Rapid-Injection Nuclear Magnetic Resonance Investigation of the Reactivity of α- and β-Alkoxy Ketones with Dimethylmagnesium: Kinetic Evidence for Chelation

Stephen V. Frye,*[1a] Ernest L. Eliel,[1a] and Roland Cloux[1b]

William R. Kenan, Jr., Laboratories of Chemistry
University of North Carolina
Chapel Hill, North Carolina 27514
Institut de Chimie Organique, Université de Lausanne
CH-1005 Lausanne, Switzerland

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Chelation is often invoked to explain the stereochemical outcome of the reaction between organometallic reagents and chiral α- and β-alkoxycarbonyl compounds.[2-8] However, evidence other than the observed stereochemistry for the role of chelation has been scarce;[9] only static NMR spectra of the chelate formed between 2-methoxycyclohexanone and $TiCl_4$ in CD_2Cl_2[10] and of two β-benzyloxy aldehydes complexed with $TiCl_4$, $SnCl_4$, and $MgBr_2$ in CD_2Cl_2[11] have been reported. These studies show that stable chelates can be observed under equilibrium conditions in nonbasic solvents such as CD_2Cl_2[12] but do not establish that such chelates are kinetic intermediates in nucleophilic additions to α- and β-alkoxycarbonyl compounds in ether solvents, rather than products of a nonproductive equilibrium.[13] We report here preliminary results of a rapid-injection NMR[14] investigation of the reaction of dimethylmagnesium ($MgMe_2$) with α- and β-alkoxy ketones **1–4** as direct evidence for the role of chelation in the transition state of this reaction.

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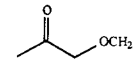

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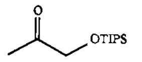

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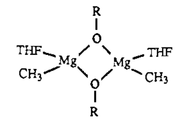

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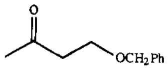

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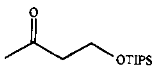

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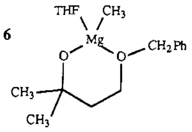

Ketones **1** and **2** were chosen because synthetic evidence[3,5,6,8] suggests that benzyl ethers chelate very effectively. In contrast, ketones **3** and **4** represent models for α- and β-alkoxy ketones which cannot chelate because of the steric bulk of the triisopropylsilyl group;[15,16] 2-hexanone served as a simple alkyl ketone reference. $MgMe_2$ was chosen as a well-characterized[17,18] organometallic reagent which exists as a single species in solution in THF.

The mechanism of $MgMe_2$ addition to benzophenone has been investigated by Ashby[17] and House.[18] The initial reaction is first order in both $MgMe_2$ and ketone and the first formed product is the methylmagnesium alkoxide. Ashby assumed rapid dimerization of this alkoxide based upon the work of Coates.[19] We restricted our study to the reaction of the first magnesium-bound methyl group disregarding the subsequent, much slower, reaction of the second methyl group. McGarrity's rapid injection technique[14] was employed, with a small amount of $MgMe_2$ in THF-d_8 (ca. 20 μL) being injected into an NMR tube containing a 0.06 M solution of ketone (or a mixture of two ketones) at low temperature in the probe of a Bruker 360-MHz NMR. The NMR singlets of the magnesium-bound methyl groups at −1.5 to −2 ppm were found to be most useful for following the reaction.[20] In the initial experiments, the ketones and $MgMe_2$ were at approximately the same concentration (0.06 M) with the temperature adjusted for a convenient rate of reaction ($t_{1/2} \approx$ minutes at 243 K for **2**, **4**, and 2-hexanone, $t_{1/2} \approx$ seconds at 213 K for **1** and **3**).

In Figure 1 is shown the −1.5 to −2 ppm NMR region recorded during reaction of $MgMe_2$ with 2-hexanone in THF-d_8 at 243 K.[21] Spectrum a shows the $MgMe_2$ singlet at −1.79 ppm; 61 s later the signal of the product methylmagnesium alkoxide had appeared at −1.61 ppm (b), and after 765 s a new signal arose at −1.67 ppm (c,d), presumed to be the dimeric methylmagnesium alkoxide **5**[17] (vide infra). After 2210 s (d) the signal assigned to the dimeric methylmagnesium alkoxide (−1.67 ppm) had grown substantially and eventually the monomer (−1.61 ppm) was completely converted to dimer. Compound **4** reacted with $MgMe_2$ at almost the same rate as 2-hexanone and with the same qualitative evolution of NMR signals. Figure 2 shows the NMR spectrum of the reaction products of a mixture of **4** and 2-hexanone with $MgMe_2$; it provides the best evidence for the dimeric nature of the slowly formed methylmagnesium alkoxide. The initially appearing signals due to the monomeric methylmagnesium alkoxides formed from **4** and 2-hexanone, appear respectively at −1.60 and −1.61 ppm, whereas at −1.65, −1.67, and −1.66 ppm are later appearing signals

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[1] (a) University of North Carolina. (b) Université de Lausanne.

