*Bull. Chem. Soc. Jpn.*, **75**, 127–129 (2002) 127

# Reaction of Magnesium Pinacolone Enolate with Benzaldehyde: Polar or ET Mechanism?

**Hiroshi Yamataka,* Makoto Shimizu, and Masaaki Mishima*,†**

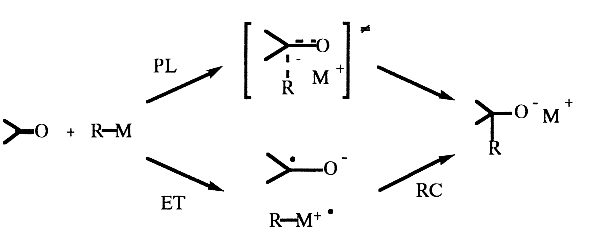
Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567-0047

†Institute for Fundamental Research of Organic Chemistry, Kyushu University, Higashi-ku, Fukuoka, 812-8581

(Received July 25, 2001)

The carbonyl-carbon kinetic isotope effect (KIE) and the substituent effect were measured for the reaction of magnesium pinacolone enolate ($CH_2{=}C(OMgBr)C(CH_3)_3$, **1**) with benzaldehyde. The results were compared with those for lithium enolate ($CH_2{=}C(OLi)C(CH_3)_3$, **2**). A normal carbonyl-carbon KIE, a medium-sized Hammett $\rho$ value and the results of chemical probe experiments indicated that the reaction of **1** proceeds via the polar mechanism as in the reaction of **2**.

Nucleophilic addition to carbonyl functions is one of the most basic organic reactions. The reaction has two possible pathways, polar addition (PL) and electron transfer (ET)–radical coupling (RC) sequence, Eq. 1, and the mechanism is highly nucleophile dependent. Current reaction designs for synthetic purpose of addition reactions of common nucleophiles to aldehydes and ketones are mostly based on the polar mechanism, but apparently the ET process is involved in reactions of the Grignard reagents and organolithium reagents.[1,2] Various experimental methods have been used so far to demonstrate the ET process, including spectroscopic methods,[1e,f,2a] product analyses,[2b,3] and secondary deuterium kinetic isotope effects (KIEs).[4,5] However, none of these methods is conclusive by itself. We have used the combination of several experimental methods, including carbon KIEs, substituent effects, and chemical probe experiments, in order to distinguish the ET process from the PL process for the addition reactions of the Grignard,[1g,6] organolithium,[2c,d,7] and the Wittig reagents.[8]



(1)

By using these methods, we have demonstrated that all lithium reagents examined react with aromatic aldehydes and ketones through the ET-RC pathway,[2c,d,7] with only one exception, i.e., the reaction of benzaldehyde with lithium pinacolone enolate, which was shown to proceed through the PL mechanism[7,9] (Eq. 1). The mechanistic change relates to the stability of the reagents measured by the intrinsic acidity of the conjugate acids of R anions in the gas phase.[7] Here, the intrinsic acidity of R–H is estimated from the gas phase heat of formation (Eq. 2) from the data compiled in the literature:[10] 416.8 kcal/mol (R = Me), 400.8 (Ph), 390.7 ($CH_2{=}CHCH_2$), 381.6 ($PhSCH_2$), 372.8 ($NCCH_2$) and 368.0 ($(CH_3)_3CC({=}O)CH_2$). The enolate reagent whose conjugate acid is most acidic reacts with benzaldehyde via the PL mechanism, whereas the reagents whose conjugate acids are less acidic go through the ET pathway. Another possible source for the mechanistic difference is the difference in the bonding mode, the O–Li bond in the lithium enolate vs the C–Li bond in other lithium reagents. Whatever the reason, the mechanistic difference between the lithium enolate and other lithium reagents raised question about the mechanism for analogous magnesium enolate because all magnesium reagents examined so far were concluded to react via the ET-RC pathways.[1g,6]

$$\mathrm{R\text{-}H} \;\overset{\Delta H_{\mathrm{gas}}}{\rightleftharpoons}\; \mathrm{R^- + H^+} \qquad (2)$$

In the present study the reaction pathway for magnesium pinacolone enolate ($CH_2{=}C(OMgBr)C(CH_3)_3$, **1**) was investigated experimentally by means of kinetic isotope effects (KIEs), substituent effects, and chemical probe experiments and the results were compared with lithium enolate ($CH_2{=}C(OLi)C(CH_3)_3$, **2**).

