α-Deuterium kinetic isotope effects in reactions of methyllithium: is better aggregation the cause of lower reactivity?

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Abstract

The values k_H/k_D for α-deuterium kinetic isotope effects for the reaction of methyllithium and methylmagnesium iodide with a series of substrates are consistently ca. 10–15% higher for the lithium reagent than for the Grignard reagent. This may indicate a pre-equilibrium between an aggregate and a reactive monomer, with a better fit of the trideuterio monomer in the aggregate. An attempt has been made to compare the equilibrium constants for the aggregation of deuterio and protio methyllithium by studying the metal–halogen equilibrium between methyllithium and methyl iodide.

Keywords: Lithium; Magnesium; Methyllithium; Methylmagnesium iodide; Kinetic isotope effects

1. Introduction

While ^{13}C and α-D kinetic isotope effects (KIEs) in reactions of alkyl halides have been extensively studied [1,2], very little is known about KIEs for reactions of alkylmetal species such as Grignard or alkyllithium reagents [3]. Better knowledge of the isotope effects is needed since it might throw light on the mechanisms of the reactions. In nucleophilic substitutions the choice is between S_N1 and S_N2 mechanisms, and in addition reactions of organometallic reagents it might be possible to decide between concerted S_N2-type mechanisms and those involving stepwise electron transfer (ET) followed by radical recombinations [4,5].

In a recent study [3] we found that in the reaction with benzophenone and 2-octanone methyllithium showed an appreciable normal KIE (k_H/k_D = 1.13 and 1.08, respectively) when methyl hydrogen was replaced by deuterium. Our interpretation was that the mechanism involved electron transfer and that the methyl radical was destabilized by α-deuterium. At the same time we found that in reactions with the same ketones the methyl Grignard reagent showed a small inverse KIE, and this was taken to indicate the operation of a polar concerted reaction mechanism. However, if reactions of methyllithium, which have a radical mechanism have an appreciable normal (i.e. not inverse) deuterium KIE, it would seem reasonable to expect a normal KIE

also in a radical type reaction of a methyl Grignard reagent. A radical type mechanism is very probable for the addition reactions of Grignard reagents to α,β-unsaturated ketones [6], and a clear example of reaction via initial ET is the 1,6-addition of methylmagnesium iodide to the sterically hindered phenylduryl ketone [7]. But do these reactions show sizable α-deuterium KIEs?

2. Results and discussion

In the present work we have measured the α-deuterium isotope effects for reactions of a variety of ketones with both methyllithium and methylmagnesium iodide, and the results are shown in Table 1. They show two main features: (1) in the reaction of methylmagnesium iodide there is very little difference in k_H/k_D between typical ET substrates and typical "polar" substrates; and (2) the KIEs for the reaction of methyllithium are 11%–18% higher than those for methylmagnesium iodide. In view of this it seems unlikely that the large α-deuterium KIEs observed for methyllithium are to be explained exclusively in terms of a shift between ET and polar reaction mechanisms.

The important difference between the alkyllithium and the Grignard reagent is the aggregated, tetrameric state of the former. There is some evidence that the reactions of the Grignard reagent involve a less aggre-

Table 1

Observed α-deuterium KIEs [a], k_H / k_D, for substitution of three hydrogens by deuterium in CH_3Li–LiI and CH_3MgI in the reaction with substrates 1–9 [b] in diethyl ether

Substrate [b]	CH_3Li–LiI	CH_3MgI
1	1.14	0.96
2	1.08	0.97
3	1.06	0.97
4	1.13	1.01
5	1.13	1.00
6	1.12	1.01
7		0.88
8		0.94
9		0.93

[a] The values given are the averages for two experiments; the deviations from average in the 15 duplicate experiments shown were in general < 0.01.
[b] (1) Benzophenone; (2) 2-octanone; (3) α,α,α-trifluoroacetophenone; (4) 1,3-diphenyl-2-buten-1-one (benzylideneacetophenone); (5) 4,4-dimethyl-1-phenylpenten-3-one (benzylidenepinacolone); (6) 2,3,5,6-tetramethylbenzophenone (phenyldurylketone); (7) isopropylidenemalonic acid diethylester; (8) nonanoic acid ethylester; (9) isobutylidenemalonic acid diethylester.

