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CYCLIZATION OF THE GRIGNARD REAGENT FROM 5-CHLORO-3-METHYL-1-HEXENE; A REVERSIBLE ORGANOMAGNESIUM REARRANGEMENT *

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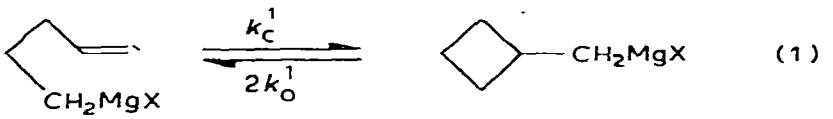
Summary

The Grignard reagent from 5-chloro-3-methyl-1-hexene cyclized reversibly to form an equilibrium mixture with two stereoisomers of the 2,4-dimethylcyclobutylmethyl-Grignard reagent. Equilibrium and rate constants for the opposing reactions have been evaluated at 80—100 and 100—120° C, respectively. Over this range, the equilibrium mixture favors the cyclic reagent by a ratio of about 3/1. Comparison with results for related compounds indicates that methyl substitution influences the equilibrium both by destabilization of the organomagnesium function and by stabilization of the strained ring. Additional comparisons of rate and equilibrium constants are discussed.

Introduction

In cyclization—ring opening rearrangements of organomagnesium compounds [1,2] such as the interconversion of I and II [3,4], the equilibrium most commonly favors cyclization for 5- or 6-membered rings and cleavage for 3- or



(1)

(I) (II)

4-membered ones [2]. This result is determined largely by differences in bond energies and by strain energies of the rings formed. The former is estimated [4]

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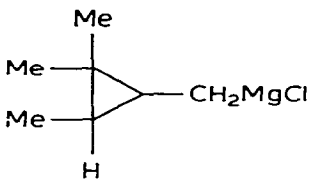
to contribute —21.7 kcal/mol to ΔH°, based on the model process:

$RCH_2—H + R'CH=CH_2 \rightarrow RCH_2CH(R')CH_2—H$

The latter may be approximated by group increment contributions to enthalpy of formation [5], 28.7, 26.2, and 6.3 kcal/mol for 3-, 4- and 5-membered rings. Some exceptions to this generalization have been found in instances involving the nortricyclyl skeleton [6] or vinylic or allylic Grignard reagents [7—10].

The relative stabilities of open-chain and cyclic isomers are also influenced by the degree of substitution. Although cyclopropylmethyl-Grignard reagents and even the substituted reagent III undergo essentially complete cleavage, 99.9% cyclization of IV to V has been reported [11].



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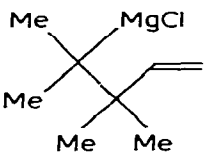

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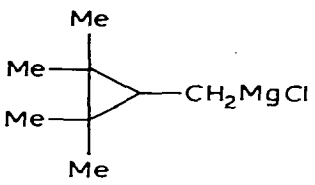
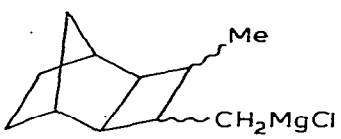


(V)

Lehmkuhl and coworkers [9,10] have also reported several examples, including VI—VIII, in which the 4-membered ring is formed by cyclization:



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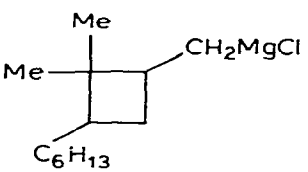

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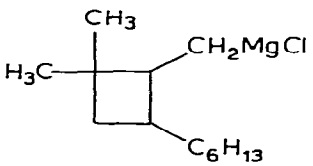
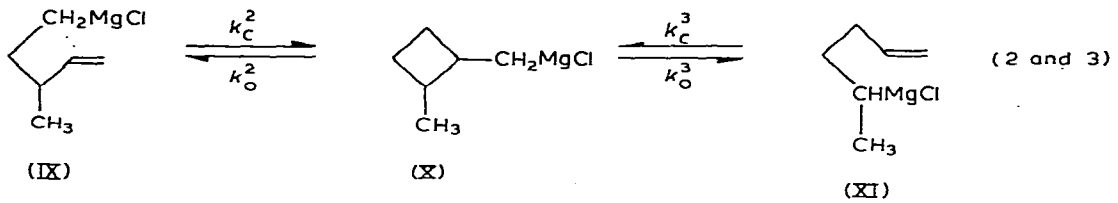


(VIII)

