Free Energies of Hydrolysis.—In Table IV are summarized the values of $\Delta F°$ and $\Delta F_{pH\ 7}$ °', the standard free energies of hydrolysis to free acetic acid and to acetate ion at pH 7.0, respectively, calculated from the results of this work and from related equilibria. The values of $\Delta F°$ refer to a standard state of 1 M reactants and products as the nonionized species, except for acetyl phosphate, which refers to the dianions of acetyl phosphate and inorganic phosphate. The vaues of $\Delta F_{pH\ 7}$ °' refer to a standard state of 1 M concentrations of the sum of all ionic species of the reactants and products at pH 7.0, except for hydrogen ion. The activity of pure water is taken as 1.0. The values for acetic acid derivatives are based on the thermodynamic pK_a for acetic acid of 4.76; the values based on a pK_a' of 4.63 ± 0.02 at ionic strength 0.2 to 1.0[29] are 180 cal./mole more negative. The calculations for ester hydrolysis, with the exception of acetylcholine, are based upon data which were extrapolated to zero ionic strength. The results for acetylcholine and for the acetyl-transfer reactions are not extrapolated to zero ionic strength, but these equilibria would not be expected to show a large dependence upon ionic strength, because increasing salt concentration should have a similar effect on the activity coefficients of the reactants and products. The values of − 9490 and −4460 cal./mole for the free energies of hydrolysis of acetylimidazole and the thiol ester group of N,S-diacetyl-β-mercaptoethylamine may be compared to the values of −7280 and −910 cal./mole, respectively, for the heats of hydrolysis of the same compounds in water.[31] The greater part of the difference between the $\Delta F°$ and ΔH values reflects the fact that the standard state for water is taken as 1.0, rather than 55.5 M; this convention contributes −2400 cal./mole to the $\Delta F°$ values.

It has been suggested that phosphorylimidazoles and possibly acylimidazoles may be involved in biological oxidative phosphorylation.[32] The rates and equilibria for acyl-transfer reactions involving acetylimidazole and phenolates reported here may conceivably be pertinent to the uncoupling or inhibitory action of acidic phenols on oxidative phosphorylation.[33]

(31) I. Wadso, *Acta Chem. Scand.*, **16**, 479, 487 (1962).

(32) P. D. Boyer, D. E. Hultquist, J. B. Peter, G. Kreil, R. A. Mitchell, M. DeLuca, J. W. Hinkson, L. G. Butler, and R. W. Moyer, *Federation Proc.*, **22**, 1080 (1963).

(33) V. H. Parker, *Biochem. J.*, **69**, 306 (1958); H. C. Hemker, *Biochim. Biophys. Acta*, **63**, 46 (1962).


Kinetics of the Ring Opening of Cyclobutylmethylorganomagnesium Compounds[1]

BY E. ALEXANDER HILL AND JOHN A. DAVIDSON[2]

RECEIVED MARCH 28, 1964

The rearrangement of cyclobutylmethyl Grignard and dialkylmagnesium reagents to 1-pent-4-enylorganomagnesium compounds was studied kinetically. The solvent dependence and the effects of α-methyl and α-deuterium substitution are most readily interpreted on the basis of a synchronous four-center process. Contribution of a π-complex structure to the transition-state resonance hybrid is proposed.

In a previous communication, we have reported ring-cleavage reactions of the cyclobutylmethylorganometallic derivations of sodium, lithium, and magnesium.[3] These cleavages, and the analogous very facile ring opening of the corresponding cyclopropyl-
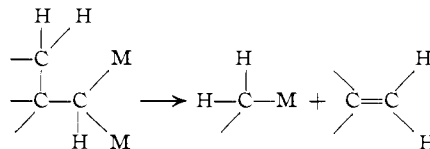

$$M=Na,\ Li,\ MgX$$
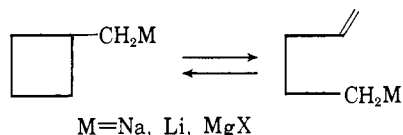
methylorganometallics,[4] undoubtedly derive their driving force from the relief of ring strain. The analogous acyclic organometallic cleavage should be endothermic by approximately 20 kcal. Some recently reported cleavages of acyclic organopotassium and organosodium compounds are apparently observed owing to

vaporization of volatile products or metallation and polymerization of the olefin formed.[5]

In the present paper, we report a kinetic study of the ring cleavages of the cyclobutylmethylorganomagnesium compounds. This study was undertaken for the purpose of distinguishing between several alternative mechanisms which have been suggested for these rearrangements.[3]

Results

The rearrangement of cyclobutylmethylmagnesium chloride to 1-pent-4-enylmagnesium chloride in tetrahydrofuran was studied kinetically at 61.5°. The corresponding dialkylmagnesium was also studied.

(3) E. A. Hill, H. G. Richey, Jr., and T. C. Rees, *J. Org. Chem.*, **28**, 2161 (1963).

(4) (a) M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 2646 (1960); (b) P. T. Lansbury, *ibid.*, **85**, 1886 (1963); (c) H. G. Richey, Jr., and E. A. Hill, *J. Org. Chem.*, **29**, 421 (1964).

(5) (a) R. A. Finnegan, *Chem. Ind.* (London), 895 (1962). (b) R. A. Finnegan, *Tetrahedron Letters*, 1303 (1962). (c) The Wittig and Stevens rearrangements, as well as several other recently reported reactions, may involve cleavages of heteroatom-substituted organometallics or organometallics in which a resonance-stabilized carbanion may be the cleavage product.[6]

(6) (a) G. Kobrick, *Angew. Chem. Intern. Ed. Engl.*, **1**, 382 (1962), and references therein; (b) P. T. Lansbury and V. A. Pattison, *J. Am. Chem. Soc.*, **84**, 4295 (1962); *J. Org. Chem.*, **27**, 1933 (1962); (c) E. Grovenstein, Jr., and G. Wentworth, *J. Am. Chem. Soc.*, **85**, 3305 (1963); (d) P. K. Freeman, D. E. George, and V. N. M. Rao, *J. Org. Chem.*, **28**, 3234 (1963).