gated species, e.g. a dimer [8] or, more often, a monomer, since the kinetics observed for the reactions of methyllithium are of fractional order with respect to the reagent (0.25–0.35) [9]. An obvious explanation is that there is an equilibrium between an aggregate (tetramer) of low reactivity and a highly reactive monomer:

$$(MeLi)_4 \rightleftharpoons 4\ MeLi \tag{1}$$

$$[MeLi] = ([(MeLi)_4] \times K)^{0.25} \tag{2}$$

Since the observed deuterium kinetic isotope effects for lithium and magnesium reagents differ, it seems possible that the observed effect in the case of methyllithium involves a combination of a small KIE for the reaction of the monomer, i.e. $k_H/k_D =$ ca. 1.0, and a relatively strong equilibrium isotope effect for equilibrium (1) in favor of the protio-monomer, i.e. $(K_H/K_D)^{0.25} =$ ca. 1.12. This combination could result in the observed overall deuterium KIE since $k_{obs} = k \times K^{0.25}$.

That the deuteriated methyllithium is more strongly aggregated than ordinary methyllithium could be attributed to the smaller steric requirements of the trideuteriomethyl group. According to Brown et. al. [10] all secondary deuterium KIEs can be explained in this way. That the C–D bond is shorter than the C–H bond makes the unit cell of the crystal lattice of solid methane-d_4 significantly smaller than that of CH_4 [11]. Also, a large body of chemical evidence shows that in any reaction in which steric hindrance is involved the deuterio reagent will react faster than the protio reagent, and in equilibria deuterium substitution will favor the side where the crowding is most severe [2]. A thermodynamic effect on equilibrium (1) is therefore not unlikely. Even if the

methyl groups are located at the periphery of the tetrameric methyllithium aggregate some repulsion may exist and the electron-deficient bonding between the negative carbon and the positive lithium atoms may be strengthed if the repulsion is partly released.

A comparison of the recently published neutron diffraction data [13] for d_3-methyllithium with the earlier X-ray diffraction data [14] for protio methyllithium do, in fact, reveal larger C–C and Li–Li distances in the aggregated CH_3Li than in the aggregated CD_3Li at 290 K. That steric hindrance to aggregation of an alkyllithium reagent could lead to very high reactivities was shown by Glaze and Freeman [12].

It would be desirable to measure the effect of deuterium substitution on the monomer–tetramer association equilibrium of methyllithium directly, but because of the extreme stability of the aggregates, which do not break down in donor solvents and are stable even in the vapor phase, this is not possible. However, as described below, information can be obtained indirectly by studying the metal–halogen exchange equilibrium between methyllithium and methyl iodide following the approach used by Applequist and O'Brien, who studied the metal–halogen exchange equilibrium between some alkyllithiums and alkyl-iodides [15].

The equilibrium between CH_3Li and CD_3Li can be represented by Eqs. (3) and (4). Adopting the nomenclature used by Applequist and O'Brien [15] we denote the equilibrium constant by K_{eq} if the concentrations in Eq. (5) involve monomeric methyllithiums, whereas when the concentrations refer to methyllithium in its normal aggregated state the equilibrium constant is denoted by K_{obsd}.
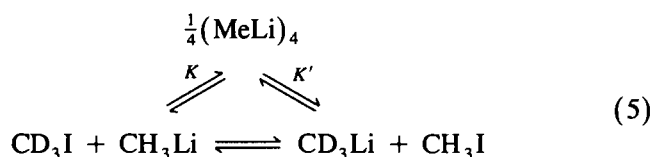
$$CH_3Li + CD_3I \rightleftharpoons CH_3I + CD_3Li \tag{3}$$
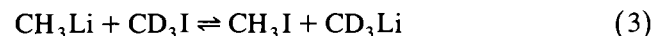
$$\frac{[CH_3I] \times [CD_3Li]}{[CH_3Li] \times [CD_3I]} = K_{eq}\ (or\ K_{obsd}) \tag{4}$$

The value of K_{eq} may be estimated theoretically by use of the fractionation factors (FFs) for CH_3Li and CH_3I. Shiner and Neumann [16] give the FF for introduction of a deuterium in methyliodide as 1.316 and the FF for one D–H exchange in methyllithium as 0.982. The latter FF was derived from the IR spectrum of monomeric methyllithium prepared from lithium atoms in an argon matrix [17]. Assuming identical zero point energy contributions for additional D–H exchanges, the FFs for CD_3I and CD_3Li will be 1.316^3, i.e. 2.28, and 0.982^3, i.e. 0.947, respectively. The value of K_{eq} for monomeric methyllithium and methyl iodide is then 0.415.

