Direct Evidence Supporting a Single-Electron Transfer Pathway in the Reduction of Ketones by Primary, Secondary, and Tertiary Grignard Reagents

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In spite of the tremendous synthetic importance involving reactions of Grignard reagents with various types of organic substrates, the mechanistic details of many of these reactions are still not well understood. Recently, in our laboratories,[1-3] as well as others,[4-7] evidence has accumulated indicating the involvement of singel-electron transfer (SET) in the reaction of Grignard reagents with aromatic ketones.

$$RMgX + Ph_2C{=}O \longrightarrow \underbrace{\left[(Ph_2C{=}O)^{-\cdot}(RMgX)^{+\cdot}\right]}_{\text{(solvent cage)}} \longrightarrow Ph_2C(R)OMgX \quad (1)$$

Frequently the SET nature of the addition reaction has been related to the stability of the intermediate alkyl radical (R·).[7] In this connection, the most convincing example of SET in Grignard reagent addition to ketones has involved reactions of benzyl[5] and *tert*-butyl Grignard reagents[1,7] with aromatic ketones. More recently we have provided information that shows that even primary Grignard reagents react with aromatic ketones by a SET pathway.[3]

Until now, there has been no direct evidence for the involvement of a SET pathway in the β-hydrogen reduction of ketones by Grignard reagents. However, Holm[8] has suggested a SET pathway to describe the reaction of benzophenone with isobutylmagnesium bromide, using data from deuterium isotope effect studies to make his point. Since the competing addition process is already proceeding by a SET pathway, it was not possible for Holm to prove that the reduction process was also proceeding by a SET mechanism. Here we wish not only to present the first direct (spectroscopic) evidence for the involvement of SET in the reduction of aromatic ketones with a wide variety of primary, secondary, and tertiary Grignard reagents, but also show that the rate of electron transfer from the Grignard reagent to the ketone is a function of the number of β-hydrogen atoms present in the alkyl group of the Grignard reagent rather then the previously suggested stability of the intermediate alkyl radical.

A sterically hindered ketone, dimesityl ketone (DMK), was chosen for the present study so that competition between addition and reduction might be reduced, the addition reaction presumably being more affected by steric effects than reduction. Fortunately, by employing DMK as the substrate, the formation of an addition product was completely eliminated while only slowing down the formation of the reduction product. Also the use of DMK allowed a clean separation of the first step of the reaction involving electron transfer from the second step involving β-hydrogen transfer. Thus, when Grignard reagents (RMgX, where R = Me, Et, Hexenyl, *i*-Bu, *sec*-Bu, *i*-Pr, *t*-Bu, *t*-$BuCH_2$, or $PhCH_2$; X = Cl or Br) and DMK were allowed to react in equimolar amounts (0.05 M) in THF, blue-colored solutions were formed. These colored solutions showed strong EPR signals (radical concentration varied from 2 to 80%) which suggested the formation of paramagnetic species. Interestingly, the solutions of all of these intermediates showed two absorption bands in the visible region, one at λ_{max} ~579 nm (major) and the other at λ_{max} ~640 nm (minor) except in the case of *t*-BuMgX reactions which showed only one band at ~640 nm. The band at ~640 nm has been assigned to the free ketyl intermediate by comparison with that of the free ketyl prepared independently and the band at ~579 nm has been assigned to the radical anion–radical cation pair. The assignment of the 579-nm band is further supported by the fact that the well-resolved EPR spectra of the solutions obtained by the reaction of different Grignard reagents with DMK are different (Figure 1). In all cases, the intensity of the visible spectrum and the EPR spectrum increased at the same rate and reached a maximum beyond which the absorption decreased as the reduction product was formed [except in the cases of RMgX (where R = *t*-Bu, *t*-$BuCH_2$, $PhCH_2$, Me) where no decrease in absorption was observed since no reduction product was formed]. The rates of formation of the paramagnetic intermeidates were found to be dependent on the nature of the Grignard reagent and followed the trend *t*-Bu > *i*-Pr > *sec*-Bu > Et > hexenyl > *i*-Bu > $PhCH_2 \simeq$ *t*-$BuCH_2$ > Me (Figure 2). Thus in the reaction of *t*-BuMgBr with DMK, over 80% radical intermediate was observed in about 1 h whereas $PhCH_2MgBr$ produced only about 2% radical intermediate, even after 15 days. In both cases no reduction product was formed, even after 2 weeks.

