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The Chemistry of Carbanions. XIV. Factors Influencing the Rate of Addition of Dimethylmagnesium to Benzophenone[1]

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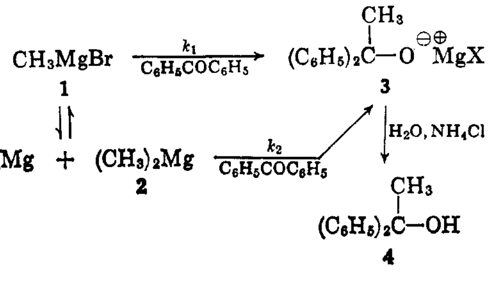
The rate of reaction of benzophenone with dimethylmagnesium in ether solution has been found to fit the bimolecular kinetic expression rate = $k_2[\mathrm{Me_2Mg}][\mathrm{C_6H_5COC_6H_5}]$. The addition of donor ligands to the reaction mixture may either accelerate or retard the rate of this addition reaction. The most effective additives are bidentate ligands such as N,N,N′,N′-tetramethylethylenediamine (**25**, retards the rate of addition) and β-methoxyethyldimethylamine (**28**, accelerates the rate of addition) which form 1:1 complexes with dimethylmagnesium in ether solution. The data are interpreted as indicating that addition occurs *without* a prior dissociation of the ligands from dimethylmagnesium. Instead, the addition is suggested to proceed *via* a transition state (or an intermediate) involving a pentacoordinated magnesium species such as structure **32**.

Although a number of studies of rate of reaction of Grignard reagents with ketones have been published,[2,3] there remains a striking diversity of opinion as to how these data should be interpreted. These difficulties in interpretation arise, at least in part, from the facts that most, if not all, Grignard reagents (*e.g.*, **1**) are in rapid equilibrium with the corresponding dialkyl- or diarylmagnesium compounds (*e.g.*, **2**)[4] and both magnesium reagents (*e.g.*, **1** and **2**) are probably capable of addition to carbonyl functions to form alkoxides (*e.g.*, **3**). Furthermore, there is general agreement[2] that the addition of dialkylmagnesium reagents to ketones is more rapid than addition of the corresponding alkylmagnesium halides (*i.e.*, $k_1 < k_2$ in Scheme I). Consequently, many supposed studies of the addition of alkylmagnesium halides may in fact be studies of only the addition of dialkylmagnesium compounds or of some combination of two different addition reactions.

SCHEME I



In continuing our study of this reaction, we have chosen to bypass the question of whether the dialkylmagnesium, the alkylmagnesium halide, or both of them are the actual reactants. Instead, we have focused our attention on the reaction of dimethylmagnesium with benzophenone. In ether solution, dimethylmagnesium,[4b] like diethylmagnesium[3d,3e,4a,5] is monomeric in the concentration range up to 0.1–0.2 *M* so that the additional complication of association to larger molecular aggregates seen[3d,3e,4a,5] with alkylmagnesium halides and magnesium halides is also avoided. Both earlier work[2] and the present study have established that the "methylmagnesium alkoxides"[4b] formed from reaction of equivalent amounts of

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[1] This research has been supported by Grant No. AF-AFOSR-573 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research.

[2] For examples, see (a) J. G. Aston and S. A. Bernhard, *Nature*, **165**, 485 (1950); (b) N. M. Bikales and E. I. Becker, *Can. J. Chem.*, **41**, 1329 (1963); (c) M. Anteunis, *J. Org. Chem.*, **26**, 4214 (1961); *ibid.*, **27**, 596 (1962); (d) R. D'Hollander and M. Anteunis, *Bull. Soc. Chim. Belges*, **74**, 71 (1965); (e) H. O. House and D. D. Traficante, *J. Org. Chem.*, **28**, 355 (1963); (f) A. V. Tuulmets, *Kinetika i Kataliz*, **5**, 71 (1964); (g) A. V. Tuulmets, *Reaktsionnaya Sposobnost Organ. Soedin. Tartusk. Gos. Univ.*, **1**, 89, 196, 212, 220 (1964); *Chem. Abstr.*, **61**, 11,866, 13,154, 13,155 (1964); (h) A. V. Tuulmets, *ibid.*, **2**, 391 (1965); *Chem. Abstr.*, **65**, 3691 (1966); (i) T. Holm, *Acta Chem. Scand.*, **19**, 1819 (1965); *ibid.*, **20**, 1139 (1966); (j) T. Holm, *Tetrahedron Lett.*, No. 28, 3329 (1966); (k) S. G. Smith and G. Su, *J. Amer. Chem. Soc.*, **88**, 3995 (1966); (l) S. G. Smith and G. Su, *Tetrahedron Lett.*, 4417 (1966); (m) S. G. Smith and J. Billet, *J. Amer. Chem. Soc.*, **89**, 6948 (1967); (n) E. C. Ashby, R. B. Duke, and H. M. Neumann, *ibid.*, **89**, 1964 (1967); (o) M. Oki, M. Hirota, H. Satonaka, and T. Hagiwara, *Tetrahedron Lett.*, 1785 (1967); (p) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

[3] For recent reviews including this subject, see (a) R. M. Salinger in "Survey of Progress in Chemistry," Vol. 1, A. F. Scott, Ed., Academic Press Inc., New York, N. Y., 1963, pp 301–324; (b) B. J. Wakefield, *Organometal. Chem. Rev.*, **1**, 131 (1966); (c) W. Tochtermann, *Angew. Chem. Intern. Ed. Engl.*, **5**, 351 (1966); (d) R. E. Dessy and W. Kitching in "Advances in Organometallic Chemistry," Vol. 4, F. G. A. Stone and R. West, Ed., Academic Press Inc., New York, N. Y., 1966, pp 280–289; (e) E. C. Ashby, *Quart. Rev.* (London), **21**, 259 (1967).

[4] (a) M. B. Smith and W. E. Becker, *Tetrahedron*, **22**, 3027 (1966); (b) H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, **32**, 2481 (1967).

[5] (a) A. D. Vreugdenhil and C. Blomberg, *Rec. Trav. Chim.*, **82**, 453 (1963); (b) E. C. Ashby and M. B. Smith, *J. Amer. Chem. Soc.*, **86**, 4363 (1964).

