Organometallic Reaction Mechanisms. 17. Nature of Alkyl Transfer in Reactions of Grignard Reagents with Ketones. Evidence for Radical Intermediates in the Formation of 1,2-Addition Product Involving Tertiary and Primary Grignard Reagents

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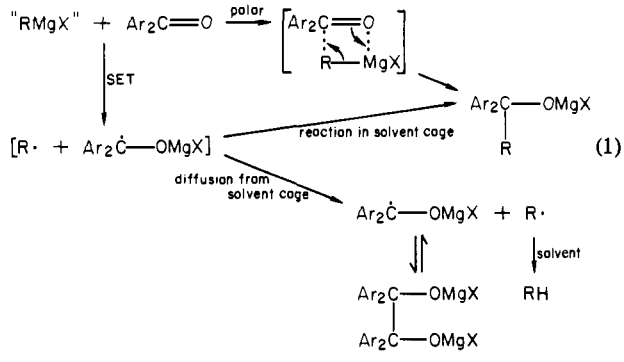
Abstract: When a Grignard reagent reacts with an aromatic ketone, a radical anion–radical cation pair is formed which can collapse to give 1,2-addition product or dissociate to form a radical anion and a free radical within the solvent cage which in turn can collapse to 1,2-addition product or a conjugate addition product or escape the solvent cage to form pinacol. The 1,2-addition products, which form after dissociation of the radical anion–radical cation pair, show free-radical character as indicated by the cyclized 1,2-addition products formed from the reaction of a tertiary Grignard reagent probe with benzophenone in THF and from the reaction of a primary Grignard reagent probe (neooctenyl Grignard reagent) with benzophenone in ether. The 1,6-addition products, which come about after dissociation of the radical anion–radical cation pair, show free-radical character as evidenced by the cyclized 1,6-addition products formed in all of the reactions which involve the tertiary probe Grignard reagent (in all solvents studied) with benzophenone and 2-MBP and also in the reaction of the neooctenyl probe Grignard reagent with 2-MBP.

The reaction of Grignard reagents with organic substrates (particularly ketones) is well recognized as a very important reaction in synthetic organic chemistry, yet the mechanism of this reaction is not completely understood. Questions concerning the nature of the Grignard reagent solution,[1] the identification of the reactive species,[2] and the kinetic order of the reactive organomagnesium species[3] have been satisfactorily answered over the past several years. At this time the description of the alkyl transfer from the Grignard reagent to the carbonyl carbon atom, i.e., whether alkyl transfer proceeds by a polar or a single-electron-transfer (SET) mechanism, is the most significant question that remains to be answered.

In 1968, Blomberg and Mosher presented evidence supporting a SET pathway to describe the reaction of a Grignard reagent with a ketone.[4] In the reaction of "neopentylmagnesium chloride" with benzophenone in THF, not only did they observe 1,2-addition but also they isolated benzopinacol and neopentane, both in 20% yield. Presumably the neopentane arose from hydrogen abstraction from the solvent by a neopentyl radical. In this study, Blomberg and Mosher also reported the observation of an ESR signal which they assigned to a ketyl. They suggested a mechanism similar to eq 1 which included both polar and SET pathways as operative in the reaction.



(1)

Fauvarque has studied the reaction of R_2Mg compounds with fluorenone and benzophenone in various solvents.[5] His ESR observations indicate that ketyl concentration depends on the polarity of the solvent and the ability of the alkyl group to stabilize the radical. Significant amounts of ketyl were observed when dibenzylmagnesium was allowed to react with fluorenone in HMPA; however, the same reaction in ether showed only a trace of ketyl to be present. The proposed SET mechanism is similar to that shown in eq 1.

More recently, Holm and Crossland have presented convincing evidence for the rate-determining SET step in the reaction of "*t*-C_4H_9MgCl" with benzophenone in diethyl ether.[6] In reactions with various substituted benzophenones, they obtained pinacol, 1,2-, 1,4-, and 1,6-addition products. For all of these reactions, however, the Hammett plot of relative rate vs. σ (substituent constant) gave a straight line (even when the substituted benzophenone had two or three ortho methyl groups). In similar reactions using "CH_3MgBr", the presence of only one ortho methyl group on benzophenone caused significant deviation from the linear free-energy relationship. On the basis of the above and several other pieces of evidence, they proposed that the rate-determining step for the reaction of "*t*-C_4H_9MgCl" with benzophenone involves SET to give an intermediate common to all products (similar to eq 1). The SET is then followed by one or more steps to give the observed products. On the other hand, they considered it likely that the reaction of "CH_3MgBr" with benzophenone proceeds through a polar pathway.

Results and Discussion

Holm and Crossland[6] have presented convincing evidence for a rate-determining single-electron-transfer (SET) step (similar to eq 1) in the reaction of "*t*-BuMgCl" with benzophenone in diethyl ether involving the intermediate formation of a "free" radical and radical anion. The ability to "trap" or "observe" the intermediate radical or radical anion would be instrumental in establishing the integrity of the proposed mechanism.

With this in mind, radical probes were incorporated into the R group of Grignard reagents such that free radical character could be observed as isomerization or cyclization of the particular probe. If cyclization or isomerization of the probe takes place,

(1) E. C. Ashby, *Bull. Soc. Chem. Fr.*, 2133 (1972).
(2) E. C. Ashby, J. Laemmle, and M. H. Neumann, *J. Am. Chem. Soc.*, **94**, 5421 (1972).
(3) E. C. Ashby, Li-Chung Chao, H. M. Neumann, and J. T. Laemmle, *Acc. Chem. Res.*, **7**, 272 (1974).
(4) C. Blomberg, R. M. Sallinger, and H. S. Mosher, *J. Org. Chem.*, **34**, 2385 (1969).
(5) J. F. Fauvarque and E. Rouget, *C. R. Hbed. Seances Acad. Sci., Ser. C*, **267**, 1355 (1968).
(6) T. Holm and I. Crossland, *Acta Chem. Scand.*, **25**, 59 (1971).

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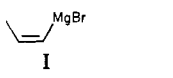
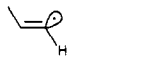
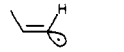
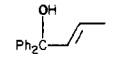
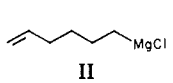
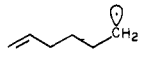
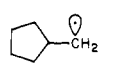
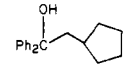
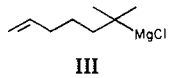
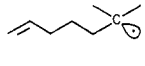
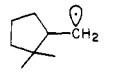
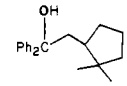
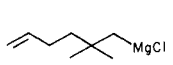
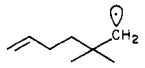
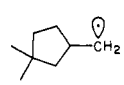
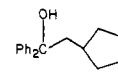
Table I. Grignard Reagent Free-Radical Probes

Grignard probes	intermediate radical	isomerized or cyclized radical	expected product[a]
 I			
 II			
 III			
 IV			

[a] Expected 1,2-addition product with $Ph_2C{=}O$ for set process.

Table II. Products from the Reaction of Propenylmagnesium Bromide with Benzophenone

expt no.	propenyl Grignard isomer ratio cis	trans	[Fe], ppm	G/K ratio	total carbinol[a]	products pinacol[a]	cis carbinol[b]	trans carbinol[b]
1	95	5	0	0.5	100	0	95.0	5.0
2	60	40	0	0.5	100	0	60.7	39.3
3	29	71	0	0.5	100	0	29.3	70.7
4	95	5	0	1.5	100	0	91.6	8.4
5	95	5	4000	1.5	93.6	6.4	90.8	9.2
6	60	40	0	1.5	100	0	43.3	56.7
7	60	40	4000	1.5	93.5	6.5	41.8	58.2
8	29	71	0	1.5	100	0	18.7	81.3
9	29	71	4000	1.5	92.7	7.3	20.0	80.0

[a] Normalized as 100% = % total carbinol + % pinacol. [b] Normalized as 100% = % *cis*-carbinol + % *trans*-carbinol.

then of course the existence of the R group of the Grignard reagent as a free radical is implied. On the other hand if cyclization or isomerization of the probe does not take place, one cannot dismiss the possibility of a SET process involving a free radical since the rate of coupling of the free radical with the radical anion could be significantly greater than the rate of cyclization or isomerization of the probe. This is not an unlikely possibility since the coupling of a primary alkyl free radical with a ketyl is speculated to take place very rapidly (10^7–10^9 L mol^{-1} s^{-1}) and probes which isomerize or cyclize at this rate are rare. The radical probes studied are illustrated in Table I.

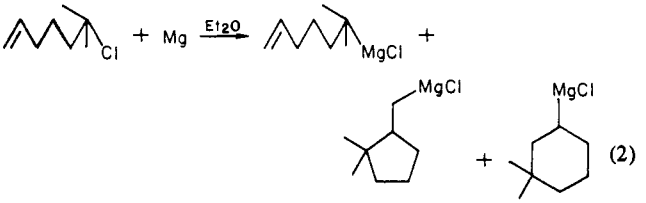
***cis*-Propenylmagnesium Bromide (I) (A Vinyl Grignard Probe).** Should the R group of *cis*-propenylmagnesium bromide (a vinyl Grignard probe) become a free radical during the course of a reaction, the *cis*-propenyl radical would isomerize ($K_{inversion} \simeq 10^8$ s^{-1})[7] to the thermodynamically more stable *trans*-propenyl radical, resulting in a product with *trans* stereochemistry (Table I). Since coupling of the free radical with the radical anion probably takes place at a comparable rate to that of isomerization (10^8), a lack of isomerization of the probe should be an indication that the reaction is not proceeding via an SET mechanism.

