

Secondary β -Deuterium Kinetic Isotope Effects in Reactions of Grignard Reagents

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Kinetic isotope effects (KIEs) for addition reactions of β -deuteriated Grignard reagents have been determined by isotopic separation of reaction products by capillary GC. Separation of products from the reactions studied required a minimum of three substitutions of deuterium for hydrogen. The method was used for the addition of β -perdeuteriated ethyl, isopropyl, and *tert*-butyl-magnesium halide to benzophenone, 2-octanone, 4,4-dimethyl-1-phenyl-1-penten-3-one, and 1,3-diphenyl-2-propen-1-one.

The observed effects were small, within $\pm 5\%$, apparently because a steric and a hyperconjugative effect were opposing each other. A relatively large KIE in the reaction of isopropylmagnesium bromide with benzophenone is interpreted as evidence of assistance from the β -hydrogen in a six-center transition state in the initial homolysis.

The mechanism of the reaction of Grignard reagents has been studied extensively in recent decades.^{1–4} According to the nature of both the reagent and the substrate at least two types of mechanism, a concerted and a stepwise, homolytic, have been demonstrated. While thermochemical calculations concerning the reaction of benzophenone⁵ indicate that the homolysis is a concerted transfer of the electron and the magnesium from the Grignard reagent, Japanese workers have suggested^{6,7} that the electron transfer is fast and reversible, and separate from the transfer of the magnesium. Evaluation of activation parameters⁵ as well as determination⁶ of primary carbon ¹⁴C KIEs have shown that there is no carbon-to-carbon bonding in the transition state, when the Grignard reagent is tertiary, but that the C–C bond is partially established in the transition state for the reaction of methylmagnesium bromide. It was thought that a study of secondary β -deuterium isotope effects might provide useful information in this area.

The effect of a deuterium in the β -position to a reaction center may be normal, $k_H/k_D > 1$, or inverse, $k_H/k_D < 1$. All isotope effects are based on changes in vibrational motion on going from the ground state to the transition state.⁸ As a pragmatic approach, however, normal secondary β -deuterium isotope effects have been ascribed to less efficient stabilisation of an electron-deficient carbon by a β -deuterium than by a β -hydrogen.^{8,9} Similarly, inverse β -deuterium isotope effects have been perceived as being of steric origin,^{8,10} since a CD₃ group is effectively smaller than a CH₃ group.

Large β -deuterium isotope effects are observed in carbenium ion chemistry, and for ethanolysis of *tert*-butyl chloride the effect amounts to ca. 10% per β -deuterium or $k_H/k_D = 2.33$ for perdeuterio-*tert*-butyl chloride.¹¹ The β -

deuterium effects in homolytic reactions are much smaller since radicals are much less electron deficient than are carbenium ions. Values of 2–3% per β -deuterium have been reported.^{8,12} Secondary β -deuterium kinetic isotope effects in the reactions of Grignard reagents have not been reported, but would, *a priori*, be expected to be small.

The best way of observing small isotope effects of this kind is through the use of competition kinetics. In this way the two reagents are in exactly the same reaction conditions and rate determinations may be performed by convenient and accurate analytical means (GC). The relationships between reaction rates observed in this way are reliable and mutually comparable.

Methods. Competition experiments were performed by mixing equal volumes (0.5–1.0 ml) of mixtures of ca. 0.5 M each of β -perdeuteriated and non-deuteriated Grignard reagents and 0.005 M substrate solutions in ether. Since the Grignard reagents were in a hundredfold excess the conditions were *pseudo*-first order. After work-up the product mixtures were analyzed by GC–MS to identify the various products, and by capillary column GC for quantification.

Calibration, the determination of the precise composition of the Grignard reagent mixtures, was performed by quantitative reaction of the reagents with an excess of 4,4-dimethyl-1-phenyl-1-penten-3-one followed by GC quantification of the 1,4-addition products. The composition of the deuterio/non-deuterio *tert*-butylmagnesium chloride mixture was also determined by quantitative conversion of the reagents into pivalic acid methyl esters, which were analyzed by GC.