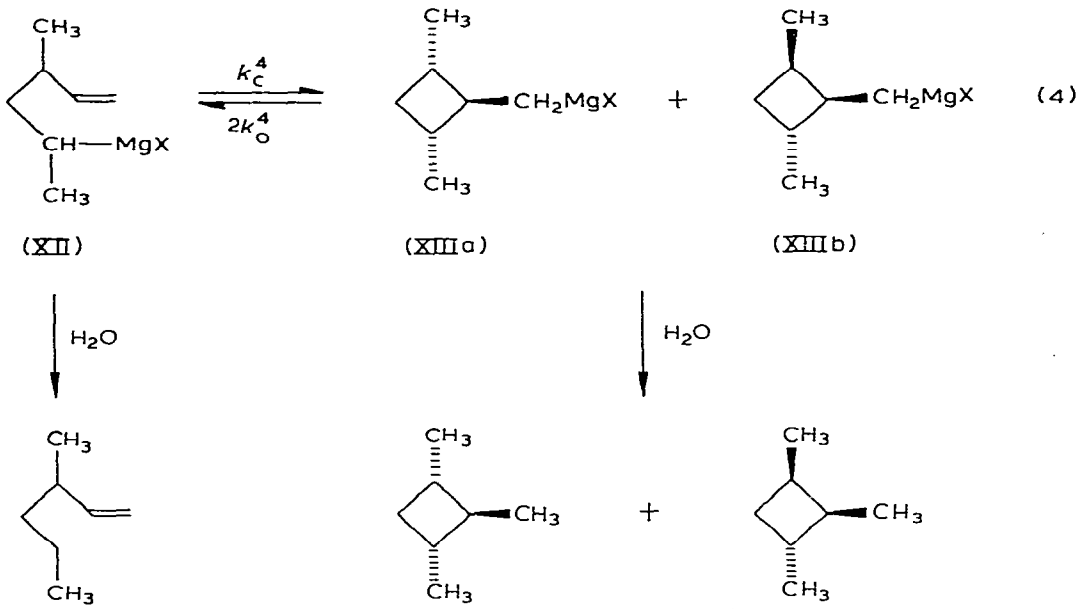
Closure of the strained ring is favored by conversion of a less stable secondary or tertiary Grignard reagent to a primary one in the cyclic isomer. This difference in stability between secondary and primary organometallic functions has been estimated variously as: $-\Delta G^\circ \approx 3$ kcal/mol ($\log K = 3.0$ to 3.4) from Li—I exchange at —70° C [12]; $-\Delta G^\circ \gtrsim 2.8$ kcal/mol ($\log K \gtrsim 2$) from Mg—Hg exchange at 33° C [13]; $-\Delta G^\circ \approx 5$ kcal/mol ($-\Delta H^\circ \approx 3.7$ kcal/mol; $\log K \approx 3$) from a rearrangement equilibrium between two cyclic organomagnesium compounds at 100° C [14]; and $-\Delta G^\circ \approx 3.3$ kcal/mol ($\log K \approx 2.1$) at 70° C derived from the unsaturated Grignard reagent rearrangement equilibrium between IX and XI in eq. 2 and 3 [10] *:

* We have some reservations about the last estimate. The authors adjust their observed free energy difference between the two Grignard reagents (3.85 kcal/mol) by —0.55 kcal/mol to account for a carbon skeleton contribution to the equilibrium constant, estimated as equal to the enthalpy difference between 1-hexene and 3-methyl-1-pentene. No source is given for the latter number, and the most recent literature value which we find for this difference is —1.88 kcal/mol [15]. This would lead to $-\Delta G^\circ$ ~2.0 kcal/mol between secondary and primary organomagnesium functions. (The skeleton contribution to ΔS° is small.) A further potential source of uncertainty arises if some of the hydrocarbon from hydrolysis of the Grignard reagent had actually been formed by attack of the secondary Grignard reagent on solvent, as found in the present study. In this event, the stability difference would have been underestimated.



(IX) (X) (XI)

We have studied a rearrangement equilibrium involving the 2,4-dimethylcyclobutylmethyl-Grignard reagent (XIII):

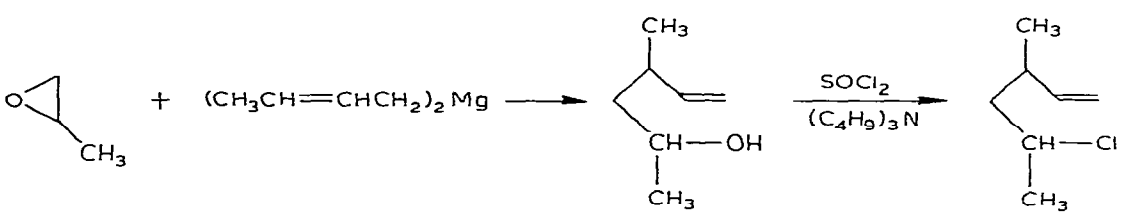


(XII) (XIIIa) (XIIIb)

In this case, the cyclic isomer is favored by a small margin, allowing both the rate and equilibrium to be studied conveniently. We report here our results for this system, and compare these results with those for the unsubstituted cyclobutylmethyl [4] (eq. 1) and the 2-methylcyclobutylmethyl system [10,16] (eq. 2 and 3).

Results

By the route shown below, the appropriate halide, 5-chloro-3-methyl-1-hexene (XV) was prepared:



(XIV) (XV)

Both XIV and XV were obtained as mixtures of two diastereomers (spectroscopic properties are reported in the experimental section). If crotylmagnesium chloride was used instead of dicrotylmagnesium, an additional alcohol product was obtained, 2,3-dimethyl-4-penten-1-ol. Apparently some addition to the secondary carbon of the epoxide occurs in the presence of the more Lewis-acidic halide. Precipitation with 1/2 mol of dioxane was sufficient to eliminate this side-reaction, even without separation of the reagent from the $MgCl_2$-dioxane complex. There was not a significant amount of product formed by reaction of the crotyl organometallic at its primary carbon, or by prior isomerization of the epoxide.