Three propenyl Grignard reagents of different cis/trans ratios were allowed to react with benzophenone (Table II). Reactions carried out in excess ketone do not result in isomerization of the propenyl group as is evidenced by the fact that the starting Grignard reagent cis/trans ratio was exactly reflected in the reaction products. The apparent slight degree of isomerization observed when the reactions are carried out in excess Grignard reagent can be explained by the relative reactivities of the cis and trans isomers. It was found that the trans isomer reacted about twice as fast as the cis isomer with benzophenone. The only effect produced by doping the reactions with iron salts was the formation of small amounts of pinacol; the alkylation product cis/trans ratios were unaffected.

5-Hexenylmagnesium Chloride (II) (A Primary Alkyl Grignard Probe). Should the R group of 5-hexenylmagnesium chloride (II) become a "free" radical during the course of a reaction, the 5-hexenyl radical (a primary alkyl radical) would cyclize ($K_{cyc} = 10^5$ s^{-1})[8-10] predominantly to the cyclopentylmethyl radical and to a minor extent to the cyclohexyl radical, resulting in products with cyclic R groups. When II (primary Grignard probe) was allowed to react with benzophenone in ether, only a straight-chain 1,2-addition product (51%) and benzhydrol (49%) were observed. The benzhydrol was apparently produced by β-hydrogen reduction of benzophenone by the Grignard reagent. This reaction was further investigated by using a sterically hindered ketone (2-methylbenzophenone) (2-MBP) and a more strongly coordinating solvent (THF) in the hope of slowing down the 1,2-addition (radical–radical anion coupling) process such that cyclization might be observed. In THF, 2-MBP and II gave straight-chain 1,2-addition (28%) and 2-methylbenzhydrol (88%) as products. Indeed, 1,2-alkylation was slowed down, allowing β-hydrogen reduction to become the major reaction pathway.

The absence of isomerization or cyclization in the 1,2-addition products of I (a vinylic Grignard) and II (a primary Grignard), respectively, with benzophenone indicates that either the reaction is polar or, if SET, no "free" radical is present or the rate of radical–ketyl coupling is significantly faster than the rate of isomerization or cyclization of the probe. Therefore a lack of isomerization or cyclization of the probe cannot be taken as conclusive evidence that a SET process involving a free radical is not in effect.

(1,1-Dimethyl-5-hexenyl)magnesium Chloride (III) (A Tertiary Alkyl Grignard Probe). Should the R group of 1,1-dimethyl-5-hexenylmagnesium chloride (III) (a tertiary Grignard) become a "free" radical during the course of a reaction, the 1,1-dimethyl-5-hexenyl radical would cyclize ($K_{cyc} \simeq 10^5$ s^{-1})[8] predominantly to the (2,2-dimethylcyclopentyl)methyl radical, resulting in products with cyclic R groups. Solutions of III prepared from the corresponding halide and magnesium in ether (eq 2),



(2)

under the best conditions found for noncyclized products contained 38–55% of the Grignard reagent as the cyclic isomers. Thus in every reaction the excess Grignard reagent added to the ketone had to be accounted for as the hydrocarbon formed on hydrolysis such that the origin (straight-chain or cyclic Grignard reagent) of the alkylation products could be determined. When III was allowed to react with benzophenone in ether and the resulting product hydrolyzed, the hydrocarbon analysis[11,12] indicated that

(7) G. M. Whitesides and C. P. Casey, *J. Am. Chem. Soc.*, **88**, 4541 (1966).

(8) C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, **94**, 6059 (1972).
(9) D. Lal, D. Griller, S. Husband, and K. U. Ingold, *J. Am. Chem. Soc.*, **96**, 6355 (1974).
(10) P. Schmid and K. Ingold, *J. Am. Chem. Soc.*, **99**, 6434 (1977).
(11) In ref 12, 16, 18, and 21, St. Chain refers to the hydrocarbon obtained by hydrolysis of (1,1-dimethyl-5-hexenyl)magnesium chloride, Cyclo 5 refers to the hydrocarbon obtained by hydrolysis of (2,2-dimethylcyclopentyl)-methylmagnesium chloride, and Cyclo 6 refers to the hydrocarbon obtained by hydrolysis of (2,2-dimethylcyclohexyl)magnesium chloride.
(12) Millimoles of Grignard I added to the reaction and mmoles of hydrocarbons recovered from reaction:

	Grignard I added		hydrocarbon recovered	difference
St. Chain	1.22 ± 0.04	St. Chain	0.77 ± 0.02	0.45 ± 0.07
Cyclo 5	0.96 ± 0.02	Cyclo 5	0.91 ± 0.02	0.05 ± 0.04
Cyclo 6	0.10 ± 0.01	Cyclo 6	0.09 ± 0.005	0.01 ± 0.01
	2.28 ± 0.07			0.51 ± 0.12

Table III. Products from the Reaction of "CH_3MgBr" [a] with 2-MBP (0.0167 M) in the Presence or Absence of *p*-Dinitrobenzene (*p*-DNB) in Diethyl Ether at Room Temperature[18]

expt no.	["CH_3-MgBr"], M	% *p*-DNB	react time, min	% 1,2-add[b]	% pinacol	% recov ketone	% recov *p*-DNB
1	0.033	0	3	23.9	trace	76.1	
2	0.033	0	9	41.4	4.1	54.9	
3	0.033	0	16	58.6	10.5	31.0	
4	0.033	0	30	63.9	31.1	23.0	
5	0.100	17	5	57.2	0	42.8	17.8
6	0.100	17	11	79.6	0	20.4	15.6
7	0.100	17	20	91.9	0	8.1	19.4
8	0.100	17	40	98.7	0	1.3	13.9

[a] Dow doubly sublimed magnesium, but obviously contaminated by a few ppm of $FeCl_3$ or other transition-metal salt. [b] Normalized as 100% = % 1,2-addition product + % pinacol + % ketone.

almost 90% of the reaction proceeded through the straight-chain Grignard. The resulting alkylation products consisted of 61% 1,6-addition and 39% 1,2-addition product. Although very little cyclization of the probe was observed in the 1,2-addition product (2% cyclized 1,2-addition product is accounted for by the amount of cyclized Grignard reagent which reacted), 73% of the 1,6-addition product was cyclized.

The ratio of cyclized to uncyclized 1,6-addition products (73:27) established the radical nature of the 1,6-addition process (heretofore *assumed* to be a radical process) and indicated that the rate of probe cyclization is comparable to the rate of 1,6-addition product formation. It is important to note that the ratio of 1,6-addition to 1,2-addition products (61:39) indicates that the rate of formation of 1,6-addition product is faster than the rate of 1,2-addition product formation. Thus, 1,2-addition product is being formed at a rate slower than that of cyclization of the probe, but little or no cyclization was observed in the 1,2-addition product. Since Holm's results argue against the possibility of a polar 1,2-addition reaction, the only reasonable rationalization of these findings is that, after the transfer of the electron from the Grignard reagent to the benzophenone in ether, R· of the Grignard is still tightly bound to the magnesium as a radical cation ($RMgX^{+}\cdot$). Collapse of the radical anion–radical cation pair to form 1,2-addition product would preclude cyclization.

We have also found that the radical anion as well may not be a "free ketyl" in reactions of either primary or tertiary Grignard reagents with benzophenone. Kornblum and co-workers[13] have pointed out that *p*-dinitrobenzene (*p*-DNB) is effective as a "radical anion scavenger" which can "short circuit" SET reactions. If the Grignard reaction with benzophenone involves a SET process described by eq 3, it should be possible for *p*-DNB to intervene

$$RMgX + Ph_2C{=}O \rightarrow [Ph_2\dot{C}O^{-}] + [RMgX]^{+}\cdot \rightarrow \text{products} \quad (3)$$

as described by eq 4 and 5, provided the coupling of the radical

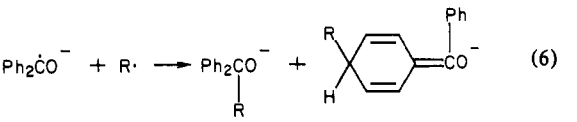
$$p\text{-DNB} + [Ph_2\dot{C}O^{-}] \rightarrow Ph_2C{=}O + [p\text{-DNB}]^{-}\cdot \quad (4)$$

$$[RMgX]^{+}\cdot[p\text{-DNB}]^{-}\cdot \rightarrow RMgX + p\text{-DNB} \quad (5)$$

anion with R· is not much faster than the rate at which [*p*-DNB] can enter into the solvent cage and react with the radical anion (eq 4).

