Kinetic Isotope Effects in the Reduction of Methyl Iodide

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Abstract: α-Deuterium (α-D) kinetic isotope effects (KIEs) have been determined for the reaction of methyl iodide with a series of reducing agents. Reagents which transfer hydride ion in an S_N2 reaction show small inverse or small normal KIEs. Reagents which transfer an electron to methyl iodide to produce methyl radical show large normal KIEs up to 20% per α-D. Large KIEs were found for the reaction of methyl iodide with sodium, for Pd-catalyzed reaction of methyl iodide with hydrogen, for electron transfer (ET) at a platinum cathode, for ET from benzophenone ketyl or from sodium naphthalenide, for iron-catalyzed ET from a Grignard reagent to methyl iodide, and for reduction of methyl iodide with tributyltin hydride or with gaseous hydrogen iodide. Very small KIEs were found for electron transfer to methyl iodide from magnesium in ether or from sodium in ammonia. The reason may be that these reactions are transport or diffusion controlled.

Introduction

Kinetic isotope effects (KIEs) are useful in the study of reaction mechanisms and may provide information which is otherwise unavailable.[1] Secondary α-deuterium (α-D) KIEs have proved very useful in making the distinction between S_N1 and S_N2 nucleophilic substitution reactions,[2,3] while the possibility of distinguishing between nucleophilic and radical type reaction mechanisms of alkyl halides by means of this type of isotope effect is largely unknown.[4]

The conversion of methyl iodide to methane may take place either by the direct displacement of iodide by hydride ion in an S_N2 reaction or by a stepwise reaction via a homolytic fission of C−I to form methyl radical followed by hydrogen abstraction from a donor. Three deuteriums in methyl iodide are expected to induce a small inverse KIE in the S_N2 substitution of iodide with hydride, <5% per D,[2] while the formation of methyl radical by electron transfer as explained below should be accompanied by a large normal KIE, because of the differences in the IR spectra of the reactant and the product.

The distinction between S_N2 and electron transfer (ET) mechanisms in the reactions of nucleophiles with alkyl halides has been extensively studied in recent years,[5] and objections have been raised against the results obtained by the use of radical probes and isotope exchange reactions.[6] It seems, however, that the measurement of secondary deuterium KIEs is very well suited to obtain the desired information.

Table 1. KIEs in the Reductions of Methyl Iodide and Trideuteriomethyl Iodide and Product Distributions[a]

run no.	reagent	solvent	CH_3I/CD_3I k_H/k_D	product ratio, ethane:methane
1	LiAlH$_4$	DEE	1.056 ± 0.01	0:100
2	NaBH$_4$	diglyme	0.98 ± 0.01	0:100
3	Pt cathode	THF	1.68 ± 0.04	21:79
4	Ph$_2$CONa	DEE	1.67 ± 0.02	
5	Na/THF	THF	1.37 ± 0.04	68:32
6	Na, NH$_3$	NH$_3$	1.02 ± 0.01	41:59
7	Bu$_3$SnH	THF	1.19 ± 0.06	0:100
8	H$_2$, Pd	THF	1.48 ± 0.08	0:100
9	RMgBr, Fe	DEE	1.48 ± 0.05	4:96
10	RMgBr, Fe	THF	1.39 ± 0.04	75:25
11	HI	gas phase, 250 °C	1.42 ± 0.01	0:100
12	(1) Mg, (2) H$_2$O	DEE	1.00 ± 0.01	2:98
13	C$_{10}$H$_8$,Na	THF	1.51	?

[a] The average of two measurements and deviations from the average are given.

Isotopic separation of reaction products by gas chromatography has proved to be a simple and accurate method for the measurement of KIEs, and the method has inter alia been used for determining the deuterium KIEs for two types of ET to methyl iodide.[4]

In the present investigation the KIEs have been measured for the reactions of methyl iodide with 12 reducing agents. Only very little supplementary kinetic and mechanistic information has been obtained about the various reactions, but the KIEs should be a useful basis for further studies. Besides for the reactions of metal hydrides, KIEs have been obtained for electron transfer reactions such as the Würtz reaction, Kharasch reaction, cathodic reduction, catalytic reduction, Grignard reagent formation, and electron transfer from sodium benzophenone ketyl and from sodium naphthalenide. The results are given in Table 1.