Gas chromatographic separation of deuterium-substituted and non-substituted compounds is possible with the

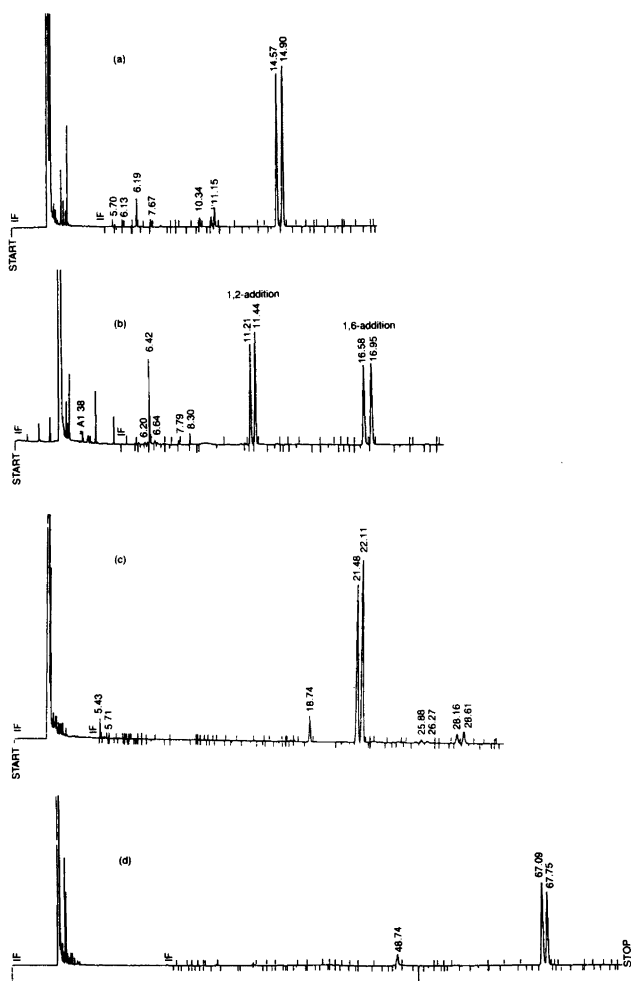


Fig. 1. Capillary column gas chromatographic separation of addition products from the reaction of β -perdeuterated/non-deuterated Grignard reagent mixtures with ketones. (a) $\text{Bu}^i\text{MgCl} + \text{C}_6\text{H}_5\text{CH}=\text{CHCOC}(\text{CH}_3)_3$, 50 m column, 160°C ; (b) $\text{Bu}^i\text{MgCl} + \text{C}_6\text{H}_5\text{COC}_6\text{H}_5$, 50 m column, 200°C ; (c) $\text{Pr}^i\text{MgCl} + \text{C}_6\text{H}_5\text{CH}=\text{CHCOC}_6\text{H}_5$, 50 m column, 190°C ; (d) $\text{EtMgBr} + \text{C}_6\text{H}_5\text{COC}_6\text{H}_5$, 100 m column, 160°C .

use of capillary columns, the substituted compound eluting earlier than the non-substituted. Depending on the ratio of the number of deuterium atoms to the molecular weight, rather long columns may be needed to effect the complete resolution required for obtaining reliable quantitative results. As shown in Fig. 1, a $50\text{ m} \times 0.2\text{ mm}$ column with a plate-count of 200 000 gave complete or nearly complete separations in cases with nine or six substitutions of hydrogen with deuterium, whereas products with only three substitutions required a 100 m column to give nearly complete separations.

Attempts were made to circumvent the necessity of completely separated peaks by using a molecular or a fragment ion in MS for quantification, but grossly erroneous results were obtained because of isotope effects on the fragmentation.

