25.26, 24.03, 23.02, 22.79, 22.49, 19.05, 17.95; HRMS-FAB ($M + H^+$) calcd for $C_{70}H_{109}N_{12}O_{14}$ 1363.8010, found 1363.8000.

Titration of hubM$_3$ with R'CA or flexM$_3$ with R''CA Monitored by ^{1}H NMR Spectroscopy. An NMR tube was charged with hubM$_3$ (0.0196 g, 0.0094 mmol) or flexM$_3$ (0.0132 g, 0.0100 mmol) and $CDCl_3$ (1.0 mL). Solid aliquots of neohexyl cyanurate (R'CA) (0.0010 g, 0.0047 mmol) or triphenylpropyl cyanurate (R''CA) (0.0020 g, 0.0050 mmol) were added to the NMR tube, and the tube was shaken until all of the solid had dissolved. The ^{1}H NMR spectrum was recorded after each aliquot was added. After the sixth aliquot was added there was no further change in the spectrum. Additional aliquots of R'CA or R''CA did not go into solution.

NOE Spectra of the hubM$_3$(R'CA)$_3$ and flexM$_3$(R''CA)$_3$ Complexes. The NOE spectra of the 1:3 complexes were recorded at 25 °C. The procedures for both complexes were identical. The complex (0.0100 mmol) was dissolved in 1.0 mL of $CDCl_3$, and the sample was degassed with five freeze-pump-thaw cycles. The NOE spectra were collected with an evolution period of 3.0 s and a relaxation delay of 6.0 s.

Gel Permeation Chromatography. Gel permation chromatography was performed using a Waters 600E HPLC with a Waters 484 UV detector (set at 254 nm) and Waters analytical gel permeation column (Ultrastyragel, 1000 Å pore size). Elutions were performed at room temperature using HPLC grade chloroform and methylene chloride as the solvents at a flow rate of 1.0 mL/min. The samples were prepared at concentrations of 1.0 mM for hubM$_3$ samples and 2.0 mM for the flexM$_3$ samples in solvent that contained *p*-xylene (3.0 mM) as an internal reference. The injection volume was 20 μL.

Molecular Weight Determinations of the hubM$_3$(R'CA)$_3$ and flexM$_3$(R''CA)$_3$ Complexes by Vapor Pressure Osmometry. Molecular weight determinations were made with a Wescan Model 233 vapor pressure osmometer operated at 35 °C. The molecular weights of the complexes were measured in HPLC grade glass-distilled chloroform at concentrations of 2, 4, 8, and 16 mM. At each concentration, 3-4 measurements were taken. Calibration curves were generated using sucrose octaacetate, perbenzoyl β-cyclodextrin, polystyrene (MW 5050, polydispersity = 1.05), and a gramacidin S derivative in which the ornithine amino groups had been converted to the *tert*-butyl carbamates (MW 1342) as molecular weight standards.

Titration of hubM$_3$ with R'CA and flexM$_3$ with R''CA Monitored by UV Spectroscopy. UV spectra were recorded on a Perkin-Elmer Model 551 spectrophotometer. A 125-mL Erlenmeyer flask equipped with a stirring bar was charged with hubM$_3$ (0.0209 g, 0.0100 mmol) or flexM$_3$ (0.0132 g, 0.0100 mmol) and 100 mL of CH_2Cl_2. Solid aliquots of neohexyl cyanurate (0.0011 g, 0.0050 mmol) or triphenylpropyl cyanurate (0.0020 g, 0.0050 mmol) were added to the flask, and the solution was stirred until all of the solid had dissolved. After each aliquot was added, a 0.30-mL sample of the solution was transferred to a 1.0-mm quartz cuvette and the UV spectrum was recorded from 390 to 190 nm. The sample was transferred back to the Erlenmeyer flask and the next aliquot was added. After the sixth aliquot was added there was no further change in the spectrum. The quartz cuvette was rinsed thoroughly with THF and dried in a stream of nitrogen between each measurement.

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Supplementary Material Available: Details of the synthesis of compounds other than hubM$_3$ and flexM$_3$ that are shown in Scheme II (9 pages). Ordering information is given on any current masthead page.

