KINETIC AND EQUILIBRIUM STUDIES OF CYCLIC
KETAL FORMATION AND HYDROLYSIS

DISSERTATION

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I: INTRODUCTION

Stimulated by theoretical and practical problems, we became interested in studying the rates of hydrolysis and formation of cyclic ketals and in determining equilibrium constants for these reactions. From a theoretical viewpoint, we wanted to see whether the effect of the gem-dimethyl grouping in promoting ring formation could be extended to larger alkyl groups, particularly the ethyl and isopropyl groups. From a practical viewpoint, we were interested in the preferential blocking or regeneration of ketonic groups in polyfunctional compounds. This objective could be attained; (a) by finding differences in the hydrolysis or formation rates of ketals, or (b) by allowing equilibrium to be established between one mole of polycarbonyl compound and the molar quantity of glycol which would achieve the maximum in selective ketone blocking once equilibrium is established.

More specifically it was of interest to discover how large a difference exists in the kinetic and thermodynamic properties of the ketals in the reaction. If a sufficient difference exists,

then, one of the glycols to be investigated might be used to block one of the types of ketonic groups in polycarbonyl compound

which contained five- and six-membered rings. This was deemed of importance because such polycarbonyl compounds are frequently encountered in steroids and terpenes. A glycol, which would block preferentially either a five- or six-membered ring ketone, would be of value.

Although rate data were desired for both the forward and reverse reactions, the kinetic work emphasized ketal hydrolysis because of experimental feasibility and the equilibrium position of the reaction. The ketals were derived from the ketones; cyclohexanone, cyclopentanone, and 2-methylcyclopentanone and the following glycols; ethylene glycol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, 2,2-diethyl-1,3-propanediol, and 2,2-diisopropyl-1,3-propanediol. The guiding philosophy in the kinetic work was that it would be better to measure the rates of a number of compounds at one temperature than to measure the rates of a few compounds at several temperatures. The principal reason for this is that the emphasis was on measuring relative rate constants and discovering a preferential blocking group rather than determining the activation energies and probability factors of the reaction. Although a change-over of rates is theoretically possible over a wide temperature range, such would not be expected to occur in the temperature range usually employed for this type of reaction.

Since the steroids are common polycarbonyl compounds, it was decided to try to find the blocking groups for such steroid ketones. An example of such a steroid is androstanedione (I).

In this compound a ketone group is found in the six-membered

ring D. For the purpose of this investigation it was thought that cyclohexanone would be a suitable simple analog to

ring A, while 2-methylcyclopentanone would fulfill a similar relationship to ring D. In truth, 2,2-dimethylcyclopentanone would be superior to 2-methylcyclopentanone for this purpose, but the dimethylcyclopentanone is much more difficult to prepare than the monomethylcyclopentanone. Finally, cyclopentanone itself was included in this study because it affords interesting comparisons with 2-methylcyclopentanone.

With respect to the previously mentioned glycols, only ethylene glycol has been used heretofore in blocking steroid ketones. However, as with other groups now used to block such ketones, ethylene glycol is in many cases not completely suitable with respect to selectivity, yield of product, and reaction time. Since 1,3-glycols are likewise capable of forming cyclic ketals, it was hoped that perhaps one of these might prove selective enough to be a blocking group for one type of ketone and not the other. The preferential character of these groups could be shown either from the point of view of rate of formation or hydrolysis or with respect to the position of equilibrium in the reaction.

Ethylene glycol was also included with the 1,3-glycols because no such study has yet been made on it, despite its importance as a blocking group for ketones in the steroids.

As stated previously, the experiments were also designed to provide information on the influence of the gem-dialkyl effect in promoting ring formation and ring stability. The gem-dimethyl group is known to exhibit this effect, but little is known about the influence of larger dialkyl groups. Rate constants were determined for the hydrolysis of three types of ketals in which, in addition to the unsubstituted compound, the gem-dialkyl groups

were dimethyl, diethyl, and diisopropyl.

II: LITERATURE REVIEW

A summary of the previous related research is included in this literature review. The discussion is separated into three parts. The methods for blocking ketone groups are reviewed in the first section. It was thought that a clearer picture of the methods of blocking ketone groups could be obtained by focusing the discussion on a particular area of organic research. The steroids were selected as the area since the research program itself was designed to apply particularly to the steroids.

The second part is devoted to the mechanism of ketal hydrolysis, the chemistry of five-membered and six-membered ring compounds, and influence of substitution on ring formation and cleavage.

The final division is concerned with the formation and hydrolysis of cyclic ketals. Kinetic data is included whenever it is available. Also, the equilibrium values for the various acetals and ketals in the accompanying reaction are considered.

A. Methods of Blocking Steroid Ketone Groups

1. Cyclic Ketals

Steroidal cyclic ketals, which have been up-to-now entirely of the 1,3-dioxolane type (A), are prepared most frequently

by the acid catalyzed reaction of the steroidal carbonyl with ethylene glycol, with the water formed being removed by azeotropic distillation. An alternate procedure for preparing steroidal cyclic ketals is the accompanying reaction, which is known as transketalization.¹

steroidal ketone + cyclic ketal $\rightleftharpoons$

steroidal ketal + low boiling ketone

In this method the removal of the low boiling ketone may be used to drive the reaction to completion. Cyclic ketals are decomposed to yield the free ketone by an acidic aqueous medium. Ketals are stable under a variety of conditions of which a partial list would include:¹

1. catalytic reduction by hydrogen

sodium in alcohol

sodium borohydride

lithium aluminum hydride

2. oxidation

Oppenauer

chromic anhydride-pyridine

silver oxide

osmium tetroxide

3. esterification

4. saponification

¹ A reference example for each type of reaction is given by H. Dauben, et al., J.Am.Chem.Soc., 76, 1359 (1954).

5. bromine addition
6. allylic bromination
7. dehydrobromination
8. cyanhydrin formation
9. Grignard reaction
10. Reformatsky reaction
11. base-catalyzed reactions or basic media

Some preferential preparation of cyclic steroidal ketals can be achieved with polycarbonyl steroids. The 3-keto groups almost always form ketals whereas their C-11 and C-12 counterparts almost never undergo the reaction.¹ Only a few cases of C-11 ketal formation have been observed.² Ketones at either C-20 or C-17 position are somewhat intermediate in reactivity. Ketones at the C-6 position do form ketals, but whether these ketones are equivalent to the readily reactive C-3 or moderately reactive C-20 ketones could not be ascertained.³ The C-7 carbonyls are probably intermediate in

- ¹ E. Oliveto, et al., J.Am.Chem.Soc., 78, 1414 (1956); H. Herzog, M. Jevnik, and E.B. Hershberg, ibid., 75, 269 (1953); E. Oliveto, T. Clayton, and E. Hershberg, ibid., 75, 486 (1953); R.H. Levin, et al., ibid., 75, 502 (1953); E.S. Rothman and M. Wall, ibid., 78, 1744 (1956).
- ² B. Magerlein and R. Levin, ibid., 77, 1904 (1955); J. Constantin, et al., ibid., 75, 1716 (1953).
- ³ E. Fernholz, and U.S.patents; 2,356,154 (Aug. 22, 1944), 2,378,918 (June 26, 1945).

reactivity, but here again information could not be located despite a diligent search of the literature. Neighboring groups, however, will modify the relative reactivity of a carbonyl group at a given position in the steroid molecule. A number of examples might be of interest at this point. The reaction of 3,11-diketostanoic acid (I) with ethylene glycol to form 3,11-diketostanoic acid-3-ethylene ketal (II) in 81 percent yield provides an example of preferential blocking of the C-3 keto group over the C-11 carbonyl.¹

The preferential formation of a C-3 ketal in the presence of C-12 and C-20 keto groups is illustrated by the conversion of 16-bromo- Δ^4 -pregnene-17 α -ol-3,12,20-trione (III) to 16-bromo- Δ^5 -pregnene-17 α -ol-3,12,20-trione-3-ethylene ketal (IV) in 90 percent yield.²

¹ E. Oliveto, et al., J.Am.Chem.Soc., 78,1414 (1956).

² E.S. Rothman and M. Wall, ibid., 78,1744 (1956).

On the other hand, the formation of pregnan-17 α -ol-3,11,20-trione-3,20-diethylene ketal (VI) in 93 percent yield from pregnan-17 α -ol-3,11,20-trione (V) provides an example of reactivity at the C-3 and C-20 positions, while the C-11 position is inert as over.¹

Reaction of the C-20 and non-reaction at the C-11 also occurs when pregnan-3 α ,17 α -diol-11,20-dione (VII) is converted to pregnan-3 α ,17 α -diol-11,20-dione-20-ethylene ketal (VIII).¹ That the C-17

ketone is more reactive than the C-11 ketone is illustrated by the conversion of andrenosterone (IX) to Δ^4 -androstene-3,11,17-triketone-3,17-diethylene ketal (X) in 35 percent yield.²

¹ E. Oliveto, T. Clayton, and E. Hershberg, J. Am. Chem. Soc., 75, 486 (1953).

² S. Bernstein, et al., J. Am. Chem. Soc., 75, 1481 (1953).

Various refinements are sometimes of value in achieving selective ketal formation. The 3-ethylene-dioxy derivative (XII)

of Δ^4 -androsterone-3,17-dione was first prepared in 25 percent yield by reaction of excess ethylene glycol and Δ^4 -androsterone-3,17-dione (XI).¹ The yield was raised to 50 percent by use of only one mole of ethylene glycol.² Finally, the same derivative was prepared in 74 percent yield by exchange dioxolation using 2-methyl-2-ethyl-1,3-dioxolane (XIII).³

XIII

- ¹ E. Fernholz and H. Stavely, 102nd Meeting of Am.Chem.Soc., Atlantic City, N.J., 39M (1941); U.S.patents; 2,356,154 and 2,378,918.
- ² H. Herzog, et al., J.Am.Chem.Soc., 75,4425 (1953).
- ³ H. Dauben, B. Loken, and H. Ringold, ibid., 76,1359 (1954).

Exchange dioxolation according to the method of Dauben, Loken, and Ringold offers selectivity in that no reaction is observed at C-17 carbonyl even when the C-17 ketone is the only carbonyl group present.¹ In other cases, exchange dioxolation affords yields which are equal to, or slightly better than, those of direct diolation with some saving in time of reaction.

With respect to selective hydrolysis, much less has been accomplished. The diketal, 4-bromopregnane-11b,17a-diol-3,20-dione-3,20-diethylene ketal (XIV) was hydrolyzed to the monoketal, 4-bromopregnane-11b,17a-diol-3,20-dione-3-ethylene ketal (XV) in 93 percent yield.² This preferential hydrolysis at the 20 position

XIV

XV

would be expected in this case because the neighboring halogen would tend to slow down the rate of hydrolysis of the ketal at the 3 position. On the other hand, treatment of Δ^5 -pregnene-11a,17a,21-triol-3,20-dione-3,20-diethylene ketal (XVI) with

¹ Presented before the Division of Organic Chemistry at the Fourth Northwest Regional Meeting of the American Chemical Society, Seattle, Wash., June 8, 1951. (cf. H. Dauben, B. Loken, and H. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

² E. Oliveto, *et al.*, *J. Am. Chem. Soc.*, **77**, 2224 (1955).

p-toluenesulfonic in acetone leads to Δ^4 -pregnene-11a,17a,21-triol-3,20-dione-20-ethylene ketal (XVII) in 63 percent yield.¹

The presence of the double bond at the Δ^5 position facilitates the hydrolysis of 3-keto-3-ethylene ketal.

Finally, we would like to mention one peculiarity which occurs in the ketalization of 3-keto- Δ^4 -steroids. The reader may have perhaps noticed that migration of the double bond takes place on ketal formation and hydrolysis in the accompanying manner.²

Ketals have found frequent use as a means of protecting steroidal ketones. From the point of view of the steroid chemist, the experimental procedure and reaction yields for preparing and hydrolyzing ketals, and the stability of ketals under various

¹ F. Sondheimer, J. Am. Chem. Soc., 75, 1282 (1953).

² R. Antonucci, et al., J. Org. Chem., 18, 70 (1953); F. Sondheimer, et al., J. Am. Chem. Soc., 75, 1282 (1953); O. Mancera, et al., ibid., 77, 5669 (1955).

conditions are quite satisfactory in a great number of cases. The selectivity which can be achieved in ketal formation is at best empirical in nature. The method of transketalization for selective ketal formation seems quite promising in certain cases. Finally, although reactions involving cyclic ketals have been used at one time or another by almost every steroid chemist, there have not been any patterned thermodynamic or kinetic studies on these or analogous compounds.

2. Hemithioketals

Hemithioketals are formed by the reaction of β -mercaptoethanols with keto steroids. In addition to β -mercaptoethanol itself, substituted β -mercaptoethanols, such as 1,1-diphenyl-3-mercaptopropane-2-ol, have been used to prepare hemithioketals.¹ Zinc chloride is a suitable catalyst. The initial ketone may be regenerated either by acid hydrolysis or by the action of Raney nickel. Hemithioketals are prepared in yields ranging up to 80 percent with carbonyl groups at C-3, C-7, C-12, C-17, and C-20 positions. The conjugated C-3 carbonyl and C-11 carbonyl groups are relatively unreactive. Examples demonstrating these statements are now given. The reactivity at the C-3, C-7, and C-12 positions is demonstrated by the formation of the trihemithioketal (II) of dehydrocholic acid (I) in 35 percent yield.² The comparative reactivities of the C-17 and C-3 (conjugated) carbonyls are indicated

¹ C. Djerassi, M. Gorman, J. Henry, J. Am. Chem. Soc., 77, 4647 (1955).

² R. Mazur and E. Brown, ibid., 77, 6670 (1955).

by the formation of Δ^4 -androstene-3,17-dione-17-ethylenehemi-

thioketal (IV) from Δ^4 -androstene-3,17-dione (III) in 41 percent yield.¹ Our final example is of selective hemithioketal formation

in the preparation of allo-pregnan-3 β -ol-11,20-dione-3-acetate-20-ethylenehemithioketal (VI) from allopregnan-3 β -ol-11,20-dione acetate (V) in 75 percent yield.² The information on selective

¹ J. Romo and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 4961 (1951).
² C. Djerassi, *et al.*, *ibid.*, **74**, 3634 (1952).

hemithioketal hydrolysis is very sketchy. When the trihemithio-ketal (II) of dehydrocholic acid is treated with acetyl chloride in methanol, the bis-hemithioketal (VII) in which only the 3-keto

group had been hydrolyzed, was obtained in 41 percent yields.¹

In comparison with the other methods for blocking steroid ketones, the hemithioketal method differs in three ways. First, the original ketone may be regenerated by the action of Raney nickel on the hemithioketal. Second, the 12-keto group reacts with *B*-mercaptoethanol. Third, *B*-mercaptoethanol is very reluctant to react with conjugated carbonyls. The last two differences contrast particularly with the reactions in the ketal formation method. Thus, the above examples show why hemithioketal formation is a useful tool to steroid chemists.

3. Thioketals

Thioketals are compounds produced from steroidal ketones and thiols by means of catalysis with zinc chloride and sodium sulfate. The thiol compounds; ethanedithiol, 1,3-propanedithiol,

¹ R. Mazur and E. Brown, *J. Am. Chem. Soc.*, 77, 6670 (1955).

benzyl mercaptan, ethanethiol, and thioglycollic acid have been used to prepare thioketals. Of the above, the dithiols form cyclic thioketals. The original ketones may be regenerated by aqueous acids. However, most frequently the thioketals are subjected to hydrogenolysis with Raney nickel, as shown by the accompanying example. Thioketals, broadly speaking, are quite similar

to sulfides in stability.

Hauptmann gives as a general rule that both monothiols and dithiols form mercaptols with keto groups in rings A and D while only the dithiols form mercaptols with keto groups in rings B and C.¹ The 11-keto group, however, is inert to reaction. Ethane-dithiol reacts readily with dehydrocholic acid to form the tri-

I

mercaptopol (I).² Yields in the above examples are only in the 60-80 percent range even for the more reactive compounds. It

¹ H. Hauptmann and M. Campos, J. Am. Chem. Soc., 74, 3179 (1952).

² H. Hauptmann, ibid., 69, 562 (1947).

is believed that the reaction of ethanedithiol with a 3-keto- Δ^4 -steroid does not lead to double bond migration as does the corresponding reaction of ethylene glycol and steroid. The reason for this is that the thioketal of Δ^4 -cholestene-3-one yields Δ^4 -cholestene on hydrogenolysis with Raney nickel.¹ Thioketals find their widest use in blocking steroid ketones when the hydrogenolysis of the ketone with Raney nickel is amenable to the synthesis desired or when other blocking groups fail to react with a hindered carbonyl.

4. "Enamine" Derivatives

The "enamine" derivatives are another type of derivative which can be used in blocking steroidal ketones. "Enamines" are formed by the condensation of the steroidal ketones with secondary amines. Pyrrolidine is the amine most frequently used, but morpholine and piperidine have also seen some service. An example follows.² The yields in "enamine" formation are usually

¹ H. Hauptmann, J. Am. Chem. Soc., 74, 3179 (1952).

² F.W. Heyl and M.E. Herr, J. Am. Chem. Soc., 75, 1918 (1953).

nearly quantitative. "Enamines" are hydrolyzed by bases. However, lithium aluminum hydride can be used to reduce other oxygenated functions in the presence of "enamine" derivatives, but hydrolysis of the reduction complex also leads to hydrolysis of the blocking group.

"Enamine" derivatives have been formed with steroidal carbonyl groups at the C-3, C-7¹, C-17², and C-22¹ positions, although reaction at the C-3 position seems to be preferred, as the previous example indicates.^{3,4}

Finally, "enamines" differ from other derivatives discussed heretofore in that they are reasonably stable in strong acids. Actually, in the presence of strong acids, "enamines" isomerize to ternary iminium salts, but for synthetic purposes "enamines" may be considered stable in strong acids.¹

Neutral medium
"enamine"

Strong acid medium
iminium salt

The stability in strong acids, hydrolysis by bases, tendency toward selective attack at C-3, and high preparative yields can be turned to advantage in a number of synthetic approaches.

¹ J. L. Johnson, et al., J. Am. Chem. Soc., 78, 430 (1956).

² M.E. Herr and F.W. Heyl, ibid., 75, 5927 (1953).

³ M.E. Herr, J.A. Hogg, and R.H. Levin, ibid., 78, 500 (1956).

⁴ F.W. Heyl and M.E. Herr, ibid., 75, 1918 (1953).

5. Other Blocking Groups

In this section a brief description will be given of a number of less widely used blocking groups. The standard carbonyl reagents; semicarbazine and 2,4-dinitrophenylhydrazine have seen some use as blocking reagents with steroids. The prevalent method of ketone regeneration seems to be treatment with pyruvic acid in an acidic medium but straight acid hydrolysis and sodium nitrite in acetic acid have also been utilized with semicarbazones.¹

Steroidal ketones react with 2,4-dinitrophenylhydrazine in the above order.² Most cases reported in the literature concern blocking of the 3-keto group only.