A Grignard reagent was prepared from chloride XV in ether. Hydrolysis of this reagent and gas chromatography yielded 3-methyl-1-hexene as the only important product. The NMR spectrum of the solution of Grignard XII showed, in addition to olefinic and methyl absorption, a sextuplet at —0.08 ppm which may be assigned to the α-hydrogen of the secondary organomagnesium function.

When the solution was heated for several hours at 100° C or higher, a doublet appeared in the NMR spectrum at —0.32 ppm, as expected for cyclized Grignard reagent (XIII). Hydrolysis yielded two new hydrocarbon components, which were isolated by preparative gas chromatography and examined spectroscopically. Both were shown to be saturated from their IR and NMR spectra, and their isolation by GLC was facilitated by prior removal of the 3-methyl-1-hexene from the mixture by ozonolysis. The major one was assigned as the *trans,trans*-isomer of 1,2,3-trimethylcyclobutane, based on the presence of only five ^{13}C NMR signals in its spectrum and its anticipated relative stability. Lower-field positions of ^{13}C and ^{1}H methyl resonances and relatively high-field tertiary ring proton resonances are consistent with this structure. The minor isomer had seven different ^{13}C NMR signals (methyl groups at 13.7, 14.7 and 19.9 ppm), and three methyl doublets could be picked out by comparing 60 and 100 MHz proton spectra. Hence it was assigned the *cis,trans* stereochemistry.

After heating for extended periods of time, the mixture of hydrocarbon hydrolysis products approached a constant limiting composition (e.g., about 23% of open-chain isomer at 100° C). It was possible also to approach equilibrium from the opposite direction. A sample of Grignard reagent which had been isomerized to a steady composition was treated with an excess of bromine in ether. The principal product component had proton and ^{13}C spectra consistent with the *trans,trans* isomer of 2,4-dimethylcyclobutylmethyl bromide. Peaks could also be assigned to a minor stereoisomer. The product appeared to be essentially free of open-chain isomer; the unsaturated Grignard reagent XII should have been converted to higher-boiling tribromide. When a Grignard reagent was prepared from the cyclic bromide, the hydrolysis product before heating consisted of 11% of 3-methyl-1-hexene and 73 and 16% of the two trimethylcyclobutanes. After 48 h at 100° C, the ratio of these hydrolysis products was 24/58/18.

The rate of approach to equilibrium, starting with XII, was followed by hydrolysis and analysis of samples heated for shorter periods of time.

Destruction of Grignard reagent by reaction with the solvent complicated

TABLE 1

COMPOSITION OF EQUILIBRATED REACTION MIXTURES OF GRIGNARD REAGENTS XII AND XIII IN ETHER

T (°C)	Concentration (*M*)	Composition (%)		
		XII	XIIIa	XIIIb
80	[a]	16.3 ± 0.4	64.5 ± 0.6	19.2 ± 0.3
100	ca. 1.0	23.4 ± 1.3	61.2 ± 1.4	15.4 ± 1.4
100	ca. 1.0 [b]	22.4 ± 0.9	61.7 ± 1.8	15.8 ± 1.0
100	ca. 1 [c]	24	58	18
100	[a]	22.5 ± 1.1	57.1 ± 1.1	20.4 ± 0.7
110	ca. 1.0	26.4 ± 1.8 [d]	59.0 ± 2.4	14.9 ± 1,5
120	ca. 1.0	23.1 ± 1.4 [e]	61.7 ± 1.5	14.9 ± 1.1

[a] Concentrated reagent produced by removal of excess solvent under vacuum. [b] Tetrahydrofuran solution. [c] Reaction starting with 2,4-dimethylcyclobutylmethylmagnesium bromide. [d] Value calculated from extrapolated equilibrium constant in concentrated reagent is 26.2%. [e] Value calculated from extrapolated equilibrium constant in concentrated reagent is 29.9%.

the effort to obtain accurate rate and equilibrium constants. The secondary Grignard reagent preferentially abstracted a proton from solvent, producing an excess of 3-methyl-1-hexene in the hydrocarbon hydrolysis product. Major errors from this source were eliminated by pumping solvent and volatile products from the Grignard reagent before hydrolysis *, since equilibration was substantially more rapid than reaction with the solvent. Some error may remain, since the apparent equilibrium mixture of Grignard reagents actually corresponds to a steady state in which the content of secondary reagent is reduced below its equilibrium value by virtue of its continuous slow removal. A lack of internal consistency suggests such a problem at 120° C. Equilibrium data were also obtained in concentrated Grignard reagents, from which most of the solvent had been removed under vacuum. In these mixtures, the rearrangement was significantly faster, allowing attainment of equilibrium at lower temperature in a reasonable period of time. Compositions of the equilibrated mixtures are shown in Table 1. In samples heated at 100° C, the final mixture had similar compositions in 1 *M* ether and THF solutions and in the concentrated reagent. The fraction of open-chain reagent was the same in all, within experimental error, though there was a small consistent difference in the relative yield of the two cyclic isomers in the concentrated mixture. In the subsequent treatment of equilibrium and rate constants, the cyclic Grignard reagent is treated as a single component. Therefore, the concentrated solution equilibrium constant at 80° C and the average of all 100° C data were used to obtain extrapolated equilibrium constants at 110 and 120° C. From equilibrium constants ($= k_c/k_0$) and the apparent rate constant for approach to equilibrium ($= k_c + k_0$), rate

