hydrocarbons: the solubility increased with the size of the halogen ($Cl<Br<I$), the length of the R group, and the type of solvent (aromatic > aliphatic).

An interesting feature of this work in addition to providing reaction of an alkyl halide and magnesium in a non-polar solvent in up to 95% yield, is that in freshly prepared solutions, analysis has detected compounds of the empirical formula R_3Mg_2X. Unfortunately the concentration is low and solids precipitate from solution on standing until products of indiscriminate empirical formulae remain. It has been suggested that R_3Mg_2X is associated in hydrocarbon solution and that predominantly MgX_2 precipitates on standing. The solid products produced in the reaction simply appear to be a mixture of R_2Mg, MgX_2, and associated species thereof. Thus one is not sure that the name 'Grignard Reagent' should be applied to the solid mixture of compounds produced when an alkyl halide is allowed to react with magnesium in hydrocarbon diluent.

Zakharkin and his co-workers[57] later expanded the work in hydrocarbon diluent demonstrating higher yields (70—95%) for most primary alkyl and aryl halides using diluents such as dodecane, 2,2,3-trimethylpentane, and sometimes no diluent at all. Essentially all of the magnesium-containing product was precipitated from solution and no attempt was made to determine the nature of the products other than to determine the empirical formula.

More recently it has been found[58] that Grignard compounds can be prepared in aromatic hydrocarbons as a solvent rather than a diluent. In this connection, 2M solutions of several typical alkylmagnesium halides (*e.g.*, C_2H_5MgBr) were prepared. The difference in this report and those of Bryce-Smith and Zakharkin

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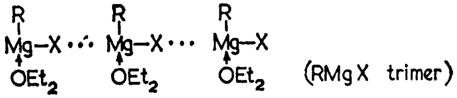
[56] D. Bryce-Smith and G. F. Cox, *J. Chem. Soc.*, 1961, 1175.
[57] L. I. Zakharkin, O. Yu. Okhlobystin, and B. N. Strunin, *Tetrahedron Letters*, 1962, 631.
[58] E. C. Ashby and R. Reed, *J. Org. Chem.*, 1966, **31**, 985.

and their colleagues is that one mole of triethylamine as a complexing agent was employed per mole of magnesium so that the actual product was $RMgX{\cdot}NEt_3$. It is interesting that use of one mol. of diethyl ether or tetrahydrofuran did not impart such solubility. The composition of the Grignard compounds reported in benzene solvent is believed to be described by the singular species $RMgX{\cdot}NEt_3$ for reasons presented earlier[49] (fractional crystallisation and molecular association).

H. Conclusions concerning the Composition of Grignard Reagents.—It appears that the following conclusions are justified. (1) RMgX species exist in diethyl ether, tetrahydrofuran, and triethylamine. (2) The compositions in the above solvents are represented as follows:

Diethyl ether. Monomeric species consist largely of RMgX along with a small amount of $R_2Mg + MgX_2$. Association is extensive above about 0.3M:

$$\text{etc.} \rightleftharpoons \text{Trimer} \rightleftharpoons \text{Dimer} \rightleftharpoons 2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \text{Dimer} \rightleftharpoons \text{Trimer} \rightleftharpoons \text{etc.}$$



$$\underset{\underset{OEt_2}{\uparrow}}{\overset{\overset{R}{|}}{Mg}}{-}X \cdots \underset{\underset{OEt_2}{\uparrow}}{\overset{\overset{R}{|}}{Mg}}{-}X \cdots \underset{\underset{OEt_2}{\uparrow}}{\overset{\overset{R}{|}}{Mg}}{-}X \quad \text{(RMgX trimer)} \qquad (17)$$

Tetrahydrofuran. Relatively little association occurs in this solvent. The prevailing monomeric species consist of substantial quantities both of RMgX and of $R_2Mg + MgX_2$. The Grignard compound EtMgCl also contains the species $EtMg_2Cl_3$ in appreciable quantity.

Triethylamine. Only one species (RMgX) is observed for simply alkylmagnesium bromides and chlorides. In solutions of alkylmagnesium iodides and aromatic Grignard compounds the situation is not so simple.[59]

Hydrocarbon. The work of Bryce-Smith and his co-workers indicates that when RX and Mg are allowed to react in hydrocarbons as diluents, a mixture of insoluble organomagnesium and inorganic magnesium compounds is produced ($R_2Mg + MgX_2$ and highly associated combinations). This mixture of insoluble compounds will behave similarly to ether solutions of Grignard compounds toward some organic functional compounds. The species R_3Mg_2X is soluble to a small extent; however, the solutions are not stable and precipitation results in time.