Two other infrequently used ketone derivatives are the enol ethers and enol acetates. Enol ethers can be prepared from ethyl orthoformate and the steroid ketone. They are very unstable in acids. The enol acetates are formed by the reaction of steroidal

enol ether

enol acetate

- ¹ E. Hershberg, U.S.patent; 2,477,463; St.Goldschmidt and W. Veer, *Rec.trav.chim.*, 65, 796 (1946); C.V. Mattox and E. Kendall, *J.Am.Chem.Soc.*, 70, 882 (1948).
- ² H. Reich, *et al.*, *J.Org.Chem.*, 18, 822 (1953).

ketones either with isopropenyl acetate or acetic anhydride and acid catalyst. Aqueous acidic or alkaline solutions regenerate the steroid ketones.

Summary

From the above we see that the steroid chemist has turned to a number of derivatives for protecting steroid ketones. Which derivative he uses in a given situation depends upon the steroid molecule and the subsequent reactions which it will undergo. The mass of steroid research has served to build up a large volume of practical information about the derivatives which should be formed in any given case. In contrast with this abundance, very little systematic work has been done in the way of kinetic and equilibrium studies of the reactions commonly used in blocking and unblocking steroid ketones. A study such as this might lead to new blocking group types, which could either make certain reactions feasible or increase the yields of compounds, which are biologically significant to all of us.

B. Theoretical Background

1. Mechanism of Ketal Hydrolysis

The hydrolysis of acetals and ketals has been thoroughly investigated from a mechanistic viewpoint. R. Taft¹ suggests that the following mechanism is in accord with all available experimental

¹ M. Kreevoy and R. Taft, Jr., J. Am. Chem. Soc., 77, 3146 (1955).

facts. Several lines of evidence support the above mechanism. An alkyl carbonium ion corresponding to the alcohol moiety of the ketal cannot be an intermediate in the reaction. This has been demonstrated in two different ways. First, optically active alcohols¹ and glycols² retained optical configuration during acetal formation and hydrolysis. Second, the only alcohol recovered on hydrolysis of a neopentyl alcohol acetal was neopentyl alcohol. Both of these support the conclusion that an alkyl carbonium ion corresponding to the alcohol cannot be an intermediate in the reaction, otherwise racemization of the optically active alcohols or rearrangement of the neopentyl alcohol would have occurred.

A second line of evidence for the aforementioned mechanism is that acetal hydrolysis exhibits specific hydronium catalysis in water.³ This is of value because it excludes general acid catalysis, which involves the transfer of a proton in the rate-determining step.

¹ J. O'Gorman and H.J. Lucas, *J. Am. Chem. Soc.*, **72**, 5489 (1950).

² E.R. Alexander, *et al.*, *ibid.*, **74**, 3173 (1952); H.K. Garner and H.J. Lucas, *ibid.*, **72**, 5497 (1950).

³ J.N. Bronsted and W.F.K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

Further mechanistic corroboration is the difference in rate of hydrolysis of acetal in water and deuterium oxide. The hydrolysis of acetal in 50 percent dioxane-H₂O is faster by a factor of three when deuterated water is used.¹ Analogous results were obtained for acetal in a completely aqueous medium.² If the rate-determining step involved proton transfer from catalyzing acid to substrate (general acid catalysis) the transfer of a deuteron because of heavier mass would be slower than the transfer of a proton. Therefore, the reaction would be slower in deuterated water than in ordinary water. However, the result is just the opposite. Most workers account for the increased speed in D₂O by the presence of a greater concentration of the activated complex.

S = substrate, specifically the ketal molecule

This large concentration of activated complex results because deuterium oxide is a weaker base than water³, thus the equilibrium is shifted further to the right in equation 2. than in equation 1. Therefore, work with deuterium oxide likewise indicates specific acid catalysis.

A final confirmation of the above mechanism is found in an analysis of the change of rate constant with change of acid

¹ M. Kreevoy and R. Taft, Jr., J.Am.Chem.Soc., 77, 3146 (1955).

² W.J. Orr and J.A. Butler, J.Chem.Soc., 330 (1937).

³ Wiberg, Chem.Rev., 55, 713 (1955).

concentration. If general acid catalysis prevailed, the following expression should hold.¹

$$3. \quad K_1 = \text{constant} \times A$$

$$K_1 = \text{rate constant at a particular } A$$

$$A = \text{acid concentration}$$

If specific acid catalysis prevailed, the following should be the controlling expression.¹

$$4. \quad \log K_1 / H_0 = \text{constant}$$

$$K_1 = \text{rate constant at a particular } H_0 \text{ value}$$

$$H_0 = - \log \frac{A_{H^+} f_B}{f_{BH^+}}$$

$$A_{H^+} = \text{activity of hydrogen ion}$$

$$\left. \begin{matrix} f_B \\ f_{BH^+} \end{matrix} \right\} \text{activity coefficients of neutral inductor and its conjugate acid}$$

That equation 4. is involved and that acetal hydrolysis involves specific acid catalysis has been verified experimentally by a number of workers.²

From a qualitative viewpoint, reaction rates themselves substantiate this mechanism. It is known that ease of formation of carbonium ion increases from primary, to secondary, to tertiary. Likewise, electron-releasing groups help carbonium ion formation, whereas electron-attracting groups hinder it. Since the product of the rate-determining step is a carbonium ion intermediate;

¹ L. Zucker and L.P. Hammett, J.Am.Chem.Soc., 61, 2791 (1939).

² L.J. Andrews and W.W. Keating, ibid., 73, 1007 (1951);
W.W. Keating and L.J. Andrews, ibid., 74, 6189 (1952);
D. McIntyre and F.A. Long, ibid., 76, 3240 (1954).

factors which increase ease of formation of carbonium ions should lead to marked rate increase. Such is seen to be the case in the following relative rate constants derived from the work of Kreevoy and Taft.¹

	<u>R₁</u>	<u>R₂</u>	<u>Relative rate constant</u>
	H	H	6 X 10 ⁻⁸
	CH ₃	H	3 X 10 ⁻³
$\begin{array}{c} R_1 - C - OEt \\ \\ R_2 - C - OEt \end{array}$	CH ₃	CH ₃ *	1
	ClCH ₂	H	1.4 X 10 ⁻⁸
	ClCH ₂	CH ₃	1 X 10 ⁻⁴

* acetone ketal taken as standard of 1.

Indeed, since the molecule in the activated complex differs from the initial molecule only by a proton, Taft has been able to apply his modified Sigma-Rho treatment to a series of 24 acetals and ketals in a very fine fashion. The modification involves a correction for hyperconjugation.

However, the last step of Taft's mechanism telescopes several actual steps. Thus, the overall mechanism for acetal preparation and hydrolysis, shown for the case of a cyclic ketal, would be as indicated in Figure 1.

According to Taft's mechanism, step K-6 would be the slow (rate-determining) step for hydrolysis. This has proved to be consistent with the experimental results obtained up to now.

¹ M. Kreevoy and R. Taft, Jr., J. Am. Chem. Soc., 77, 5590 (1955).

FIGURE 1

MECHANISM OF CYCLIC KETAL FORMATION

However, the possibility always exists for more than one step in acetal or ketal hydrolysis to be slow with a given compound. Aldehydes, such as chloral, which form stable hydrates, may also form relatively stable hemiacetals. The hydrolysis of an acetal of such an aldehyde might demonstrate complex kinetics.

2. Chemistry of Ring Compounds

a. Cyclopentanone and Cyclohexanone

H.C. Brown, J.H. Brewster, and H. Shechter¹ postulate that in comparable cases "exo double bonds stabilize a 5-membered ring and destabilize a 6-membered ring." The generalization is made that, other things being equal, reactions will proceed in such a manner as to favor the formation or retention of an exo double bond in a 5-membered ring and to avoid the formation or the retention of an exo double bond in a 6-membered ring. This generalization can be applied to:

1. equilibria involving endo and exo double bond isomers
2. olefin formation
3. stability of cyclic esters, lactones, hemiacetals, and imides
4. preference for formation of furanose and pyranose structures in the sugars

The authors give numerous applications of the above generalization¹, several of which will be mentioned presently.

¹ H.C. Brown, J.H. Brewster, and H. Shechter, J.Am.Chem.Soc., 76, 467 (1954).

The fact that under comparable conditions the enol contents are 0.48 percent for cyclopentanone and 2.0 percent for cyclohexanone is further support for the postulated generalization.¹

Brown, Brewster, and Shechter give the following reason for the phenomena. The cyclopentane ring is almost planar. In idealized structures, the bond oppositions are reduced from ten to six in going from saturated cyclopentane derivatives to cyclopentanone derivatives.

10 bond oppositions
10 Keal strain

6 bond oppositions
6 Keal strain

On the other hand, the cyclohexane structure is staggered with no bond oppositions. Introduction of the trigonal ketone group introduces in some measure unfavorable conformations.²

b. 1,3-Dioxolanes and 1,3-Dioxanes

The reaction of carbonyl compounds, either aldehydes or ketones, with 1,2- and 1,3-glycols yield 1,3-dioxolanes and 1,3-dioxanes, respectively.

1,3-dioxolane

1,3-dioxane

¹ G. Schwarzenbach and Ch. Wittwer, *Helv.Chim.Acta.*, 30, 669 (1947).

² H.C. Brown, *et al.*, *J.Am.Chem.Soc.*, 76, 467 (1954).

In his famous rules on ring formation, Hudson stated that in the reaction of a polyglycol with formaldehyde or benzaldehyde, beta-rings (1,3-dioxanes) are favored.¹ In the corresponding reaction of acetone, there is a marked preference for the five-membered ring.²

The case of D-sorbitol (I) is an excellent specific example of the above rules. The monoacetal of D-sorbitol and benzaldehyde is the 2,4-benzylidene-D-sorbitol (II)³ while the corresponding diacetal is the 2,4-benzylidene-D-sorbitol (II)³ while the corresponding diacetal is 1,3; 2,4-dibenzylidene-D-sorbitol (III).⁴ On the other hand, the monoketal of acetone and D-sorbitol (I) is 1,2-isopropylidene-D-sorbitol (IV) while the corresponding diketal is 1,2; 5,6-diisopropylidene-D-sorbitol (V).⁵

- ¹ R.M. Hann and C.S. Hudson, J.Am.Chem.Soc., 66, 1909 (1944).
- ² S.A. Barker and E.J. Bourne, Advances in Carbohydrate Chemistry, 7, 137 (1952).
- ³ L. vonVargha, Ber., 68, 18, 1377 (1935); F. Michael and K. Hasse, ibid., 68, 1582 (1935).
- ⁴ S.J. Angyal and J.V. Lawler, J.Am.Chem.Soc., 66, 837 (1944); R.M. Hann, A.T. Ness, and C.S. Hudson, ibid., 66, 73 (1944); J.K. Wolfe, R.M. Hann, and C.S. Hudson, ibid., 64, 1493 (1942).
- ⁵ B.C. Pressman, L. Anderson, and H.A. Landy, ibid., 72, 2404 (1950).

Numerous other experimental examples¹ have led to the generalization that aldehydes tend to form the 1,3-dioxane rings whereas ketones tend to form the 1,3-dioxolane rings.

Since a six-membered ring is usually considered to be more strain free than the five-membered ring, it is necessary to explain the observation that acetone forms a 1,3-dioxolane (VI) in preference to a 1,3-dioxane (VII) on reaction with a polyglycol.

VI

VII

Brown, et al.,² suggest that the result is probably due to steric strain. That is, a six-membered isopropylidene derivative would have a gem-dimethyl in a homomorphic cyclohexane structure. One methyl group must then be in the axial position. Presumably, this results in sufficient destabilization to favor the formation of the five-membered ring in the reaction of glycerin with acetone.

It would seem that increase of donor ability (H-bonding) of the ketal oxygen might lead to increased reactivity in an acid catalyzed reaction such as ketal hydrolysis. An investigation of hydrogen bonding in cyclic ethers was made by two independent

¹ S.A. Barker and E.J. Bourne, *Advances in Carbohydrate Chemistry*, 7, 137 (1952).

² H.C. Brown, J.H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, 76, 467 (1954).

methods.¹ One method was based upon the heat of mixing the cyclic ether with chloroform. The other was based upon the shift in O-D vibration in a solution of cyclic ether in deuterated methanol. The authors found that the extent of hydrogen bonding of a cyclic ether varies with the ring size in the order as follows.

∠-substitution (presumably electron repelling groups) definitely increases donor ability of all ethers regardless of structure.

The fact that with acetals the five-membered ring reacts faster than the six-membered ring, while with ketals the six-membered ring reacts faster than the five-membered ring², points out the difficulty of separating the influence of hydrogen bond formation

on reactivity of these compounds.

3. Influence of Alkyl Groups on Ring Formation

It has been known for a long time that substituents, particularly the so-called gem-dialkyl groups, tend to facilitate ring formation. This effect has been shown in formation of cyclic anhydrides, lactones, ketones, and small rings containing oxygen

¹ S. Searles and M. Tamres, J. Am. Chem. Soc., 73, 3704 (1951).
² R. Leutner, Monatsh. Chem., 66, 222 (1935); O. Ceder, Arkiv Kemi, 6, 523 (1954).

or nitrogen to mention a few of the best known cases. Several typical examples of the gem-dimethyl effect will now be described.

a. Anhydrides

In 1890, K. Auwers and V. Meyer noted that substituted succinic and glutaric acids form cyclic anhydrides much more easily than the corresponding non-substituted succinic and glutaric acids.¹ Nevertheless, the position of the substituent plays an important role. Thus, $\beta, \beta, \beta', \beta'$ tetramethyl adipic acid (I) forms an anhydride which is hydrolyzed by boiling water or carbonate solution.² Under these conditions the anhydride of $\alpha, \alpha, \alpha', \alpha'$ tetramethyl adipic acid (II) is inert.² Incidentally,

by contrast, the anhydride of adipic acid is hydrolyzed by the moisture of the air.²

b. Lactones

These substituent effects occur also in somewhat more esoteric reactions. Thus, 2,2-diphenyl-4-pentenoic acid (III) on treatment with cyanogen iodide leads to 2,2-diphenyl-5-iodo-4-pentanolactone (IV) in 82 percent yield. The corresponding

¹ K. Auwers and V. Meyer, Ber., 23, 101 (1890).

² E.H. Farmer and J. Kracovski, J.Chem.Soc., 680 (1927).

reaction with *l*-pentanoic acid (V) gives only a 20 percent yield of *l*-iodo-*l*-pentanolactone (VI) in 60 days.¹

c. Three-membered Rings

A good quantitative example of this substituent effect is the report on the rate of formation of a series of substituted ethylene oxide.² A large increase in rate is observed on increasing the number of alkyl groups.

¹ R.T. Arnold and K.L. Lindsay, *J. Am. Chem. Soc.*, **75**, 1048 (1953).

² L. Smith, *Z. physik. Chem.*, **156A**, 135 (1933).

Substituent Effects on Rates of Formation of Ethylene Oxides

<u>R₁</u>	<u>Substituents</u>		<u>R₂</u>	<u>Rate constant K at 18°</u>
	<u>R₁</u>	<u>R₂</u>		
H	H	H	H	0.31
CH ₃	H	H	H	6.5
H	H	CH ₃	H	1.7
CH ₃	CH ₃	H	H	78.0
H	H	CH ₃	CH ₃	77.0
CH ₃	CH ₃	CH ₃	H	424.0
H	CH ₃	CH ₃	CH ₃	633.0
CH ₃	CH ₃	CH ₃	CH ₃	3600.0

The following equilibrium constants between the open-chain keto acid and the closed cyclic acid were observed.¹ Besides

<u>R</u>	<u>R₁</u>	<u>% VII</u>
H	H	0
CH ₃	CH ₃	0
C ₂ H ₅	C ₂ H ₅	62
n - propyl	n - propyl	71
R - R ₁ (CH ₂) ₅		100

¹ Laufen and Thorpe, J.Chem.Soc., 123, 1683 (1923).

these, there are numerous other examples in which the substituents contribute to ease of ring formation, stability of the ring, or resistance to reactivity.

Explanations of the Gem-Dimethyl Effect

Ingold relates the gem-dimethyl effects to the spatial requirements of the atoms involved.¹ Thus, in the series from glutaric to dimethyl glutaric, Ingold calculates that the following angles are present:

		<u>A</u>	<u>B</u>	<u>Angle "x"</u>
glutaric acid	H	H	115.3
	methyl glutaric acid	CH ₃	H	112.5
	dimethyl glutaric acid	CH ₃	CH ₃	109.5

While these theoretical values are most likely incorrect, the fundamental idea is quite plausible. The decrease in the angle "x" would bring the other molecules in the chain close together, thus facilitating any possible ring closure.

Dr. Newman has suggested that a conformational argument might also be applied. Thus, in unsubstituted glutaric acid, three rotamers (conformations) are possible.

¹ E.K. Ingold, J.Chem.Soc., 119, 305 (1921); 121, 2676 (1921).

The eclipsing effect of the large (acidic) groups would tend to make B and C unfavored rotamers. Therefore, most molecules would exist as rotamer A, which is non-reactive. Furthermore, it is necessary for the molecule to go through an unfavored rotamer before cyclization can take place. Hence, with glutaric acid there is little tendency toward cyclic anhydride formation.

On the other hand, in β,β -dimethyl glutaric acid, the eclipsing effects are somewhat different. In this case, the reactive

conformers (B and C) would be almost as favored as conformer A. Since it is not necessary for the molecule to attain an unfavored conformation before reaction can take place, cyclic anhydride formation occurs more rapidly with β,β -dimethyl glutaric acid than with glutaric acid. An argument such as this can be extended to explain the superior influence of alkyl groups larger than methyl in promoting ring formation. G. Hammond¹ proposes the explanation that whenever ring formation occurs, the reaction is accompanied by a decrease in entropy. This negative entropy is ascribed to a loss of certain vibrational and rotational degrees

¹ G. Hammond, in M.S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, New York, N.Y., 1956, p.468.

of freedom on going from the open-chain molecule to a cyclic molecule.¹ Correspondingly, the ring cleavage reaction would then be accompanied by a positive entropy. However, if rotations about

bonds, e.g., a and b, is restricted by alkyl groups, then the entropy of ring formation would be less negative than the corresponding ring formation with the methylene compound. That is, the gem-dialkyl substituted compound would not have these degrees of freedom to lose on ring formation or to gain on ring cleavage. Since a less positive or more negative entropy effect should be accompanied by a decreased reaction speed, the overall effect of gem-dialkyl substitution would be the retarding of ring cleavage and the helping of ring formation.

While the arguments put forth seem to furnish strong leads about this amazing dimethyl effect, there is still much to be explained from a theoretical viewpoint in this area of chemistry. Indeed, no general quantitative measurement of the magnitude of the gem-dialkyl effect for related reactions has as yet been proposed.

C. Reactions of Cyclic Ketals

1. Rates of Hydrolysis of Cyclic Ketals

Kinetic measurements for hydrolysis of cyclic acetals and ketals have been reported only infrequently. The accompanying table summarizes most of the information available for hydrolysis

¹ A.A. Frost and R.G. Pearson, in "Kinetics and Mechanism," John Wiley and Sons, New York, N.Y., 1953, p.106.

of cyclic acetals and ketals at 25° in an aqueous medium. The information in Table 1. provides a number of salient points.