* In preliminary experiments before this precaution was taken, the concentration of trimethylcyclobutanes in the hydrolysis product appeared to reach a maximum, and then decreased with further heating. As the more reactive secondary Grignard reagent XII was selectively converted to hydrocarbon by reaction with solvent, ring-cleavage of XIII occurred to replenish the XII which had been lost.

TABLE 2

RATE AND EQUILIBRIUM CONSTANTS [a] FOR EQUILIBRATION OF GRIGNARD REAGENTS XII AND XIII

T (°C)	Solvent	K_{obs}	$10^5 k_{obs}$	$10^5 \times (k_c^4)$ [b]	$10^5 \times (k_0^4)_{obs}$ [c]
100	Ether	3.41 ± 0.2 [d]	2.65 ± 0.15	2.05 ± 0.10	0.60 ± 0.04
110	Ether	2.82 ± 0.3 [e]	6.35 ± 0.4	4.7 ; ± 0.3	1.66 ± 0.20
120	Ether	2.35 ± 0.3 [f]	11.8 ± 1.2	8.3 ± 0.8	3.5 ± 0.4
100	THF	3.44 ± 0.16	0.875	0.678	0.197

[a] Equilibrium and rate constants defined on the basis of XIIIa and b as a single component. Error limits were assigned subjectively as the maximum variation which appeared consistent with the precision of the raw data. [b] $\Delta H^{\neq}$ 19.6 ± 2.2 kcal/mol; $\Delta S^{\neq}$ −28 ± 6 eu in ether. [c] $\Delta H^{\neq}$ 25.0 ± 2.2 kcal/mol; $\Delta S^{\neq}$ −16 ± 6 eu in ether. [d] Average of all determinations at 100°C. [e] Extrapolated from concentrated reagent at 80 and 100°C; average observed value 2.79 ± 0.25. [f] Extrapolated from concentrated reagent at 80 and 100°C; average observed value 3.15 ± 0.3.

constants for the opposing processes were evaluated. Results are listed in Table 2.

Discussion

It is instructive to compare rate and equilibrium constants in the present system with those for eq. 1 (I ⇌ II, the unsubstituted cyclobutylmethyl system) and eq. 2 and 3 (IX ⇌ X ⇌ XI, the 2-methylcyclobutylmethyl system). Relevant data are not available under identical conditions, but reasonable extrapolations and estimates may be made. The numbers obtained are listed in Table 3, and the two paragraphs following are devoted to explanation and justification of the quantities tabulated. To allow comparison throughout the series, constants have been calculated for a "one-sided" reaction involving only one bond of the cyclobutane ring (i.e., for I ⇌ II or XII ⇌ XIII, $K_{obs} = k_c/2k_0$, where k_0 is half of the total ring cleavage rate constant $(k_0)_{obs}$; the tabulated equilibrium constant is k_c/k_0). In subsequent discussion, superscripts 1—4 will identify equilibrium and rate constants for equations so labelled in the text and in Table 3.

TABLE 3

RATE AND EQUILIBRIUM CONSTANTS FOR CYCLIZATION-RING OPENING REACTIONS OF THE CYCLOBUTYLMETHYL GRIGNARD REAGENT AND METHYLATED ANALOGS AT 100°C IN TETRAHYDROFURAN [a, b]

Reaction	K	k_c (sec^{-1})	k_0 (sec^{-1})
1 (I ⇌ II)	*1.8 × 10^{-4} (5.6 × 10^{-4})*	*2 × 10^{-8} (6 × 10^{-8})*	1.1 × 10^{-4}
2 (IX ⇌ X)	*7.5 × 10^{-3}*	*5.2 × 10^{-7}*	7 × 10^{-5}
3 (XI ⇌ X)	*1.33*	1.6 × 10^{-6}	*1.2 × 10^{-6}*
4 (XII ⇌ XIII)	6.9	6.8 × 10^{-6}	1 × 10^{-6}

[a] k_0 is defined as the rate of cleavage of one cyclobutane ring C—C bond, or half of the total observed ring-opening rate for II and XIII. K is similarly defined for one ring C—C bond, and is twice the observed equilibrium constant for cyclization of I or XII. [b] See text for details of the origin of rate and equilibrium constants. Values in italics were obtained by extrapolation or estimation by processes which may have introduced substantial errors.