The errors on peak area integrations due to the small overlaps of peaks are probably insignificant, when, as in

our case, peaks are of nearly the same size and non-tailing. This is strongly supported by the fact that many of the analyses were carried out at very different temperatures with differing, but still small, degrees of peak overlap, without significant differences in the quantitative results. The relative standard deviations on GC determinations of peak area ratios were $< 0.5\%$ in all cases except one. Competition and calibration experiments were performed at least twice. No cases showed significantly deviating results. Mean values were used for the calculations.

The β -deuterium kinetic isotope effects, k_H/k_D , were calculated by dividing the ratios of peak areas of isotopically substituted and unsubstituted products from calibration experiments with the corresponding ratios from competition experiments. In this way possible differences in FI detector responses of substituted and unsubstituted compounds are internally compensated. Information about FI responses of deuterium substituted compounds seems unavailable in the literature. For the sake of interest an experiment was conducted showing that, on a molar basis, benzene and hexa-deuteriobenzene gave equal responses to within 0.1% .

Results and discussion

In the choice of reagents and substrates a serious limitation is that the reactions should ideally lead only to one product in almost quantitative yield. Reactions of Grignard reagents, however, very often lead to more than one product or even to complex mixtures, including polymeric residues. Furthermore, since the purpose of the investigation was to establish a possible correlation between reaction mechanism and β -deuterium isotope effects, mechanistic information about the reactions studied should be obtainable by independent means.

Among the most studied and best known reactions of Grignard reagents are the reactions with aliphatic and aromatic ketones, and therefore 2-octanone and benzophenone were included in the investigation. Furthermore, two α,β -unsaturated ketones were included about which recent mechanistic information was obtainable.

Additions of primary and secondary Grignard reagents to 4,4-dimethyl-1-phenyl-1-penten-3-one (benzylidenepinacolone) are known to give high yields of only the 1,4-addition products and the reaction mechanism has been shown to be concerted.¹³ Reaction of primary Grignard reagents with aliphatic ketones such as 2-octanone gives high yields of addition product and the mechanism is assumed to be concerted. The same applies to the reaction of secondary reagents with aliphatic ketones, although enolisation and reduction now become more competitive. Benzophenone and 1,3-diphenyl-2-propen-1-one (benzylideneacetophenone) react with Grignard reagents by mechanisms assumed to be homolytic or hybrid concerted-homolytic.^{5,13}

Of the Grignard reagents used ethylmagnesium bromide behaves ideally, giving 95% or more of the main products. Isopropylmagnesium bromide tends to give reduction prod-

Table 1. β -Deuterium kinetic isotope effects, k_H/k_D , in the reactions of Grignard reagents with ketones as determined by competition kinetics. Maximum deviations are given.

	CD_3CH_2MgBr	$(CD_3)_2CHMgBr$	$(CD_3)_3CMgCl$
$CH_3COC_6H_{13}$	0.985 ± 0.003	0.940 ± 0.005	
$C_6H_5COC_6H_5$			
1,2-addition	1.014 ± 0.003	1.050 ± 0.003	1.016 ± 0.003
1,6-addition		1.016 ± 0.003	0.954 ± 0.005
$C_6H_5CH=CHCOC(CH_3)_3$	1.034 ± 0.003	0.987 ± 0.005	0.974 ± 0.007
$C_6H_5CH=CHCOC_6H_5$	1.050 ± 0.010	1.001 ± 0.008	0.997 ± 0.007

ucts and, like *tert*-butylmagnesium chloride, produces both 1,2- as well as conjugate addition products. In the present work, however, only the 1,4-additions to the α,β -unsaturated ketones gave the desired high reproducibility. The amount of alternative products (1,2-addition, etc.) was, furthermore, very small using the actual reaction conditions. For benzophenone 1,6-addition accounts for a large part of the reaction if the alkyl of the Grignard reagent is isopropyl or *tert*-butyl. The products are unstable 1,6-dihydroalkylbenzophenones. In order for these products to be measured by GC they need to be oxidised to the alkylbenzophenones. Exposing the solutions to air results in almost complete aromatisation of the dihydro compounds in the course of 24 hours, and quantification is possible as seen in Fig. 1(b).