The rates of hydrolysis of cyclic acetals are much slower than the corresponding rates of the non-cyclic acetals. The relationship for rates of hydrolysis is generally maintained in going from the acyclic to cyclic series. The only exception is in the pinacol series.

With acetals, increase of ring size seems to lead to greater stability. This idea is exemplified by the following examples.

k min.⁻¹ 0.78

0.13

0.022

k min.⁻¹ 0.0002

0.000053

Ketals seem to be in a different category. A comparison of the rates of hydrolysis in Table 1. of the following 1,3-dioxanes and 1,3-dioxolanes indicates that the 1,3-dioxanes (six-membered ring ketal) are more unstable than the 1,3-dioxolanes (five-membered ring ketal) when ketones are involved.

TABLE 1
RATES OF HYDROLYSIS FOR ACETALS AND KETALS AT 25°

	Formaldehyde	Acetaldehyde	Acetone
Ethylene Glycol	0.0002 ^a	0.78 ^a	8.74 ^a
Trimethylene Glycol	0.000053 ^a	0.13 ^a	189.0 ^c
1,3-Butylene Glycol	0.000048 ^a	0.21 ^a	338.0 ^a
Pinacol	0.000027 ^a	0.0415 ^a	0.0120 ^a
Pentaerythritol	0.00000098 ^b	0.0061 ^b	10.35 ^b
Ethanol	0.013 ^b	60.0 ^b	135,000.0 ^b
1,4-Butylene Glycol		0.022 ^a	

$$k = \text{min.}^{-1}$$

	Benzaldehyde	Acetophenone	Benzophenone	Cinnamylaldehyde
Ethylene Glycol	103.0 ^c	27.6 ^c	3.04 ^c	1370.0 ^c
Trimethylene Glycol	26.0 ^c	154.0 ^c	12.0 ^c	429.0 ^c

- ^a R. Leutner, *Monatsh. Chem.*, 60, 317 (1932); 66, 222 (1935).
^b A. Skrabel and M. Zlatewa, *Z. physik. Chem.*, 119, 305 (1926).
 A. Skrabel and F. Bilger, *ibid.*, 130, 29 (1927).
 A. Skrabel and H. Eger, *ibid.*, 122, 349 (1926).
 A. Skrabel and K. Mirtl, *ibid.*, 111, 98 (1924).
^c O. Ceder, *Arkiv Kemi*, 6, 354 (1954).

However, with increasing substitution, the rates of hydrolysis of the 1,3-dioxanes decrease and approach in magnitude those of the 1,3-dioxolanes. Pentaerythritol ketal (the rate constant of this has already been halved to account for presence of 2 ketal groups) and ethylene glycol ketal are examples.

Further examples of this are given by Leutner.¹

¹ R. Leutner, Monatsh.Chem., 60, 317 (1932).

Activation energies and frequency factors are reported in Table 2.² It is to be noticed that both activation energies and probability factors increase on going from the five- to six-membered rings. In the case of the ketones, the entropy change outweighs the activation energy change, thus making the five-membered ring ketals more stable for ketones. In the case of aldehydes, the activation energy changes, thus making the six-membered ring acetals more stable for aldehydes. Ceder concludes that aldehydes prefer to form six-membered acetal rings whereas ketones prefer to form the five-membered ketal rings. He also states that the magnitude of activation energy and entropy factors are of the same order for cyclic ketals as for those of non-cyclic acetals and ketals. He also concludes that activation energies depend more on the carbonyl portion of the compound than on the alcohol moiety.

The high rate of hydrolysis of the cinnamylaldehyde acetal is explained on the basis that the intervening carbonium ion would be stabilized by the allylic double bond. Also, with respect to these cinnamyl acetals, Ceder measured both the rate of disappearance of the acetal and the rate of appearance of the aldehyde. The rate differences observed were out of range of the experimental error, but Ceder did not think them of sufficient size to demonstrate conclusively a mechanism for ketal hydrolysis which involves

¹ O. Ceder, Arkiv Kemi, 6, 523 (1954).

TABLE 2

ACTIVATION ENERGIES AND FREQUENCY FACTORS FOR
HYDROLYSIS OF CYCLIC ACETALS AND KETALS

COMPOUND	E_a	S
27.1	1.6×10^{14}
19.8	1.8×10^{15}
14.8	1.3×10^{11}
20.9	8.6×10^{14}
17.5	2.9×10^{12}
19.3	3.8×10^{14}
17.2	2.1×10^{11}
17.4	1.0×10^{12}
12.7	4.4×10^{10}
14.7	4.2×10^{11}

two slow steps and two rate constants. The experimental results are:

<u>compound</u>	<u>wave length</u>	<u>Ks 20°</u>	<u>Ks 30°</u>	<u>Ea</u>	<u>S</u>
ethylene	2520	559.	1129	12.4	1.7
acetal	2920	954.	1955	12.7	4.0
trimethylene	2500	212.	453	13.4	3.4
acetal	2920	281.	647	14.7	4.2

The readings at 2920 measure the rate of appearance of the ketone, whereas those at 2500-2520 represent rate of disappearance of ketal.

2. Equilibrium Constants of Cyclic Ketal Reactions

The equilibrium pictured below lies largely to the left.

Evidence for this is shown by the fact that early workers experienced considerable difficulty in the direct preparation of ketals, even when such stratagems as using a large excess of the alcohol or ketone were employed. Good yields of ketals were not achieved until some method was employed to remove the water produced from the reaction system.

Few quantitative equilibrium measurements have been reported for this reaction. Probably this can be traced to low values of K_e which would be experienced except in special cases.

$$K_e = \frac{(\text{ketal})(\text{water})}{(\text{ketone})(\text{glycol})}$$

The following equilibrium constants for a series of cyclic ketals of acetone have been reported.¹ The large decrease in

<u>glycol</u>	<u>Ke 18°</u>
ethylene glycol	0.14
1,2-propanediol	0.44
1,3-propanediol	0.026
glycerin	0.74
2-monochlorohydrin	0.28
<u>cis</u> -cyclopentanediol	10.0
<u>cis</u> -cyclohexanediol	0.16
<u>trans</u> -cyclohexanediol	0.00

equilibrium constant in going from ethylene glycol to 1,3-propanediol is consistent with the previously mentioned tendency of ketones to form five-membered rings. That substituents seem to help in shifting the equilibrium to the ketal side is seen with 2-monochlorohydrin, glycerin, and 1,3-propanediol.

The behavior of cis-cyclopentanediol in the above equilibrium contrasts markedly with the behavior of the cyclohexanediols in the same reaction. Current interpretations of the stereochemistry of five- and six-membered ring compounds might lead one to expect this result. Since an equilibrium reaction is involved, the relative stabilities of the reactants and products are of prime importance rather than any considerations involving the intermediates in this reaction. The four atoms which will enter the 1,3-dioxolane ring occupy essentially the same planar configuration in cis-cyclopentanediol as they occupy in the cyclic ketal. The cis-cyclopentanediol and the ketal derived from it should be equivalent with

¹ P.H. Hermans, Z.physik.Chem., 113, 337 (1924).

respect to degree of strain in the cyclopentane ring. (In this case, then, there should be no increase in ring strain due to ketal formation.) Moreover, whenever the geometric arrangement of the atoms which enter the ring is essentially the same in both a non-cyclic compound and its cyclic derivative or analog, there is a marked tendency for the cyclic form to predominate. This would seem to apply to this cis-cyclopentanediol ketal system. The combination of the above effects is sufficient to yield a high equilibrium constant for the cis-cyclopentanediol case.

Trans-cyclopentanediol (I) does not react with acetone.¹ The

alcohol groups would have to undergo too much twisting to form the planar 1,3-dioxolane ring.

Also, the oxygen distances in the rigid trans structure are too far apart to be bridged by a single carbon atom. With the cyclohexanediols, the cyclohexane moiety of the cyclic ketal has to assume unfavorable conformations with both the cis and the trans isomers in order to form the cyclic ketal. Since by comparison in the cis and trans cyclohexanediols the cyclohexane rings are relatively strain free, the equilibrium constants should be quite low in these reactions. The experimental results bear this out. S.J. Angyal and C.G. MacDonald² offer an explanation for the difference in reactivity of cis and trans cyclohexanediols. They state that the rotation necessary to enable the cis-diol to form

¹ L.P. Kuhn, J. Am. Chem. Soc., 76, 4323 (1954).

² S.J. Angyal and C.G. MacDonald, J. Chem. Soc., 686 (1952).

the ketal does not introduce much ring puckering or strain (Case I).

On the other hand, the rotation necessary to enable the trans-diol to form the cyclic ketal does introduce greater ring puckering and strain (Case II). The reader should note the increase in axial group interaction that the indicated rotation (Case II) could cause. It might be mentioned that the axial bond distance of 3.66 Å is too large to be bridged by a single carbon atom.¹

With respect to the effect of temperature and substituents on equilibrium constants, the dearth of published material on ketals necessitates turning to acetals for examples. Equilibrium constants for the accompanying reaction have been reported at two temperatures.²

$$K_e = \frac{(\text{acetal})(\text{water})}{(\text{aldehyde})(\text{methanol})^2}$$

<u>Aldehyde involved in equilibrium</u>	<u>K_e 2°</u>	<u>K_e 25°</u>
Salicylaldehyde	0.0722	0.0325
o-Methoxybenzaldehyde	0.591	0.256
3-Hydroxy-2-naphthaldehyde	0.337	0.141
2-Hydroxy-1-naphthaldehyde	0.012	0.0067

¹ S.J. Angyal and C.G. MacDonald, J.Chem.Soc., 686 (1952).

² N. Melchior, J.Am.Chem.Soc., 71, 3651 (1949).

The increase in temperature causes a shift to the left. The application of LeChatelier's principle reveals that acetal hydrolysis is endothermic and acetal formation is exothermic. In other words, the complete equation would be

As in the case of acetal and ketal hydrolysis, the position of equilibrium of acetals and ketals is particularly influenced by polar and resonance effects, especially those due to α -carbon substituents as the following indicates.¹

<u>Ethanol acetal of</u>	<u>K_e 25°</u>
Aminoacetaldehyde (acid medium probably NH ₃)	0.1340
Bromoacetaldehyde	0.1121
Cyanoacetaldehyde	0.1070
Propionaldehyde	0.0782
Acetaldehyde	0.0744
Butyraldehyde	0.0691
iso-Butyraldehyde	0.0355
Glycolic aldehyde	0.0202
Acrolein	0.00455
Benzaldehyde	0.00163
Cinnamaldehyde	0.00089
Crotonaldehyde	0.00063

Electron-withdrawing groups in the carbonyl component usually shift the equilibrium to the ketal side while electron-donating groups shift equilibrium to the ketone side. The ketone side of the equilibrium is also favored when the carbonyl group is conjugated. Acetals and ketals provide another example of the influence of the inductive effects of substituents upon equilibrium constants. The inductive effect, at the carbonyl, increases from

¹ W.A. Hartung and H. Adkins, J. Am. Chem. Soc., 49, 2517 (1927).

aldehydes to ketones while the equilibrium shifts to favor the free carbonyl component in the same order.

Finally, with respect to the alcohols utilized in acetal formation, change from primary to secondary alcohol seems to shift the equilibrium to the ketone side as shown by the following.¹

<u>Acetaldehyde acetals</u>	<u>K_e 25°</u>
Methyl acetal	0.0834
Ethyl acetal	0.0804
iso-Propyl acetal	0.0127

In summary, the inductive effects in the carbonyl fragment are extremely important. Those in the alcohol portion of the molecule seem to be smaller, but nevertheless distinct. Steric effects seem to show up more in cyclic ketals than in their non-cyclic analogs. Research in this area, however, has not been plentiful.

3. Rates of Formation of Cyclic Ketals

The absence of information regarding the rates of formation of cyclic acetals and ketals necessitates turning to qualitative information on ease of formation of cyclic ketals.

The acid-catalyzed reaction of a cyclic ketone with ethylene glycol by the standard benzene azeotrope method takes 1.5 hours with cyclohexanone and 1.4 hours with 2-methylcyclohexanone² to go to completion. From this one would not expect overwhelming

¹ H. Adkins and E.W. Adams, J.Am.Chem.Soc., 47, 1368 (1925).

² M. Sulzbacher, et al., ibid., 70, 2827 (1948).

differences in the rates of formation of ketals derived from cyclohexanones or their monomethyl analogs and a particular glycol.

On the other hand, the difference between ethylene and trimethylene glycol in tendency toward cyclic ketal formation can be noted in the synthetic results of early workers. Methyl ethyl ketone and acetone reacted with ethylene glycol to give cyclic ketals, but the same ketones did not give any products on reaction with trimethylene glycol under similar conditions.¹ Similarly, the ethylene glycol ketal of cyclohexanone was prepared in 80 percent yield, while the corresponding ketal of trimethylene glycol was produced only in 24 percent yield even at a much higher temperature.² Later workers achieved higher yields in these reactions because they utilized a superior method for the removal of the water produced in the reaction.³

An interesting corollary to the above is the exchange reaction reported by Bergmann and Bograchov.⁴ The following reaction

¹ R. Dworzak and K. Herrman, *Monatsh.Chem.*, 52, 83 (1929).

² J. Boeseken and F. Tellegen, *Rec.trav.chim.*, 57, 133 (1938).

³ E. Salmi, *Ber.*, 71B, 1803 (1938); E. Salmi and V. Ronnikko, *ibid.*, 72B, 600 (1939).

⁴ E. Bergmann and E. Bograchov, *J.Am.Chem.Soc.*, 73, 1774 (1951).

was run by refluxing the reactants in benzene for three or four hours in the presence of naphthalenesulfonic acid. The product crystallized from the reaction mixture on standing. Each of the ketones used; cyclopentanone, cyclohexanone, and 3-methylcyclohexanone afforded product in 90 percent yield after a reaction time of three hours. Methyl isobutyl ketone, acetophenone, fluorenone, β -ionone, and ethyl acetoacetate did not yield any product in this reaction.

The authors explain the above reaction of cyclic ketones as due to a tendency toward spirane formation. The unusual preference of ketal formation over acetal formation is difficult to explain. However, it might be mentioned that there is usually a tendency towards the carbonyl side of acetal and ketal hydrolysis equilibrium in which a conjugated carbonyl is involved.

III: DESCRIPTION OF RESEARCH PROGRAM

The specific approach to the problem outlined will be briefly elaborated on at this point. Particular emphasis will be placed on the type reactions which were to be performed and the anticipated results.

As stated previously, the kinetics and equilibrium of the accompanying reaction comprise most of the research reported in this dissertation. Rate data were desired for both the forward

and reverse reactions, but ketal hydrolysis comprised all of the kinetic work for two reasons. First, the equilibrium position in the above reaction usually lies largely to the left. In other words, the hydrolysis constant, k_2 , is larger than the formation constant, k_1 . In order to avoid complicated calculations it was desired to run the reaction under such conditions that it would be essentially complete and irreversible. This was accomplished by studying the hydrolysis reaction in a partially aqueous medium so that pseudo-first order kinetics would be obtained. Second, this approach would permit the utilization of a convenient spectrophotometric procedure¹ for measuring the rate of ketal hydrolysis.

¹ M.M. Kreevoy and R.W. Taft, Jr., J.Am.Chem.Soc., 77, 5590 (1955).

The rate of ketal formation and equilibrium studies were limited in comparison with the hydrolysis work. In the equilibrium studies non-equilibrium solutions of the various components of the reaction were prepared. The initial concentrations of components were chosen so that at equilibrium the concentrations of

the free ketone and its corresponding ketal would be about equal. The equilibrium was approached from both sides and a spectrophotometric procedure was again used for analysis. In the ketal formation studies, the reaction velocity was measured by the amounts of water removed by azeotropic distillation in various periods of time.

One of the purposes of this research was the discovery of a compound which would preferentially block one type of ketone of a polycarbonyl compound which contains five- and six-membered ring ketones. It was decided to work with simple ring ketones and to extrapolate the information to more complex molecules rather than to work with a particular polycarbonyl compound. Cyclopentanone, cyclohexanone, and 2-methylcyclopentanone were the simple ketones selected for investigation. Actually, 2,2-dimethylcyclopentanone would have been superior to 2-methylcyclopentanone for comparison with steroids containing a 17-keto group, but the dimethyl ketone is more difficult to prepare. The compounds which were tested for their efficacy as blocking groups for cyclopentanones and cyclohexanones were the 1,3-propanediols. So that another purpose of this research might be fulfilled, a group of 1,3-diols were selected

which would increase our knowledge of the gem-dialkyl effect in promoting ring formation and stability. The specific 1,3-diols used were 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, 2,2-diethyl-1,3-propanediol, and 2,2-diisopropyl-1,3-propanediol. Ethylene glycol was also studied because it is currently the most widely used ketone blocking group and as such it would provide a good basis for comparison with the various 1,3-diols.

Since this research was to emphasize ketal hydrolysis, the first step was the preparation of the various ketals possible from the above ketones and glycols. These ketals are listed in Table 3. The rest of the synthetic work was confined essentially to the preparation of starting materials which were not available. The most interesting synthesis was that of 2,2-diisopropyl-1,3-propanediol, which was prepared according to the accompanying scheme, much of which was developed by Marshall.¹

Scheme:

¹ F. Marshall, J.Chem.Soc., 2754 (1930).

TABLE 3
KETALS PREPARED IN THIS RESEARCH

I

II

III

IV

V

VI

VII

VIII

IX

X

XI

XII

XIII

XIV

XV

Subsequent to the kinetic, equilibrium, and preparative work outlined, calculations were made to demonstrate the selectivity of 1,3-diols in blocking five- and six-membered ring ketones in comparison with the selectivity of ethylene glycol in a similar function. These calculations apply to both the kinetic and equilibrium approach in so far as the experimental information permits.

In the light of the literature survey of the previous section, several items should be emphasized. There is no direct published evidence on the relative rates of formation and hydrolysis of ethylene glycol ketals of cyclohexanone and cyclopentanone. However, in steroid molecules such as Δ^4 -androstene-3,17-dione the ketone in the 6-membered ring forms the cyclic ketal faster and to a greater extent at equilibrium than that in the 5-membered ring.¹ Although other factors such as steric and inductive effects contribute to this difference, there is reason to believe that the above relationship would hold with monocyclic analogs. Thus, Brown, Brewster, and Shechter² postulated the generalization (which is supported by numerous experimental examples) that in comparable cases cyclohexanones react to a greater extent or at a greater speed than cyclopentanones. Also, where similar compounds are involved, the 5-membered ring ketone would be produced more quickly in a reaction than the 6-membered ring ketone. Therefore, both the 1,3-diols and

¹ E. Fernholz and H. Stavely, 102nd Meeting of Am.Chem.Soc., Atlantic City, N.J., 39M (1941); U.S.patents; 2,356,154; 2,378,918; H. Herzog, et al., J.Am.Chem.Soc., 75, 4425 (1953).

