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Cyclizations during the Grignard Reactions of ω-Bromoalkynes*

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The Grignard reactions of a number of ω-bromoalkynes have been shown to undergo regioselective cyclizations in certain instances to give the smaller possible carbocycle. These cyclizations are shown to result from two competing processes, whose relative efficiencies depend upon the chain length and the remote substitutent on the acetylene. These are interpreted as a radical cyclization which occurs only during the time the Grignard is being formed from the bromide and an organometallic reaction which slowly transforms the Grignard reagent into its cyclic isomer. The mechanistic details of these transformations are discussed.

INTRODUCTION

Cyclizations that occur during the Grignard reactions of olefinic halides and the reverse ring-opening processes have been examined in some detail.[1] Less effort has been devoted to the corresponding acetylenic derivatives in spite of the greater synthetic potential of cyclizations of such compounds. Richey and coworkers demonstrated some time ago the slow, but highly regioselective transformation of a pre-formed 5-alkynylmagnesium halide to the corresponding alkylidenecyclopentane derivative in THF at 100 °C.[2] While this conversion was exceedingly slow (6 days), it was estimated to be more facile than that of an olefinic analog.[3] Trimethylsilyl substitution at the acetylene terminus,[4] the strategic incorporation of aromatic rings into

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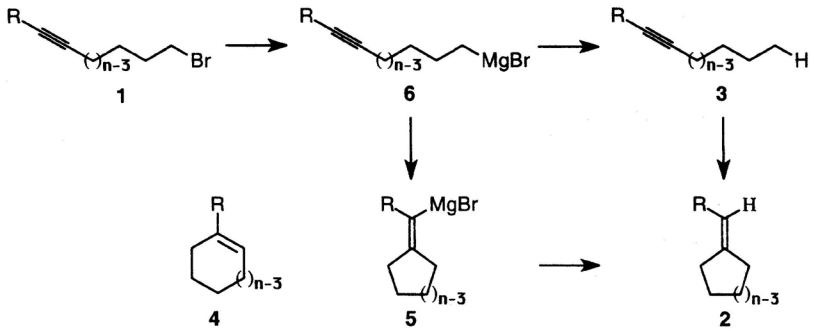
the system,[5] and the use of a more reactive allylic Grignard reagent[6] all appear to facilitate the cyclizations of acetylenic Grignard reagents considerably.

The evidence for the involvement of radical intermediates during the formation of Grignard reagents has accumulated over the years, although there remains considerable controversy concerning whether these radicals are localized on the magnesium surface or are freely diffusing in solution.[7] Independent radical cyclizations of acetylenic halides using various methods have been extensively examined since our initial studies[8,9] and such reactions are now established in the synthetic methodology for cyclic compounds.[10] However, synthetic interest in the Grignard cyclizations has decreased in view of the more recent discovery of suitable conditions for the clean metal-halogen exchange of alkyl iodides to provide the organolithium reagents, since the latter organometallic reagents are substantially more reactive towards cyclization.[11] Nonetheless, the systematic examination of the Grignard chemistry of bromoacetylenes in this study illustrates several interesting mechanistic aspects which are of more general concern to our understanding of the nature of the Grignard reaction.

RESULTS

The Grignard reactions of a number of ω-haloalkynes of general structure **1** with substituents R and chain lengths n were investigated.[9] All reactions were performed in flame-dried glassware under an argon atmosphere using anhydrous solvents. Reactions were normally run by adding the starting halide all at once to an excess of triply sublimed magnesium chips (other sources of magnesium gave different results) in the specified solvent at its reflux temperature. Quantities were adjusted to provide approximately 1% solutions of Grignard reagent. Prior to the introduction of the reactant, a small amount of a simple Grignard reagent was prepared in the reaction medium from a reactive alkyl halide containing the same halogen as the reactant. This served to activate the magnesium surface and also to scavenge traces of moisture and oxygen. The progress of reactions was followed by hydrolysis of aliquots and analysis by gas chromatography (GC). The Grignard reagents were formed rapidly from bromides and iodides under these conditions as shown by the disappearance of the starting material within 15 minutes. The hydrolysis products from these reactions were isolated by preparative GC and characterized by spectroscopic methods, usually with the aid of authentic samples obtained by unambiguous synthetic routes.[9]

As expected, cyclization was most facile with the n = 4 series. Thus, the phenyl-substituted alkynyl bromide **1a** (R = Ph) was transformed into benzylidenecyclopentane (**2a**) in 90% distilled yield in a preparative reaction in



Ia, R=Ph, n=4; **Ib**, R=*p*FPh, n=4; **Ic**, R=*p*MePh, n=4; **Id**, R=*p*MeOPh, n=4; **Ie**, R=Bu, n=4; **If**, R=Ph, n=5; **Ig**, R=Bu, n=5; **Ih**, R=Ph, n=3; **Ii**, R=Bu, n=3;**Ij**, R=Ph, n=6

Scheme 1.

refluxing THF (66 °C) run for 9 days. Less than 1% of acyclic acetylene **3a** was observed by GC at the end of this period. There was no detectable amount (<1%) of 1-phenylcyclohexene (**4a**), the product expected from the alternate regiochemistry in the intramolecular addition reaction. In an identical reaction that was hydrolyzed after 1 hour, the ratio of **2a** to **3a** was 57 : 43. The presence of organometallic reagent was determined by the quenching of aliquots with D_2O. After one hour, both **2a** and **3a** showed 99% deuterium incorporation; whereas at 24 hours, the level of incorporation in these products had decreased to 95% and 96%, respectively. Thus, essentially complete conversion to the cyclic Grignard reagent **5a** can be achieved in good yield and with excellent regioselectivity, providing this organometallic intermediate cleanly for further synthetic transformations.