TABLE I

RATE CONSTANTS FOR CYCLOBUTYLMETHYL GRIGNARD AND
DIALKYLMAGNESIUM RING CLEAVAGES, 61.5°,
TETRAHYDROFURAN[a]

Run	Concentration[b]	No. of points	$k \times 10^6$, sec.$^{-1}$	Added reagents
A.	Cyclobutylmethylmagnesium chloride			
1	0.114	6	3.16 ± 0.12	
2	.6	4	3.57 ± .14	
3	.97	7	4.24 ± .19	
4	1.14	4	4.54 ± .04	
5	1.14	6	4.56 ± .06	
6	1.14	3	4.38 ± .04	
7	1.27	3	4.35 ± .14	
8	0.8	6	8.33 ± .33	2.4 M C$_4$H$_9$MgCl
9	.57	6	2.82 ± .03	0.25 M MgCl$_2$
10	.8	5	3.31 ± .34	.01 M H$_2$O
11	.8	5	3.38 ± .11	.1 M C$_6$H$_5$OH
12	.6	5	3.30 ± .08	.075 M H$_2$O
13	.43	4	6.35 ± .19	.47 M (C$_2$H$_5$)$_3$N[c]
14	1.1[d]	5	3.98 ± .04	
15	1.1[d,e]	7	3.89 ± .27	
16	1.43[d,e]	5	3.65 ± .24	
17	2.56[d,e]	4	7.4 ± .7	
18	2.80[d,e]	5	5.78 ± .14	
19	4.18[d,e]	5	11.2 ± .5	
20	0.66[d,e]	6	32.6 ± 2.7	CH$_3$OCH$_2$CH$_2$OCH$_3$[c,f]
21	0.55[d,e,g]	9	4.85 ± 0.26	
22	1.1[d,e,g]	7	5.06 ± .16	
23	1.9[d,e,g]	5	4.76 ± .20	
24	1.0[d,e,h]	8	4.15 ± .29	
B.	Di(cyclobutylmethyl)magnesium			
25	0.11	7	4.71 ± 0.12	
26	1.1	5	5.13 ± .35	
27	1.1	5	5.39 ± .11	
28	0.85	6	5.24 ± .12	0.01 M H$_2$O
29	.7	6	6.62 ± .21	37% (C$_2$H$_5$)$_3$N
30	.9	7	8.92 ± .70	60% (C$_2$H$_5$)$_3$N
31	.5	8	10.67 ± .12	55% C$_6$H$_6$
32	1.14	7	8.90 ± .25	50% isooctane
33	0.44	8	31.5 ± 3.9	60% 1,2-dimethoxyethane
34	0.44	10	17.69 ± 1.2	60% 1,2-dimethoxyethane

[a] Water content of solvent 2.8 × 10^{-3} M, ampoule kinetic technique and sublimed magnesium unless otherwise specified. [b] Concentration of alkyl groups (determined as total base). [c] White precipitate present. [d] Water content of solvent 5 × 10^{-3} to 1 × 10^{-2} M. [e] Pot kinetic technique used. [f] Solvent replaced by 1,2-dimethoxyethane. [g] "Grignard grade" magnesium. [h] "Grignard grade" magnesium fused under hydrogen.

The reaction was followed by hydrolysis of the organometallic and analysis of the product for methylcyclobutane and 1-pentene. It was found that on long heating the rearrangement proceeds at least 99.8% to completion, so an infinity point of 100% rearrangement was assumed for the kinetic calculations. The n.m.r. spectrum of the initial Grignard solution had a doublet absorption at 10.39 τ which is in the region characteristic of hydrogens α to a magnesium.[4a] On partial rearrangement, a new triplet at 10.70 τ and vinyl group absorption appeared. These spectra are consistent with the proposed structures of the original and rearranged Grignard reagents, and make improbable any alternative structures for the rearrangement product (such as an allylic or vinyl organometallic).

Rearrangements were followed 50 to 90% to completion. The kinetics were found to be first order in unrearranged Grignard (or unrearranged alkyl group) within a run. The observed rate constants are listed

in Table I. Uncertainties are 70% confidence limits.[7] The several runs included with only 3 or 4 points are from control ampoules for various preparations of the reagents. These were included because of their close adherence to first-order kinetics, and their agreement with other runs.

The rate of reaction was affected by the purity of the magnesium used in preparing the Grignard. A reagent prepared from ordinary "Grignard reagent" grade magnesium rearranged about 25% faster than comparable reagents made from very high purity sublimed magnesium (compare run 22 with runs 14–16). Among other impurities, the less pure magnesium probably contained about 20 times as much iron and 100 times as much manganese as the sublimed magnesium. In one run in which the "Grignard reagent" grade magnesium was fused in a stream of hydrogen before being transferred to the reaction flask, the rate was closer to that obtained with sublimed magnesium (compare run 24 with runs 14–16).

The rate of rearrangement is nearly independent of total Grignard reagent concentration up to over 1 M. Over a tenfold concentration change from 0.114 to 1.14 M, the reaction rate changes by a factor of only 1.35. However, further increase to 3 or 4 M (see runs 8 and 19) increases the rate two- and threefold. This increase occurs when the Grignard present is all cyclobutylmethylmagnesium chloride and its rearrangement product, or if it contains largely another alkyl group (run 8, with added butylmagnesium chloride). Addition of magnesium chloride decreased the reaction rate.

The rate of reaction was also affected by small amounts of water in the solvent. Thus, a water content of 6 to 11 × 10^{-3} M decreased the rate of about 80–90% of the value in the driest solvents used (about 3 × 10^{-3} M water). Addition of enough water to hydrolyze 25% of the Grignard, or addition of phenol instead of water, had about the same effect as an amount of water sufficient to hydrolyze only about 3% of the organometallic (runs 10–12).

In an attempt to study the effect of solvent, triethylamine was added to run 14, and the solvent was replaced by 1,2-dimethoxyethane in run 20. In both instances a white precipitate formed, and the rate of rearrangement increased.

To avoid difficulties from precipitation, the rearrangement of di(cyclobutylmethyl)magnesium was studied. As with the Grignard reagent, the rate of rearrangement was nearly independent of concentration up to at least 1 M. The rate of rearrangement was faster than that of the Grignard reagent at equal "alkyl group" concentration by about 25%, and appeared to be less sensitive to low solvent water concentrations (run 28). Dilution of the solvent with triethylamine, benzene, isooctane, or 1,2-dimethoxyethane gave clear solutions, and increased the rate of reaction. In all cases except with added dimethoxyethane, tetrahydrofuran appeared to be present in the volatile fraction produced on hydrolysis of the organomagnesium. This probably indicates its importance in the role of solvating the magnesium.