The results obtained using ethylmagnesium and isopropylmagnesium bromide and *tert*-butylmagnesium chloride in reaction with four different types of ketone are given in Table 1.

Conclusions

From the results one may conclude that β -deuterium isotope effects in the reaction of Grignard reagents are indeed small. For reactions of the unhindered ethylmagnesium bromide k_H/k_D increased from 0.985 for 2-octanone to 1.014 for benzophenone and 1.034 and 1.05 for α,β -unsaturated ketones. The increasing values may indicate an increasing need for hyperconjugative stabilisation of the α -carbon in the transition states.

The bulky hexadeuterio isopropylmagnesium bromide shows an inverse isotope effect in the reaction with 2-octanone. In this presumably concerted reaction, the steric effect seems to dominate. With benzophenone a rather large isotope effect is observed. The effect is three times larger than that observed with *tert*-butylmagnesium chloride. The two reagents differ in that the isopropyl reagent produces 20% reduction product by transfer of a β -hydrogen, while *tert*-butyl reagent produces none at all. It has been suggested⁴ that electron transfer or homolysis may

take place either in a four-center or a six-center transition state. Homolysis via the six-center transition state with assistance from the β -hydrogen normally leads to reduction products (primary cage product), but some of the radical pairs combine carbon to carbon to give the addition products, which is the secondary cage product. β -Deuterium substitution in this way suppresses not only the reduction process, but also, to some extent, the addition process.

Small isotope effects are seen with *tert*-butylmagnesium chloride. The nine β -hydrogens should allow increased hyperconjugation in the hydrogen reagent but, since *tert*-butyl is extremely bulky, the deuterium reagent has a steric advantage, and this effect seems to dominate in the reaction with α,β -unsaturated ketones, while the hyperconjugative effect dominates in 1,2-addition to benzophenone as seen in Table 1. The amount of 1,6-addition product, however, is much higher using the deuterium reagent. Since this product results from escape of *tert*-butyl radical out of the solvent cage² one could ascribe the effect to a greater mobility of the deuterated radical. Another explanation would be that the diffused d_0 -radicals disproportionate much more slowly than ordinary *tert*-butyl radicals, increasing the probability of reaction with the ketyl radical.

Our hopes of being able to assign specific mechanisms to the reaction of Grignard reagents on the basis of β -deuterium isotope effects are only partly supported by the results shown in Table 1, mainly because of opposing steric and the electronic effects.

Experimental

Materials. Nondeuterio *tert*-butyl chloride was purchased from Cambridge Isotope Laboratory. CD_3CH_2Br and $(CD_3)_2CHBr$ were prepared by $LiAlH_4$ reduction of CD_3COOH and $(CD_3)_2CO$, respectively, to the alcohols and conversion into bromides by means of PBr_3 . The isotopic purity of all labelled compounds was > 99%.

For preparation of Grignard reagents sublimed magnesium and ether distilled from $LiAlH_4$ were used. Substrates were prepared as described.¹³

Kinetics. Approximate equimolar amounts of ca. 1 M deuterated and non-deuterated Grignard reagents were mixed. The exact composition was determined by reacting a sample with a 30% excess of benzylidenepinacolone and analyzing the reaction product by means of GC. For the competition experiments 1 ml of 0.005 M substrate dissolved in ether was mixed via a syringe with 1 ml of the deuterio/non-deuterio Grignard reagent. The reaction mixture was mixed with saturated ammonium chloride and the ether layer was separated, washed with water and dried with magnesium sulphate.

GC and GC-MS. GC analyses were performed on an HP 5890 gas chromatograph equipped with a standard injector and FI detector. The columns used were 50 and 100 m \times 0.2 mm \times 0.33 μ HP-5 capillary columns. The carrier gas was hydrogen; injection split 50:1. Peak areas were measured with an HP 3394 A integrator. GC-MS analyses were carried out using a VG TRIO-2 mass spectrometer.

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