TABLE I

RATES OF ADDITION OF DIMETHYLMAGNESIUM TO BENZOPHENONE IN ETHER SOLUTION

Me_2Mg concn, *M*	$C_6H_5COC_6H_5$ concn, *M*	% reaction after 0.14 sec at *ca.* 25°	k_2,[a] M^{-1} sec^{-1}	$10^{-2}k_3$,[b] M^{-2} sec^{-1}	k_1, sec^{-1} [c]	k_1', sec^{-1} [d]
0.048	0.024	14	23	4.2	0.46	0.95
0.072	0.024	16	17	2.8	0.41	1.3
0.096	0.024	20	17	2.0	0.40	1.7
0.144	0.024	26	15	1.1	0.31	2.1
0.192	0.024	34	16	0.85	0.31	2.9
0.384	0.024	63	19	0.48	0.30	7.0
0.096	0.012	25	22	2.3	0.23	2.0
0.096	0.036	25	23	3.9	0.70	2.6
0.096	0.048	25	23	2.6	0.96	2.1
0.158	0.083	32	19	1.4	1.3	2.7
0.198	0.104	39	20	1.2	1.7	3.6
0.258	0.135	46	20	0.92	2.0	4.4
		Average	20 ± 2	1.8 ± 0.9	0.76 ± 0.5	2.8 ± 1

[a] Rate = $k_2[Me_2Mg][C_6H_5COC_6H_5]$. [b] Rate = $k_3[Me_2Mg]^2[C_6H_5COC_6H_5]$. [c] Rate = $k_1[Me_2Mg]$. [d] Rate = $k_1'[C_6H_5COC_6H_5]$.

ketone and dimethylmagnesium are substantially less reactive in addition reactions than the starting dimethylmagnesium. Therefore, by limiting our studies to reactions of benzophenone with at least a twofold molar excess of dimethylmagnesium, we believe that we are studying the process by which a methyl group is transferred from dimethylmagnesium to benzophenone without serious competition from other reactions.

Our rate studies utilized the previously described[2e,p] flow reactor in which ether solutions of benzophenone and dimethylmagnesium were mixed in a capillary tube and then quenched 0.14 sec after mixing. Gas chromatographic analysis of the quenched reaction mixture provided a measure of the amount of carbinol **4** produced. By utilizing various initial concentrations of reactants, the data summarized in Table I were obtained. Among the simple kinetic expressions, which might be written for this reaction, our data fit best the simple bimolecular relationship (eq 1) rather

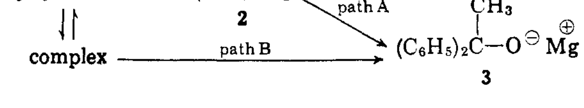
$$\text{rate} = k_2[CH_3MgCH_3][C_6H_5COC_6H_5] \qquad (1)$$

than a dependence on only the concentration of one reactant or on a higher order in one of the reactants. Although other, more elaborate kinetic expressions could probably be derived which would fit our data, we question that the quality of our data justifies such treatments. In particular, our measurements were necessarily performed under adiabatic conditions with the result that the reaction temperatures could not be controlled after the reactants were mixed.[6]

The same type of first-order kinetic dependence on each of the reactants has been observed for the reaction of dimethylmagnesium with benzophenone in tetrahydrofuran solution[2b] and with 4-methylmercaptoacetophenone.[2m] In another study of the reaction of benzophenone with dimethyl magnesium in an ether–benzene mixture,[2c] an order higher than one was suggested for the dimethylmagnesium dependence. These data, which did not appear to fit any simple kinetic relationship, suffered from several deficiencies[2b] including the use of *almost* equal concentration of reactants so that all of the rate constant calculations employed the small differences between two relatively large numbers. In all cases,[2b,c,e,i,m] there appears to be agreement that the reaction rate is dependent on both the concentration of the dialkylmagnesium and the concentration of the ketone. We believe the present data are most consistent with the presence of one molecule of the dialkylmagnesium compound and one molecule of ketone in the rate-limiting step of this addition reaction.

Even in the early discussions[3e,7] of the mechanism of addition of organomagnesium compounds to ketones, the idea was often expressed that the organometallic reagent and the ketone formed an intermediate complex which then underwent further reaction to form the alkoxide product (*e.g.*, **3**). Only very recently has there been quantitative evidence[2i–m] for the extremely rapid formation of a complex between organomagnesium reagents and ketones. Many workers[2c,2e,8] have observed the formation of transient colors which appeared to persist in reaction mixtures only as long as both unchanged organomagnesium reagent and unchanged ketone were present in the reaction. However, early claims to have isolated intermediate complexes as precipitates have been refuted.[2b,9] The general questions raised by observation of transient complexes in this reaction mixture (illustrated in Scheme II) are about the actual nature of these complexes and whether these complexes are intermediates in product formation (*i.e.*, path B) or if they are merely side equilibria competing with the formation of the product (*i.e.*, path A). Since the formation of these spectroscopically (and sometimes

SCHEME II



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[6] As a result, all of our "per cent reaction at 25°" measurements (Tables I–III) are influenced by a systematic error which causes them to be too large. The reported[2b] value of the activation energy for reaction of benzophenone with methylmagnesium bromide is 10–13 kcal/mol and the maximum temperature rise for complete reaction with solutions more concentrated than those employed in this study was 10°.[2e] From these data we estimate that none of our data is too large by more than a factor of 1.5. Since most of our measurements involved reactions which proceed only 20–40% to completion, the actual systematic error in these measurements is probably substantially smaller and remains relatively constant.

(7) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp 138–142.

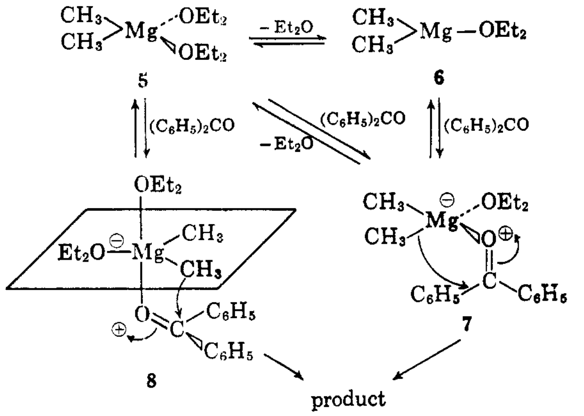
(8) (a) H. Gilman and R. E. Fothergill, *J. Amer. Chem. Soc.*, **51**, 3149 (1929); (b) R. MacLeod and coworkers, "Petroleum Research Fund Reports," 1959, p 93; 1961, p 50.