It was determined[14] that *p*-DNB is capable of removing the electron from the ketyl radical anion to regenerate the ketone although not with 100% efficiency. A study was carried out to determine the effect of *p*-DNB on the reactions of "CH_3MgBr" and "*t*-BuMgCl" with 2-MBP.[14] From the data in Tables III and IV, it is concluded that the reaction of "CH_3MgBr" and "*t*-BuMgCl" with 2-MBP in the presence of *p*-DNB is not significantly slower than the same reaction without *p*-DNB. The important feature of this data is that *p*-DNB completely eliminates pinacol formation. The fact that *p*-DNB prevents pinacol formation but cannot trap the radical anion leading to 1,2- or 1,6-addition product is again indicative of a tight radical anion–radical cation pair in a solvent cage or that the reaction rate of radical anion coupling with R· is much faster than *p*-DNB can enter into the solvent cage and be reduced by the radical anion.

Additional evidence as to the possible "bound" nature of the R group radical and ketyl was obtained from ketyl cross over experiments. Garst and co-workers[15] have shown that benzophenone ketyl is a very effective trap for alkyl free radicals forming predominantly 1,6- and 1,2-addition products (eq 6). The reaction



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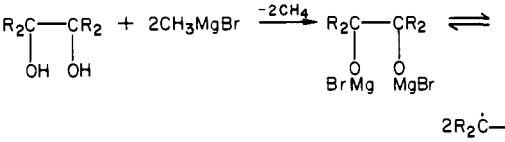
of excess Grignard reagent with pinacol produces ketyl (eq 7) but



$$2R_2\dot{C}{-}O^{-}Mg^{+}Br \quad (7)$$

does not react further.[14] The only product upon subsequent hydrolysis is the starting pinacol. Thus, by forming ketyl with an excess of Grignard reagent and then adding another ketone (eq 8, 9), it should be possible to conduct a Grignard reaction with

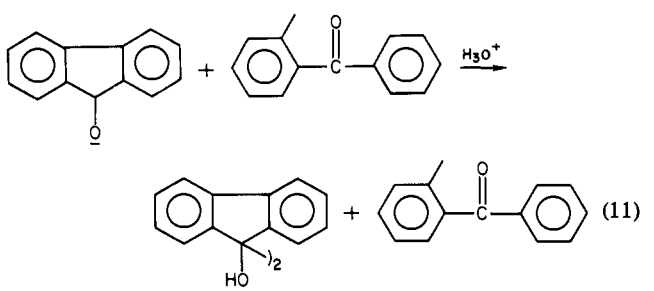
$$R_2\dot{C}{-}O^{-} + R'_2C{=}O + CH_3MgBr \rightarrow R_2\dot{C}{-}O^{-} + R'_2{-}\dot{C}{-}O^{-} + CH_3\cdot \quad (8)$$

$$R_2\dot{C}{-}O^{-} + R'_2\dot{C}{-}O^{-} + CH_3\cdot \xrightarrow{H_3O^{+}} R_2(CH_3)COH + R'_2(CH_3)COH \quad (9)$$

a ketone in the presence of a ketyl which could serve as a free radical trap. However, if the ketyl transfers an electron to the ketone, forming a new ketyl and a new ketone, an apparent and erroneous cross-over product would be indicated (eq 10). This

$$R_2\dot{C}{-}O^{-} + R'_2C{=}O \rightarrow R_2C{=}O + R'_2\dot{C}{-}O^{-} \quad (10)$$

problem is overcome by insuring that the ketone corresponding to the added ketyl (fluorenone reduction potential = 1.3 V vs. SCE) has a lower reduction potential than the ketone added to the reaction (2-MBP, reduction potential = 1.8 V vs. SCE). This was found to be the case when 2 equiv of "CH_3MgBr" were added to 1 equiv of fluorenone pinacol to produce the ketyl without an excess of Grignard (eq 7) and then 2-MBP was added. Upon subsequent hydrolysis, 2-MBP and fluorenone pinacol were the only products (eq 11). The reverse reaction, fluorenone added



(11)

to 2-MBP ketyl, also gave 2-MBP and fluorenone pinacol in 98% yield. The other 2% yield appeared to be present in the form of a mixed pinacol. Apparently when an appreciable concentration of both ketyls are present, mixed dimagnesium pinacolates form which slow down the exchange process. In any case, the important

(13) N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, **14**, 734 (1975).
(14) E. C. Ashby and T. L. Wiesemann, *J. Am. Chem. Soc.*, **100**, 189 (1978).
(15) J. F. Garst and C. D. Smith, *J. Am. Chem. Soc.*, **98**, 1520 (1976).

Table IV. Products from the Reaction of "*t*-BuMgCl" with 2-MBP (0.0167 M) in the Presence or Absence of *p*-DNB in Diethyl Ether at Room Temperature[18]

expt no.	["*t*-BuMgCl"], M	% *p*-DNB	react time, min	% 1,6-add[a]	% 1,2-add	% pinacol	% recov ketone	% recov *p*-DNB
1	0.033	0	3	71.2 (78.4)[b]	19.6 (21.6)	9.1	0	
2	0.033	0	6	76.4 (83.7)	14.9 (16.3)	8.7	0	
3	0.033	0	9	73.5 (79.7)	18.7 (20.3)	7.8	0	
4	0.033	0	18	74.2 (83.5)	14.7 (16.5)	11.2	0	
5	0.133	12.5	4	83.0	17.0	0	0	0
6	0.133	12.5	7	84.3	15.7	0	0	3.1
7	0.133	12.5	16	84.0	16.0	0	0	4.6
8	0.133	12.5	29	85.0	15.0	0	0	10.5

[a] Normalized 100% = % 1,6-addition product + % 1,2-addition product + % pinacol + % ketone. [b] Normalized 100% = % 1,6-addition product + % 1,2-addition product.

Table V. Reactions of "CH_3MgBr" and "t-C_4H_9MgCl" with 2-Methylbenzophenone in the Presence of Fluorenone Ketyl in Diethyl Ether

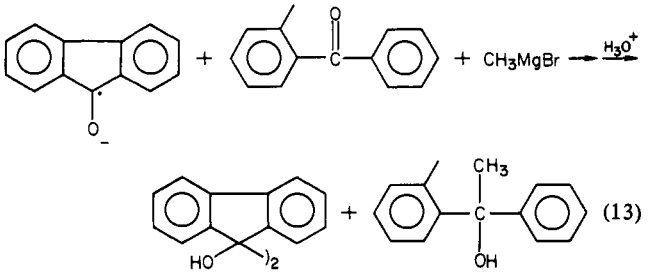
					products[a]			
expt no.	Grignard reagent	[pinacol], M	[RMgX], M	[2-MBP], M	recov ketone	2-MBP + 1,2-add	2-MBP + 1,6-add	fluorenone alkylation
1	CH_3MgBr	0.017	0.034	0.067	100	0	0	0
2	CH_3MgBr	0.017	0.050	0.067	100	0	0	0
3	CH_3MgBr	0.017	0.067	0.067	100	0	0	0
4	CH_3MgBr	0.017	0.083	0.067	95	5	0	0
5	CH_3MgBr	0.017	0.100	0.067	77	23[b]	0	0
6	CH_3MgBr	0.017	0.133	0.067	50	50[b]	0	0
7	CH_3MgBr	0.017	0.250	0.067	0	100[b]	0	0
8	*t*-BrMgCl	0.033	0.133	0.017	0	12[b]	88	0
9	*t*-BuMgCl	0.033	0.200	0.017	0	13[b]	87	0

[a] Normalized as 100% = % recovered ketone + % 1,2-addition product + % 1,6-addition product + % fluorenone alkylation. [b] Traces of 2-methylbenzopinacol present, probably from ppm of Fe present in Mg from which Grignard reagent was prepared.

result is that no 2-MBP ketyl was formed in the reaction of 2-MBP with fluorenone ketyl. Thus, we postulated that if the Grignard reaction involves the SET process described by eq 12, it should

$$RMgX + Ph_2C{=}O \rightarrow Ph_2\dot{C}{-}O^{-}\overset{+}{M}gBr + R\cdot \rightarrow \text{product} \quad (12)$$

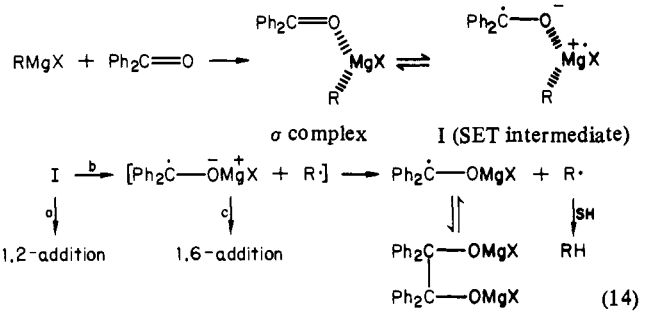
be possible for fluorenone ketyl to intercept some of the R group radicals (especially those generated in forming 1,6-addition products with 2-MBP) to form fluorenone addition products as described (eq 9), provided the subsequent coupling of R· and the ketyl is not much faster than the rate at which another ketyl can enter the solvent cage and abstract an electron from the ketyl already present. When "CH_3MgBr" was allowed to react with 2-MBP in the presence of fluorenone ketyl (Table V), the only product observed was the 1,2-addition product of 2-MBP. Also *t*-butyl 1,2- and 1,6-addition products were the only products (eq 13) observed from the reaction of "*t*-BuMgCl" with 2-MBP in



(13)

the presence of fluorenone ketyl. These results indicate that while the R group radical is free enough to cyclize (in the case of tertiary probe Grignard), it is not trapped by a free-radical scavenger.

