CHEMISTRY LETTERS, pp. 643-646, 1987.

Carbon-14 Kinetic Isotope Effect in Reduction of Benzophenone with Lithium Isopropoxide

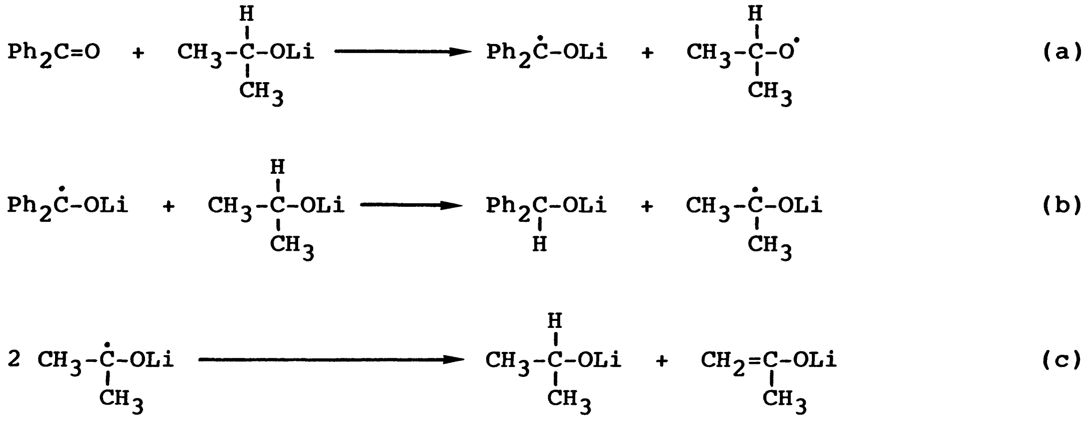
Hiroshi YAMATAKA* and Terukiyo HANAFUSA
The Institute of Scientific and Industrial Research,
Osaka University, Ibaraki, Osaka 567

The carbon-14 kinetic isotope effect (KIE) was determined for the reduction of benzophenone-carbonyl-^{14}C with lithium isopropoxide in THF at 25 °C. The observed KIE ($^{12}k/^{14}k$ = 1.045) suggested that there is considerable bonding change at the carbonyl carbon in the transition state. This is the first example of carbon KIE in a reaction which proceeds via initial electron transfer followed by a slow radical process.

In recent years evidence has been accumulated which indicates the involvement of single electron transfer (SET) in a variety of organic reactions such as the Grignard reaction$^{1)}$ and the reactions of ketones with organolithium reagents.$^{2)}$ Experimental methods generally used in these studies are spectroscopic observation of radical intermediates and radical probe experiments; these methods have been shown to be useful to detect a possible involvement of a SET process in these reactions. However, a SET mechanism is by nature a multi-step process (an ET step and subsequent radical processes to give products), and hence it is important to clarify which step is rate determining. The methods cited above may not be suitable for this purpose.

Kinetic isotope effects have successfully been used to investigate the rate-determining step of chemical reactions.$^{3)}$ For example, α-deuterium KIE has been shown to be useful in identifying the rate-determining step in Winstein's ion-pair scheme of solvolytic reactions.$^{4)}$ The KIE technique is applicable in general to any reaction in which the magnitude of KIE is known in each step of a multi-step reaction. The magnitude of primary KIE in the ET step is often assumed to be unity.$^{5,6)}$ Here we wish to report the first example of carbon KIE in such a reaction that proceeds via initial ET followed by slow radical processes. The reaction we investigated is the reduction of benzophenone with lithium isopropoxide (Scheme 1), which has recently been shown to proceed via a SET mechanism.$^{7,8)}$