[2] Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.

[3] Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, 1031. Still, W. C.; Schneider, J. A. *Ibid.* **1980**, 1035.

[4] Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

[5] (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, 265. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, 1879, 1883.

[6] Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.

[7] Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 125.

[8] Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, 3223.

[9] Kauffmann et al. (Kauffmann, T.; Möller, T.; Rennefeld, H.; Welke, S.; Wieschollek, R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 348) have determined the relative rate of nucleophilic addition to $RCO(CH_2)_nCHOHR'$ (A) vs. $RCO(CH_2)_{n+1}R'$ (B) (n = 0, 1) and find A to react much faster than B with organometallics which do not deprotonate the OH group. (Reagents which form alkoxides, RO^-M^+, with A show little discrimination.) Unfortunately, the authors themselves recognize—and the present work strongly suggests—that the acceleration seen with A (n = 0) may be due to the inductive effect of the α-oxygen rather than to chelation. This factor is eliminated in the present work by comparing compounds with OCH_2Ph and $OSi(i\text{-}Pr)_3$ groups at the α position.

[10] Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem. Suppl.* **1983**, 1511.

[11] Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

[12] We have been able to observe (by NMR) chelates similar to those observed by Reetz[10] and Keck[11] for **1** or **2** and $MgBr_2$ in $CDCl_3$ and CD_2Cl_2 but no chelates are observed in THF, presumably due to its greater coordinating ability toward $MgBr_2$. Ketones **3** and **4** show (NMR) evidence of complexation to $MgBr_2$ in $CDCl_3$ without chelation.

[13] Ashby has presented an excellent discussion of this problem.[17a] In brief, it is very difficult to design experiments to distinguish between eq 1 and 2:

$$\text{chelate} \rightleftharpoons \text{ketone} + \text{dimethylmagnesium} \rightarrow \text{product (chelate not intermediate)} \quad (1)$$

$$\text{ketone} + \text{dimethylmagnesium} \rightleftharpoons \text{chelate} \rightarrow \text{product (chelate intermediate)} \quad (2)$$

[14] McGarrity, J. F.; Olgle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810. McGarrity, J. F.; Prodolliet, J. *J. Org. Chem.* **1984**, *49*, 4465.

[15] The basicity of ethers and alkoxysilanes has been shown to be quite similar by West et al. (West, R.; Wilson, L. S.; Powell, D. L. *J. Org. Met. Chem.* **1979**, *178*, 5); therefore we consider the major effect of the triisopropylsilyl group to be steric.

[16] For synthetic evidence regarding prevention of chelation by sterically demanding silicon protecting groups cf. ref 4 and references therein, ref 5a, ref 8, and: Reetz, M. T.; Hüllmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600.

[17] (a) Laemmle, J.; Ashby, E. C.; Neumann, H. M. *J. Am. Chem. Soc.* **1971**, *93*, 5120. (b) Parris, G. E.; Ashby, E. C. *ibid* **1971**, *93*, 1206.

[18] (a) House, H. O.; Oliver, J. E. *J. Org. Chem.* **1968**, *33*, 929. (b) The NMR spectra of a number of methylmagnesium species in diethyl ether are reported in: House, H. O.; Latham, R. A.; Whitesides, G. M. *Ibid.* **1967**, *32*, 2481.

[19] Coates, G. E.; Heslop, J. A.; Redwood, M. E.; Ridley, D. *J. Chem. Soc. A* **1968**, 1118.

[20] The signals due to the ketones and the alkoxide products downfield from Me_4Si are consistent with our observations based on the CH_3–Mg resonances. Thus the disappearance of dimethylmagnesium coincides with disappearance of the resonances due to the ketones and appearance of signals due to the corresponding alkoxides. Also, when two alkoxides (monomer, dimer) are indicated by the CH_3–Mg signals, this is corroborated by the observation of two sets of signals for some resonances due to the alkoxy portion of the methylmagnesium alkoxides. Workup of the reactions after completion gives the expected alcohols essentially pure according to NMR.