In light of the possible "bound" nature of the R group radical and ketyl, it seems that the mechanism of "*t*-BuMgCl" with benzophenone might involve a radical anion–radical cation pair in which the R group radical is still tightly bound to the magnesium such that it cannot isomerize or cyclize. This radical anion–radical cation pair (I) may be thought of as originating via the σ complex which is undoubtedly formed very rapidly in a simple acid–base reaction. The radical anion–radical cation pair would then either (a) collapse to a 1,2-addition product (which would preclude cyclization) or (b) dissociate to form a radical anion and a free radical within the solvent cage which in turn could collapse to form 1,2- and conjugate addition products or escape the solvent cage to from benzopinacol as illustrate in eq 14.



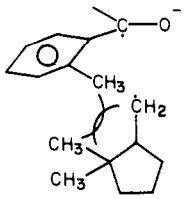
(14)

Further investigation of the tertiary Grignard probe reaction with ketones, in ether, centered on the effect of increased steric hindrance at the carbonyl carbon atom on the reaction products. Thus, when the tertiary Grignard probe was allowed to react with 2-MBP instead of benzophenone in ether, the resulting hydrocarbon analysis[11,16] indicated that 91% of the reaction proceeded through the straight-chain isomer. The alkylation products consisted of 71% 1,6-addition product, 21% 1,2-addition product, and 8% 2-methylbenzhydrol. Although no cyclization was observed in the 1,2-addition product, cyclization was observed for 71% of the 1,6-addition product. In view of our proposed mechanism, the increase in 1,6-addition with the concomitant decrease in 1,2-addition could simply be due to the increased steric hindrance to 1,2-addition due to the 2-methyl group on benzo-

(16) Millimoles of Grignard H added to the reaction and mmoles of hydrocarbon recovered from reaction:

	Grignard H added		hydrocarbon recovered	difference
St. Chain	2.97 ± 0.09	St. Chain	1.25 ± 0.03	1.72 ± 0.11
Cyclo 5	2.60 ± 0.07	Cyclo 5	2.44 ± 0.04	0.16 ± 0.11
Cyclo 6	0.18 ± 0.02	Cyclo 6	0.17 ± 0.007	0.01 ± 0.09
	5.75 ± 0.18			1.89 ± 0.31

phenone. The lack of cyclized 1,2-addition product could be due to selective 1,2-addition by the straight-chain radical in competition with the more sterically hindered cyclized radical. No such selectivity should be observed for 1,6-addition product.



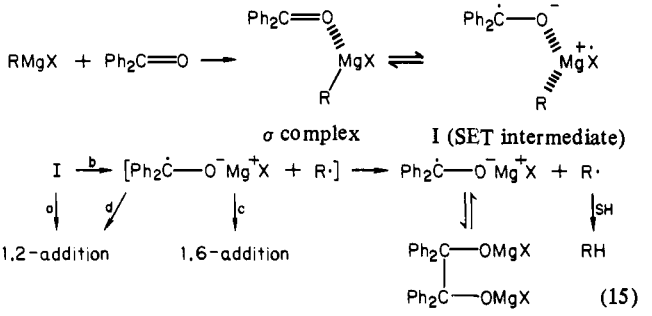
In the reaction of tertiary Grignard probe with benzophenone, the effects of changing the solvent basicity and viscosity were determined by employing THF and di-*n*-butyl ether as reaction solvents. Tetrahydrofuran is a more strongly coordinating solvent than diethyl ether and is about twice as viscous (THF, η_{40} (cP) = 0.389; diethyl ether, η_{40} (cP) = 0.194).[17] Di-*n*-butyl ether is less basic than diethyl ether, since basicity is diminished for di-*n*-alkyl ethers with increasing chain length; however, at the same time its viscosity is $>5/2$ times that of diethyl ether (di-*n*-butyl ether, η_{40} (cP) = 0.506).[17]

Only 82% of the reaction proceeded through the straight-chain isomer when the tertiary Grignard probe was allowed to react with benzophenone in di-*n*-butyl ether.[11,18] The alkylation products consisted of 61% 1,2-addition products and 39% 1,6-addition products. Cyclized 1,2-addition product accounted for 27% of the 1,2-addition products. However, the absolute yield of cyclized 1,2-addition product matches within experimental error the amount of cyclized Grignard reagent that reacted. Thus, cyclized 1,2-addition product did not originate from straight-chain Grignard reagent. Cyclized 1,6-addition product accounted for 69% of the 1,6-addition product produced in the reaction. Observing the dramatic decrease in the yield of 1,6-addition product in di-*n*-butyl ether compared to the same reaction in diethyl ether, one would be inclined to attribute this to the increase in solvent viscosity (a slowing down of radical migration to the 6-position). However, if viscosity were the determining factor, a large increase in the ratio of cyclized to uncyclized 1,6-addition product would be expected because of the extended lifetime of the radical. This is not what is observed; in fact, the ratio of cyclized to uncyclized 1,6-addition product actually decreased slightly. There are two alternative explanations for this data, and both are concerned with the coordinating ability of di-*n*-butyl ether. In terms of our proposed mechanism, once the electron transfer has occurred, the stability of the radical anion–radical cation pair would be very dependent upon the coordinating ability of the solvent to stabilize the ketyl. A poorly coordinating solvent such as di-*n*-butyl ether would not be expected to stabilize the ketyl very effectively, thus the radical anion–radical cation pair would tend to collapse to 1,2-addition rather than dissociate to ketyl and free radical and in turn to 1,6-addition product.

An alternate explanation is that electron transfer, itself, is very dependent upon solvent polarity as demonstrated by Fauvarque[5] and suggested earlier by Walborsky.[19] A poorly coordinating solvent such as di-*n*-butyl ether would not be expected to effectively promote electron transfer, thus allowing a polar reaction to become competitive. It is also interesting to note that 16% of the reaction took place through the cyclic Grignard, but no benzhydrol (from β-hydrogen reduction) was detected. Cyclopentylmethyl Grignard reagent and other Grignard reagents which contain a tertiary β-hydrogen (isopropyl and isobutyl Grignard reagents) usually give in excess of 80% benzhydrol on reaction with benzophenone.[20]

The situation is quite different when the tertiary probe Grignard was allowed to react with benzophenone in THF rather than diethyl ether when 91% of the reaction proceeded through the straight-chain Grignard reagent.[11,21] The alkylation products consisted of 58% 1,2-addition products and 42% 1,6-addition products. Cyclization was observed in 41% of the 1,2-addition products and in 81% of the 1,6-addition products. Since only 9% of the tertiary probe Grignard which reacted was the cyclic isomer then at least 45% of the cyclized 1,2-addition product had to originate from straight-chain Grignard reagent. These results produce solid evidence that in the reaction of a tertiary Grignard reagent with benzophenone, 1,2-addition products come about through a radical process. These data suggest that the strongly coordinating solvent THF promotes dissociation of the radical anion–radical cation pair through stabilization of the ketyl and then retards migration (viscosity effect) of the alkyl radical to the 6-position as evidenced by a decrease in 1,6-addition products (compared to the same reaction in ether). Other viscosity effects observed were an increase in the ratio of cyclized to uncyclized 1,6-addition products (due to the increased lifetime of the radical) and the appearance of cyclized 1,2-addition product which is probably formed via internal return of the dissociated alkyl radical to the carbonyl carbon (solvent viscosity causes longer residence time at the site of radical anion–radical cation pair dissociation).

To be consistent with these new data, it is necessary for the mechanism described in eq 14 to involve a second pathway for the formation of 1,2-addition product (path d), that is, by reaction of the free alkyl radical (from dissociation of the radical anion–radical cation pair) with the carbonyl carbon of the ketyl within the solvent cage illustrated in eq 15.



(15)

Thus far the description of the mechanism of the reaction of a Grignard reagent with benzophenone has dealt with only a tertiary Grignard reagent. Only with a tertiary Grignard reagent reacting with an aromatic ketone has any evidence of electron transfer been observed. It is possible however, that all Grignard reactions with aromatic ketones proceed through a SET pathway by the proposed mechanism (eq 15). The stability of the radical anion–radical cation complex (I) should be determined by the stabilities of the incipient radical (R·) and the ketyl ($Ph_2\dot{C}$—O^-) and the coordinating ability of the solvent, which in turn would determine the amount of SET character observed in the reaction. With tertiary Grignard reagents, the intermediate complex (I) would be unstable because of the stability of the *tert*-alkyl radical, thus making path b competitive with path a or even the predominant reaction pathway. The choice between path c and d would be dependent upon solvent viscosity, radical reactivity (primary radicals are more reactive than tertiary radicals), and steric

(17) G. A. Hill and G. M. Bramann, "Collected Volume of Organic Syntheses", Wiley, New York, 1941, Vol. I, p 81.

(18) Millimoles of Grignard L added to the reaction and mmoles of hydrocarbon recovered from reaction:

	Grignard L added		hydrocarbon recovered	difference
St. Chain	1.50 ± 0.04	St. Chain	1.08 ± 0.03	0.42 ± 0.07
Cyclo 5	1.39 ± 0.03	Cyclo 5	1.31 ± 0.04	0.08 ± 0.07
Cyclo 6	0.11 ± 0.01	Cyclo 6	0.12 ± 0.006	

(19) H. M. Walborsky and M. S. Aronoff, *J. Organomet. Chem.*, **51**, 31 (1973).

