JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 2, 205–213 (1989)

MECHANISM OF THE GRIGNARD REACTION

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ABSTRACT

Mechanism of the Grignard reactions of aromatic ketones in THF was studied by spectroscopic and kinetic methods. The stable radical intermediates generated in the initial electron transfer from Grignard reagent to ketones are in a state of aggregated dimer of corresponding ion–radical pairs; in which two ketone anion radicals are bridged by a dimer di-cation of Grignard reagent. Subsequent alkyl radical transfer from dimeric Grignard reagent cation moiety to ketone anion radical aggregated each other are promoted by a participation of another neutral Grignard reagent. Proposed mechanism by present authors is able to explain well addition products/reduction products ratios in the Grignard reactions.

INTRODUCTION

Since the discovery of the Grignard reagent in 1901,[1] the reaction mechanism with carbonyl compounds has been studied extensively by using product analysis and kinetic methods. As a result, the contribution of concerted or polar processes in the reactions has long been believed. However, application of ESR technique has disclosed that the Grignard reactions with ketones are essentially of radical processes, initiated by an electron transfer from the Grignard reagent.

While a radical pathway of the reaction was proposed tentatively in 1929 by Blicke and Powers on the basis of reduction by-products,[2] there has been no experimental evidence for the radical mechanism.

In 1964, K. Maruyama, by using ESR and visible spectroscopy, observed the formation of distinct amounts of stable radical species in the reactions of Grignard reagents with benzophenones in THF. Based on these results, the contribution of radical species was suggested to be major.[3] Independently, analogous results were reported by G. A. Russell's group[4] and by C. Blomberg's group.[5] These results stimulated organometallic chemists, as well as physical organic chemists.[6] Unfortunately, in those days, it was difficult for the radical mechanism of the Grignard reaction to gain general acceptance.

Afterwards, several reports questioning the radical mechanism have been published by E. C. Ashby's group,[7] who insist that on the radical formation in Grignard reactions heavy metal contaminants in magnesium metal, from which Grignard reagents are prepared, are responsible, but the same group have withdrawn from this question.

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0894–3230/030205–09$05.00

Received 22 February 1988
Revised 4 July 1988

In 1971, T. Holm and I. Crossland proposed a radical mechanism based on the linear free energy studies,[8] insisting that the rate-determining step was the initial electron transfer process by thermographic procedure. However, their mechanism excluded participation of 'stable' radical intermediates, inconsistent with our ESR results.

E. C. Ashby's group proposed in 1977 a radical mechanism of the Grignard reaction based on the ESR and product analysis.[9] Ashby's mechanism was thrown in doubt by T. Holm[10] and W. Kaim,[11] because of the instability of paramagnetic organometal cation-radical.[12]

Anyway, by the early 1980's the electron transfer initiation in the Grignard reaction is in the state of general acceptance by chemists.[8,9] In spite of this situation, the mechanism of the Grignard reaction still remains to be solved. That is; there was no reliable information on the alkyl radical transfer process which should be followed to the initial electron transfer. In addition, the structure of stable radical intermediates observed in the reaction was controversial.

Recently, we have disclosed that the Grignard addition reactions of aromatic ketones in THF solutions proceed stepwise—initial electron transfer from Grignard reagent to ketone followed by alkyl radical transfer.[13–18] At the same time, the structures of the stable radical intermediates, not so simple as considered so far, have been proposed.[13]

The purpose of this paper is to give a brief review on recent studies on the Grignard addition reactions.

STRUCTURE OF RADICAL INTERMEDIATE

As was mentioned above, the life-time and structure of radical species which could be generated in the Grignard reaction have been the center of controversy. One of the difficulties in solving this problem arises from the extremely short life-time of the radical intermediates under the usual Grignard reaction conditions. However, by selection of suitable conditions stable radical species of unexpectedly longer life-time were able to be observed.[13] To observe the stable radical species in the Grignard reactions, an excess amount of ketones over a Grignard reagent in THF has to be mixed under strictly dry and deoxygenated conditions.

For example, when phenylmagnesium bromide (PhMgBr) dissolved in THF was allowed to react with an excess amount of benzil under strictly dry and deoxygenated conditions, a purple colored radical intermediate (PCR) appeared in the reacting solution. This radical is quite stable even at room temperature; the concentration of the PCR remained constant for several years, so long as one kept the ratio of benzil/Grignard reagent (B/G) constant.[13] PCR showed a well resolved ESR spectrum as given in Figure 1A, which was compatible with an ion-paired anion radical of benzil. With a gradual increase in the concentration of PhMgBr to that of benzil further PCR disappeared once, and again a stable golden colored radical (GCR) appeared. Analysis of the ESR spectrum of GCR disclosed that GCR corresponded to an ion-paired anion radical of α-phenyl benzoin salt. Irrespective of the species of Grignard reagents, e.g. methylmagnesium bromide (MeMgBr), ethylmagnesium bromide (EtMgBr) or allylmagnesium bromide, the two corresponding radical intermediates were able always to be observed under suitable conditions.

