Concerning the Addition of Grignard Reagents to Ketones. Evidence for a Termolecular Mechanism

Sir:

The mechanism of Grignard reagent addition to ketones has been the subject of considerable controversy for some years. While it appeared that the controversy had subsided regarding the several mechanisms in question,[1] Smith and Su[2] suggested still another reaction

$$\text{ketone} + \text{grignard} \overset{K}{\rightleftharpoons} \text{complex} \quad (1)$$

$$\text{complex} \xrightarrow{k_1} \text{product} \quad (2)$$

path. In addition, they reported spectroscopic evidence supporting the formation of a complex.

We have studied the kinetics of the reaction of benzophenone with methylmagnesium bromide in diethyl ether solvent at Grignard:ketone ratios ranging from 25:1 to 150:1.[3] The maximum concentration of methylmagnesium bromide employed was 1.52×10^{-2} *M* since association studies have shown that the former is predominantly monomeric at and below this concentration. Under these conditions, the reaction was found to be pseudo first order. The kinetic data were obtained at 25° by quenching individual samples of the reaction mixture at appropriate intervals of time and following the disappearance of ketone by ultraviolet analysis (λ_{max} 251 mμ).

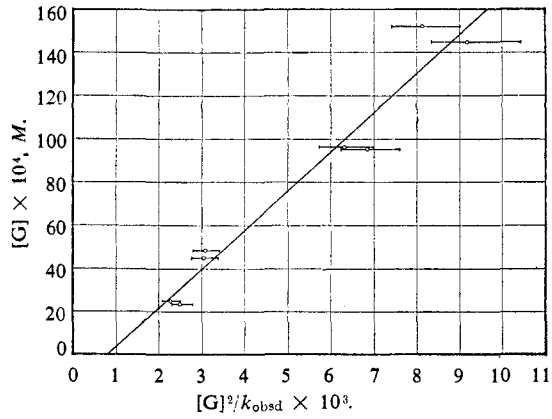


Figure 1. Graphical test of proposed mechanism.

A mechanism which fits the experimental data is one similar to that originally suggested by Swain.[4]

$$G + K \overset{K}{\rightleftharpoons} C \quad (3)$$

$$C + G \xrightarrow{k_2} \text{product} \quad (4)$$

In this case the observed pseudo-first-order rate constant is given by

$$k_{obsd} = \frac{k_2 K[G]_0^2}{1 + K[G]_0} \quad (5)$$

The data obtained in this study are summarized in Table I. A quantitative test of this mechanism is demonstrated by the plot (Figure 1) of $[G]_0$ *vs.* $[G]^2/k_{obsd}$ since

$$[G]_0 = k_2 \frac{[G]_0^2}{k_{obsd}} - \frac{1}{K} \quad (6)$$

Within experimental error, the points fall on a line, and the slope and intercept have the signs required for meaningful interpretation. It is clear that the kinetic expression (eq 5) can resolve to a simple second- or third-order expression depending on the value of *K*. This possibility is currently being investigated using substituted benzophenones.

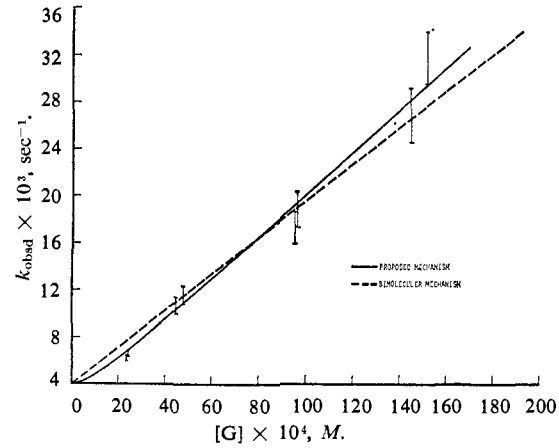


Figure 2. Graphical test for bimolecular mechanism.

Table I

$[G]_0 \times 10^4$, *M*	$[K]_0 \times 10^4$, *M*	$k_{obsd} \times 10^3$, sec^{-1}
23.8	1.027	2.26
24.5	1.027	2.65
24.7	1.010	2.71
45.2	1.010	6.73
48.3	1.010	7.61
95.4	1.027	13.28
96.4	1.010	14.79
145	1.065	22.9
152	1.065	28.4

In attempting to see if a simple bimolecular mechanism would fit the data as well as the proposed mechanism does, the dependence of k_{obsd} on $[G]_0$ was examined. The solid curve (Figure 2) represents values of k_{obsd} computed for the proposed mechanism using the numerical values of *K* and k_2 obtained graphically from Figure 1. It appears clear that the solid curve fits the data better than the dashed line. Therefore the data do not satisfy a simple bimolecular mechanism.