Results and Discussion

The prediction of a kinetic isotope effect requires a knowledge of the changes in the bonding of the isotopically exchanged

(1) Melander, L. *Isotope Effects on Reaction Rates*; Ronald Press: New York, 1960.

(2) Willi, A. V. In *Isotopes in Organic Chemistry;* Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, Oxford, New York, 1977; Vol. 3, p 237.

(3) Westaway, K, C. In *Isotopes in Organic Chemistry;* Buncel, E., Lee C. C., Eds.; Elsevier: Amsterdam, Oxford, New York, Tokyo, 1987; Vol 7, p 275.

(4) Holm, T.; Crossland, I. *Acta Chem. Scand.* **1996**, *50,* 90.

(5) (a) Ashby, E. C.; Pham, T. N.; Amrollah-Madjdabadi, A. *J. Org. Chem.* **1991**, *56*, 1596. (b) Ashby, E. C.; Sun, X.; Duff, J. L. *J. Org. Chem.* **1994**, *59,* 1270. (c) Ashby, E. C.; Welder, C. O.; Doctorovich, F. *Tetrahedron Lett.* **1993**, *34,* 7235. (d) Welder, C. O.; Ashby, E. C. *J. Org. Chem.* **1997**, *62,* 4829.

(6) Newcomb, M.; Varick, T. R.; Choi, S. Y. *J. Org. Chem.* **1992**, *57,* 373 and references therein.

atoms on going from the ground state to the transition state. Going from methyl iodide to the S_N2 transition state does not change the bonds between carbon and hydrogen significantly, and KIEs are as mentioned above small. Bonds between α-hydrogen and carbon in a free radical, however, are much less "stiff" and more pliable than the bonds in methyl iodide. This is known from the available IR spectroscopic data.[7] A crude estimate of the equilibrium

$$CD_3^{\bullet} + CH_3I \rightleftharpoons CD_3I + CH_3^{\bullet} \qquad (1)$$

$$[CD_3I][CH_3]/[CD_3][CH_3I] = K_1$$
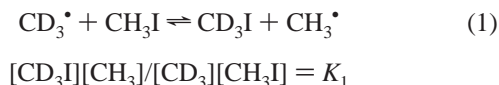
which is the equilibrium isotope effect (EIE) for complete homolysis of methyl iodide, may be obtained[8] from the formula

$$K = \exp[0.7193(\nu_{R1} - \nu_{R2} - \nu_{P1} + \nu_{P2})/T]$$

where the ν values are the normal-mode frequencies for reactants and products using only the frequencies which directly involve hydrogen motion. Using literature values for C−H vibrations and calculated values for C−D vibrations, it is found that the right side in (1) is favored by the zero point energy corresponding to 664 cal or $K_1 = 3.07$ at 25 °C.

The rate at which the equilibrium (1) is established is not known. It might be possible that the results obtained are influenced by reaction of the methyl radicals with methyl iodides before hydrogens are abstracted from the donor. The values found for k_H/k_D might in such cases tend to be too large. Since the observed KIEs, however, in no case approach the calculated EIE, it may be assumed that hydrogen abstraction and radical recombination are faster than attack on methyl iodide.

The reactions listed in Table 1 may be grouped according to the predicted reaction mechanisms.

The reactions with $NaBH_4$ and with $LiAlH_4$ (LAH) have low KIEs, confirming that these reagents react via an S_N2 transition state by direct hydride transfer. This is most obvious for the borohydride, for which the KIE is slightly inverse, corresponding to a slightly smaller steric bulk of the CD_3 group than of the CH_3 group.[9] LAH likewise has a small, normal KIE and reacts as a nucleophile.

