Relative Reactivities of Cycloalkanone Dimethyl Ketals to Hydrogenolysis by Dichloroaluminum Hydride

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The relative rates of hydrogenolysis of a series of cycloalkanone dimethyl ketals by $AlCl_2H$ to the corresponding cycloalkyl methyl ethers have been determined. The order of reactivity varies with ring size in the following manner: $C_7 > C_8 > C_9 \approx C_5 > C_{11} \approx$ 3-pentanone $> C_{10} > C_6 > C_{12} > C_4$. These results are consistent with the concept of I (internal) strain, and it is suggested that formation of the oxocarbonium ion is the rate-controlling step in the hydrogenolysis reaction.

Following the discovery of lithium aluminum hydride (LAH) and its many applications to the reduction of organic compounds, it had been found that LAH in combination with other reagents gave compounds with reducing properties[2] different from those of LAH itself. LAH and aluminum halides give hydridoaluminum halides, "mixed hydrides," which unlike LAH have the ability to hydrogenolyze acetals and ketals to ethers. The "mixed hydrides" which exist in ether as an etherate, complex with an oxygen of the acetal or ketal. This complex **1** decomposes to give the oxocarbonium ion **2** which in turn is attacked by hydride to yield the ether **3**. Brown and Leggetter have studied[3] the ease
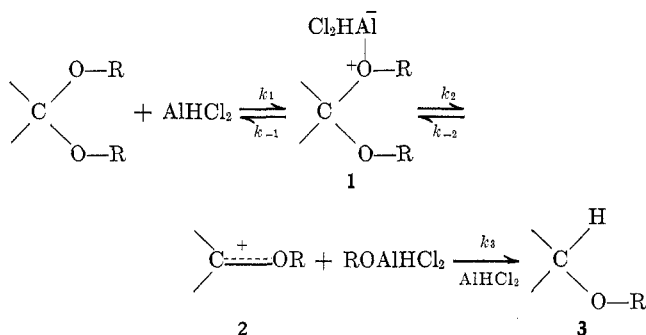
and direction of ring opening hydrogenolysis of a large number of substituted 1,3-dioxolanes. They concluded that the results were consistent with the formation of the oxocarbonium ion being the rate-controlling step because the predominant product is the one resulting from the more inductively stabilized oxocarbonium ion. Eliel, *et al.*,[4] later pointed out that evidence available from the hydrogenolysis of substituted 1,3-dioxolanes, 2-tetrahydropyranyl ethers and 2-tetrahydrofuranyl ethers did not necessarily indicate which step was rate controlling. With such unsymmetrical acetals and ketals, that reduction product which passes through the more stable carbonium ion normally predominates.[3,5,6] Eliel argued that since the oxocarbonium ion **2** was a relatively unstable intermediate, the energies of both the transition state leading to the oxocarbonium ion **2** and the transition state leading to the product **3** reflect the stability of the intermediate oxocarbonium ion **2**. Thus, no information was obtained as to

whether the formation of the oxocarbonium ion, *i.e.*, $k_3 \gg k_{-2}$, or whether the acquisition of hydride, *i.e.*, $k_3 \ll k_{-2}$, was rate determining.

The formation of an oxocarbonium ion **2** from a ketal **1** involves a change in the coordination number of the reacting carbon from four to three, and the formation of an ether **3** from an oxocarbonium ion **2** involves a change in the coordination number from three to four. In the reaction of any cyclic series of compounds such as the reduction of cycloalkanone dimethyl ketals, the relative reactivities of the members will vary in a unique way depending on the change in coordination number (4 to 3 or 3 to 4). The changes of reaction rates and equilibria as a function of ring size in homologous series have been extensively researched[7-17] and the explanation for such changes can be found in the steric strains inherent in ring compounds. These steric strains and their effects on the reactivity of cyclic compounds are qualitatively understood.[11,17-19]

Results

Direct determination of the rate constants for the hydrogenolysis of the cycloalkanone dimethyl ketals is experimentally difficult because of the rapidity with which the reaction proceeds. Competitive reductions among the cycloalkanone dimethyl ketals, however, would give the desired trend in reactivity. Each ketal was competitively reduced at least twice, either both times against a second ketal or against two different ketals which had been reduced against each other.