It was possible to obtain good kinetic data on the cyclization of the initially formed acyclic Grignard reagent **6a** in the higher boiling solvent dimethoxyethane (DME) at its reflux temperature (85 °C), where cyclizations proceeded at a more reasonable rate. It is important to note that the data for these determinations were obtained by monitoring reactions until the starting halide was totally consumed and only then measuring the rate of the subsequent cyclization of **6a** to **5a** by GC analysis of the evolution of the mixture of cyclic and acyclic products in hydrolyzed aliquots. Reactions were usually followed for several half lives and the conversion to **2a** was essentially complete (>99%) after 24 hours. The data fit first-order kinetics to provide the rate constant for the organometallic cyclization starting from bromide **1a** that is listed in the Table. Similar reactions of **1a** were also run at the lower temperatures of 67 and 51 °C. Measurements over this range of more than 30 °C permit estimation of the Arrhenius parameters for the cyclization process, which are: $\log A = 7.5 \pm 0.1$ and $E_a = 18.1 \pm 0.1$ kcal/mole (correlation coefficient = 0.9999).

The DME solvent system was also convenient for comparison of the cyclizations of the Grignard reagents derived from the *p*-F (**1b**), *p*-Me (**1c**) and *p*-OMe (**1d**) analogs of **1a**. The products of these reactions were isolated for characterization from reactions interrupted at a point when comparable amounts of the cyclic and acyclic products were present. The kinetic data for the cyclizations of the corresponding Grignard reagents are given in the Table. The rates of these cyclizations vary over a factor of less than three. A Hammett plot of the rate data for the cyclizations of the four aryl-substituted Grignard reagents of type **6** against σ values[12] gives a reasonable correlation with $\rho = +1.3 \pm 0.1$ (correlation coefficient = 0.9907). The modest positive ρ value indicates that the cyclization of **6** to **5** is influenced relatively little by the *para* aryl substituent in these $n = 4$ cases.

More detailed consideration of the rate plots for these kinetic runs reveals an important feature of these Grignard reactions. Thus, the rates for the cyclization of the Grignard reagents **6** are much too slow to account for the total amount of cyclic product observed experimentally. This is most obvious from the intercepts of the least-squares kinetic lines ($-\ln A/A_0$), which are substantially greater than zero, indicating that not all of the cyclic product was formed by the process being measured. This means that a second cyclization process must have been operative prior to the start of the kinetic measurements, namely during the time that the Grignard reagent was being generated from haloalkyne **1**. A conservative estimate of the amount of cyclization occuring by this transient pathway during the Grignard formation stage of the reaction can be obtained from the intercepts of the kinetic lines, where zero time is defined as the instant of injection of halide **1** into the reaction vessel. The corresponding values for the amount of cyclization at the intercept (assuming instantaneous conversion of the halide to the Grignard reagent) are given in the Table as percentages of **2** at t_0. These cyclization values for **1a–d** fall in the 60% range (see Table I). Consequently, the transient cyclization process in these cases actually accounts for more of the cyclic product **2** than that derived from isomerization of the preformed Grignard reagent **6**.

The alkyl-substituted bromide **1e** ($n = 4$; R = Bu) was found to cyclize more slowly than its phenyl analog. Pentylidenecyclopentane (**2e**) was the only significant product other than alkyne **3e**. Six-membered cycloalkene **4e** was specifically shown to be absent (<1%). In refluxing THF, **2e** constituted 27% of the product mixture after 0.5 hours and further heating only very slowly increased this cyclic product to the maximum 33% achieved after 6 days. The cyclization to **2e** was more facile in refluxing DME, where the 29% of **2e** present after 1 hour increased to 92% after 7 days. Under these conditions, the rate of cyclization of **6e** was estimated to be slower than that of the phenyl-substituted derivative **6a** by a factor of about 34 (see Table I for rate data). Cyclization during the formation of the Grignard reagent was

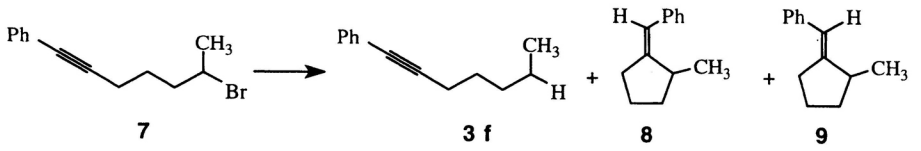
TABLE I

Kinetic data for the cyclization reaction of **1**

	$\frac{T}{°C}$	R group	n	$\frac{k}{sec^{-1}}$	intercept	% of **2** at t_o	correl. coeff.	half-life / h	run time / h
1a	85	C_6H_5	4	$3.41 \pm 0.09 \times 10^{-4}$	1.08	66%	0.9936	0.56	2.0
1a	85	C_6H_5	4	$3.43 \pm 0.06 \times 10^{-4}$	1.07	66%	0.9983	0.56	1.5
1a	67	C_6H_5	4	$8.38 \pm 0.40 \times 10^{-5}$	1.32	73%	0.9886	2.30	4.0
1a	51	C_6H_5	4	$2.12 \pm 0.05 \times 10^{-5}$	1.20	70%	0.9925	9.08	10
1b	85	p-FC_6H_4	4	$3.28 \pm 0.10 \times 10^{-4}$	1.02	64%	0.9924	0.57	1.25
1b	85	p-FC_6H_4	4	$3.24 \pm 0.12 \times 10^{-4}$	0.95	61%	0.9848	0.59	1.25
1c	85	p-MeC_6H_4	4	$1.83 \pm 0.04 \times 10^{-4}$	1.04	64%	0.9981	1.05	1.0
1c	85	p-MeC_6H_4	4	$1.80 \pm 0.07 \times 10^{-4}$	1.07	66%	0.9847	1.07	3.5
1d	85	p-$MeOC_6H_4$	4	$1.51 \pm 0.02 \times 10^{-4}$	0.97	62%	0.9981	1.27	4.0
1d	85	p-$MeOC_6H_4$	4	$1.54 \pm 0.04 \times 10^{-4}$	0.85	57%	0.9909	1.25	1.5
1e	85	C_4H_9	4	$1.01 \pm 0.02 \times 10^{-5}$	0.31	27%	0.9997	19.1	27
1h	85	C_6H_5	3	$1.72 \pm 0.05 \times 10^{-5}$	0.00	0%	0.9934	11.2	5.0

also important for **1e**, as indicated by the intercept of the kinetic line, although this process was only about half as significant (31%) for alkyl-substituted **1e** relative to phenyl-substituted **1a**.

