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Ketyl Radicals Formed in Grignard Reaction. III.[1] Steric Effects on the Formation of Radicals

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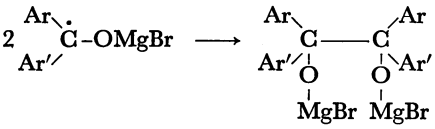
In the reaction of benzophenone with phenylmagnesium bromide, the concentration and life-time of the ketyl radical were influenced greatly by the substitution of *ortho*-hydrogen atoms of both the two reactants by methyl group. From the results of visible absorption and ESR measurements and also of product-analysis, the ketyl radical was considered to be a common intermediate towards normal and abnormal reaction products. The existence of an equilibrium between monomeric and dimeric states of the ketyl radical was also proposed.

The peculiarity of the ketyl radical observed in the Grignard reaction of *o*-methylbenzophenone was discussed in comparison with that of potassium-ketyl of the same ketone,[1] but the reason for the ketyl radical having a long "life time" remained ambiguous. The effects of the *o*-methyl group of benzophenone as well as those of the phenyl-Grignard reagent on the formation of ketyl radicals have been studied more precisely.

Results and Discussion

The formation of ketyl radicals was followed by observation of the characteristic coloration of the reaction solution by means of visible absorption spectroscopy and ESR spectroscopy. Results obtained by use of these techniques will be discussed separately.

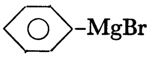
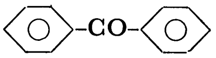
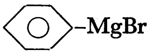
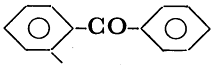
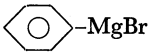
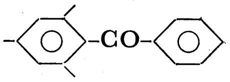
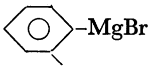
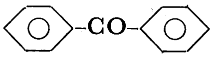
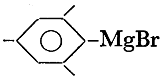
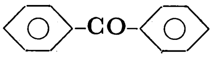
"Life Time" of Ketyl Radicals. When *o*-methyl-substituted benzophenones were treated with arylmagnesium bromide (ArMgBr) in tetrahydrofuran (THF) under N_2-atmosphere or in vacuum and at room temperature, the colorless solution turned to purple or wine-red. The coloration, which is due to the formation of ketyl radicals,[1] lasted in most cases for as long as several months. Benzopinacol, as a minor product, has often been isolated from the reaction mixture of benzophenone and Grignard reagents, being considered to be the product formed by dimerization of the ketyl radical (Scheme 1).[2]


(1)

The time during which the characteristic coloration was observed is tentatively denoted in this paper as the "life time" of a ketyl radical. The "life time" at 50 °C was greatly influenced by the number of *o*-methyl groups. The "life times" of radicals and the yields of carbinols and pinacols are given in Table 1. The increasing number of *o*-methyl groups on the ketone prolongs the "life time" exceedingly (experiments 1, 2 and 3). That of *o*-methyl groups on ArMgBr also prolongs it, but the effect is smaller (experiments 1, 4 and 5). The fair yield of benzopinacol in experiment 5 can be attributed to the steric hindrance effect of *o*-methyl groups of mesityl-MgBr. However, the absence of the pinacol, despite the appearance of the characteristic color, in experiment 4 must be noted. This fact shows that the ketyl radical formed does not necessarily dimerize to the pinacol. When the velocity of the formation of *o*-methyltriphenylcarbinol in experiment 4 was compared with that of the same product in experiment 2, the unsubstituted benzophenone was

Table 1. "Life times" of radicals and yields of carbinols and pinacols

0.9 M ketone and 1.35 M ArMgBr, at 50 °C.

No.	ArMgBr	Ketone	"Life Time" (min)	Yield (%)	
				Carbinol	Pinacol
1			0	100	0
2			210	69	10
3			>1100	8	trace
4			5	100	0
5			10	1.8	45