The most convenient and accurate method of measuring the ratio of products is by gas chromatography. Unfortunately, the ketals are unstable on the gas chromatograph owing to fragmentation to enol ethers. However, under the experimental work-up conditions the

(1) Abstracted in part from the thesis of K. J. Byrne presented to Villanova University in partial fulfillment for the M.S. degree, 1969.

(2) M. N. Rerick, "Reduction," R. L. Augustine Ed., Marcel Dekker, New York, N. Y., 1968.

(3) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **42**, 990 (1964).

(4) E. L. Eliel, B. E. Nowak, R. A. Diagnault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).

(5) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **41**, 2671 (1963).

(6) B. E. Leggetter and R. K. Brown, *ibid.*, **42**, 1005 (1964).

(7) M. Anteunis, F. Alderweireldt, and M. Acke, *Bull. Soc. Chim. Belg.*, **72**, 797 (1963).

(8) H. C. Brown, R. S. Fletcher, and R. B. Johannessen, *J. Amer. Chem. Soc.*, **73**, 212 (1951).

(9) H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952).

(10) H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

(11) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 211 (1957).

(12) R. Heck and V. Prelog, *Helv. Chim. Acta*, **38**, 1541 (1955).

(13) J. E. Kilpatrick K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, **69**, 2483 (1947).

(14) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(15) J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, **73**, 5030 (1951).

(16) L. Scholsmans, P. J. C. Fierens, and T. Verlie, *Bull. Soc. Chim. Belg.*, **68**, 580 (1959).

(17) M. Havel, J. Krupicka, M. Svoboda, J. Zavada, and J. Sicher, *Collect. Czech. Chem. Commun.*, **33**, 1429 (1968).

(18) D. Lloyd, "Alicyclic Compounds," Elsevier, New York, N. Y., 1963, p 73.

(19) J. Sicher, "Progress in Stereochemistry," Vol. III, P. B. D. de la Mare and W. Klyne, Ed., Butterworths, Washington, D. C., 1962, p 202.

ketals were quantitatively converted to ketones. The gas chromatograms of the reaction mixtures of the competitive reductions then showed methyl ethers produced by reduction and ketones which corresponded to unreacted ketal. The exception is cyclobutanone dimethyl ketal which does not hydrolyze readily and, since it is reasonably stable on the gas chromatograph, it was examined as the ketal.

It had been the original plan to obtain corrections for detector responses for all ketones and methyl ethers and to express the results as percent ketal reduced. However, it became apparent that there was a material loss for ketones of some ring sizes. Cyclopentanone had the largest shortage in material balance. A possibility is that the ketones produced in the work-up of the unreacted ketals undergo condensation reactions. Eliel[20] has reported that, for the reduction of ketones by hydride transfer from alkoxyaluminum dichloride, some condensation of the ketones especially cyclopentanone had occurred. Another possibility is that the ketal could lose methanol to form an enol ether which under acidic conditions polymerizes. This loss of some of the unreacted ketal does not interfere with the results here because it occurs after the competitive reduction.

When competitive reactions are controlled such that only small percentages of products are formed, the molar ratio of products approximates the ratio of rate constants for the formation of these products. Detector responses (see Experimental Section) were used to correct the measured ratio of cycloalkyl methyl ethers to a molar ratio. The relative reactivities thus obtained are in Table I.

TABLE I

RELATIVE REACTIVITIES OF DIMETHYL KETALS
TO HYDROGENOLYSIS BY DICHLOROALUMINUM HYDRIDE

Dimethyl ketal of	Relative reactivity	Dimethyl ketal of	Relative reactivity
Cyclobutanone	0.06	Cyclononanone[a]	1.6
Cyclopentanone	1.3	Cyclodecanone[a]	0.7
Cyclohexanone	0.5	Cycloundecanone[a]	1.0
Cycloheptanone	7.0	Cyclododecanone	0.3
Cyclooctanone	1.7	3-Pentanone	1.0

[a] Reduced on one-tenth the scale of the other reductions.

Discussion

The relative reactivities of the cycloalkanone dimethyl ketals should increase when there is a decrease in strain in the rate-controlling step and decrease when there is an increase in strain in the rate-controlling step. The change in the strain present in the cycloalkanone dimethyl ketal rings will be in the opposite direction in the two steps of the hydrogenolysis because the change in coordination number is four to three in the first step (1 → 2) and three to four in the second step (2 → 3). That k_{-2} is unimportant (dissociation is irreversible) has been demonstrated by Leggetter and Brown[21] in the hydrogenolysis of the *cis*- and *trans*-2,4-dimethyl-1,3-dioxolanes. No isomerization is detectable in the hydrogenolysis reaction of these compounds. If one then assumes that k_1/k_{-1} is the same for all ketals then the observed rate will reflect oxocarbonium ion 2 formation.

