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Direct Rate Measurements of the Reactions of Benzophenone with RMgX and RLi: Effects of Substituents and Reagent Concentration on Rates

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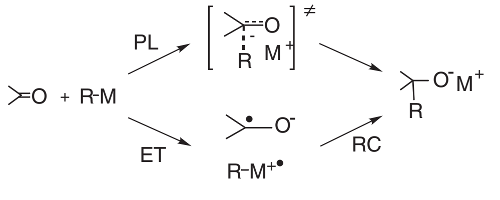
Rates of reactions of MeMgBr and MeLi with substituted benzophenones (BPs) were determined by using a stopped-flow method. The Hammett plots for the reactions of MeMgBr in THF and in Et_2O at 0 °C gave ρ values of 0.99 ± 0.09 and 0.99 ± 0.08, respectively; such values were in excellent agreement with the ρ value determined previously by competition experiments in THF. The Hammett ρ value (0.40 ± 0.07) for the reaction of MeLi in Et_2O at 0 °C also agreed with that determined by competition experiments within experimental errors. A logarithmic plot of the rate constant vs the reagent concentration for the reaction of BP and MeMgBr in THF gave a linear plot with a slope of close to unity, whereas that in Et_2O showed saturation at a higher MeMgBr concentration, reflecting different aggregation states in different solvents. An analogous plot for MeLi in Et_2O gave a curved logarithmic plot with a slope of $1/4$ at a higher reagent concentration and a slope of $1/2$ at a lower reagent concentration range, suggesting that the aggregation of MeLi is concentration dependent.

The mechanism of the reactions of benzophenone (BP) with Grignard reagents (RMgX) and organolithium reagents (RLi) has previously been investigated by means of carbonyl-carbon kinetic isotope effects (KIEs) and substituent effects on the reaction rates.[1,2] On the basis of the results, together with some chemical probe experiments,[3,4] we have concluded that the reactions proceed via the electron transfer (ET)–radical combination (RC) pathway in a general reaction scheme (Eq. 1), with the exception for enolate reagents, which were shown to react via the polar (PL) pathway.[1c,2d] An important mechanistic point is that for MeMgX and PhMgX the rate-determining step is the RC step in the ET–RC pathway, whereas for MeLi and PhLi the ET step is rate determining. The measurements of the substituent effects and KIEs for these reactions were carried out by using competition experiments, in which a deficient amount of a reagent was allowed to react with a mixture of two substrates competitively. Although the competition experiment is a common practice to determine relative reactivities of reactions for which direct rate measurement is not easy with conventional procedures, it has a well-known limitation that it cannot be used for very fast reactions because mixing may mask the relative reactivity in such cases. As for the reactions of RMgX and RLi, recent reports claimed that these reactions were so fast that the competition experiment gave erroneous results.[5,6]



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In the present paper, we report the results of direct rate measurements of these reactions with a stopped-flow method; such results indicate that previous competition experiments gave reliable relative reactivities. We also report the effect of the concentration of these reagents on their reactivities and provide new insight on the aggregation of these reagents in ethereal solvents.

Results and Discussion

Rate Measurements. The rates of the reactions of MeMgBr and MeLi with BP and benzaldehyde (BA) were measured with the standard UV stopped-flow spectroscopic method by following the decrease of the absorbance of the carbonyl compound at 280–290 nm under pseudo first-order conditions with excess reagents. The observed rate constants are summarized in Table 1. Two points are clear from the data in Table 1. First, BA reacted about 10^4 times faster than BP with MeMgBr, whereas the reactivity difference was much smaller for the reactions with MeLi. This is consistent with the difference of the rate-determining step for these two classes

Table 1. Pseudo First-Order Rate Constants of the Reactions of BP and BA with MeLi and MeMgBr at 0 °C[a)]

Substrate	Reagent	Solvent	k/s^{-1}	Relative rates (BA/BP)
BA	MeLi	Et_2O	1680	
BP	MeLi	Et_2O	35.5	47
BA	MeMgBr	THF	46.9	
BP	MeMgBr	THF	0.005	9380

a) [BA] = 2.5 mM, [BP] = 2.5 mM, [MeLi] = 21.5 mM, and [MeMgBr] = 100 mM.

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Table 2. Pseudo First-Order Rate Constants for the Reactions of BP with MeMgBr in Et_2O[a)]

Temperature/°C	k_{obs}/s^{-1}
0.0	0.073
10.0	0.159
20.0	0.237

a) [BP] = 1.0 mM and [MeMgBr] = 500 mM.