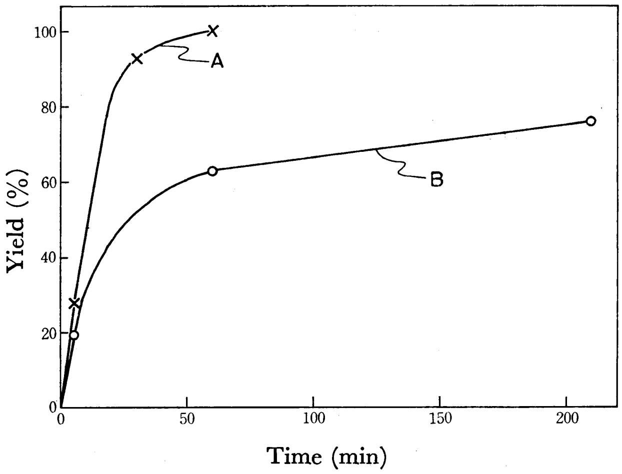
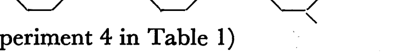
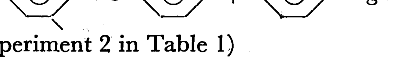


Fig. 1. Yields of *o*-methyltriphenylcarbinol at 50 °C.

A: 

(experiment 4 in Table 1)

B: 

(experiment 2 in Table 1)

0.9×10^{-2} mol ketone and 1.35×10^{-2} mol ArMgBr.

found to yield the carbinol rapidly and quantitatively (Fig. 1). The short "life time" of the ketyl radical in experiment 4 can thus be attributed to the rapidity of the normal addition reaction.

These facts make it possible to assume that the ketyl radical is a common intermediate in Grignard reaction. If the ketyl radical is pictured tentatively as shown in Fig. 2, the normal addition product and the dimerization product can be explained in terms of steric hindrance, effects of which can be classified as (i) the effect caused by the Grignard moiety, and (ii) that caused by the ketone moiety. When (i) is large and (ii) small, the Grignard-aryl group cannot come close to the carbonyl-carbon atom and the radical would tend towards the sterically less-hindered dimerization process,[2] this being the case in experiment 5. The dimerization process is retarded by effect (ii), which is shown in experiment 3. In this case (i) is small and (ii) very large, and the Grignard reagent attacks the unsubstituted phenyl group of the ketone as reported by Fuson *et al.*[3] (Scheme 2). This nuclear phenylation has been explained recently on the basis of an electron-transfer mechanism.[4]

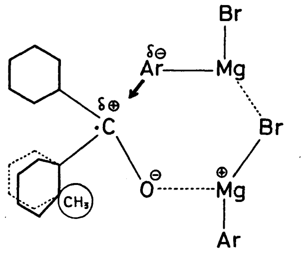
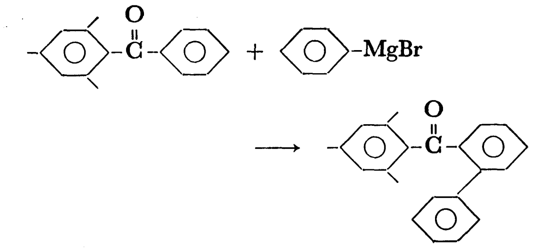


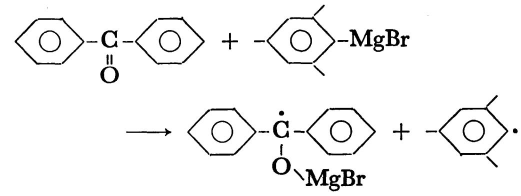
Fig. 2. Attempted depiction of ketyl-type radical intermediate.
At present, it cannot be decided on which of the two (or more) Ar groups delocalizes the other free electron.



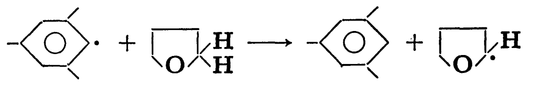
(2)

The rapidity of the formation of the carbinol in experiment 4 is explained in terms of the energy level of the reaction intermediate, ketyl radical. The delocalization of the free electron spin is favored owing to the small twisting angle of the two phenyl groups of benzophenone out of plane of its carbonyl group, thus lowering the energy level. The same effect can be expected also in experiment 5, but the enhanced effect of steric hindrance of the Grignard-mesityl group makes it impossible to produce the carbinol.