Benzene-soluble Grignard compounds have been prepared, but the solubility and composition ($RMgX{\cdot}NR'_3$) is a result of complex-formation with 1 mole of a tertiary amine for each mole of organomagnesium compound.

3 Mechanisms of Grignard Reactions

The mechanism of the addition of Grignard reagents to ketones has been a

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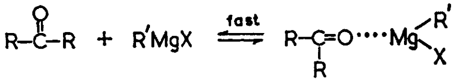
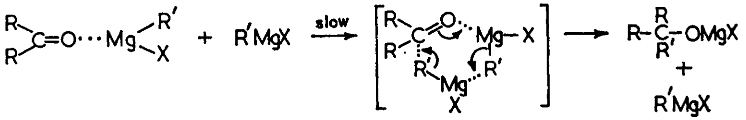
[59] E. C. Ashby and T. Bickley, unpublished work.

subject of much controversy for some years.[60] The first serious mechanistic suggestion (18, 19) concerning this reaction was made by Swain and Boyles[61] in 1951. They suggested the mechanism to be third order; first order in ketone and second order in Grignard reagent. This mechanism was criticised after 1957 when the Grignard reagent was reported to have the $R_2Mg{\cdot}MgX_2$ structure. Almost simultaneously Miller *et al.*,[62] Bikales and Becker,[63] and Hamelin and Hayes[64] suggested a bimolecular mechanism involving one molecule of ketone and one molecule of unsymmetrical dimeric Grignard reagent (20).



(18)



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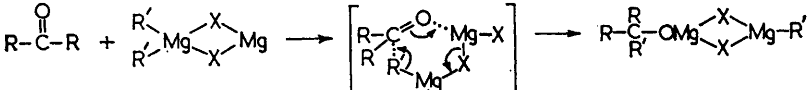

(20)

In the years ensuing since 1957 an apparent impasse was reached concerning the two different mechanistic descriptions of this reaction. On the one hand, Mosher, Becker, and Hamelin upheld the conclusion that the mechanism of addition of Grignard compounds to ketones is best represented in terms of a six-centre transition state involving one molecule of ketone and one molecule of Grignard dimer, $R_2Mg{\cdot}MgX_2$. On the other hand, Anteunis[65] has held that the mechanism originally suggested by Swain and Boyles correctly represents the course of this reaction. It is clear that neither group of workers possessed kinetic data which were consistent with their suggested mechanism. This was because, although each of these workers recognised that the mechanism was complex, the kinetic data were analysed as if the reaction was simple; more specifically, as if the reaction should be either first or second order in Grignard reagent. The second-order kinetics reported by Bikales and Becker actually represented only the first 30% of the reaction. After 30% reaction, the simple second-order plot showed a serious deviation. On the other hand, Becker has criticised the kinetic data presented by Anteunis for several reasons, the

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[60] M. S. Kharasch and Otto Reinmuth, Grignard Reactions of Nonmetallic Substances, Prentice-Hall Inc., New York, 1954.

[61] C. G. Swain and H. B. Boyles, *J. Amer. Chem. Soc.*, 1951, **73**, 870.

[62] J. Miller, G. Gregarion, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1961, **83**, 3955.

[63] N. M. Bikales and E. I. Becker, *Canad. J. Chem.*, 1962, **41**, 1329.

[64] R. Hamelin and S. Hayes, *Compt. rend.*, 1961, **252**, 1616.

[65] M. Anteunis, *J. Org. Chem.*, 1961, **26**, 4214: 1962, **27**, 596; *Bull. Soc. chim. belges.*, 1964, **73**, 655.

most important of which is that the actual data presented, when calculated correctly and plotted, do not substantiate a third-order mechanism. In the meantime Mosher quoted Swain in a person communication footnote[62] saying that Swain no longer maintains that the Grignard–ketone mechanism proceeds by third-order kinetics. Thus, until recently, it appeared that there were two distinct views concerning the mechanism of this reaction; on the one hand Mosher, Becker, and Hamelin maintain that the Grignard–ketone addition reaction proceeds by second-order kinetics and on the other hand Anteunis maintains that the reaction proceeds by third-order kinetics.