The effect of α-substitution was investigated by rearrangement of the Grignard reagent from α-cyclo-

(7) F. S. Acton, "Analysis of Straight-Line Data," John Wiley and Sons, Inc., New York, N. Y., 1959, pp. 23 and 24.

butylethyl chloride. The rate constant for rearrangement at a concentration of 0.5 M was $(5.47 \pm 0.16) \times 10^{-6}$ sec^{-1}. This value is about 40% greater than the rate constant for the unsubstituted compound at the same concentration.

α-Cyclobutylethyl chloride was prepared by reaction of the corresponding alcohol with thionyl chloride and tri-n-butylamine under conditions which give no rearrangement with cyclobutylmethyl chloride itself. However, the reaction product was found by vapor phase chromatography to be a mixture of several chlorides, probably including the two isomers of 2-methylcyclopentyl chloride and 1-methylcyclopentyl chloride in addition to the desired chloride.[8] The major peak in the chromatogram (52%) contained mostly the desired product. Preparative chromatography was not used for a kinetics sample, since considerable decomposition occurred on the column even under mild conditions. It was found, however, that hydrolysis of the Grignard reagent produced a considerably simplified mixture of hydrocarbons. About 95% of the monomeric hydrocarbon product consisted of ethylcyclobutane and methylcyclopentane in a ratio of 44:56. The remaining 5% of the product originated during Grignard formation, probably by disproportionation from the tertiary chloride. Since it was found previously that the rate of rearrangement of cyclobutylmethylmagnesium chloride is independent of concentration at low concentration, the rearrangement was studied with Grignard prepared from the mixed chloride. It was shown by examination of solvent pumped from the Grignard before hydrolysis that competing solvent cleavage did not complicate the situation. The internal consistency of the kinetics confirms the suitability of the treatment used for the data.

The hydrocarbon derived from the rearranged Grignard reagent was an almost equal mixture of *trans*- and *cis*-2-hexenes. The composition was constant from the beginning of the reaction through 5.6 half-lives.

The secondary α-deuterium isotope effect on the reaction was studied by rearranging an equimolar mixture of Grignard reagents from cyclobutylmethyl chloride and α,α-d_2-cyclobutylmethyl chlorides. Samples were examined after 9.4 and 70.2% rearrangement. The isolated hydrocarbons were analyzed for the ratio (mass 70)/(mass 72) by mass spectroscopy. From the mass ratio and the extent of reaction, the isotope effect k_H/k_D was evaluated. A value of 1.02 $\pm$ 0.02 was obtained, taking the probable errors in the analysis into consideration.

The α,α-d_2-cyclobutylmethyl chloride was prepared by reduction of methyl cyclobutanecarboxylate with lithium aluminum deuteride (prepared *in situ*), followed by conversion of the alcohol to chloride with thionyl chloride–tributylamine. Dideuterated methylcyclobutane and 1-pentene were obtained by hydrolysis of the deuterated Grignard reagent. The n.m.r. spectra were consistent with essentially complete α-deuteration in the chloride and alcohol, with dideuteration of the methyl group of the methylcyclobutane, and with complete deuteration of the terminal methylene group

(8) C. F. Wilcox, Jr., and M. E. Mesirov, *J. Am. Chem. Soc.*, **84**, 2757 (1962), have estimated a driving force of 4.3 kcal. owing to participation in the solvolysis of α-cyclobutylethyl tosylate.

of 1-pentene. Mass spectra of the methylcyclobutane and the 1-pentene both had 70/72 ratios of about 0.01. Infrared spectra of these compounds were changed markedly by deuteration. The most readily interpreted features in all the spectra were a doublet due to symmetric and asymmetric carbon–deuterium stretching modes. This appears to be a useful group frequency for structural studies.[9]

Discussion

Three distinctly different types of mechanism seem reasonable for the ring-cleavage reactions of cyclobutylmethylorganometallics and for related reactions. The organometallic may ionize to a carbanion, which then rearranges. Such a mechanism seems most probable for the most polar organometallics, such as the alkylsodiums, and is supported by an apparent increase in reactivity with polarity of the carbon–metal bond.[3,10] Alternatively, dissociation may occur to a univalent magnesium species and a free radical, which undergoes rearrangement before recombination. The participation of free radicals in Grignard reactions, particularly in the presence of extraneous metal salts, has received considerable attention,[11] and analogies for the radical ring cleavage or its reversal are plentiful.[12] In this case, rearrangement and recombination would probably have to occur in a solvent cage, since little reaction with solvent to yield hydrocarbon was observed during the course of a kinetic run. Finally, a concerted cyclic process might be proposed, in which changes in carbon–carbon bonding occur simultaneously with transfer of the magnesium from one carbon atom to another. These mechanistic possibilities are represented in Scheme I. It is to be understood in all

Scheme I
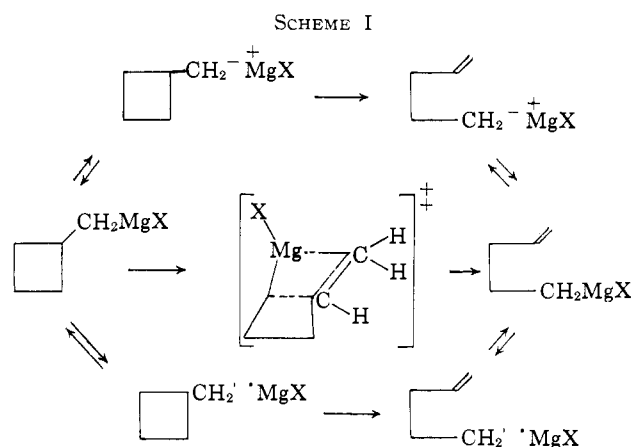
cases that solvent is coordinated to the magnesium.

The most striking feature of the kinetic results reported in this paper is the insensitivity of the rate to solvent and structural variations. Rearrangement of the dialkylmagnesium was studied in pure tetrahydro-

(9) (a) W. T. King and B. Crawford, Jr., *J. Mol. Spectry.*, **8**, 58 (1962). (b) 1-Pentene obtained from reaction of the deuterated chloride with sodium contained a third C–D stretching band owing to an additional atom of deuterium in the methyl group.