A considerable amount of mesitylene was found in experiment 5. When a larger scale reaction was carried out using 28% excess molar mesityl-MgBr and the reaction mixture was decomposed by D_2O-D_2SO_4, the content of monodeuteriomesitylene in the recovered sample of mesitylene was about 30% on the basis of NMR absorption. Thus the mesityl radical, produced as a result of the electron-transfer from the Grignard reagent to the ketone (Scheme 3), would abstract hydrogen from the THF molecule (Scheme 4).

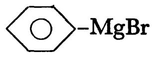
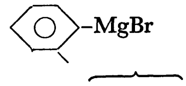
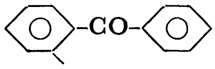
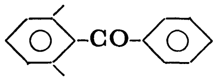
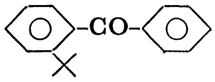
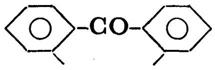
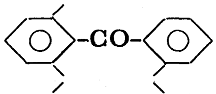
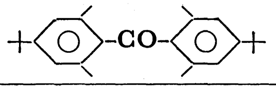


(3)



(4)

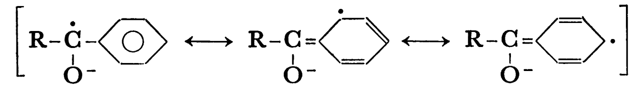
TABLE 2. VISIBLE ABSORPTION BANDS OF RADICAL SPECIES
Ketone: 3.3×10^{-4}M, ArMgBr: 5.0×10^{-4}M
s: strong, m: medium, w: weak.

No.	Ketone	 –MgBr λ_{max}(nm)	temp. (°C)	ε	 –MgBr λ_{max} (nm)	temp. (°C)	Mg(Hg) λ_{max} (nm)
I		553 s 610m	25	>8500	553 s, 610m	25	60—610 s (broad)
II		434, 540 s, 580m	25	>8000	383, 530m, 570w	50	434, 540 s, 580w
III		380, 534 s, 565m	25	>4000	380, 555w	50	438, 534 s, 565w
IV		564 s, 620m	25	~2000	564 s, 620w	50	620 s
V		450, 560m, 615w	50	~150	not observed	50	438, 570 s, 610w
VI		430, 580w, 610w	50	~30	not observed	50	————

Thus, all the results are explained by considering the formation of a ketyl radical to be an essential process in the Grignard reaction.

Visible Absorption Spectra. Evacuated optical cells were used for the measurements of visible absorption spectra of ketyl radicals. Main absorption bands appear at 530—580 nm. They are accompanied by weaker bands at longer wavelength side (570—620 nm) in all cases. Absorption spectra of Mg-ketyls of respective ketones were also measured (Table 2).

The values of absorbance give a rough estimate obtained when the absorbance of main band becomes almost maximum after a certain time of reaction of each ketone with phenyl-MgBr. High absorbances observed in the cases of ketones bearing at least one unsubstituted phenyl group can be attributed to the spin delocalization given by:



Though the nearly planar structure of unsubstituted benzophenone favors spin delocalization, the ketyl of this least-hindered ketone favors, at the same time, normal addition and/or dimerization (Table 1, experiments 1, 4 and 5). For this reason, any high absorbance cannot be realized in the Grignard reaction of benzophenone itself.

The temperatures listed in Table 2 are those necessary to realize a velocity of color development suitable for ordinary measurements under the conditions of the described molar concentrations. In reactions with phenyl-MgBr, ketones I—IV easily reveal colors at room temperature but V and VI need higher temperatures. In reactions with *o*-tolyl-MgBr, only ketone I reveals color at room temperature, II—IV need higher temperatures, and V and VI do not reveal color after warming for several hours. Thus the initial electron-transfer process is affected by two kinds of steric hindrance; one due to ketones, and the other to Grignard reagents.