(9) D. O. Cowan and L. A. Dolak, *J. Org. Chem.*, **31**, 4296 (1966).

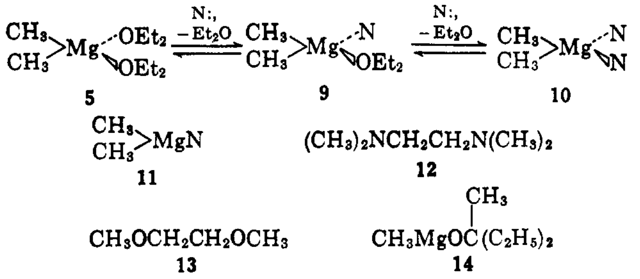
visually) observable complexes is much faster[2i–m] than the formation of addition products (*i.e.*, **3**), a rigorous differentiation between these possibilities will be exceedingly difficult.[10]

However, it did appear possible to get information about whether it was necessary to dissociate one[11] of the solvent ligands from the organomagnesium reactant[12,13] (*e.g.*, **5** → **6** → **7** in Scheme III) prior to addition. Alternative possibilities would involve formation of a pentacoordinate intermediate[14] such as **8** without loss of one of the initial solvating ligands, or the direct displacement of one of the ligands by the ketone (*i.e.*, **5** → **7**) without the intervention of the tricoordinate species **6**. We have noted earlier[4b] that the rate of exchange of alkyl groups between two different dialkylmagnesium derivatives can be retarded substantially by the addition of materials which are better donor ligands than diethyl ether. Addition of the same materials has been found to enhance the rate of reaction of organomagnesium compounds with alkyl halides,[15] and to retard the rate of abstraction of the acidic hydrogen atom from terminal acetylenes.[16]

SCHEME III



SCHEME IV



The addition of these donor ligands (*e.g.*, N: in Scheme IV) presumably favors the formation of coordination complexes such as **9** and **10** and reduces the probability of forming tricoordinated magnesium species such as **6** and **11**. In the case of certain bidentate ligands such as **12** and **13** it has been possible to isolate crystalline complexes corresponding to structure **10** from ether solutions.[13a,17] It appears reasonable to expect that reactions which require prior dissociation of one of the ligands bound to magnesium will be retarded by the presence of these good donor ligands since the concentration of partially coordinated forms such as **6** and **11** will be lowered. Reactions which do not require such prior dissociation may be accelerated by such ligands especially in cases where the C–Mg bond is undergoing heterolytic cleavage in the sense that $\text{Mg–CH}_3 \rightarrow \text{Mg}^{\oplus}\text{CH}_3^{\ominus}$.

With this view in mind we have examined the effect on the rate of addition of excess dimethylmagnesium to benzophenone in ether solution, when a number of additives have been added in concentrations comparable to the concentration of the organometallic reagent. The data are summarized in Table II along with the corresponding data for the reaction with methylmagnesium bromide and with the previously studied[4b,18] methylmagnesium alkoxide **14**.

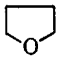
In general, the donor ligands studied fell into three classes. The ligands **15–20**, which probably all function as monodentate ligands under the conditions studied,[19] had little if any effect when only 1–2 mol of the material was present per mole of the magnesium reagent. Although the addition of a 50- to 100-fold excess of tetrahydrofuran did retard the rate of addition significantly,[2j] it is not clear how much of this effect is to be attributed to a change in the bulk properties of the solvent, rather than to a change in the donor ligands surrounding magnesium. The second group of additives studied, **21–24**, had various effects (see Experimental Section) but all suffered from the defect that insoluble materials were formed when these materials were added to ethereal solutions of dimethylmagnesium. Consequently, we were unable to examine the effects of these materials over a useful range of

CH_3OCH_3

15

$CH_3C(CH_2OCH_3)_3$

16



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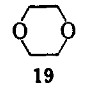
$(C_2H_5)_3N$

18



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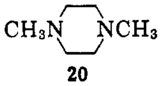

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(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, pp 127–194.

(11) W. French and G. F. Wright [*Can. J. Chem.*, **42**, 2474 (1964)] have presented evidence that at least one ether ligand is present in the transition state by demonstrating induced asymmetry in the product from dimethylmagnesium and benzaldehyde when an optically active ether was used as part of the solvent.

(12) The presently available X-ray data suggest that each magnesium atom in organomagnesium reagents is normally surrounded by four ligands arranged tetrahedrally around the metal atom. See (a) E. Weiss, *J. Organometal. Chem.*, **2**, 314 (1964); (b) G. Stucky and R. E. Rundle, *J. Amer. Chem. Soc.*, **85**, 1002 (1963); **86**, 4821, 4825 (1964); (c) L. J. Guggenberger and R. E. Rundle, *ibid.*, **86**, 5344 (1964).

(13) The stoichiometries and molecular weights of the amine and ether complexes derived from organomagnesium compounds are also consistent with the idea that these substances are normally tetracoordinate: (a) G. E. Coates and J. A. Heslop, *J. Chem. Soc., Sect. A*, 26 (1966); (b) G. E. Coates and D. Ridley, *J. Chem. Soc.*, 56 (1967).

(14) Although the organomagnesium compounds appear normally to exist as tetracoordinate species[12,13] the existence of hexacoordinate derivatives of magnesium with octahedral symmetry has been demonstrated for the magnesium halide hexahydrates [R. W. G. Wyckoff, "Crystal Structures," Vol. 3, 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1965, p 785] and suggested for the magnesium cation solvated with methanol [S. Nakamura and S. Meiboom, *J. Amer. Chem. Soc.*, **89**, 1765 (1967)]. In an oxymagnesium bromide–ether complex, each magnesium atom is pentacoordinate (ref 12b). Also the magnesium atom in porphyrins is believed to be pentacoordinate: J. N. Phillips, "Comprehensive Biochemistry," Vol. 9, M. Florkin and E. H. Stotz, Ed., Elsevier Publishing Co., New York, N. Y., 1963, pp 34–72.

(15) (a) L. I. Zakharkin, O. Y. Okhlobystin, and B. N. Strunin, *J. Organometal. Chem.*, **4**, 349 (1965); (b) L. I. Zakharkin, O. Y. Okhlobystin, and K. A. Bilevitch, *Tetrahedron*, **21**, 881 (1965); (c) H. F. Ebel and R. Schneider, *Angew. Chem. Intern. Ed. Engl.*, **4**, 878 (1965).