Table 3. Pseudo First-Order Rate Constants for the Reactions of Substituted BPs with MeMgBr and MeLi at 0 °C

Substituent	k_{obs}/s^{-1}		
	MeMgBr/THF[a)]	MeMgBr/Et_2O[b)]	MeLi/Et_2O[c)]
p-Me	8.0×10^{-3}	5.93×10^{-2}	48.6
m-Me	8.5×10^{-3}	nd[d)]	57.8
H	13.3×10^{-3}	7.25×10^{-2}	65.6
p-F	15.5×10^{-3}	nd[d)]	75.5
p-Cl	21.5×10^{-3}	12.1×10^{-2}	86.2
m-Cl	28.1×10^{-3}	18.8×10^{-2}	84.5
m-CF_3	33.9×10^{-3}	26.0×10^{-2}	92.4

a) [BP] = 1.0 mM and [MeMgBr] = 250 mM. b) [BP] = 1.0 mM and [MeMgBr] = 500 mM. c) [BP] = 1.0 mM and [MeLi] = 55 mM. d) Not determined.

of reagents: RC for MeMgBr and ET for MeLi. Second, it can be seen that MeLi reacted much faster than MeMgBr in diethyl ether; the reactivity difference amounted to 2730 for the reactions with BP, although the concentration of MeLi was lower than that of MeMgBr. In Table 2 are listed rate constants for the reaction of BP and MeMgBr in diethyl ether at three different temperatures. The pseudo first-order rate constant at 20 °C agreed with the reported value (MeMgBr [500 mM] + BP [50 mM] in Et_2O, $k = 0.30\ s^{-1}$).[7] The Eyring plot with the three pseudo first-order rate constants gave a good straight line ($R^2 = 0.998$), from which the activation enthalpy and entropy were calculated to be 7.7 kcal mol^{-1} and -42 cal mol^{-1} K^{-1}, respectively.

Substituent Effect. Rate constants for substituted BPs with MeLi and MeMgBr were measured in ethereal solvents at 0 °C, and are summarized in Table 3. Figure 1 shows the plots of the relative reactivities against the standard Hammett σ values for the reactions of substituted BPs with MeMgBr determined by the stopped-flow method in diethyl ether (open circle) and in THF (open triangle), together with the plot obtained previously from a competition experiment (filled triangle). It is clear that the both competition and direct rate measurements gave essentially the same Hammett ρ values. In Fig. 2 are shown the Hammett plots for the reactions of substituted BPs with MeLi in diethyl ether at 0 °C. Here again, the ρ values determined by both methods are the same within the experimental error. The results clearly indicate that the reactions of BP with MeMgBr and MeLi are not too fast to be deteriorated by mixing control, and thus the competition experiment gave reliable results.

Holm has recently proposed that competition kinetics for the Grignard reactions with aromatic ketones gave erroneous relative reactivities because the reactions were too fast.[5] The argument was primarily based on the competition between different Grignard reagents in reactions with ketones in diethyl ether. However, since Grignard reagents in diethyl ether are known to form aggregates[8] and hence the formation of mixed aggregates may deteriorate the relative reactivity results, arguments based on mixed reagents should be made with care. It has also been reported that the reactivity ratios between BA and BP for the reactions with MeMgBr and $CH_2{=}CHCH_2MgBr$ were >3000:1 and 1.9:1, respectively.[5] These results are qualitatively in line with our results with the direct rate measurements, in that the reactivity ratio is roughly 10000 for MeMgBr and 50 for MeLi; one should consider here that both MeLi and $CH_2{=}CHCH_2MgBr$ react with these substrates via the rate-determining ET mechanism and hence the reactivity between ketone and aldehyde is small, whereas the reaction of MeMgBr proceeds with the RC step as rate-determining and thus suffers a large steric effect.

Maclin and Rickey have claimed that the previously observed small Hammett ρ values and negligible carbonyl-^{14}C KIE for the reactions of MeLi and PhLi with benzophenone

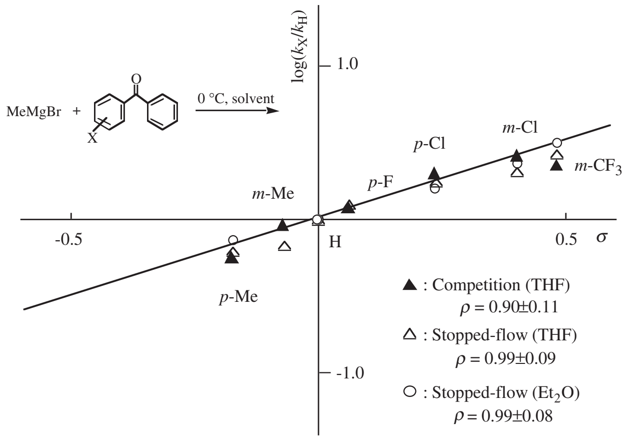

Fig. 1. Hammett plots for the reactions of substituted benzophenones with MeMgBr at 0 °C. Closed triangles are the data determined by competition experiment in THF, open triangles by stopped-flow measurement in THF, and open circles by stopped-flow measurement in Et_2O.