The results of the competitive reduction of cyclobutanone, cyclopentanone, cyclohexanone, and cyclo-

(20) E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, **30**, 3809 (1965).
(21) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **43**, 1030 (1965).

heptanone dimethyl ketals suggest that the formation of the oxocarbonium ion intermediate 2 is the rate-controlling step of these "mixed hydride" reductions. Cyclobutanes possess considerable angle strain. The formation of an oxocarbonium ion would increase this angle strain. Cyclobutanone dimethyl ketal is 17 times less reactive than 3-pentanone dimethyl ketal. Cyclohexanes are able to stagger all their bonds and formation of an oxocarbonium ion would introduce some eclipsing. Cyclohexanone dimethyl ketal is only half as reactive as 3-pentanone dimethyl ketal. The slowness of these reductions show that the strain increasing step (formation of the oxocarbonium ion) is rate controlling. Cyclopentanone dimethyl ketal is reduced 1.3 times as fast as 3-pentanone dimethyl ketal. Cycloheptanone dimethyl ketal is reduced seven times as fast as 3-pentanone dimethyl ketal. There is a decrease in eclipsing strain in the five- and seven-membered-ring dimethyl ketals with the formation of the oxocarbonium ion intermediate. This decrease in strain in the rate-controlling step causes these ketals to be more reactive than an open-chain ketal.

Because cycloalkanone dimethyl ketals of medium rings would greatly reduce their transannular strain in forming the oxocarbonium ion intermediate, their reductions were expected to be very rapid. This is not the case. Cyclooctanone and cyclononanone dimethyl ketals are reduced only slightly faster than 3-pentanone dimethyl ketal, and cyclodecanone, cycloundecanone and cyclododecanone dimethyl ketals are reduced at the same rate or slightly slower than 3-pentanone dimethyl ketal (Table I). The hydrogenolysis of cycloalkanone dimethyl ketals does not show the large release of strain found for other ring reactions such as SN1 displacements.

One explanation might be that the transannular strain in the medium rings has other effects besides being a driving force for the formation of the oxocarbonium ion. It can hinder the complexing of a ketal by dichloroaluminum hydride which has ether and ketal as ligands in rapid equilibrium. The transannular strain in cycloalkanone dimethyl ketals of medium rings could decrease their association with dichloroaluminum hydride (k_1/k_{-1} is not the same for these ketals). Thus, the relative reactivities of cycloalkanone dimethyl ketals of ring sizes eight to twelve might more accurately reflect the degree of association of the ketal and dichloroaluminum hydride than the rate (k_2) of oxocarbonium ion formation.

A second explanation might be that the hydrogenolysis of ketals may resemble an SN2 displacement. This mechanism involves a change of coordination number of four to five to four. While a pentacoordinated intermediate 4 is not usually considered as an intermediate
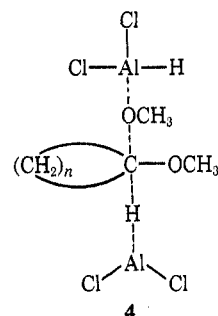
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in ketal hydrogenolysis, the results do not exclude the possibility. This type of intermediate has been postulated to account for the stereochemistry of similar hydrogenolysis reactions.[22,23] For this the methoxide complexed with a dichloroaluminum hydride would be the leaving group and a second dichloroaluminum hydride would approach from the other side. The introduction of a fifth coordinating group in the rate-controlling step would not change the interpretation of results for the smaller cycloalkanone dimethyl ketals, but would be expected to slow the hydrogenolysis of the ketals of medium ring size because the rate-controlling step would increase the transannular strain.

Experimental Section

Preparation of Compounds.—Cyclobutanone was prepared by the procedure described by Roberts and Sauer.[24] The remaining ketones were obtained from Aldrich Chemical Co., Inc. Cyclobutanone, cyclopentanone, and cyclohexanone dimethyl ketals were prepared by the method of Lorette and Howard.[25] A modification of the method of Helferich and Hausen[26] was employed for the synthesis of the ketals of seven- to twelve-membered rings.