Information about the stereochemistry of the $n = 4$ cyclization reaction was provided by a study of the analogous secondary bromide **7**, whose methyl group serves to label the two ends of the chain. Reaction of **7** with magnesium in THF at reflux gave a mixture of acetylene **3f** and two cyclized products identified as *syn*- and *anti*-benzylidene-2-methylcyclopentane (**8** and **9**, respectively). The secondary starting bromide **7** was less reactive than the primary bromides **1**, but was completely consumed after 2 hours, at which time hydrolysis of an aliquot showed a 16 : 36 : 48 mixture of **3f** : **8** : **9**, respectively. Further heating resulted in only slow evolution of the product mixture, but it reached the proportions of 8 : 36 : 56 after 7 days. Thus, **7** appears to undergo a slightly more facile cyclization than analog **1a** by the transient reaction occuring during the formation of the Grignard reagent. This cyclization process is clearly not stereoselective and leads to a mixture of *syn* and *anti* cyclic products. However, the subsequent slow cyclization of the acyclic Grignard reagent, while modest in amount, appears to result in an increase of the *anti* isomer **9** uniquely. This process corresponds to an intramolecular *syn* addition of the carbon-magnesium bond to the acetylene group.



Scheme 2.

In order to define the behavior of the corresponding radical, bromide **7** was also reduced with tributyltin hydride in dilute solution in refluxing benzene.[9] The same three products, **3f**, **8**, and **9**, were observed, this time as a 3 : 60 : 37 mixture. Thus, cyclization of the secondary radical derived from **7** is similar to that of the primary radical generated from **1a**.[8] As expected, this radical cyclization does not show significant stereoselectivity owing to the well-known characteristics of the intermediate vinyl radical.[13]

The identity of cyclic products **8** and **9** was confirmed by independent synthesis. In a one-pot process, methylenetriphenylphosphorane was monoalkylated with 1,4-dibromopentane, after which the resulting phosphonium salt was both cyclized and deprotonated to the ylide by treatment with two equivalents of *n*-butyllithium. Finally, benzaldehyde was added to the re-

sulting ylide to give a mixture of the benzylidenecyclopentanes **8** and **9**. The compound with the shorter retention time was assigned the *syn* structure **8** on the basis of a more shielded methyl group (δ = 1.01 ppm) in the ^{1}H-NMR spectrum than that of isomer **9** (δ = 1.18 ppm). The methyl group of **8** is situated close to and above benzene ring so as to experience a shielding influence[14] in the minimium-energy conformation as determined by a molecular mechanics calculation. The *syn* isomer **8** also shows a lower intensity band (255 nm; ε = 4500) associated with the styrene chromophore in its UV spectrum relative to *anti* isomer **9** (257 nm; ε = 6100). Greater distortion of the chromophore from planarity for *syn* isomer **8**, owing to steric interactions between the methyl and phenyl groups in the *syn* structure, may account for this feature.

Cyclization of higher homologs with n = 5 was less facile. Thus, phenyl-substituted bromide **1f** gave a 65 : 35 mixture of phenylalkyne **3f** and benzylidenecyclohexane (**2f**) after 1 hour in refluxing THF. However, heating for a further 8 days did not modify this ratio. In refluxing DME, 49% of cyclic **2f** was present after one hour; but after 6 days this product had increased to only 61% . No 1-phenylcycloheptene (**4f**) was detected in these product mixtures (>1%). In this instance, it is clear from the very slow product evolution data that almost all of the cyclic product was formed during the generation of the Grignard reagent and not by subsequent isomerization of acyclic Grignard reagent **6f** to the cyclic Grignard **5f**. It was not possible to obtain reliable kinetic information for the organometallic process in this case, owing to its very slow cyclization. The presence of organometallic intermediates in these reactions was probed by quenching aliquots with D_2O. In refluxing THF, **2f** and **3f** both showed 98% incorporation of one deuterium after 1 hour. Incorporation decreased to 77% and 82%, respectively, after 6 days. Interestingly, in refluxing DME, deuterium incorporation was somewhat less efficient, being 99% and 94%, respectively, after 1 hour; these values decreased to 25% and 46% over 6 days. Thus, the initial conversion to the organometallic species appears to be highly efficient, although the Grignard reagents do slowly undergo decomposition upon prolonged heating, presumably by proton abstraction from the solvent.

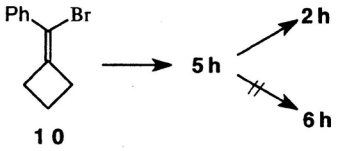
The corresponding n = 5, alkyl-substituted bromide **1g** (R = Bu) gave only 3–6% of pentylidenecyclohexane (**2g**) in a mixture with **3g** in diethyl ether, THF or DME at reflux and no 1-butylcycloheptene (**4g**) was observed at all. The amount of **2g** remained constant upon further heating, suggesting that all of the cyclic product from this particular acetylenic halide was generated during the formation of the Grignard reagent.