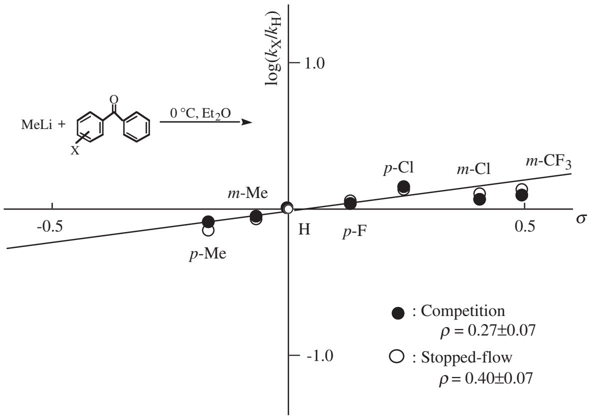

Fig. 2. Hammett plots for the reactions of substituted benzophenones with MeLi in Et_2O at 0 °C. Filled circles are the data determined by competition experiment and open circles by stopped-flow measurement.

were due to slower rates of mixing than the addition reactions themselves.[6] A significant KIE detected for the reaction of Me_2CuLi with benzophenone was, on the other hand, attributed to a slower addition step than the mixing. It was suggested that these reactions proceed via the same rate-determining step, although such a mechanistic assignment disagrees with spectroscopic observation and enone-isomerization experiment, which strongly suggested different rate-determining steps for the reactions of MeLi and Me_2CuLi.[4] Similarly, significant KIEs observed for MeMgBr and MeMgI with benzophenone and a smaller KIE for *t*-BuMgCl were explained as due to slow mixing rates compared to the rates of addition for *t*-BuMgCl. However, the argument is inconsistent with the large Hammett ρ value (3.0) reported for the reaction of *t*-BuMgCl,[9] because the reaction with rate-determining slow mixing should give a negligible ρ value. Clearly, interpretation of small ρ values and KIEs in terms of mixing control does not fit other available experimental results.

Effect of Concentration. The chemistry of aggregation has been extensively studied for RMgX, RLi, and Li enolates. Ashby has summarized that the aggregation state of RMgX depends on the solvent, and that RMgX, where R = Me or Et, and X = Cl, Br, or I, exists basically as a monomer in THF, whereas it forms a higher aggregate in a higher concentration in diethyl ether.[8]

Smith et al. have carried out some kinetics measurements for the reaction of MeMgBr and 2,4-dimethyl-4′-methylthiobenzophenone in diethyl ether by a stopped-flow technique,[10] and found that, under the condition that the concentration of the ketone (10^{-4} M) was much lower than that of the Grignard reagent (0.01–0.4 M), the pseudo first-order rate constant did not follow a linear dependence on the reagent concentration but exhibited a saturation curve. The logarithmic plot was not linear and a linear regression gave an apparent slope of 0.65.

Ashby et al. have measured the rates of reactions of MeMgBr with BP in diethyl ether under the conditions that the concentration of MeMgBr was lower than 1.52×10^{-2} M and that the concentration ratio of the reagent to ketone was 25–150.[11] At the low MeMgBr concentration, low enough for the reagent to exist as a monomer but for the concentration to be sufficiently larger than that of the ketone, the rate was functionally dependent on the reagent concentration. It was proposed that the results supported Swain's suggestion, i.e., ketone and Grignard reagent form a complex, which by the attack of another molecule of the reagent gives the product (Eq. 2).

$$\text{Ketone} + \text{RMgX} \rightleftharpoons \text{complex} \xrightarrow{\text{RMgX}} \text{Product}. \qquad (2)$$

We examined the effect of concentration of the reagent for the reaction of MeMgBr with BA in diethyl ether and in THF. Figure 3 shows the plot of pseudo first-order rate constants against the concentration of MeMgBr and the logarithmic plot for the reaction of BA with MeMgBr in THF at 0 °C. The observed linear logarithmic plot with a slope of nearly unity is consistent with the notion that the reagent exists as a monomer in THF. No complication due to the initial complex formation or to the attack by a second molecule of the reagent was detected for the reaction with BA. The reaction in diethyl ether, however, gave a curved logarithmic plot as shown in Fig. 4. The slope in Fig. 4B is 1.0 at a lower concentration range ([MeMgBr] < 100 mM) and then gradually decreases as the concentration increases. The different behavior in THF and diethyl ether is reasonably interpreted as due to the different aggregation states of the reagent in these solvents.