Ring-opening rate constants ($k_{obs} = 2k_0^1$) for II at 60, 80 and 100° C in THF have been reported by Hill and Ni [4]. The cyclization of I to II was studied by following the equilibration of label in I-d_2 (deuterated α to magnesium). Upper limits of about 2×10^{-8} sec^{-1} for k_c^1 and 1.8×10^{-4} for K^1 at 100° C may be estimated from the failure to observe significant equilibration in 170 h at 110°C [17]. Somewhat larger values of 6×10^{-8} sec^{-1} and 5.6×10^{-4} respectively are derived from kinetics at 140° C, utilizing an estimated ΔS° for K^1 in the extrapolation to 100° C. A number of explanations for this discrepancy have been suggested [4].

In the 2-methylcyclobutylmethyl system, k_0^2 for the ring opening X → IX in THF at 61.5° C is similar to that for II → I [16]; extrapolation to 100° C was made assuming the same activation energy as for k_0^1. The alternative ring cleavage X → XI to yield a secondary Grignard reagent comprises only about 2% of the total ring-opening reaction of X. The corresponding rate constant k_0^3 was taken as $0.02 \times k_0^2$, and extrapolated to 100° C using the activation enthalpy determined in the present study for k_0^4 in ether. (We have found virtually identical activation enthalpies for k_0^1 in ether and THF.) The rate constant k_c^3 for cyclization of XI to X at 100° C in THF has been reported by Richey and coworkers [17]. The remaining rate constant k_c^2 for cyclization of IX to X may be estimated with the help of an equilibrium constant for XI ⇌ IX, determined by Lehmkuhl to be 290 at 70° C in ether. If there is little solvent effect on the position of that equilibrium, and an enthalpy change of —4 kcal/mol is assumed ($\Delta G^\circ = -3.85$ kcal at 70° C, and ΔS° is likely to be small), then the extrapolated equilibrium constant [IX]/[XI] = K^3/K^2 becomes about 180 at 100° C. From this ratio, and $K^3 \sim 1.3$, values for K^2 and k_c^2 were calculated.

In comparing reactions 1—4, we will neglect any complications which might arise from different extents of exchange and association processes (Schlenk equilibrium) for the various organomagnesium components. While this is not strictly justified, the small effects of solvent (ethyl ether vs. THF) and halogen (chloride vs. bromide) suggest that these equilibria do not have a major influence on the results presented.

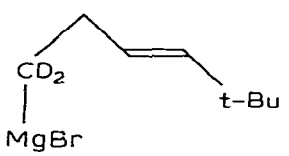
Despite uncertainties in some of the estimates and extrapolations, it is clear from the trend to the results in Table 3 that methyl substitution increases the equilibrium extent of cyclization. Increases are found for substitution both at the α-position of the open-chain organometallic, and at the more remote γ-position. The cyclization equilibrium constant is increased by α-substitution by factors of about 7×10^3 (K^3/K^1) and 920 (K^4/K^2), corresponding to free energy differences of —6.6 and —5.1 kcal/mol. Methyl substitution in the γ-position produces a smaller effect: $K^2/K^1 \sim 42$ and $K^4/K^3 \sim 5.2$, again corresponding to —2.8 and —1.2 kcal/mol in free energy. The consequences of methyl substitution may reasonably be interpreted as arising from a combination of two effects: destabilization of secondary Grignard reagent relative to a primary one, and stabilization of the strained ring relative to the open-chain isomer by alkyl substitution. (The latter effect does not appear to be reflected in group contribution to enthalpy of formation [5].)

The changes produced in the equilibrium constant by α- and γ-methyl substitution may be dissected into changes in the rates of the opposing cyclization and ring-opening processes k_c and k_0. The α-methyl effect is the consequence of

significant changes in both k_c (80 X and 13 X) and k_0 (92 X and 70 X). On the other hand, γ-methyl substitution appears to exert its influence largely upon k_c (26 X and 4.2 X), and leaves k_0 unaffected within the accuracy of the numbers *.

Fewer comparisons are possible for enthalpy or entropy changes. For the unsubstituted cyclobutylmethyl system, ΔS° for cyclization was estimated as about —10 eu, based on the difference in entropy between 1-pentene and methylcyclobutane. A very similar estimate may be made for the present system (eq. 4) based on the group increments of Benson et al., assuming that the organomagnesium function behaves in a fashion similar to a variety of typical functional groups. The observed value for eq. 4 was —12 ± 3.1 eu. Its similarity to the estimated values for both equations 1 and 4 suggests that there is not a large solvation-related entropy difference between primary and secondary organomagnesium functions, and that the "ring-methyl stabilization" is not an entropy effect which the group increments fail to take into account. The difference in equilibrium constant between reactions 1 and 4 rests primarily with differences in enthalpy of reaction (~+2 to +3 kcal/mol vs. —5.4 ± 1.1 kcal/mol).

Activation parameters for the ring-opening reaction are available for eq. 1 and 4. Enthalpies of activation appear to be similar (25.8 ± 0.3 and 26.55 ± 0.2 kcal for 1 in ether and THF, and 25.0 ± 2.2 for 4 in ether). The decreased cleavage rate in 4, in which a secondary organomagnesium function is being generated, appears to result largely from a more negative entropy of activation (—3.4 ± 0.6 and —4.6 ± 0.5 eu for 1 in ether and THF, and —16 ± 6 eu for 4 in ether). From this result, it might be concluded that the decreased cleavage rate does not reflect the difference in stability of the final product as much as it does increased constraint in a more congested transition state. The importance of steric effects in determining transition-state stability for the organomagnesium cyclization-cleavage rearrangements is also supported by the especially large decrease in cyclization rate found by Maercker and Streit [18] for the t-butyl substituent in XVI.