(16) J. H. Wotiz and G. L. Proffitt, *J. Org. Chem.*, **30**, 1240 (1965).

(17) L. I. Zakharkin, *J. Gen. Chem., USSR*, **34**, 3166 (1964).

(18) H. O. House and W. L. Respess, *J. Org. Chem.*, **30**, 301 (1965).

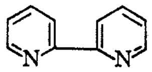
(19) We presume that for reasons of unfavorable geometry the triether **16** and the heterocycles **19** and **20** are not apt to function as bidentate ligands when an excess of a second donor solvent, diethyl ether, is present.

TABLE II

RATES OF ADDITION OF METHYLMAGNESIUM DERIVATIVES TO BENZOPHENONE IN THE PRESENCE OF VARIOUS ADDITIVES

Organometallic reagent (concn, *M*)	Additive (concn, *M*)	Concn of benzophenone, *M*	% reaction after 0.14 sec at *ca.* 25°
Me_2Mg (0.047)[a]		0.024	22
Me_2Mg (0.047)[a]	THF (**17**, 0.047)	0.024	19[b]
	THF (**17**, 0.094)		20[b]
	THF (**17**, 0.23)		17[b]
	THF (**17**, 0.47)		16[b]
	THF (**17**, 2.3)		6[b]
	THF (**17**, 4.7)		3[b]
Me_2Mg (0.053)[a]	Me_2O (**15**, 0.051)	0.024	20[b]
	Me_2O (**15**, 0.15)		23[b]
	Me_2O (**15**, 0.20)		24[b]
Me_2Mg (0.047)[a]	Triether **16** (0.047)	0.024	20
	Triether **16** (0.094)		23
Me_2Mg (0.055)[a]		0.038	36[b]
Me_2Mg (0.055)[a]	Et_3N (**18**, 0.73)	0.038	38[b]
Me_2Mg (0.047)[c]		0.024	15
Me_2Mg (0.047)[c]	Dioxane (**19**, 0.047)	0.024	15
Me_2Mg (0.047)[c]	Diamine (**20**, 0.047)	0.024	15
Me_2Mg (0.047)[c]	Triamine **23** (0.024)	0.024	30[b,d]
	Triamine **23** (0.047)		30[b,d]
	Triamine **23** (0.094)		14[e]
Me_2Mg (0.055)[c]	Triether **22** (0.055)	0.024	17[d]
Me_2Mg (0.047)[a]	HMP (**24**, 0.023)	0.024	36
	HMP (**24**, 0.047)		56–67
	HMP (**24**, 0.070)		74[b]
	HMP (**24**, 0.094)		38–67[e]
	HMP (**24**, 0.18)		11–14[e]
$MeMgOC(CH_3)(C_2H_5)_2$[c] (0.037)		0.024	1.7
MeMgBr (0.047)		0.024	1.5
MeLi (0.050)	$MgBr_2$ (0.025)	0.024	30
MeLi (0.050)	$MgBr_2$ (0.028)	0.024	26
Me_2Mg (0.047)[a]	DME (**27**, 0.047)	0.024	29
	DME (**27**, 0.094)		29
	DME (**27**, 0.23)		45
	DME (**27**, 0.47)		54
Me_2Mg (0.047)[a]	Diamine **25** (0.012)	0.024	20
	Diamine **25** (0.023)		15
	Diamine **25** (0.037)		15
	Diamine **25** (0.047)		7
	Diamine **25** (0.094)		7
	Diamine **25** (0.23)		7
Me_2Mg (0.055)[c]	Amino ether **26** (0.055)	0.024	3[b]
	Amino ether **26** (0.11)		3[b]
Me_2Mg (0.038)[c]		0.024	13[b]
Me_2Mg (0.038)[c]	Amino ether **28** (0.018)	0.024	29[b]
	Amino ether **28** (0.028)		37[b]
	Amino ether **28** (0.038)		36
	Amino ether **28** (0.055)		45
	Amino ether **28** (0.075)		40
	Amino ether **28** (0.15)		40[b]
	Amino ether **28** (0.18)		41[b]
	Amino ether **28** (0.37)		36[b]

[a] This dimethylmagnesium solution was from preparation no. 1. [b] These data were obtained from a single run. [c] This dimethylmagnesium solution was from preparation no. 2. [d] In this experiment the reacting solutions were mixed rapidly before a precipitate began to form in the organomagnesium solution. [e] In this experiment, a precipitate began to form in the organomagnesium solution before the reactants could be mixed.



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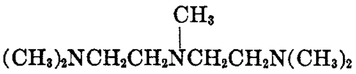
$CH_3OCH_2CH_2OCH_2CH_2OCH_3$

22



$(CH_3)_2NCH_2CH_2N(CH_3)CH_2CH_2N(CH_3)_2$

23

$[(CH_3)_2N]_3P{=}O$

24

$(CH_3)_2NCH_2CH_2N(CH_3)_2$

25

$(CH_3)_2NCH_2CH_2OCH_2CH_2N(CH_3)_2$

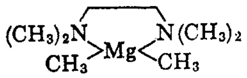
26

$CH_3OCH_2CH_2OCH_3$

27

$CH_3OCH_2CH_2N(CH_3)_2$

28



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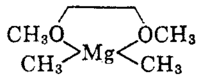

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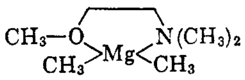

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concentrations. The final group of additives were the bidentate ligands, **25**–**28**, which differed from the earlier additives, **15**–**20**, in that the addition of 1–2 mol of these materials per mole of dimethylmagnesium had a substantial effect on the rate of addition but addition of excess material produced relatively little if any further change. These observations argue strongly, as do the isolation experiments,[13a,17] that these additives, **25**–**28**, have converted the dimethylmagnesium largely into the monomeric[13a] complexes such as **29**–**31** when even 1 molar equiv of the additive was present in ether solution. The two diamine additives **25** and **26** retarded the rate of addition by about a factor of 4 while the ethereal additives **27** and **28** accelerated the rate of addition by a factor of 2–3. The ability of added 1,2-dimethoxyethane to enhance the rate of addition of methylmagnesium bromide has been noted previously.[2p] A brief investigation (Table III) of the effect of concentration changes on the rate of addition in the presence of the amino ether **28** indicated that the reaction was still following bimolecular kinetics rather than an alternative process dependent on the concentration of only one of the reactants. In an accompanying study of the stereochemistry of the addition process,[20] the relative proportions of *cis* and *trans* isomers produced from the addition of an ethereal solution of dimethylmagnesium to the carbonyl group of 5-methyl-2-cyclohexenone were essentially the same irrespective of whether the reaction was run without an additive or in the presence of the diamine **25** or the amino ether **28**.