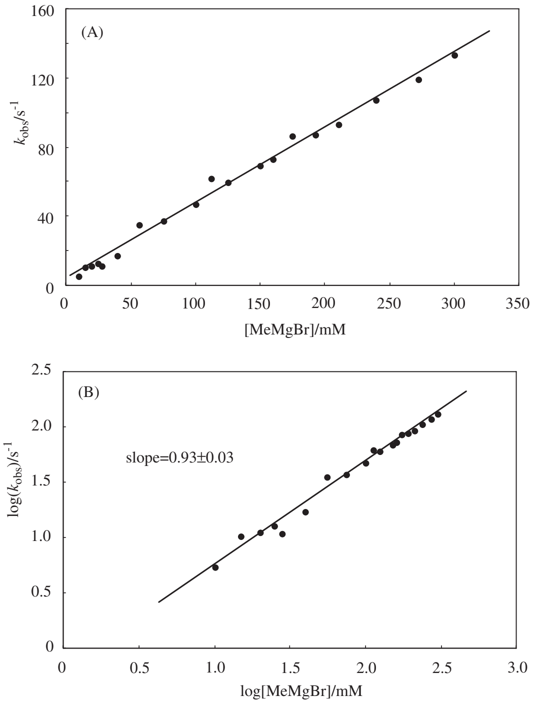

Fig. 3. (A) Plot of pseudo first-order rate constants against the concentration of MeMgBr and (B) logarithmic plot for the reaction of BA with MeMgBr in THF at 0 °C.

The state of aggregation of RLi in various solvents has been extensively investigated by a variety of methods, including vapor pressure technique, NMR and UV spectroscopic methods, and kinetics.[12–27] These studies have shown that MeLi and BuLi are mostly tetrameric, PhLi is dimeric, and benzyllithium is monomeric in THF.[12–15] In diethyl ether, tetrameric and dimeric structures coexist for PhLi.[13,15] Lithium enolates of aromatic ketones exist as a monomer–dimer or monomer–tetramer mixture in THF, depending on the structures of ketones.[27a,c]

Measurement of rate constants is a unique method that provides information not only on the rate process but on the reactant state as well. Smith and co-workers succeeded in measuring the rate constants of the reaction of MeLi with a carbonyl compound at various reagent concentrations with a stopped-flow/rapid scan spectroscopic method, and demonstrated that the reaction exhibited a fractional kinetic order.[19a,c] Thus, the reaction of 2,4-dimethyl-4′-methylthiobenzophenone with MeLi in diethyl ether at 25 °C showed one-fourth order in MeLi. The monomer was considered the reactive species that exists in equilibrium with the tetramer. Fractional reaction orders with respect to RLi in reactions with electrophiles repeatedly reported in the literature were attributed to monomer/tetramer equilibrium.[17,19,20]

In the present study, we reexamined the effect of the reagent concentration on the rate of the reaction of MeLi with BP in diethyl ether at 0 °C. As shown in Fig. 5A, the plot of the rate

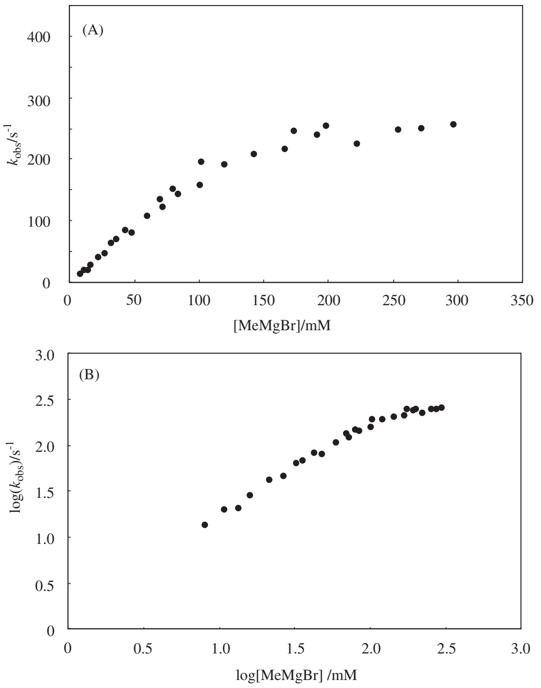

Fig. 4. (A) Plot of pseudo first-order rate constants against the concentration of MeMgBr and (B) logarithmic plot for the reaction of BA with MeMgBr in Et_2O at 0 °C.

