

α -Deuterium and α - ^{13}C KIEs in the Reaction of Alkylolithium and Alkylmagnesium Reagents with Benzophenone and 2-Octanone

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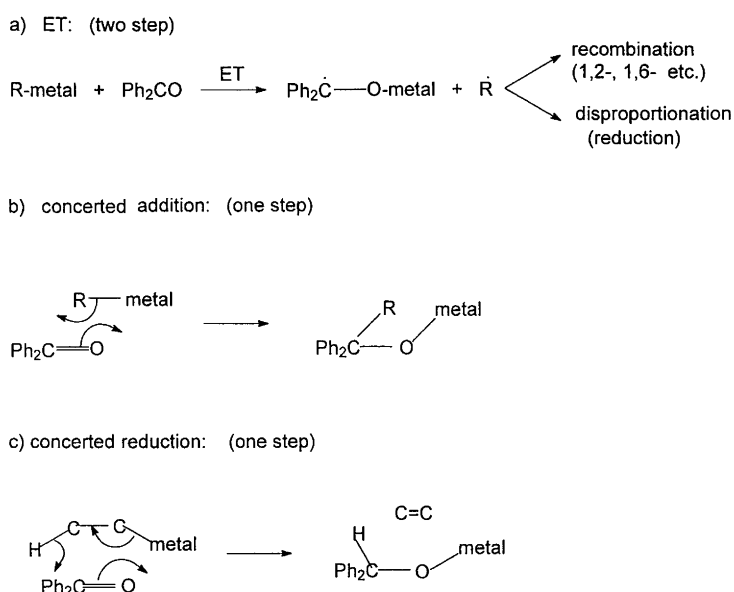
Holm, T., 1994. α -Deuterium and α - ^{13}C KIEs in the Reaction of Alkylolithium and Alkylmagnesium Reagents with Benzophenone and 2-Octanone. – Acta Chem. Scand. 48: 362–366 © Acta Chemica Scandinavica 1994.

The addition reactions of methylmagnesium iodide and of ethylmagnesium bromide to benzophenone and 2-octanone proceed via concerted reaction mechanisms, while the addition of the corresponding alkylolithium reagents have electron transfer mechanisms. This is concluded from the observation of large normal α -deuterium KIEs for the reaction of RLi and small and inverse α -deuterium KIEs for the reaction of RMgX. An ET mechanism for the reaction of ethyllithium with benzophenone is supported by the finding of a 1,6-addition product (5%) and of an *O*-alkyl product (traces) and by the observation that suppression of the reduction process by β -deuteriation of the reagent causes an increase in the rate of addition. With ethyllithium and benzophenone addition and reduction therefore have a common precursor (radicals), while with ethylmagnesium bromide addition and reduction are independent reactions.

^{13}C KIEs for substitution at the α -carbon of the reagents are of little diagnostic value.

The mechanism of the reaction of Grignard reagents with benzophenone has been studied very intensely for many years.^{1–8} The reaction of *tert*-butylmagnesium chloride was found to occur via an electron transfer mechanism

meaning that *tert*-butyl and ketyl radicals are produced in the rate-determining step [Scheme 1(a)].⁵ This conclusion was drawn on the basis of the following criteria: (1) the magnesium ketyl was observed by ESR³ and by



Scheme 1.

UV-VIS spectroscopy during the reaction; (2) significant amounts of radical by-products such as benzopinacol⁴ and hydrocarbons from the alkyl radicals were found; (3) more than 50% of the reaction product was alkyl-dihydrobenzophenones⁵ formed by 1,6-addition across the aromatic ring; (4) the reactivity series for various alkyls was⁶ *tert*-butyl > isopropyl > ethyl > butyl > methyl; (5) the use of substituted benzophenones including *ortho* derivatives showed that the overall rates measured for the substituted benzophenones gave a satisfactory Hammett plot, when correlated with the respective substitution constants, even though the product distribution was very sensitive to steric factors.⁵ An *ortho* methyl group in the benzophenone did not cause any steric rate retardation.

The sum of the evidence from these criteria, and especially from (5) constitutes proof of a stepwise, radical mechanism for the reaction of tertiary and secondary Grignard reagents with benzophenone.