It is interesting to note here that in these reactions the rate of electron transfer is dependent on the number of β-hydrogen atoms present in the alkyl group of the Grignard reagent and not on the stability of the incipient alkyl radical. For example, the ethyl Grignard reagents were found to transfer an electron to DMK at a much faster rate then the benzyl Grignard reagents, whereas such behavior should be reversed if radical stability was the major factor. However, since the benzyl group has no β-hydrogens, it *should* transfer an electron to DMK at a much slower rate than the ethyl group which has three β hydrogens.

Reduction of organic substrates (such as ketones) by organometallic reagents containing the isobutyl group (e.g., *i*-Bu_3Al and *i*-BuMgBr) involve β-hydrogen transfer and is considered a very important reaction. However, during the present investigation involving reactions of DMK with Grignard reagents, we have found that the rate of β-hydrogen atom transfer is indeed dependent on the nature of the alkyl group of the Grignard reagent but follows the trend Et > hexenyl > *i*-Pr > *sec*-Bu > *i*-Bu ≫ *t*-Bu (Figure 3). Since the order of Grignard reagent activity is just the reverse for the first step of reaction (electron transfer), maybe it is not surprising that the overall rate of the reaction is most favorable for an isobutyl group when the rates of both steps are comparable.

It appears that the rate of β-hydrogen atom transfer is a function of the steric requirement of the alkyl group. Thus the ethyl group which is sterically much smaller than the isobutyl group gives the reduction product at a much faster rate. Since in these reactions we suggest the formation of a radical anion–radical cation pair, it is not surprising that the steric effect of the alkyl groups plays a major role in the hydrogen atom transfer. The overall mechanism of this reaction is outlined in Scheme I. The other possible mechanisms (shown by Schemes II–IV) can be ruled out for the following reasons:

(1) High concentrations of the radical intermediate present in the reactions studied (as high as 80%) rule out the possibility of a polar mechanism (Scheme II) and the radical chain mechanism (Scheme III), as the major reaction pathway, although it is possible that to a minor degree the polar pathway is competing with the SET pathway.

(2) The presence of different EPR spectra for different reactions of Grignard reagents with DMK not only supports the presence of a radical pair (Scheme I) but also rules out Scheme IV where