The reaction of benzophenone with lithium isopropoxide was carried out as follows. In a flame-dried test tube capped with a rubber septum benzophenone (91 mg, 0.5 mmol) and diphenoxyethane (40 mg, 0.19 mmol, an internal standard) were placed and dissolved in 1.97 mL of freshly distilled THF. To this 3.03 mL of THF solution of LiOPr$\underline{\text{i}}$$^{12)}$ (3.3 M, 1 M = 1 mol dm^{-3}) was added and the test tube was placed in a constant-temperature bath maintained at 25.0±0.1 °C. At appropriate



$$Ph_2C{=}O + CH_3\text{-}\underset{CH_3}{\overset{H}{C}}\text{-}OLi \longrightarrow Ph_2\dot{C}\text{-}OLi + CH_3\text{-}\underset{CH_3}{\overset{H}{C}}\text{-}O^{\bullet} \qquad (a)$$

$$Ph_2\dot{C}\text{-}OLi + CH_3\text{-}\underset{CH_3}{\overset{H}{C}}\text{-}OLi \longrightarrow Ph_2\underset{H}{C}\text{-}OLi + CH_3\text{-}\underset{CH_3}{\dot{C}}\text{-}OLi \qquad (b)$$

$$2\ CH_3\text{-}\underset{CH_3}{\dot{C}}\text{-}OLi \longrightarrow CH_3\text{-}\underset{CH_3}{\overset{H}{C}}\text{-}OLi + CH_2{=}\underset{CH_3}{C}\text{-}OLi \qquad (c)$$

Scheme 1.

time intervals a small portion of the reaction solution was withdrawn, added to water, and extracted with ether. The ethereal solution was then subjected to GLPC analysis (2 m-glass column, PEG-HT at 190 °C). As shown in Fig. 1, the material balance was excellent and no side product was detected. The kinetic isotope effect was measured by running the reaction of benzophenone-*carbonyl*-^{14}C (10 mmol) with LiOPr^{i} (200 mmol) in 100 mL THF. A small portion of the reaction solution (20 mL) was withdrawn from the reaction vessel at appropriate time intervals, poured into water, and worked up as usual. The product alcohol and the recovered ketone were separated by TLC and purified by repeated recrystallization. Radioactivities were determined by a liquid scintillation counter (Beckman LS9000) as reported previously.[11] KIEs were calculated by using four equations of Tong and Yankwich.[13] These equations allow KIE calculations in four ways by using any three of the measured parameters, fraction of reaction, *f*, radioactivity of the starting ketone, R_0, activity of the recovered ketone, R_r, and activity of the product alcohol, R_p. Agreement among the KIEs calculated by four different equations was excellent as shown in Table 1, indicating the high reliability of the results.

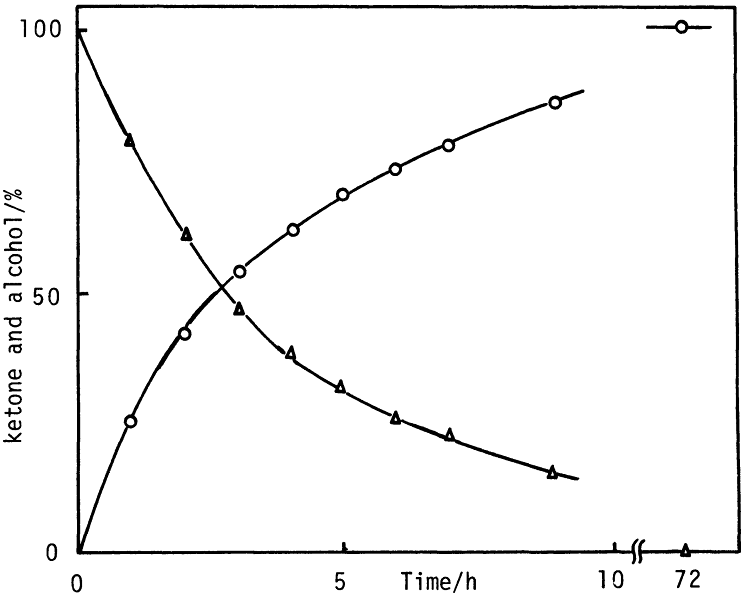


Fig. 1. Reaction of Benzophenone with lithium isopropoxide: (▲) benzophenone; (○) Benzhydrol.