[21] The reaction of 2-methyl-2-hexanol with dimethylmagnesium gives identical signals in this region, albeit at a much faster rate.

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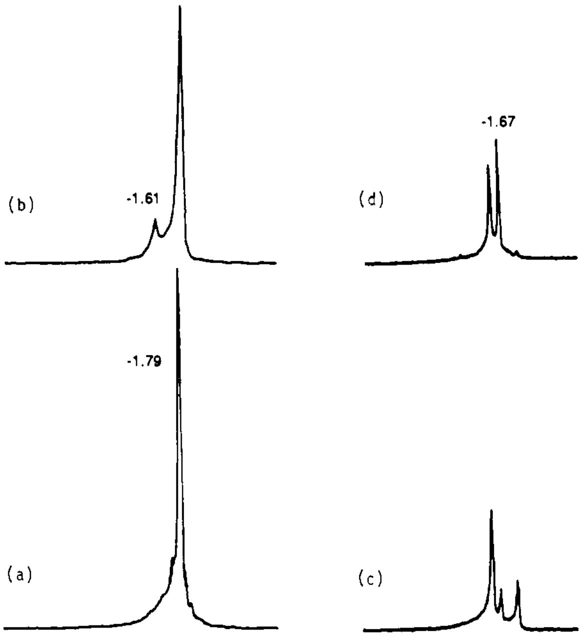

Figure 1. NMR spectra of 2-hexanone reacting with dimethylmagnesium in THF-d_8 at 243 K: (a) 1 s after injection; (b) 61 s; (c) 765 s; (d) 2210 s.

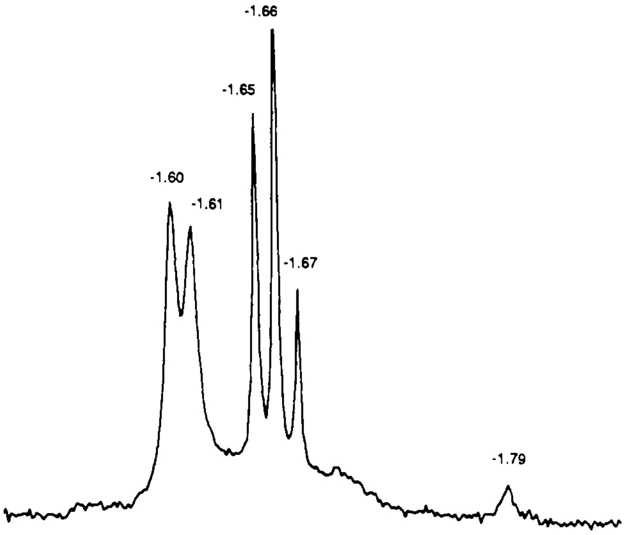

Figure 2. NMR spectrum of 2-hexanone and **4** reacting with dimethylmagnesium in THF-d_8 at 243 K.

assigned to the homo dimers from **4** and 2-hexanone and the corresponding mixed dimer, respectively.[22] Spectra of ketone **2** reacting with $MgMe_2$ showed only the signal due to $MgMe_2$ and a single methylmagnesium alkoxide species at −1.59 ppm over several hours. A tentative explanation is that chelation in the monomeric magnesium alkoxide prevents dimerization, as depicted in **6**.[23]

Table I. Relative Rate[a] of Reaction with Dimethylmagnesium

k_1/k_3	>100[b] (213 K)
k_2/k_4	1.18 (283 K), 1.72 (243 K), 1.99 (223 K), 2.54 (203 K)[c]
$k_4/k_{2\text{-hexanone}}$	0.90 (243 K)

[a] Determined by integration of initial and final (before reaction of the active methyl group of the methylmagnesium alkoxide) ketone signals vs. internal pentamethylbenzene. [b] 100 is an estimate of the upper limit measurable by NMR techniques. [c] $\Delta\Delta S^{\ddagger}{}_{2\text{-}4} = -3.4 \pm 0.3$ cal deg^{-1} mol^{-1}, $\Delta\Delta H^{\ddagger}{}_{2\text{-}4} = -1.08 \pm 0.10$ kcal mol^{-1}.