The chemistry of the n = 3 system provides an interesting contrast with the longer-chain homologs.[4] The phenyl-substituted bromide **1h** gives mixtures of benzylidenecyclobutane (**2h**) and acetylene **3h**. Once again the cyclization is highly regioselective, since no 1-phenylcyclopentene (**4h**) was ob-

served. In one experiment in refluxing DME, only 1% of **2h** was formed in 0.5 hours, but cyclization proceeded to 56% in 24 hours and on to a maximum of 62% over 15 days. Kinetic plots showed a pronounced curvature at longer reaction times, which is attributable to hydrogen abstraction from the solvent competitive with these slow cyclizations. However, it was possible to estimate a rate constant (see Table I) assuming first-order kinetics for the data for the first 10 hours of reaction (< one half-life). On this basis, the cyclization of Grignard reagent **6h** is approximately 20 times slower than that of the analogous n = 4 Grignard **6a**. Furthermore, the intercept of the kinetic line corresponds to essentially zero cyclization in agreement with the composition evolution data. This indicates very little, if any, cyclization during Grignard reagent formation. In refluxing THF, only 10% of cyclic product **2h** was observed over 8 days and 21% during 30 days.

Cyclization of the alkyl-substituted analog **1i** (n = 3; R = Bu) was even less efficient. In refluxing DME, there was <1% of cyclization after 5 h, whereas a maximum of only 11% was achieved after 7 days. In THF, only a trace (<1%) of **2i** was seen by GC after 8 days. Although it was difficult to achieve much cyclization here, it is clear that the cyclization that occurs is of the organometallic type.

Since alkylidenecyclopropane[15] and cyclobutylcarbinyl[1] Grignard reagents isomerize to ring-opened isomers, it was deemed prudent to examine the stability of the corresponding cyclobutane derivative **5h**, in order to ascertain whether this strained Grignard reagent is in equilibrium with observable amounts of its acyclic isomer **6h** under the reaction conditions. Consequently, cyclic bromide **10** was reacted with magnesium in both DME and THF and shown to produce only benzylidenecyclobutane (**2h**) during 144 hours at reflux. An experiment in THF which was quenched with D_2O after 1 hour gave **2h** which had incorporated 99% deuterium at the vinyl position. This demonstrates clean formation of cyclic Grignard reagent **5h** from **10**. Thus, equilibrium appears to be almost completely on the side of cyclic Grignard reagent **5h**, even in this case where the cyclic isomer possesses substantial ring-strain. This is in agreement with the observation that the corresponding free-radical also does not ring-open.[9] The increased strength of a vinyl-magnesium bond over that of an alkyl-magnesium bond,[16] should only increase the thermodynamic advantage of the cyclobutane isomer.



Scheme 3.

In the case of **1j** (n = 6; R = Ph), it was the corresponding iodide which was examined under typical Grignard conditions. However, this attempt to extend the range of these cyclization reactions to the formation of a seven-membered ring was not successful. In both THF and DME, the only product observed during the course of prolonged heating was acyclic acetylene **3j**.

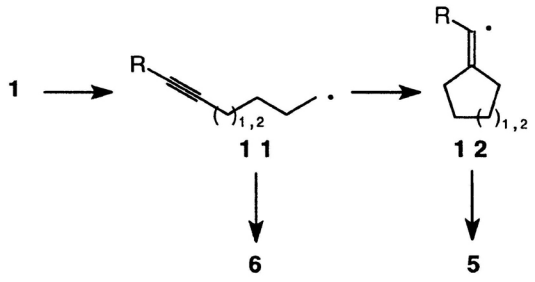
A similar situation was found upon reacting 4-bromo-1-phenyl-1-butyne with magnesium in THF. Reaction of this shorter-chain analog yielded neither cyclopropyl nor cyclobutyl derivatives, but only the corresponding acetylene. In this case, the strained, cyclic Grignard reagent is known to open to its acyclic isomer.[15]

DISCUSSION

The Grignard chemistry of bromoalkynes of type **1** consists of two different cyclization processes, both of which fortuitously lead to the same final product, a feature which tends to obscure the mechanistic complexity of this system. There is a transient cyclization process which gives cyclic products of type **2**, but which operates only during the time the Grignard reagent is being generated. This is almost certainly a free-radical process.[7] Once formed, the acyclic Grignard reagent is subject to slow isomerization to the cyclic isomer by a second type of reaction, one that probably proceeds by a concerted organometallic mechanism.[1] The balance between these two competing processes depends on the chain-length between the two reactive centers and the nature of the substituent at the remote end of the acetylene, among other variables. It should be noted, however, that the conditions utilized for formation of the Grignard reagent in this study are not those typically used for this classic organometallic reaction. The coordinating solvent DME, the high temperatures, and the high concentrations of alkyl halides utilized in this study can all influence the course of these reactions, especially the transient cyclization process, whose importance may well be magnified under the reaction conditions we have used.

The accumulated evidence has established with a reasonable degree of certainty that free-radical intermediates are involved in the very complex, heterogeneous transformation of an alkyl halide into a soluble alkylmagnesium halide.[7] Furthermore, the study of free radicals of type **11** by alternate means[8,9] has established that there is high regioselectivity for the new carbon bond formation at the more proximate center of the acetylene function. This selectivity is, of course, just that observed in the global Grignard reaction. Furthermore, a phenyl substitutent at the remote alkyne site facilitates cyclizations of radical **11** relative to an alkyl group. Radical cyclizations of **11** are facile with the n = 4 case to form five-membered radicals of type **12**. They are also competent, though less efficient, in generating six-membered carbocycles in the n = 5 situation, but radical cyclizations of the

n = 3 system have not been observed.[8,9] It is probably an unfavorable kinetic situation which prevents this last cyclization from being competitive with other reactions of intermediate radical **11** in the n = 3 situation, since cyclic radical **12** appears to be more stable than its acyclic isomer. The observation that cyclic radical **12** (n = 3; R = Ph) does not ring-open to its acyclic counterpart **11** is consistent with this view.[9] A characteristic feature of radical cyclizations to acetylenes is that they are not stereoselective, as shown in the present study by the radical cyclization of bromoalkyne **7** with tributyltin hydride to give a mixture of geometrical isomers **8** and **9**, and as frequently demonstrated elsewhere.[10] Thus, the results of this study are in accord with expectations for radical intermediates in the transient cyclizations that occur during the preparation of the Grignard reagent, specifically the formation of five-membered rings more readily than six-membered ones with a phenyl group facilitating both cyclizations, the absence of cyclobutyl products, and the randomization of stereochemistry in the cyclization of **7** to isomeric five-membered ring products **8** and **9**.