² H.C. Brown, J.H. Brewster, and H. Shechter, ibid., 76, 467 (1954).

ethylene glycol would react more quickly with cyclohexanone than with cyclopentanone. Conversely, with ketals derived from any one of the glycols, the cyclopentanone ketal should hydrolyze faster than the cyclohexanone ketal. The accompanying equilibrium would

be shifted further towards the left for the 5-membered ring ketone reaction than for the 6-membered ring ketone reaction. The hope in this research, then, was to discover in the above reaction a larger kinetic or equilibrium differential between the cyclohexanone and 2-methylcyclopentanone ketals of one of the 1,3-diols than that differential which exists between the cyclohexanone and 2-methylcyclopentanone ketals of ethylene glycol in the above reaction.

The kinetic work of Leutner¹ and Ceder² would lead one to expect that ketals formed from trimethylene glycol hydrolyze faster than the corresponding ketals derived from ethylene glycol. Previous work would also lead the reader to suspect that increased gem-dialkyl substitution in cyclic ketals would be marked by increases in compound stability and by decrease in rates of hydrolysis.

It is hoped that the information presented in this section will permit the reader to grasp quickly the significance of the experimental detail and critique which will follow in the ensuing sections of this dissertation.

¹ R. Leutner, Monatsh.Chem., 60, 317 (1932); 66, 222 (1935).

² O. Ceder, Arkiv Kemi, 6, 523 (1954).

IV: HYDROLYSIS OF CYCLIC KETALS

A. Experimental Procedure and Method of Calculation of Rates of Hydrolysis of Cyclic Ketals

The reaction which we wished to follow kinetically was ketal hydrolysis. The experimental procedure selected should provide

the necessary information and have the adaptability to cope with the experimental requirements and yet should be as simple and convenient as possible. R. Taft has used a thermostated Beckmann D.U. Spectrophotometer to measure the rates of hydrolysis of acetals and ketals by running the reaction in the instrument cells and following the increase of carbonyl absorption. Taft employed a 50-50 mixture of dioxane-water and under these conditions a first order rate law was obeyed.

The same basic experimental procedure was employed in this research with some modifications. An aqueous dioxane solution was selected because dioxane is a good solvent, inert, water miscible, and readily available. However, the solvent ratio was changed to 70-30 dioxane-water rather than the 50-50 ratio which Taft used. This change was necessary to keep the initial concentration of ketal in solution. The maximum amount of water within

the solubility limit was used to insure that the reaction would go essentially to completion. This is necessary for a true infinite time reading. With the 70-30 dioxane-water ratio and with the initial concentration of ketal, such that an infinite time optical density ($O.D._{\infty}$) reading of 0.5 to 0.8 will be obtained, the initial mole ratio of water to ketal will be four hundred to one. The information currently available indicates that under these conditions the ketals would be more than 99 percent hydrolyzed even in the more unfavorable cases. This method led to the observation of pseudo-first order kinetics. A fixed acid concentration (0.003 N HCl) was used throughout these experiments. With the slower reacting ketones, either one or two modifications were usually employed. First, glass-stoppered cells were used to reduce evaporation and to limit the contact of oxygen with reaction mixture. Second, an infinite time reading was obtained by running the same experiment at a higher acid concentration. Kinetic runs which were made at two acid concentrations gave infinity readings which agreed within the precision limits of the D.U. Spectrophotometer. This justifies the use of this procedure, which offers a time advantage and eliminates some possible errors due to evaporation, peroxide formation, and slow side reactions. The kinetic measurements were made at $30.0 \pm .15^{\circ}$. This temperature was selected because it was felt that a temperature only a few degrees above room temperature would be easier to hold (the thermostating on the cell compartment would be more effective) and the use of refrigeration coils would be eliminated.

Kinetic Procedure

All rate measurements were made by following the increase of the carbonyl peak in the ultraviolet with a Beckmann D.U. Spectrophotometer. For each of the ketal experiments 3.00 ml. of 0.01 N hydrochloric acid and enough dioxane to give a total volume of 10.00 ml. were added to 5.00 ml. of stock solution of ketal in dioxane. All the components were brought to 30° before mixing. Part of this mixture was then transferred to a 1.00 cm. quartz cell and placed in a water-jacketed cell compartment for the course of reaction. Water was pumped through the jackets from a bath thermostated at $30.00 \pm .05^\circ$, and the cell temperature was found never to differ from that of the circulating bath water by more than 0.1° . The optical density was determined at convenient intervals and usually at least twenty to twenty-five readings were obtained. With the slower reactions, the optical density at infinite time was obtained by running the same reaction at a higher acid concentration.

Since in ketal hydrolysis the optical density is directly proportional to the sum of the hydrolyzed material throughout the course of the reaction, it is possible to obtain hydrolysis rates directly from the time change in the optical density of the system. Using this method, Taft has observed that ketal hydrolysis follows a first order rate law. The accompanying forms of

the first order rate equation indicate that a plot of $\log (O.D._{\infty} - O.D._t)$ against time yields a straight line from whose

$$1. \quad \frac{k}{2.303} t = \log \frac{(O.D._{\infty})}{(O.D._{\infty} - O.D._t)}$$

$$2. \quad -\frac{k}{2.303} t = -\log (O.D._{\infty}) + \log (O.D._{\infty} - O.D._t)$$

k = rate constant

$O.D._{\infty}$ = optical density at infinite time

$O.D._t$ = optical density at time t

slope the rate constant (k) can be evaluated. A sample plot is shown. For convenience in calculating, we added a constant to each side of the equation and $3 + \log (O.D._{\infty} - O.D._t)$ was plotted against the time.

$$3. \quad 3 - \frac{k}{2.303} t = -\log (O.D._{\infty}) + \log (O.D._{\infty} - O.D._t) + 3$$

The utilization of the above kinetic method and calculation procedure led to a considerable amount of rate data which will be reported in the next section.

FIGURE 2

SAMPLE PLOT FOR KETAL HYDROLYSIS

Run 132

70-30 dioxane-water

Ketal VIII

0.003 N HCl

 $30. \pm .15^{\circ}$ $3 + \log(O.D._{\infty} - O.D._t)$ Slope = $-0.0083 \text{ min.}^{-1}$ $k_1 = 0.0192 \text{ min.}^{-1}$

B. Experimental Results

The following section contains tables for the individual hydrolysis runs and summary tables for composite rate constants, average rate constants, and relative rate constants.

TABLE 4
KINETIC RUN 182

Compound I

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm 15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.088 M

Slit - 0.150

O.D. _{∞} - 0.765Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
167	-0.002	0.767	2.885
235	0.002	0.763	2.883
339	0.003	0.762	2.881
595	0.007	0.758	2.880
763	0.011	0.754	2.877
1227	0.016	0.749	2.875
1255	0.017	0.748	2.874
1955	0.027	0.738	2.868
2340	0.031	0.734	2.866
2830	0.040	0.725	2.860
3433	0.047	0.718	2.856
4418	0.062	0.703	2.847
5106	0.071	0.694	2.841
6303	0.088	0.677	2.831
6928	0.097	0.668	2.825
8223	0.114	0.651	2.814
8943	0.127	0.638	2.805
10034	0.139	0.626	2.797
12440	0.167	0.598	2.777
12960	0.174	0.591	2.772

Slope = -0.00051 min.⁻¹ $k_1 = 0.00117 \text{ min.}^{-1}$

TABLE 5
KINETIC RUN 183

Compound I

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.088 M

Slit - 0.150

O.D. - 0.782

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
392	0.022	0.760	2.881
1130	0.037	0.745	2.872
4460	0.081	0.701	2.846
8218	0.128	0.654	2.816
8335	0.144	0.638	2.805
9443	0.146	0.636	2.804
12713	0.183	0.599	2.777
14825	0.204	0.578	2.762
15875	0.217	0.565	2.752
16738	0.229	0.553	2.743
16988	0.227	0.555	2.744
17480	0.233	0.549	2.740
17953	0.239	0.543	2.735
18557	0.247	0.535	2.728
21575	0.278	0.504	2.702
21640	0.278	0.504	2.702
21826	0.279	0.503	2.702
23432	0.304	0.478	2.679
24360	0.303	0.479	2.680
24646	0.303	0.479	2.680

Slope = $-0.00050 \text{ min.}^{-1}$ $k_1 = 0.00115 \text{ min.}^{-1}$

TABLE 6
KINETIC RUN 184

Compound I

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.088 M

Slit - 0.150

O.D. _{∞} - 0.764

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
1143	0.027	0.737	2.867
1907	0.046	0.718	2.856
2336	0.038	0.726	2.861
2375	0.040	0.724	2.860
3122	0.051	0.713	2.853
3576	0.056	0.708	2.850
4908	0.073	0.691	2.840
5603	0.088	0.676	2.830
6658	0.099	0.665	2.823
8922	0.128	0.636	2.804
9575	0.138	0.626	2.797
10308	0.145	0.619	2.792
12708	0.173	0.591	2.772
13255	0.179	0.585	2.767
13894	0.189	0.575	2.760
14430	0.196	0.568	2.754

Slope = $-0.00051 \text{ min.}^{-1}$

$k_1 = 0.00117 \text{ min.}^{-1}$

TABLE 7
KINETIC RUN 185

Compound I

Initial Ketal Conc. - 0.088 M

O.D._∞ - 0.764

Solvent - 70-30 Dioxane-water

Temp. - 30. ± .15°

Acid Conc. - 0.003 N HCl

Slit - 0.150

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D.</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
261	0.007	0.757	2.879
850	0.014	0.750	2.875
1407	0.023	0.741	2.870
2785	0.042	0.722	2.859
3480	0.057	0.707	2.849
4578	0.072	0.692	2.840
6918	0.102	0.662	2.821
7008	0.103	0.661	2.820
7438	0.108	0.656	2.817
8175	0.116	0.648	2.812
10608	0.147	0.617	2.790
11143	0.151	0.613	2.788
11763	0.161	0.603	2.780
12411	0.168	0.596	2.775

$$\text{Slope} = -0.00051 \text{ min.}^{-1}$$

$$k_1 = 0.00116 \text{ min.}^{-1}$$

TABLE 8
KINETIC RUN 186

Compound I

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.088 M

Slit - 0.150

O.D. _{∞} - 0.778Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
242	0.013	0.765	2.884
1222	0.043	0.735	2.866
2826	0.047	0.731	2.864
2952	0.049	0.729	2.863
5832	0.089	0.689	2.838
9720	0.139	0.639	2.806
11310	0.149	0.629	2.799
11400	0.153	0.625	2.796
15918	0.211	0.567	2.761
17325	0.225	0.553	2.743
18095	0.232	0.546	2.737
18940	0.243	0.535	2.728
19275	0.242	0.536	2.729
20058	0.255	0.523	2.719
22923	0.277	0.501	2.700
23030	0.284	0.494	2.694
23280	0.287	0.491	2.691
23355	0.287	0.491	2.691
25665	0.307	0.471	2.673
26107	0.311	0.467	2.669

Slope = $-0.00050 \text{ min.}^{-1}$ $k_1 = 0.00115 \text{ min.}^{-1}$

TABLE 9
KINETIC RUN 196

Compound II

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.085 M

Slit - 0.150

O.D. $_{\infty}$ - 0.776Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.$_t$</u>	<u>O.D.$_{\infty}$ - O.D.$_t$</u>	<u>$3 + \log(\text{O.D.}_{\infty} - \text{O.D.}_t)$</u>
188	0.046	0.730	2.863
739	0.139	0.637	2.804
818	0.152	0.624	2.795
913	0.166	0.610	2.785
1103	0.194	0.582	2.765
1260	0.219	0.557	2.746
1442	0.244	0.532	2.726
1755	0.282	0.494	2.694
1998	0.311	0.465	2.668
2158	0.328	0.448	2.651
2255	0.337	0.439	2.643
2670	0.380	0.396	2.598
2798	0.396	0.380	2.590
2953	0.408	0.368	2.566
3165	0.428	0.348	2.542
3332	0.441	0.335	2.525
3450	0.450	0.326	2.513
4638	0.538	0.238	2.377
5140	0.563	0.213	2.328
5541	0.583	0.193	2.286

Slope = -0.00649 min. $^{-1}$ $k_1 = 0.0149 \text{ min.}^{-1}$

TABLE 10
KINETIC RUN 197

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.085 M

Slit - 0.150

O.D._∞ = 0.776

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
183	0.047	0.729	2.863
300	0.068	0.708	2.850
427	0.093	0.673	2.828
603	0.125	0.651	2.814
740	0.148	0.628	2.798
860	0.169	0.607	2.783
1110	0.206	0.570	2.756
1310	0.234	0.542	2.734
1440	0.250	0.526	2.721
1573	0.268	0.508	2.706
1716	0.290	0.486	2.687
1950	0.317	0.459	2.662
2197	0.343	0.433	2.637
2400	0.358	0.418	2.621
2586	0.377	0.399	2.601
3425	0.452	0.324	2.511
3987	0.505	0.271	2.433
4260	0.526	0.250	2.398
4603	0.547	0.229	2.360
5568	0.590	0.186	2.270
6390	0.630	0.146	2.164
6875	0.645	0.131	2.117

Slope = -0.00665 min.⁻¹

k₁ = 0.0153 min.⁻¹

TABLE II
KINETIC RUN 198

 Compound II
 Solvent - 70-30 Dioxane-water
 Temp. - 30. $\pm$.15°
 Acid Cono. - 0.003 N HCl
 Initial Ketol Cono. - 0.085 M Slit - 0.150
 O.D._∞ - 0.775 Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
282	0.076	0.699	2.815
426	0.108	0.667	2.821
570	0.131	0.644	2.809
783	0.163	0.612	2.787
967	0.192	0.583	2.766
1102	0.213	0.562	2.750
1299	0.242	0.533	2.727
1480	0.262	0.513	2.710
1699	0.289	0.486	2.687
2009	0.327	0.448	2.651
2179	0.350	0.425	2.628
2457	0.378	0.397	2.599
2728	0.408	0.367	2.565
3438	0.468	0.307	2.487
3683	0.488	0.287	2.458
3864	0.500	0.275	2.439
4228	0.530	0.245	2.389
4470	0.547	0.228	2.358
4938	0.569	0.206	2.314
6123	0.624	0.151	2.179
6636	0.637	0.138	2.140
7200	0.656	0.119	2.076

$$\text{Slope} = -0.00661 \text{ min.}^{-1}$$

$$k_1 = 0.0152 \text{ min.}^{-1}$$

TABLE 12
KINETIC RUN 199

 Solvent - 70-30 Dioxane-water
 Temp. - 30. $\pm$.15°
 Compound II
 Acid Conc. - 0.003 N HCl
 Initial Ketol Conc. - 0.085 M
 Slit - 0.150
 O.D. $_{\infty}$ - 0.778
 Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D. $_t$</u>	<u>O.D. $_{\infty}$ - O.D. $_t$</u>	<u>$3 + \log(O.D. $_{\infty}$ - O.D. $_t$)$</u>
250	0.062	0.716	2.855
343	0.079	0.699	2.844
703	0.139	0.639	2.806
881	0.169	0.609	2.785
1045	0.193	0.585	2.767
1410	0.243	0.535	2.728
1685	0.279	0.499	2.698
1805	0.292	0.486	2.687
2018	0.318	0.460	2.663
2400	0.364	0.414	2.617
2570	0.382	0.398	2.600
2722	0.398	0.380	2.580
3045	0.422	0.356	2.551
3234	0.436	0.342	2.534
3437	0.455	0.323	2.509
3587	0.467	0.311	2.493
3809	0.483	0.295	2.470
4157	0.505	0.273	2.436
4290	0.517	0.261	2.417
4543	0.531	0.247	2.393
4703	0.538	0.240	2.380
5055	0.559	0.219	2.340
5366	0.572	0.206	2.314
5729	0.592	0.186	2.270

$$\text{Slope} = -0.00642 \text{ min.}^{-1}$$

$$k_1 = 0.0148 \text{ min.}^{-1}$$

TABLE 13
KINETIC RUN 200

Compound II

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Katal Conc. - 0.005 M

Slit - 0.150

O.D._∞ - 0.776

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞-O.D._t</u>	<u>3 + log(O.D._∞-O.D._t)</u>
215	0.053	0.723	2.859
358	0.084	0.692	2.841
473	0.108	0.668	2.825
588	0.131	0.647	2.811
655	0.143	0.633	2.801
935	0.187	0.589	2.770
1032	0.202	0.574	2.759
1119	0.217	0.559	2.747
1243	0.239	0.537	2.730
1396	0.250	0.526	2.721
1476	0.260	0.516	2.713
1625	0.281	0.495	2.695
1959	0.308	0.468	2.670
2099	0.323	0.453	2.656
2344	0.347	0.429	2.633
2568	0.372	0.404	2.606
2841	0.396	0.380	2.580
2965	0.410	0.366	2.564
3173	0.410	0.349	2.542
3525	0.456	0.320	2.505
3813	0.477	0.299	2.476
4086	0.492	0.284	2.453
4252	0.505	0.271	2.431
4508	0.523	0.253	2.403

Slope = -0.00654 min.⁻¹k₁ = 0.0151 min.⁻¹

TABLE 11
KINETIC RUN 210

Compound II

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.078 M Slit - 0.150

O.D. _{∞} - 0.710

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
223	0.043	0.667	2.824
317	0.055	0.655	2.816
427	0.075	0.635	2.803
544	0.091	0.619	2.792
665	0.110	0.600	2.778
781	0.126	0.584	2.766
917	0.143	0.567	2.754
1020	0.157	0.553	2.743
1158	0.176	0.534	2.728
1355	0.202	0.508	2.706
1920	0.268	0.442	2.645
2133	0.298	0.412	2.615
2268	0.313	0.397	2.599
2573	0.348	0.362	2.559
2884	0.366	0.344	2.537
3193	0.396	0.314	2.497
3464	0.411	0.299	2.476
3913	0.446	0.264	2.422
4235	0.469	0.241	2.382
4857	0.502	0.208	2.318
5400	0.528	0.182	2.260
5713	0.544	0.166	2.220
6270	0.567	0.143	2.155

Slope = -0.00658 min.⁻¹k₁ = 0.0152 min.⁻¹

TABLE 15
KINETIC RUN 211

Compound II

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.078 M

Slit - 0.150

O.D._∞ - 0.710

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 $\log$(O.D._∞ - O.D._t)</u>
196	0.036	0.674	2.829
298	0.049	0.661	2.820
437	0.073	0.637	2.804
573	0.098	0.612	2.787
712	0.116	0.594	2.774
902	0.143	0.567	2.754
1022	0.159	0.551	2.741
1179	0.178	0.532	2.726
1318	0.198	0.512	2.709
1502	0.219	0.491	2.691
1715	0.244	0.466	2.668
2068	0.284	0.426	2.629
2381	0.316	0.394	2.596
3023	0.374	0.336	2.526
3547	0.409	0.301	2.479
3887	0.436	0.274	2.438
4449	0.468	0.242	2.384
4813	0.488	0.222	2.346
5058	0.502	0.208	2.318
5242	0.516	0.194	2.288
5712	0.542	0.168	2.225
6104	0.554	0.156	2.193
6553	0.569	0.141	2.149

$$\text{Slope} = -0.00647 \text{ min.}^{-1}$$

$$k_1 = 0.0149 \text{ min.}^{-1}$$

TABLE 16
KINETIC RUN 212

Compound II

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.078 M

Slit - 0.150

O.D. _{∞} - 0.710

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 $\log$(O.D._{∞} - O.D._t)</u>
222	0.047	0.663	2.822
359	0.073	0.637	2.804
546	0.099	0.611	2.786
699	0.127	0.583	2.766
873	0.149	0.561	2.749
1013	0.168	0.542	2.734
1182	0.192	0.508	2.706
1439	0.226	0.484	2.685
1639	0.246	0.464	2.667
1908	0.279	0.431	2.635
2040	0.292	0.418	2.621
2592	0.349	0.361	2.558
2751	0.366	0.344	2.537
2970	0.384	0.326	2.513
3217	0.403	0.307	2.487
3401	0.417	0.293	2.467
3815	0.447	0.263	2.420
4277	0.483	0.227	2.356
4522	0.498	0.212	2.326
5086	0.527	0.183	2.263
5413	0.544	0.166	2.220
6100	0.575	0.135	2.130
6387	0.583	0.127	2.104