A ketone, tetramethoxylsilane and methanol were mixed in a molar ratio of 1:3.1:4.0. A catalytic amount of dry hydrogen chloride was added and the mixture was allowed to stir at room temperature for 3 days. The mixture was then made basic with sodium methoxide, distilled to separate it from the silicon polymer which causes bumping and distilled again to purify the ketal.

The boiling points, °C (mm), for dimethyl ketals[27] are as follows: cyclobutanone, bp 112–113; cycloheptanone, 73 (10); cyclooctanone, 88 (7.7); cyclononanone, 58–61 (0.5); cyclodecanone, 63–64 (0.2); cycloundecanone, 87–88 (0.7); Methyl ethers[27] obtained by preparative glc are cyclononyl, cyclodecyl, and cycloundecyl.

The methyl ethers expected from the competitive reductions of the cycloalkanone dimethyl ketals were synthesized either by the "mixed hydride" reduction of individual ketals or by the sodium borohydride reductions of the corresponding ketones and methylation of the resulting alcohols by the procedure of Diner, Sweet, and Brown.[28]

Competitive Reductions.—Into a 500-ml three-neck flask equipped with a mechanical stirrer, rubber septum, and drying tube was placed 400 ml of anhydrous ether. To the ether was added 0.300 g (0.00750 mol) of 95% LAH and 3.00 g (0.0225 mol) of aluminum chloride. The mixture was allowed to stir for 0.5 hr. The reaction flask was cooled using a Dry Ice–acetone bath and a mixture of 0.025 mol of two ketals was syringed into reaction flask and allowed to warm for another 0.5 hr. Then 20% sodium hydroxide (about 4.5 ml) was added dropwise until a granular precipitate formed leaving a clear ether layer. The ether was filtered and evaporated to concentrate the products. Suitable precautions were taken depending upon the volatilities of the products. The hydrolysis of the aluminum salts initially produces a large amount of hydrochloric acid. Ketals are not stable under acidic conditions and they were always found to be partially hydrolyzed to the ketones. The hydrolysis was completed by adding two drops of dilute hydrochloric acid to the ether solution. The ether solution was examined by gas chromatography; peaks corresponding to the cycloalkylmethyl ethers were measured under conditions identical with those used to measure the competitive reductions. The gas chromatograms were obtained on a F & M Model 720 thermal conductivity gas chromatograph equipped with a 0.25 in. × 6 in. 10% Carbowax column. The helium gas flow was adjusted to 10 cc/sec. The injection port and detector were 250 and 360°, respectively. The column was set at 65° and programmed 10°/min.

The detector response corrections for the cycloalkyl methyl ethers are as follows: cyclobutyl, 0.82; cyclopentyl, 0.93; cyclohexyl, 1.00; cycloheptyl, 1.07; cyclooctyl, 1.12; cyclononyl, 1.21; cyclodecyl, 1.29; cycloundecyl, 1.36; cyclododecyl, 1.44; and 3-pentyl, 0.76.

Registry No.—Dichloroaluminum hydride, 13497-97-7; cyclobutanone dimethyl ketal, 4415-90-1; cyclopentanone dimethyl ketal, 931-94-2; cyclohexanone dimethyl ketal, 933-40-4; cycloheptanone dimethyl ketal, 25632-02-4; cyclooctanone dimethyl ketal, 25632-03-5; cyclononanone dimethyl ketal, 25632-04-6; cyclodecanone dimethyl ketal, 25632-05-7; cycloundecanone dimethyl ketal, 25632-06-8; cyclododecanone dimethyl ketal, 950-33-4; 3-pentanone dimethyl ketal, 25636-49-1.

(22) P. C. Loewen, W. W. Zajac, Jr., and R. K. Brown, *Can. J. Chem.*, **47**, 4059 (1969).

(23) S. S. Bhattacharjee and P. A. J. Gorin, *ibid.*, **47**, 1195 (1969).

(24) J. D. Roberts and C. W. Sauer, *J. Amer. Chem. Soc.*, **71**, 3925 (1949).

(25) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

(26) B. Helferich and J. Hausen, *Ber.*, **57B**, 795 (1924).

(27) Satisfactory combustion analytical data (±0.4%) were obtained on these compounds, Ed.

(28) U. E. Diner, F. Sweet, and R. K. Brown, *Can. J. Chem.*, **44**, 1592 (1966).