The absorption bands at 380—450 nm appear when at least one of the two aryl groups of ketone twists almost perpendicularly out of plane of the carbonyl group, but these bands were not assigned in this work. The following discussion is concerned mainly with *o*-methyl- and *o,o'*-dimethylbenzophenone. The variation of the relative absorbance $\varepsilon_{564}/\varepsilon_{620}$ in the time-course of the reaction of *o,o'*-dimethylbenzophenone with phenyl-MgBr is interesting. For convenience, the relative height at $\lambda_{\max}$'s of the respective band was taken as the value of $\varepsilon_{564}/\varepsilon_{620}$. The relative absorbance is small in the initial stage, and becomes larger as the reaction proceeds under each molar concentration (Fig. 3). It becomes smaller when the solution is diluted. The convergence of the relative absorbance to the value of 1.65—1.70 after 24 hr suggests the existence of an equilibrium. As the 620 nm band of the Grignard ketyl can be assigned to its monomeric state on the basis of the fact that the Mg-ketyl has a simple band at the same wavelength, the 564 nm band could be assigned to its dimeric state. This assignment is supported by the following results. When the concentration of ketone is low (experiments iii, iv and v), the relative absorbance is larger as the molar ratio of ketone is higher (experiments iv and v). The higher relative absorbances in the initial stage of experiment iii than that of iv can be explained as follows: a much higher amount of the monomeric ketyl initially formed by the action of the much higher amount of Grignard reagent in experiment iii affords a higher amount of the dimeric aggregate than in experiment iv.[6] This is reasonable since the velocity of the initial developement of absorbance decreases in the order: ii>iii>i~iv>v (not represented in Fig. 3).

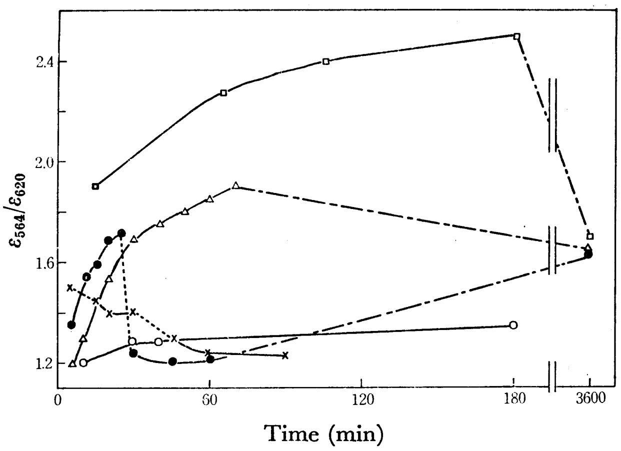
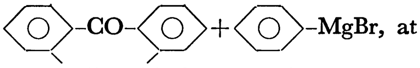


Fig. 3. Variation of relative absorbance $\varepsilon_{564}/\varepsilon_{620}$ with respect to time.

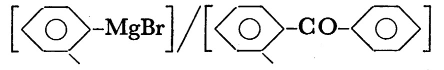


at 25 °C

······: Diluted before the subsequent measurement.
-·-·-·: Left to stand for 24 hr.
Molar concentration: [Grignard]/[Ketone], × 10⁴ M.
i) ○, 5.0/3.3=1.5 ii) ×, 30.0/3.3=9.0
iii) ●, 30.0/0.66=45.0 iv) △, 5.0/0.66=7.6
v) □, 1.0/0.66=1.5

In the reaction of *o*-methylbenzophenone with *o*-tolyl-MgBr, a similar phenomenon was observed (Table 3). The absorption band of Mg-ketyl of this ketone broadened from 560 to 610 nm probably owing

TABLE 3. VARIATION OF RELATIVE ABSORBANCE $\varepsilon_{553}/\varepsilon_{610}$ WITH RESPECT TO TIME



$=[5.0\times10^{-4}]/[3.3\times10^{-4}]$
$=1.5$

Reaction time (min)	Extent of dilution	temp. (°C)	$\varepsilon_{553}/\varepsilon_{610}$
5	×1	25	1.63
10	×1	25	2.12
20	×1	25	2.41
25	×1	25	2.45
45	×1	25	3.11
60	×5	25	2.09
⋮	⋮	⋮	⋮
3600	×5	25	1.25
3605	×5	5	1.32
3610	×5	25	1.25