In the reactions of fluorenone, 1-methylfluorenone, benzophenone, and 2-methylbenzophenone in THF, similarly, ion-paired ketone anion radicals were observed by ESR (see Figure 1C–F, respectively).[18] The hyperfine splitting constants of these radical intermediates are summarized in Table 1. However, a possible counter cation radical which might be produced from Grignard reagent was not detected by ESR in any cases.

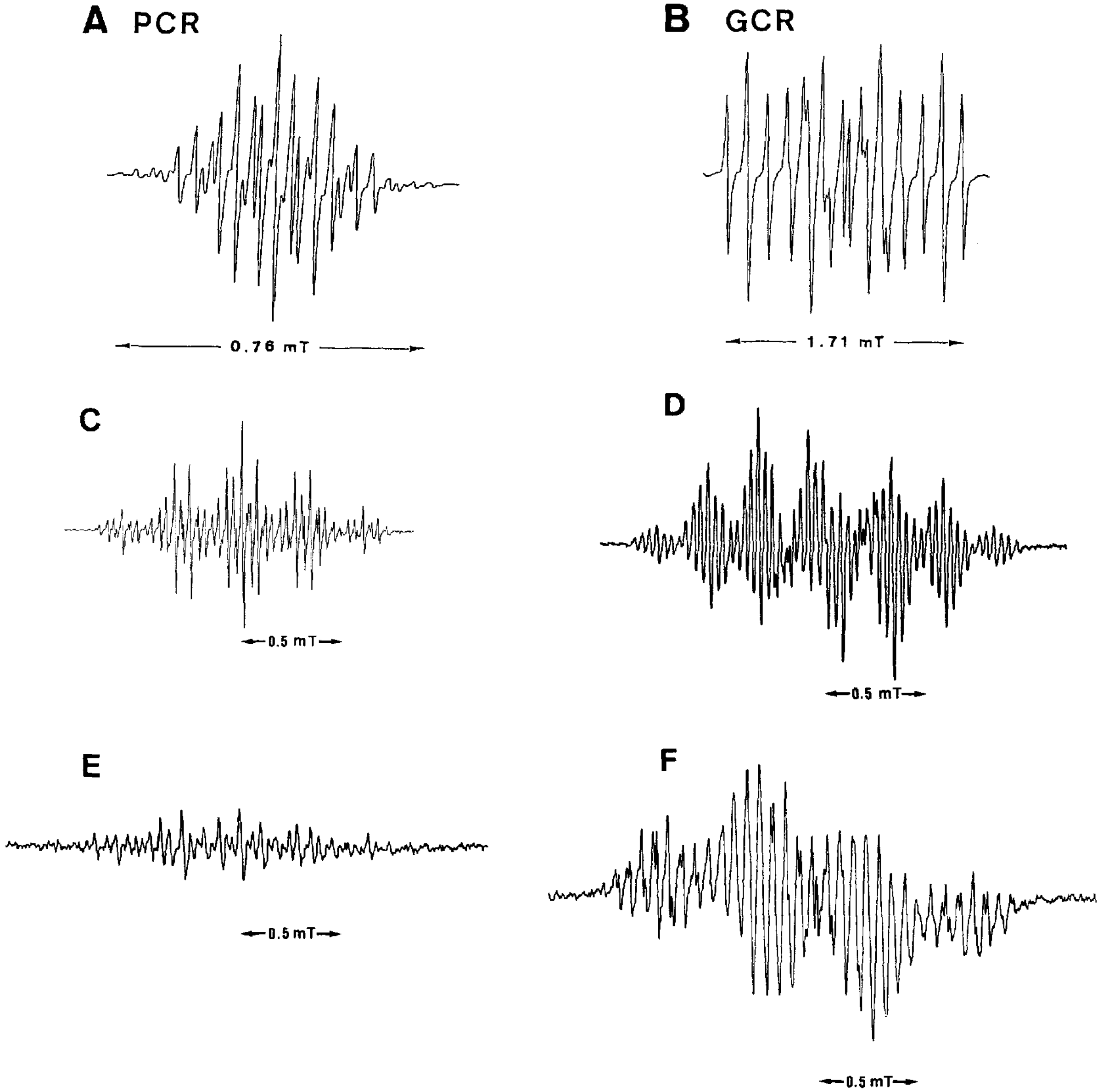


Figure 1. ESR spectra of radical intermediates generated in the Grignard reaction in THF at room temperature: A) PCR in the reaction of PhMgBr with benzil, B) GCR in the reaction of PhMgBr with benzil, C) reaction of MeMgBr with fluorenone, D) reaction of MeMgBr with 1-methylfluorenone, E) reaction of MeMgBr with benzophenone, F) reaction of MeMgBr with 2-methylbenzophenone