It has been shown by Ashby et al. that LAH reacts with 1-halobornanes[5b] and with sterically hindered, neopentyl-like alkanes[5a,c] by ET mechanisms. With halobornane the S_N2 mechanism is impossible, and with branched alkyls the ET mechanism is very much favored. Using the primary octyl iodide, the Ashby group found[4d] an electron transfer mechanism in the later phases of the reaction, while the initial phase was strictly S_N2. AlH_3 reacted largely by ET. The determinations were based on isotopic D/H exchange in the reaction product. The normal H/D KIE found in the present competition experiments is within the limits for KIEs for nucleophilic substitution.[2] When the reaction was carried out in perdeuteriodiethyl ether, only a trace amount of isotope exchange was, however, found in the methane. ET is therefore of no importance in this reaction.

High KIEs on the order of $k_H/k_D = 1.40-1.70$ (12−20% per D) are found for ET to methyl iodide from a platinum cathode, from benzophenone ketyl, and from sodium metal, for the Kharasch reaction, for the reaction with hydrogen iodide, and

for the reaction with sodium naphthalenide. For these reactions the high KIE indicates a reaction mechanism in which electron transfer with formation of a methyl radical is the rate-determining step. The KIE is only a fraction of the EIE, but the variation observed indicates that the degree to which the ET transition state has developed radical hybridization varies for the individual reaction. C−I bond-breaking which is assumed to be concerted with ET[10] is probably not complete in the TS.

For two reactions in which the mechanism obviously must include electron transfer to methyl iodide, very low KIEs are found: (i) the reaction with magnesium to form the Grignard reagent and (ii) the reduction with sodium in ammonia to form methane.

Concerning (i), it was shown by the Whitesides group[11] that in the reaction of alkyl bromides and alkyl iodides with magnesium the rate of the reaction did not vary with the nature of the alkyl group. The reaction is mass transport or diffusion controlled, and for the same reason the KIE for the reaction must be unity as is actually found. The ^{13}C KIE for the reaction was likewise and for the same reason found to be unity.[12]

Concerning (ii), a high value for k_H/k_D in the reaction with HI and a low value in the reaction with sodium in liquid ammonia were interpreted as being characteristic for inner sphere ET with a high KIE and for outer sphere ET with a low KIE, respectively.[4]

In light of the new results it seemed to be a possibility that low KIEs for this reaction are found because the ET for the reaction is diffusion controlled. In the present study it has been found that the reaction in flow stream experiments is complete at the end of the mixing period, $\sim10^{-3}$ s, meaning that the half-life is less than 200 μs. The reaction is extremely fast and is mixing controlled if not diffusion controlled. Competition kinetics tend to be unreliable with very fast reactions.[13] Whether the distinction between outer sphere and inner sphere ET to methyl iodide is relevant is therefore dubious. The rather significant ^{13}C KIE found for the reaction is dubious as well.[4]

Whether formation of methylsodium (anionic methyl) is a reaction step in the reduction of methyl iodide with sodium in ammonia should be considered. Monomeric methyllithium is presumably a good model for methylsodium, and the position of equilibrium (2) indicates the size of a possible KIE for

$$CH_3^{\bullet} + CH_3Li \rightleftharpoons CD_3Li + CH_3^{\bullet} \qquad (2)$$

electron transfer from methylsodium to methyl iodide. K_2 is found by combining (1) with (3) since $K_2 = K_1/K_3$. Since K_3

$$CD_3Li + CH_3I \rightleftharpoons CD_3I + CH_3Li \qquad (3)$$
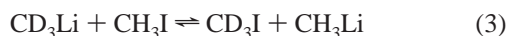
has been found[14] to be 2.4, K_2 is as low as 1.28. A rate-determining step consisting of ET to methyl radical to form methyl anion would therefore have a low KIE. A scheme for

(7) Pacansky, J.; Koch, W.; Miller, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 317.