## Results and Discussion

Kinetic isotope effects were determined for the reaction of benzaldehyde with **1** in $Et_2O$ by comparing reactivities in $C_6D_5CHO/C_6H_5CHO$ and $C_6H_5{}^{13}CHO/C_6D_5CHO$ as reported previously,[7] and from the two values the carbonyl-carbon KIE (${}^{12}k/{}^{13}k$) was calculated. The indirect method was adopted in order to avoid the interference of $^{13}C$ natural abundance in the intensity measurement with the FT-ICR mass spectrometer. The results listed in Table 1 showed a small but normal (larger than unity) carbonyl-carbon KIE for the reaction. A heavy atom KIE is usually considered to be normal when the total bonding at the labeled atom decreases in the TS and to be in-

Table 1. Kinetic Isotope Effects in the Reaction of **1** and **2** with Benzaldehyde at 0 °C

| Reagent | $k_H/k_{D5}$ | $k_{D5}/^{13}k$ | $^{12}k/^{13}k$ b) |
|---|---|---|---|
| **1** | 1.022 ± 0.001 | 0.988 ± 0.002 | 1.010 ± 0.003 |
| **2** a) | 1.031 ± 0.004 | 0.988 ± 0.002 | 1.019 ± 0.004 |

a) Data taken from Ref. 7. b) Calcd from $k_H/k_{D5}$ and $k_{D5}/^{13}k$.

verse (less than unity) when the bonding increases. In addition to the tight/loose character of the TS, however, there is an equally or even more important factor that determines the size of a primary KIE, the dynamic character of the TS;[11] KIE is larger if the labeled atom is involved to a greater extent in the reaction-coordinate motion at the TS. The importance of the reaction-coordinate contribution has well been demonstrated by calculations of primary carbon KIEs.[12] Thus, the carbonyl-carbon KIE is expected to be of considerable magnitude if the reaction proceeds via the polar mechanism or if the rate-determining step is RC in the ET-RC route since the motion of the labeled carbon is directly involved in the reaction coordinate in these cases. In contrast, the KIE would be much smaller and close to unity for the rate-determining ET mechanism since there is no contribution from the reaction-coordinate motion.

The normal carbonyl-carbon KIE observed for **1** eliminates the possibility that the reaction would proceed through the rate-determining ET mechanism, for which carbon KIEs of unity ($^{12}k/^{13}k$ = 1.000) have indeed been observed.[2c,d] It should be noted that the normal KIE has also been reported for the reaction of benzaldehyde with **2**.[7a]

Substituent effects for the reactions of substituted benzaldehydes with **1** were measured in $Et_2O$ at 0 °C by competition experiments as before.[7] The reaction of benzophenone with **1** was too slow to determine reliable substituent effects. Figure 1 illustrates the relationship between log ($k_X/k_H$) and the substituent constant $\sigma$.

A large to medium-sized substituent effect is reasonably expected for the polar mechanism, and the $\rho$ value would also be of considerable magnitude for the rate-determining RC mechanism because this mechanism involves ET pre-equilibrium, for which the Hammett $\rho$ value is quite large.[13] Thus, the PL and the rate-determining RC mechanism would show similar kinetic behavior. In contrast to the above two cases, the magnitude of the $\rho$ value for the rate-determining ET mechanism is not easily predictable, because the character of the ET TS is not clear. However, previous results suggested that the $\rho$ value could be rather small,[1g,2c,2d] which was rationalized in terms of the predominant contribution of solvent reorganization in the activation process of the charge-separation type ET step.[2c]

The reaction of **1** gave a medium-sized $\rho$ value with substituted benzaldehydes (0.85 ± 0.06). The $\rho$ value is again similar to that observed previously for reaction of **2** with benzaldehyde. The present results can be rationalized by assuming a mechanism in which the reaction of **1** with benzaldehyde proceeds via the polar mechanism as for **2**, or via the ET-RC pathway with the RC step rate-determining.

Two chemical probe experiments, enone isomerization[12] and dehalogenation,[6] have been shown to be useful in distinguishing the two mechanistic alternatives by estimating the possible intervention of a radical ion pair.[6,9,14b] These experiments are the probes that measure whether a reagent has enough ability to transfer electron to enone and halobenzophenone, respectively. In the enone-isomerization probe, isomerization of the starting cis enone to trans upon mixing with a reagent is taken as indication of the occurrence of ET from the reagent to the enone. Since *Z*-2,2,6,6-tetramethylhept-4-en-3-one has more negative reduction potential (−2.28 V vs SCE) than benzaldehyde (−1.84 V) and benzophenone (−1.82 V),[15] a positive response in the enone-isomerization experiment then indicates the possible occurrence of ET to the aromatic aldehyde and ketone. A dehalogenation experiment measures the occurrence of ET from a reagent to halobenzophenone.[6] As indicated by Savéant[16] and Tanner,[17] halobenzophenone radical anion undergoes dehalogenation with rate constants ranging over $10^2$–$10^6$ when the halogen is Br or I, and this reaction can compete with the RC step when a radical ion-pair intermediate was formed by ET. Although the dehalogenation rate for the actual reaction intermediate would be much slower than reported because of a strong interaction between the ketyl and the counter radical cation of the nucleophile, there would be a good possibility for dehalogenation to occur if one uses *o*-halobenzophenones, for which the RC step is slowed down by the steric reason.[1g] If these two probes were positive there would be a good