^{13}C Kinetic Isotope Effects in the Reactions of Grignard Reagents with Benzophenone

Torkil Holm

Contribution from the Department of Organic Chemistry, Building 201, Technical University of Denmark, DK-2800 Lyngby, Denmark. *Received July 8, 1992. Revised Manuscript Received October 5, 1992*

Abstract: The rate-determining step for the reaction of benzophenone with Grignard reagents is an inner sphere electron transfer (ET) with a simultaneous transfer of magnesium to produce the magnesium benzophenone ketyl and the alkyl radical. For tertiary and secondary reagents the alkyl radical is free to escape from the cage, while for primary reagents and methyl partial bond formation between the radicals stabilizes the transition state and prevents escape. Substitution in the carbonyl group with isotopic carbon gives rise to a kinetic isotope effect (KIE), which for ^{14}C has been reported to be near unity for the reaction of *tert*-butylmagnesium chloride. In the present investigation, the KIE when ^{13}C was used was found to be high and of the same magnitude when either *tert*-butylmagnesium chloride or methylmagnesium bromide was used. The reported and confirmed very low KIE for allylmagnesium bromide is not evidence for, but rather evidence against, the formation of ketyl during the reaction.

Introduction

The reaction of benzophenone with Grignard reagents has been studied for several decades, and the list of probes and mechanistic tools which have been used is long.[1-5] The more recent publications on the subject,[6-8] however, leave the impression that the problem is totally unsettled and that results obtained more than 10-15 years ago are obsolete and should be revised. This author holds almost the opposite view, and the intention of the present article is to examine the logical and experimental foundation of

Scheme I

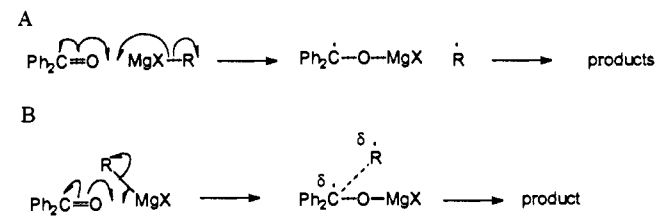

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Table I. Carbonyl ^{13}C Kinetic Isotope Effects at 20 °C in Reactions of Benzophenones with Grignard Reagents[a]

reagent	$k_D/^{12}k$	$k_D/^{13}k$	$^{12}k/^{13}k$
CH_3MgBr	1.0141 ± 0.0037 (5)	1.0442 ± 0.0057 (5)	1.0296 ± 0.0061
t-BuMgCl	0.9135 ± 0.0071 (10)	0.9383 ± 0.0053 (9)	1.0271 ± 0..0075
C_3H_5MgBr	1.0034 (1)	1.0107 (1)	1.0072

[a] k_D is the rate of reaction of decadeuteriobenzophenone. Error limits are standard deviations; the number of experiments is given in parentheses.

the new theories, taking as a starting point the investigations made about 20 years ago.

Evidence was found that for *tert*-butylmagnesium chloride the reaction with benzophenone was stepwise and was initiated by the production of the magnesium ketyl and a free *tert*-butyl radical.[9] It also was found that for an extended series of Grignard reagents the rates of reaction were correlated with the oxidation potentials of the reagents.[10] Measurements of the activation parameters and of the heats of formation of the transition states[11] finally led to the conclusion that the mechanism is an induced homolysis of the Grignard reagent followed by a fast recombination of the radicals formed, as shown in Scheme IA.

The reaction is an inner sphere electron transfer (ET), in which an electron is donated from the Grignard reagent to the ketone with the simultaneous transfer of magnesium. The estimate of the heat of formation of the transition state (TS) for the reaction of *tert*-butylmagnesium chloride with benzophenone was nearly identical with the sum of the heats of formation of *tert*-butyl radical and the magnesium ketyl radical. The operation of an outer sphere ET would require a TS, in which the highly stable O–Mg bond was not established; therefore, outer sphere ET is ruled out. The thermochemical calculations showed that TS's for reactions of secondary Grignard reagents were 1.2–2.5 kcal mol^{-1} more stable than the two free radicals; for primary reagents the numbers were 4.0–5.6, and for methylmagnesium bromide the TS was 9.9 kcal mol^{-1} more stable than the separated radicals.