For the reaction of benzophenone with methyl, phenyl and primary Grignard reagents, however, only (1) and (4) indicated a radical mechanism, and the observed ketyl radicals might very well be an unimportant by-product. The question of radical or concerted mechanism [Scheme 1(b) and (c)] was therefore unanswered. Nevertheless it was widely assumed that caged radicals were actually produced in the main process, but that no escape from the cage was taking place because of the high reactivity of the radicals.^{1,2,7,8}

The kinetic isotope effect (KIE) resulting from the replacement of the carbonyl carbon in benzophenone with ^{14}C has been measured by Yamataka *et al.* for a number of Grignard reagents,⁸ and for methyl-, phenyl- and allyl-lithium.^{9,10} Values of $^{12}k/^{14}k$ for the reactions of the lithium reagents were near unity, similar to the values found in the reactions of allylmagnesium and *tert*-butylmagnesium halide.^{8,11} From theoretical calculations⁸ it was considered likely that a unity ^{14}C KIE should be expected for a reaction in which electron transfer is rate limiting. This conclusion has been questioned since it was reported that the $^{12}k/^{13}k$ KIE for reaction of *tert*-butylmagnesium chloride and methylmagnesium bromide with ^{13}C benzophenone were both significant and of the same magnitude.¹¹

Yamataka *et al.* found a low value of Hammett's ρ in the reaction of methyl- and phenyl-lithium (and also allylmagnesium bromide) in the reaction with substituted benzophenones.^{12,13} This was taken as evidence of an electron transfer as the rate determining step even if it, *a priori*, would seem strange that the transfer of a negative charge should be independent of polar substituents in the acceptor molecule. Unpublished kinetic measurements in this laboratory have shown that methyllithium reacts with benzophenone in diethyl ether in a reaction in which the initial rate is almost independent of the concentration of the substrate. Since the rate is invariant with the concentration of benzophenone it is hardly surprising that it is invariant with isotopic or polar substitutions in the benz-

ophenones. It seems possible, that because of the aggregated nature of alkyllithium reagents,¹⁴ benzophenone does not play an important part in the rate-determining step. The experiments are being continued.

If electron transfer from *tert*-butylmagnesium chloride to ^{13}C benzophenone actually has a significant carbon KIE as found in Ref. 11, a unity ^{14}C KIE is no proof for or against electron transfer in the reaction of alkyllithium with benzophenone. A different approach, however, seems to give more obvious results.

Results and discussion

In the present work benzophenone and 2-octanone were reacted with methyl- and ethyl-lithium and with methyl and ethyl Grignard reagents, and KIEs were measured for substitution of the metal carrying ^{13}C in alkylmetal reagents and for substitution of the α -hydrogens with deuterium in the two reagents. The ^{13}C effects measured (Table 2) did not vary much and were difficult to interpret, but the effect of α -deuterium substitution was large and apparently meaningful. The results are given in Table 1 and Table 2.

It is seen (Table 1) that methyllithium (entry 1) and ethyllithium (entry 9) in reaction with both substrates have high values for $k_{\text{H}}/k_{\alpha\text{D}}$ (about 5% per α -deuterium), while the values obtained for methylmagnesium iodide (3) and ethylmagnesium bromide (14) are small and inverse.

The interpretation of secondary deuterium KIEs requires knowledge of the changes in all vibrational frequencies in the transition state, but an empirical rule for α -deuterium KIEs has been proposed by Streitwieser,¹⁵ which states that a decrease in p-character on going to the transition state will result in a decrease in rate if hydrogen is replaced by with deuterium. For an $\text{S}_{\text{N}}1$ reaction, in which the α -atom must rehybridize from sp^3 to sp^2 , a much larger effect (of the order of 10% per deuterium) is observed than for $\text{S}_{\text{N}}2$, which requires less rehybridization and for which observed effects are smaller than 5% per α -deuterium.¹⁶

In analogy with this, the typical ET reaction, in which a free radical is produced, would require much more rehybridization at the α -carbon than would a concerted reaction, although not as much as required by a carbonium ion. The ET will therefore give rise to both α - and β -deuterium KIEs.

β -Deuterium KIEs have been used¹⁷ for distinguishing $\text{S}_{\text{N}}2$ from ET reactions since the vibrational frequencies are loosened at the transition state in ET leading to $k_{\text{H}}/k_{\text{D}} > 1$. In the present work the interference of primary KIEs on the reduction process makes this approach difficult (see below).