Ketones **1** and **3** reacted with $MgMe_2$ much faster ($t_{1/2} \approx 10$ s at 213 K) than **2**, **4**, or 2-hexanone, so that it proved impossible to measure their rate of reaction at any temperature where **2**, **4**, and 2-hexanone reacted at reasonable rates. This must be due to the inductive activation of the carbonyl of **1** and **3** by the α-alkoxy group. (The β-alkoxy group in **2** and **4** has a very small effect as seen by the similar rates of reaction of **4** and 2-hexanone, cf. Table I.) At 213 K the reaction of **1** and **3** with $MgMe_2$ produced species with essentially identical NMR spectra in the region −1.5 to −2 ppm consisting of only two signals for CH_3 bound to magnesium: one at −1.79 ppm from $MgMe_2$ and one at −1.67 ppm due to the methylmagnesium alkoxide product. The nature of the aggregation state of the methylmagnesium alkoxide products in these two cases is unknown and further study of these products is under way.

Quantitative analysis of the kinetics of the above reactions with concentrations of the ketone and $MgMe_2$ approximately equal proved difficult,[17a] and therefore competition experiments were performed to determine the relative rates of reaction of the ketones studied[9,24] (cf. Table I). The most important result is the finding that the benzyl-protected ketone **1** reacts with $MgMe_2$ much faster than its triisopropylsilyl counterpart **3**; in fact the difference in rates was too great to be measured. Benzyl-protected ketone **2** also reacts faster than **4** but only by a factor of about 2. We interpret the rate difference between **1** and **3** to result from rate enhancement due to chelation in the reaction of the α-alkoxy benzyl-protected ketone **1**. The smaller difference in rates between **2** and **4** does not allow firm interpretation but is consistent with the synthetic finding that chiral α- but not β-alkoxy ketones react stereoselectively with Grignard reagents and alkyllithiums.[4,25] This interpretation assumes that there is no inherent difference between the reactivity of the α-benzyloxy and triisopropylsilyloxy ketones other than that due to the benzyl ethers' ability to chelate. To test this asumption we carried out competition experiments between **1** and **3** (and **2** and **4**) using the nonchelating reagent[8,26] diisobutylaluminum hydride (DIBAL). Preliminary results indicate that corresponding benzyl- and triisopropylsilyl protected ketones are reduced at approximately the same rate with DIBAL, supporting the assumption that their difference in reactivity with $MgMe_2$ is not due to effects, electronic or steric, other than the ability or inability to chelate.

On the basis of the evidence presented, we believe the large difference in reaction rate with $MgMe_2$ between **1** and **3** is, in fact, due to chelation in the transition state during the reaction of **1**. This appears to be the first strong kinetic evidence that chelation—long postulated in Cram's chelate rule[2,7]—does occur during the reaction of α-alkoxy ketones with alkylmagnesium reagents. In β-alkoxy ketones these experiments suggest that chelation is of minor importance, which is in accord with synthetic findings.[4,25]

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(22) On the basis of the fact that CH_3MgO-*t*-Bu is a tetramer in benzene and diethyl ether,[19] a referee has suggested that we may be observing a dimer to tetramer equilibrium for the product of **2** and 2-hexanone with $MgMe_2$. Such an equilibrium cannot explain the NMR spectra presented in Figure 2 as readily as a monomer to dimer equilibrium, and the extrapolation of structural results in benzene and diethyl ether to a more disaggregating solvent such as THF may not be justified. For example, Ashby et al. (Ashby, E. C. *Pure Appl. Chem.* **1980**, 52, 545) have reported that Grignard reagents which aggregate strongly in diethyl ether are monomers over a wide concentration range in THF.

(23) Reaction of a mixture of **2** and **4** with $MgMe_2$ shows no evidence for formation of mixed dimers, which supports this hypothesis. However, even if the reaction of **2** with $MgMe_2$ forms the monomeric chelated product **6** this is *not* necessarily evidence for chelation in the transition state.

(24) Experiments carried out under pseudo-first-order conditions (excess ketone[17a]) for **2**, **4**, and 2-hexanone are in agreement with the relative rates reported in Table I. **1** and **3** react too rapidly to be examined under pseudo-first-order conditions but their relative rate of reaction is in agreement with their qualitative absolute rates.

(25) Reference 6 reports that the stereoselectivity of additions to substrates where both α- and β-chelation was possible was best explained in terms of exclusive or near exclusive α-chelation control.

(26) Ko, K.-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333.