Kinetic Isotope Effects for Addition of Lithium Pinacolone Enolate to Benzaldehyde

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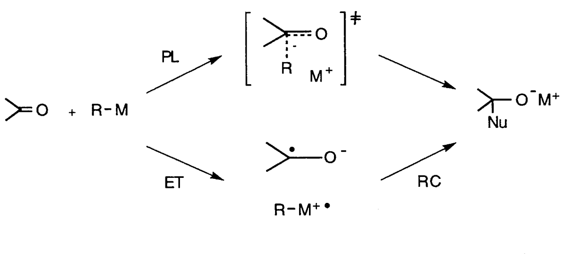
The carbonyl-carbon-13 and phenyl-D_5 kinetic isotope effects (KIEs) were measured for the reaction of benzaldehyde and lithium pinacolone enolate. The KIEs together with ab initio MO calculations indicated that a CC bond formation process is involved in the rate-determining transition state of the reaction. It was concluded that the enolate addition reaction proceeds in a different manner from those for MeLi and PhLi, for which the rate-determining step was judged to be an electron transfer step.

Although the nucleophilic addition to carbonyl functions is one of the most basic reactions in organic synthesis, understanding of the mechanism of this fundamental transformation is still premature. There are two possible reaction routes, the polar addition (PL) mechanism and the electron transfer (ET) - radical coupling (RC) sequence (Eq. 1), and the mechanism is highly nucleophile dependent. For example, the reactions of RMgX[1] and RLi,[2] here R is an alkyl group, are known to have different rate-determining steps and hence to show different steric effects.



(1)

Lithium enolate is an important reagent in its versatile synthetic utility, especially for enantioselective reactions. Design of the reaction, which is critical to attain high selectivity, requires the knowledge of the mechanistic details. Recently Arnett reported that the reaction of lithium pinacolone enolate with benzaldehyde (Eq. 2) proceeds via the polar mechanism on the basis of the comparison of the experimental activation energy with the energy required for ET determined electrochemically.[3] The conclusion was different from that for the reaction of the same nucleophile with benzophenone drawn by Ashby on the basis of kinetic analysis of an EPR active species detected during the reaction,[4] and also different from our conclusion for the reactions of MeLi, PhLi and CH_2=$CHCH_2Li$ with benzophenone based on KIE measurements.[2,5] The discrepancy should be due to either the difference of reagents or the difference of the mechanistic criteria. The report by Arnett let us to study the reaction of lithium pinacolone enolate and benzaldehyde with our KIE methods, which have been applied previously to other lithium reagents. The present KIE results clearly show that the mechanism for the enolate is different from other RLi.

(2)

Lithium pinacolone enolate was prepared from the reaction of pinacolone and lithium diisopropylamide in THF at -78 °C, and allowed to react with benzaldehyde at 0 °C. The carbonyl carbon-13 and C_6D_5 KIEs were measured by using FT ion-cyclotron resonance mass spectrometry (FT-ICR MS).[6] Ab initio MO calculations were carried out to estimate the magnitude of equilibrium IEs for the polar process by using the Gaussian 92 and 94 packages of program.[7,8]

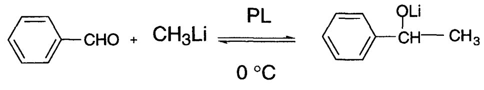
Among the three possible mechanistic alternatives, PL, rate-determining ET, and rate-determining RC, distinction of the rate-determining ET mechanism from PL and rate-determining RC can be achieved in a rather straightforward manner by using primary carbonyl-carbon KIE as a probe. A carbon KIE is larger if the labeled carbon atom is involved to a greater extent in the reaction-coordinate motion at the rate-determining transition state,[9,10] and thus the carbonyl-carbon KIE is expected to be large for the PL and the rate-determining RC mechanism and to be small for the rate-determining ET mechanism. We have reported mechanistic study of the addition reactions of RLi, RMgX, Wittig reagents by using the KIE criterion, and discussed the usefulness of this method.[11]

The isotope effects were determined for C_6D_5CHO *vs.* C_6H_5CHO and $C_6H_5{}^{13}CHO$ *vs.* C_6D_5CHO in order to avoid the interference of ^{13}C natural abundance in intensity measurement. The observed KIEs are $k_H/k_{D5} = 1.031 \pm 0.004$ and $k_{D5}/{}^{13}k = 0.988 \pm 0.002$, and these values give ${}^{12}k/{}^{13}k = 1.019 \pm 0.004$.

The carbonyl carbon KIE for the present reaction was small positive and different from those observed for nucleophilic additions to benzophenone of other lithium reagents; all the reactions of MeLi, PhLi, and CH_2=$CHCH_2Li$ with benzophenone as well as the reaction of PhLi with benzaldehyde gave very small carbonyl carbon KIEs.[2,5] The KIEs of near unity have been considered to show negligible reaction-coordinate contribution, suggesting that neither bond formation nor bond breaking to the carbonyl carbon is involved in the rate-determining TS. This, together with other evidence, let us to conclude that the these reactions proceed via a rate-determining ET mechanism.[2,5]