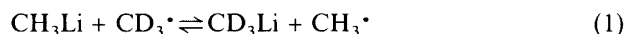
A more quantitative approach to secondary KIEs is the calculation of fractionation factors, which are the equilibrium constants for the exchange of deuterium between compounds with C-H bonds of different types.¹⁸

For α -deuterium KIEs a theoretical maximum value of the effect might be calculated from the fractionation

Table 1. Relative reactivity, k_{II}/k_I , for the addition reaction of 0.15 M ethereal organometallic reagents (II) competing with 0.15 M reference reagents (I) for a 0.002 M concentration of various substrates. The value presented is the average of n experiments and the maximum deviation from the average is also given (in parentheses).

| Reagent | | k_{II}/k_I for | |
|--|--|--------------------|--|
| I | II | Ph ₂ CO | CH ₃ COC ₆ H ₁₃ |
| (1) CD ₃ Li, Lil | CH ₃ Li, Lil | 1.136 ± 0.007(2) | 1.096 ± 0.002(2) |
| (2) CD ₃ Li, Lil | ¹³ CH ₃ Li, Lil | 1.114 ± 0.002(2) | 1.080 ± 0.004(2) |
| (3) CD ₃ Mgl | CH ₃ Mgl | 0.960 ± 0.001(2) | 0.977 ± 0.005(3) |
| (4) CD ₃ Mgl | ¹³ CH ₃ Mgl | 0.943 ± 0.001(2) | 0.955 ± 0.002(3) |
| (5) CD ₃ CD ₂ Li, LiBr | CH ₃ CH ₂ Li, LiBr | 1.056 ± 0.011(5) | 1.149 ± 0.006(2) |
| (6) CD ₃ CD ₂ Li, LiBr | CH ₃ ¹³ CH ₂ Li, LiBr | 1.026 ± 0.013(2) | 1.120 ± 0.003(2) |
| (7) CD ₃ CD ₂ Li, LiBr | CH ₃ CD ₂ Li, LiBr | 0.953 ± 0.008(2) | 1.057 ± 0.006(2) |
| (8) CD ₃ CH ₂ Li, LiBr | CH ₃ CH ₂ Li, LiBr | 0.952 ± 0.005(3) | 1.052 ± 0.004(2) |
| (9) CH ₃ CD ₂ Li, LiBr | CH ₃ CH ₂ Li, LiBr | 1.104 ± 0.019 | 1.087 ± 0.012 |
| (10) CD ₃ CD ₂ MgBr | CH ₃ CH ₂ MgBr | 0.999 ± 0.007(4) | 0.948 ± 0.005(2) |
| (11) CD ₃ CD ₂ MgBr | CH ₃ ¹³ CH ₂ MgBr | 0.975 ± 0.005(3) | 0.926 ± 0.002(3) |
| (12) CD ₃ CD ₂ MgBr | CH ₃ CD ₂ MgBr | 1.011 ± 0.004(2) | 0.985 ± 0.003(1) |
| (13) CD ₃ CH ₂ MgBr | CH ₃ CH ₂ MgBr | 1.014 ± 0.003(3) | 0.985 ± 0.003(3) |
| (14) CH ₃ CD ₂ MgBr | CH ₃ CH ₂ MgBr | 0.991 | 0.965 |

factors for methyllithium and the methyl radical, which would allow calculation of the equilibrium constant K for equilibrium (1).



The fractionation factor for methyllithium has been calculated,¹⁸ but no reliable value is known for the methyl radical. The fractionation factor for the hypothetical S_N2 transition state is also unknown. Qualitatively, however, it must be assumed that the bonds from carbon to α -hydrogens are looser in the radical than in an S_N2 transition state and the conclusion is that methyl- and ethyl-lithium react by ET and have a radical-type transition state, while the corresponding Grignard reagents react in a concerted way.

That ethyllithium reacts by electron transfer with benzophenone [Scheme 1(a)] and ethylmagnesium bromide reacts by a concerted mechanism [Scheme 1(b) and (c)] is indicated not only by the KIEs measured, but also by experiment. The reaction products obtained in the two reactions are different. While the Grignard reagent produces only the addition and the reduction product, ethyllithium with benzophenone produces, in addition, 5% of the 1,6-addition product and trace amounts of *O*-alkylated products as observed by GC-MS of the reaction product. Addition of ethyllithium to an excess of benzophenone produces the blue lithium ketyl. Methyllithium like methylmagnesium bromide produces a high yield of the 1,2-addition product and no trace of 1,6-addition product. When methyllithium is added to an excess of benzophenone no ketyl is produced if the ketone solution has been protected against light. Photochemically produced benzopinacol is converted into blue ketyl by the addition of methyllithium.

