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STRUCTURE OF RADICAL INTERMEDIATES APPEARING IN THE GRIGNARD REACTION OF MONOKETONES

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ABSTRACT

The structure of radical intermediates appearing in the reactions of MeMgBr with aromatic monoketones was investigated by using ESR and visible spectroscopy. Stable radical intermediates in the reacting solutions were assigned to the dimeric radical ion pairs.

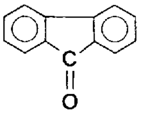
INTRODUCTION

Since the discovery of radical intermediates in the Grignard reaction with benzophenones,[1,2] evidence indicating participation of radicals in the reactions has accumulated.[3–8]

Recently, we reported the reaction mechanism of the Grignard reaction of benzil (a diketone) in THF.[3a] The structure of stable radical intermediates observed in the reaction was assigned to the aggregated structure of the radical ion pair consisting of two anion radicals of ketone and dication of dimeric Grignard reagents. We extended similar investigations to other aromatic ketones.

RESULTS AND DISCUSSION

The reaction products of methylmagnesium bromide (MeMgBr) with fluorenone (**1**), 1-methylfluorenone (**2**), benzophenone (**3**), and 2-methylbenzophenone (**4**), in tetrahydrofur-



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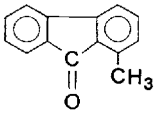

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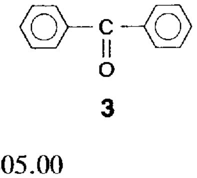

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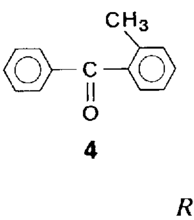

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an (THF) were pure 1,2-addition products, i.e., 1,1-di-substituted ethanols, without any reduction product. This fact is quite suitable for investigating the details of the reaction mechanism.[9]

When we allowed the fluorenone to react with MeMgBr in THF at room temperature under strictly dry and anaerobic conditions, a certain quantity of amber colored radical intermediate (λ_{max} = 454 nm) accumulated in the reacting solution. The radical intermediate showed a well-resolved ESR spectrum of a fluorenone anion radical (a_{2H} = 0·342 mT, a_{2H} = 0·266 mT, a_{2H} = 0·075 mT, and a_{2H} = 0·043 mT, see Figure 1A), In the reaction of 1-methylfluorenone with MeMgBr a similar amber colored radical species (λ_{max} = 453 nm) appeared in the reacting solution. The radical intermediate showed a well-resolved ESR spectrum of a 1-methylfluorenone anion radical (a_{1H} = 0·423 mT, a_{5H} ~ 0·258 mT, a_{2H} ~ 0·074 mT, and a_{2H} ~ 0·037 mT, see Figure 1B).

In the reaction of benzophenone with MeMgBr a stable pink colored radical intermediate (λ_{max} = 550 nm) appeared, which showed a well-resolved ESR spectrum of a benzophenone anion radical (a_{2H} = 0·357 mT, a_{4H} = 0·290 mT, and a_{4H} = 0·104 mT, see Figure 1C). (The other blue colored intermediate appeared initially in the reacting solution, but could not be observed by ESR because of its extremely short lifetime [$<\sim$ 200 ms].[3b]) Similarly, in the reaction of 2-methylbenzophenone a pink colored radical intermediate (λ_{max} = 540 nm) appeared, which showed a well-resolved ESR spectrum of a 2-methylbenzophenone anion radical (a_{1H} = 0·540 mT, a_{2H} = 0·481 mT, a_{2H} = 0·193 mT, a_{5H} ~ 0·057 mT, and a_{2H} ~ 0·019 mT, see Figure 1D).

By ESR spectroscopy, we did not detect any possible counter cation radical; the free Grignard cation radical was derived from MeMgBr.[10,11] As in the case of benzil,[3a] this was indicative of participation of the dimeric radical intermediates in the reactions. In the case of benzil, we observed triplet ESR spectra due to dimeric radical intermediates in rigid media.