(XVI)

In the cyclization direction, comparisons may be made among cyclizations of the primary Grignard reagent I in eq. 1, and the secondary Grignard reagents XI and XII in eq. 3 and 4. (The data for I and XI are in THF and for XII in ether. Parameters for cyclization of I may be of limited accuracy.) The entropy of activation is more negative for the two secondary Grignard reagents (about

* As previously noted, alternative larger estimates might have been chosen for k^1 and k_c^1. Smaller values than those tabulated for K^2 and k_c^2 would also be more appropriate if the possible attack by Grignard reagent XI on solvent influenced the data in ref. 10. If the true values for these constants differ from those tabulated in the direction suggested then the rate and equilibrium effects of the first and second methyl groups would become more nearly equal.

—24 and —28 ± 6 eu vs. about —15 eu for I), probably reflecting again a greater degree of congestion in the former transition states. Activation enthalpies for cyclization of I, XI and XII are about 28.5, about 23, and 19.6 ± 2.2 kcal/mol, respectively. It is likely that both the difference in Grignard reagent stability and the stabilization of the ring by methyl substitution contribute to the differences in $\Delta H^{\ddagger}$. This would imply that both bond reorganization at the organomagnesium center and the bond-bending necessary for formation of the strained ring have developed to a rather advanced extent in the transition state.

A concerted four-center mechanism has been supported earlier for rearrangements of the type studied here [1,2]. The present results are consistent with a transition state with structural features resembling the cyclobutylmethyl product. It is stabilized by ring methyl substitution to about the same extent as the fully-formed ring, and its enthalpy does not reflect most of the α-methyl destabilization present in the secondary open chain reagent. However, α-methyl substitution also introduces additional steric congestion in the transition state, not present in either product or reactant, which decreases its entropy and slows the reaction in either direction.

It had been hoped that the comparisons above would provide an additional quantitative estimate of the stability difference between primary and secondary organomagnesium functions. If α-methyl substitution (K^3/K^1 and K^4/K^2) affects the stabilities of both the organometallic function and the ring, while γ-methyl substitution (K^2/K^1 and K^4/K^3) affects only the latter, then the effect of methyl substitution on the organomagnesium grouping should be isolated in the quantities $(K^3/K^1)/(K^2/K^1)$ and $(K^4/K^2)/(K^4/K^3)$. Unfortunately, in either case the result is simply the ratio (K^3/K^2). This is the equilibrium constant [IX]/[XI] determined by Lehmkuhl and coworkers [10] as 290 at 70°C ($\Delta G^{\circ} \approx -3.85$ kcal/mol), and extrapolated here as 180 at 100°C. Its value is independent of any data for reactions 1 and 4, and as noted previously, it may be a lower limit because of attack of Grignard reagent on solvent. A minor ambiguity also arises in the definition of the stability difference. The ratio K^3/K^2 was "corrected" by Lehmkuhl for the difference in stability between the two carbon skeletons. The net result is a hypothetical equilibrium comparison:

which corresponds to the traditional measure of organometallic stability in an acid—base sense (metal—hydrogen exchange). The "uncorrected" ratio K^3/K^2 is equivalent to an intramolecular exchange of methyl for hydrogen between an alkyl site and the site α to the metal, or to the exchange of metal for alkyl between two sites:

This is a "homodesmotic reaction" [19], in which the numbers of CH_3, CH_2, CH, and C groups remain invariant; these have been recommended for comparison of thermodynamic stability with theoretical calculations. In the present instance, the two definitions differ by the difference between the group contributions to ΔH_f from two CH_2 groups, and CH + CH_3.

Experimental

NMR spectra were obtained on Varian Associates T-60, HA-100, and CFT-20 NMR spectrometers, and IR spectra were run on Beckman IR-8 and Perkin—Elmer 137 spectrometers. Boiling points are uncorrected. Gas chromatograms were obtained on Varian-Aerograph A-90 chromatographs, using the columns: A, 10 ft × 1/2 in Apiezon J; B, 10 ft × 1/4 in tricresyl phosphate; C, 10 ft × 1/4 in Tide.

In equilibrium and kinetic experiments, sublimed magnesium was used, and ethyl ether and THF solvents were distilled from lithium aliminum hydride in a slow stream of dry nitrogen. Dioxane was freshly-opened spectroscopic grade solvent, redistilled from lithium aluminum hydride.