Slope = -0.00670 min.⁻¹k₁ = 0.0154 min.⁻¹

TABLE 17
KINETIC RUN 213

Compound II

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Slit - 0.150

Initial Ketal Conc. - 0.078 M

Acid Conc. - 0.003 N HCl

O.D._∞ - 0.710

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
275	0.047	0.663	2.822
360	0.062	0.648	2.812
480	0.079	0.631	2.800
604	0.099	0.611	2.786
810	0.132	0.578	2.762
987	0.156	0.554	2.744
1120	0.175	0.535	2.728
1260	0.194	0.516	2.713
1447	0.216	0.494	2.694
1713	0.247	0.463	2.666
2057	0.283	0.427	2.630
2952	0.306	0.404	2.606
2481	0.327	0.383	2.583
2757	0.353	0.357	2.553
2970	0.370	0.340	2.532
3450	0.410	0.300	2.477
3788	0.432	0.278	2.444
3957	0.445	0.265	2.423
4119	0.455	0.255	2.407
4405	0.467	0.243	2.386
4587	0.481	0.229	2.360
4800	0.495	0.215	2.332
5136	0.510	0.200	2.301
5307	0.518	0.192	2.283

Slope $\pm -0.00646 \text{ min.}^{-1}$ $k_1 = 0.0149 \text{ min.}^{-1}$

TABLE 18
KINETIC RUN 216

Compound III

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .17^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.073 M

Slit - 0.150

O.D. _{∞} - 0.743

Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
235	0.058	0.685	2.836
365	0.067	0.676	2.830
497	0.081	0.652	2.821
624	0.094	0.649	2.812
746	0.108	0.635	2.803
1020	0.133	0.610	2.785
1239	0.152	0.591	2.772
1402	0.168	0.575	2.760
1758	0.200	0.543	2.735
1875	0.208	0.535	2.728
2438	0.254	0.489	2.689
2888	0.291	0.452	2.655
3270	0.316	0.427	2.630
3852	0.354	0.389	2.590
4027	0.364	0.379	2.579
5302	0.433	0.310	2.491
5816	0.458	0.285	2.455

Slope = -0.00411 min.⁻¹

$k_1 = 0.00946 \text{ min.}^{-1}$

TABLE 19
KINETIC RUN 219

Compound III

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.073 M

Slit - 0.150

O.D. _{∞} - 0.744

Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
1755	0.202	0.542	2.734
1898	0.217	0.527	2.722
2047	0.229	0.515	2.712
2212	0.242	0.502	2.701
2393	0.257	0.487	2.688
2560	0.269	0.475	2.679
2733	0.284	0.460	2.663
2972	0.302	0.442	2.645
3193	0.316	0.428	2.631
3407	0.331	0.413	2.616
3670	0.348	0.396	2.598
4085	0.373	0.371	2.569
4335	0.390	0.354	2.549
4540	0.399	0.345	2.537
4998	0.421	0.323	2.509
5317	0.436	0.308	2.489
5549	0.447	0.297	2.473
6076	0.469	0.275	2.439
6681	0.496	0.248	2.395
8199	0.548	0.196	2.292

Slope = $-0.00406 \text{ min.}^{-1}$

$k_1 = 0.00935 \text{ min.}^{-1}$

TABLE 20
KINETIC RUN 220

Compound III

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.073 M

Slit - 0.150

O.D. ∞ - 0.743Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.$\cdot$t</u>	<u>O.D.$\cdot\infty$ - O.D.$\cdot$t</u>	<u>3 + log(O.D.$\cdot\infty$ - O.D.$\cdot$t)</u>
10	0.053	0.690	2.839
183	0.072	0.671	2.827
352	0.091	0.652	2.814
528	0.109	0.634	2.802
683	0.122	0.621	2.793
859	0.142	0.601	2.779
897	0.158	0.585	2.767
1228	0.177	0.566	2.753
1448	0.197	0.546	2.737
1710	0.218	0.525	2.720
1925	0.237	0.506	2.704
2241	0.259	0.484	2.685
2482	0.278	0.465	2.668
2682	0.291	0.452	2.655
2893	0.305	0.438	2.642
3154	0.322	0.421	2.624
3403	0.338	0.405	2.608
3688	0.357	0.386	2.587
3863	0.367	0.376	2.575
4243	0.387	0.356	2.551
4858	0.419	0.324	2.511
6355	0.487	0.256	2.408
6620	0.495	0.248	2.395
7003	0.508	0.235	2.371

Slope = -0.00401 min. $^{-1}$ $k_1 = 0.00923$ min. $^{-1}$

TABLE 21
KINETIC RUN 226

Compound III

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.065 M

Slit - 0.150

O.D. _{∞} - 0.646

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞}-O.D._t</u>	<u>3 +log(O.D._{∞}-O.D._t)</u>
308	0.045	0.601	2.779
550	0.060	0.586	2.769
812	0.083	0.563	2.751
1238	0.117	0.529	2.724
1499	0.137	0.509	2.707
1893	0.168	0.478	2.679
2085	0.186	0.460	2.663
2355	0.203	0.443	2.647
2489	0.211	0.435	2.639
2796	0.233	0.413	2.616
3133	0.253	0.393	2.594
3480	0.273	0.373	2.572
3848	0.294	0.352	2.547
4074	0.307	0.339	2.530
4326	0.318	0.328	2.516
4566	0.331	0.315	2.498
4800	0.342	0.304	2.483
5261	0.363	0.283	2.452
5533	0.371	0.275	2.439
5882	0.386	0.260	2.415
6238	0.400	0.246	2.391
6727	0.415	0.231	2.364
7266	0.433	0.213	2.328

$$\text{Slope} = -0.00400 \text{ min.}^{-1}$$

$$k_1 = 0.00921 \text{ min.}^{-1}$$

TABLE 22
KINETIC RUN 228

Compound III

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.065 M

Slit - 0.150

O.D. _{∞} - 0.646Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>$3 + \log(\text{O.D._{∞} - O.D._t)$</u>
322	0.036	0.610	2.785
464	0.052	0.594	2.774
968	0.093	0.553	2.743
1098	0.103	0.543	2.735
1392	0.128	0.518	2.714
1615	0.145	0.501	2.700
1936	0.174	0.472	2.674
2133	0.187	0.459	2.662
2323	0.202	0.444	2.647
2445	0.212	0.434	2.638
2618	0.223	0.423	2.626
2730	0.230	0.416	2.619
2948	0.242	0.404	2.606
3242	0.260	0.386	2.587
3763	0.288	0.358	2.554
3938	0.299	0.347	2.540
4488	0.327	0.319	2.504
4961	0.348	0.298	2.474
5678	0.378	0.268	2.428
6400	0.408	0.238	2.377

Slope = -0.00403 min.⁻¹ $k_1 = 0.00928 \text{ min.}^{-1}$

TABLE 23
KINETIC RUN 229

Compound III

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.065 M

Slit - 0.150

O.D. _{∞} - 0.646

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
323	0.038	0.608	2.784
475	0.055	0.591	2.772
653	0.072	0.574	2.759
785	0.084	0.562	2.750
937	0.099	0.547	2.738
1205	0.122	0.524	2.719
1444	0.139	0.507	2.705
1953	0.176	0.470	2.672
2112	0.190	0.456	2.659
2416	0.209	0.437	2.641
2577	0.223	0.423	2.626
2744	0.234	0.412	2.615
2920	0.244	0.402	2.604
3220	0.264	0.382	2.582
3674	0.277	0.369	2.567
3873	0.302	0.344	2.537
4325	0.321	0.325	2.512
4604	0.335	0.311	2.493
4965	0.353	0.293	2.467
5517	0.376	0.270	2.431
6120	0.403	0.243	2.386
6984	0.432	0.214	2.330

$$\text{Slope} = -0.00406 \text{ min.}^{-1}$$

$$k_1 = 0.00935 \text{ min.}^{-1}$$

TABLE 24
KINETIC RUN 157

Compound IV

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$ 1.5°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.077 M

Slit - 0.150

O.D. ∞ - 0.660Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.-t</u>	<u>O.D.∞ - O.D.-t</u>	<u>3 + log(O.D.∞ - O.D.-t)</u>
303	0.146	0.514	2.711
364	0.167	0.493	2.693
420	0.181	0.479	2.680
501	0.203	0.457	2.660
575	0.224	0.436	2.640
676	0.249	0.411	2.614
734	0.261	0.399	2.601
793	0.276	0.384	2.584
856	0.292	0.368	2.566
948	0.311	0.349	2.543
1031	0.326	0.334	2.524
1080	0.338	0.322	2.508
1176	0.354	0.306	2.486
1256	0.369	0.291	2.464
1348	0.386	0.274	2.438
1443	0.400	0.260	2.415
1510	0.410	0.250	2.398
1590	0.422	0.238	2.377
1680	0.436	0.224	2.350
1750	0.443	0.217	2.337

Slope = -0.0156 min.⁻¹k₁ = 0.0359 min.⁻¹

TABLE 25
KINETIC RUN 158

Compound IV

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketol Conc. - 0.077 M

Slit - 0.150

O.D._∞ - 0.660

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞-O.D._t</u>	<u>2.3 log(O.D._∞-O.D._t)</u>
270	0.126	0.534	2.729
344	0.147	0.513	2.709
473	0.169	0.491	2.691
503	0.194	0.464	2.667
597	0.218	0.442	2.645
667	0.238	0.422	2.625
732	0.253	0.407	2.610
787	0.265	0.395	2.596
851	0.280	0.380	2.580
917	0.293	0.367	2.567
993	0.311	0.349	2.543
1048	0.321	0.339	2.530
1106	0.333	0.327	2.515
1312	0.371	0.289	2.461
1505	0.405	0.255	2.407
1685	0.430	0.230	2.362

Slope = -0.0155 min.⁻¹

k₁ = 0.0355 min.⁻¹

TABLE 26
KINETIC RUN 159

Compound IV

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketol Conc. - 0.077 M

Slit - 0.150

O.D._∞ - 0.660

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._c</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
275	0.134	0.526	2.721
305	0.143	0.517	2.714
363	0.160	0.500	2.699
420	0.176	0.484	2.685
485	0.194	0.466	2.668
542	0.208	0.452	2.655
598	0.222	0.438	2.642
670	0.240	0.420	2.623
741	0.258	0.402	2.604
836	0.277	0.383	2.583
905	0.294	0.366	2.564
995	0.313	0.347	2.540
1056	0.324	0.336	2.526
1136	0.341	0.319	2.504
1205	0.356	0.304	2.483
1287	0.364	0.296	2.471
1377	0.379	0.281	2.449
1478	0.398	0.262	2.418
1590	0.417	0.243	2.386
1767	0.438	0.222	2.346

Slope = -0.0153 min.⁻¹k₁ = 0.0352 min.⁻¹

TABLE 27

KINETIC RUN 128

Compound V

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.075 M

Slit - 0.150

O.D. _{∞} - 0.688

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
198	0.361	0.327	2.515
220	0.384	0.304	2.483
243	0.408	0.280	2.447
270	0.433	0.255	2.407
300	0.454	0.234	2.369
328	0.476	0.212	2.326
362	0.497	0.191	2.281
393	0.515	0.173	2.238
423	0.533	0.155	2.190
465	0.553	0.135	2.130
523	0.578	0.110	2.041
578	0.598	0.090	1.954
622	0.608	0.080	1.903
667	0.620	0.068	1.833
735	0.635	0.053	1.724
823	0.648	0.040	1.602
905	0.661	0.027	1.431

Slope = -0.0870 min.⁻¹k₁ = 0.200 min.⁻¹

TABLE 28
KINETIC RUN 129

Compound V

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.075 M

Slit - 0.150

O.D. _{∞} - 0.688

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._c</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 $\log$(O.D._{∞} - O.D._t)</u>
195	0.354	0.334	2.524
216	0.376	0.312	2.494
230	0.393	0.297	2.473
250	0.414	0.274	2.438
265	0.428	0.260	2.415
283	0.444	0.244	2.387
302	0.458	0.230	2.362
329	0.477	0.211	2.324
362	0.498	0.190	2.279
398	0.518	0.170	2.230
429	0.537	0.1515	2.179
470	0.557	0.131	2.117
510	0.573	0.115	2.061
569	0.592	0.096	1.982
625	0.607	0.081	1.909
696	0.622	0.066	1.820
696	0.622	0.066	1.820
763	0.640	0.048	1.681
848	0.648	0.040	1.602

Slope = -0.0866 min.⁻¹k₁ = 0.199 min.⁻¹

TABLE 29
KINETIC RUN 130

Compound V

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.075 M

Slit - 0.150

O.D._∞ - 0.691

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
197	0.354	0.337	2.528
220	0.379	0.312	2.494
239	0.398	0.293	2.467
266	0.423	0.268	2.428
292	0.445	0.246	2.391
312	0.459	0.232	2.366
330	0.473	0.218	2.339
364	0.496	0.195	2.290
433	0.537	0.154	2.188
466	0.552	0.139	2.143
496	0.567	0.124	2.093
543	0.583	0.108	2.033
582	0.595	0.096	1.982
619	0.606	0.085	1.929
662	0.615	0.076	1.881
723	0.630	0.061	1.781
820	0.645	0.046	1.663

Slope = $-0.0862 \text{ min.}^{-1}$

$k_1 = 0.199 \text{ min.}^{-1}$

TABLE 30
KINETIC RUN 165

Compound VI

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketol Conc. - 0.070 M

Slit - 0.150

O.D._∞ - 0.744

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
198	0.506	0.238	2.377
217	0.529	0.215	2.332
236	0.551	0.193	2.286
252	0.562	0.182	2.260
270	0.581	0.163	2.212
286	0.593	0.151	2.179
302	0.605	0.139	2.143
332	0.625	0.119	2.076
361	0.641	0.103	2.013
390	0.653	0.091	1.959
420	0.667	0.077	1.887
448	0.676	0.068	1.832
487	0.687	0.057	1.756
518	0.698	0.046	1.663
563	0.708	0.038	1.580
626	0.717	0.027	1.431
705	0.725	0.019	1.279
810	0.734	0.010	1.000
989	0.741	0.003	0.477

Slope = -0.1307 min.⁻¹k₁ = 0.301 min.⁻¹

TABLE 31
KINETIC RUN 166

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.150

O.D. _{∞} - 0.736

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
182	0.493	0.243	2.386
198	0.512	0.224	2.350
211	0.531	0.205	2.312
228	0.556	0.180	2.255
242	0.603	0.133	2.124
274	0.616	0.120	2.079
310	0.616	0.120	2.079
328	0.622	0.114	2.057
354	0.641	0.095	1.978
374	0.647	0.089	1.949
403	0.659	0.077	1.887
427	0.665	0.071	1.851
471	0.677	0.059	1.771
523	0.692	0.044	1.644
579	0.702	0.034	1.532
632	0.712	0.024	1.380
698	0.720	0.016	1.204
787	0.728	0.008	0.903
957	0.732	0.004	0.602

Slope = -0.131 min.⁻¹

k₁ = 0.302 min.⁻¹

TABLE 32
KINETIC RUN 167

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.150

O.D. $_{\infty}$ - 0.743

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D.$_t$</u>	<u>O.D.$_{\infty}$ - O.D.$_t$</u>	<u>3 + log(O.D.$_{\infty}$ - O.D.$_t$)</u>
205	0.538	0.205	2.312
218	0.552	0.191	2.281
235	0.568	0.173	2.238
250	0.583	0.160	2.204
270	0.598	0.145	2.161
287	0.610	0.133	2.124
303	0.621	0.122	2.086
319	0.632	0.111	2.045
339	0.641	0.102	2.009
359	0.650	0.093	1.969
403	0.671	0.072	1.857
422	0.678	0.065	1.813
449	0.685	0.058	1.763
488	0.696	0.047	1.672
532	0.706	0.037	1.568
593	0.715	0.028	1.447
666	0.724	0.019	1.279
772	0.734	0.009	0.954

Slope = -0.134 min.^{-1}

$k_1 = 0.308 \text{ min.}^{-1}$

TABLE 33
KINETIC RUN 168

Compound VI

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.150

O.D. $_{\infty}$ - 0.740Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.$_t$</u>	<u>O.D.$_{\infty}$ - O.D.$_t$</u>	<u>$3 + \log(\text{O.D.}_{\infty} - \text{O.D.}_t)$</u>
138	0.440	0.300	2.477
159	0.467	0.273	2.436
177	0.490	0.250	2.398
196	0.513	0.227	2.356
213	0.532	0.208	2.318
232	0.548	0.192	2.283
248	0.565	0.175	2.243
267	0.581	0.159	2.201
281	0.591	0.149	2.173
300	0.604	0.136	2.134
325	0.619	0.121	2.083
342	0.629	0.111	2.045
366	0.640	0.100	2.000
390	0.648	0.092	1.964
422	0.661	0.079	1.898
464	0.678	0.062	1.792
504	0.688	0.052	1.716
602	0.708	0.032	1.505
720	0.721	0.019	1.279
905	0.731	0.009	0.954

Slope = -0.126 min. $^{-1}$ $k_1 = 0.290 \text{ min.}^{-1}$

TABLE 34
KINETIC RUN 148

Compound VII

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.085 M

Slit - 0.150

O.D._∞ - 0.735

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
829	0.009	0.726	2.861
1093	0.017	0.718	2.856
1423	0.026	0.709	2.851
1839	0.036	0.699	2.845
2615	0.058	0.677	2.831
3080	0.068	0.667	2.824
3404	0.077	0.658	2.818
3745	0.085	0.650	2.813
4268	0.099	0.636	2.804
4748	0.113	0.622	2.794
5183	0.122	0.613	2.788
5725	0.134	0.601	2.778
6172	0.144	0.591	2.772
6650	0.161	0.574	2.759
7220	0.169	0.566	2.753
8675	0.202	0.533	2.727
9750	0.224	0.511	2.708
10575	0.237	0.498	2.697
11602	0.256	0.479	2.680
14057	0.302	0.433	2.637