The Meerwine-Pondorf-Verley reduction of ketones has long been considered to proceed via a polar mechanism involving a cyclic transition state.[14]

Table 1. Kinetic Isotope Effects in Reduction of Benzophenone at 25 °C[a)]

Reagent/Solvent	$\underline{R}_0,\underline{R}_r,\underline{R}_p$	$\underline{f},\underline{R}_0,\underline{R}_r$	$\underline{f},\underline{R}_0,\underline{R}_p$	$\underline{f},\underline{R}_r,\underline{R}_p$	$^{12}\underline{k}/^{14}\underline{k}$ (av)
$LiOPr^{\underline{i}}$/THF	1.044±0.002	1.048±0.003	1.042±0.003	1.045±0.002	1.045±0.004

a) For definitions of $\underline{R}_0$, $\underline{R}_r$, $\underline{R}_p$, and $\underline{f}$, see text. Listed values are averages from 5 runs whose fractions of reaction are in the range 32-73%. Error limits are the standard deviations.

However in 1978, the reduction of fluorenone with lithium alkoxide was shown to give lithium fluorenone ketyl to the extent of 65%, suggesting that there occured the transfer of single electron from lithium alkoxide to the ketone.[7)] More recently, Ashby and Argyropoulos provided strong evidence which indicates that the reduction of benzophenone with lithium isopropoxide proceeds via an initial ET to the ketone to yield lithium benzophenone ketyl.[8b)] In particular, they observed that the intensity of the EPR signal of the ketyl intermediate decreased in a first-order fashion with $\underline{k} = 2.0 \times 10^{-5}\ s^{-1}$ in THF at 22 °C, which is in good agreement with the rate constant ($\underline{k} = 2.5 \times 10^{-5}\ s^{-1}$) for the pseudo-first-order formation of benzhydrol. The results suggested that the product formation from the radical intermediate is the rate-determining step of the reaction under these reaction conditions. The proposed mechanism is summarized in Scheme 1, in which the ketyl intermediate formed via SET abstracts a hydrogen atom from another molecule of lithium isopropoxide in step b to give lithium benzhydrolate as well as lithium acetone ketyl, and the latter rapidly disproportionates to lithium isopropoxide and the lithium enolate of acetone in step c.

Kinetic analysis of the present results shown in Fig. 1 gave the pseudo-first-order rate constant of $3.0 \times 10^{-5}\ s^{-1}$ at 25 °C, which is in agreement with the reported value. The carbonyl-^{14}C KIE determined in the present study is of considerable magnitude, and indicates that there is considerable bonding change at the carbonyl carbon in the rate-determining transition state. The observed KIE is a composite of the two effects: the equilibrium IE (EIE) in step a and the KIE in step b. Although no experimental data are available for the EIE in the SET process, it should be larger than unity because the C=O bond should be weakened by accepting an electron in its anti-bonding molecular orbital. Ab initio MO calculations at the HF/3-21G level for SET to $H_2C=O$ revealed that the C-O bond is indeed lengthened from 1.207 to 1.318 Å, and the EIE was calculated as 1.071 at 25 °C.[15)] Although the benzophenone ketyl has an unpaired electron much more delocalized into the phenyl groups and therefore the EIE should be much smaller than the calculated value for $H_2C=O$, it seems reasonable to conclude that the EIE in step a is of considerable magnitude. Step b is formally a bond forming process, and hence the KIE of this step may be small although KIE is generally larger than the EIE of the same reaction.[16)]

It is interesting to note that the overall KIE is comparable in magnitude to those reported for typical additions to ketones (e.g., $^{14}\underline{k}/^{12}\underline{k} = 1.043$ for $(C_6H_5)_2C=O + LiBH_4$[17)] and 1.054 for $C_6H_5COCH_3 + 2,4\text{-}(NO_2)_2C_6H_3NHNH_2$[18)]). This suggests that the effective transition state of the two-step process (the electron transfer and hydrogen transfer sequence) is similar to that of the direct nucleophilic addition. In conclusion, the present study shows that the ^{14}C KIE in the reaction which proceeds via SET followed by a slow radical process is as large as that expected for the conventional nucleophilic reaction. The results suggest that the ^{14}C KIE technique may be a useful method to determine the rate-determining step of a SET reaction.

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(Received January 26, 1987)