TABLE III

RATES OF ADDITIONS OF THE COMPLEX FROM DIMETHYLMAGNESIUM AND β-METHOXYETHYLDIMETHYLAMINE (**28**) TO BENZOPHENONE IN ETHER SOLUTION

Concn of Me_2Mg + $CH_3OCH_2CH_2N(CH_3)_2$, *M*	PhCOPh concn, *M*	% reaction after 0.14 sec at *ca.* 25°	$10^{-2}k_2$,[a] M^{-1} sec^{-1}	k_1,[b] sec^{-1}
0.038	0.024	36	1.0	1.9
0.038	0.018	39	1.1	1.5
0.038	0.012	39	1.0	0.95

[a] Rate = $k_2[Me_2Mg\ complex][C_6H_5COC_6H_5]$. [b] Rate = $k_1[Me_2Mg\ complex]$.

The foregoing data are most consistent with the idea that addition of the dimethylmagnesium to ketones follows the same general reaction path irrespective of whether the ligands bound to magnesium are two ether molecules (*i.e.*, **5**) or a bidentate ligand (*e.g.*, **29**–**31**). However, the activation energy for the transfer of a methyl group from magnesium to the carbon atom of the carbonyl group is altered by the nature of the donor ligands bound to magnesium. As a result the methyl transfer can either be accelerated or retarded when the ether ligands are replaced by other species. These observations then argue that the donor

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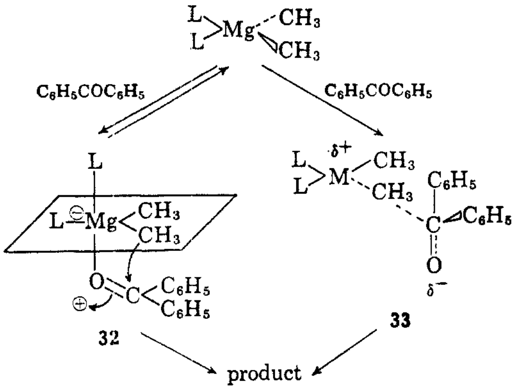
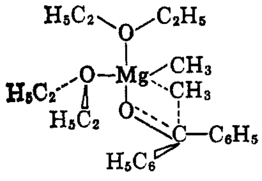
(20) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).

ligands are *not* dissociated from the magnesium prior to ketone addition (as in **5** → **6** → **7** in Scheme III) but rather that the addition involves a pentacoordinate intermediate (as in **8** and **32**), the direct displacement of a donor ligand by the ketone (*i.e.*, **5** → **7**), or the transfer of a methyl group to the carbonyl carbon atom without concurrent association of the oxygen and magnesium atoms (as in **33**). We regard the process **33** as unlikely for two reasons. In the relative nonpolar reaction medium employed, formation of the indicated alkoxide ion without aid from solvation by a second magnesium species seems unlikely. This alternative process would also suggest that the configuration of the alkyl group should be inverted during its transfer to the carbonyl carbon atom. Although we do not yet have direct evidence bearing on the stereochemical outcome of adding an alkylmagnesium reagent to a ketone, both the addition of a cyclopropylmagnesium derivative to carbon dioxide[21] and the transfer of a primary alkyl group from one magnesium atom to another[4b] are known to occur with retention of configuration. It seems likely that a comparable stereochemical result will be found for the ketone addition. Our data do not allow a choice to be made between the formation of a pentacoordinate intermediate (*e.g.*, **32**) and the direct displacement of a donor ligand to form a tetrahedral intermediate (*e.g.*, **5** → **7**). However, the observations[2i–m] indicating a rapid formation of a ketone–organomagnesium complex followed by the rate-limiting formation of the addition product appear to us to be more consistent with the formation of a pentacoordinate intermediate such as **32** in which no bond breaking is required. Subsequent rate-limiting decomposition of this pentacoordinate intermediate would then yield the tetracoordinate addition product.



The reasons for the differing rates of reaction (retarded with **29** and accelerated with **30** and **31**) when the bidentate complexes are employed as reactants are open to speculation. However, it is appropriate to note that in pentacoordinate transition states **34**–**36** for the transfer of a methyl group to benzophenone, both the diethyl ether ligands in **34** and the relatively rigid diamine ligand in **35** have alkyl groups which may interfere sterically with the approach of the benzophenone. By contrast, the amino ether complex in **36** has a conformation in which the O-methyl group lies away from the direction of approach of the benzophenone. The same possibility exists for the 1,2-dimethoxyethane complex **30** which was also found to add to benzophenone more rapidly than the diethyl ether complex **5**.



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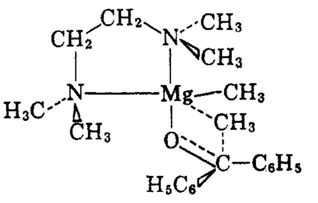

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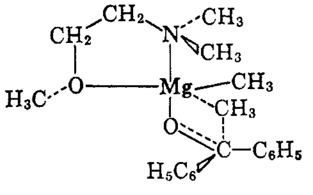

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Experimental Section[22]