Slope = $-0.00101 \text{ min.}^{-1}$ $k_1 = 0.00233 \text{ min.}^{-1}$

TABLE 35
KINETIC RUN 149

Compound VII

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.085 M

Slit - 0.150

O.D._∞ - 0.735

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
261	0.000	0.735	2.866
659	0.008	0.727	2.862
990	0.018	0.717	2.856
1418	0.028	0.707	2.849
2075	0.046	0.689	2.839
2530	0.060	0.675	2.829
3220	0.079	0.656	2.817
3857	0.097	0.638	2.805
4421	0.108	0.627	2.797
4870	0.124	0.611	2.786
5204	0.127	0.608	2.784
5778	0.142	0.593	2.773
6255	0.153	0.582	2.765
6743	0.164	0.571	2.757
7367	0.177	0.558	2.747
7880	0.188	0.547	2.738
8669	0.209	0.526	2.721
9860	0.223	0.512	2.709

Slope = $-0.00100 \text{ min.}^{-1}$ $k_1 = 0.00230 \text{ min.}^{-1}$

TABLE 36
KINETIC RUN 150

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.085 M

Slit - 0.150

O.D._∞ - 0.735

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>$3 + \log(O.D._\infty - O.D._t)$</u>
410	0.021	0.714	2.854
570	0.014	0.721	2.858
855	0.024	0.711	2.852
1300	0.035	0.700	2.845
1638	0.047	0.688	2.838
1975	0.054	0.681	2.833
2528	0.069	0.666	2.824
3038	0.082	0.653	2.815
3465	0.094	0.641	2.807
3840	0.103	0.632	2.801
4398	0.117	0.618	2.791
4877	0.129	0.606	2.783
5472	0.143	0.592	2.772
5820	0.151	0.584	2.766
7015	0.178	0.557	2.746
8097	0.199	0.536	2.729
8523	0.208	0.527	2.722
9224	0.224	0.511	2.708

$$\text{Slope} = -0.00102 \text{ min.}^{-1}$$

$$k_1 = 0.00235 \text{ min.}^{-1}$$

TABLE 37
KINETIC RUN 131

Compound VIII

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Katal Conc. - 0.080 M

Slit - 0.150

O.D._∞ - 0.726

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
422	0.087	0.649	2.812
519	0.104	0.622	2.794
640	0.128	0.598	2.777
738	0.144	0.582	2.765
855	0.164	0.562	2.750
962	0.184	0.542	2.734
1105	0.208	0.518	2.714
1230	0.224	0.502	2.701
1375	0.252	0.474	2.676
1527	0.270	0.456	2.659
1638	0.287	0.439	2.643
1787	0.306	0.420	2.623
1961	0.327	0.399	2.601
2124	0.351	0.375	2.574
2238	0.363	0.363	2.560
2433	0.384	0.342	2.534
2601	0.404	0.322	2.508
2966	0.437	0.289	2.461
3275	0.463	0.263	2.420
3471	0.477	0.249	2.396

Slope = -0.00828 min.⁻¹k₁ = 0.0191 min.⁻¹

TABLE 38
KINETIC RUN 132

Compound VIII
 Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

8lit - 0.150

Optical Density measured at 287 mμ

 Initial Ketal Conc. - 0.080 M

 O.D._∞ - 0.726

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
320	0.071	0.655	2.816
424	0.093	0.733	2.801
548	0.117	0.609	2.785
686	0.143	0.583	2.766
813	0.167	0.559	2.747
929	0.187	0.539	2.732
1071	0.208	0.518	2.714
1166	0.226	0.500	2.699
1293	0.245	0.481	2.682
1386	0.259	0.467	2.669
1540	0.284	0.442	2.645
1724	0.308	0.418	2.621
1878	0.327	0.399	2.601
2014	0.344	0.382	2.582
2135	0.360	0.366	2.564
2407	0.389	0.337	2.528
2498	0.399	0.327	2.515
2876	0.436	0.290	2.462
3090	0.454	0.272	2.435
3287	0.471	0.255	2.407

Slope = -0.00832 min.⁻¹

k₁ = 0.0192 min.⁻¹

TABLE 39
KINETIC RUN 133

Compound VIII

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.080 M

Slit - 0.150

O.D._∞ - 0.726

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>$3 + \log(O.D._\infty - O.D._t)$</u>
324	0.071	0.655	2.816
453	0.099	0.627	2.797
580	0.123	0.603	2.780
672	0.140	0.586	2.768
797	0.164	0.562	2.750
905	0.183	0.543	2.735
1052	0.207	0.519	2.715
1244	0.236	0.490	2.690
1364	0.257	0.469	2.671
1448	0.270	0.456	2.659
1549	0.283	0.443	2.646
1697	0.308	0.418	2.621
1814	0.322	0.414	2.606
1937	0.336	0.390	2.591
2078	0.353	0.373	2.572
2165	0.364	0.362	2.559
2264	0.374	0.352	2.547
2633	0.417	0.309	2.490
3073	0.455	0.271	2.433
3643	0.500	0.226	2.354

Slope = $-0.00826 \text{ min.}^{-1}$

$k_1 = 0.0190 \text{ min.}^{-1}$

TABLE 40
KINETIC RUN 99

Compound IX

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.066 M Slit - 0.150

O.D. ∞ - 0.667

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D. t</u>	<u>O.D. ∞ - O.D. t</u>	<u>$3 + \log(\text{O.D. } \infty - \text{O.D. } t)$</u>
281	0.119	0.548	2.739
345	0.136	0.531	2.725
423	0.154	0.513	2.710
483	0.169	0.498	2.697
551	0.183	0.484	2.685
606	0.198	0.469	2.671
684	0.212	0.455	2.658
752	0.224	0.443	2.646
810	0.237	0.430	2.634
903	0.256	0.411	2.614
962	0.263	0.404	2.606
1022	0.275	0.392	2.593
1080	0.286	0.381	2.581
1140	0.296	0.371	2.569
1200	0.307	0.360	2.556
1323	0.326	0.341	2.533
1472	0.343	0.324	2.511
1739	0.383	0.284	2.453
1993	0.412	0.255	2.407
2085	0.424	0.243	2.386

Slope = $-0.0117 \text{ min.}^{-1}$ $k_1 = 0.0269 \text{ min.}^{-1}$

TABLE 41
KINETIC RUN 100

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.066 M

Slit - 0.150

O.D._∞ - 0.667

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞-O.D._t</u>	<u>3 + log(O.D._∞-O.D._t)</u>
301	0.128	0.539	2.732
361	0.141	0.526	2.720
418	0.154	0.513	2.710
491	0.169	0.498	2.697
543	0.181	0.486	2.687
602	0.195	0.472	2.674
687	0.211	0.456	2.659
749	0.225	0.442	2.645
818	0.240	0.427	2.630
887	0.255	0.412	2.615
949	0.264	0.403	2.605
1020	0.276	0.391	2.592
1080	0.287	0.380	2.580
1298	0.323	0.344	2.537
1502	0.355	0.312	2.494
1723	0.382	0.285	2.455
1885	0.401	0.266	2.425
2102	0.425	0.242	2.384
2235	0.438	0.229	2.360
2422	0.458	0.209	2.320

Slope = -0.0116 min.⁻¹

k₁ = 0.0267 min.⁻¹

TABLE 42
KINETIC RUN 101

Compound IX

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.066 M

Slit - 0.150

O.D. $_{\infty}$ - 0.667Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.$_t$</u>	<u>O.D.$_{\infty}$ - O.D.$_t$</u>	<u>$3 + \log(\text{O.D.}_{\infty} - \text{O.D.}_t)$</u>
256	0.109	0.558	2.747
323	0.127	0.540	2.732
390	0.143	0.524	2.719
427	0.150	0.517	2.714
490	0.164	0.503	2.702
555	0.178	0.489	2.689
617	0.192	0.475	2.677
690	0.207	0.460	2.663
796	0.229	0.438	2.642
888	0.246	0.421	2.624
962	0.259	0.408	2.611
1095	0.282	0.385	2.586
1169	0.297	0.370	2.568
1482	0.344	0.323	2.509
1708	0.374	0.293	2.467
1997	0.414	0.253	2.403
2345	0.445	0.222	2.346
2619	0.470	0.197	2.295
2832	0.487	0.180	2.255
3005	0.501	0.166	2.220

Slope = $-0.0115 \text{ min.}^{-1}$ $k_1 = 0.0265 \text{ min.}^{-1}$

TABLE 43
KINETIC RUN 173

Compound X

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.151

O.D. ∞ - 0.636Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.t</u>	<u>O.D.∞ - O.D.t</u>	<u>3 +log(O.D.∞ - O.D.t)</u>
270	0.017	0.619	2.792
478	0.024	0.612	2.787
738	0.027	0.609	2.785
1272	0.022	0.614	2.788
1440	0.023	0.613	2.788
3003	0.034	0.602	2.780
3015	0.036	0.600	2.778
3966	0.048	0.588	2.769
5553	0.058	0.578	2.762
6300	0.070	0.566	2.753
7053	0.075	0.561	2.749
7695	0.082	0.554	2.744
8838	0.094	0.542	2.734
10800	0.109	0.527	2.722
13508	0.133	0.503	2.702
14832	0.144	0.492	2.692

Slope = -0.00044 min.⁻¹k₁ = 0.00101 min.⁻¹

TABLE 44
KINETIC RUN 174

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.151

O.D. $_{\infty}$ - 0.636

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D.$_{\infty}$</u>	<u>O.D.$_{\infty}$-O.D.$_{\infty}$</u>	<u>3 + log(O.D.$_{\infty}$-O.D.$_{\infty}$)</u>
465	0.033	0.603	2.780
660	0.034	0.602	2.780
1140	0.046	0.594	2.774
1865	0.048	0.588	2.769
3187	0.061	0.575	2.760
5085	0.079	0.557	2.746
7645	0.102	0.534	2.728
9138	0.116	0.520	2.716
11332	0.134	0.502	2.701
12427	0.144	0.492	2.692
14430	0.158	0.478	2.679
16322	0.177	0.459	2.662
17758	0.186	0.450	2.653
19548	0.201	0.435	2.639

Slope = -0.000447 min.⁻¹

k₁ = 0.000103 min.⁻¹

TABLE 45
KINETIC RUN 175

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.151

O.D. _{∞} - 0.636

Optical Density measured at 287 mu

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
300	0.028	0.608	2.784
1800	0.043	0.593	2.773
3472	0.057	0.579	2.763
6270	0.085	0.551	2.741
7753	0.102	0.534	2.728
9778	0.119	0.517	2.714
10868	0.128	0.508	2.706
13025	0.147	0.489	2.689
13725	0.152	0.484	2.685
14820	0.163	0.473	2.675
16233	0.174	0.462	2.665
18029	0.191	0.445	2.648

Slope = -0.00045 min.⁻¹

k₁ = 0.000104 min.⁻¹

TABLE 46
KINETIC RUN 137

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.150

O.D._∞ - 0.678

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
240	0.027	0.651	2.814
300	0.035	0.643	2.808
437	0.048	0.630	2.799
629	0.066	0.612	2.787
788	0.081	0.597	2.776
963	0.097	0.581	2.764
1084	0.107	0.571	2.757
1327	0.126	0.552	2.742
1520	0.140	0.538	2.731
1750	0.158	0.520	2.716
1958	0.173	0.505	2.703
2190	0.193	0.485	2.686
2407	0.205	0.473	2.675
2640	0.226	0.452	2.655
3004	0.242	0.436	2.640
3797	0.292	0.386	2.587
4150	0.313	0.365	2.562
4824	0.349	0.329	2.517
5379	0.379	0.299	2.476
5664	0.394	0.284	2.453

Slope = $-0.00384 \text{ min.}^{-1}$

$k_1 = 0.00884 \text{ min.}^{-1}$

TABLE 47
KINETIC RUN 138

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.150

O.D. ∞ - 0.678

Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.$\cdot$t</u>	<u>O.D.$\cdot\infty$ - O.D.$\cdot$t</u>	<u>3 + log(O.D.$\cdot\infty$ - O.D.$\cdot$t)</u>
351	0.030	0.648	2.812
587	0.056	0.622	2.794
690	0.064	0.614	2.788
933	0.087	0.591	2.772
1207	0.111	0.567	2.754
1355	0.121	0.557	2.746
1562	0.140	0.538	2.731
1799	0.156	0.522	2.718
2361	0.194	0.484	2.685
2677	0.218	0.460	2.663
2802	0.234	0.444	2.647
3120	0.251	0.417	2.620
3398	0.268	0.410	2.613
3677	0.281	0.397	2.599
4058	0.307	0.371	2.569
4346	0.325	0.353	2.548
4704	0.340	0.338	2.529
5018	0.357	0.321	2.507
5389	0.373	0.305	2.484
6405	0.417	0.261	2.417

Slope = -0.00388 min.⁻¹

k₁ = 0.00893 min.⁻¹

TABLE 48
KINETIC RUN 139

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.070 M

Slit - 0.150

O.D. ∞ - 0.678

Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.t</u>	<u>O.D.∞-O.D.t</u>	<u>3 + log(O.D.∞-O.D.t)</u>
284	0.032	0.646	2.810
480	0.048	0.630	2.799
737	0.071	0.607	2.783
984	0.094	0.584	2.766
1308	0.118	0.560	2.748
1599	0.146	0.532	2.726
1858	0.163	0.515	2.712
2160	0.184	0.494	2.694
2477	0.207	0.471	2.673
2851	0.236	0.442	2.645
3065	0.249	0.429	2.633
3319	0.263	0.415	2.618
3614	0.280	0.398	2.600
3867	0.296	0.382	2.582
4201	0.316	0.362	2.559

Slope = -0.00384 min.⁻¹

k₁ = 0.00884 min.⁻¹

TABLE 49
KINETIC RUN 112

Compound XII

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.066 M

Slit - 0.150

O.D._∞ - 0.670

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 log(O.D._∞ - O.D._t)</u>
248	0.060	0.610	2.785
300	0.072	0.598	2.777
420	0.086	0.584	2.766
540	0.101	0.569	2.755
662	0.113	0.557	2.746
779	0.129	0.541	2.732
900	0.144	0.526	2.721
1022	0.158	0.512	2.709
1148	0.174	0.496	2.696
1262	0.187	0.483	2.684
1388	0.200	0.470	2.672
1504	0.208	0.462	2.665
1678	0.223	0.447	2.650
1865	0.248	0.422	2.625
2051	0.264	0.406	2.609
2200	0.275	0.395	2.597
2437	0.295	0.375	2.574
2679	0.314	0.356	2.551
3058	0.343	0.327	2.515
3438	0.371	0.299	2.476

Slope = -0.0057 min.⁻¹

k₁ = 0.0131 min.⁻¹

TABLE 50
KINETIC RUN 113

Compound XII

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^{\circ}$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.066 M

Slit - 0.150

O.D._∞ - 0.670

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D.</u>	<u>O.D._∞ - O.D._t</u>	<u>$3 + \log(O.D._∞ - O.D._t)$</u>
302	0.067	0.603	2.780
420	0.082	0.588	2.769
601	0.104	0.566	2.753
659	0.113	0.557	2.746
777	0.123	0.547	2.738
900	0.138	0.532	2.726
1027	0.157	0.513	2.710
1139	0.167	0.503	2.702
1273	0.185	0.485	2.686
1446	0.201	0.468	2.671
1611	0.211	0.459	2.662
2060	0.260	0.410	2.613
2240	0.275	0.395	2.597
2520	0.298	0.372	2.571
2736	0.313	0.357	2.553
3052	0.342	0.328	2.516
3291	0.357	0.313	2.496
3603	0.382	0.288	2.459

Slope = -0.0566 min.⁻¹ $k_1 = 0.0132 \text{ min.}^{-1}$

TABLE 51
KINETIC RUN 114

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.066 M

Slit - 0.150

O.D. _{∞} - 0.670

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
306	0.073	0.597	2.776
454	0.097	0.573	2.758
549	0.108	0.562	2.750
657	0.118	0.552	2.742
778	0.133	0.537	2.730
916	0.148	0.522	2.718
1024	0.159	0.511	2.708
1144	0.176	0.494	2.694
1258	0.188	0.482	2.683
1392	0.202	0.468	2.670
1520	0.214	0.456	2.659
1620	0.223	0.447	2.650
1833	0.244	0.426	2.629
2067	0.268	0.402	2.604
2214	0.278	0.392	2.593
2400	0.296	0.374	2.573
2605	0.312	0.358	2.554
2917	0.337	0.333	2.522
3354	0.366	0.304	2.483
3630	0.383	0.287	2.458

Slope = - 0.0568 min.⁻¹

k₁ = 0.131 min.⁻¹

TABLE 52
KINETIC RUN 187

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.069

Slit - 0.170

O.D._∞ - 0.619

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
195	0.051	0.568	2.754
1260	0.053	0.566	2.753
3240	0.052	0.567	2.754
9828	0.075	0.544	2.736
14555	0.092	0.527	2.722
16860	0.098	0.521	2.717
17400	0.102	0.517	2.714
19860	0.106	0.513	2.710
21540	0.115	0.504	2.702
24240	0.124	0.495	2.695
27840	0.140	0.479	2.680
31380	0.149	0.470	2.672
47580	0.188	0.431	2.635
49680	0.192	0.427	2.630
84600	0.290	0.329	2.517
88800	0.286	0.333	2.522
89340	0.290	0.329	2.517
96180	0.304	0.315	2.498
100680	0.318	0.301	2.478
103920	0.323	0.296	2.471

Slope = -0.000169 min.⁻¹

k₁ = 0.000389 min.⁻¹

TABLE 53
KINETIC RUN 188

Compound XIII

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.069 M

Slit - 0.170

O.D. _{∞} - 0.619

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>$3 + \log(O.D._{\infty} - O.D._t)$</u>
735	0.049	0.570	2.756
1355	0.047	0.572	2.757
8175	0.064	0.555	2.744
8250	0.067	0.552	2.742
12780	0.083	0.536	2.729
15312	0.092	0.527	2.722
15695	0.093	0.526	2.721
18280	0.100	0.519	2.715
19980	0.109	0.510	2.708
22690	0.120	0.499	2.698
26340	0.136	0.483	2.684
29805	0.141	0.478	2.679
43080	0.174	0.445	2.648
46020	0.179	0.440	2.644
48120	0.185	0.434	2.638
83100	0.282	0.337	2.528
87360	0.279	0.340	2.532
95820	0.298	0.321	2.507
99120	0.309	0.310	2.491
102420	0.317	0.302	2.480

Slope = -0.000165 min.⁻¹

$k_1 = 0.000380 \text{ min.}^{-1}$

TABLE 54
KINETIC RUN 189

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.069 M

Slit - 0.170

O.D._∞ - 0.619

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D. <i>t</i></u>	<u>O.D._∞ - O.D. <i>t</i></u>	<u>3 <i>t</i> log(O.D._∞ - O.D. <i>t</i>)</u>
838	0.071	0.548	2.739
1560	0.076	0.543	2.735
3235	0.083	0.536	2.729
5940	0.103	0.516	2.713
9608	0.113	0.506	2.704
13065	0.125	0.494	2.694
25770	0.160	0.459	2.662
29220	0.171	0.448	2.651
31380	0.172	0.447	2.650
66420	0.273	0.346	2.539
70620	0.273	0.346	2.539
78020	0.288	0.331	2.520
82320	0.299	0.320	2.505
113780	0.364	0.255	2.407

Slope = -0.00167 min.⁻¹

k₁ = 0.00385 min.⁻¹

TABLE 55
KINETIC RUN 193

Compound XIII

Solvent - 70-30 Dioxane-water

Temp. $\pm 30.$ - $.15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.069 M