(10) G. E. Coates, "Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1960, pp. 1, 2, 43.

(11) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice–Hall, Inc., New York, N. Y., 1954, pp. 116–137.

(12) R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Am. Chem. Soc.*, **85**, 3483 (1963); E. Renk, P. R. Shafer, W. H. Graham, R. H. Mazur, and J. D. Roberts, *ibid.*, **83**, 1987 (1961); work reported by L. H. Slaugh, R. D. Mullineaux, and J. H. Raley, *ibid.*, **85**, 3180 (1963), may be interpreted as intramolecular addition and cleavage of free radicals.

furan (with a trace of dioxane remaining from precipitation of the magnesium chloride) and in mixtures of tetrahydrofuran diluted with isooctane, benzene, triethylamine, and 1,2-dimethoxyethane. In the mixtures containing 50% isooctane, 55% benzene, and 60% triethylamine, the reaction rates were very similar, and exceeded that in pure tetrahydrofuran by factors of 1.7 to 2.1. In each of these mixtures, the dielectric constant of the medium should be lower than in tetrahydrofuran solution.[13] The dependence upon solvent polarity is consistent with a mechanism in which the transition state is somewhat less polar than the reactants, but would be difficult to explain in terms of a mechanism which involves ionization of the organometallic. It is tempting to draw attention to the similarity in estimated dielectric constants for the three mixtures (~4.5). However, in all of these solutions, the dialkylmagnesium concentration is fairly high, and the dielectric constant of all solutions certainly exceeds that estimated for the solvents alone.[14] The effect of triethylamine appears to be mainly an effect on medium polarity, since a solution with only 37% of amine reacts at an intermediate rate. The vapor phase chromatogram of the volatiles, pumped from the magnesium salts after hydrolysis contained a peak corresponding to tetrahydrofuran, suggesting that even with added amine, some tetrahydrofuran was coordinated with the magnesium.

Dimethoxyethane has a more marked rate-accelerating effect, despite the fact that its dielectric constant (6.8)[15] is nearly as high as that of tetrahydrofuran. It seems likely that the strong tendency of dimethoxyethane for solvating cations is important here,[15,16] leading to a general weakening of the carbon–metal bond, and perhaps even to a significant change in the nature of the transition state. These runs showed less reproducibility than most of the other data, with occasionally widely deviating points.

The α-deuterium isotope effect was found to be 1.02 ± 0.02. In numerous studies, isotope effects, in reactions where a bond to tetrahedral carbon is broken, have been found to be remarkably constant at about $k_H/k_D = 1.10$ to 1.20 per deuterium, regardless of
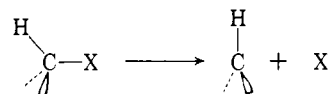
whether the carbon atom is left as a cationic, anionic, or radical center, or whether the C–X bond is broken in a dissociation or abstraction step.[17] The small observed isotope effect in the reaction suggests that the rate-determining step is *not* a simple breaking of the carbon–magnesium bond, as it would be if the first

steps of either the free radical or the carbanion mechanism were rate-determining. On the basis of explanations advanced for these secondary isotope effects,[17b] it appears that a reaction whose rate-determining step follows a pre-equilibrium dissociation should have a similar isotope effect.[18] In that case, the carbanion or radical mechanisms with the second step rate-determining are also unlikely.

The weak electron-releasing inductive effect of deuterium might also be taken into account.[17b,19] A simple σ^*–ρ treatment, assuming σ^* for –CH$_2$D as -0.0027,[19] the fall-off factor per carbon atom as 2.8, and a ρ-value of $+4.0$, would predict a maximum value of $k_H/k_D = 1.14$ for the inductive effect in the carbanion mechanism. An inverse effect of about 0.97 might be estimated for loss of all of the 20% partial ionic character[20] of the C–Mg bond. Neither of these figures will help much in explaining the small observed isotope effect.

Two reservations might be noted in the interpretation of the small isotope effect. First, there are a few reported instances of small or even inverse α-deuterium isotope effects.[21] Second, the usual model for secondary α-deuterium isotope effects considers the conversion of an sp^3 carbon atom to sp^2, and examples of the normal effect are mostly of this type (particularly if free radicals are considered planar). In the present case, however, a carbanion intermediate might maintain a nonplanar sp^3 configuration.

The rearrangement of α-cyclobutylethylmagnesium chloride provides information about the effect of α-alkyl substitution on the rearrangement rate. The observed small rate increase (relative $k = 1.53$) is interpreted as inconsistent with either free-radical or anionic processes, but compatible with a concerted cyclic mechanism. Either a free-radical or ionic cleavage of the carbon–magnesium bond should be a fairly endothermic process, and so the transition state for such a step might be expected to have considerably more radical or ionic character, respectively, than the original carbon–magnesium bond.[22] In that case, the added α-methyl substituent should be expected to stabilize strongly a free radical or destabilize a carbanion intermediate relative to the reactant states, and produce an accordingly large rate increase or decrease, respectively. If the radical or carbanion forms reversibly and rearranges in the rate-determining step, the substituent effect should still be sizable, and in the same direction. In a cyclic process, the small rate increase is understood if some of the partial negative charge caused by the polar carbon–magnesium bond[20] is distributed onto a second carbon atom in the transition state.[23]

(13) For dielectric constants of the pure solvents, see F. E. Critchfield, J. A. Gibson, and J. L. Hall. *J. Am. Chem. Soc.*, **75**, 6044 (1953); A. A. Maryott and E. R. Smith, "Table of Dielectric Constants of Pure Liquids," National Bureau of Standards, Washington, D. C., Circular No. 514, 1951; A. Weissberger, E. S. Proskaner, J. A. Riddick, and E. E. Toops, Jr., "Organic Solvents." Interscience Publishers, Inc., New York, N. Y., 1955.

(14) R. E. Dessy and R. M. Jones, *J. Org. Chem.*, **24**, 1685 (1959); R. E. Dessy. *ibid.*, **25**, 2260 (1960).

(15) G. Wittig and E. Stahnecker, *Ann.*, **605**, 69 (1957).