The observed stabilization is interpreted as an interaction or partial bond formation between the two spins, which for primary radicals and methyl prevents the escape of the radicals from the cage. Even for methyl, however, the TS must be assumed to have some radical character, as indicated by the observation of ketyl signals in ESR and UV–vis spectra.[15,16] The ketyl observed, of course, may be a byproduct, but its presence does not seem to depend on metallic impurities. Possibly a biradical somewhat like the TS shown in Scheme IB may live long enough to make the reaction involve two steps (see below).

Japanese workers have objected to the homolytic mechanism and have proposed as the rate-determining step either a slow rearrangement[8] or a slow radical combination.[6] The electron transfer was assumed to be outer sphere, fast, and reversible. The evidence was kinetic measurements of the rate of appearance of ketyl absorption and, lately, the measurements of kinetic isotope effects (KIEs) using benzophenone labeled with ^{14}C in the carbonyl group. The reaction mechanisms for methyl and *tert*-butyl Grignard reagents were considered to be unrelated, since a rather significant KIE ($^{12}k/^{14}k$ = 1.050) was observed for methylmagnesium bromide, while *tert*-butylmagnesium chloride and allylmagnesium bromide reacted with benzophenone with a carbonyl ^{14}C KIE of around unity.[8]

An obvious objection against the introduction of a rate-determining step with no correlation to the oxidation potentials of the Grignard reagents is that the observed correlation[10] is then unexplained. An electron-transfer preequilibrium followed by a slow rearrangement was suggested, leading to the rate expression:

$$k_0 = K_{ET}k$$

but this will fit the observations only if k is invariant or itself correlated to E_{ox}.

The presence of a carbon KIE for the reaction of methyl and its absence for the *tert*-butyl Grignard reagent was, however, surprising, since it would indicate that the reaction mechanisms for the two Grignard reagents were qualitatively different, while the linear correlation of E_{ox} and log rate suggests that they are qualitatively alike. Work was therefore started to determine whether the reported KIEs could be confirmed.

Results and Discussion

A simple and accurate method was recently developed for the determination of KIEs based on isotopic separation of reaction products by means of capillary GC.[12] The method has now been applied to the reaction of [*carbonyl*-^{13}C]benzophenone with methyl- and *tert*-butylmagnesium halides, and the results show for methylmagnesium bromide a ratio $^{12}k/^{13}k$ = 1.030 ± 0.008 and for *tert*-butylmagnesium chloride $^{12}k/^{13}k$ = 1.027 ± 0.009. In a single experiment using allylmagnesium bromide, the absence of a KIE for this reagent seemed to be confirmed (Table I).

Since the origin of KIEs lies exclusively in the difference in mass, ^{13}C KIEs should be on the order of one-half of the ^{14}C KIEs. While this is consistent with the results obtained with methylmagnesium bromide, a large discrepancy exists between the new values of ^{13}C KIEs and the earlier values of ^{14}C KIEs for the reaction of *tert*-butylmagnesium chloride. Instead of being below 1% the effect is actually above 5%!

The KIE for the reaction of benzophenone with *tert*-butyl Grignard reagent is thus not significantly lower than the KIE for reaction of methylmagnesium bromide, and the mechanistic interpretations proposed by Yamataka et al. seem to be invalidated. It is now indicated that the effect observed is mainly the KIE for the ketyl formation, which includes the breaking of the π C=O with a simultaneous O—Mg bond formation, but not necessarily with a simultaneous C—C bond formation.

In earlier work (refs 8 and 9) the greatly differing electronic and steric effects of substitutions in the reactions of methyl and *tert*-butyl reagents were taken as evidence of widely different mechanisms. Of course there are, in the two cases, differences in how close an approach is required in the TS and how large a development of charge must take place. *tert*-Butyl is bulky, but no close approach to the carbonyl is needed to form the rather stable radicals, of which the ketyl, however, is strongly electron deficient (Scheme IA). Methyl is unhindered, which facilitates an approach and allows about 12% partial C–C bond formation in the TS (Scheme IB). This assistance reduces the electron deficiency at the central carbon, but would not be expected to perturb the ^{13}C KIE significantly.