4-Methyl-5-hexen-2-ol (XIV) [20]. A Grignard reagent was prepared from crotyl chloride (50 g, 0.55 mol) and magnesium (45 g, 1.85 g-at) in a total of 450 ml of ether. To this solution, dioxane (22 g, 0.28 mol) was added dropwise with stirring, and the mixture was allowed to stand for 1 h. Propylene oxide (50 g, 0.86 mol) was added to the reagent with stirring at 0° C, and after 15 min stirring, the mixture was hydrolyzed with water, filtered, dried ($MgSO_4$), and concentrated. Distillation yielded 31 g (49%) of product: b.p. 135—140° C; IR (neat) 3300 (OH), 3040, 2900, 1635, 1170, 1040, 996, and 910 cm^{-1}; PMR (CCl_4) δ 6.1—5.4 (m, 1, =CH), 5.2—4.7 (m, 2, $=CH_2$), 4.1 (s, 1, OH), 3.8 (m, 1, CHOH), 2.3 (m, 1, CH), ~1.4 (m, 2, CH_2), 1.14 (d, 3, *J* 6 Hz, CH_3), 1.01 ppm (d, 3, *J* 6 Hz, CH_3). First order analysis of the multiplet at 6.1—5.4 ppm was made assuming the presence of two diastereomers having the $CH_\alpha CH{=}CH_cH_t$ grouping. Values of J_{trans} 17 Hz, J_{cis} 9.4 Hz, J_α 7 Hz were found for both isomers; the chemical shift of the major component was 0.055 ppm to higher field than the minor component. Gas chromatography (column 3) showed the presence of two components in a ratio of about 1/2. The ^{13}C NMR spectrum (neat) also indicated the presence of diastereomers. Observed shifts for the major and minor diastereomers, and estimated [21] values (in parenthesis) are as follows: δ 143.75, 144.23 (146.4 =CH); 112.59, 111.89 (112.1, $=CH_2$), 64.75, 64.75 (64.9, CHOH), 45.80, 45.99 (46.3, CH_2), 34.18, 34.18 (32.4, allylic CH), 23.63, 23.05 (21.6, terminal CH_3), and 20.51, 19.72 ppm (20.1, CH_3). Anal.: Found: C, 73.39; H, 12.30. $C_7H_{14}O$ calcd.: C, 73.63; H, 12.36%.

When reaction between the crotyl Grignard reagent and propylene oxide was carried out without addition of dioxane, a third component was present in the alcohol mixture. It appeared at longer GLC retention time, and its NMR spectrum had a doublet at δ 3.75 ppm ($J \simeq 5.5$ Hz, CH_2OH). It was assigned the probable structure, 2,3-dimethyl-4-penten-1-ol [22].

5-Chloro-3-methyl-1-hexene (XV). To a mixture of XIV (28 g, 0.245 mol) and tri-n-butylamine (45.4 g, 0.245 mol) in 125 ml of anhydrous ether cooled to 0° C, thionyl chloride (29.1 g, 0.245 mol) was added dropwise over one hour.

After addition was complete, the mixture was stirred for 5 h, and the ether was distilled at reduced pressure. The temperature of the flask was then gradually increased to 80° C over a period of 1 h, while the pressure was maintained at about 12 mmHg to distill product from the mixture as it was formed. Redistillation yielded 23 g (71%): b.p. 132—134° C; IR (neat) 3030, 2900, 1635, 995, and 912 cm^{-1}. Gas chromatography (Column A) showed that the product was a mixture of two isomers, in a ratio of 55 : 45. The isomers were separated by preparative gas chromatography (Column A) and PMR spectra were run individually: (a) δ 5.9—5.3 (m, 1, =CH), 5.2—4.8 Hz, (m, 2, $=CH_2$), 3.96 (sextuplet, 1, $J \simeq 7$ Hz, CHCl), 2.40 (m, 1, allylic), 1.8—1.5 (m, 2, CH_2); 1.40 (d, J 6.5 Hz, CH_3), and 1.00 ppm (d, 3, J 6.5 Hz, CH_3); (b) δ 6.0—5.4 (m, 1, J 7.5, 9.5, 17.5 Hz, =CH), 5.1—4.7 (m, 2, $=CH_2$), 3.97 (sextuplet, 1, $J \simeq 7$ Hz, CHCl), 2.37 (m, 1, allylic), 1.83—1.5 (m, 2, CH_2), 1.40 (d, 3, J 6.5 Hz, CH_3), and 1.00 (d, 3, J 6.5 Hz, CH_3). ^{13}C NMR shifts (neat) for the major and minor isomers (estimated [21] values in parentheses) are as follows: 142.29, 142.3 (146.3, =CH); 113.97, 112.7 (112.4 $=CH_2$), 55.77, 55.2 (51.6, CHCl), 46.99, 46.9 (49.4, CH_2), 35.37, 34.9 (31.1, CH), 25.50, 24.9 (24.7, terminal CH_3); 20.42, 19.0 (20.0, CH_3). Anal.: Found: C, 63.45; H, 9.81. $C_7H_{13}Cl$ calcd.: C, 63.39; H, 9.88%.