While it appeared that the controversy had died down because of the difficulty in obtaining better results, Smith and Su[66] suggested a quite different mechanism. This was that the ketone reacts with monomeric Grignard compound in a fast step (21) to produce a complex and then the complex rearranges in a first-order fashion (22) to produce the product. Smith and Su reported some very important observations. When methylmagnesium bromide and 2,4-dimethyl-4′-methylmercaptobenzophenone were allowed to react, two bands were observed in the ultraviolet spectrum. One band (315 mμ) was the π–π^* carbonyl band of the ketone and the other band (355 mμ) was attributed to the shifted carbonyl band due to the formation of a complex between ketone and Grignard reagent. The two bands were found to decrease concurrently establishing that an equilibrium does exist between ketone and complex. In a pseudo-first-order kinetic study, disappearance of the ketone and complex took place in a first-order fashion.

$$\mathrm{K} + \mathrm{G} \overset{K}{\rightleftharpoons} \mathrm{C} \tag{21}$$

$$\mathrm{C} \xrightarrow{k_3} \mathrm{P} \tag{22}$$

K = Ketone G = Grignard C = Complex P = Product

Attempts by Smith and Su to establish the mechanism presented earlier (eqns. 21, 22) meet with much difficulty. The kinetic data were consistent with the suggested mechanism up to a Grignard concentration of 0·3M. At higher concentrations serious deviation from expected results in the plot of k_{obs} against [G] was observed. Smith suggested an effect due to the medium to explain the deviation. This is not unreasonable and there is precedence for the mathematical forms (23) put forward.

$$k = k_0\,(1 + b[\mathrm{G}]) \tag{23}$$

Eqn. (23) now leads to (24)

$$k_{\mathrm{obs}}\ K[\mathrm{G}]k(1 + b[\mathrm{G}]) \tag{24}$$

$$K[\mathrm{G}] + 1$$

The weakness in this interpretation is that the major effect of [G] on the rate is exerted *via* the medium effect, rather than on how G enters the mechanism. Thus the mechanism is not demonstrated in a positive way.

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[66] S. G. Smith and G. Su, *J. Amer. Chem. Soc.*, 1964, **86**, 2750; 1966, **88**, 3995.

One problem which appears regularly in a study of this type is the uncertainty of the aggregation of Grignard reagents at the concentrations being studied. Realising this, Smith and Su suggest an alternative mechanism at Grignard concentrations $>0{\cdot}3\text{M}$ which approaches in essence the mechanism originally reported by Becker, Mosher, and Hamelin. As a matter of fact with the constants (K_1 and K_3) that Smith and Su use to fit their mechanistic scheme, most of the reaction proceeds *via* the path involving reaction of the dimer G_2.[66]

$$G_2 + K \xrightarrow{K_3} C_2;\ C_2 \xrightarrow{k_4} P \tag{25}$$

Smith and Su concluded their very detailed study by saying that many other reaction mechanisms could be written which, with suitable choice of numerical parameters, are consistent with their experimental results.

Ashby and his co-workers[67] studied the kinetics of the reaction of benzophenone with methylmagnesium bromide in diethyl ether using concentrations of the latter so small that the reagent is predominantly monomeric, and at the same time sufficiently greater than the ketone concentration that the concentration of Grignard remains constant during a given experiment. Each reaction was then pseudo-first order; and the variation of its rate constant, k_{obs}, was observed as the Grignard concentration, [G], was varied from one experiment to another. The kinetic results were obtained by quenching individual samples of the reaction mixture at appropriate intervals and following the disappearance of ketone (250 mμ) by ultraviolet analysis. The functional dependence of k_{obs} on [G] was used as a test of possible mechanisms.