What is common for the two mechanisms is that the fundamental reaction is homolysis of C–Mg induced by the concerted O–Mg bond formation. The evidence for this comes from the satisfactory correlation between the oxidation potential and log rate for the various reagents. The oxidation potential relates to the homolytic reaction at the platinum anode:

$$RMgX - e^- \rightarrow R^\bullet + {}^+MgX$$

It has been customary[3,4] to assume that the first step in a reaction of a Grignard reagent is the formation of a coordinative bond between magnesium and the lone pairs of carbonyl oxygen. It is, however, not clear whether these complexes are true steps on the reaction path or whether they represent "blind alleys".[13] For the sake of simplicity they have been omitted from Scheme I.

The absence of a KIE for allylmagnesium bromide reacting with benzophenone was taken as evidence that the rate-determining step in this case was an electron transfer.[7] According to the new results the conclusion must be quite the opposite. If there is no

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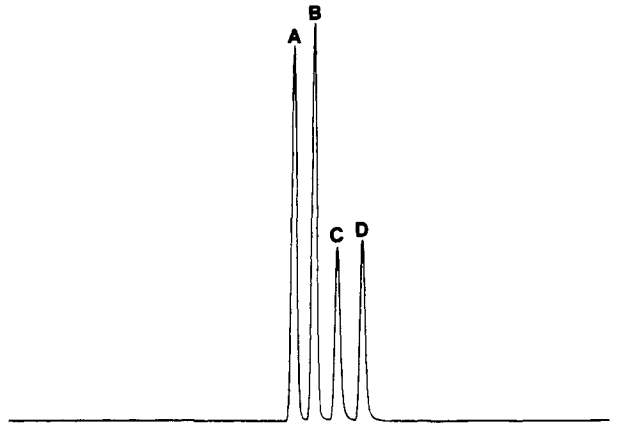

Figure 1. Gas chromatogram of the reaction mixture from the reaction of 0.025 M methylmagnesium bromide with a mixture of 0.025 M decadeuteriobenzophenone and 0.025 M benzophenone. Retention time was ca. 31 min at 140 °C. A = decadeuteriobenzophenone, B = benzophenone, C = methylbis(pentadeuteriophenyl)carbinol, D = methyldiphenylcarbinol.

KIE, the reaction is not dissociative and there is no ketyl formation. A concerted 6-center reaction or an S_E2' mechanism must be imagined with C—C bond formation taking place simultaneously with the breaking of π C=O. As actually observed, this mechanism is faster than the rate of the homolytic mechanism, which would be predicted on the basis of the oxidation potential of allylmagnesium bromide.[10] In keeping with this interpretation, the reaction of allylmagnesium bromide with benzophenone takes place without any transient coloration.

Determinations of carbon KIEs must be considered to be of the utmost importance in mechanistic work with benzophenone, but the finding of values around unity must not, as has been done repeatedly, be taken as proof *for*, but rather as proof *against*, the participation of ketyl as an intermediate.

Methods

^{13}C and ^{12}C benzophenone have the same retention time in GC, but on a suitable capillary column decadeuteriobenzophenone elutes fast enough that the GC peaks for this compound and for nondeuterated benzophenones are completely separated from each other. The same applies to derivatives of the benzophenones, for example, the Grignard addition products (Figure 1). It is therefore possible to relate the reactivities of ^{12}C and ^{13}C benzophenone by using decadeuteriobenzophenone as a common reference. The use of perdeuteriobenzophenone as the internal standard in this way allows the use of normal competition kinetics, which gives the necessary high precision and reliability.[14]

Methylmagnesium bromide reacts with benzophenone to produce only the 1,2-addition product in a very high yield. KIEs may be determined simply by letting the ketones compete for the Grignard reagent by using an insufficient amount of reagent. From the ratios between unreacted ketones and between reaction products formed, the relative reactivities of the ketones may be estimated. Both ratios are obtained from a single gas chromatogram (Figure 1).