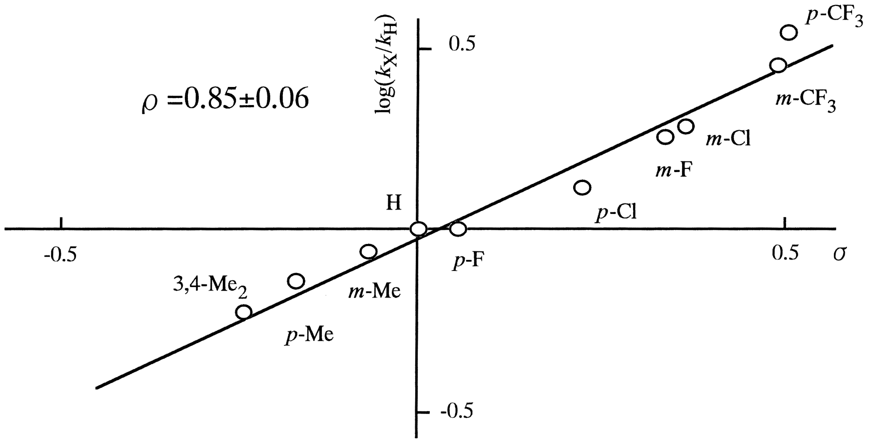


Fig. 1. Variations of reactivity with $\sigma$ values for the reaction of substituted benzaldehydes and **1** in $Et_2O$ at 0 °C.

Table 2. *Z–E* Isomerization during the Reaction of (*Z*)-Enone with Magnesium Pinacolone Enolate (**1**) in $Et_2O$ at 0 °C

| Reagent | Time/min | Recovered *Z*:*E* |
|---|---|---|
| Enolate | 10 | 98.5:1.5 |
| | 30 | 98.2:1.8 |
| | 60 | 98.2:1.8 |
| Blank | 0 | 97.9:2.1 |

possibility that the reaction proceeds via the ketyl intermediate of sufficient lifetime.

The enone-isomerization experiments applied for **1** gave the results summarized in Table 2. Clearly, no isomerization was detected for the prolonged reaction time (1 h). Similarly dehalogenation experiments gave quantitative recovery of the starting *o*-iodobenzophenone after 1 h, showing no evidence for the presence of a radical ion-pair intermediate of sufficient lifetime. These results are consistent with the polar mechanism.

In conclusion, the reaction of magnesium pinacolone enolate **1** with benzaldehyde is concluded to proceed via the polar mechanism as for the reaction of lithium pinacolone enolate **2**. The difference in stability of anions as well as the difference in the bonding mode (O–Mg vs C–Mg) is considered the primary source for the mechanistic changes. Clearly, enolate reagents with oxygen–metal bonds belong to a different class of reagents from organometallic reagents with carbon–metal bonds from the mechanistic point of view.

## Experimental

Diethyl ether was dried over sodium/benzophenone and distilled immediately before use. All substituted benzaldehydes were commercially available and were purified either by distillation or recrystallization. Benzaldehyde-carbonyl-$^{13}C$ was synthesized by the pyridinium dichromate oxidation of benzyl alcohol-7-$^{13}C$, which was prepared by carbonylation of phenylmagnesium bromide with $^{13}CO_2$ gas (99%, Aldrich) and the borane reduction of the resultant benzoic acid-7-$^{13}C$. Benzaldehyde-$d_5$ was prepared according to the same sequence of reactions, starting with bromobenzene-$d_5$. Magnesium pinacolone enolate (**1**) was synthesized by mixing equimolar amounts of pinacolone and *i*-$Pr_2NMgBr$, which was prepared from *i*-$Pr_2NH$ and *i*-PrMgBr. All reactions were carried out in $Et_2O$ at 0 °C under dry nitrogen using the Schlenk tube technique.[18] Relative reactivity measurement, carbon-13 KIE measurement and probe experiments were carried out as reported previously.[7]

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture.

## References

1 a) T. Holm and I. Crossland, "Grignard Reagents: New Developments," ed by H. G. Richeky, Jr., Wiley, New York (2000), Chapter 1. b) T. Holm, *J. Am. Chem. Soc.*, **115**, 916 (1993). c) E. C. Ashby and J. R. Bowers, Jr., *J. Am. Chem. Soc.*, **103**, 2242 (1981). d) T. Holm, *Acta Chem. Sand.*, **37**, 567 (1983). e) Y. Zhang, B. Wenderoth, W. Su, and E. C. Ashby, *J. Organomet. Chem.*, **292**, 29 (1985). f) K. Maruyama and T. Katagiri, *J. Am. Chem. Soc.*, **108**, 6263 (1986). g) H. Yamataka, T. Matsuyama, and T. Hanafusa, *J. Am. Chem. Soc.*, **110**, 4912 (1989).