(8) Shiner, V. J., Jr.; Neumann, T. E. *Z. Naturforsh.* **1989**, *44a*, 337.

(9) Brown, H. C.; Azzaro, M. E.; Koelling, J. G.; McDonald, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 2520.

(10) (a) Lexa, D.; Saveant, J. M.; Su, K. B.; Wang, D. L. *J. Am. Chem. Soc.* **1988**, *110, 7617*. (b) Saveant, J. M. *Adv. Phys. Org. Chem.* **1990***, 26*, 1.
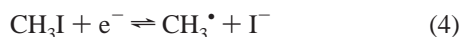
(11) Barber, J. J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *10*, 02, 239

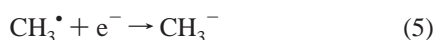(12) Vogler, E. A.; Stein, R. L.; Hayes, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3163.

(13) (a) Francis, A. W. *J. Am. Chem. Soc.* **1926**, *48*, 655. (b) Tolgyesi, W. S. *Can. J. Chem.* **1965**, *43*, 3, 343. (c) Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1970**, 1045.

(14) Holm, T. *J. Organomet. Chem.* **1996**, *506*, 37.

reduction of methyl iodide could include reversible formation of a methyl radical
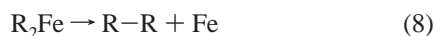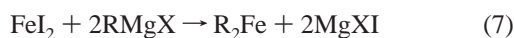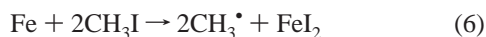
$$CH_3I + e^- \rightleftharpoons CH_3^\bullet + I^- \tag{4}$$

followed by rate-determining ET

$$CH_3^\bullet + e^- \rightarrow CH_3^- \tag{5}$$

and proton abstraction from the solvent. The k_H/k_D expected would, however, still include the EIE for (1) as a factor, and methyl anion formation therefore cannot explain the very low KIEs.

The KIE for catalytic Pd-catalyzed hydrogenation of methyl iodide is high. For this reaction a mechanism which includes the formation of methyl radical is not self-evident, but the KIE found indicates that methyl radical is a true intermediate and that the mechanism is dissociative. Associative and concerted reaction mechanisms would be expected to have small KIEs. It is possible that a hydrogen atom abstracts iodine from the molecule and that the methyl radical reacts with another hydrogen atom, but with the two events being separated.

The mechanism of the Kharasch reaction is not known in detail,[15] but is assumed to involve three or four extremely fast chain reaction steps. ET takes place from an iron species to methyl iodide with generation of methyl radicals. The oxidized iron species exchanges halogens with alkyls from the Grignard reagent to form dialkyliron, which eliminates iron:

$$Fe + 2CH_3I \rightarrow 2CH_3^\bullet + FeI_2 \tag{6}$$

$$FeI_2 + 2RMgX \rightarrow R_2Fe + 2MgXI \tag{7}$$
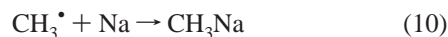
$$R_2Fe \rightarrow R-R + Fe \tag{8}$$

The methyl radicals abstract hydrogen from the solvent or recombine to form ethane. Since large KIEs are not expected for the alkyl exchange or for the elimination (neither of which involve free radicals), the rate-determining step must be a radical-producing step like (6).[16] A surprising observation is that, while the use of THF as a solvent gives a high ratio of ethane to methane, the use of ether leads to the production of methane with only traces of ethane. The change in the product distribution is seen with concentrations of THF in ether as low as 5%.

ET from benzophenone ketyl sodium to methyl iodide generates methyl radical and was studied by Garst.[17] The reaction is at least 10^4 times slower than ET from sodium in ammonia. Since the ketyl is a very efficient radical scavenger, methyl attacks it at positions of high spin density, and 1,2-, 1,4-, and 1,6-addition products to benzophenone are formed as shown by Garst. The last two compounds mentioned are dihydrobenzophenones which oxidize easily to benzophenones. On an efficient GC column the 4-(trideuteriomethyl)benzophenone is separated from its protio analogue, and the KIE for ET to methyl iodide can be calculated.

