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# Kinetic Isotope Effect and Substituent Effect Study on the Grignard Reaction of MeMgI with Benzophenone. A Rate-Determining C-C Bond Formation[#]

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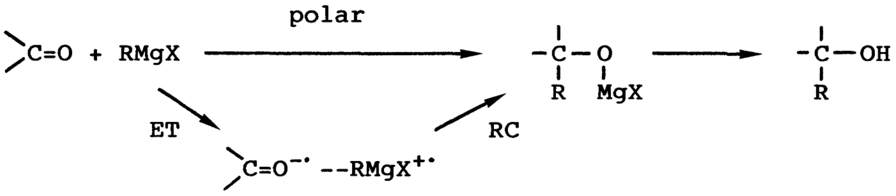
The carbonyl carbon-14 kinetic isotope effect and substituent effects were determined for the reaction of MeMgI with benzophenone. The observed large carbon isotope effect ($^{14}k/^{12}k=1.056$) together with the large steric effect on reactivity introduced by *o*-substituents on benzophenone indicated that the C-C bond formation is the rate-determining step of the Grignard reaction.

The mechanism of the Grignard reaction has been investigated for many years by numerous investigators.[1)] Among several mechanistic aspects, recent studies were focused on the involvement of single-electron transfer (SET) in the reaction of RMgX with aromatic ketones. In 1964, Maruyama presented spectroscopic evidence for the formation of radical species in the reaction of benzophenone with ArMgBr.[2)] Later in 1971, Holm and Crossland reported experimental results which indicated that the reaction of MeMgBr was different in mechanism from that of *t*-BuMgCl.[3)] Absence of steric effect on rate and presence on product distribution led them to conclude that ET is rate determining in the reaction of *t*-BuMgCl with benzophenone. In contrast, the reaction of MeMgBr was noted to suffer a large steric rate retardation although no relevant data were given; the results were interpreted in terms of a polar mechanism. However, a huge amount of studies in the past two decades by means of spectroscopic measurements of radical intermediates,[2,4)] kinetic studies of the intermediates,[5-9)] product analyses,[10-13)] and radical probe experiments[14-17)] appear to indicate that SET is involved in the reaction not only of *t*-BuMgCl but of MeMgBr. Although no evidence in support of the SET mechanism has yet been obtained for the simplest system, i.e., $Ph_2C=O$ + $CH_3MgX$, it is widely accepted at present that the system also reacts via SET.



Scheme 1.

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[#]This paper is dedicated to the late Professor Ryozo Goto, Kyoto University.

Table 1. Kinetic Isotope Effect in the Reaction of Benzophenone with MeMgI[a)]

| $R_0, R_r, R_p$ | $f, R_0, R_r$ | $f, R_0, R_p$ | $f, R_r, R_p$ | $^{12}k/^{14}k$ (av) |
|---|---|---|---|---|
| 1.056±0.001 | 1.057±0.004 | 1.056±0.002 | 1.057±0.002 | 1.056±0.002 |

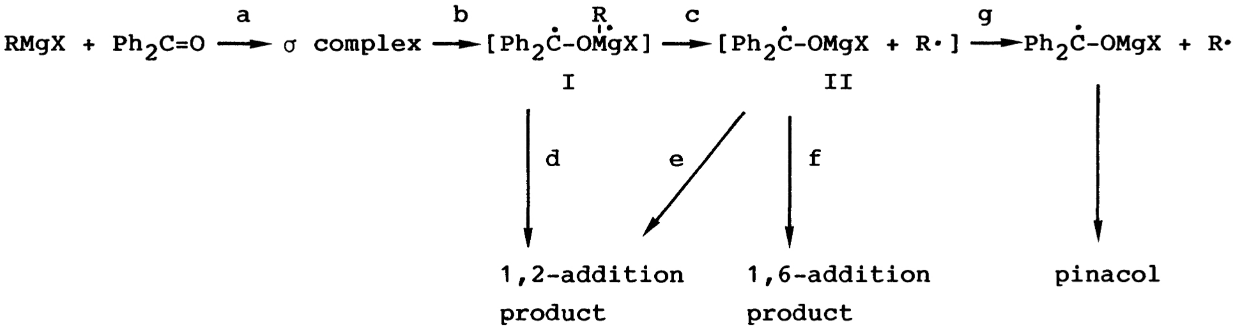
a) Reactions were carried out in diethyl ether at 0.0±0.1 °C. The KIEs were calculated according to the four equations of Tong and Yankwich. For definition of $f$, $R_0$, $R_r$, and $R_p$, see: J. Y.-P. Tong and P. E. Yankwich, J. Phys. Chem., 61, 540 (1957). Each KIE value is the average of 4 runs with fractions of reaction in the range of 30 to 80%. Error limits are the standard deviations.

Under such circumstances, it seems important to reconsider the difference in the reaction mechanism between the *t*-BuMgCl and MeMgX reagents. Here we report the results of kinetic isotope effect (KIE) and substituent effect measurements in the reaction of MeMgI with benzophenone; these two methods are known to be useful to elucidate the rate-determining transition state of chemical reactions.

KIE was determined by the procedure reported before.[20)] Substituent effects on the rate of the Grignard reaction were measured by a competitive method,[19)] in which a pair of ketones were allowed to react with a deficient amount of reagent. Some *o*-substituted benzophenones were included in this experiment to confirm the earlier report.[3)] The relative reactivity determined was plotted against the Hammett $\sigma$ constant in Fig. 1.