2 a) H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976). b) H. O. House and C.-Y. Chu, *J. Org. Chem.*, **41**, 3067, 3076, 3083 (1976). c) H. Yamataka, N. Fujimura, Y. Kawafuji, and T. Hanafusa, *J. Am. Chem. Soc.*, **109**, 4305 (1987). d) H. Yamataka, Y. Kawafuji, K. Nagareda, N. Miyano, and T. Hanafusa, *J. Org. Chem.*, **54**, 4706 (1989).

3 See also, E. C. Ashby and T. L. Wiesemann, *J. Am. Chem. Soc.*, **100**, 3101 (1978). E. C. Ashby, J. Bowers, and R. Depriest, *Tetrahedron Lett.*, **21**, 3541 (1980). See, also: M. Newcomb and D. P. Curran, *Acc. Chem. Res.*, **21**, 206 (1988). M. Newcomb, T. R. Verick, and S.-Y. Choi, *J. Org. Chem.*, **57**, 373 (1992).

4 W. A. Pryer and W. H. Hendrickson, Jr., *J. Am. Chem. Soc.*, **97**, 1582 (1975); **105**, 7114 (1983).

5 J. J. Gajewski, W. Bacian, N. J. Harris, L. P. Olson, and J. P. Gajewski, *J. Am. Chem. Soc.*, **121**, 326 (1999).

6 H. Yamataka, K. Yamaguchi, T. Takatsuka, and T. Hanafusa, *Bull. Chem. Soc. Jpn.*, **65**, 1157 (1992).

7 a) H. Yamataka, D. Sakaki, Y. Kuwatani, M. Mishima, and Y. Tsuno, *J. Am. Chem. Soc.*, **119**, 9975 (1997). b) H. Yamataka, D. Sakaki, Y. Kuwatani, M. Mishima, M. Shimizu, and Y. Tsuno, *J. Org. Chem.*, **66**, 2131 (2001).

8 H. Yamataka, K. Nagareda, Y. Takai, M. Sawada, and T. Hanafusa, *J. Org. Chem.*, **53**, 3877 (1988). H. Yamataka, K. Nagareda, T. Takatsuka, K. Ando, T. Hanafusa, and S. Nagase, *J. Am. Chem. Soc.*, **115**, 8570 (1993).

9 See also: E. M. Arnett and C. A. Palmer, *J. Am. Chem. Soc.*, **112**, 7354 (1990). C. Palmer, C. A. Ogle, and E. M. Arnett, *J. Am. Chem. Soc.*, **114**, 5619 (1992).

10 S. G. Lias, J. E. Bartmess, J. L. Holmes, R. D. Levin, and G. W. Mallard, *J. Phys. Chem., Ref. Data*, **17**, Supple. 1 (1988).

11 L. Melander and W. H. Saunders, Jr., "Reaction Rates of Isotopic Molecules," Wiley-Interscience, New York (1980).

12 H. Yamataka and T. Ando, *J. Phys. Chem.*, **85**, 2281 (1981). H. Yamataka, S. Tamura, T. Hanafusa, and T. Ando, *J. Am. Chem. Soc.*, **107**, 5429 (1985). L. B. Sims and D. E. Lewis, "Isotopes in Organic Chemistry," ed by E. Buncel and C. C. Lee, Elsevier, Amsterdam, (1984), Vol. VI, Chap. 4.

13 P. Zuman, O. Exner, R. F. Rekker, and W. Nauta, *Th. Coll. Czechoslov. Chem. Commun.*, **33**, 3213 (1968).

14 a) H. O. House and P. D. Weeko, *J. Am. Chem. Soc.*, **97**, 2770 (1975). b) E. C. Ashby and T. L. Wiesemann, *J. Am. Chem. Soc.*, **100**, 3101 (1978).

15 H. Yamataka, K. Nagareda, T. Hanafusa, and S. Nagase, *Tetrahedron Lett.*, **30**, 7187 (1989).

16 L. Nadjo and J. M. Savéant, *J. Electroanal. Chem.*, **30**, 41 (1971).

17 D. D. Tanner, J. F. Chen, L. Chen, and C. Luelo, *J. Am. Chem. Soc.*, **113**, 8074 (1991).

18 Schriver, D. F. "Manipulation of Air Sensitive Compounds," McGraw-Hill, New York (1969), Chap. 7.