Scheme 4.

The radicals **11** are thought to be formed by approach of alkyl halide **1** to the magnesium surface where it reacts by single-electron transfer and subsequent (or simultaneous) dissociation of the resulting radical-anion into alkyl radical **11** and halide anion (or a magnesium halide species of some sort).[7] The radical thus generated, whether adsorbed on the magnesium surface or freely diffusing in solution, clearly has enough molecular integrity and sufficient lifetime to undergo its characteristic intramolecular addition to give cyclic radical **12** in the n = 4 and n = 5 examples. Further evolution on to the corresponding Grignard reagents **6** and **7** takes place with both the acyclic radical **11** and its cyclic isomer **12**. (Not much information has been developed with respect to this part of the overall process leading to the Grignard reagent.) Two aspects of these putative radical processes are noteworthy for the specific reactions under examination in this study. First of all, the radical cyclizations are not trivial side-reactions; they account for

the majority of the cyclic products generated in the efficient phenyl-substituted, $n = 4$ system and also in the $n = 5$ examples. Secondly, these radical species do not partake of other potential radical reactions to any significant degree, since essentially all of the intermediate radicals (cyclic and acyclic) ultimately end up as a Grignard reagent. This point is clearly demonstrated by the various hydrolysis experiments with D_2O, which give high incorporation of deuterium into both cyclic and acyclic hydrolyzed products at a stage of the reaction when all of **1** has been converted to Grignard reagents. This result also implies that, if the radical intermediates are freely diffusing, return of radicals **11** and **12** to the surface and conversion on to Grignards **6** and **5**, respectively, takes place much faster than hydrogen abstraction from the solvent to give the corresponding hydrocarbons directly.[17]

The organometallic part of the cyclizations appears to involve a totally different type of mechanism. The Hammett correlation with $\rho = +1.3$ suggests that a large amount of charge is not built up at the remote acetylenic carbon in the transition state for the rate-determining step of the cyclization reaction. This speaks persuasively against mechanisms (Figure 1) in which processes such as electron-transfer from the organometallic unit to the triple bond gives a radical-anion at the acetylenic site (path a), or carbanionic attack (from an ion pair derived from heterolysis of the carbon-magnesium bond) on the triple bond leads to a cyclic anion (path b). The observed ρ value is similar to that obtained by Hill in a study of an olefinic Grignard rearrangement, who argues cogently that the ρ value is much smaller than expected for an anionic process by comparison with known ρ values for a variety of reactions which involve substantial anionic character.[18]

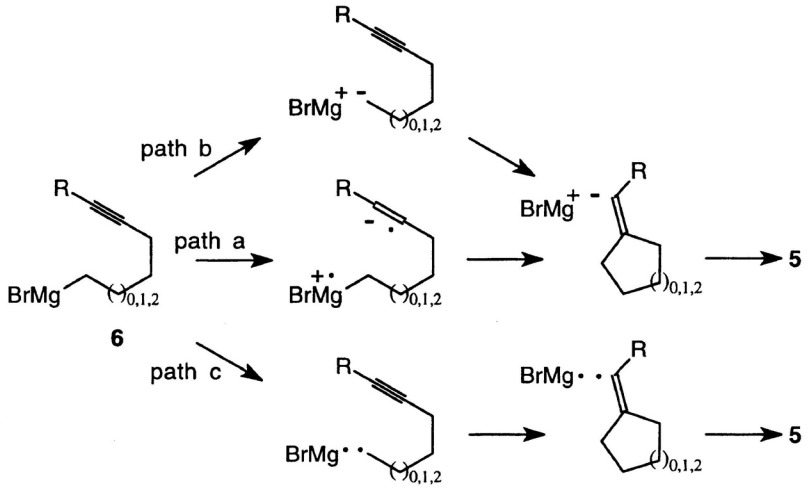
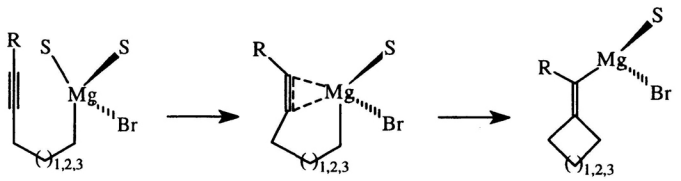


Figure 1. Possible mechanisms for the cyclizations of **6**.

Radical-pair formation by homolysis of the carbon-magnesium bond followed by radical cyclization (path c) also seems unlikely. The organometallic reagents in the $n = 3$ examples cyclize to four-membered rings and, furthermore, these isomerizations occur more easily than those of the $n = 5$ Grignard reagents, unlike independently generated free-radicals of this type. In addition, the ρ of +0.38 that was estimated[9] for radical cyclizations of para-substituted aryl derivatives with $n = 4$, while of the same sign, is significantly smaller than the observed ρ for the organometallic transformations. Thus, a radical mechanism is not considered to explain satisfactorily the characteristics of the organometallic cyclizations in this study. These conclusions about radical and anionic mechanisms mirror those previously put forth for cyclizations of unsaturated Grignard reagents.[1]