to the unsymmetrical molecular structure. The twisting vibration of *o*-tolyl group out of plane of the benzoyl group is considered to be easier in Mg-ketyl than in Grignard-ketyl.[1] The mixing of the electronic transition corresponding to the benzoyl group with that corresponding to the *o*-tolyl group could be expected. In contrast to the Mg-ketyl, the Grignard-ketyl has bands at 553 and 610 nm, resembling the Grignard-ketyl of *o,o'*-dimethylbenzophenone. Taking into account the previous observation of the very high spin density on the unsubstituted phenyl group of the Grignard-ketyl of *o*-methylbenzophenone,[1] one could ascribe the absorption bands of this ketyl mainly to the electronic transition corresponding to the unsubstituted benzoyl group. A discussion on the relative absorbance is thus significant in this case. It becomes larger as the reaction proceeds, smaller when the solution is diluted, and again larger when the temperature is lowered.

The existence of another equilibrium between the original ketone and the monomeric ketyl is suggested from the effect of temperature and that of the steric hindrance caused by the Grignard reagent (Table 2). The existence of this equilibrium is also suggested from the relative velocity of the initial developement of absorbance found in the experiments (Fig. 3). A higher velocity was realized by the higher molar ratio of the Grignard reagent and also by the higher concentrations of the two reactants. The two equilibrium processes can be represented as follows (Scheme 5).

$$2G + 2B \overset{K_1}{\rightleftarrows} 2G^{+\cdot} + 2B^{-\cdot}$$

$$\overset{K_2}{\rightleftarrows} [B^{-\cdot} \cdots G^{+\cdot} \cdots B^{-\cdot}] + G^{+\cdot} \qquad (5)$$

G: Grignard reagents
B : Benzophenones

The ketyl radical in Fig. 2 depicts the monomeric state "$2G^{+\cdot}+2B^{-\cdot}$," a part of which is the precursor of carbinol. The dimeric species $[B^{-\cdot}\cdots G^{+\cdot}\cdots B^{-\cdot}]$ is considered to be the precursor of pinacol. The Grignard reagent represented tentatively as monomeric in this scheme may exist as more aggregated state.[6,7]

Radical Concentration. The radical concentration, determined by ESR technique, was also affected by the structure of ketone and that of the Grignard reagent. A single sample tube was used throughout the measurement, and conditions of the ESR spectrometer were kept constant as far as possible. The results for the respective combinations of reactants differ considerably (Fig. 4), and thus it is feasible to discuss the relative effect of substituent.

The maximum concentration of the ketyl radicals formed in reactions with phenyl-MgBr decreases in the order:

2-*t*-Butyl- > 2,6-Dimethyl- > 2,2'-Dimethyl- >
(C) (D) (A)
2-Methyl- > 2,6,2'-Trimethylbenzophenone
(B) (F)

A different order, A>B>C>D>F, is found for the velocity of electron-transfer in the initial stage of the reaction. The two orders can be explained in terms of steric hindrance. In cases A and B, the initial electron-transfer is relatively rapid owing to the small steric hindrance which in turn favors the subsequent normal addition and dimerization, and thus the concentration of the ketyl radicals begin to come down in short times. In cases C and D, the large steric hindrance retards the initial electron-transfer as well as the subsequent processes,[4] and thus the remarkably high radical concentrations are realized after long times of reaction. The high radical concentrations in these cases are ascribed to the small equilibrium constant K_2 of Scheme 5. The low concentration in case F would be due mainly to the largest (of cases A—F) steric hindrance against the initial electron-transfer. If case E is compared with B, the effect of *o*-methyl group of Grignard reagent can be discussed. The velocity of the initial electron-transfer from *o*-tolyl-MgBr, being lower than that from phenyl-MgBr, becomes comparable to that of subsequent processes, thus depressing the radical concentration.