Slit - 0.170

O.D. ∞ - 0.619Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.∞</u>	<u>O.D.∞ - O.D.t</u>	<u>$3 \log(O.D.\infty - O.D.t)$</u>
360	0.062	0.567	2.754
1230	0.065	0.564	2.751
10246	0.096	0.523	2.719
11040	0.097	0.522	2.718
16800	0.113	0.506	2.704
18420	0.119	0.500	2.699
22860	0.138	0.481	2.682
30000	0.160	0.459	2.662
63780	0.245	0.374	2.573
66840	0.254	0.365	2.562
71880	0.268	0.351	2.545
74940	0.277	0.342	2.534
90600	0.308	0.311	2.493
90780	0.311	0.308	2.489
99240	0.327	0.292	2.465
103800	0.333	0.286	2.456
107580	0.342	0.277	2.443
111240	0.352	0.267	2.427
113880	0.359	0.260	2.415

Slope = $-0.000172 \text{ min.}^{-1}$ $k_1 = 0.000396 \text{ min.}^{-1}$

TABLE 56
KINETIC RUN 195

Compound XIII

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.069 M

Slit - 0.170

O.D. ∞ - 0.619Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
240	0.063	0.556	2.745
33900	0.167	0.452	2.655
34560	0.665	0.454	2.657
37440	0.178	0.441	2.644
42120	0.191	0.428	2.631
45420	0.201	0.418	2.621
61140	0.240	0.379	2.579
61320	0.240	0.379	2.579
69720	0.260	0.359	2.555
73680	0.270	0.349	2.543
78060	0.281	0.338	2.529
81720	0.289	0.330	2.519
82860	0.291	0.328	2.516
84300	0.296	0.323	2.509
84660	0.297	0.322	2.508
121200	0.364	0.255	2.407
123300	0.367	0.252	2.401
124980	0.369	0.250	2.398
129600	0.377	0.242	2.384

Slope = -0.000169 min.⁻¹ $k_1 = 0.000389 \text{ min.}^{-1}$

TABLE 57
KINETIC RUN 169

Compound XIV

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.18°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.068 M

Slit - 0.150

O.D. $_{\infty}$ - 0.712Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D.$_{\infty}$</u>	<u>O.D.$_{\infty}$ - O.D.$_{\infty}$</u>	<u>3 + log(O.D.$_{\infty}$ - O.D.$_{\infty}$)</u>
242	0.077	0.635	2.803
307	0.079	0.633	2.801
547	0.087	0.625	2.796
633	0.088	0.624	2.795
847	0.095	0.617	2.790
940	0.099	0.613	2.787
1287	0.108	0.614	2.781
1850	0.124	0.588	2.769
2292	0.138	0.574	2.759
2693	0.152	0.560	2.748
3118	0.165	0.547	2.738
3402	0.172	0.540	2.732
4012	0.188	0.524	2.719
4323	0.198	0.514	2.711
4806	0.209	0.503	2.702
5270	0.223	0.489	2.689
6086	0.243	0.469	2.671
6567	0.257	0.455	2.658
7106	0.268	0.444	2.647

Slope = - 0.00136 min.⁻¹ k_1 = 0.00313 min.⁻¹

TABLE 58

KINETIC RUN 171

Compound XIV

Solvent - 70-30 Dioxane-water

Temp. - $30. \pm .15^\circ$

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.064 M

Slit - 0.150

O.D._∞ - 0.712

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._∞ - O.D._t</u>	<u>3 + log(O.D._∞ - O.D._t)</u>
288	0.082	0.630	2.799
593	0.091	0.621	2.793
945	0.105	0.607	2.783
1350	0.115	0.597	2.776
1840	0.132	0.580	2.763
2943	0.164	0.548	2.739
4285	0.195	0.517	2.714
5825	0.236	0.476	2.678
6422	0.251	0.461	2.664
7285	0.269	0.443	2.646
7834	0.281	0.431	2.635
8253	0.292	0.420	2.623
11787	0.353	0.359	2.555
12263	0.362	0.350	2.544

$$\text{Slope} = -0.00133 \text{ min.}^{-1}$$

$$k_1 = 0.00306 \text{ min.}^{-1}$$

TABLE 59
KINETIC RUN 179

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.064 M

Slit - 0.151

O.D. _{∞} - 0.694

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D._t</u>	<u>O.D._{∞} - O.D._t</u>	<u>3 + log(O.D._{∞} - O.D._t)</u>
310	0.066	0.628	2.798
687	0.079	0.615	2.789
1458	0.112	0.582	2.765
1863	0.126	0.568	2.754
2285	0.140	0.554	2.744
2699	0.153	0.541	2.733
3162	0.169	0.629	2.724
3608	0.186	0.508	2.706
4175	0.203	0.491	2.691
4680	0.219	0.475	2.677
5158	0.233	0.461	2.664
5683	0.249	0.445	2.648
6297	0.262	0.432	2.636
6708	0.273	0.421	2.624
7148	0.285	0.409	2.612
7732	0.299	0.395	2.597
8187	0.312	0.382	2.582
8696	0.322	0.372	2.571
9157	0.333	0.361	2.558

Slope = -0.00165 min.⁻¹

k₁ = 0.00380 min.⁻¹

TABLE 60
KINETIC RUN 180

Compound XV

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.064 M

Slit - 0.151

O.D. _{∞} - 0.694

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D. t</u>	<u>O.D._{∞} - O.D. t</u>	<u>3. + log(O.D._{∞} - O.D. t)</u>
98	0.067	0.627	2.797
690	0.083	0.611	2.786
980	0.099	0.595	2.775
1402	0.116	0.578	2.762
1854	0.132	0.562	2.750
2431	0.152	0.542	2.734
2923	0.174	0.520	2.716
3420	0.186	0.508	2.706
3946	0.203	0.491	2.691
4483	0.219	0.475	2.677
4962	0.232	0.462	2.665
5400	0.245	0.449	2.652
5918	0.260	0.434	2.638
6438	0.273	0.421	2.624
6935	0.286	0.408	2.611
7410	0.301	0.393	2.594

Slope = -0.00167 min.⁻¹ $k_1 = 0.00385 \text{ min.}^{-1}$

TABLE 61
KINETIC RUN 223

Compound XV

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.067 M

Slit - 0.150

O.D. ∞ - 0.680Optical Density measured at 287 m μ

<u>Time/seconds</u>	<u>O.D. t</u>	<u>O.D. ∞ - O.D. t</u>	<u>3 + log(O.D. ∞ - O.D. t)</u>
296	0.043	0.637	2.804
695	0.058	0.622	2.794
882	0.066	0.614	2.788
1063	0.072	0.608	2.784
1862	0.102	0.578	2.762
2136	0.111	0.569	2.755
2308	0.119	0.561	2.749
2560	0.128	0.552	2.742
2936	0.143	0.537	2.730
3293	0.157	0.523	2.719
3631	0.166	0.514	2.711
4060	0.182	0.498	2.697
5323	0.233	0.447	2.650
6448	0.261	0.419	2.622
7630	0.286	0.394	2.596
8953	0.312	0.368	2.566
10112	0.335	0.345	2.538
10815	0.355	0.325	2.512
11970	0.375	0.305	2.484
13281	0.398	0.282	2.450

Slope = -0.00163 min.⁻¹ k_1 = 0.00375 min.⁻¹

TABLE 62

KINETIC RUN 224

Compound XV

Solvent - 70-30 Dioxane-water

Temp. - 30. $\pm$.15°

Acid Conc. - 0.003 N HCl

Initial Ketal Conc. - 0.067 M

Slit - 0.150

O.D._∞ - 0.680

Optical Density measured at 287 mμ

<u>Time/seconds</u>	<u>O.D. t</u>	<u>O.D._∞ - O.D. t</u>	<u>3 flog(O.D._∞ - O.D. t)</u>
400	0.033	0.647	2.811
702	0.046	0.634	2.802
983	0.058	0.622	2.794
1462	0.077	0.603	2.780
1869	0.093	0.587	2.769
2217	0.104	0.576	2.760
3628	0.172	0.508	2.706
4610	0.198	0.482	2.683
4773	0.203	0.477	2.679
5197	0.212	0.468	2.670
5517	0.223	0.457	2.660
5732	0.228	0.452	2.655
5936	0.233	0.447	2.650
6600	0.244	0.436	2.640
7191	0.261	0.419	2.622
7784	0.273	0.407	2.610
8350	0.289	0.391	2.592
9883	0.327	0.353	2.548
11380	0.354	0.326	2.513
11558	0.358	0.322	2.508

Slope = -0.00165 min.⁻¹k₁ = 0.00380 min.⁻¹

TABLE 63

SUMMARY OF KINETIC HYDROLYSIS RUNS FOR KETALS I, II, and III

Temp. - 30. $\pm$.15°

Solvent - 70-30 Dioxane-water

Acid Conc. - 0.003 N HCl

<u>Compound</u>	<u>Table #</u>	<u>Run #</u>	<u>Rate constant/minutes⁻¹</u>
I	4	182	0.00117
I	5	183	0.00115
I	6	184	0.00117
I	7	185	0.00116
I	8	186	0.00115
			avg. 0.00116
II	9	196	0.0149
II	10	197	0.0153
II	11	198	0.0152
II	12	199	0.0148
II	13	200	0.0151
II	14	210	0.0152
II	15	211	0.0149
II	16	212	0.0154
II	17	213	0.0149
			avg. 0.0151
III	18	216	0.00948
III	19	219	0.00935
III	20	220	0.00923
III	21	226	0.00921
III	22	228	0.00928
III	23	229	0.00935
			avg. 0.00931

TABLE 6h

SUMMARY OF KINETIC HYDROLYSIS RUNS FOR KETALS IV - IX

Temp. - $30. \pm .15^{\circ}$

Solvent - 70-30 Dioxane-water

Acid Conc. - 0.003 N HCl

<u>Compound</u>	<u>Table #</u>	<u>Run #</u>	<u>Rate constant/minutes⁻¹</u>
IV	24	157	0.0359
IV	25	158	0.0355
IV	26	159	0.0352
			avg. 0.0355
V	27	128	0.200
V	28	129	0.199
V	29	130	0.199
			avg. 0.199
VI	30	165	0.301
VI	31	166	0.302
VI	32	167	0.308
VI	33	168	0.290
			avg. 0.300
VII	34	148	0.00233
VII	35	149	0.00230
VII	36	150	0.00235
			avg. 0.00233
VIII	37	131	0.0191
VIII	38	132	0.0192
VIII	39	133	0.0190
			avg. 0.0191
IX	40	99	0.0269
IX	41	101	0.0267
IX	42	101	0.0265
			avg. 0.0267

TABLE 65

SUMMARY OF KINETIC HYDROLYSIS RUNS FOR KETALS X - XV

Temp. - $30. \pm .15^{\circ}$

Solvent - 70-30 Dioxane-water

Acid Conc. - 0.003 N HCl

<u>Compound</u>	<u>Table #</u>	<u>Run #</u>	<u>Rate constant/minutes⁻¹</u>
X	43	173	0.00101
X	44	174	0.00103
X	45	175	0.00104
			avg. 0.00103
XI	46	137	0.00884
XI	47	138	0.00893
XI	48	139	0.00884
			avg. 0.00887
XII	49	112	0.0131
XII	50	113	0.0132
XII	51	114	0.0131
			avg. 0.0131
XIII	52	187	0.000389
XIII	53	188	0.000380
XIII	54	189	0.000385
XIII	55	193	0.000396
XIII	56	195	0.000385
			avg. 0.000388
XIV	57	169	0.00313
XIV	58	171	0.00316
			avg. 0.00314
XV	59	179	0.00380
XV	60	180	0.00385
XV	61	223	0.00375
XV	62	224	0.00380
			avg. 0.00380

TABLE 66
RATES OF KETAL HYDROLYSIS

Temp. - 30. $\pm$.15°

Solvent - 70-30 Dioxane-water

Acid Conc. - 0.003 N HCl

$k \text{ min.}^{-1}$	0.0012 I	0.015 II	0.0093 III
$k \text{ min.}^{-1}$	0.036 IV	0.20 V	0.300 VI
$k \text{ min.}^{-1}$	0.0023 VII	0.019 VIII	0.027 IX
$k \text{ min.}^{-1}$	0.0010 X	0.0089 XI	0.013 XII
$k \text{ min.}^{-1}$	0.00039 XIII	0.0031 XIV	0.0038 XV

TABLE 67
RELATIVE RATES OF KETAL HYDROLYSIS

Temp. - $30. \pm .15^{\circ}$

Solvent - 70-30 Dioxane-water

Acid Conc. - 0.003 N HCl

1.00
I

13.02
II

8.02
III

30.60
IV

171.6
V

258.6
VI

2.009
VII

16.47
VIII

23.02
IX

0.888
X

7.65
XI

11.29
XII

0.335
XIII

2.672
XIV

3.276
XV

Compound I is taken as a standard with a relative rate of 1.0.

C. Discussion of Relative Rates of Hydrolysis of Cyclic Ketals

The preceding relative rate constants evoke comment in three basic areas. First, the feasibility of separating the various cyclic ketones by selective hydrolysis of certain cyclic ketals will be evaluated. Next, the influence of the gem-dialkyl groups in promoting ring stability will be thoroughly appraised. Finally, the comparative reactivities of ketals derived from ethylene glycol or 1,3-propanediols will be noted and discussed.

If the reader desires to use chemical reactivity to distinguish the steroidal D ring ketone from the A ring ketone, he should be attentive to the accompanying ratios of the hydrolysis rates of ketals derived from 2-methyl cyclopentanone and cyclohexanone.

<u>ethylene glycol</u>	<u>1,3-propanediol</u>	<u>2,2-dimethyl-1,3-propanediol</u>	<u>2,2-diethyl-1,3-propanediol</u>	<u>2,2-diisopropyl-1,3-propanediol</u>
8.02	8.45	11.46 = $\frac{\text{cyclopentanone}}{\text{cyclohexanone}}$	12.7	9.49

While these ratios are not overwhelmingly different; they do demonstrate that 2,2-dimethyl-1,3-propanediol and 2,2-diethyl-1,3-propanediol offer some advantage over ethylene glycol for separation of 2-methylcyclopentanone from cyclohexanone. As such, ketals made from the above propanediols should be superior to ethylene glycol for the selective hydrolysis of ketals derived from steroidal ketones. Later on, calculations will be made to extrapolate the above rate constants in terms of percent product differentiation possible on a hypothetical steroid molecule.

In the case of the ratio of the hydrolysis constants for the cyclopentanone and cyclohexanone ketals, a different situation arises. Here the hydrolysis rate ratio is from fifty to one hundred

<u>ethylene glycol</u>	<u>1,3-propanediol</u>	<u>2,2-dimethyl-1,3-propanediol</u>	<u>2,2-diethyl-1,3-propanediol</u>	<u>2,2-diisopropyl-1,3-propanediol</u>
13.0	5.6	8.2 = $\frac{\text{cyclopentanone ketal}}{\text{cyclohexanone ketal}}$	8.6	8.0

percent higher with the ketals derived from ethylene glycol than it is for those ketals derived from the 1,3-propanediols. Therefore, if the preferential formation of cyclopentanone over cyclohexanone via selective ketal hydrolysis is desired, then ethylene glycol should be employed in the preparation of the ketals.

Before giving any reasons for the ratios observed heretofore, we will report the ratios of rate constants for the ketals derived from 2-methylcyclopentanone and cyclopentanone. These constants show that the introduction of the Δ -methyl group leads to a rate

<u>ethylene glycol</u>	<u>1,3-propanediol</u>	<u>2,2-dimethyl-1,3-propanediol</u>	<u>2,2-diethyl-1,3-propanediol</u>	<u>2,2-diisopropyl-1,3-propanediol</u>
.62	1.51	1.40 = $\frac{\text{cyclopentanone ketal}}{\text{2-methylcyclopentanone ketal}}$	1.48	1.23

increase with the ketals prepared from the 1,3-propanediols and a rate decrease with the ketal prepared from ethylene glycol.

It is to be noted that in all cases, the change from cyclohexanone ketal to the corresponding cyclopentanone ketal is marked by an increase in the rate of hydrolysis. The generalization of

Brown, Brewster, and Shechter¹ predicts that the preceding results should be observed. In one form this generalization postulated that, other things being equal, when the change in coordination number is from four to three, the reaction should proceed quickly for the cyclopentane derivative and slowly for the cyclohexane derivative. This four to three change in coordination number occurs in ketal hydrolysis. As such, in the hydrolysis of cyclopentanone

and cyclohexanone ketals, cyclopentanone is formed more quickly than cyclohexanone. However, the difference in the rates of formation of cyclopentanone and cyclohexanone is not as large as many of the examples which inspired Brown, Brewster, and Shechter's generalization.

The introduction of the methyl group $\angle$ to the carbonyl in cyclopentanone causes results in ketal hydrolysis which defy complete explanation at this time. In alicyclic acetals and ketals, the introduction of methyl group alpha to the carbonyl has a two-fold effect. The increased inductive effect tends to stabilize the intermediate carbonium ion and, hence, to promote ketal hydrolysis. At the same time, the reduced number of hydrogens available for hyperconjugation leads to decreases in the stabilization which

¹ H.C. Brown, J.H. Brewster, and H. Shechter, J.Am.Chem.Soc., 76, 467 (1954).

the intermediate carbonium ion receives by way of hyperconjugation. This tends to reduce the rate of ketal hydrolysis. The inductive and hyperconjugative effects work against each other and as such it would be difficult to predict which would predominate. Furthermore, in cyclic ketals the introduction of a methyl group would have a modifying influence on the strains present in the ring system. This modifying influence would effect the rates of hydrolysis of the ketals but it would be difficult to predict. The rate orders which were observed differ according to the glycol employed in forming the ketal. With 1,3-dioxanes (I) the 2-methyl-

cyclopentanone ketals hydrolyze faster than the cyclopentanone ketal. With

the 1,3-dioxolanes (II) the cyclopentanone ketal hydrolyzes faster than the 2-methylcyclopentanone ketal. Possibly related work is

found in some dipole moment on cyclic ketals. The accompanying dipole

moments have been reported.¹ The authors state that an increase

D

1.08

1.07

1.24

of dipole moment leads to a decrease in the angle $\angle$, according to the accompanying scheme. Furthermore, decrease in angle $\angle$ causes structural instability in the ketal. The conclusion is

¹ Bergmann, et al., Rec.trav.chim., 71, 213 (1952).

Dipole	$\angle$
1.1	111°
1.45	130°
1.90	120°

that the ketal derived from cyclopentanone and ethylene glycol is an unstable compound. The rate with which this com-

pound hydrolyzes would seem to verify this viewpoint although certainly more than one factor is involved in this matter. However, the influence of the methyl group on the dipole moment and angle cannot be stated at the present time. But basically, there isn't any convincing explanation for the relative hydrolysis rates of cyclic ketals formed from 2-methylcyclopentanone and cyclopentanone.