If the reaction were second order overall (26), first order in Grignard and first order in ketone, the simplest interpretation of such a law would be a

$$\text{Rate} = k_2[\text{K}][\text{G}] \tag{26}$$

bimolecular reaction (27). In such a case, k_{obs} should be given by (28). A plot

$$K + G \xrightarrow{k_2} P \tag{27}$$

of k_{obs} against [G] was not linear.

$$k_{\text{obs}} = k_2[\text{G}] \tag{28}$$

If the mechanism suggested by Smith and Su were correct, then k_{obs} is related

$$k_{\text{obs}} = \frac{k_3K[\text{G}]}{1 + K[\text{G}]} \tag{29}$$

to [G] by the expression (29). Quantitative adherence to this expression was tested graphically by use of eqn. (30).

$$[\text{G}] = k_3\,\frac{[\text{G}]}{k_{\text{obs}}} - \frac{1}{K} \tag{30}$$

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[67] E. C. Ashby, R. Duke, and H. M. Neumann, *J. Amer. Chem. Soc.*, 1967, **89**, 1964.

A plot of [G] against $[G]/k_{obs}$ produced a line through the data points with a negative slope, which is meaningless physically.

A mechanism (31)—(33) which did fit the experimental results is similar to that originally suggested by Swain.

$$G + K \overset{K}{\rightleftharpoons} C \tag{31}$$

$$C + G \xrightarrow{k_3} P' \tag{32}$$

$$P' \rightleftharpoons P + G \tag{33}$$

In this case

$$k_{obs} = \frac{k_3K[G]^2}{1 + K[G]} \tag{34}$$

and a quantitative test of this mechanism was a plot of [G] against $[G]^2/k_{obs}$ since

$$[G] = k_3\frac{[G]^2}{k_{obs}} - \frac{1}{K} \tag{35}$$

Such a plot is shown in Figure 5.

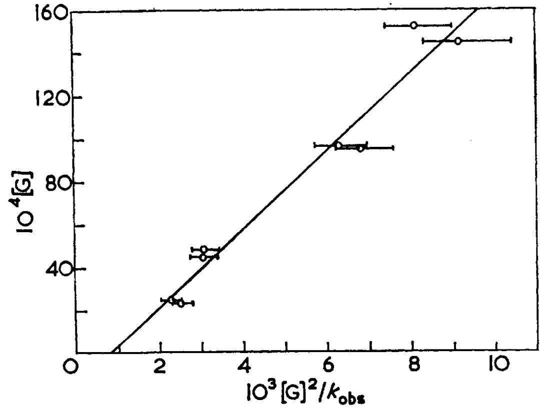


Fig. 5 *Graphical test of suggested termolecular mechanism.*

Within experimental error the points fall on a line, and the slope and intercept have signs required for meaningful interpretation.

The mechanism suggested by Becker and others (36)—(38) is somewhat similar to the one suggested by Ashby and his co-workers, except that the components are brought together in a different manner.

$$2\mathrm{G} \overset{Kg}{\rightleftharpoons} \mathrm{G}_2 \tag{36}$$

$$\mathrm{K} + \mathrm{G}_2 \xrightarrow{K} \mathrm{C} \tag{37}$$

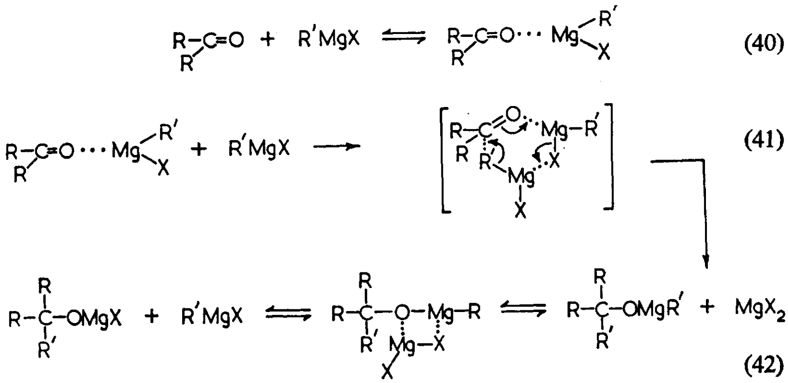
$$\mathrm{C} \xrightarrow{k_3} \mathrm{P} \tag{38}$$

In this case

$$k_{\mathrm{obs}} = \frac{k_3 Kg[\mathrm{G}]^2}{1 + KgK[\mathrm{G}]^2} = \frac{k_3 K'[\mathrm{G}]^2}{1 + K'[\mathrm{G}]^2} \tag{39}$$

This is true for conditions such that the concentration of dimer G_2 is small with respect to that of monomer G. The test of the mechanism is whether or not a plot of k_{obs} against $k_{\mathrm{obs}}/[\mathrm{G}]_0$ is linear, which it is not.