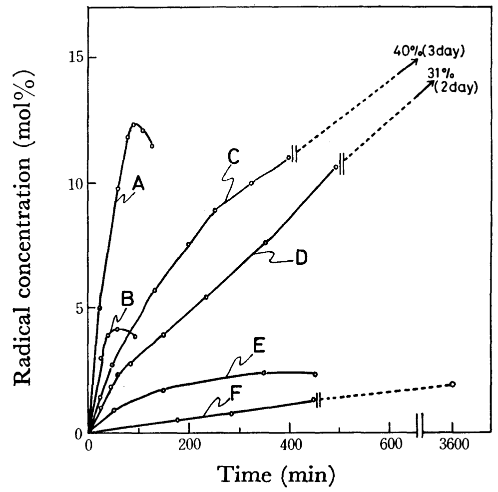
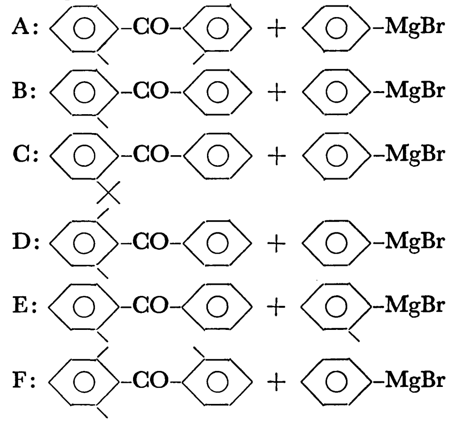


Fig. 4. Variation of radical concentration based on original ketones at 20 °C.
ArMgBr: 7.0×10⁻⁴, Ketone: 3.3×10⁻⁴.



ESR measurement provides further evidence for the existence of the monomer-dimer equilibrium. The effect of temperature in the case of mesityl phenyl ketone and phenyl-MgBr is as follows: the radical concentration decreased to 89—91% at −30 °C and to 69—73% at −50 °C based on a concentration observed at +20 °C, and the variation was reproducible.

Another evidence obtained from the effect of dilution is as follows: when a volume of the solvent twice as much as that of the reaction solution was added just after the radical concentration reached the maximum (reaction A, Fig. 4), the resulting concentration was 21% higher than that expected from the extent of dilution.

Conclusion. The characteristics of the Grignard reaction are considered by a large number of investigators to be ionic, and the contribution of radical processes has been recognized only in a few cases.(2) Ashby and his co-workers(8) proposed that heavy metal impurities in magnesium initiate the formation of benzopinacol in the reaction of benzophenone with methyl-MgBr. However, they later observed the formation of the ketyl radical in the reaction of *o*-methylbenzophenone with the same Grignard reagent.(9) The reason for the long "life time" of the Grignard–ketyl of *o*-methylbenzophenone(1) can now be given: (a) the steric hindrance of the ketyl radical against the normal addition and dimerization, or (b) the enhanced delocalization of the free spin on the phenyl group.(1) The latter may cause a trend towards a slow nuclear phenylation similar to that observed in the reaction of mesityl phenyl ketone, though the detection of such a minor product was difficult.(4)

The effect of steric hindrance on the formation of the ketyl radical due to the initial electron-transfer is evidently consistent with the same effect on the decay of the radicals due to the subsequent processes.

Experimental

Materials and Reaction. *ortho*-Methyl-substituted benzophenones were prepared according to the method previously reported.(10) Grignard reagents in THF were prepared as usual and transferred to storage bottles under N_2-atmosphere. A definite aliquot of Grignard solution was pipetted out under N_2-stream, and transferred to a reaction flask. Benzophenone and its derivatives dissolved in THF were added at once. The reaction mixture was stirred at 50 °C for a certain time as long as the characteristic color was observed, and hydrolyzed with aqueous ammonium chloride. The products were analyzed by means of glc and tlc.

Visible Absorption Measurements. The apparatus for measurements was constructed from an optical cell and a reaction vessel equipped with a container for ketone connected with a breakable seal. An aliquot of ArMgBr solution was transferred under N_2-stream to the reaction vessel, frozen with liquid N_2, evacuated by means of a vacuum line, and diluted to an appropriate volume by vacuum distillation of THF. The apparatus was sealed off. Immediately after the breakable seal was broken, the optical measurement was begun. A Hitachi EPS-3T model spectrophotometer was used.

ESR Measurements. The apparatus for measurements was constructed as described previously.(11) Preparation of samples was similar to that for the optical measurements. Radical concentration was determined by the over-modulation technique. JEOL ME-3X model and PE-1X model spectrometers were used.

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