In discussing the observed KIEs in the present study, it is useful to examine the magnitudes of IEs on the corresponding equilibria. Theoretical isotope effects on the polar addition process were computed by using ab initio MO methods. Here benzaldehyde and the benzaldehyde-methyl lithium adduct were fully optimized at HF/6-31+G* and their vibrational frequencies were calculated. MeLi was used here instead of lithium pinacolone enolate for simplicity assuming that the equilibrium IE (EIE) is not much different for the MeLi adduct and for the lithium enolate adduct. The equilibrium IEs for carbonyl-^{13}C, and phenyl-D_5 species were obtained from the vibrational frequencies[12] of the isotopemers by using Bigeleisen's equation (Eq. 3) and shown below.

$$\frac{k_1}{k_2} = \left[\frac{\nu^{\neq}_{L1}}{\nu^{\neq}_{L2}}\right] \frac{\prod\limits^{3n-6} \frac{u_{2i}}{u_{1i}} \prod\limits^{3n-6} \left(\frac{1 - e^{-u_{1i}}}{1 - e^{-u_{2i}}}\right) \exp\left[\sum\limits^{3n-6} (u_{1i} - u_{2i})/2\right]}{\prod\limits^{3n-7} \frac{u^{\neq}_{2i}}{u^{\neq}_{1i}} \prod\limits^{3n-7} \left(\frac{1 - e^{-u^{\neq}_{1i}}}{1 - e^{-u^{\neq}_{2i}}}\right) \exp\left[\sum\limits^{3n-7} (u^{\neq}_{1i} - u^{\neq}_{2i})/2\right]} \quad (3)$$



$^{12}K/^{13}K = 1.006 \quad K_H/K_{D5} = 1.094$

Theoretical EIE at the carbonyl ^{13}C for the MeLi addition to benzaldehyde was calculated to be small ($^{12}k/^{13}k = 1.006$). The experimental carbonyl-^{13}C KIE is small positive ($^{12}k/^{13}k = 1.019$) and is larger than the EIE, suggesting that there is reaction-coordinate contribution. The observed KIE of 1.9% corresponds to 3.8% of ^{14}C KIE, which is within the range expected for the carbonyl-^{14}C KIE in the polar nucleophilic additions; $^{12}k/^{14}k = 1.035$ (BH_3/THF), 1.021 (AlH_3/Et_2O), $LiAlH_4/THF$ (1.017), $LiAlH_4/Et_2O$ (1.024), $LiBH_4/Et_2O$ (1.043), and $NaBH_4$/2-PrOH (1.066).[13] Thus, the observed positive KIE is consistent with the PL mechanism, although the IE result by itself does not exclude the possibility that the reaction proceeds via fast ET followed by a slow rate-determining RC step.

Since the D_5 KIE is a secondary effect, the contribution from reaction-coordinate motion to the IE is negligible or very small if any. The magnitude of the KIE should thus be in between 1.0 and the EIE (1.094), depending on the position of the TS along the reaction coordinate. The observed D_5 KIE of 1.031 is one-third of the EIE, which suggests that the TS is reached at one-third of the reaction coordinate if the reaction proceeds via the PL mechanism.

In summary, the present isotope effect results clearly indicated that reaction of lithium pinacolone enolate and benzaldehyde proceeds in a different mechanism from that of MeLi or PhLi. Whether the reaction proceeds via the PL mechanism like the $LiAlH_4$ reduction or via the ET-RC pathway with the rate-determining RC step as for MeMgX is not clear at this stage. Further mechanistic study on related reactions incluing the one with benzophenone is in progress.

References and Notes

1 H. Yamataka, T. Matsuyama, and T. Hanafusa, *J. Am. Chem. Soc.*, **111**, 4912 (1989).

2 H. Yamataka, N. Fujimura, Y. Kawafuji, and T. Hanafusa, *J. Am. Chem. Soc.*, **109**, 4305 (1987).

3 C. A. Palmer, C. A. Ogle, and E. M. Arnett, *J. Am. Chem. Soc.*, **114**, 5619 (1992); E. M. Arnett and C. A. Palmer, *J. Am. Chem. Soc.*, **112**, 7354 (1990).

4 E. C. Asby and J. N. Argyropoulos, *J. Org. Chem.* **51**, 472 (1986).

5 H. Yamataka, Y. Kawafuji, K. Nagareda, N. Miyano, and T. Hanafusa, *J. Org. Chem.*, **54**, 4706 (1989).

6 For previous measurement by this method, see: H. Yamataka, M. Mishima, Y. Kuwatani, and Y. Tsuno, *J. Am. Chem. Soc.*, **117**, 5829 (1995).

7 M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andress, K. Rachavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, *GAUSSIAN 92*, Gaussian Inc., Pittsburgh, PA (1992).

8 M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y.Ayala, W. Chen, M. W. Wong, J. L. Andress, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, *GAUSSIAN 94*, Revision C.2, Gaussian, Inc., Pittsburgh, PA (1995).

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

10 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, In *Isotopes in Organic Chemistry*; ed by E. Buncel and C. C. Lee, Elsevier, Amsterdam (1984), Vol. VI, Chap. 4.

11 See, for example: H. Yamataka, K. Nagareda, T. Takatsuka, K. Ando, T. Hanafusa, and S. Nagase, *J. Am. Chem. Soc.*, **115**, 8570 (1993).

12 Frequencies were scaled down by the factor of 1.12 to correct for the overestimation at this calculation method.

13 H. Yamataka and T. Hanafusa, *J. Am. Chem. Soc.*, **108**, 601 (1986); H. Yamataka and T. Hanausa, *J. Org. Chem.*, **53**, 772 (1988).