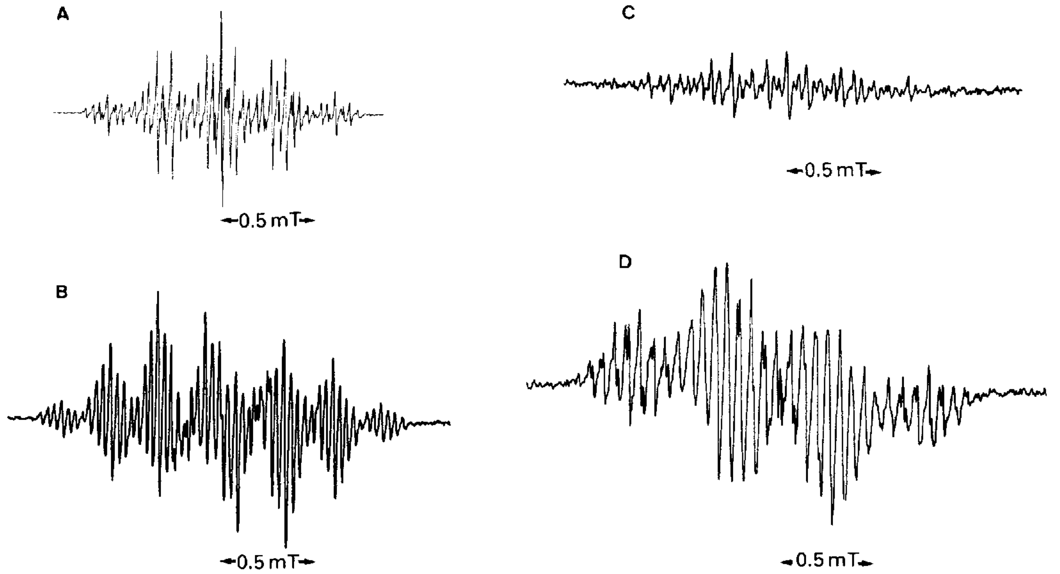


Figure 1. ESR spectra of the radical intermediates generated in the reaction of MeMgBr in THF at room temperature; A) reaction with fluorenone, B) reaction with 1-methylfluorenone, C) reaction with benzophenone and D) reaction with 2-methylbenzophenone

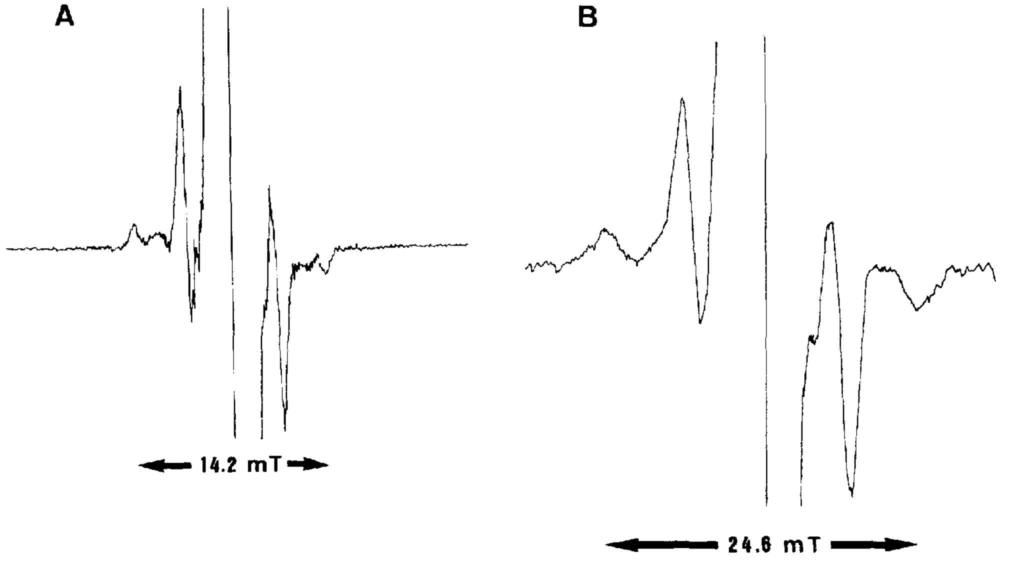
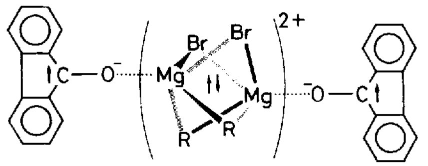


Figure 2. Triplet ESR spectra, observed at 77 K, of the radical intermediates in the reaction of MeMgBr in MTHF; A) reaction with 1-methylfluorenone and B) reaction with 2-methylbenzophenone

Actually, both the amber colored radical intermediate generated in the reaction of fluorenone with MeMgBr and the pink colored radical intermediate generated in the reaction of 2-methylbenzophenone with MeMgBr showed the respective triplet ESR spectra. Similarly, a well resolved triplet ESR spectrum was observed at 77 K in a 2-methyltetrahydrofuran (MTHF) solution of the amber colored radical generated in the reaction of 1-methylfluorenone with MeMgBr (Figure 2). Although fluorenone showed a weak triplet ESR spectrum in the reaction with MeMgBr in MTHF, non-substituted benzophenone showed no appreciable triplet ESR spectrum under the same conditions, because of the lower concentration of the radical intermediate in MTHF solution.