5-Chloro-2,3-dimethyl-1-pentene. This compound formed from the corresponding alcohol in the crude mixtures noted above, had NMR (CCl_4) δ 5.9—5.3 (m, 1, =CH), 5.2—4.8 (m, 2, $=CH_2$), 3.3 (d, 2, J 6 Hz, CH_2), 2.5—2.0 (m, 1, CH), 1.9—1.3 (m, 1, CH), 0.9 (d, 6, $J \simeq 6.5$ Hz, CH_3). ^{13}C NMR shifts (neat) of two diastereomers are as follows (estimated [21] value in parentheses): 141.81, 140.14 (144.6, =CH), 113.88, 114.56 (113.3, $=CH_2$) 48.84, 48.54 (49.4, CH_2Cl), 39.95, 40.24 (42.1, CH), 39.95, 39.64 (37.2, allylic CH), 15.64, 17.31 (16.9, CH_3), 14.08, 13.76 (15.0, CH_3).

Grignard reagent from XV. Grignard reagents (ca. 1 *M* concentration) were prepared in ether or THF from 1—2 g samples of XV. The solvent and any volatile products were removed under vacuum and replaced with fresh dry solvent. The solution was transferred by syringe to several nitrogen-filled ampules (~1—1.5 ml each) and, in some cases, to an NMR tube. Ampules and tubes were sealed under reduced pressure. An NMR spectrum of the Grignard reagent solution had a somewhat broadened high field sextuplet, $J \simeq 8$ Hz at —0.08 ppm vs. TMS internal reference. There were overlapping methyl doublets, $J \sim 7$ Hz, at 0.965 and 0.945 ppm, multiplets at about 1.5 and 2.1 ppm, and olefinic absorption centered at 5.65 ppm (=CH) and at 4.8, 4.9 and 5.0 ppm ($=CH_2$). Hydrolysis of the Grignard reagent yielded a single major hydrocarbon component, which was isolated by preparative gas chromatography (Column A). The NMR spectrum was identical with a published spectrum of 3-methyl-1-hexene [23].

Sealed samples of the Grignard reagent were heated for periods of time at 100, 110, and 120° C. The NMR spectrum of the heated Grignard reagent had a doublet at about —0.32 ppm (J 6.9 Hz) and absorptions attributed to the open-chain Grignard reagent became less prominent. The tubes were opened and volatile materials were pumped to a trap under vacuum. Nitrogen was admitted to the ampules and after fresh solvent (ether or octane) was added, they were cooled to Dry Ice temperature and hydrolyzed with water. The

organic phase was analyzed by gas chromatography (Column A and B). In addition to 3-methyl-1-hexene, two new components were present. The major one of these was isolated by gas chromatography. Its PMR spectrum (CCl_4) showed no unsaturation; there was a methyl doublet (J 6.5 Hz) at 0.97 ppm, and ring hydrogen multiplets at 2.1, 1.6 and 1.3 ppm; ^{13}C NMR (CCl_4) δ 18.74 (1 C, CH_3), 20.51 (2 C, CH_3), 35.83 (2 C), 36.02 and 47.35 ppm. The minor isomer was incompletely resolved from 3-methyl-1-hexene by GLC, so the alkene was removed from the hydrolysis product by ozonolysis. Ozone was passed slowly through an octane solution of the product at —78° C until a blue color persisted. After brief purging with nitrogen, the ozonide was reduced by addition of dimethyl sulfide. The minor hydrocarbon product was then isolated by preparative GLC. The proton NMR spectrum contained several peaks in the methyl region. These were analyzed by comparison of 60 and 100 MHz spectra to yield three doublets: δ 1.013 (J 6.1 Hz), 0.971 (J 7.2 Hz), and 0.895 ppm (J 6.5 Hz). Ring protons were at δ 2.25 (1 H), 1.6—1.9 (3 H) and 1.2 ppm (1 H). The ^{13}C NMR spectrum had signals at δ 13.84, 14.92 and 20.11 (CH_3), and 28.32, 33.97, 34.98 and 39.55 ppm (ring carbons).

In some experiments, most of the solvent was pumped from the Grignard reagent before sealing and heating. Rearrangement occurred more rapidly, but the molar concentration of Grignard reagent was not known.

2,4-Dimethylcyclobutylmethyl bromide and its Grignard reagent. A sample of Grignard reagent from 2 g (15 mmol) of XV, which had been heated for 48 h at 100° C, was added slowly to a stirred solution of 1.2 g of bromine in 50 ml of ether cooled to 0° C. Excess bromine was removed by shaking the solution with 1.0 M aqueous sodium thiosulfate. The solution was dried ($MgSO_4$) and distilled to yield 0.25 g of product: b.p. 73° C (10 mmHg): NMR (neat) δ 3.7 (d, J 6 Hz, CH_2Br), 2.5—1.5 (m) and 1.4 ppm (d, J 4 Hz, CH_3). The ^{13}C NMR spectrum (neat) had five major peaks: δ 21.19 (2 C, CH_3), 33.69 (2 C, $CHCH_3$), 34.47, 36.52, 53.11 ppm (CH_2Br); in addition, seven weak absorptions attributable to a stereoisomer were present: δ 14.83 and 16.10 (CH_3), 28.02, 28.51, 33.19, 35.15, and 47.07 ppm (CH_2Br).

The bromide sample was allowed to react with excess magnesium in ether. Half of the mixture was hydrolyzed without heating, and the other half was sealed in an ampule, and heated 48 h at 100° C. The sample was hydrolyzed as described above after removal of volatiles.

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