(16) H. Zook and T. Russo, *J. Am. Chem. Soc.*, **82**, 1258 (1960); H. E. Zaugg, *ibid.*, **83**, 837 (1961).

(17) (a) S. Seltzer, *ibid.*, **83**, 2625 (1961); (b) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *ibid.*, **80**, 2326 (1958); (c) A. Streitwieser, Jr., and D. E. Van Sickle, *ibid.*, **84**, 254 (1962); (d) A. A. Zavitsas and S. Seltzer, Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964, p. 4C; (e) S. Seltzer, *ibid.*, p. 4C.

(18) The usual explanations consider the effect due mainly to decrease in a vibrational frequency as a bending mode of a tetrahedral carbon–hydrogen bond converted to an out-of-plane bending frequency of trigonal carbon.[17b]

(19) A. Streitwieser, Jr., and H. S. Klein, *J. Am. Chem. Soc.*, **85**, 2759 (1963).

(20) G. Fraenkel, D. G. Adams, and J. Williams, *Tetrahedron Letters*, 767 (1963).

(21) (a) M. M. Kreevoy and B. M. Eisen, *J. Org. Chem.*, **28**, 2104 (1963); (b) M. M. Kreevoy and L. T. Ditsch, *J. Am. Chem. Soc.*, **82**, 6127 (1960); (c) R. E. Weston and S. Seltzer, *J. Phys. Chem.*, **66**, 2192 (1962). Inverse isotope effects have also been noticed in bimolecular nucleophilic displacements on carbon, but these are not relevant to the present case, since they also involve an attacking nucleophile.

(22) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(23) Preliminary work by R. A. Doughty (M.S. Thesis, University of Minnesota, 1963) is also in agreement with the cyclic mechanism. The primary hydrolysis product after rearrangement of the Grignard reagent

An observation in the α-cyclobutylethylmagnesium chloride reaction which appears to be significant is the production of almost equal amounts of *cis*- and *trans*-2-hexene. The *cis* content of the mixture is considerably greater than expected on the basis of the approximately 1:3 equilibrium ratio of *cis*:*trans*.[24]

An attractive explanation for the relative abundance of *cis*-2-hexene in the product is that the transition-state resonance hybrid contains a significant contribution from a metal–olefin π-complex structure. The known preference of π-complexes for *cis*- over
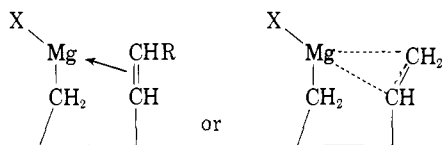
trans-olefins would then stabilize the isomeric transition state leading to the *cis*-double bond in the product organomagnesium compound.[25] A π-complex might possibly be an intermediate following the rate-determining transition state. Somewhat analogous π-complexes have been suggested as intermediates in polymerizations of olefins by complex organometallic catalysts.[26] The present ring cleavage is an intramolecular analog to the reverse of the addition step in such polymerizations. A π-complex contribution to the transition state would also be in accord with the small α-deuterium isotope effect. Kreevoy and Eisen[21a] have found a small *inverse* effect of hydrogens α to the mercury in the deoxymercuration of 2-phenyl-2-methoxyethylmercuric iodide, which proceeds through a mercury–olefin complex.

Small amounts of water in the solvent were found to produce a slight decrease in the Grignard rearrangement rate. This does not appear to be a general inhibiting effect due to the basic magnesium salts which would be formed by reaction of water with the Grignard, since essentially the same rate was found whether the added water was sufficient to hydrolyze 3 or 25% of the reagent. Added phenol had an identical effect. The most likely explanation appears to be that a part of the rearrangement in the driest solvents involves trace impurities in the magnesium, which are effectively inactivated by a small amount of water. The slightly faster rate found when ordinary "Grignard reagent" grade magnesium was used is consistent with this interpretation. When water was added to the dialkylmagnesium solution, some precipitation occurred, but there was no change in rate. Perhaps the catalytic impurity is removed during precipitation of the magnesium chloride.

A definite dependence of the first-order rate constant upon total Grignard reagent concentration was

found. Between 0.1 and 1.1 M the rate increased by a factor of about 1.35, but the increase is more marked at higher concentrations. A maximum rate nearly three times that in 1 M solution was observed with a sirupy solution of about 4 M concentration.

Ashby and Becker[27] have found that the ethyl Grignard reagent is monomeric in tetrahydrofuran, but dimeric in ether. Diethylmagnesium appears to be partially dimerized in tetrahydrofuran.[28] It is possible that the rate increase at higher concentration is then caused by some reaction proceeding through a small amount of more rapidly rearranging dimer (or more highly associated species). In that case, the pseudo-first-order rate constant might be represented by

$$k_\psi = k_1 + k_2[\text{total Grignard}]$$

A reasonably good, though perhaps fortuitous, fit to such a relation is found for the lower concentration runs in dry tetrahydrofuran. There is too much scatter in other runs, possibly owing to variable water content, to test this correlation further. Another explanation, which might also require a term in total Grignard, is the catalysis of part of the reaction by a trace metallic impurity. Alternatively, the concentration dependence might be caused by a "medium effect," possibly associated with the availability of solvent molecules for coordination with the magnesium. Judging from results presented by Dessy and co-workers on the dielectric constant of Grignard solutions,[14] the medium must undergo a very great change through the concentration range covered in the kinetics, and some medium effect should at least be superimposed upon any other effects. It seems that the concentration effect is small with the dialkylmagnesium.

The observed difference in rate between the Grignard reagent and the dialkylmagnesium is not unexpected in light of previous studies of reaction rates of organomagnesium compounds.[29] Excess magnesium chloride further decreased the rearrangement rate. At the present time, we find it difficult to attach any important mechanistic or structural significance to these results. It has been shown that Grignard reagent solutions have a higher dielectric constant than dialkylmagnesium solutions of similar concentration, and that addition of magnesium halide to the Grignard reagent further increases the dielectric constant.[14] Thus, the rate changes observed might be caused by a simple dielectric constant effect, and are in the direction expected on the basis of the solvent effect.

Experimental[30]

Cyctobutylmethyl chloride was prepared as described previously.[3c] Most samples used were at least 99.9% pure by v.p.c., although there was no detectable difference in kinetics when some low-boiling impurities (<1%) were present. The n.m.r. spec-

from 2-methylcyclobutylmethyl chloride is 3-methyl-1-pentene. This olefin arises by kinetically controlled cleavage of the Grignard in the direction leading to a primary rather than a secondary organometallic.