If the mechanism suggested by Smith and Su is correct, then k_{obsd} is related to $[G]_0$ by the expression

$$k_{obsd} = \frac{k_1 K[G]_0}{1 + K[G]_0} \quad (7)$$

Quantitative adherence to this expression can be tested graphically by noting that

$$[G]_0 = k_1 \frac{[G]_0}{k_{obsd}} - \frac{1}{K} \quad (8)$$

A plot of $[G]_0$ *vs.* $[G]_0/k_{obsd}$ does not suggest a fit. The best line through the data points has a negative slope, which has no physical meaning.

(1) E. C. Ashby and M. B. Smith, *J. Am. Chem. Soc.*, **86**, 4363 (1964).
(2) S. G. Smith and G. Su, *ibid.*, **88**, 3995 (1966).
(3) Concentrations of Grignard reagents were determined by the Gilman method which involves hydrolysis with excess standard H_2SO_4 followed by back-titration with standard NaOH. Halide was determined by the Volhard method.
(4) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, 73, 870 (1951).

The mechanism suggested by Mosher[5] and Becker[6] is similar to the one suggested here, but it brings the components together in a somewhat different manner.

$$2G \overset{K_g}{\rightleftharpoons} G_2 \quad (9)$$

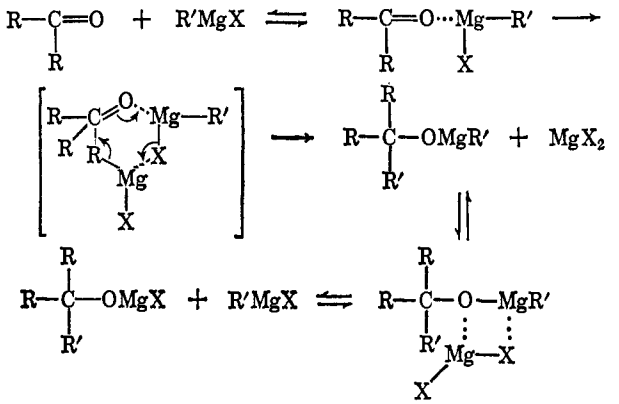
$$K + G_2 \overset{K'}{\rightleftharpoons} C \quad (10)$$

$$C \xrightarrow{k_3} P \quad (11)$$

In this case $k_{obsd} = k_3k_g[G]^2/(1 + K_gK[G]^2) = k_3K'[G]^2/(1 + K'[G]^2)$ for conditions such that the concentration of dimer G_2 is small with respect to that of monomer G. The test of the mechanism is whether a plot of k_{obsd} *vs.* $k_{obsd}/[G]_0$ is linear. The plot is not linear.

The ultimate test of the mechanism proposed here is whether the rate behavior in solutions where Grignard and ketone are in comparable concentration is consistent with the numerical values of K and k_2 obtained under pseudo-first-order conditions. Such experiments are currently in progress and indicate already that this is the case.

The fact that at low Grignard:ketone ratios the rate of reaction decreases markedly after 50% of the available R groups are utilized[6] can be readily explained by assuming that the product (eq 4) does not readily regenerate the active Grignard species as originally proposed by Swain.



Calculations of our kinetic data at low Grignard:ketone ratios have produced agreement with this concept.[7]

(5) J. Miller, G. Gregoriou, and H. S. Mosher, *J. Am. Chem. Soc.*, **83**, 3966 (1961).

(6) N. M. Bikales and E. I. Becker, *Can. J. Chem.*, 41, 1329 (1962).

(7) It should be noted that the conclusion drawn here is compatible with the existence of the Schlenk equilibrium, but that the data cannot indicate which of the species ($RMgX$, MgX_2, or R_2Mg) may be involved in the mechanism, if specificity indeed occurs.

(8) Sloan Fellow, 1965–1967; to whom inquiries should be addressed.