(20) Unpublished results of T. L. Wiesemann and D. P. Campbell.

(21) Millimoles of Grignard K added to the reaction and mmoles of hydrocarbon recovered from reaction:

	Grignard K added		hydrocarbon recovered	difference
St. Chain	1.20 ± 0.03	St. Chain	0.26 ± 0.007	0.94 ± 0.037
Cyclo 5	1.20 ± 0.03	Cyclo 5	1.13 ± 0.03	0.07 ± 0.06
Cyclo 6	0.26 ± 0.02	Cyclo 6	0.24 ± 0.007	0.02 ± 0.027
	2.66 ± 0.08			1.03 ± 0.12

considerations. On the other hand, vinylic Grignard reagents, e.g., *cis*-propenylmagnesium bromide, and primary alkyl Grignard reagents, e.g., 5-hexenylmagnesium chloride, may react by a polar mechanism or, if by SET, may form a more stable complex which would collapse via path a to give only 1,2-addition product with no SET character observed (as in the cases reported here).

(2,2-Dimethyl-5-hexenyl)magnesium Chloride. To observe electron-transfer character in a reaction between a primary Grignard reagent and benzophenone, assuming the postulated mechanism to be in effect, it became apparent that the rate of path a (eq 15) would have to be slowed sufficiently to allow at least partial reaction through path b. When neopentylmagnesium bromide was allowed to react with benzophenone, a very slow reaction took place which produced mainly 1,2-addition product, but also about 10% of the 1,6-addition product.[22] This is the first example of electron-transfer behavior (1,6-addition) displayed in the reaction of a primary Grignard reagent with a ketone. On the basis of this information a neopentyl-type probe was prepared ((2,2-dimethyl-5-hexenyl)magnesium chloride) and allowed to react with benzophenone. The neooctenyl Grignard reagent when prepared contains a substantial quantity of cyclic (5-membered ring) isomer. Unlike the tertiary Grignard probe, the neooctenyl cyclic Grignard reagent is much more reactive toward benzophenone than is its straight-chain isomer. Thus, in a reaction with benzophenone, large amounts of cyclic 1,2-addition products and benzhydrol are produced before the Grignard of interest has started to react. It was established that by adding 1 equiv of acetone to a solution of neooctenyl Grignard reagent, which contains 1 equiv of the cyclic Grignard, that the cyclic Grignard reacts completely with the acetone (1,2-addition, β-hydrogen reduction and enolization) leaving the straight-chain isomer intact. It was also established that the acetone–cyclic Grignard reagent reaction products had no effect on the stability or stereochemical integrity of the neooctenyl straight-chain Grignard reagent. Thus, by prereacting out the cyclic Grignard, we were able then to conduct a reaction between the neooctenyl Grignard and benzophenone. This reaction proceeded 100% through the straight-chain isomer.[23,24] The alkylation products consisted of 100% 1,2-addition with cyclization observed in 12% of the 1,2-addition product. This is the first example of electron-transfer behavior exhibited in the formation of 1,2-addition product from the reaction of a primary Grignard reagent with a ketone. Thus the increase in steric bulk apparently slowed down the collapse of the radical anion–radical cation complex such that dissociation via path b (eq 15) and recombination via path d could occur. Because of the importance of this finding and the fact that only 12% cyclization of the R group was observed, this reaction was repeated several times. In each case, 10–15% of cyclized 1,2-addition product was observed.

The absence of 1,6-addition product (path c) is somewhat surprising when compared to the neopentyl Grignard reaction with benzophenone which produced about 10% 1,6-addition product. However, when the increased difficulty of migration of the neooctenyl radical (due to its larger size) is coupled with the fact that the primary radical is very reactive (compared to a tertiary radical), it is possible that internal return (path d) predominates over migration (path c).

The effect of increased steric hindrance about the carbonyl carbon atom on the formation of 1,2- and 1,6-addition was determined when neooctenyl Grignard reagent was allowed to react with 2-MBP. The extremely slow reaction produced 1,2-addition product and 14% 1,6-addition product. No cyclization was observed in the 1,2-addition product, but cyclization was observed in 69% of the 1,6-addition products. The introduction of a 2-methyl group in benzophenone apparently slowed even more the collapse of the radical anion–radical cation complex (path a) and also provided enough steric interference to prevent internal return (path d), leaving path c as the only alternative for coupling of the "free" neooctenyl radical.

Summary

It has been established that not only tertiary Grignard reagents but also primary Grignard reagents react with aromatic ketones in both diethyl ether and THF by an electron-transfer process. The free-radical nature of the R group of the Grignard reagent coupling with the ketyl has been established for both primary and tertiary Grignard reagents, although under selective conditions the electron transfer has been shown to proceed through a radical cation–radical anion intermediate. The electron-transfer nature of the reaction of Grignard reagents with ketones clearly appears to be a function of the oxidation potential of the Grignard reagent, the reduction potential of the ketone, and the polarity of the solvent. As long as the reduction potential is low enough (at least −1.8 eV), the reactions proceed by SET whether the Grignard reagent is primary or tertiary. It appears that the mechanistic pathway is polar when the R group is vinyl although this system is being tested further. Ketones that are not aromatic but that have reduction potentials lower than benzophenone (e.g., $(CF_3)_2C{=}O$) are also being tested for their SET mechanistic behavior with Grignard reagents.

Experimental Section

Materials. Solvents. Fisher reagent grade anhydrous diethyl ether and practical grade di-*n*-butyl ether were stored over sodium and then distilled under nitrogen from $LiAlH_4$ or sodium benzophenone ketyl just prior to use. Fisher reagent grade tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were dried over $NaAlH_4$ and distilled under nitrogen just prior to use.

Ketones. Eastman highest purity 2-methylbenzophenone (2-MBP) and benzophenone were distilled under vacuum. Eastman highest purity 9-fluorenone was used without further purification. Fisher Certified A.C.S. grade acetone was dried over $MgSO_4$, filtered, distilled from P_2O_5, and stored over 4 A molecular sieves. Solutions of these ketones were stored in a glovebox and shielded from light prior to use.

Alkyl Halides. Fisher reagent grade bromobenzene and *tert*-butyl chloride, Aldrich 6-chloro-1-hexene, and Chemical samples 6-bromo-1-hexene, 5-bromo-1-pentene, and 4-bromo-1-butene were distilled from calcium hydride just prior to use. Aldrich 1-bromo-1-propene was fractionally distilled on a Nester-Faust Teflon annular spinning band column to give pure *cis*-1-bromo-1-propene. The *trans*-1-bromo-1-propene could not be obtained pure.

Organometallic Compounds. Grignard reagent solutions were prepared as previously described[3] unless otherwise indicated. Triply and doubly sublimed magnesium (Dow) was milled with a carbide tool prior to use. ROC/RIC magnesium crystals were used without further purification. Grignard reagents in THF were prepared and analyzed in the same manner as Grignard reagents prepared in ether. Grignard reagents in di-*n*-butyl ether were prepared by removing the diethyl ether from the Grignard reagent under vacuum after the di-*n*-butyl ether had been added. $LiAlH_4$ (Alfa Inorganic) was suspended in refluxing ether for 24 h and then filtered. The clear solutions were standardized by standard aluminum analysis (EDTA titration) prior to use.

Other Compounds. Authentic samples of 1-hexene, 1-heptene, cyclohexene, 1,5-hexadiene, cyclohexane, 1,1-dimethylcyclohexane, and methylcyclopentane were obtained from Aldrich Chemical Co. Authentic

(22) Unpublished results of E. C. Ashby and R. S. Smith.

(23) In ref 24 and 25 St. Chain refers to the hydrocarbon obtained by hydrolysis of (2,2-dimethyl-5-hexenyl)magnesium chloride, cyclo 5 refers to the hydrocarbon obtained by hydrolysis of (3,3-dimethylcyclopentyl)-methylmagnesium chloride, cyclo-5-ole refers to the hydrocarbon olefin obtained when Cyclo 5 undergoes β-hydrogen reduction of a ketone, Ace refers to acetone, IPA refers to isopropyl alcohol, and 1,2-add refers to 1,1-dimethyl-2-(3,3-dimethylcyclopentyl)ethanol.

(24) Millimoles of Grignard M added to the reaction and mmoles of hydrocarbons and other products recovered:

	Grignard M added		product recovered	difference
St. Chain	1.4 ± 0.04	St. Chain	0.04 ± 0.001	1.0 ± 0.05
Cyclo 5	1.4 ± 0.05	Cyclo 5	0.29 ± 0.01	1.11 ± 0.05
	2.8 ± 0.08	Cyclo-5-ole	0.16 ± 0.01	
Ace	1.4 ± 0.01	Ace	0.24 ± 0.01	
		IPA	0.15 ± 0.01	−1.11 ± 0.03
		1,2-add	0.96 ± 0.02	

(25) Millimoles of Grignard M added to the reaction and mmoles of hydrocarbons recovered from the reaction:

	Grignard M added		hydrocarbon recovered	difference
St. Chain	2.0 ± 0.1	St. Chain	0.18 ± 0.01	1.82 ± 0.11
Cyclo 5	7.5 ± 0.2	Cyclo 5	0.30 ± 0.01	7.20 ± 0.21
	9.5 ± 0.3	Cyclo-5-ole	7.15 ± 0.10	−7.15 ± 0.10

samples of 6-methyl-1-heptene, methylenecyclopentane, 2-methyl-1,5-heptadiene, and 1,1,3-trimethylcyclopentane were obtained from Chemical Samples Co. Aldrich (Spectro Grade) nitromethane and methyl crotonate and Eastman highest purity benzaldehyde were distilled prior to use. Aldrich diisopropylamine was refluxed over and distilled from calcium hydride prior to use. Aldrich isobutyric acid was refluxed over and distilled from P_2O_5. Aldrich triphenylphosphine was dried over P_2O_5 in a vacuum dessicator for 48 h prior to use. Aldrich crotonic acid (*trans*-2-butenoic acid) was recrystallized twice from ethanol–water followed by vacuum drying over P_2O_5 for 24 h.