The basic idea in utilizing carbon KIE is that a primary carbon KIE arises only when the isotopically labeled carbon atom changes its bonding in the rate-determining transition state. Thus, some magnitude of KIE is expected at the carbonyl carbon if the reaction takes place via initial fast ET followed by slow recombination of the radical ion pair formed (rate-determining RC, Scheme 1) whereas little or no KIE may be expected if the ET step is rate determining.[21)]

Carbonyl carbon-14 KIE observed for the reaction of MeMgI with bonzophenone is large as listed in Table 1. It is important to point out that the magnitude is comparable to that observed in the reduction of benzophenone with lithium isopropoxide.[21)] This large KIE clearly indicates that the bonding at the carbonyl carbon changes in the rate-determining transition state of the Grignard reactions. The magnitude of the Hammett $\rho$ value (0.69±0.19) determined in the present study



Scheme 2.

is in qualitative agreement with the values reported for related reactions of MeMgX,[3,22] and smaller than the ρ value (3.0) reported for the reaction of t-BuMgCl.[3] The important point in Fig. 1 is that large rate retardations were observed for the o-substituted derivatives. This is in sharp contrast to the absence of steric rate retardation in the t-BuMgCl reaction.[3] The steric effects clearly eliminates the possibility that the SET step is rate determining in the MeMgI reaction; the observed rate retardations for the o-substituted derivatives are much larger than those expected from the difference in reduction potential (e.g., $E_{red}$ = 1.776, 1.835, and 1.851 eV vs. SCE, respectively, for unsubstituted, p-Me and o-Me derivative.[23]). Thus, it can be concluded that the rate-determining step of the Grignard reaction of MeMgI with benzophenone is the C-C bond formation.

On the basis of the radical probe experiments, Ashby et al. have proposed a sequence of steps for the SET mechanism (Scheme 2), in which there are two pathways for the formation of 1,2-addition product.[14] The present study on the rate-determining step of the Grignard reaction of MeMgI supports the proposed scheme. If there is only one intermediate to give the 1,2-addition product in the SET mechanism as simply shown in Scheme 1, it is highly unlikely that the rate-determining step of the MeMgI reaction is the RC step while that of the t-BuMgCl reaction is ET because the change in reagent from MeMgI to t-BuMgCl should make the RC step slower and the ET step faster and therefore this should make the RC step rate determining for the t-BuMgCl reaction. It is reasonable to conclude

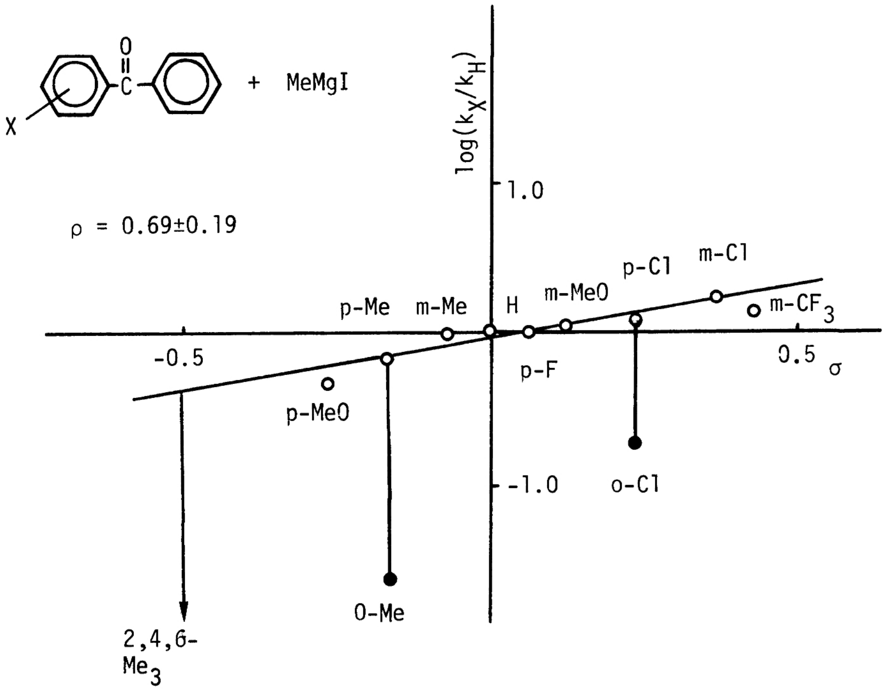


Fig. 1. Variation of reactivity with the Hammett σ constants. Points of o-substituted derivatives were shown by closed circles. Reactivity of 2,4,6-trimethylbenzophenone was too low to obtain a reliable value.

that the reaction of MeMgI proceeds via an a-b-d sequence in Scheme 2 if it indeed follows the SET mechanism and that step d is rate determining. In the reaction of *t*-BuMgCl, on the other hand, path d should be slowed down because of the steric reason, and path c, becomes favorable. Thus, the reaction proceeds via the sequence of steps, a-b-c-(e, f, and g).

It is also important to point out here that the available experimental evidence does not necessarily mean that the ET step, b, is rate determining for the *t*-BuMgCl reaction; the all experimental results are consistent with the mechanism in which step c is rate determining. Since ET from *t*-BuMgCl to benzophenone is easier than that from MeMgI, it is probable that ET from *t*-BuMgCl to benzophenone is a fast step and that the subsequent step, c, becomes rate determining. The considerably large $\rho$ value reported for the reaction of *t*-BuMgCl with benzophenones seems to support this possibility. Studies to further clarify this point is in progress.

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