From careful inspection of the ESR hyperfine splitting constants of the stable radical intermediates, it is suggested that the stable anion radical moiety should be 'tightly' ion-paired with a diamagnetic cation moiety derived from Grignard reagent.[13,15]

Thus, it may be deduced that the cation moiety of the intermediate is not in the state of a simple cation radical,[13–16] but in dimeric, i.e. non-paramagnetic, state such as Structure **1**. In

$$\mathrm{B} + \mathrm{G} \xrightarrow{k_1} \mathrm{MIP} \quad (1)$$

$$2\ \mathrm{MIP} \xrightarrow{k_2} \mathrm{D} = \mathrm{PCR} \quad (2)$$

$$\mathrm{D} + \mathrm{G} \xrightarrow{k_3} \mathrm{A} + \mathrm{MIP} + \mathrm{G} \quad (3)$$

(B: benzil, G: Grignard reagent, MIP: monomer ion radical pair, D: dimer ion radical pair = PCR A: addition product.)

$$d[\mathrm{D}]/dt = -k_3[\mathrm{G}]_0[\mathrm{D}] = -k_{obs.}[\mathrm{D}] \quad (4)$$

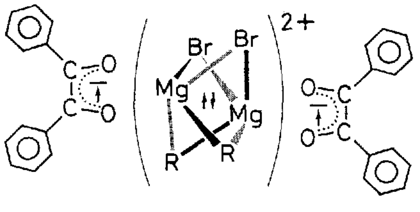
Scheme 1

Table 1. Hyperfine splitting constants of the radical intermediates

ketone	Grignard reagent	hyperfine splittings (mT)
benzil	EtMgBr*	PCR 0·099(6H), 0·041(4H)
		GCR 0·568(1H), 0·456(2H), 0·106(2H), 0·148(2H)
fluorenone	MeMgBr	0·342(2H), 0·266(2H), 0·075(2H), 0·043(2H)
1-methylfluorenone	MeMgBr	0·423(1H), ~0·258(5H), ~0·074(2H), ~0·037(2H)
benzophenone	MeMgBr	0·357(2H), 0·290(4H), 0·104(4H)
2-methylbenzophenone	MeMgBr	0·540(1H), 0·481(2H), 0·193(2H), ~0·057(5H), ~0·019(2H)

*No reduction by-product was obtained under this reacting condition.

fact, this was confirmed as follows. By means of a low temperature (77 K) ESR investigation, typical triplet ESR spectra of stable Grignard radical intermediates (PCR and GCR) were observed in glassy 2-methyltetrahydrofuran (MTHF) solutions.[13] From the fine structure of the triplet ESR spectra, average distances between two parallel spins on two anion radical moieties were estimated in a variety of reacting Grignard systems. The estimated values are



1 PCR

Structure 1. Structure of the dimer radical intermediate generated in the Grignard reaction, PCR summarized in Table 2. These estimated distances are reasonably explained by taking into consideration dimer intermediates such as Structure **1**. Although the major component of stable radical intermediates could be in a dimeric state such as given in Structure **1**, there would be some highly aggregated states in solution.