The experimental information concerning the organometallic cyclization appears to be most consistent with a concerted rearrangement of the type generally proposed for intramolecular additions of unsaturated Grignard reagents.[1] Substituent effects in the phenyl ring of **6** are relatively small, since the new bonds are formed without much charge development at the remote carbon of the acetylene. This is consistent with the relatively small ρ value observed. The variant of this mechanism which invokes prior coordination of the unsaturated center to the metal finds support in acetylene coordination chemistry, where such complexes are frequently formed. For example, hydroalumination and carboalumination of acetylenes appear to involve complex formation.[19] Thus, a cyclic complex such as **13** is a potential intermediate on the way to cyclic Grignard **5**. Alternatively, a four-center addition leading directly to **5** can be considered. In this case, the two reacting bonds can be oriented in the same plane in a rectangular array or they can react in a crossed arrangement. Either rearrangement of the complex or concerted reaction *via* a rectangular geometry gives *syn* addition, whereas the crossed form of the four-center process should lead to *anti* addition. *Syn* addition is typically observed in reactions of organometallic reagents with alkynes. In accord with this, the results with methyl-labeled alkyne **7** suggest that the modest amount of Grignard cyclization observed after all of the **7** has been converted to Grignard reagent occurs by selective *syn* addition. This stereoselectivity was not seen in the initial study of these cyclizations using an alkyl-substituted acetylene,[2] where the product mixture contained both *syn*- and *anti*-addition products, but this could easily be a result of the subsequent isomerization of the vinyl Grignard reagent under the rather drastic conditions of the cyclization. A later examination of silyl-substituted alkynes showed clean *syn* addition.[4] Analogous organolithium reagents also add intramolecularly in a *syn* manner, although equilibration of the cylic vinyllithium intermediate does take place later in certain instances.[11] It should also be noted that cyclizations of these organolithium reagents are facilitated by phenyl substitution at the remote acetylenic carbon (relative to an alkyl group). Furthermore, cyclization of the $n = 4$ organolithium is much faster than its $n = 3$ analog, which in turn appears to be more reactive than

the $n = 5$ example. This is the same reactivity pattern observed for the Grignard cyclizations studied in this work.



6 **13** **5**

Scheme 5.

Cyclobutane products are not usually found in Grignard cyclizations of the olefinic analogs of **5**, but there is ample evidence that this is a thermodynamic problem, since the rearrangements of several substrates show that such species are kinetically accessible.[1] In the cyclization of alkyne **6**, the additional driving force of forming a more stable vinyl Grignard reagent **5**[16] is a significant factor favoring the cyclic product at equilibrium, even in the $n = 3$ case where the product is a strained cyclobutane.[4] The fact that benzylidenecyclobutane (**2h**) is formed with reasonable efficiency suggests to us that a mechanism involving complex formation is operative, since complexation of the metal to the alkyne poses no particular geometric problem, whereas the short $n = 3$ chain effectively prohibits a rectangular arrangement with close approach of the two carbon centers which form the new carbon-carbon bond. Sliding of the carbon attached to the magnesium over to the near acetylenic center should be facilitated in complex **13**. This is similar what is thought to happen in a variety of organometallic additions to triple bonds. The low Arrhenius factor observed in the temperature study of **1a** in the $n - 4$ series is indicative of a highly ordered transition state. One that resembles complex **13** would seem to satisfy this requirement since substantial rotational restriction of the chain is implied. It is even possible that complex formation is the rate-determining step.

EXPERIMENTAL

General procedures, apparatus, starting materials, products and references to these materials can be found in an earlier paper.[9]

*Preparative Grignard Cyclization of 6-Bromo-1-phenyl-1-hexyne (**1a**)*

To 2 g of Mg in 125 ml of anhydrous THF under argon was added 100 mg of 1-bromobutane. The solution was refluxed for 2 h, 6.80 g of **1a** was added and heating was continued for 9 days. After the addition of 2 ml of water, the solution was

dried, concentrated, and the residue was distilled to give 4.35 g (90%) of benzylidenecyclopentane (**2a**): b.p. 70–72 °C (0.3 mm). GC analysis of this distilled product showed less than 0.2% of **3a** and no detectable **4a**. An identical reaction was quenched with water after 1 h to give **2a** and 1-phenyl-1-hexyne (**3a**) in a 57 : 43 ratio. The products were separated by preparative GC and identified by comparison with authentic samples.

Analytical Grignard Reactions and Kinetic Determinations

Analytical reactions were performed in 100-mL, 3-neck, round-bottomed flasks equipped with an argon inlet on a reflux condenser, a glass stopper and a septum cap. The flask was flame-dried under a stream of argon. Solvents were distilled from lithium aluminum hydride immediately before use. An excess of triply sublimed magnesium (Dow Chemical Company; 99.9948%) was used. (The use of other sources for the magnesium gave moderately different kinetic results.) Reaction was initiated by the addition of 10 mg of a simple halide. Quantities were adjusted to give concentrations of the Grignard reagent of approximately 1% (w/v) starting from several hundred milligrams of **1**. The reaction mixture was checked by GC after 15 min to ensure that **1** was gone before kinetic runs were started. The kinetics were measured at the reflux temperature of the solvent held constant to ±1 °C or in a constant temperature bath. Cyclizations were monitored by periodically removing aliquots, hydrolysis and analysis by GC. Percentage-composition data were obtained by integrated GC peak areas. In several cases checked against an internal standard, there was no appreciable change in the material balance during a kinetic run. The products were identified by GC retention times and, where present in more than trace amounts, by isolation and comparison of spectral properties with authentic samples. Data for the kinetic experiments described briefly below are summarized in the Table I. For determination of the amount of Grignard reagent present in reaction mixtures, aliquots were quenched with 99.95% deuterium oxide and samples were isolated by GC and analyzed by mass spectrometry using low-energy ionization.