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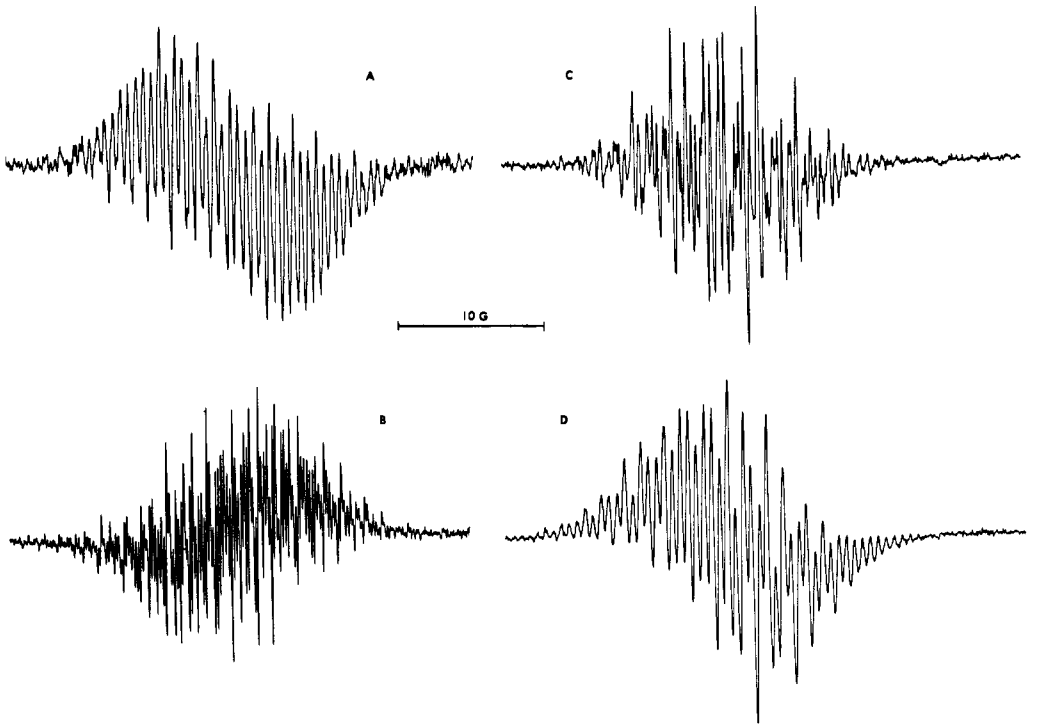
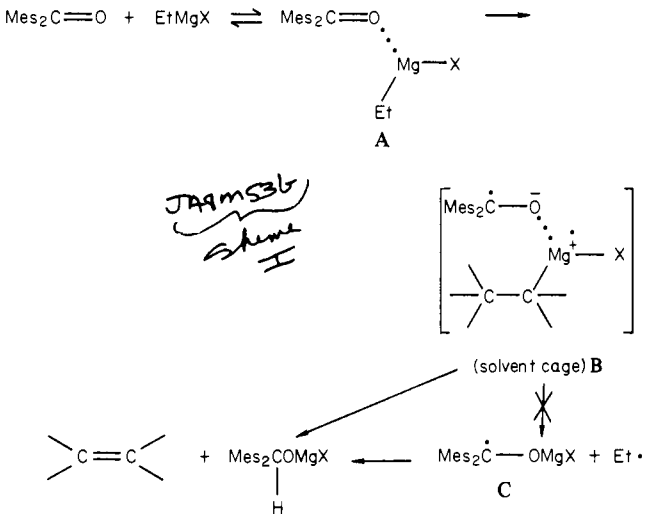
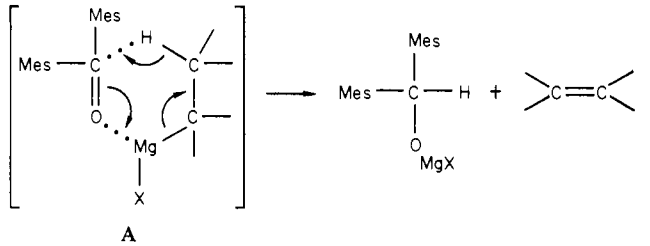


Figure 1. EPR spectrum of the reaction of dimesityl ketone with Grignard reagent RMgX [where R = (A) $PhCH_2$, (B) *t*-$BuCH_2$, (C) Me, (D) Et], in THF at room temperature.

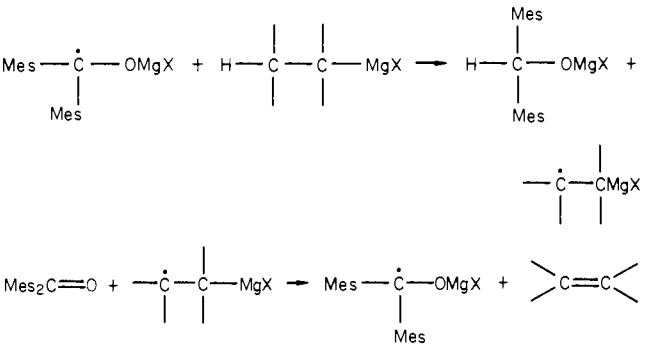
Scheme I. Radical Pair Mechanism



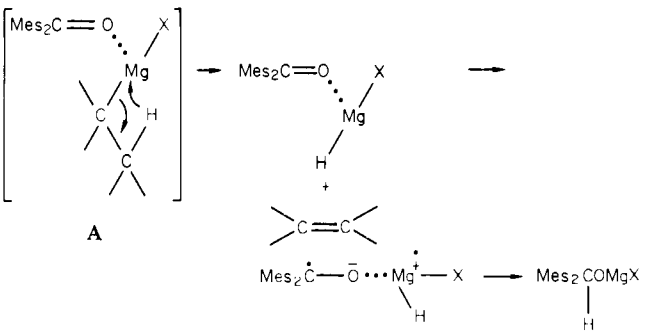
Scheme II. Polar Mechanism



Scheme III. Radical Chain Mechanism[10]



Scheme IV. β-Hydrogen Elimination Prior to Electron Transfer to Give HMgX



β-hydrogen elimination of an alkyl group generates HMgX which after electron transfer should produce the radical intermediate (D).[11] In this case one should observe similar EPR spectra regardless of the nature of the alkyl group.