Preparation of Reagents.—Ethereal solutions of dimethylmagnesium were prepared from dimethylmercury and triply sublimed magnesium and standardized by reaction with dimethylphenylsilyl chloride.[23] Ethereal solutions of methyllithium and of methylmagnesium bromide were either commercial samples or were prepared by the reaction of methyl bromide with lithium or triply sublimed magnesium and standardized by the same procedure.[23] Benzophenone was recrystallized from aqueous ethanol, dried under reduced pressure, and sublimed, mp 48–49°. Reagent samples of ether and tetrahydrofuran (**17**) were distilled from $LiAlH_4$ prior to use. 1,2-Dimethoxyethane (**27**) was refluxed with sodium overnight and then distilled and redistilled from $LiAlH_4$. N,N,N′,N′-Tetramethylethylenediamine (**25**) was distilled and then redistilled from $LiAlH_4$, bp 120–121°. Hexamethylphosphoramide (**24**) was stirred over molecular sieves (Linde type 4A) for 2 days, and then filtered, stirred with sodium overnight, and distilled under reduced pressure, bp 67° (0.6 mm). Bis(N,N-dimethylaminoethyl) ether (**26**, obtained from Union Carbide Chemicals Corp., Charleston, W. Va.) was stirred overnight with BaO and then distilled, bp 77–78° (12–13 mm). A sample of the triamine **23** was distilled, from $LiAlH_4$ and then redistilled, bp 80° (12 mm). The triether **22** was stirred successively over KOH and BaO and then distilled and redistilled from $LiAlH_4$, bp 65° (20 mm). N,N′-Dimethylpiperazine (**20**) was distilled from $LiAlH_4$, bp 128–130°. Dioxane (**19**) was refluxed over KOH, distilled, and redistilled from $LiAlH_4$, bp 100.5°. The material was degassed by five cycles of freezing and thawing at 0.1 mm and then used promptly. 2,2′-Bipyridyl (**21**) was crystallized from hexane and then dried under reduced pressure, mp 70.5–71°. Triethylamine (**18**) was distilled from $LiAlH_4$, bp 88–89.5°. Dimethyl ether was distilled from a commercial cylinder (Matheson) into a cold trap under a nitrogen atmosphere.

A mixture of 100 ml of aqueous 37% formaldehyde and 100 ml of aqueous 90% formic acid was added, dropwise and with stirring, to 25.0 g of 2-methoxyethylamine. The exothermic reaction which occurred during the addition was moderated with an ice bath. After the addition was complete, the mixture was heated on a steam bath overnight and then 25 ml of concentrated aqueous HCl was added and the mixture was concentrated under reduced pressure. The residual crude amine hydrochloride (55.8 g of yellow oil) was mixed with 200 ml of saturated aqueous K_2CO_3 and continuously extracted with pentane. The pentane extract was dried, concentrated, and distilled to separate 21.3 g

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[21] H. M. Walborsky and A. E. Young, *J. Amer. Chem. Soc.*, **86**, 3288 (1964).

[22] All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The nmr spectra were determined at 60 Mc with a Varian Model A-60 nmr spectrometer. The chemical shift values are expressed either in cycles per second (cps) or δ values (ppm) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a Hitachi (Perkin-Elmer) mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates. All transfers and reactions of organometallic reagents were performed under a nitrogen atmosphere.

[23] H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965).

(63%) of the amino ether **28** as a colorless liquid, bp 98–100°. Redistillation from $\mathrm{LiAlH_4}$ afforded the pure[24] **amino ether 28:** bp 98–100°; $n^{26}\mathrm{D}$ 1.3972; nmr ($\mathrm{CDCl_3}$), δ 3.47 (2 H triplet, J = 5.5 cps, $\mathrm{CH_2{-}O}$), 3.35 (3 H singlet, $\mathrm{CH_3O}$), 2.48 (2 H triplet, J = 5.5 cps, $\mathrm{CH_2{-}N}$), and 2.27 (6 H singlet, $\mathrm{CH_3N}$); mass spectrum, molecular ion, *m/e* 103, abundant fragment peaks, *m/e* 58, 45, and 42.

Anal. Calcd for $\mathrm{C_5H_{13}NO}$: C, 58.21; H, 12.70; N, 13.58. Found: C, 58.33; H, 12.61; N, 13.35.

A mixture of 90.0 g (0.751 mol) of 1,1,1-tris(hydroxymethyl)ethane, 57.5 g (2.50 mol) of sodium hydride (from washing an oil dispersion with pentane), and 1500 ml of tetrahydrofuran was heated under reflux for 12 hr. To the resulting suspension was added, dropwise and with stirring, over a 6-hr period, 400 g (2.85 mol) of methyl iodide. The resulting mixture was stirred at room temperature for 140 hr and then filtered and the residue was washed with tetrahydrofuran. The combined filtrates were concentrated under reduced pressure and the residue was dissolved in 500 ml of pentane and again filtered to remove additional amounts of NaI which separated. After this filtrate had been concentrated, the residual yellow liquid (104 g) was distilled from $\mathrm{LiAlH_4}$ to separate 97.2 g (80%) of **1,1,1-tris(methoxymethyl)ethane** (16)[25] as a colorless liquid: bp 61–62° (13 mm), $n^{26}\mathrm{D}$ 1.4701; nmr ($\mathrm{CCl_4}$), δ δ 3.22 (9 H singlet, $\mathrm{OCH_3}$, 3.12 (6 H singlet, $\mathrm{O{-}CH_2}$) and 0.84 (3 H singlet, $\mathrm{CH_3{-}C}$); mass spectrum, weak molecular ion peak at *m/e* 162, abundant fragment peaks, *m/e* 85, 75, 71, 55, and 45.

Anal. Calcd for $\mathrm{C_8H_{18}O_3}$: C, 59.23; H, 11.18. Found: C, 59.11; H, 10.99.