*6-Bromo-1-phenyl-1-hexyne (**1a**)*

The reaction of **1a** was performed in DME at reflux to give **2a** and **3a**; **1a** was completely gone after 15 min. Aliquots were removed between 15 min and 2 h. After 24 h, **3a** was <1% of the mixture. Hydrolysis of a reaction in THF with D_2O gave the following amounts of deuterium incorporation by mass-spectrometry: **2a** incorporated 99% after 1 h, 95% after 24 h; **3a** showed 99% incorporation after 1 h, 96% after 24 h by mass spectrometry.

Runs at lower temperatures were performed with **1a** using a constant-temperature bath. The temperature of the solutions increased slightly during the period of formation of the Grignard reagent (approximately 15 min) and were equilibrated prior to taking aliquots. A reaction at 67 °C was sampled between 30 min and 4 h. After 24 h, the amount of **3a** was <1%. A reaction at 51 °C was sampled between 1 and 11 h; after 5 days, the amount of **3a** was <1%.

*6-Bromo-1-*para*-fluorophenyl-1-hexyne (**1b**)*

Aliquots were removed from kinetics runs between 15 min and 2 h; after 24 h, the proportion of **3b** was <1%. A run on 3.8 g of **1b** for 30 min gave 3.1 g (92%) of **2b** and **3b** in a 79 : 21 ratio.

*6-Bromo-1-*para*-tolyl-1-hexyne (**1c**)*

Aliquots were removed between 15 min and 3 h; after 48 h, the amount of **3c** was 3–4%. A reaction on 4.0 g of **1c** for 30 min gave 3.2 g (89%) of **2c** and **3c** in a 73 : 27 ratio.

*6-Bromo-1-*para*-anisyl-1-hexyne (**1d**)*

Aliquots were removed between 15 min and 4 h; after 48 h, **3d** was 1% of the product. A run on 3.8 g of **1d** for 30 min gave 3.2 g (93%) of **2d** and **3d** in a 69 : 31 ratio.

*1-Bromo-5-decyne (**1e**)*

Reaction of **1e** in refluxing DME gave a mixture of 5-decyne (**3e**) and the following percentages of pentylidenecyclopentane (**2e**): 1 h, 29%; 3 h, 33.5%; 15 h, 58%; 27 h, 71%; 168 h, 92%. Cyclization kinetics were estimated using data through 27 h. Reaction of **1e** in THF gave the following percentages of **2e**: 0.5 h, 26%; 4.5 h, 27%; 17 h, 28%; 42 h, 29%; 70 h, 31%; 144 h, 33%. It was shown by GC that <1% of **4e** was present in either reaction.

*7-Bromo-1-phenyl-1-heptyne (**1f**)*

Reaction of **1f** showed only slight changes in the ratio of benzylidenecyclohexane (**2f**) to 1-phenyl-1-heptyne (**3f**) upon refluxing for extended periods. The following percentages of **2f** were detected: in DME at 1 h, 49% and at 150 h, 61%; in THF at 1 h and 200 h, 35%. It was shown by GC that <<1% of **4f** was present. Hydrolysis of a reaction in THF with D_2O gave the following amounts of deuterium incorporation by mass-spectrometry: **2f** incorporated 98% after 1 h, 82% after 150 h; **3f** showed 98% incorporation after 1 h, 77% after 150 h. In refluxing DME, deuterium incorporation was: 94% after 1 h and 25% after 150 h for **2f** and 99% and 46% for **3f**.

*11-Bromo-5-undecyne (**1g**)*

Reaction of **1g** gave pentylidenecyclohexane (**2g**) and 5-undecyne (**3g**) in several solvents. Aliquots removed periodically and analyzed by GC showed no noticeable change in the product ratios upon heating for extended periods. The following percentages of **2g** were observed: ether, 3%; THF, 5%; DME, 6%. No **4g** (<<1%) was detected.

*5-Bromo-1-phenyl-1-pentyne (**1h**)*

Reaction of **1h** in DME gave a mixture of 1-phenyl-1-pentyne (**3h**) and the following percentages of benzylidenecyclobutane (**2h**): 1 h, 7%; 3 h, 19%; 5 h, 30%; 7 h, 37%; 9 h, 42%. The rate of cyclization was estimated using the data for the first 5 h. In another experiment in DME, the 1% of **2h** present at 0.5 h was converted to 62% in 15 days. The following percentages of **2h** were observed in THF: 10% at 200 h, and 21% after 720 h. No **4h** (<<1%) was present in either reaction.

*1-Bromo-4-nonyne (**1i**)*

A sample of **1i** in refluxing DME disappeared after 15 min. Analysis of aliquots over time showed mainly 4-nonyne (**3i**) with the following amounts of pentylidenecyclobutane (**2i**): 5 h, 1%; 120 h, 7%; 167 h, 10%. GC showed <<1% of **4i**. An experiment in refluxing THF gave only a trace (<<1%) of material with the GC behavior of **2i**.

*8-Iodo-1-phenyl-1-octyne (**1j**)*

Reaction of iodide **1j** in refluxing DME gave 1-phenyl-1-octyne (**3j**) as >99% of the product by GC. The crude reaction product was spectroscopically identical with authentic **3j**.

4-Bromo-1-phenyl-1-butyne

Reaction in refluxing DME gave 1-phenyl-1-butyne as >99% of the product at all times. The spectra of the crude product were essentially identical with pure material.

*Grignard Reaction of 1'-Bromobenzylidenecyclobutane (**10**)*

The Grignard reaction of 200 mg of **10** was performed in both refluxing THF and DME as described above for a number of days. Aliquots showed only **2h** as a product; >>1% of **3h** was present. Hydrolysis of a reaction in THF with D_2O after 1 h gave **2h** which had incorporated 99% of one deuterium by mass spectrometry; ^{1}H-NMR confirmed this measurement and demonstrated that uptake of the deuterium was at the vinyl position.