The reaction in THF of methyl iodide with sodium naphthalenide produced methanes and to a smaller degree methylated naphthalenes and dihydronaphthalenes. Ethanes were not looked for. The KIE given in Table 1 is for methane formation without correction for the H/D ratios in byproducts.

In the Würtz reaction ethane is generated from methyl iodide via methylsodium:

$$CH_3I + Na \rightarrow CH_3^\bullet + NaI \tag{9}$$

$$CH_3^\bullet + Na \rightarrow CH_3Na \tag{10}$$

$$CH_3Na + CH_3I \rightarrow CH_3CH_3 + NaI \tag{11}$$

Methane is formed as a byproduct via methyl radical or via methylsodium reacting with the solvent. The ratio k_H/k_D for methane was 1.37 and for the methyl groups in ethane 1.03, which indicates that the nucleophilic attack of methylsodium on methyl iodide, (11), has a large inverse deuterium KIE. This is likely since CD_3I is faster than CH_3I by a factor 1.15 in nucleophilic hydrolysis[18] and CD_3Na is expected to be a better nucleophile than the protio analogue because it is less bulky.[9]

The reaction of tributyltin hydride with methyl iodide showed values of k_H/k_D near 1.2. The reagent reacts by a chain mechanism:

$$Bu_3Sn^\bullet + CH_3I \rightarrow Bu_3SnI + CH_3^\bullet \tag{12}$$

$$CH_3^\bullet + Bu_3SnH \rightarrow CH_4 + Bu_3Sn^\bullet \tag{13}$$

The rate constant of (12) is 2.5×10^9 M^{-1} s^{-1} for methyl iodide[19] and apparently 20% lower for the trideuteriomethyl iodide.

Experimental Section

Materials. Deuterium-labeled compounds were obtained from Cambridge Isotope Laboratories with isotopic purity 99%. Solvents were dried over benzophenone ketyl (ether) or LAH (THF). Other chemicals were standard laboratory grade.

Gas Chromatography. A Hewlett-Packard 5890, Series II instrument equipped with a standard injector and FI detector was used. The column was a 75 m × 0.32 mm 5 C molecular sieve capillary column (Chrompack) with a layer thickness of 30 μm. The carrier gas was hydrogen, injection split 50:1. Retention times for methane and trideuteriomethane were 21.57 and 21.99 min, respectively. Elution of ethane followed heating to 150 °C, the total retention time being 50.04, 50.48, and 50.93 min for ethane-d_6, ethane-d_3, and ethane, respectively. An HP 3394 A integrator was used.

Kinetic Isotope Effects. A standard 1:1 molar mixture was prepared from methyl iodide and trideuteriomethyl iodide. The exact H/D ratio of the mixture was found by reducing 2 μL of the mixture in 1 mL of ether with 20 mg of LAH for 20 min and analyzing the methanes formed by GC. For determination of a KIE 50 μL (1 mmol) of the standard methyl iodide mixture was dissolved in 1 mL of solvent in a test tube closed with a rubber septum. A 0.1 mequiv sample of the reducing agent was added, and the mixture was kept for a sufficient period, which depended on the nature of the reagent. The methanes produced were analyzed by GC by injecting 20 μL of headspace gas. Since the ratio of methyl iodides to reductive agent in the competition experiments was always well above 10:1, the KIEs were calculated simply as the ratio between the peak areas [PA(CH₄)/PA(CD₃H)] corrected for the peak area ratio obtained for the standard mixture after complete reduction. All determinations were repeated at least once, and the averages and deviations from the averages are given in Table 1.

Electrolytic Reduction. A mini test tube (3 mL) was fitted with two platinum electrodes and a rubber septum. A solution of 220 mg of tetraoctylammonium perchlorate in 1 mL of THF was added under vacuum. A 50 μL sample of the H/D methyl iodide mixture was added. A current of 1 mA was applied for 20 min, after which 20 μL of headspace gas was analyzed.