The value of K_{obsd} for the halogen–metal exchange in ethereal solutions of aggregated methyllithiums and methyl iodides was found experimentally by the procedure used by Applequist and O'Brien. Ideally this should

be performed with halogen-free solutions of the methyllithiums, but in our work they were prepared in ether from the methyl iodides. Since the Wurtz reaction, which produces lithium iodide, always competes with the metal–halogen exchange, and since the concentrations of methyllithiums are low, the use of halogen-free reagents is not possible, and is probably not essential. A series of experiments at 0°C gave a value of K_{obsd} of 0.40 ± 0.04, implying that the experimental value of α-D IE is ca. 4% lower than the value calculated for the nonaggregated reagents.

When aggregation is taken into account Eq. (1) has to be modified as in Eq. (5):

$$\frac{1}{4}(MeLi)_4$$

$$\overset{K}{\nearrow} \quad \overset{K'}{\nwarrow} \qquad\qquad (5)$$

$$CD_3I + CH_3Li \;\rightleftharpoons\; CD_3Li + CH_3I$$

The aggregate is in a fluxional state, a fast exchange between the deuterio and the nondeuterio reagent taking place, presumably in a random way. For this situation Applequist and O'Brien showed that Eq. (6) applies

$$\frac{K_{obsd}}{K_{eq}} = \left(\frac{K}{K'}\right)^{1/4} \qquad\qquad (6)$$

If we assume that the isotope effect for the splitting off of a monomeric methyllithium is on average unchanged in the mixed aggregates, the concentration of the monomers will according to Eq. (2), be a function of $(K/K')^{1/4}$, and for a $1:1$ mixture of the normal and the deuterio reagent the relationship shown in Eq. (7) will apply:

$$\frac{[CH_3Li]}{[CD_3Li]} = \frac{K_{obs}}{K_{eq}} \qquad\qquad (7)$$

If the protio and the deuterio reagent had the same reactivity the ratio between K_{obsd} and K_{eq} would be identical to $(k_H/k_D)_{obs}$, but if the monomeric methyllithium reacts with a value of k_H/k_D of f, the observed deuterium KIE in the reaction of methyllithium will be:

$$(k_H/k_D)_{obs} = f \times \frac{K_{eq}}{K_{obs}} \qquad\qquad (8)$$

The ratio between the calculated K_{eq} and the measured K_{obs} is ca. 0.97. If the reaction of methyllithium takes place via the solvated monomer, and the two monomers are of equal reactivity, a value of $(k_H/k_D)_{obs}$ of 0.97 should be found for the reaction. The results obtained with methylmagnesium iodide and substrates of various types indicate that the deuterated monomer is about as reactive as an electron donor as the protio monomer. By analogy with this one may assume a value of f of 1.0 in

Eq. (8). If the α-deuterium KIE observed for reaction of methyllithium with several substrates were due to more effective aggregation of the deuterio reagent the ratio between K_{eq} and K_{obs} should have been 1.13.

The equilibrium (3) refers to the unsolvated methyllithium species, whereas Eq. (5) applies in ether solution. Unsolvated methyllithium tetramer, for example in the vacuum of the mass spectrometer, is highly stable implying that equilibrium (1) lies entirely over to the left-hand side. In ether, however, the right-hand side of equilibrium (1) is favored by the much better solvation of four monomers than of the aggregate. The deuterium isotope effect on this solvation is difficult to predict, and is not taken into account in the calculation.

α-Deuterium KIEs are small and the procedure used is crude. The prediction of K_{eq} within $\pm 15\%$ by use of fractionation factors is, however, remarkably good. Possibly a more refined treatment, in which solvation isotope effects are taken into account, will give agreement between calculation and experiment.