In both reactions of fluorenone and benzophenone, we could only trap too small an amount of the radical species to detect clear triplet ESR spectra in rigid MTHF at 77 K, because of the faster decay of both the above radical intermediates to form final 'addition products'. Concentrations of the trapped radicals were estimated to be about 5 μM in the reaction of fluorenone and about 20 μM in the reaction of benzophenone (compared with standard 1,1-diphenyl-2-picrylhydrazyl (DPPH); about 1/100 of the radical amount accumulated in the case of 2-methylbenzophenone). The electron transfer rates from Grignard reagents to ketones and rates of alkyl or aryl radical transfer in the stable dimeric radical ion pair to form a stable 'addition product' were already reported[3b–d] (electron transfer rates: fluorenone > benzophenone > 1-methylfluorenone >> 2-methylbenzophenone; and alkyl radical transfer rates: benzophenone > fluorenone >> 1-methylfluorenone > 2-methylbenzophenone). (The rate constants of electron transfer and successive methyl radical transfer in the reaction of fluorenone in THF at 25 °C were $15\,\mathrm{M^{-1}s^{-1}}$ and $0{\cdot}07\,\mathrm{M^{-1}s^{-1}}$ respectively, while in that of 1-methylfluorenone they were $7\,\mathrm{M^{-1}s^{-1}}$ and $< 0{\cdot}005\,\mathrm{M^{-1}s^{-1}}$.)

From the fine structure of the triplet ESR spectrum, we determined D' and E', the energy parameters of spin–spin interaction, which enabled us to estimate the average distance between two spins on two anion radicals aggregated with cation moiety in the radical



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intermediate (Structure **5**). The energy parameters *D'* and *E'* for the radical intermediates generated in the Grignard reactions are given in Table 1, together with the estimated distances between two spins on two anion radicals. Interestingly, the distance observed in the reaction of 2-methylbenzophenone with *p*-anisylmagnesium bromide (*p*AniMgBr) is slightly larger than that in the reaction with MeMgBr (entries 3–5). This is clear evidence that the alkyl or aryl moiety of Grignard reagent affects the distance of two spins on the aggregated radical ion pair.

Table 1. Energy parameters (*D'* and *E'*) and average distance (*r*) of spin–spin interaction between two anion radicals in the Grignard reaction intermediate

entry	ketone	RMgBr	*D'*(mT)	*E'*(mT)	*r*(Å)
1	fluorenone	MeMgBr	~ 7·4	~ 0	~ 7·2
2	1-methylfluorenone	MeMgBr	7·1	~ 0	7·3
3	2-methylbenzophenone	MeMgBr	12·3	~ 0	6·1
4		EtMgBr	12·3	~ 0	6·1[3c]
5		*p*AniMgBr	11·8	~ 0	6·2

Since the monomer–dimer equilibrium of fluorenone alkali metal ketyls has been well investigated using electronic spectroscopy,[12] the extent of the dimeric aggregation of the radical intermediate in the reaction of fluorenone with MeMgBr was determinable by means of visible spectroscopy. The visible spectrum of fluorenone lithium ketyl in THF solution showed two absorption maxima at 450 nm and 530 nm (Figure 3B), while the amber colored radical intermediate generated in the reaction of fluorenone with MeMgBr showed only one absorption maximum at 454 nm with a very weak shoulder at about 530 nm (Figure 3A).

For the fluorenone metal ketyl, both of these two absorption bands were assigned; the band at $\lambda_{max} = 530$ nm to the monomeric ion radical pair, and the other band at $\lambda_{max} = 450$ nm to the dimeric ion radical pair, in which two cation moieties aggregated. Thus, it could be concluded that the radical intermediates generated in the reaction of fluorenone with MeMgBr mostly were in the dimeric state in the THF solution. Based on the reported molar extinction coefficients of a monomer and a dimer of fluorenone metal ketlys,[12d] we roughly estimated the association constant of the amber colored intermediate to be no less than $7 \times 10^6\,\mathrm{M}^{-1}$ at 25 °C.