(24) J. E. Kilpatrick, E. J. Prosen, K. S. Pitzer, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **36**, 559 (1946).

(25) (a) H. J. Lucas, R. S. Moore, and D. Pressman, *J. Am. Chem. Soc.*, **65**, 227 (1943); (b) M. M. Kreevoy, L. L. Schaleger, and J. C. Ware, *Trans. Faraday Soc.*, **58**, 2433 (1962), have found that the transition states for oxymercuration of *cis*- and *trans*-2-butene are of nearly equal energy. The transition states are considered to resemble the olefin–mercuric salt π-complex.

(26) W. L. Carrick, in "Unsolved Problems in Polymer Science," National Academy of Sciences, National Research Council, Publication 995 (1962); W. Cooper in "Progress in High Polymers," Vol. 1, J. C. Robb and F. W. Peaker, Ed., Academic Press, Inc., New York N. Y., 1961, pp. 287–306.

(27) E. C. Ashby and W. E. Becker, *J. Am. Chem. Soc.*, **85**, 118 (1963).

(28) S. J. Storfer and E. I. Becker, *J. Org. Chem.*, **27**, 1868 (1962).

(29) See, for instance, H. O. House and D. D. Traficante, *J. Org. Chem.*, **28**, 355 (1963); J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *ibid.*, **21**, 1063 (1956).

(30) Infrared spectra were taken on a Perkin-Elmer 421 or Beckman IR5 spectrometer. Nuclear magnetic resonance spectra were run by Dr. W. B. Schwabacker on a Varian Model HR 60 spectrometer with super-stabilizer at 56.4 Mc. Mass spectra were run by A. Swanson on a Consolidated Electrodynamics Corp. Model 21-402 spectrometer. Microanalyses were performed by Mrs. O. Hammerston of the University of Minnesota. Boiling points are uncorrected.

trum had a doublet at 6.53 τ corresponding to the methylene hydrogens α to the chlorine. The lack of appropriate absorption showed the absence in quantities greater than 1% of cyclopentyl chloride or olefinic unsaturation. A Grignard reagent prepared in tetrahydrofuran and hydrolyzed yielded mainly methylcyclobutane, along with about 3% of 1-pentene. The hydrocarbons were identified by comparison of the infrared spectra of samples trapped from the v.p.c. with published spectra.[31] There were also some very small peaks (about 0.2%) corresponding in retention time to cyclopentene and either methylenecyclobutane or cyclopentane. Heating the Grignard reagent solution for extended periods of time increased the 1-pentene at the expense of the methylcyclobutane. When the Grignard solution was refluxed for a total of about 80 hr., followed by removal of volatile materials under vacuum before hydrolysis, the methylcyclobutane peak comprised about 0.2% of the total hydrocarbon.

The n.m.r. spectrum of a sample of Grignard reagent in tetrahydrofuran had a doublet at 10.39 τ (J = 8.5 c.p.s.). Solvent masked most of the rest of the spectrum. After heating for several hours at 60°, a new triplet centered at 10.70 τ appeared, along with new multiplet absorption in the vinyl region at 4.7 to 5.5 τ.

Cyclobutylmethanol-α,α-d_2.—Methyl cyclobutanecarboxylate (b.p. 132.5–133.5°) was prepared by Fischer esterification of the acid.

Aluminum bromide (29.8 g. 0.11 mole of somewhat yellow material) was added in portions with stirring under a stream of nitrogen to 100 ml. of anhydrous ether. This solution was then dropped into 4.0 g. (0.44 mole) of lithium deuteride (97%) in 25 ml. of ether over a period of 2 hr., and refluxed for 3 hr. more. Then 25 g. (0.22 mole) of methyl cyclobutanecarboxylate in additional ether was added dropwise. Product work-up in the customary manner with dilute sulfuric acid and distillation through a 6-in. wire spiral column produced a total of 13.75 g. (71%) boiling from 137–141°. A center fraction (b.p. 139.5–141°) was shown by v.p.c. to contain 4% of the starting ester. Cyclopentanol was absent (<1% by v.p.c.). The infrared spectrum showed a doublet owing to carbon–deuterium stretching at 2180 and 2080 cm.$^{-1}$, and also had several differences from the undeuterated material in the fingerprint region.

Cyclobutylmethyl chloride-α,α-d_2 was prepared in 68% yield by the procedure used for undeuterated material. A center fraction boiling at 109.5–110° was shown by v.p.c. to contain about 1% of methyl cyclobutanecarboxylate, and very small traces of lower-boiling impurities. The infrared spectrum contained the carbon–deuterium stretching doublet at 2230 and 2150 cm.$^{-1}$. The n.m.r. doublet at 6.53 τ, characteristic of the α-protons in cyclobutylmethyl chloride, was absent. A maximum of 1% of cyclopentyl chloride was present, as estimated from v.p.c of the Grignard hydrolysis product, which contained a small peak with the same retention time as cyclopentane and methylenecyclobutane.

The mass spectrum of methylcyclobutane obtained by hydrolysis of the Grignard reagent showed less than 3% of material not doubly deuterated. The deuterated methylcyclobutane had an n.m.r. multiplet centered at about 8.99 τ, corresponding approximately to the methyl doublet in undeuterated methylcyclobutane. The multiplet had eight equally spaced peaks, approximately in the ratio 1:2:3:3:3:3:2:1. Such a spectrum is consistent with the structure of methylcyclobutane-α,α-d_2, if the geminal H–D coupling constant is about 2.0 c.p.s. and the vicinal H–H coupling constant is about 6.0 c.p.s. The latter is similar to the splitting of the doublet in undeuterated methylcyclobutane. The infrared spectrum has a C–D stretching doublet at 2150 and 2215 cm.$^{-1}$. The n.m.r. spectrum of deuterated 1-pentene from the rearranged Grignard has only the nonterminal olefinic absorption of the vinyl group, which appears as a complex multiplet. In the infrared, the C–D stretching absorption comes at 2225 and 2310 cm.$^{-1}$.