3. Conclusion

The rate of formation of radicals by electron transfer from an alkylmagnesium or a monomeric alkyllithium compound seems not to be very significantly changed by the introduction of α-deuterium. The large α-deuterium KIEs observed for ethereal alkyllithium reagents is likely to arise from a stronger binding of the deuterio monomer in the aggregate.

4. Experimental details

4.1. Materials

Diethyl-ether was distilled from sodium benzophenone ketyl. Commercial methyl iodide (Merck) and d_3-methyl-iodide (isotropic purity $> 99\%$; Cambridge Isotope Laboratories, Inc.) were used. Solutions of methyllithium and d_3-methyllithium were prepared by the addition of the iodides, separately or as a $1:1$ mixture, to a large excess of freshly cut lithium in diethyl ether. The solutions were used on the day of preparation. Oxygen was excluded by use of ampoules and disposable syringes.

4.2. Halogen–metal exchange equilibrium

The method used for the determination of K_{obsd} involved keeping the concentrations of the methyl iodides high and equal and the concentrations of the methyllithiums low and variable, since according to Eq.

(4) the ratio between the lithium reagents are then equal to K_{obsd}, which preliminary tests indicated was ca. 0.5. To 5 ml of an ether solution 0.300 M in methyl iodide and 0.300 M in trideuteriomethyl iodide was added 0.5 ml of an ethereal solution 0.1 M in methyllithium. LiI and 0.05 M in trideuteriomethyllithium. Samples withdrawn after 30, 60, and 90 min were treated with an excess of p,p'-dimethylbenzophenone, and after workup the ratio D/H of deuterio to nondeuterio product was found by GLC. The value obtained after 90 min at 0°C, $D/H = 0.403$, was taken as K_{obs}. A duplicate experiment gave the same result.

4.3. Kinetic isotope effects

The procedure described in Ref. [4] was used. The concentrations of protio and deuterio reagents were each 0.15 M and the concentration of substrates 0.002 M. The value of k_H/k_D was determined from the ratio of hydrogen and deuterium products as determined by GLC.

Alkyllithiums form mixed aggregates with reaction products such as alcoholates. For this reason the ratio of methyllithium to ketone was kept at 75:1. An even higher ratio was desirable, but would have reduced the accuracy of the analysis of the products.

References

[1] A.V. Willi, in E. Buncel and C.C. Lee (eds.), Isot. Org. Chem., 3 (1977) 237.
[2] K.C. Westaway, Isot. Org. Chem., 7 (1987) 275.
[3] T. Holm, Acta Chem. Scand., 48 (1993) 362.
[4] T. Holm, Acta Chem. Scand. Ser., B37 (1983) 567, and references therein.
[5] E.C. Ashby, Pure. Appl. Chem., 52 (1980) 545, and references therein.
[6] T. Holm, Acta Chem. Scand., 45 (1991) 925.
[7] R.C. Fuson, B.C. McKusiek and J. Mills, J. Org. Chem., 11 (1946) 60.
[8] K.C. Williams and T.L. Brown, J. Am. Chem. Soc., 88 (1966) 4134.
[9] B. Wakefield, The Chemistry of Organolithium Compounds, Pergamon, Oxford, 1980.
[10] H.C. Brown, J.G. Azzaro, J.G. Koelling and G.J. McDonald, J. Am. Chem. Soc., 88 (1966) 2520.
[11] S.C. Greer and L. Meyer, J. Chem. Phys., 52 (1970) 468.
[12] W.H. Glaze and C.H. Freeman, J. Am. Chem. Soc., 91 (1969) 7198.
[13] E. Weiss, T. Lambertsen, B. Schubert, J.K. Cockcroft and A. Wiedenmann, Chem. Ber., 123 (1990) 79.
[14] E. Weiss and G. Heneken, J. Organomet. Chem., 21 (1969) 265.
[15] D.E. Applequist and D.F. O'Brien, J. Am. Chem. Soc., 85 (1963) 743.
[16] V.J. Shiner, Jr. and T.E. Neumann, Z. Naturforsh., A44a (1989) 337.
[17] L. Andrews, J. Chem. Phys., 47 (1967) 4834.