Evidence that the radical anion–radical cation (B) in Scheme I does not dissociate to free radicals (C) is suggested by the fact that 5-hexenylmagnesium bromide does not result in the formation of cyclized olefins.

The reaction of *tert*-butylmagnesium chloride with di-*tert*-butyl ketone did not result in the formation of a radcial species. Indeed we do not believe, at this point, that SET takes place in the

(11) We have shown recently that HMgX reacts with dimesityl ketone via a single electron process to give the reduction product. E. C. Ashby, A. B. Goel, and R. N. DePriest, *J. Am. Chem. Soc.*, **102**, 7779 (1980).

(12) We are grateful to the National Science Foundation (Grant CHE-78-00757) for support of this work.

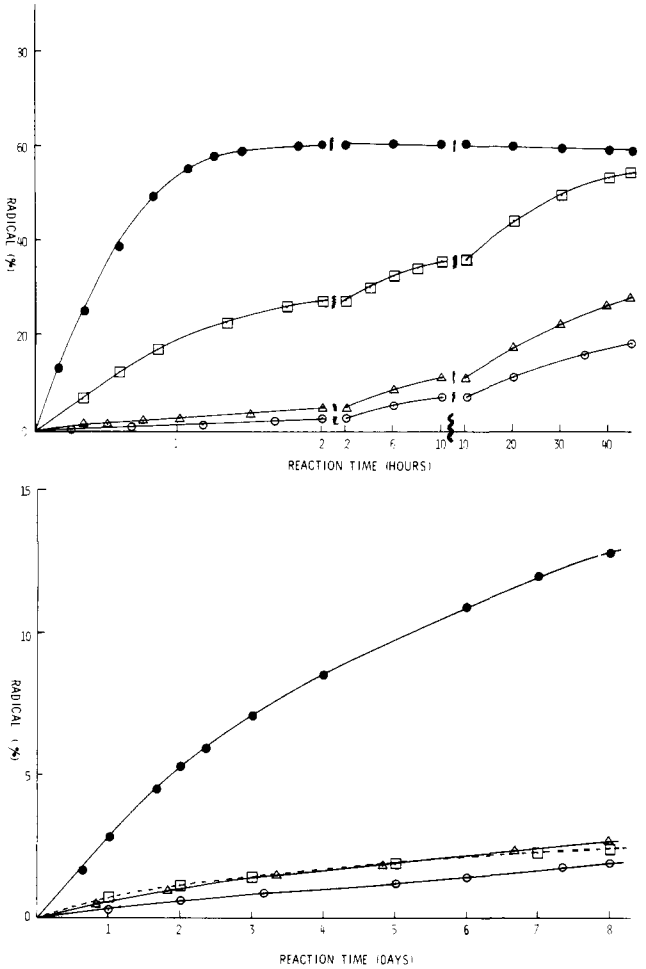


Figure 2. Formation of the radical intermediates with time determined by EPR and visible spectroscopy in the reaction of dimesityl ketone (DMK) with Grignard reagents. (a) *i*-PrMgCl (●), *sec*-BuMgCl (□), EtMgCl (△), 5-hexenylmagnesium bromide (○). (b) *i*-BuMgCl (●), *t*-$BuCH_2MgBr$ (△), $PhCH_2MgBr$ (□), MeMgBr (○).