Methyl cyclobutyl ketone was prepared by the addition of an ethereal solution of methyllithium (from 134.5 g., 0.95 mole, of methyl iodide and 13.3 g. 1.92 moles, of lithium wire) to cyclobutanecarboxylic acid (39.5 g., 0.395 mole) in ether. Decomposition with water and distillation yielded 3.0 g., b.p. 130–133°; 15.4 g., b.p. 133–137°; lit.[32] b.p. 137.° The infrared spectrum (smear) showed a carbonyl stretching band at 1715 cm.$^{-1}$, as well as a very weak hydroxyl band at 3450 cm.$^{-1}$.

α-Cyclobutylethanol was prepared by lithium aluminum hydride reduction of methyl cyclobutyl ketone. The product was worked

up under nonacidic conditions, and distilled at 139–141°, lit.[32] 144°.

α-Cyclobutylethyl Chloride.—Thionyl chloride (18.5 g., 0.155 mole) was added over 1 hr. to a mixture of α-cyclobutylethanol (15.5 g., 0.153 mole) and tri-n-butylamine (28.6 g., 0.155 mole) in 100 ml. of anhydrous ether maintained at 0°. The reaction mixture was allowed to stir and warm to room temperature over a period of 2 hr. Then the ether was removed under reduced pressure, and the temperature was raised over a period of 2 hr. to 110°, while evacuated at 15 mm. through a Dry Ice trap. The liquid in the trap was redistilled at atmospheric pressure, b.p. 122–127.5°.

Anal. Calcd. for $C_6H_{11}Cl$: C, 60.75; H, 9.35. Found: C, 61.07; H, 9.56.

A Grignard reagent was prepared in ether from a small portion of the product, and hydrolyzed by pouring into a mixture of ice-water and isooctane. The monomeric hydrocarbon product was found by v.p.c. (Apiezon J) to consist to the extent of 95% of a pair of partly overlapping peaks. These were isolated by preparative chromatography, and identified as ethylcyclobutane and methylcyclopentane by determination of their infrared[31] and n.m.r. spectra. From the kinetic experiments (*vide infra*) the ratio of ethylcyclobutane to methylcyclopentane was shown to be 44:56. The remainder of the product (5%) was eluted after the major peaks, and appears to be a mixture, although it was not resolved by v.p.c. Infrared and n.m.r. spectra gave evidence for both terminal methylene and trisubstituted double bonds. In another Grignard reagent prepared in tetrahydrofuran, all volatile materials were pumped into a cold trap before hydrolysis of the reagent. The hydrolyzed reagent contained only the ethylcyclobutane and methylcyclopentane, along with traces of rearrangement product (*vide infra*); all of the hydrocarbon mixture of longer retention time distilled off before hydrolysis. When the solution was heated for several hours before hydrolysis, the ethylcyclobutane peak decreased in size, and was replaced by a pair of partly resolved peaks of shorter retention time. These were separated preparatively, and shown to consist of *trans*- and *cis*-2-hexene, in order of increasing retention time. Identification was by comparison of the infrared spectra of the separated components with published spectra.[31] The two hexene isomers were formed in very nearly equal amounts, and the ratio did not change appreciably during the course of the rearrangement.

Vapor phase chromatography of the chloride showed the presence of at least four components. There was obviously some decomposition on the column, and rechromatography of a fraction which had been trapped out had appreciable material with retention time appropriate for C_6 hydrocarbons. The largest peak appeared by its n.m.r. spectrum to be mainly α-cyclobutylethyl chloride (doublet at 8.61, quintet at 6.08, broad multiplet at about 8.1 τ), probably contaminated with one of the isomers of 2-methylcyclopentyl chloride.

Magnesium used for most of the kinetic work was high purity sublimed magnesium.[33] Some "Grignard" grade magnesium (Fisher Scientific, lot 794064) which was also used was found by a qualitative emission spectrographic analyses[34] to contain about 0.1% of manganese and about 0.01% of iron. In one run, a sample of "Grignard reagent" magnesium was fused in a Pyrex tube under a stream of hydrogen. Some dark sublimate was noted on the tube. The magnesium was transferred to the reaction flask without exposure to air.

Tetrahydrofuran (Baker, White Label) was refluxed over potassium hydroxide for several hours and distilled. Then it was redistilled from lithium aluminum hydride under a slow flow of helium in an all-fused apparatus shortly before use. The water content was 2.8×10^{-3} M or less (by Karl Fischer titration). For some of the work solvent containing 5.5×10^{-3} to 1.1×10^{-2} M water was prepared by passage through molecular sieves (Linde 4A) instead of the final distillation. The table of kinetics results indicates the solvent used for various runs.

Dioxane was purified by reflux over sodium, distillation, passage through an alumina column, and distillation from lithium aluminum hydride in a stream of helium immediately before use. It had about 5.5×10^{-3} M water.

1,2-Dimethoxyethane was passed through an alumina column and distilled from lithium aluminum hydride in a stream of helium.

(31) Infrared Spectral Data, American Petroleum Institute, Research Project 44.

(32) R. Jacquier and H. Christol, *Bull. soc. chim. France*, 600 (1957).

(33) We are indebted to Dr. R. S. Busk of the Dow Metal Products Co. for a gift of magnesium which was used for this work.

(34) We wish to express appreciation to Dr. W. Erickson of Minneapolis-Honeywell Regulator Co. for this analysis.

Triethylamine was dried over molecular sieves.

Benzene (thiophene-free reagent) was distilled from lithium aluminum hydride. Spectrograde isooctane was used without further treatment.

Preparation of Grignard Reagents.—Grignard reagents were prepared in a specially constructed flask sealed to a reflux condenser. A small side-tube to provide access to the flask was sealed with a glass stopper and a Teflon sleeve fitting which was capable of holding a vacuum of 100 μ. The flask could be attached to a cold trap by ground glass connections at the top of the condenser.

The flask, containing an excess of magnesium, was flamed out under vacuum and filled with helium. The chloride was added in tetrahydrofuran, and refluxed under a small positive pressure of helium. In most cases, a small amount of ethyl chloride or methyl iodide was added to help initiate the reaction. More solvent was usually added after the reaction had started. Reflux was continued for about 0.5 hr. Grignard reagents so obtained were clear, and colorless to pale yellow. In most cases, it was found that a small amount of rearrangement had occurred during formation of the reagent. This was usually about 3 to 8% when the concentration was below 2 M, but much higher degrees of rearrangement were found in more concentrated solutions.