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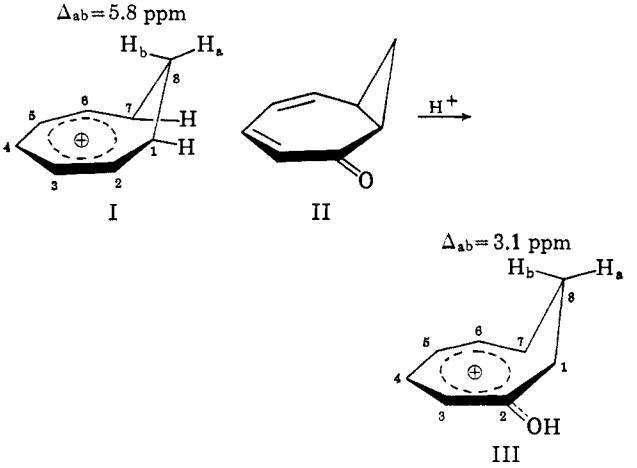
The Homoaromatic 1-Hydroxyhomotropylium Cation[1,2]

Sir:

Known homotropylium cationic species include the parent $C_8H_9^+$ cation[3,4a] I and its $Mo(CO)_3$ complex,[3a] as well as the 1-methylhomotropylium ion[4b] and its 1-phenyl analog.[4b] Another instructive case is the conjugate acid[4c] of the bicyclic ketone II (monohomotropone), whose nmr spectrum, especially the big chemical shift (Δ_{ab}) between inside H_b and outside H_a protons, is indicative of a nonclassical 2-hydroxyhomotropylium structure III. Even with the hydroxyl substituent on the cationic system, the nonclassical homoconjugative involvement of the cyclopropane ring in the cyclic electron delocalization is very substantial. The fact that a relatively high energy cyclopropane ring is present in the parent ketone II favors nonclassical character in species III; thus, an even more instructive monohomotropylium species which we report in the present communication is the 1-hydroxy isomer V, the conjugate acid of cyclooctatrienone (IV).

As reported recently by Roberts and his co-workers,[5] cyclooctatrienone displays a temperature-dependent nmr spectrum in CS_2 solvent. The high-temperature spectrum (35°) contains a doublet signal at τ 7.0 for the C_8 methylene protons, a quartet at τ 4.23 for the C_7 proton, and a complex multiplet between τ 3.4 and 3.9 for the other five protons. In the low-temperature spectrum, *e.g.*, at −73°, the signal for H_a and H_b is that of the AB part of the ABX spectrum with the chemical shift (Δ_{ab}) between inside H_b and outside H_a being 0.42 ppm. We observe similar temperature dependence of the nmr spectrum of cyclooctatrienone in other solvents. In none of them is there any indication of pronounced monohomotropylium oxide character in IV.



In strongly acidic media, such as SO_2–FSO_3H or SO_2–FSO_3H–SbF_5, however, the nmr spectrum of the conjugate acid of IV does correspond to a homoaromatic homotropylium species V. Using CH_2Cl_2 as a secondary standard (τ 4.70), the signal for the inside H_b appears as a triplet at τ 8.68, considerably upfield from the H_b signal in the neutral parent ketone, while the signal for the outside H_a appears as a quartet of doublets at τ 5.60, downfield from the position of H_a in IV. Thus the chemical shift between H_a and H_b (Δ_{ab}) is now 3.1 ppm. The signal for H_7 appears as a quartet at τ 4.05,[6] while the signals for the protons

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) Reported in part at The Chemical Society International Symposium on Aromaticity, Sheffield, England, July 6–8, 1966.

(3) (a) S. Winstein, H. D. Kaesz, C. G. Kreiter, and E. C. Friedrich, *J. Am. Chem. Soc.*, 87, 3267 (1965); (b) S. Winstein, C. G. Kreiter, and J. I. Brauman, *ibid.*, 88, 2047 (1966).

(4) (a) J. L. Rosenberg, J. E. Mahler, and R. Pettit, *ibid.*, 84, 2842 (1962); (b) C. E. Keller and R. Pettit, *ibid.*, 88, 604 (1966); (c) J. D. Holmes and R. Pettit, *ibid.*, 85, 2531 (1963).

(5) C. Ganter, S. M. Pokras, and J. D. Roberts, *ibid.*, 88, 4235 (1966).

(6) In SO_2–FSO_3H at −26° the signal for H_1 and H_7 in the monohomotropylium ion I appears as a quartet at τ 3.52. The signal for H_b appears as a doublet of triplets at τ 10.73, that for H_a as a quartet at τ 4.87, and those for H_{2-6} as a multiplet centered at τ 1.50. Coupling