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EFFECTS OF STRUCTURE ON INTRAMOLECULAR CYCLIZATIONS OF ALKENYL GRIGNARD REAGENTS

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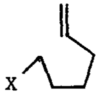
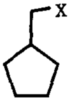
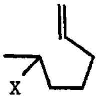
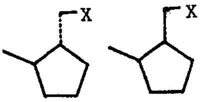
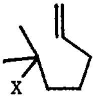
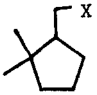
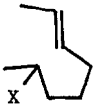
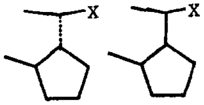
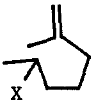
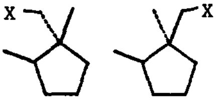
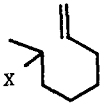
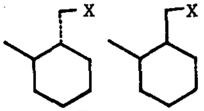
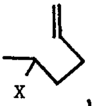
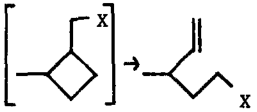
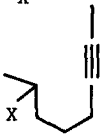
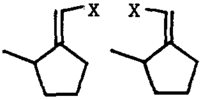
Intermolecular additions of Grignard reagents to isolated multiple bonds of hydrocarbons ordinarily are not observed.[1] However, *intramolecular* additions to alkenes,[2-6] alkynes,[7,8] and allenes[9] and the reverse of these additions, cleavages[10-12] of strained cyclic Grignard reagents to alkenyl isomers, have been reported. This communication reports the rates and products of addition of the Grignard function to the multiple bond in a series of alkenyl Grignard reagents.

The effects of methyl substituents on rate were unusual. A secondary Grignard reagent (2) cyclized more rapidly than either a primary (1) or a tertiary (3) reagent. Similarly, the rearrangements (that must involve rate-determining cyclizations) of 7[13] and of the corresponding primary[14] (1-but-3-enyl) and tertiary (2-methyl-2-pent-4-enyl) reagents had relative rates of 1, <0.02, and ~0.01. The relative rates of 2, 4, and 5, indicated a large rate-retarding effect by a methyl group when placed at *either end of the double bond*. Less surprising was the more rapid cyclization of an alkynyl Grignard reagent (8) than of a similarly substituted alkenyl (4) reagent or (as indicated by the rates of 2, 7, and 6) the more rapid formation of a five- than of a four- or six-membered ring.[15]

The available information is not sufficient to permit assigning a mechanism to these cyclizations. Nevertheless, if 1-8 cyclize by a common mechanism, then the large kinetic effects of the position, substitution, and nature (alkene or alkyne) of the multiple bond preclude any mechanism with a rate-determining step preceding involvement of the multiple bond. The unusual effect of α-methyl substitution could be rationalized by mechanisms in which a substituent exerts opposite effects on reversible formation of some activated species and a subsequent, slower

Table. Rates and Products of Reactions of Grignard Reagents in Tetrahydrofuran at 100°.

	reactant[a]	products	initial conc (M)	ratio trans:cis	rate x 10^6 [b] (sec^{-1})	relative rate
1			0.24-0.32	---	9.2 ± 2.2	69
2			0.31-0.38	>10	373 ± 47	2800
3			0.11-0.20	---	3.15 ± 0.68	24
4			0.17-0.20	~5	0.303 ± 0.057	2.3
5			0.19-0.22	c	0.316 ± 0.113	2.4
6			0.26-0.30	>3	0.134 ± 0.069	1
7			0.65-0.67	---	1.6 [d]	11.9
8[e]			0.30-0.36	~5 [f]	22.9 ± 3.7	170

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[a] Grignard reagents 1-7 were prepared from the corresponding chlorides (X = Cl). Grignard reagent 8 was prepared from the bromide (X = Br); the rate of cyclization of the reagent prepared from the chloride probably was about the same,[8,11,16] but could not be determined accurately since its formation was slower than its cyclization.

[b] Standard deviations are of several rate constants; rate constants usually were determined both by appearance of the product hydrocarbon and disappearance of the reactant hydrocarbon.