tert-Butylmagnesium chloride produces with benzophenone a series of reaction products, of which the most important, the 4-*tert*-butyl-1,4-dihydrobenzophenone, is unstable and reverts to benzophenone by heating.[9] To avoid contamination from this source the unreacted benzophenones therefore have to be quantitatively converted to a GC-measurable compound by the reaction with a suitable reagent. The reagent used for this purpose should fulfill three requirements: (1) it should react quantitatively and without byproducts; (2) it should react extremely fast; and (3) it should react without any ^{13}C carbonyl KIE. Yamataka et al. used methyllithium for this purpose, which was added to the reaction mixture.[8] A large part of this reagent, however, must have reacted with magnesium halide and formed methylmagnesium halide. As a quenching reagent, methylmagnesium chloride falls short of all three requirements mentioned above, since it reacts slowly and incompletely and has a rather high ^{13}C carbonyl KIE. Also the use of high concentrations of Grignard reagent may result in the production of byproducts such as diphenylmethanol.[4] A better quenching reagent was found to be allylmagnesium bromide, which is the fastest Grignard reagent known[10] and which reacts quantitatively and cleanly and without a ^{13}C carbonyl KIE.[7]

Competition between the benzophenones may be obtained either by using an insufficient amount of Grignard reagent or by using an excess of Grignard reagent for an insufficient time.

In the Japanese work an excess of ketones was used. In the present work this was found to be rather inappropriate when using *tert*-butylmagnesium chloride, since in this case varying amounts of byproducts were formed, apparently by totally different reaction mechanisms. Among the others found was diphenylmethyl *tert*-butyl ether. This product seems to be formed by O-attack of a *tert*-butyl radical on free benzophenone.[15]

In the present work competition was therefore obtained by stopping the reaction after 0.5–2 half-lives by quenching the reaction mixture in a large excess of allylmagnesium bromide and measuring the quantitatively formed allyldiphenylcarbinol.

Experimental Section

Materials. [^{13}C]Benzophenone was obtained from ICN Biomedicals Inc. (Cambridge, MA). Isotopic purity was 99%. Benzophenone-d_{10} was prepared from C_6D_6[17] with an isotopic purity of >99%. Grignard reagents were prepared from sublimed magnesium and ether distilled from $LiAlH_4$.

Kinetics. Two test solutions were prepared which were (1) 0.025 M in both benzophenone and decadeuteriobenzophenone and (2) 0.025 M each of carbonyl ^{13}C substituted benzophenone and decadeuteriobenzophenone. Also prepared was a 0.025 *M* solution of methylmagnesium bromide. The kinetic runs were carried out at room temperature, 20 °C. Using disposable syringes, 1 mL of test solution was added to 1 mL of the Grignard reagent. The reaction mixture was added to saturated aqueous ammonium chloride, and the ether layer washed with water and dried with magnesium sulfate.

Competition between benzophenones reacting with *tert*-butylmagnesium chloride was obtained by mixing ether solutions, 0.002 M in both decadeuteriobenzophenone and either ^{13}C or ^{12}C carbonyl benzophenone, with 1.0 M *tert*-butylmagnesium chloride in a simple flow stream arrangement. The solutions were contained at room temperature in two 2 cm^3 disposable syringes connected to a mixing "T" from which a polyethylene reaction tube, 0.5 mm inner diameter, led to a flask containing 4 mL of 1 M allylmagnesium bromide. The syringes were emptied simultaneously in about 0.5 s, corresponding to a liquid speed in the reaction tube of about 7 m s^{-1}. The reaction tube was either 10 or 22 cm, which corresponds to a reaction time of 7 or 14 ms. The half-life of benzophenone in 0.5 M *tert*-butylmagnesium chloride is about 7 ms at room temperature. Work-up was as described above.

GC. GC analyses were performed on an HP 5890 gas chromatograph equipped with a standard injector and FI detector and a 50 m × 0.2 mm × 0.33 μm HP-5 capillary column. The carrier gas was hydrogen; injection split 50:1. Peak areas were measured with an HP 3394 A integrator. The exact ratios between the ketones of the test solutions were found by GC.

The relative reactivities of a pair of ketones with starting concentrations A_0 and B_0 were calculated from the concentrations of unreacted ketones A and B according to

$$\frac{k_A}{k_B} = \frac{\ln (A/A_0)}{\ln (B/B_0)} = \frac{\ln [(B_0/A_0)(A/B)]}{\ln (B/B_0)} + 1$$

Peak areas were weighted for the respective carbon counts.

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