*6-Bromo-1-phenyl-1-heptyne (**7**)*

To 50 ml of dry THF under N_2 was added 31 ml of 1.6 M *n*-butyllithium in hexane. The dropwise addition of 5.1 g of phenylacetylene was followed by the addition of 0.58 g of tetramethylethylenediamine. After heating to reflux for 2 h, the reaction mixture was cooled and 11.5 g of 1,4-dibromopentane was added. After heating to reflux for 24 h, the solvents were removed, the residue was dissolved in ether and the ether extract was washed with dilute aqueous HCl and dried ($MgSO_4$). Removal of the solvent and distillation gave **7**: 7.5 g (60%); b.p. 115–120 °C (0.25 mm); IR (neat) ν_{max}/cm^{-1}: 3030, 2220, 1600, 1570, 755, 690; ^{1}H-NMR ($CDCl_3$) δ/ppm: 1.74 (d, 3, J = 6 Hz), 1.6–2.1 (m, 4), 2.48 (t, 2, J = 6 Hz), 4.18 (sextet, 1, J = 6 Hz) 7.1–7.5 (m, 5); HRMS: m/z 250.0351 (M^+); calcd. for $C_{13}H_{15}Br$, 250.0358.

syn- *and* anti-*Benzylidene-2-methylcyclopentane (**8** and **9**)*

A suspension of sodium hydride in oil (70 mmol), was washed several times with dry pentane, before 35 ml of anhydrous THF was added under N_2, followed by 21.4 g of methyltriphenylphosphonium bromide and two drops of ethanol. After heating to reflux for 8 h, the solution was cooled, the solid was removed by filtration under N_2, and the orange solution was added to 6.9 g of 1,4-dibromopentane dropwise. After heating for 5 h at 50 °C, the solution was cooled to room temperature and 37.5 ml of a 1.6 M solution of *n*-butyllithium in hexane was added dropwise. The resulting deep red solution was stirred for 0.5 h before 6.4 g of benzaldehyde was added. After heating to reflux for 1 h, the solvents were removed and the residue was dissolved in ether, washed with water and dried ($MgSO_4$). Concentration and distillation afforded 4.0 g of an oil, b.p. 85–90 °C (0.5 mm), from which pure samples of **8** and **9** were isolated by preparative GC.

The *syn* isomer **8**, which was eluted first, showed UV(cyclohexane) λ_{max}/nm: 206 (ε = 4500), 255 (ε = 4500); IR (neat) ν_{max}/cm^{-1}: 3030, 1650, 1600, 910, 750, 695; ^{1}H-NMR ($CDCl_3$) δ/ppm: 1.01 (d, 3, J = 6 Hz), 1.4–2.0 (m, 4), 2.3–2.5 (m, 2), 3.0 (m, 1), 6.20 (m, 1), 7.0–7.3 (m, 5); ^{13}C-NMR ($CDCl_3$) δ/ppm: 18.9, 22.6, 34.93, 34.97, 35.2, 121.0, 125.2, 127.5 (4), 137.8, 150.3; MS m/z , 172 (83), 157 (33), 129 (69), 128 (25), 117 (49), 115 (33), 105 (35), 91 (72), 81 (100), 79 (25), 77 (41).

The *anti* isomer **9** showed UV (cyclohexane) λ_{max}/nm: 208 (ε = 4300), 257 (ε = 6100); IR (neat) ν_{max}/cm^{-1}: 3030, 1650, 1600, 965, 930, 910, 860, 750, 690; ^{1}H-NMR ($CDCl_3$) δ/ppm: 1.18 (d, 3, J = 7 Hz), 1.6–2.0 (m, 4), 2.56 (m, 3), 6.14 (m, 1), 7.0–7.3 (m, 5); ^{13}C-NMR ($CDCl_3$) δ/ppm: 19.3, 24.5, 31.2, 34.4, 40.5, 120.3, 125.1, 127.5 (2), 127.7 (2), 138.3, 149.9; MS: m/z 172 (78), 157 (39), 155 (36), 143 (20), 129 (69), 128 (26), 117 (71), 115 (38), 91 (79), 81 (100), 79 (100), 79 (20), 77 (19); HRMS: m/z 172.1242 (M^+); calcd. for $C_{13}H_{16}$, 172.1253.

Grignard Reaction of **7**

A mixture of 0.2 g of Mg and 12.5 ml of THF was heated to reflux with several drops of allyl bromide for 2 h, before a solution of 0.72 g of **7** in 60 ml of dry THF was added dropwise. After 2 h at reflux, an aliquot showed a 16 : 36 : 48 mixture of **3f** : **8** : **9**. Evolution of this mixture was slow, but after 7 days the product ratio was 8: 36 : 56. Hydrolysis and isolation of the products by preparative GC gave pure samples that were identical with the authentic materials.

Reaction of **7** *with Tributyltin hydride*

To a solution of 0.50 g of **7** in 28 ml of benzene (0.07 M) at reflux, was added dropwise a solution of 0.64 g of tributyltin hydride in 6 ml of benzene also containing 6 mg of AIBN. After heating for 1 h, GC analysis showed a 3 : 60 : 37 mixture of **3f** : **8** : **9**.

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SAŽETAK

Ciklizacije ω-bromalkina tijekom Grignardovih reakcija

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Pokazalo se da Grignardove reakcije brojnih ω-bromalkina teku uz regioselektivnu ciklizaciju i u određenim slučajevima daju manje moguću cikličku strukturu. Također se pokazalo da su te ciklizacije rezultat dvaju kompeticijskih procesa, čiji relativni utjecaj ovisi o duljini lanca te o udaljenim supstituentima na acetilenu. Te ciklizacije teku radikalskim mehanizmom koji je djelatan samo tijekom stvaranja Grignardova reagensa iz bromida i organometalnog spoja u reakciji koja polako transformira Grignardov reagens u njegov ciklički izomer. Raspravlja se o mehanističkim detaljima tih transformacija.