Procedure for Kinetic Studies.—An ether solution (*ca.* 19 ml) containing known concentrations of benzophenone and phenanthrene (an internal standard for gas chromatographic analysis) was mixed with an ether solution (20.0 ml) containing known concentrations of dimethylmagnesium and any additives under a positive nitrogen pressure of 5 cm of Hg in the previously described[2e,2p] flowing-stream reactor fitted with a 30-cm reaction tube. The volumes of solution were adjusted so that an excess of the organometallic solution was always present. Control experiments established that the changes in viscosity (and corresponding changes in flow rate and mixing ratio) caused by the concentrations of reactant and additives we employed were less than the experimental error of our analytical method and could be neglected. Repetition of previously described[2e,p] calibration procedures established the flow rate (11.7 ml/sec), the mixing ratio, and the reaction time (0.14 sec) for all of the rate measurements made. The temperature of the initial reaction solutions before mixing were brought to 22–26°, but no effort was made to thermostat the flowing-stream apparatus. The reaction mixtures were quenched in cold (0–5°) aqueous methanol (3:4 v/v) and the resulting solutions were mixed with saturated, aqueous $\mathrm{NH_4Cl}$ to cause separation of the ether phase. The aqueous phase was extracted with ether and the combined ether solutions were washed with aqueous NaCl, dried, and concentrated under reduced pressure to a volume of 4–5 ml. After these concentrated solutions had been mixed with *ca.* 1 mg of *p*-toluenesulfonic acid and *ca.* 0.1 g of $\mathrm{CaSO_4}$ to adsorb any residual water, the solutions were analyzed by gas chromatography[26] employing equipment which had been calibrated with known mixtures of authentic samples. As demonstrated previously,[4b] the diphenylmethylcarbinol (4) present in the reaction mixtures was converted quantitatively into 1,1-diphenylethylene when the acidified reaction mixture was injected into the heated inlet system of the gas chromatograph. The retention times of the components being analyzed follow: 1,1-diphenylethylene, 2.8 min; benzophenone, 8.4 min; and phenanthrene, 15.6 min. Benzhydrol (corresponding retention time 18 min) was not detected in any of the reactions. The average analytical values from three gas chromatograms were employed for each run. In all cases the material balances exceeded 95% and control experiments demonstrated that the quenching, isolation, and analysis procedures did not alter the composition of known mixtures of authentic samples. The "per cent reaction" figures listed in Tables I, II, and III were obtained by dividing the corrected area of the diphenylethylene peak by the total corrected area of the diphenylene and benzophenone peaks. Unless otherwise noted, all of the "per cent reaction" values listed in Table II are average values from duplicate runs which agreed with one another to within 3% or less. The estimated errors in measuring volumes and concentrations of reaction solutions are 3% or less. The molar concentrations of reactants listed in Tables I, II, and III refer to the initial concentrations of reactants after the solutions have been mixed. The extent of reaction in the standard reactions of dimethylmagnesium with benzophenone in ether solution were found to vary somewhat with different lots of dimethylmagnesium. This effect presumably arose because the different lots of reagent contained slightly different amounts of alkoxide impurities. Although a single lot of dimethylmagnesium was used for all of the concentration studies listed in Tables I and III, two different lots of reagent were used for the data listed in Table II. A set of standard reactions (dimethylmagnesium plus benzophenone in ether) was run for each lot of dimethylmagnesium. Data concerned with the effect of additives should be compared with the standard reaction utilizing the same lot of dimethylmagnesium. The methylmagnesium 3-methyl-3-pentoxide solutions were prepared by the addition of 3-methyl-3-pentanol to an ether solution containing an equimolar amount of dimethylmagnesium as previously described.[4b]

Because of the immediate formation of a light orange-brown precipitate when 2,2′-bipyridyl (21) was mixed with ethereal dimethylmagnesium no rate measurements were possible with this additive. The slower formation of precipitate with the additives **22–24** permitted us to obtain crude estimates of their effect which are summarized in Table II. The results with hexamethylphosphoramide varied substantially depending on whether the formation of a precipitate had started before the solutions of benzophenone and the methylmagnesium derivative were mixed. In general the addition of 0.5–1.5 molar equiv of the phosphoramide to an ethereal solution resulted in the slow separation of a white solid. Addition of 2 molar equiv of the phosphoramide resulted in the rapid separation of a white solid. Collected samples of this white solid did not melt below 350° and were insoluble in water, tetrahydrofuran, and hexamethylphosphoramide but did dissolve in dilute, aqueous HCl.[27] No precipitate was observed after several hours when equal volumes of hexamethylphosphoramide and ethereal 0.46 *M* dimethylmagnesium were mixed. Several runs were made with organometallic reagents prepared from 2 molar equiv of ethereal methyllithium and 1 molar equiv of anhydrous magnesium bromide since earlier experiments[4b] suggested that the reagent formed in this mixture was equivalent to dimethylmagnesium. The reagent prepared in this fashion appears to be slightly more reactive than an equivalent concentration of ethereal dimethylmagnesium which is free from lithium bromide.

Preparation of Complexes from Dimethylmagnesium. A. With N,N,N′,N′-Tetramethylethylenediamine (25).—Following the previously described procedure,[13a] a solution of 3.2 mmol of dimethylmagnesium in 5.0 ml of ether was treated with 0.60 ml (*ca.* 6 mmol) of the diamine **25** and the resulting solution was concentrated to dryness under reduced pressure. Sublimation of the residual white solid at 80° and 0.1 mm afforded the **complex 29** as white solid which was soluble in ether at room temperature to the extent of at least 0.5 *M*. The complex crystallized from solution when the ether solution was cooled below 0°. However, solutions of the complex in chlorobenzene[28] could be cooled to *ca.* −60° without separation of the complex from solution. The nmr spectrum of a chlorobenzene solution of the complex **29** at *ca.* 30° exhibited, in addition to solvent absorption, two singlets at δ 1.97 ($\mathrm{CH_3N}$ and $\mathrm{CH_2N}$) and −1.30 (78 cps above TMS, $\mathrm{CH_3Mg}$) in a ratio of about 8:3. For comparison, the spectrum of a chlorobenzene solution of the diamine **25** exhibited two singlets (separation 11.5 cps) at δ 2.22 (4 H, $\mathrm{CH_2N}$) and 1.95 (12 H, $\mathrm{CH_3N}$). The nmr spectrum of the diamine solution was essentially the same at *ca.* 30° and at *ca.* −63°. A cold (−54°) solution of the complex **29** in chlorobenzene retained the highfield singlet attributable to the $\mathrm{CH_3{-}Mg}$ protons. However, the signal for the $\mathrm{CH_2N}$ and $\mathrm{CH_3N}$ protons separated into two singlets separated by 4.5 cps with the higher field peak being of lower intensity. These peaks may represent the separate signals for

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[24] A gas chromatographic column packed with 1,2,3-tris(β-cyanoethoxy)propane (TCEP) suspended on Chromosorb P was employed for this analysis.

[25] The preparation and characterization of this substance was performed in our laboratories by Mr. W. F. Fischer, Jr.

[26] A gas chromatographic column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis.

[27] This material may be the insoluble, presumably polymeric bisdimethylaminomagnesium described previously by Coates and Ridley.[13b]

[28] The complex was previously reported[13a] to give monomeric solutions in benzene.

the CH_2N and CH_3N protons which are no longer accidentally equivalent at low temperatures. A chlorobenzene solution containing approximately equimolar amounts of the diamine **25** and the complex exhibited, in addition to solvent absorption and the high field singlet for the CH_3–Mg protons, two singlets (separation 5 cps) with the higher field absorption being the more intense as would be expected if the free diamine **25** were exchanging rapidly with the diamine in the complex **29**. This pattern persisted down to *ca.* −30°. Below this temperature the less intense, lower field peak broadened. However, at no point down to −63°, was there evidence for two different sets of peaks attributable to free and complexed diamine. We therefore concluded that exchange of this ligand on dimethylmagnesium is relatively rapid at or above −30°.