After the reaction solution had cooled, the solvent and any volatile materials were pumped into a trap, leaving behind the Grignard reagent as a viscous oil which often crystallized. The desired amount of fresh solvent was added under a flow of helium. The solution was then transferred by syringe to ampoules for storage, or was used directly for kinetics. It was found that the Grignard reagent could be stored for several weeks in a freezer without appreciable rearrangement or decomposition. In all transfers, a helium atmosphere was maintained. Dialkylmagnesium[35] solutions were prepared by addition of a 10% molar excess of dioxane to a Grignard solution in an ampoule. The tube was then sealed, shaken for at least 20 hr., and centrifuged to produce a clear solution. It was shown by titration that chloride precipitation was virtually complete.

Kinetics.—Small samples of the solution to be studied were sealed in ampoules which were fitted with an extended male ground glass joint. These were immersed for the desired time in a bath maintained at 61.5 ± 0.1°. The ampoules were broken open in a "dry bag" filled with nitrogen or helium, and then attached by means of the ground glass joint to an adapter with a stopcock, which could be connected to a vacuum line. All volatile materials were pumped into a spiral cold trap. (The pumping procedure was highly effective, since 1-hexene added to several of the ampoules was not detected in the Grignard hydrolysis product.) Helium was admitted to the system at atmospheric pressure. The solid or oily liquid remaining in the tube was then hydrolyzed by addition of alcohol. Butanol was used for work with the cyclobutylmethyl organomagnesium compounds because it did not interfere with the hydrocarbon analysis. Methanol was used for the α-cyclobutylethyl reagent. The alcohol–hydrocarbon mixture was then quantitatively distilled from the magnesium salts into another spiral cold trap, and analyzed by v.p.c. In the case of the α-cyclobutylethyl reagent, a small amount of isooctane was added, and the solution was extracted three times with ice-water to remove tetrahydrofuran and methanol. A control experiment showed that identical results were obtained when a Grignard solution was hydrolyzed by the usual technique, by addition of the solution directly to butanol, and by addition to a mixture of water and n-heptane.

In several runs, a pot technique was utilized. The reagent solution was transferred to a helium-swept flask, with a long neck capped by a glass stopper with Teflon sleeve. The neck had a side-arm attached to a helium line which served to maintain a positive pressure of helium in the pot, and to sweep the neck of the flask whenever a sample was being removed. Samples were transferred by syringe to an ampoule, and worked up as before.

(35) C. Noller and W. White, *J. Am. Chem. Soc.*, **59**, 1354 (1937).

Loss of solvent from the pot limited the reaction times which could be studied in this manner.

Vapor phase chromatographic analysis for methylcyclobutane and 1-pentene was carried out with a $^3/_8$ in. × 20 ft. column of 30% SE 30 methyl silicone gum rubber on 40–60 mesh Chromosorb P at 120°. Peak heights were measured. Calibration with pure samples showed linearity of peak height with sample weight, and gave the factor for correction of both hydrocarbons to the same concentration scale.

Products from α-cyclobutylethylmagnesium chloride were chromatographed on a 0.5 in. × 10 ft. column of 17% Apiezon J on 60–80 mesh Chromosorb P at 90°; *trans*- and *cis*-2-hexene were eluted first as a pair of overlapping peaks, followed in order by a partially resolved pair caused by ethylcyclobutane and methylcyclopentane. Tracings were weighed to determine relative quantities in the two fractions. From the last ampoule, methylcyclopentane was found to comprise 56% of the total product. (At this point, about 2% of the rearranging Grignard was estimated to remain, by assuming that the methylcyclopentane curve was similar to the curve for the pure hydrocarbon. The estimate is consistent with predictions from the finally obtained rate constant.) Then, 56% of the total hydrocarbon was subtracted from the ethylcyclobutane–methylcyclopentane peak to obtain a value for unrearranged Grignard.

The concentrations of unchanged reactant and product within a run are proportional to the fractions of total hydrocarbon derived from the reactant and product, respectively. Therefore, a plot of log (methylcyclobutane/(methylcyclobutane + 1-pentene)) *vs.* time should be linear if the reaction is first order in unrearranged alkyl groups. This was found to be the case. Rate constants were calculated from the integrated first-order rate equation, using unweighted linear least-squares analysis.[7] Confidence limits are 70% limits derived from Student's distribution, with n − 2 degrees of freedom, where n = number of points. Calculation were performed on a Control Data 1604 computer by M. F. Cheng of the University of Minnesota Numerical Analysis Center.

α-**Deuterium Isotope Effects.**—A Grignard reagent was prepared under usual conditions for kinetic samples using 0.999 g. (9.56 mmoles) of cyclobutylmethyl chloride and 1.000 g. (9.39 mmoles) of its dideuterated analog, with 0.4887 g. (0.00203 g.-atom) of sublimed magnesium. A portion was immediately hydrolyzed, and found to be 9.4% rearranged. The remainder was sealed in a glass ampoule, and heated at 61.5° for 64 hr. It was found on hydrolysis to have rearranged to the extent of 70.2%. The methylcyclobutane and 1-pentene from each fraction were isolated and analyzed by mass spectroscopy at low ionizing voltage for mass 70 and 72. Results are:

| | | Mass 70/mass 72 | |
Sample	Rearrangement, %	Methylcyclobutane	1-Pentene
1	9.4	1.019	0.987
2	70.2	0.984	1.008

Results are probably accurate to about 1% and are not corrected for the mass 70 peak in the deuterated hydrocarbon or the mass 72 peak in the undeuterated material.

Using the extent of reaction and the isotopic compositions of the samples, the isotope effect for reaction between a pair of samples may be calculated from

$$\frac{k_H}{k_D} = \frac{\log (a_1{}^H/a_2{}^H)}{\log (a_1{}^D/a_2{}^D)}$$

a^H is the fraction of undeuterated material which is not rearranged, a^D is the fraction of deuterated material which is not rearranged, and the subscripts 1 and 2 refer to initial and final samples. In this manner, k_H/k_D is found to be 1.018. An additional source of error arising from traces of tetrahydrofuran collected with the hydrocarbons was shown to be no greater than 1% in the isotope ratios.