(15) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316.

(16) (a) Tamura, M.; Kochi, J. *J. Organomet. Chem.* **1971**, *31*, 289. (b) Lehr, G. F.; Lawler, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 4048.

(17) Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 1520.

(18) Llewellyn, J. A.; Robertson, R. E.; Scott, J. M. W. *Can. J. Chem.* **1960**, *38*, 222.

(19) Neumann, W. P. *Synthesis* **1987**, 665.

Reaction with Hydrogen over Pd. A 10 mg sample of a 5% Pd on carbon was placed in a test tube fitted with a rubber septum. A 1 mL portion of THF and 50 μL of methyl iodide mixture were added together with 10 mL of hydrogen. A 20 μL sample of headspace gas was analyzed by GC initially and after 5, 15, and 60 min of shaking.

Iron-Catalyzed Reaction with Grignard Reagent. To 1 mL of 0.1 M butylmagnesium bromide in ether was added 50 μL of H/D methyl iodides. A 0.5 mg sample of anhydrous $FeCl_3$ dissolved in 50 μL of ether was added. After 5 min 20 μL of headspace gas was analyzed by GC. The experiment was performed also using THF as the solvent.

Reaction with Sodium. To 3 mg of sodium in a test tube fitted with a rubber septum were added 1 mL of THF and 50 μL of the methyl iodide mixture. The tube was shaken, and the sodium went into solution. A 20 μL sample of headspace gas was analyzed.

Reaction with Magnesium. A 2 mg portion of magnesium was dissolved in 1 mL of ether containing 50 μL of the methyl iodide mixture. After the reaction 100 μL of water was added and 20 μL of headspace gas was analyzed.

Reaction with Benzophenone Ketyl. A 20 mg portion of benzophenone in 10 mL of ether was shaken with 100 mg of sodium for 20 min, producing a dark blue solution. A 5 mL sample of the solution was added to a solution of 50 μL of standard H/D methyl iodide mixture in 5 mL of ether. The color disappeared after 50 s. A 10 mL portion of saturated aqueous ammonium chloride was added, and the ether layer was isolated and kept overnight with admission of air. The solution was analyzed by GC using a silicone capillary column as described.[20] The ratio between the peaks for the para adducts 4-methylbenzophenone

and 4-(trideuteriomethyl)benzophenone was found. The corresponding ratios for the ortho adduct and for the 1,2-addition product were almost identical.

Reaction of LAH in diethyl ether-d_{10}. To 2 mg of LAH in 0.1 mL of perdeuterio ether in a 5 mL ampule with a rubber septum was added 40 μL of methyl iodide. After 4 h 50 μL of headspace gas was injected into the molecular sieve column, which was attached to a mass spectrometer. Analysis of the eluted methane peak showed a content of CH_3D of less than 0.5% relative to CH_4.

Reaction with Sodium Naphthalenide. To 1 mg of sodium in 2.5 mL of THF was added 100 mg of naphthalene. A dark green solution formed. A 50 μL sample of H/D methyl iodide was added. A 50 μL portion of headspace gas was analyzed by GC as above. GC of the solution showed trace amounts of methylated naphthalenes and dihydronaphthalenes.

Kinetics. Two 20 mL reservoirs were charged with liquid ammonia. To one was added 200 μL of methyl iodide and to the other 3 mg of sodium to produce a dark blue solution. The reservoirs were connected to a mixing chamber and a glass reaction tube, i.d. 0.9 mm. The reservoirs were stoppered, and after a sufficient pressure had built up, the outlets were opened. The liquid speed in the reaction tube was 1 mL s^{-1} or 1.5 mL ms^{-1}. The blue color was visible for less than 2 mm corresponding to 0.0013 s.

Supporting Information Available: List of gas chromatographic integrals for experiments listed in Table 1 and calculation of K_1 and K_3 (2 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

(20) Holm, T. *J. Am. Chem. Soc.* **1993**, *115*, 916.