The diamine complex **29** was also prepared from methylmagnesium bromide by the following procedure. To 50 ml of an ethereal solution containing 0.15 mol of methylmagnesium bromide was added 15 ml (0.18 mol) of dioxane. The resulting mixture was diluted with 50 ml of ether and stirred at room temperature for 30 min after which the ether solution was separated from the insoluble dioxane complex by filtration through a filter stick. The residual solid was washed with ether and the combined ether filtrates were treated with 12 ml (*ca.* 0.1 mol) of the diamine **25**. The resulting solution was concentrated under reduced pressure and the residual white solid was sublimed (0.1–0.2 mm and 80–100°) to separate 2.4 g (21%) of the diamine complex **29**, mp 94.5–96.5° in a sealed evacuated tube (lit.[13a] mp 97–98°). This complex appears not to decompose at its melting point since the resolidified sample from the melting point determination had the same melting point as the original sample.

B. **With 1,2-Dimethoxyethane (27).**—A solution prepared from 3.2 mmol of dimethylmagnesium and 1.0 ml of 1,2-dimethoxyethane in 5.0 ml of ether was cooled in a Dry Ice–acetone bath and then allowed to warm to room temperature. Once crystallization of the complex **30** had been initiated at low temperatures, it continued at room temperature in agreement with an earlier report.[13a] The solid was separated (centrifugation followed by removal of the supernatant liquid through a cannula), washed with a 5-ml portion of ether, and then dried under reduced pressure. During this drying process partial decomposition of the complex appeared to occur. The portion of the residue which was still soluble was taken up in benzene[28] for nmr examination. Apart from absorption attributable to benzene and small amounts of ether, the sample exhibited singlets at δ 3.21 (OCH_2), 3.12 (OCH_3), and −0.90 (54 cps above TMS, CH_3–Mg). The ratio of peak areas corresponded approximately to the 1:1 complex **30**. For comparison, the nmr spectrum of a benzene solution of 1,2-dimethoxyethane has singlets at δ 3.37 (OCH_2) and 3.18 (OCH_3).

C. **With β-Methoxyethyldimethylamine (28).**—To 4.4 ml of an ether solution containing 2.8 mmol of dimethylmagnesium was added 0.55 ml (5 mmol) of the methoxyamine **28** and the resulting solution was concentrated to dryness under reduced pressure. The residual crystalline complex **31** was soluble in ether at room temperature to the extent of at least 0.5 *M* but crystallized from solution when the solution was cooled below 0°. Attempts to sublime the complex at 80–90° and 0.08 mm were not successful; the complex appeared to dissociate leaving polymeric dimethylmagnesium behind in the manner noted previously[13a] for the 1,2-dimethoxyethane complex **30**. A chlorobenzene solution of the amino ether complex **31** has nmr signals at δ 3.28 (2 H triplet, J = 5.5 cps, CH_2O), 3.21 (3 H singlet, CH_3O), 2.31 (2 H triplet, J = 5.5 cps, CH_2N), 2.12 (6 H singlet, CH_3N) and −1.25 (75 cps above TMS, 6 H singlet, CH_3Mg). For comparison, a chlorobenzene solution of the amino ether **28** has nmr peaks at δ 3.39 (2 H triplet, J = 6 cps, CH_2O), 3.22 (3 H singlet, OCH_3), 2.41 (2 H triplet, J = 6 cps, CH_2N), and 2.17 (6 H singlet, CH_3N).

Registry No.—Dimethylmagnesium, 2999-74-8; benzophenone, 119-61-9; **16**, 15476-20-7; **25**, 110-18-9; **28**, 3030-44-2; **29**, 15405-88-6; **30**, 15405-89-7; **31**, 15405-87-5.

Acknowledgments.—The authors are indebted to Dr. Francis Johnson of the Dow Chemical Co. for a generous sample of triply sublimed magnesium, to the Union Carbide Chemicals Co. for a sample of bis (N,N-dimethylaminoethyl) ether, and to Professor Stanley G. Smith for providing us with a preprint of his manuscript prior to publication.

The Chemistry of Carbanions. XV. The Stereochemistry of Alkylation of 4-*t*-Butylcyclohexanone[1a]

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Alkylation of the enolate anion 1 of 4-*t*-butylcyclohexanone with triethyloxonium fluoroborate yielded a mixture of O-alkylated product and a mixture of approximately equal amounts of the stereoisomeric 2-ethyl-4-*t*-butylcyclohexanones. A comparable mixture of C-alkylated products was obtained from reaction of the enolate anion with ethyl iodide for short periods of time. Quenching the enolate anion 1 in a mixture of deuterium oxide and deuterioacetic acid yielded a mixture of the axial deuterio ketone (*ca.* 70%) and the equatorial deuterio ketone (*ca.* 30%). These results are interpreted as evidence that the transition states for alkylation and protonation have geometries resembling the enolate anion 1 rather than the products.

With specific methods in hand for generating the enolate anions of simple ketones,[2] we were interested in examining the preferred direction of alkylation of an enolate anion derived from a simple cyclohexanone.[3,4] For this purpose we elected to study the alkylation and the protonation of the enolate anion **1** derived from 4-*t*-butylcyclohexanone (**2**). Solutions of this enolate anion **1** in 1,2-dimethoxyethane (DME) were obtained either by reaction of the ketone **2** with triphenylmethyllithium or by reaction of the enol acetate **3** with 2 equiv of methyllithium. The latter

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[2] (a) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); (b) H. O. House and B. M. Trost, *ibid.*, **30**, 1341, 2502 (1965).

[3] For recent reviews of the stereochemistry of C alkylation, see (a) L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965); (b) J.-M. Conia, *Rec. Chem. Progr.* (Kresge-Hooker Sci. Lib.), **24**, 43 (1963).

[4] For recent studies pertinent to the stereochemistry of alkylation of simple cyclohexanone derivatives, see (a) R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 1194 (1958); (b) E. J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 3476 (1960); C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *ibid.*, **83**, 4433 (1961); M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967); (c) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **84**, 2611 (1962); (d) J. M. Conia and P. Briet, *Bull. Soc. Chim. Fr.*, 3881, 3888 (1966).