A similar visible spectrum of the amber colored radical intermediate was observed in the reaction of 1-methylfluorenone. For comparison, the visible spectrum of the radical intermediate in the Grignard reaction and that of 1-methylfluorenone lithium ketyl in solution were given in Figures 3C and 3D, which indicate the major component in the dimeric state.

The visible spectrum of the pink colored intermediate which appeared in the reaction of benzophenone discloses the major contribution of the dimeric state ($\lambda_{max} = 550$ nm) of the

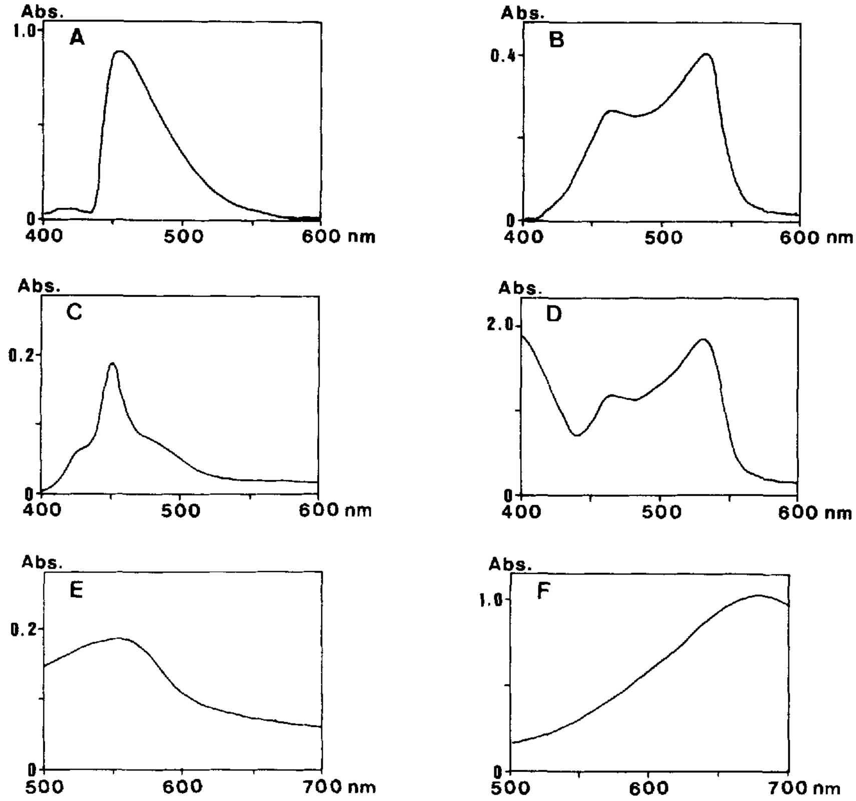


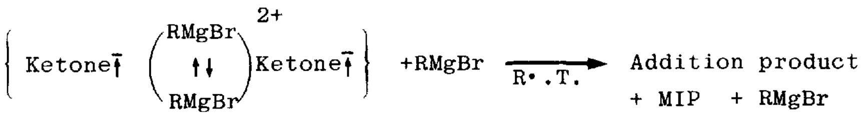
Figure 3. Visible spectra of radical intermediates together with the ketone lithium ketyls in THF at 25°C; A) radical intermediate in the reaction of fluorenone, B) fluorenone lithium ketyl, C) radical intermediate in the reaction of 1-methylfluorenone, D) 1-methylfluorenone lithium ketyl, E) radical intermediate in the reaction of benzophenone and F) menzophenone lithium ketyl

radical intermediate species, but this is not so clear as in the case of fluorenones, because of the broad bands (Figure 3E and 3F).