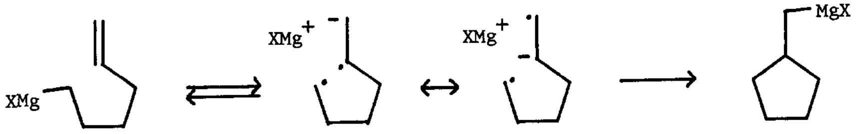
[c] Not determined since both isomers give the same hydrocarbon on hydrolysis.

[d] Interpolated from data at other temperatures.

[e] Data for this compound are taken from reference 8.

[f] It is not known which isomer predominates nor if the vinyl Grignard reagents are configurationally stable under the reaction conditions.

cyclization step; such a mechanism in which the reversible step is electron transfer to the double bond (as shown below) rationalizes the effects of methyl substitution at the double bond more readily than would reversible homolysis or heterolysis of the carbon-magnesium bond.[17] The results could be rationalized instead by mechanisms in which small rate-increasing electronic effects of α-methyl substituents are countered by large steric effects of vinyl and α-methyl substituents, for example a mechanism in which the requisite bond formations and cleavages are relative concerted.



The reactions were followed by hydrolyzing aliquots of the Grignard solutions and analyzing (by glc) the resulting hydrocarbon mixtures. The only hydrocarbons detected in significant amounts had the structures (X = H) shown in the Table. The reported first-order rate constants are for cyclizations of Grignard reagents after their formation, and the *cis*-*trans* ratios refer to that portion of each product mixture that arose from cyclization of the Grignard reagent. Grignard reagent preparation led to varying degrees to formation of rearranged Grignard reagent, a complicating reaction presumably due to the intermediacy of radicals[18] or unsolvated organomagnesium compounds[19] in the reaction of a halide with magnesium. Fortunately, uncertainties introduced into the rates by this process as well as by slow disappearance of the Grignard reagents (partly by proton abstraction and partly in ways unknown), noticeable in the slower reactions, are small compared to the large variations due to changes in structure of the organic group. It is assumed that effects on the relative rates due to different degrees of association[20] of the Grignard reagents also are small relative to the large effects due to structure; it has been determined for some systems that Grignard reagent concentration, excess magnesium halide, and the halogen (Cl, Br, or I) used have only relatively small effects on rate.[8,16]

Only compounds having the smaller of the two possible ring sizes (for example, cyclopentanes rather than cyclohexanes from **1**-**5**) were formed, even from **4** in which both carbons of the double bond are monoalkyl substituted. Formation of the smaller rings can be rationalized by the suggestions made earlier of particular geometries of approach of the functional groups necessary for addition.[4,7,21] Cyclization of the alkenyl Grignard reagents led to predominantly *trans* hydrocarbon products. Interestingly, the process during Grignard reagent formation that produced cyclic

Grignard reagent led to hydrocarbon mixtures with strikingly low *trans*:*cis* ratios: <2, <0.4, and <0.6 for **2**, **4**, and **6**, respectively.[22]

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13. Attack by **7** on tetrahydrofuran is less significant than once thought.[3] By scrupulous purification of reagents and exclusion of air, yields of up to 90% of the hydrocarbon resulting from rearrangement of **7** have been obtained.
14. Rearrangement of the primary (α-D_2) Grignard reagent was not detected, permitting the assignment of the rate limit. A recent study [E. A. Hill and H.-R. Ni, submitted for publication] at even higher temperatures suggests that the rearrangement rate is close to the assigned limit.
15. Formation of a three-membered ring must be far more rapid than formation of a five-membered ring. A rate constant of ~0.1 sec^{-1} can be estimated for rearrangement of 2-pent-4-enylmagnesium chloride in tetrahydrofuran at 100° from the data reported[2] for 1-but-3-enylmagnesium bromide in ether, by extrapolating to 100° and applying the corrections observed in other series for the changes in solvent, halogen, and α-substitution.[8,16]
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17. Methyl groups destabilize aryl radical anions [R. G. Lawler and C. T. Tabit, *J. Amer. Chem. Soc.*, **91**, 5671 (1969) and references cited therein].
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22. Substantial cyclization during Grignard reagent formation could account for the very different ratio reported recently[5] for hydrolysis products obtained from a reaction of **2**.