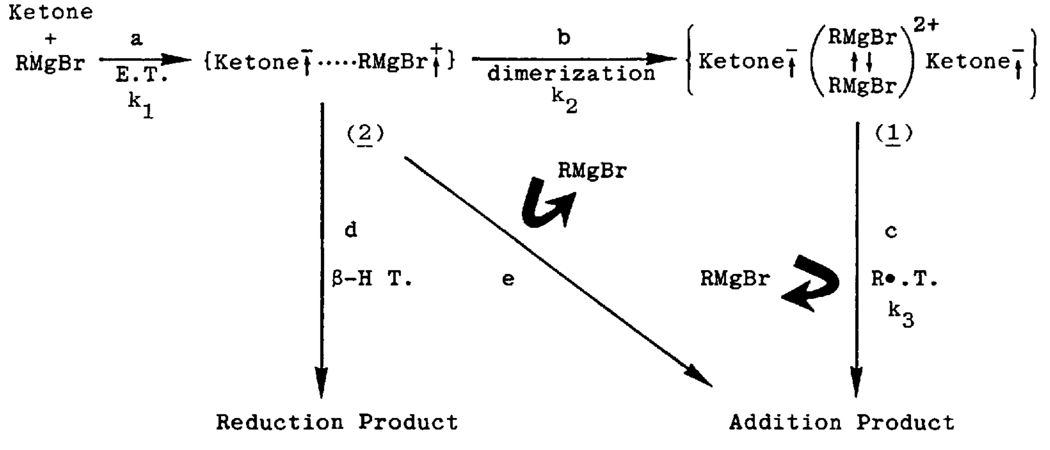
Recently, the reaction of benzophenone with organolithium compounds was investigated by means of kinetic isotope effects.[19] To be consistent with our results, the work indicated that initial fast electron transfer process was followed by rate determining R• transfer process in the reaction.

The Grignard reaction of benzil was reinvestigated by a Danish chemist.[20] By recognizing formation of O-addition product accompanied with normal C-addition product, this investigator threw a doubt on the reaction mechanism (see Scheme 2) proposed by present authors,[13] but the results did not contradict the mechanism. Taking into consideration the distribution of free spins on benzil anion radical, ignoring the cation moiety in radical intermediates, the resonance form will be depicted as shown in Figure 2. Therefore, formation of both C-addition product and O-addition product in some 'limiting' Grignard reactions is a support of fast electron transfer from a Grignard reagent and the electron transfer is followed by slow rate-determining R• transfer from the cation moiety of Grignard reagent. On this point, we will publish a paper soon.

Table 2. Estimated distances between the two spins on aggregated anion radicals

ketone	Grignard reagent	estimated distance (Å)
benzil	EtMgBr*	PCR 5·0
		GCR 5·9
fluorenone	MeMgBr	~7·2
1-methylfluorenone	MeMgBr	7·3
2-methylbenzophenone	MeMgBr	6·1

Solvent: 2-methyltetrahydrofuran. Temperature: 77 K.
*No reduction by-product was obtained under this reacting condition.



Scheme 2

Figure 2. Resonance structures of benzil anion radical

KINETIC STUDIES ON THE BEHAVIOR OF RADICAL INTERMEDIATES

Technical exploitation of producing stable radical intermediates gave us a clue to measuring the kinetic behavior of the radical intermediates.[13,17] By means of stopped-flow method, the decay process of PCR was followed under pseudo-first order conditions (in the presence of a large excess of Grignard reagent). The first order decay rate constants of PCR were proportional to the initial concentrations of the Grignard reagent used in each case. In addition, the rate constants varied widely depending on the species of Grignard reagents.[13,14] The results were explained well by Scheme 1, which assumed: i) one molecule of Grignard reagent is enough for initial electron transfer, ii) the produced monomer ion–radical pairs instantly aggregate to form a dimer radical intermediate, PCR, and, iii) alkyl radical transfer in the dimer radical intermediate is induced by assistance of another neutral Grignard molecule.

By assuming equations (1), (2), and (3), equation (4) can be derived, which consists with the experimental results.

In the Grignard reactions of benzophenones and fluorenones, like the benzil case, alkyl radical transfer processes were second order; first order to the dimer radical intermediate and first order to the neutral Grignard reagent.[17,18] This is the reason why the radical intermediate survives for a long time (even several years) under the limiting conditions of excess amount of a ketone over a Grignard reagent.

The second order rate constants of the alkyl radical transfer process, k_3 ($\mathrm{M}^{-1}\ \mathrm{s}^{-1}$) varied widely in the range of 10^7, depending upon the species of Grignard reagents and ketones examined.[17]

Similarly, the second order rate constants of initial electron transfer processes, k_1 ($\mathrm{M}^{-1}\ \mathrm{s}^{-1}$) vary in the range of 10^6. Recently reported results on the rate constant of initial electron transfer in the reaction of PhMgBr with benzil, determined by means of thermographic method, is in good agreement with our results.[20]

CHANGE OF ADDITION/REDUCTION RATIO

Since the reducing property of Grignard reagents containing β-hydrogen was first observed by V. Grignard in 1901,[1] control of addition/reduction selectivity has been the subject of numerous investigations. The problem was investigated in view of relative reaction rates,[21–24] stereochemistry,[25] and H–D isotope effects.[26] To our knowledge, however, there is no systematic investigation on the subject.