CONCLUSION

The present study has focused on the structure of the radical intermediate in the Grignard reaction of an aromatic monoketone in THF. It was concluded that the stable radical intermediate in the reaction consists of two molecules of ketone anion radicals aggregated with

$$2\ \text{ketone} + 2\ \text{RMgBr} \xrightarrow[\text{E.T.}]{} 2\ \underset{\text{(MIP)}}{[\ \text{ketone}^{\bar{\cdot}} \cdots \text{RMgBr}^{\overset{+}{\cdot}}\ ]} \xrightarrow[\text{dimerization}]{}$$



$$\left\{ \text{Ketone}^{\bar{\uparrow}} \left(\begin{matrix} \text{RMgBr} \\ \uparrow\downarrow \\ \text{RMgBr} \end{matrix} \right)^{2+} \text{Ketone}^{\bar{\uparrow}} \right\} + \text{RMgBr} \xrightarrow[\text{R}^{\bullet}\text{.T.}]{} \begin{matrix} \text{Addition product} \\ + \text{MIP} + \text{RMgBr} \end{matrix}$$

(5)

a dimer dication of the Grignard reagent. The possible scheme of the Grignard addition reaction with aromatic monoketones in THF could be depicted as given in Scheme 1.[3a,d]

EXPERIMENTAL

Materials and Methods

Fluorenone (**1**, guaranteed reagent grade) was recrystallized from ethanol. Benzophenone (**3**, guaranteed reagent grade) was recrystallized from hexane and from ethanol. 1-Methylfluorenone **2** prepared by Ullmann synthesis[13] from 2-amino-2′-methylbenzophenone was recrystallized from methanol, m.p. 98·5 °C; ^{1}H-NMR(CCl_4) δ 2·60(s,3H), 6·9–7·6(m,7H). 2-Methylbenzophenone **4** prepared by Friedel–Crafts reaction of *o*-toluoyl chloride with benzene by $AlCl_3$ catalyst was distilled twice, b.p. 140 °C(12 Torr); ^{1}H-NMR(CCl_4) δ 2·31(s,3H), 7·0–7·8(m,9H). Commercially available pure tetrahydrofuran (THF) and 2-methyltetrahydrofuran (MTHF) were distilled in vacuo from reservoirs containing sodium benzophenone ketyl. Preparation of Grignard reagents was described previously.[3a]

A JEOL JES-FE1XG X-band ESR spectrometer system was used. Absolute amounts of radicals were determined by comparison with standard 1,1-diphenyl-2-picrylhydrazyl (DPPH). For the fine and the hyperfine splitting constants determinations a Mn^{2+} marker and a Fremy's salt standard were used. A JEOL JNM-100 MHz ^{1}H-NMR spectrometer was used for final product analysis.

Reactions

Preparation of samples and ESR observation at room temperature, ESR measurement at 77 K, and visible spectroscopy were undertaken as described previously.[3a] In general, we used two times excess amount of ketone over Grignard reagent (initial concentration of the reacting solution ca. 0·04 M) to make the decay of the intermediate slow. Fine splitting constants and hyperfine splitting constants were determined by mean values of three experiments.

Product analysis was carried out as follows: to 1 mmol of ketone dissolved in a strictly anaerobic and dried THF solution (5 ml) was added 1 mmol of a Grignard reagent solution at an ice cooled temperature. The reaction was continued for 4 days at room temperature. The reacting solution was quenched and hydrolyzed with 2 ml of a saturated aqueous NH_4Cl solution under strictly anaerobic conditions. The hydrolyzed mixture was extracted with ether, and dried over anhydrous magnesium sulfate. A mixture of products was subjected to ^{1}H-NMR measurement.

In the reaction of fluorenone with MeMgBr in THF, the sole product was 9-methylfluorene-9-ol (^{1}H-NMR($CDCl_3$) δ 1·68(s,3H), 2·03(br,1H) 7·2–7·6 (m,8H)). A possible reduction product, fluorene-9-ol was not detected.

In the reaction of 1-methylfluorenone with MeMgBr in THF, the sole product was 1,9-dimethylfluorene-9-ol (^{1}H-NMR($CDCl_3$) δ 1·76(s,3H), 1·90(br,1H), 2·56(s,3H), 6·9–7·6(m,7H)). Another possible reduction product, 1-methylfluorene-9-ol was not detected.

In the reaction of benzophenone with MeMgBr in THF, the sole product was 1,1-diphenylethanol (^{1}H-NMR($CDCl_3$) δ 1·75(s,3H), 2·70(br,1H), 7·0–7·6(m,10H)), together with no benzhydrol.

In the reaction of 2-methylbenzophenone with MeMgBr in THF, the product was solely 1-phenyl-1-(*o*-tolyl)ethanol (^{1}H-NMR(CCl_4) δ 1·81(s,3H), 1·92(s,3H), 2·50(br,1H), 7·0–7·7(m,9H)), together with no phenyl(*o*-tolyl)-methanol, a possible reduction product.

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