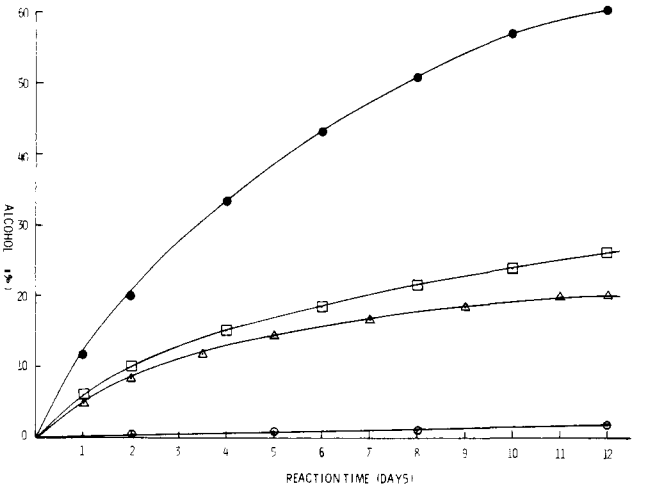


Figure 3. Formation of reduction product (Mes_2CHOH) with time determined by GLC in the reaction of DMK with Grignard reagents: (●) EtMgCl, (□) *i*-PrMgCl, (△) *sec*-BuMgCl, (○) *i*-BuMgCl.

reactions of Grignard reagents with aliphatic ketones but only with aromatic ketones or in special cases with aliphatic ketones that possess low reduction potentials (<−2.0 eV).

Preliminary results concerning the reactions of Grignard reagents with mesityl phenyl ketone indicate a similar behavior. Kinetic studies of the reactions of Grignard reagents with DMK and mesityl phenyl ketone are in progress.

Mechanism of the Zr-Catalyzed Carboalumination of Alkynes. Evidence for Direct Carboalumination[1]

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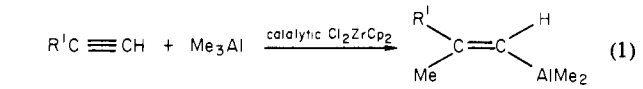
We wish to present unequivocal evidence for direct carboalumination in some representative reactions of terminal alkynes with organoalanes and zirconocene derivatives. We have recently discovered and developed controlled carbometalation of alkynes with Me_3Al and zirconocene dichloride[2] (eq 1) suitable for efficient



(1)

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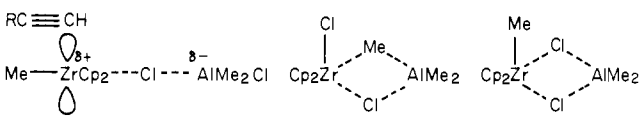
and highly stereo- and regioselective syntheses of trisubstituted olefins, especially those of terpenoid origin. In addition, this and related carboalumination reactions undergoing a clean single-state addition under homogeneous conditions appear to be well suited for detailed mechanistic studies that might be expected to shed useful light on the mechanism of carbometalation involving early transition-metal catalysts, such as the Ziegler–Natta polymerization.[3]

Since carbometalation of terminal alkynes requires the simultaneous presence of an organoalane and a Zr-containing species,[2] the reaction must involve an Al-assisted carbozirconation and/or a Zr-assisted carboalumination in the crucial carbon–carbon bond-forming step. We earlier suggested that the reactions shown in eq 1 might involve an Al-assisted carbozirconation as, for example, might be represented by **2**, on the basis of the following previous findings. First, Me_3Al and Cl_2ZrCp_2 undergo



2 3 4

a Me–Cl exchange to form species containing the $Me(Cl)ZrCp_2$ moiety, such as **3** and **4**, which is rapid on the NMR time scale at ambient temperature.[2] Cleavage of a bridging Zr–Cl bond in **4** would give the Al–Zr species in **2**. Second, the reaction of a 1-alkynyldimethylalane, e.g., *n*-PrC≡$CAlMe_2$, with preformed $Me(Cl)ZrCp_2$[4] in a 1:1 ratio gives cleanly and quantitatively the carbozirconated product **5**, thereby providing a clean-cut example of carbozirconation of alkynes[5] (eq 2). It should be emphasized here again that no reaction is observed between 1-pentyne itself and $Me(Cl)ZrCp_2$ under comparable conditions. An Al–Zr species **6** analogous to **2** appears to be a plausible active species for this reaction. Third, although **5** itself is somewhat unreactive toward

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