This section deals with the change of the addition/reduction ratio in the Grignard reaction, depending upon the species of Grignard reagents and properties of solvents. The reactions were carried out at room temperature in strictly dry and deoxygenated solutions which were prepared under vacuum. The addition product/reduction product values are changed depending on the relative concentration of two reactants in THF solution, as well as on the properties of the solvents. The product ratios are summarized in Tables 3 and 4.

Table 3. Ratio of addition, and reduction products in the Grignard reaction depending upon the various mixing ratios of the reagents in THF at room temperature

ketone (M)	Grignard reagent (M)	G/K[a]	conversion (%)[b]	addition/reduction
fluorenone	EtMgBr[d]			
(0·079)	(0·157)	2·00	96	2·58
(0·126)	(0·157)	1·25	94	2·34
(0·157)	(0·157)	1·00	92	2·12
(0·188)	(0·157)	0·83	74	1·75
(0·134)	(0·157)	0·50	50	1·75
fluorenone	*n*-BuMgBr[c]			
(0·077)	(0·153)	2·00	95	3·38
(0·122)	(0·153)	1·25	92	3·01
(0·153)	(0·153)	1·00	90	1·88
(0·184)	(0·153)	0·83	83	1·30
(0·306)	(0·153)	0·50	45	1·14
benzophenone	EtMgBr[d]			
(0·079)	(0·157)	2·00	99	0·214
(0·126)	(0·157)	1·25	98	0·144
(0·157)	(0·157)	1·00	96	0·138
(0·188)	(0·157)	0·83	78	0·144
(0·314)	(0·157)	0·50	50	0·139
benzophenone	*n*-BuMgBr[c]			
(0·077)	(0·153)	2·00	99	0·176
(0·122)	(0·153)	1·25	99	0·111
(0·153)	(0·153)	1·00	98	0·142
(0·184)	(0·153)	0·83	84	0·114
(0·306)	(0·153)	0·50	49	0·116

[a] The ratio of initial concentrations of Grignard reagent and ketone; G/K = ['RMgBr']/[ketone].
[b] Conversion yield based on consumed ketone.
[c] Ratios of addition/reduction were determined both by weight of two isolated products and by ^{1}H-NMR of product mixture.
[d] Ratios were determined by ^{1}H-NMR.

Table 4. Solvent effect on the ratio of addition and reduction products in the Grignard reaction at room temperature. (RMgBr/Ketone = 2·0)

ketone (M)	RMgBr (M)	solvent[a]	addition/reduction[b]
fluorenone (0·079)	EtMgBr (0·159)	DEE	3·81 ± 0·20
fluorenone (0·079)	EtMgBr (0·157)	THF	2·58 ± 0·18
benzophenone (0·079)	EtMgBr (0·159)	DEE	1·55 ± 0·09
benzophenone (0·079)	EtMgBr (0·157)	THF	0·214 ± 0·018
benzophenone (0·077)	n-BuMgBr (0·153)	DEE	0·366 ± 0·039
benzophenone (0·077)	n-BuMgBr (0·153)	THF	0·176 ± 0·010

[a] DEE = diethyl ether.
[b] Ratios of addition/reduction were determined by ^{1}H-NMR.

Inspection of these results illustrates the following facts:

(1) The larger amounts of Grignard reagents compared with ketones lead to formation of greater amounts of addition products.

(2) The reactions in diethyl ether compared with those in THF give the greater amounts of addition products.

The result (1) is consistent with the mechanism proposed by the present authors on the basis of kinetic and ESR studies.[13] The mechanism requires participation of another neutral Grignard reagent molecule for an alkyl radical transfer process in the stable anion radical aggregates. On the other hand, reduction could proceed without any assistance of another neutral Grignard reagent. These results are hardly explainable by the mechanism proposed by other investigators.[8,9]

The result (2) is explainable in terms of the well-known Schlenk equilibrium of Grignard reagents in solution.

$$2\ \mathrm{RMgX} \rightleftarrows \mathrm{R_2Mg \cdot MgX_2} \rightleftarrows \mathrm{RMgX \cdot RMgX} \qquad (5)$$

It is reported that this equilibrium shifts toward the left hand side in THF, and in diethyl ether toward right hand side.[27] According to our reaction mechanism (see Scheme 2),[13] the addition reaction will be favored under a higher concentration of Grignard reagent or in the presence of dimeric Grignard reagent, because alkyl radical transfer in the dimeric anion radical intermediate will be facilitated by another nearby neutral Grignard reagent (path b and c). A possible participation of path e can not be excluded at this stage.

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