Preparations. Miscellaneous Procedures. The preparations of 1-(2-methylphenyl)-1-phenylethylene and 1-(2-methylphenyl)-1-phenylethanol were carried out as previously described.[26]

2,2′-Dimethylbenzopinacol and fluorenone pinacol were prepared according to the procedure of Gomberg and Bachmann from the reaction of the appropriate ketone with magnesium and iodine.[27] The preparation of 1,1-dimethyl-5-hexen-1-ol was carried out as previously described by reacting 4-pentenylmagnesium bromide with acetone.[28]

(1,1-Dimethyl-5-hexenyl)magnesium Chloride. To a 250-mL round-bottom flask equipped with a side arm stopcock, a reflux condenser, pressure-equalizing addition funnel stoppered with a septum cap, and a magnetic stirring bar and attached to an ether/$LiAlH_4$ still was added 0.05 mol (3.6 g) of activated 3 A triply sublimed magnesium. The entire apparatus was flamed under vacuum and then flushed with nitrogen. Enough dry ether was distilled into the flask to just cover the magnesium. Through the side arm of the flask (under N_2 flush) 0.2 mL of ethyl bromide was added with stirring. After the vigorous reaction had stopped, the ether solution was removed by syringe and fresh ether distilled into the flask. This procedure was continued until 90% of the ethylmagnesium bromide was accounted for by acid titration of the removed ether. With a syringe, 20 mmol (2.93 g) of 1-chloro-1,1-dimethyl-5-hexene was added to the addition funnel. About 0.5 mL of the neat halide was added to the magnesium–ether mixture with stirring. The remaining halide was diluted with 10 mL of dry ether. The reaction started within 10 min. Additional ether was distilled into the reaction vessel, and additional halide–ether mixture was added at a rate such that refluxing was held to a minimum. The reaction was allowed to stir an additional 8 h after the addition of the halide was complete and then allowed to settle until clear. The Grignard reagent was used without being filtered. The isomer composition of the Grignard reagents prepared were determined by GLC analysis: Grignard reagents (0.142 ± 0.006 M) were composed of 0.076 ± 0.0025 M (53.6%) (1,1-dimethyl-5-hexenyl)magnesium chloride, 0.056 ± 0.0025 M (39.4%) [(2,2-dimethylcyclopentyl)methyl]magnesium chloride, and 0.010 ± 0.007 M (7.0%) (2,2-dimethylcyclohexyl)magnesium chloride.

(1,1-Dimethyl-5-hexenyl)magnesium chloride was also prepared in THF by the above procedure and in *n*-butyl ether as described earlier. The isomer composition of these Grignard reagents was determined in the same manner and shown by GLC analysis to be as follows.

Grignard reagents in THF (0.266 ± 0.008 M) were composed of 0.12 ± 0.03 M (45.1%) (1,1-dimethyl-5-hexenyl)magnesium chloride, 0.12 ± 0.003 M (45.1%) (2,2-dimethylcyclopentyl)methylmagnesium chloride, and 0.026 ± 0.002 M (9.8%) (2,2-dimethylcyclohexyl)magnesium chloride.

Grignard reagents in *n*-butyl ether (0.26 ± 0.008 M) were composed of 0.13 ± 0.004 M (50.0%) (1,1-dimethyl-5-hexenyl)magnesium chloride, 0.12 ± 0.003 M (46.2%) [(2,2-dimethylcyclopentyl)methyl]magnesium chloride, and 0.01 ± 0.001 M (3.8%) (2,2-dimethylcyclohexyl)magnesium chloride.

(2,2-Dimethyl-5-hexenyl)magnesium Chloride. To a 50-mL round-bottom flask equipped with a side arm stopcock, a reflux condenser, pressure-equalizing addition funnel stoppered with a serum cap, and magnetic stirring bar and attached to an ether/$LiAlH_4$ still was added 0.042 mol (1.0 g) of activated[29] triply sublimed magnesium. The entire apparatus was flamed under vacuum and then flushed with nitrogen. Enough dry ether was distilled into the flask to just cover the magnesium. Through the side arm of the flask (under N_2 flush) was added with stirring 0.2 mL of ethyl bromide. After the vigorous reaction had stopped, the ether solution was removed by syringe and fresh ether distilled into the flask. This procedure was continued until 90% of the ethylmagnesium bromide was accounted for by acid titration of the removed ether. About 30 mL of ether was distilled into the flask. To this was added (by syringe through the side arm) 4.7 mmol (0.34 g) of 1-chloro-2,2-dimethyl-5-hexene. The reaction, which never procedes rapidly, was allowed to mix for 3 days, and then allowed to settle until clear. The Grignard reagent was used without being filtered. The isomer composition of the Grignard reagents were determined by GLC analysis: 0.07 ± 0.002 M (50.0%) (2,2-dimethyl-5-hexenyl)magnesium chloride and 0.07 ± 0.002 (50.0%) [(3,3-dimethylcyclopentyl)methyl]magnesium chloride.

Methods. Apparatus and Procedures

Reactions were performed under nitrogen or argon at the bench with use of Schlenk-tube techniques or in a glovebox equipped with a recirculating system using manganese oxide columns to remove oxygen and dry ice–acetone traps to remove solvent vapors.[30] Calibrated syringes equipped with stainless-steel needles were used for transfer of reagents. Glassware and syringes were flamed and cooled under a flow of nitrogen or argon. Ketone, metal salt, and internal-standard solutions were prepared by weighing the reagent in a tared volumetric flask and diluting with the appropriate solvent. All melting points are corrected, and all boiling points are uncorrected.

Reactions in General. Reactions were carried out in round-bottomed flasks equipped with T-bore stopcocks attached to male 24/40 standard taper joints (allows nitrogen flush while reagents are being added or removed through the stopcock by syringe) and a Teflon-coated magnetic stirring bar. The appropriate amounts of solvents, organometallic reagents, ketones, and catalysts were syringed into the flask under a nitrogen or argon flush. After complete reaction, the mixture was hydrolyzed with saturated aqueous NH_4Cl solution under nitrogen atmosphere. In some cases the ether layer was separated, dried over anhydrous $MgSO_4$ and filtered, and the solvent removed under vacuum. In other cases the solvent and other volatile compounds of interest were removed under vacuum and collected in a liquid nitrogen or dry ice–acetone trap.

Analytical Methods. Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump.[31] Magnesium was determined by titrating hydrolyzed samples with standard EDTA solution at pH 10 with the use of Eriochrome-Black T as an indicator. Aluminum was determined by adding excess standard EDTA solution to hydrolyzed samples and then back-titrating with standard zinc acetate solution at pH 4 with use of dithizone as an indicator. Lithium reagents were analyzed by the standard Gilman double titration method.[32] Halide was determined by titration with $AgNO_3$ and back-titration by KCNS with ferric alum indicator. The amount of active C–Mg and C–Li was determined by titrating the active reagent with dry 2-butanol in xylene with use of 2,2′-biquinoline as an indicator. Carbon and benzene analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA.

Where organometallic reagents could have more than one isomer, the isomer distribution was determined by hydrolyzing an aliquot of the reagent with a minimum of saturated NH_4Cl solution, adding an internal standard (1-heptene or cyclohexene), and analyzing the resulting hydrocarbons by GLC. Hydrocarbons were identified by comparison with authentic samples. An alternate method used where appropriate involved carbonating a Grignard reagent with freshly crushed dry ice and determining the isomer composition of the resulting carboxylic acids by NMR analysis vs. an internal standard.

Analysis of all products from the reactions of methylmagnesium bromide with benzophenone and 2-methylbenzophenone, from the reactions of *cis*- and *trans*-propenylmagnesium bromide, 5-hexenylmagnesium chloride, 5-hexenyllithium, tris(5-hexenyl)aluminum, (1,1-dimethyl-5-hexenyl)magnesium chloride, and (2,2-dimethyl-5-hexenyl)magnesium chloride with benzophenone and 2-methylbenzophenone were determined by NMR analysis based upon isolated or synthesized authentic compounds. NMR analyses employed $CDCl_3$ as a solvent with internal Me_4Si.

For the products arising from reaction of methylmagnesium bromide with benzophenone, 1,2-addition was determined by the observation of the methyl group attached to the carbonyl carbon (1.92 ppm), benzopinacol was determined by the OH hydrogen (3.05 ppm), and benzhydrol was determined by the hydrogen attached to the carbonyl carbon (5.80 ppm).