Table 2. ¹³C KIEs for the addition reaction of α -C-substituted alkyllithium and Grignard reagents with benzophenone and 2-octanone in diethyl ether at 20 °C.

| Reagent | ¹² k/ ¹³ k | |
|------------------------------------|----------------------------------|---------------|
| | Ph ₂ CO | 2-Octanone |
| CH ₃ Li, Lil | 1.020 ± 0.009 | 1.015 ± 0.006 |
| CH ₃ Mgl | 1.023 ± 0.002 | 1.026 ± 0.007 |
| C ₂ H ₅ Li | 1.025 ± 0.020 | 1.026 ± 0.009 |
| C ₂ H ₅ MgBr | 1.027 ± 0.012 | 1.024 ± 0.007 |

ophenone produces the blue lithium ketyl. Methyllithium like methylmagnesium bromide produces a high yield of the 1,2-addition product and no trace of 1,6-addition product. When methyllithium is added to an excess of benzophenone no ketyl is produced if the ketone solution has been protected against light. Photochemically produced benzopinacol is converted into blue ketyl by the addition of methyllithium.

The two-step radical-type mechanism in the reaction of ethyllithium with benzophenone was also indicated by a study of the secondary KIE, which resulted from introducing three deuterium atoms into the β -position of the reagent. As seen in Table 1 this caused a significant acceleration of the addition reaction to benzophenone, but slowed down the addition to 2-octanone. The interpretation is that with benzophenone the ET reaction produces an ethyl and a ketyl radical, which may either combine to form the addition product or disproportionate to give the reduction products benzhydrol and ethene, Scheme 1. If the β -hydrogens are exchanged with deuterium the disproportionation is hindered (a primary deuterium KIE) and recombination is favored, resulting in an increased rate of the addition reaction. The fraction of 1,2-addition product increases from 62% to 73% after exchange of the β -hydrogens with deuterium atoms, Table 3. If the rate of the initial ET is unchanged and

Table 3. Product distributions for the reactions of 0.15 M ethyllithium-LiBr with 0.003 M ethereal solutions of ketones as determined by GC given in per cent. Both reagents produced, in addition, with benzophenone ca. 5% 1,6-addition product and with 2-octanone 1.6% 2-octanone enolate.

| | Benzophenone | | 2-Octanone | |
|--|--------------|-----------|------------|-----------|
| | Addition | Reduction | Addition | Reduction |
| CH ₃ CH ₂ Li, LiBr | 62 | 33 | 94 | 4.8 |
| CD ₃ CH ₂ Li, LiBr | 73 | 22 | 94 | 4.6 |

there is no loss of radicals in alternative ways the rate of formation of addition product should increase by 17%. The observed rate increase is only 5% which indicates a β -deuterium KIE on the ET step of 10–12%. As mentioned above $k_{\text{H}}/k_{\text{D}} > 1$ is expected for an ET reaction since the bond to the β -hydrogen becomes 'looser'.

It remains uncertain as to whether the reactions of the radicals take place within the solvent cage or whether they react after diffusion out of the cage.¹⁹

For 2-octanone the fraction of reduction product is not changed significantly relative to the amount of addition product, when β -H is exchanged with β -D, Table 3.

It is apparent that the isotope effects observed with the aliphatic ketone are smaller than the effects seen with benzophenone. This may mean that less radical character is developed in the reactions of alkyllithium with aliphatic ketones.

α -deuterium KIEs seen for the addition reaction of ethylmagnesium bromide to both benzophenone and 2-octanone are inverse and seem to be explained by steric effects, the groups containing deuterium being effectively smaller because of the smaller vibration amplitudes of the heavier D-atom.

The ^{13}C KIEs were found from the rates measured relative to those of the deuteriated reagents and are shown in Table 2. The values are of the order of 1.5–2.7%. The uncertainty is given as the sum of the deviations from average found for the two rate relationships, which are used for finding $^{12}\text{k}/^{13}\text{k}$. There seems to be no decisive correlation of the ^{13}C KIEs to reagent, substrate or reaction mechanism.