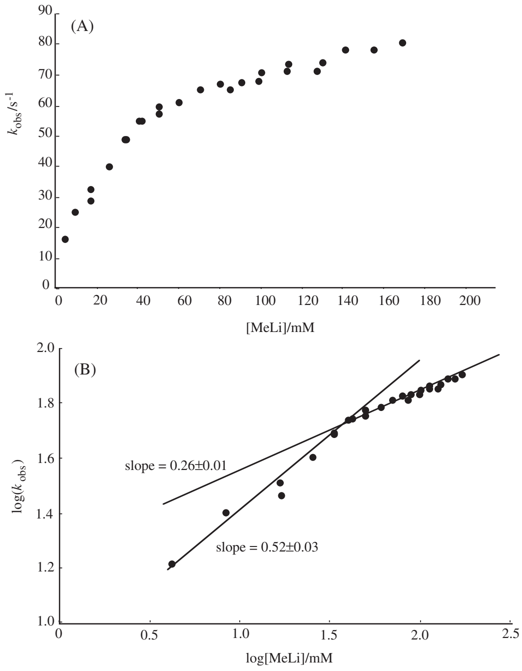

Fig. 5. (A) Plot of pseudo first-order rate constants against the concentration of MeLi and (B) logarithmic plot for the reaction of BP with MeLi in Et_2O at 0 °C.

constants against the reagent concentration gave a curved correlation as expected. The logarithmic plot in Fig. 5B, however, gave a biphasic correlation, which suggested that the kinetic order with respect to the reagent varies with the reagent concentration. At a higher concentration range (>40 mM) the slope of the correlation is one-fourth, which agrees with the reported examples,[19a,c] indicating that the monomer is the reactive species that exists in equilibrium with the tetramer. On the other hand, the observed, much larger, slope of about 0.5 at a lower concentration (<40 mM) suggests that MeLi exists primarily as a dimer under these dilute conditions and that the monomer is the reactive species. If such biphasic correlation arose from the aggregation nature of MeLi in diethyl ether, the same trend should be observed for a reaction of a different substrate. As can be seen in Fig. 6, this was indeed found for the reaction of 2,4-Me_2-BP, in which the logarithmic plot showed a break at the MeLi concentration of about 40 mM. Thus, the notion that MeLi exists as the tetramer in diethyl ether needs to be modified in such a way that a lower aggregate is important in highly dilute solution.

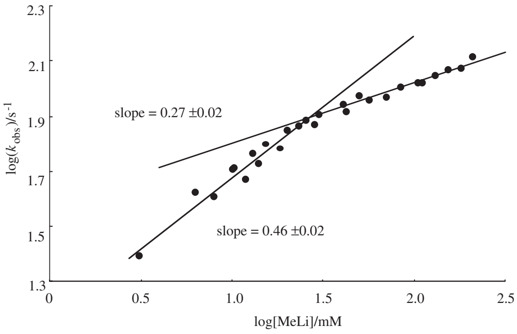

Fig. 6. Logarithmic plot for the reaction of 2,4-Me_2-BP with MeLi in Et_2O at 0 °C.

Experimental

Materials. THF was dried over sodium/benzophenone and distilled immediately before use. All substituted benzaldehydes were commercially available and were purified either by distillation or recrystallization. Substituted benzophenones were obtained as described in the literature.[28] Grignard reagents were prepared from doubly-sublimed Mg (Aldrich); MeLi in diethyl ether is a commercial sample (Aldrich). These reagents were standardized according to the literature and doubly checked by the reaction with benzaldehyde of known concentration.[29]

Rate Measurement. The rates of the reactions of organometallic reagents with BP and BA were measured with the standard UV stopped-flow photometer (Otsuka Electronics RA-401) having rapid-scan capability equipped with gas-tight reservoir. The apparatus was maintained at ±0.1 °C by means of an ethanol–water bath. The reactions were carried out under pseudo first-order conditions with excess reagent for more than 2 half-lives of reactions. Data was collected on a PC, and least-squares analysis of absorbance vs time yielded pseudo first-order rate constants with reproducibility of better than 5%. Typical measurement conditions are as follows: MeMgBr (250 mM) + benzophenone (1 mM) in THF, total sampling time, 5 s; data point, 256, slit width 1.4 nm, Y-scale 1.0 Abs. at 290 nm; MeLi (250 mM) + benzophenone (1 mM) in THF, total sampling time, 100 ms; data point, 256, slit width 1.4 nm, Y-scale 1.0 Abs. at 280 nm.

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