For the products arising from reaction of methylmagnesium bromide with 2-methylbenzophenone, 1,2-addition was determined by observation of the methyl group attached to the carbonyl carbon (1.85 ppm) and the methyl group bound to the ring (1.96 ppm), and 2,2′-dimethyl-

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benzopinacol was determined by observation of the OH hydrogen (2.15 ppm) and the methyl group bound to the ring (2.26 ppm).

For the products arising from the reaction of *cis*-propenylmagnesium bromide with benzophenone, 1,2-addition was determined by observation of the allylic methyl group (doublet of doublets, 1.46 ppm). For the products arising from the reaction of *trans*-propenylmagnesium bromide with benzophenone, 1,2-addition was determined by observation of the allylic methyl group (doublet of doublets, 1.77 ppm).

For the products arising from the reaction of 5-hexenylmagnesium chloride with benzophenone, 1,2-addition straight-chain product was determined by observation of the vinyl protons (4.75–6.17 ppm), and 1,2-addition cyclized product was determined by observation of the methylene group attached to the carbonyl carbon (doublet, 2.25 ppm).

For the products from the reaction of (1,1-dimethyl-5-hexenyl)magnesium chloride with benzophenone, straight-chain 1,2-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet, 4.67–6.17 ppm) and the *gem*-dimethyl group attached to the carbonyl carbon (1.11 ppm), cyclized 1,2-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet, 4.67–6.17 ppm) and the *gem*-dimethyl group attached to the carbonyl carbon (1.11 ppm), cyclized 1,2-addition product was determined by observation of the chemical shift of the *gem*-dimethyl groups attached to the cyclopentyl ring (doublet, 0.83 ppm), straight-chain 1,6-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet, 4.67–6.17 ppm) and the *gem*-dimethyl group attached to the aromatic ring (1.34 ppm), and cyclized 1,6-addition product was determined by observation of the chemical shift of the *gem*-dimethyl group attached to the cyclopentyl ring (doublet, 0.97 ppm).

For the products arising from the reaction of (1,1-dimethyl-5-hexenyl)magnesium chloride with 2-methylbenzophenone, straight-chain 1,2-addition product was determined by observation of the chemical shift of the protons (multiplet, 4.67–6.17 ppm) and the *gem*-dimethyl group attached to the carbonyl carbon (1.15 ppm), cyclized 1,2-addition product was determined by observation of the chemical shift of the *gem*-dimethyl group attached to the cyclopentyl ring (doublet, 0.95 ppm by comparison with the equivalent benzophenone product), straight-chain 1,6-addition product was determined by observation of the chemical shift of the vinyl protons (multiplet, 4.7–6.17 ppm) and the *gem*-dimethyl group attached β to the substituted ring (0.85 ppm), and cyclized 1,6-addition products were determined by observation of the chemical shift of the *gem*-dimethyl group attached to the cyclopentyl ring (0.80 ppm) and by the methylene group attached to the substituted aromatic ring (doublet, 2.30 ppm). The 1,6-addition products were reduced to the corresponding hydrols with $LiAlH_4$ to facilitate separation from the 1,2-addition products by column chromatography prior to NMR analysis. Thus the chemical shifts for the 1,6-addition products are for the reduced (hydrol) form of the ketone. Comparison of the NMR spectra of the 1,6-addition product from the tertiary Grignard probe with benzophenone indicates that there is little change in the chemical shift values between ketone and hydrol form of the products.

Reactions of *cis*- and *trans*-Propenylmagnesium Bromide with Benzophenone. To a THF solution of 1.5 mmol of *cis*-propenylmagnesium bromide (Grignard A) or *cis*-propenylmagnesium bromide–*trans*-propenylmagnesium bromide (Grignard B,C) was added 1.0 mmol (2.0 mL, 0.5 M) of benzophenone in THF. In those cases where the reactions were doped, the $FeCl_3$, 0.0075 mmol (0.75 mL, 0.01 M) in THF, was added just prior to the addition of the ketone. After 6 h, the reaction was hydrolyzed and extracted with ether, the ether layer separated and dried, and the ether removed under vacuum. The resulting liquid was taken up in $CDCl_3$ and analyzed by NMR.

Reaction of 5-Hexenylmagnesium Chloride in Ether with Benzophenone. To 1.0 mmol of 5-hexenylmagnesium chloride (Grignard D) in 9.15 mL of ether was added 0.5 mmol (0.85 mL, 0.59 M) of benzophenone. After 6 h, the reaction was hydrolyzed, and all volatile compounds were removed under vacuum and collected in a liquid nitrogen trap. GLC analysis with use of 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 20-ft. column at 50 °C with a flow rate of 40 mL/min of helium and with cyclohexene as the internal standard indicated the following distribution of hydrocarbons: 0.47 ± 0.01 mmol of 1-hexene, 0.24 ± 0.007 mmol of 1,5-hexadiene, and 0.029 ± 0.0002 mmol of methylcyclopentane.

The residue left after vacuum stripping was dissolved in ether and washed with water, the ether layer was separated and dried, and the ether was removed under vacuum. The remaining liquid (internal standard CH_3NO_2) was taken up in $CDCl_3$ and analyzed by NMR: 0.25 mmol (51%) of 1,1-diphenyl-5-hepten-1-ol and 0.24 mmol (49%) of benzhydrol.

From a preparative-scale reaction, the nonvolatile reaction products were chromatographed on alumina eluting with 8% ethyl acetate–hexane. Fraction 1 consisted of a liquid identified as 1,1-diphenyl-5-hepten-1-ol, n^{25}_D 1.5551; IR(neat, film) 3480 (broad OH), 3030 (aromatic CH), 2960 (aliphatic CH), 1645 (vinyl C=C), 1600 cm^{-1} (aromatic C=C); NMR($CDCl_3$, Me_4Si) 1.0–2.5 (m, 8 H), 2.13 (br, s, 1 H), 4.75–6.17 (m, 3 H), 7.08–7.60 ppm (m, 10 H); mass spectrum, *m/e* (relative intensity) 266 (M^+, <1), 248 (1), 183 (100), 105 (75), 77 (33), 41 (17). Anal. Calcd for $C_{19}H_{22}O$: C, 85.71; H, 8.27. Found: C, 85.54; H, 8.32.

Fraction 2 consisted of a solid which was recrystallized from ethanol–water to give white crystals of benzhydrol: mp 66–67 °C (lit.[33] 68 °C); NMR($CDCl_3$, Me_4Si) 2.25 (br s, 1 H), 5.80 (s, 7 H), 7.37 ppm (s, 10 H).

Reaction of (1,1-Dimethyl-5-hexenyl)magnesium Chloride in THF with Benzophenone. To 2.66 mmol of (1,1-dimethyl-5-hexenyl)magnesium chloride (Grignard K) in 25 mL of THF was added 1.0 mmol (1.0 mL, 1.0 M) of benzophenone in THF. The reaction was allowed to run for 6 h. Application of the same workup procedure as used in the previous reaction gave by GLC analysis (same GLC column and conditions as the previous reaction) the following distribution of hydrocarbons: 1.13 ± 0.03 mmol of 1,1,2-trimethylcyclopentane; 0.26 ± 0.007 mmol of 2-methyl-6-heptene; 0.24 ± 0.007 mmol of 1,1-dimethylcyclohexane. NMR analysis gave the following: 0.32 mmol (34.3%) of 1,1-diphenyl-2,2-dimethyl-6-hepten-1-ol; 0.22 mmol (23.6%) of 1,1-diphenyl-2-(2,2-dimethylcyclopentyl)ethanol; 0.076 mmol (8.1%) of 4-(1,1-dimethyl-5-hexenyl)benzophenone; 0.317 mmol (34.0%) of 4-((2,2-dimethylcyclopentyl)methylene)benzophenone.

Reaction of (1,1-Dimethyl-5-hexenyl)magnesium Chloride in *n*-Butyl Ether with Benzophenone. To 3.0 mmol of (1,1-dimethyl-5-hexenyl)-magnesium chloride (Grignard L) in *n*-butyl ether was added 0.5 mmol (1.0 mL, 0.5 M) of benzophenone in *n*-butyl ether. The reaction was allowed to run for 6 h. GLC analysis (same GLC column and conditions as the previous reaction) gave the following distribution of hydrocarbons: 1.31 ± 0.04 mmol of 1,1,2-trimethylcyclopentane; 1.08 ± 0.03 mmol of 2-methyl-6-heptene; 0.12 ± 0.006 mmol of 1,1-dimethylcyclohexane. NMR analysis gave the following: 0.22 mmol (44.9%) of 1,1-diphenyl-2,2-dimethyl-6-hepten-1-ol; 0.08 mmol (16.3%) of 1,1-diphenyl-2-(2,2-dimethylcyclopentyl)ethanol; 0.06 mmol (12.12%) of 4-(1,1-dimethyl-5-hexenyl)benzophenone; 0.13 mmol (26.6%) of 4-((2,2-dimethylcyclopentyl)methylene)benzophenone.