Since, according to the present results, methyl- and ethyl-magnesium bromide have concerted mechanisms in the reaction with benzophenone, the linear correlation of log rate and the oxidation potential of the Grignard reagents¹ is not proof of identical mechanisms and the very low reaction rates for methyl- and phenyl-magnesium bromide should be explained, for example, by low polarization of the carbonyl group in benzophenone.

Conclusion

α -Deuterium KIEs of about 5% per deuterium in the reaction of methyl- and ethyl-lithium indicate a rate-determining electron transfer step in the reaction with ketones. Reactions of methyl and ethyl Grignard reagents with ketones have inverse α -deuterium KIEs, indicating concerted reaction mechanisms. α - ^{13}C KIEs for alkyllithium and Grignard reagents provide no obvious indications of the mechanisms of their reactions with ketones.

Experimental

Materials. Diethyl ether was distilled from benzophenone ketyl. Labelled iodomethane was prepared from labelled methanol by reaction with phosphorus and iodine. Deu-

terium-substituted bromoethane was prepared from deuterium-substituted ethanol and phosphorus tribromide. (1 - ^{13}C)ethanol, pentadeuterioethanol, 1,1-dideuterioethanol, 2,2,2-trideuterioethanol, and (^{13}C)methanol were obtained from Cambridge Isotope Laboratories (all > 99% isotopically pure).

Kinetic isotope effects. The determination of KIEs by GC isotopic separation has been described.^{11,20} A 100 m \times 0.2 mm \times 0.33 μm HP-5 capillary column was used. For the competition experiments ether solutions containing a mixture of a test reagent and a reference reagent in the combinations shown in Table 1 were prepared. For example 1.5 mM of methyl iodide was mixed with 1.5 mM of trideuteriomethyl iodide and the mixture added slowly to 0.8 g magnesium in 10 ml ether with cooling to produce a Grignard reagent ca. 0.15 M in each reagent. The same procedure was used for the six combinations of alkyl halides listed in Table 1. From the same six combinations of alkyl halides alkyllithium solutions were prepared. For example a mixture of 1.5 mM of ethyl bromide and 1.5 mM of pentadeuterioethyl bromide was added slowly to a suspension of 0.4 g of lithium thread in 10 ml of ether. The solution was shaken for 20 min with occasional cooling. While the Grignard reagents were stable, the solutions of ethyllithium were used the day they were prepared.

KIEs in the reactions with substrates were determined by reacting 0.5 ml of 0.002 M solutions of the substrate in ether with 0.5 ml of a mixed (deuterio/non-deuterio) reagent in disposable syringes. The composition of the reaction mixture after normal work-up was determined by GC since the peak from the deuteriated product (or most deuteriated) eluted 0.4–0.6 min ahead of the non- (or least) deuteriated product. The kinetic isotope effects, shown in Table 1, were calculated as the ratios between the two integrals after correcting for the exact D/H composition of the reagent mixtures. These were determined by reacting the D/non-D reagents with an excess of 4-methylbenzophenone (methyl-reagents) or 4,4-dimethyl-1-phenyl-1-penten-3-one (ethyl-reagents), and analysing the product mixture by GC.^{11,20}

The use of α -dideuterio reagents in competition with the protio reagent resulted in reaction mixtures in which separation of the deuterio/protio products was insufficient. To be able to measure KIEs for α -dideuterioethyl reagents their reactivities were measured relative to the pentadeuteriated reagents, which again were measured relative to the protio reagent. The KIEs calculated in this indirect way are listed with the experimental values in Table 1.

The competition experiments and the calibrations were repeated up to five times as shown in Table 1. The maximum deviation from the average is given for each experiment.

Integration of the GC signals were reproducible to within 0.3%, while a complete $k_{\text{D}}/k_{\text{H}}$ determination, which includes a competition experiment and calibration

of the D/H ratio was normally reproducible to within $\pm 1\%$. Values which were found as the ratio between two competition experiments such as $^{12}k/^{13}k$ or the KIEs for α,α -dideuterioethyl reagents have about twice the uncertainty of that for a single D/H competition experiment. This means that the $^{12}k/^{13}k$ KIEs found are of the order of one to two times the experimental uncertainty, while the α -deuterium effects exceed the experimental uncertainty by a factor 5–10.

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Received October 28, 1993.