The fact that at low Grignard-to-ketone ratios, the rate of reaction decreases markedly after 50% of the available R groups are utilised can readily be explained by assuming that P′ (eqn. 33) does not readily regenerate the active Grignard species as originally suggested by Swain. The detailed mechanism suggested by Ashby and his co-workers is shown in (40)—(43).



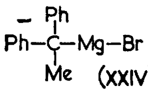
(40)

(41)

(42)

When benzophenone and methylmagnesium bromide were allowed to react in 1:2 stoicheiometry, the products were (XXIV) and (XXV).[68]

This does not exclude the possibility that (XXVI) may be an intermediate in the reaction since the alkoxymagnesiumalkyl and magnesium bromide were shown to redistribute rapidly to form the alkoxymagnesium halide.[68]

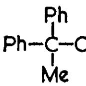


$\mathrm{Ph{-}\overset{Ph}{\underset{Me}{C}}{-}Mg{-}Br}$

(XXIV)

MeMgBr

(XXV)



$\mathrm{Ph{-}\overset{Ph}{\underset{Me}{C}}{-}OMgMe}$

(XXVI)

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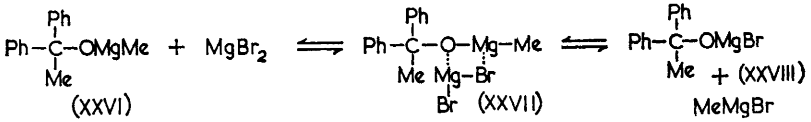
[68] E. C. Ashby and R. Arnott, unpublished results.

The ultimate test of the suggested mechanism is whether the rate behaviour in solutions where Grignard and ketone are in comparable concentration is consistent with the numerical values of k_3 and K (eqns. 34 and 35) obtained under pseudo-first-order conditions. Ashby and his co-workers claim this to be so.

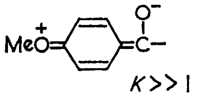


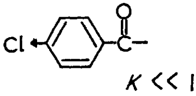
(43)

It should be noted that the suggested mechanism is compatible with the existence of the Schlenk equilibrium, but that the data cannot indicate which of the species (RMgX, MgX_2, or R_2Mg) may be involved in the equilibrium step or the rate-determining step of the mechanism, if specificity indeed occurs. This is because the fraction of the Grignard reagent present in any one specific form is constant under the conditions employed. Thus, if G_I is the species of Grignard involved in the equilibrium step, G_{II} the species in the rate-determining step, and F_I and F_{II} the corresponding fractions, eqn. (44) follows. The functional dependence of k_{obs} on [G], the total concentration of Grignard compound, is thus no different than it would be if the Grignard existed solely in the RMgX form.

$$k_{obs} = \frac{(kF_{II})\,(KF_I)\,[G]^2}{1 + (KF_I)\,[G]} \qquad (44)$$

From eqn. (34) it is clear that the reaction can exhibit simple second- or third-order kinetics depending on the magnitude of K[G]. If $K[G] >> 1$ then the reaction should exhibit simple second-order kinetics. If $K[G] << 1$, then the reaction should exhibit simple third-order kinetics. Thus discussions as to whether the reactions is second- or third-order are meaningless unless the nature of the ketone and Grignard are known so that the magnitude of the equilibrium constant (K) is known. For example, K can be made very small by placing a strong electron-withdrawing group in the *para* position of benzophenone, or K can be made very large by placing a strong electron-donating group in that position.





$$K + G \overset{K}{\rightleftharpoons} C \qquad (45)$$

In the case report by Ashby and his co-workers K is 1040; however $[G] = 10^{-3}$ therefore K[G] is neither large nor small compared with unity. Thus a more accurate picture of the mechanism is expressed in terms of molecularity rather than reaction order.

Thus it appears that the mechanism of Grignard addition to ketones is much better understood especially in terms of the suggested mechanism's being consistent with the available data. The termolecular mechanism is consistent with the kinetic data and the isolated intermediates and also explains the much lower reactivity of the second 50% of the R groups in the Grignard compound. All the questions concerning Grignard compound composition and reaction mechanisms certainly have not been answered, however, it looks as if chemists are pointed in right direction.