Reaction of (2,2-Dimethyl-5-hexenyl)magnesium Chloride in Ether with Acetone. To 0.28 mmol of (2,2-dimethyl-5-hexenyl)magnesium chloride (Grignard M) in 2.0 mL of ether was added 0.15 mmol (0.8 mL, 0.188 M) of acetone in ether. After 1 h, the reaction was hydrolyzed with a minimum amount of saturated aqueous NH_4Cl and dried with anhydrous $MgSO_4$, internal standards were added, and the reaction mixture was analyzed by GLC. Using 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 20-ft. column at 40 °C with a flow rate of 30 mL/min of helium with 1-heptene as the internal standard, gave the following hydrocarbon distribution: 0.14 ± 0.004 mmol of 2,2-dimethyl-5-heptene; 0.041 ± 0.001 mmol of 1,1,3-trimethylcyclopentane; 0.032 ± 0.001 mmol of 3,3-dimethylmethylenecyclopentane. Using 10% Carbowax 20M on Chromosorb W (AW), 60/80 mesh on a 10-ft. column at 50 °C with a flow rate of 60 mL/min of helium with THF as the internal standard, gave the following products: 0.039 ± 0.002 mmol of acetone; 0.033 ± 0.002 mmol of isopropyl alcohol. Using the same column and flow rate of helium at 150 °C with dodecane as the internal standard gave 0.065 ± 0.002 mmol of 1,1-dimethyl-2-(3,3-dimethylcyclopentyl)ethanol.

From a preparative-scale reaction, 1,1-dimethyl-2-(3,3-dimethylcyclopentyl)ethanol was isolated by preparative GLC to give a colorless liquid: n^{25}_D 1.4489; IR(neat, film) 3380 (br, OH), 2950 (aliphatic CH), 1760 cm^{-1} (C=O); NMR($CDCl_3$, Me_4Si) 0.9–2.7 (undistinguishable m), 1.0 (apparent s), 1.22 ppm (apparent s); mass spectrum, *m/e* (relative intensity) 155 (13), 137 (8), 97 (22), 81 (31), 59 (100), 55 (29), 41 (18), 32 (18), 28 (72). Anal. Calcd for $C_{11}H_{22}O$: C, 77.65; H, 12.94. Found: C, 77.52; H, 13.00.

This reaction was repeated allowing 72 h before hydrolysis. The same results were obtained within experimental error.

Reaction of (2,2-Dimethyl-5-hexenyl)magnesium Chloride in Ether with Acetone and Benzophenone. To 2.8 mmol of (2,2-dimethyl-5-hexenyl)magnesium chloride (Grignard M) in 20 mL of ether was added 1.4 mmol (7.4 mL, 0.188 M) of acetone in ether. After 1 h, 1.0 mmol (2.0

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mL, 0.5 M) of benzophenone in ether was added. After 48 h, the reaction was hydrolyzed and all volatile compounds were removed under vacuum at 65 °C and collected in a dry ice–acetone trap. GLC analysis with the use of the two columns and conditions described in the previous reaction gave the following products: 0.40 ± 0.01 mmol of 2,2-dimethyl-5-heptene; 0.29 ± 0.01 mmol of 1,1,3-trimethylcyclopentane; 0.16 ± 0.008 mmol of 3,3-dimethylmethylenecyclopentane; 0.24 ± 0.01 mmol of acetone; 0.15 ± 0.007 mmol of isopropyl alcohol; 0.96 ± 0.02 mmol of 1,1-dimethyl-2-(3,3-dimethylcyclopentyl)ethanol.

The residue left after vacuum stripping was dissolved in ether and washed with water, the ether layer separated and dried, and the ether removed under vacuum. The remaining liquid was shown by IR to have no C=O absorption between 1600–1750 cm^{-1}; NMR analysis indicates 0.38 mmol (88%) of straight-chain 1,2-addition product and 0.12 mmol (12%) of cyclized 1,2-addition product (by difference between mmoles indicated by vinyl protons and mmoles indicated by aromatic protons).

The nonvolatile reaction products were hydrogenated at 40 psig with use of 5% Pd–C in ethanol for 12 h. The resulting hydrocarbon mixture was separated by preparative GLC with use of 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 12-ft. column at 220 °C with a flow rate of 70 mL/min of helium. The first compound eluted (retention time 82 min) was identified as 1,1-diphenyl-3,3-dimethylheptane: IR(neat, film) 3030 (aromatic CH), 2950 (aliphatic CH), 1600 cm^{-1} (aromatic CH); NMR($CDCl_3$, Me_4Si) 0.78 (s, 6 H), 0.79–1.8 (m, 9 H), 2.10 (d, 2 H), 4.03 (t, 1 H), 6.90–7.40 ppm (m, 10 H); mass spectrum, *m/e* (relative intensity) 280 (M^+, 6), 22 (4), 168 (3), 167 (100), 166 (7), 165 (14), 152 (9), 91 (4), 71 (8), 57 (18), 43 (8), 41 (5), 28 (15). Anal. Calcd for $C_{21}H_{28}$: C, 90.00; H, 10.00. Found: C, 89.98; H, 10.00.

The second compound eluted (retention time 100 min) was identified as 1,1-diphenyl-2-(3,3-dimethylcyclopentyl)ethane: IR(neat, film) 3030 (aromatic CH), 2945 (aliphatic CH), 1600 cm^{-1} (aromatic C=C); NMR($CDCl_3$, Me_4Si) 0.95 (d, 6 H), 1.10–2.35 (m, 9 H), 3.98 (t, 1 H), 6.9–7.45 ppm (m, 10 H); mass spectrum, *m/e* (relative intensity) 278 (M^+, 4), 168 (19), 167 (100), 166 (4), 165 (9), 152 (8), 91 (4), 69 (5), 57 (8), 55 (5), 28 (20).

Anal. Calcd for $C_{21}H_{26}$: C, 90.51; H, 9.49. Found: C, 90.25; H, 9.67.

The ratio of peak areas for compound 1 to compound 2 were about 90:10 on the preparative GLC chromatogram.

Acknowledgment. We thank the National Science Foundation, Grant No. MPS 7504127, for support of this work.

Supplementary Material Available: All compounds used in this study whose proportion is not reported in the Experimental Section and the results of reactions of all probes with the substrates studied (17 pages). Ordering information is given on any current masthead page.

Synthesis and Hydrolysis of Hexakis(imidazolyl)cyclotriphosphazene

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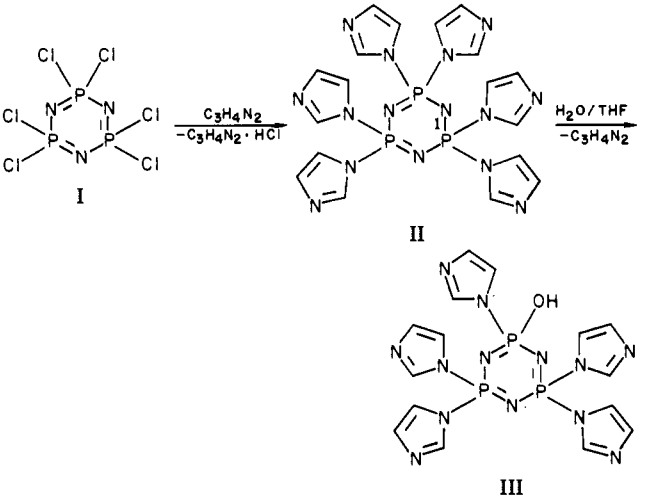
Abstract: The reaction of imidazole with hexachlorocyclotriphosphazene (I) has yielded hexakis(imidazolyl)cyclotriphosphazene (II). Compound II has been studied as a model for the analogous linear high polymer which is a prospective biodegradable carrier macromolecule. Compound II is hydrolytically unstable and decomposes to hydroxyphosphazenes, imidazole, and phosphate in aqueous media. A kinetic analysis of the removal of the first imidazolyl group from II in unbuffered 20% aqueous tetrahydrofuran within the pH range of 6.5–7.8 has shown that the hydrolysis is autocatalyzed by the free imidazole liberated in this step. Initially, the displacement of imidazole is a first-order process with respect to [II], but the release of imidazole gives rise to faster, second-order reaction in which the rate depends on the first powers of [II] and [imidazole]. The evidence favors the influence of free imidazole as a general-base catalyst and not via the formation of hydroxide ion. *N*-Methylimidazole reacts with I to form an unusual series of highly reactive yellow salts of the general formula $[N_3P_3Cl_{6-x}(C_4H_6N_2)_x]^{x+}xCl$ (VII). The chemistry of II and VII is discussed in terms of its relationship to the synthesis and reactions of the analogous linear high polymeric phosphazenes.

The hydrolysis behavior of cyclo- and polyphosphazenes is of some importance in view of the prospective biomedical use of these compounds.[1,2] In earlier papers we described the kinetics of hydrolysis of aryloxy- and fluoroalkoxycyclophosphazenes in basic media.[3,4] This paper contains an analysis of the hydrolysis reactions of an *amino*-substituted cyclophosphazene. It represents an attempt to deduce the mechanism of hydrolysis in a way that may be relevant to future biomedical studies, and it comprises the use of a small-molecule *cyclo*phosphazene as a model for the reactions of the analogous high polymer.[5]

The cyclophosphazene chosen for this study was hexakis(imidazolyl)cyclotriphosphazene (II). The imidazolyl substituent group was employed for the following reasons. First, the prospect exists that this side group might be used as a coordinative ligand



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for transition metals, especially for the coordination of high polymeric analogues of II to metalloporphyrins.[6] Second, the

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