In summary, for separation of 2-methylcyclopentanone from cyclohexanone, selective hydrolysis of ketals formed from 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol is superior to selective hydrolysis of ketals formed from ethylene glycol. However, for the separation of cyclopentanone from cyclohexanone the selective hydrolysis of ketals formed from ethylene glycol offers a definite advantage over the selective hydrolysis of ketals formed from the 1,3-propanediols.

An examination of the relative rate constants demonstrate the profound influence of gem-dialkyl substitution on the hydrolysis rates of cyclic ketals derived from the 1,3-propanediols. If the rate of hydrolysis of each unsubstituted ketal be taken as one, then the relative rates of the others in a given series would be as shown in Table 68.

This table reveals that in each series a major rate decrease takes place with introduction of the gem-dimethyl group. Further

TABLE 68

RELATIVE RATE CONSTANTS FOR HYDROLYSIS OF CYCLIC KETALS

Temp. - $30. \pm .15^\circ$

Solvent - 70-30 Dioxane-water

Acid Conc. - 0.003 N HCl

<u>Series 1</u>	<u>Series 2</u>	<u>Series 3</u>
1.00	1.00	1.00
0.066	0.0960	0.0890
0.029	0.045	0.044
0.011	0.016	0.013

Unsubstituted compounds were taken as standard of 1.0 in each series.

though less pronounced reductions in rate of hydrolysis occur with the introduction of the gem-diethyl and gem-diisopropyl groups in the cyclic ketals. Each gem-dialkyl group exerts an approximately parallel effect in each series. When each unsubstituted cyclic ketal is assigned a relative rate constant of 1.0, the relative rates of hydrolysis are

from 0.066 to 0.096 for the gem-dimethyl ketals,

from 0.029 to 0.045 for the gem-diethyl ketals, and

from 0.011 to 0.016 for the gem-diisopropyl ketals.

From another viewpoint, it is interesting to note that while the unsubstituted ketals are 10-15 times more reactive than the dimethyl ketals, the dimethyl ketals are only 2-2.5 times more reactive than the diethyl ketals, and the diethyls are only 2.5-3.3 times more reactive than diisopropyl ketals. All the preceding calculations demonstrate that gem-dialkyl groups promote ring stability and that the larger dialkyl groups are more effective than smaller dialkyl groups in this respect. However, the big jump in promoting ring stability occurs with the replacement of the hydrogens with the gem-dimethyl group, increasing the size of the dialkyl groups has a positive but smaller effect on the stability of the ring in question.

The problem of explaining this so-called gem-dimethyl effect from a theoretical point of view arises. The cyclic ketals studied in this work seem ideally suited for testing the explanation of the gem-dialkyl effect which is based upon activation energies

and entropy factors. The explanation states that in the hydrolysis of a series of cyclic ketals the entropy change would be progressively less positive as the ketals are substituted with larger dialkyl groups. The progressive decrease in the observed hydrolysis rates would be ascribed to a less positive entropy value. The determination of the activation energies and entropy values of a series of such ketals might provide an experimental verification of a theory which explains the baffling gem-dimethyl effect.

The conformational argument seems applicable here only on the basis that the restricted rotation in the more substituted ketal would prevent the alcohol group from wandering away from the center where the carbonium ion would form. The argument that

more substituted

restricted rotation

slow reaction

unsubstituted

free rotation

fast reaction

end groups are brought closer together by the introduction of the gem-dialkyl groups does not seem to be borne out experimentally. In a private communication, Dr. L. Kuhn reports that the alcohol groups in 2,2-diisopropyl-1,3-propanediol are further apart than the alcohol groups in 2,2-dimethyl-1,3-propanediol.

Another area which furnishes interesting comparison is the ratio of the rates of hydrolysis of 1,3-dioxanes to those of the 1,3-dioxolanes as shown in the accompanying data.

Ratio of rate of hydrolysis of 1,3-dioxanes to rate of hydrolysis of 1,3-dioxolanes

<u>New ketals</u>		<u>Ceder's work</u>	
<u>Ratio</u>	<u>Ketone</u>	<u>Ratio</u>	<u>Ketone</u>
30.6	cyclohexanone	6.0	acetophenone
13.2	cyclopentanone	21.6	acetone
32.2	2-methylcyclopentanone	4.0	benzophenone

These data indicate that in all observed cases of ketal hydrolysis, the 1,3-dioxanes hydrolyze faster than 1,3-dioxolanes.

The lower ratio of the cyclopentanone ketals results from the high rate of hydrolysis of ketal (II) which has been commented

II

on previously. It has been suggested

that the 2,2-dialkyl-1,3-dioxane are

relatively unstable because of the presence of two alkyl groups at one position in a homomorphic cyclohexane structure. Therefore, one group is axial and the other equatorial and a bulky group in the axial position is believed to be quite unfavored.

However, on this basis ketal (VII) should be even more unstable

VII

than ketal (IV), but the experimental facts are just the opposite since the former hydrolyzes more slowly than the latter. A much better case can be made on the basis of activation

IV

energies and probability factors. Ceder's work¹ shows that activation energies favor faster hydrolysis of the 1,3-dioxolanes but that the probability factors favor faster hydrolysis of 1,3-dioxanes. Since the 1,3-dioxanes do hydrolyze faster than 1,3-dioxolanes, the entropy effects must be more overwhelming as the accompanying example indicates. There is no reason for believing that these

<u>Compound</u>	<u>k 20°</u>	<u>E_a</u>	<u>S</u>
16.7	17.5	2.9×10^{12}
88.4	19.3	3.8×10^{14}
68.6	14.8	1.3×10^{11}
14.2	20.9	8.6×10^{14}

relationships should change for the ketals (I) and (VI) prepared in this work, since the relative rate ratios are in the same direction as those reported by Ceder. Interestingly enough, the pattern of activation energies favoring hydrolysis of the 1,3-dioxolanes and entropy factors for the 1,3-dioxanes and 1,3-dioxolanes derived from cyclohexanone, cyclopentanone, and 2-methylcyclopentanone would certainly be of considerable interest and should be determined.

Several reasonable conclusions have been drawn from the relative rate constants reported in this dissertation and will be summarized at this point. For the separation of 2-methylcyclopentanone from cyclohexanone via selective ketal hydrolysis,

¹ O. Ceder, Arkiv Kemi, 6, 523 (1954).

2,2-dimethyl-1,3-propanediol and 2,2-diethyl-1,3-propanediol rather than ethylene glycol should be used in preparing the ketals to be hydrolyzed. On the other hand, for the separation of cyclopentanone from cyclohexanone via selective ketal hydrolysis, the ketals prepared from ethylene glycol offer a definite advantage over the ketals prepared from 1,3-propanediols. As a further corollary, the ketals formed from the accompanying 1,3-propanediols rather than ethylene glycol should be used whenever the selective unblocking of the D ring ketone as compared to the A ring ketone is desired in steroid chemistry. With respect to the so-called gem-dimethyl effect, we found that ring stability is heightened with an increase in the size of the gem-dialkyl group. However, the increase in ring stability is not proportional to the enlargement of the gem-dialkyl group for the significant jump in stability occurs when the hydrogens are first replaced with the methyl groups. Subsequent replacements with ethyl and isopropyl groups are not proportionately effective in increasing ring stability. Finally, in 1,3-dioxanes and 1,3-dioxolanes derived from cyclohexanone, cyclopentanone, or 2-methylcyclopentanone and the unsubstituted glycols, the 1,3-dioxanes always hydrolyzed faster than the 1,3-dioxolanes. This same relationship had previously been found with 1,3-dioxanes and 1,3-dioxolanes derived from other ketones.¹

¹ O. Ceder, *Archiv Kemi*, 6, 523 (1954).

V: EQUILIBRIA INVOLVING CYCLIC KETALS

A. Experimental Procedure and Calculation Method for Equilibrium Studies

As stated earlier, we desired to determine the equilibrium constants for the acid catalyzed reaction pictured below. Dioxane

$$K_e = \frac{(\text{ketal})(\text{water})}{(\text{ketone})(\text{glycol})}$$

was chosen as the solvent because of its previous use in the kinetic work. The equilibrium constants were determined at 30° in order to conform with the hydrolysis work.

A lack of time necessitated that the equilibrium work be restricted. The equilibrium work was limited to ketals VII, VIII, and IX for the following reasons. First, the ketals derived from

VII

VIII

IX

2,2-dimethyl-1,3-propanediol were among the most promising for separation of cyclic ketones by selective hydrolysis. Second, the effect of the gem-dimethyl group might make for an equilibrium position farther to the right. Third, the ketals derived from

2,2-dimethyl-1,3-propanediol were easily prepared. Fourth, quantities of the pure glycol are readily available, a fact important for any application to practical processes.

Before outlining the specific experimental procedure chosen, we would like to mention certain factors which governed the choice. These factors concerned the solvent, the catalyst, the analytical method and its accuracy, and the demonstration that equilibrium had been achieved. Dioxane, the solvent, easily forms hydroperoxides by reaction with the oxygen in the air. Likewise, it has a tendency to absorb moisture from the air. For these reasons dioxane was carefully purified by redistillation immediately before use. The reaction mixtures were kept free from contact with the air and moisture by sealing in small ampoules under nitrogen. For convenience and for assurance of relative constancy of catalyst concentration, aqueous acid was used rather than acid in any other form.

The use of a Beckmann D.U. Spectrophotometer provided a convenient means of determining the carbonyl concentration without disturbing the equilibrium. The concentrations of the other reactants were calculated from the ketone concentration. In order that the percent error be kept as low as possible for each component, the initial concentrations of components were chosen so that the equilibrium concentrations of the free ketone and its corresponding ketal were about equal. This was not achieved until the approximate value of the equilibrium constant was known from

early runs. Approximate equilibrium constants showed the necessity of using a large initial molar excess of 2,2-dimethyl-1,3-propanediol to achieve equivalency of ketone and ketal concentrations at equilibrium in the reactions involving the cyclopentanones. The approximate equilibrium values were also quite helpful for setting up solutions whose optical densities at equilibrium were in an accurately readable range. The final major consideration in setting up this equilibrium procedure was the demonstration that equilibrium had been achieved. In this work, aliquots of the initial solutions were sealed in vials. Periodically, a vial was opened and the optical density measured. Relative constancy of optical density was taken as an indication that equilibrium had been achieved. The attainment of equilibrium was also shown by approaching the equilibrium point from both directions. In doing this, we used initial solutions of ketone, glycol, and aqueous acid to approach the equilibrium point from one direction and we used initial solutions of ketal and aqueous acid or of ketal, glycol, and aqueous acid to approach the equilibrium point from the other direction.

The following specific experimental procedure was employed in the equilibrium work. The initial components were weighed into a 50 ml. volumetric flask (cal. 49.9 ml. for 30°). Then, the mixture was diluted to volume at 30° with freshly distilled dioxane. Aliquots were introduced into 5 ml. ampoules by means of a special capillary funnel. The solutions in the vials were frozen; nitrogen was bubbled over the frozen solution for a short while and the vials

were sealed while nitrogen was still being introduced into the vials. The sealed vials were put in brown bottles, which were then placed in a constant temperature bath at $30.0 \pm 0.1^\circ$. Periodically (every 1 or 2 weeks) a vial was opened and the optical density of the solution was measured. If the solutions in several successive vials showed a relatively constant optical density, it was assumed that equilibrium had been attained. In a few cases a modification was employed after equilibrium had been attained. After the optical density of the aliquot was measured, three milliliters each of the equilibrium solution and 0.2 N hydrochloric acid were mixed together. The optical density of this solution was measured after a three hour waiting period. The difference between the two readings represented the unhydrolyzed ketal present at equilibrium.

Calculations

Equilibrium constants were calculated in three basic methods. Experience proved that the equilibrium values so obtained were accurate only to plus or minus 25 percent. This accuracy applied both to a given calculation method and to any comparison among the calculation methods.

Method 1. Uncorrected Approach

This is the standard approach for calculating the equilibrium constant based upon the optical density of the solution measured against dioxane, the extinction coefficient of the carbonyl compound, and initial reactant concentrations.

Method 2. Corrected O.D. Approach

The optical density of the reaction was measured against pure dioxane and pure water standards. The difference between the two readings was subtracted from future O.D. measurements against the water standard. The accompanying example demon-

Sept.

O.D. against H ₂ O	0.460
O.D. against dioxane	0.450
<u>difference</u>	<u>0.010</u>

Oct.

Subsequent O.D. against H ₂ O	0.470
<u>difference correction</u>	<u>0.010</u>
corrected O.D.	0.460

strates this method. Once the corrected O.D. was obtained, the calculation procedure was then the same as in the uncorrected approach (Method 1.).

Method 3. Approach Based on Equilibrium Ketal Concentration

The difference between the optical density of the completely hydrolyzed solution and the optical density at equilibrium was used to determine the concentration of ketal at equilibrium. This in turn led to equilibrium constants which should agree with the constants obtained by the preceding methods. Several unusual corrections were applied in the method under discussion. First, an approximate five percent decrease in solution volume occurs in mixing equal volumes of dioxane and dilute acid. Second, the extinction coefficient of a carbonyl compound differs with the solvent medium. In these calculations, it was assumed

that the presence or absence of the glycol did not effect the extinction coefficient of the carbonyl compound. A sample solution of a hypothetical case shows the mode of calculation employed.

Data

Initial ketone concentration	$C_{\text{one}}^{\text{in}}$	0.0
Initial ketal concentration	$C_{\text{al}}^{\text{in}}$	0.6
Reaction volume in dioxane	V_d	3 ml.
Reaction volume in dioxane-water	V_{d-w}	6 ml.
Extinction coefficient for ketone in dioxane	E_d	15
Extinction coefficient for ketone in dioxane-water	E_{d-w}	20
Corrected optical density at equilibrium	O.D. eq.	0.450
Optical density of dioxane-water sol.(completely hydrolyzed)	O.D.unc.	0.637
Absorption correction for dioxane in dioxane-water mixture		0.005

Steps in Determination of Equilibrium Concentration of Ketal

A. The optical density of a solution is inversely proportional to its volume. Therefore, the optical density of the solution, if no contraction had occurred, ($O.D._{\infty}$), would be 0.95 of the observed figure.

$$1. \quad 0.637 \times \frac{95}{100} = 0.605 = O.D._{\infty}$$

Then the absorption correction for the dioxane in the dioxane-water solution is subtracted to give the true optical density at infinity ($O.D._{\infty}^t$) of a ketone.

$$2. \text{O.D.}_{\infty} - \text{correction} = \text{O.D.}_{\infty}^t$$

$$0.605 - 0.005 = 0.600$$

$$\text{O.D.}_{\infty}^t = 0.600$$

B. This optical density of the completely hydrolyzed solution (O.D._{∞}^t) arises from two sources, the ketone present at equilibrium $\left[\text{O.D.}_{\infty}^{\text{one}} (\text{eq.}) \right]$ and the ketone formed from the ketal present at equilibrium $\left[\text{O.D.}_{\infty}^{\text{al}} (\text{eq.}) \right]$.

$$3. \text{O.D.}_{\infty}^t = \text{O.D.}_{\infty}^{\text{al}} (\text{eq.}) + \text{O.D.}_{\infty}^{\text{one}} (\text{eq.})$$

C. Since the optical density of a solution is directly proportional to the extinction coefficient of the absorbing molecule and inversely proportional to the volume of the solution, the accompanying expression leads to evaluation of $\text{O.D.}_{\infty}^{\text{one}} (\text{eq.})$.

$$4. \text{O.D.}_{\infty}^{\text{one}} (\text{eq.}) = \text{O.D. eq.} \times \frac{E_{d-w} \times V_d}{E_d \times V_{d-w}}$$

$$\text{O.D.}_{\infty}^{\text{one}} (\text{eq.}) = 0.450 \times \frac{20}{15} \times \frac{3}{6}$$

$$5. \text{O.D.}_{\infty}^{\text{one}} (\text{eq.}) = 0.300$$

D. By substituting the values obtained in equations 2. and 5. into equation 3., the part of the optical density of the completely hydrolyzed solution due to the ketone formed from the ketal present at equilibrium $\left[\text{O.D.}_{\infty}^{\text{al}} (\text{eq.}) \right]$ is obtained.

$$3. \text{O.D.}_{\infty}^t = \text{O.D.}_{\infty}^{\text{one}} (\text{eq.}) + \text{O.D.}_{\infty}^{\text{al}} (\text{eq.})$$

$$0.6 = 0.3 + \text{O.D.}_{\infty}^{\text{al}} (\text{eq.})$$

$$\text{O.D.}_{\infty}^{\text{al}} (\text{eq.}) = 0.3$$

E. The ketal concentration at equilibrium ($C_{al}^{eq.}$) is equal to the sum of the initial concentration of ketal and ketone times the fraction of the total optical density due to the ketone formed from the ketal present at equilibrium.

$$6. \quad C_{al}^{eq.} = \frac{O.D._{al}^{(eq.)}}{O.D._t} \times [C_{al}^{in} + C_{al}^{in}]$$

$$C_{al}^{eq.} = \frac{0.3}{0.6} \times [0.0 + 0.6]$$

$$C_{al}^{eq.} = 0.3 \text{ M}$$

From the ketal equilibrium concentration and the initial concentrations of reactants, it is now possible to calculate the equilibrium of the reaction as in Method 1.

B. Equilibrium Data and Calculation Results

The ensuing tables contain data and the results of the calculation procedures which were outlined in the preceding section. In the calculations average values of the U.V. readings were used. Comprehensive calculations indicated that the average equilibrium constants so obtained might actually be plus or minus fifteen percent.

TABLE 69
Equilibrium Run 7

Ketal VII

Initial components:

0.5062 g. - ketal VII

Temp. - $30.0 \pm 0.1^\circ$

0.0606 g. - 1 N HCl

U.V. Readings at 287 mu

in 49.9 ml. dioxane

Optical Density Readings

<u>Time/days</u>	<u>21</u>	<u>35</u>	<u>50</u>	<u>80</u>	<u>80</u>
vs. dioxane	0.365	0.403	0.420	0.387	0.394
vs. water	0.404	0.444	0.458	0.447	0.444

Method

1. O.D. at equilibrium	0.395
2. Corrected O.D. at equilibrium	0.405
3. Optical density of equal volumes of dilute acid and equilibrium solution measured against water	0.525

Molar Concentrations of Reactants

	<u>Ketone</u>	<u>Glycol</u>	<u>Water</u>	<u>Ketal</u>	<u>Ke</u>	<u>% Ketone</u>
Initial Conc.	0	0	0.0648	0.0550		
Equil. Conc. Method 1.	0.0258	0.0258	0.0390	0.0292	1.72	47
Equil. Conc. Method 2.	0.0265	0.0265	0.0383	0.0285	1.55	48
Equil. Conc. Method 3.	0.0264	0.0264	0.0384	0.0286	1.57	48

TABLE 70
Equilibrium Run 9

	Initial components:
0.4039 g. - 2,2-dimethyl- 1,3-propanediol
Ketal VII	0.3490 g. - cyclohexanone
Temp. - 30.0 ± 0.1°	0.0329 g. - 1 N HCl
U.V. Readings at 287 mμ	In 49.9 ml. dioxane

Optical Density Readings

<u>Time/days</u>	<u>20</u>	<u>33</u>	<u>49</u>	<u>80</u>	<u>92</u>
vs. dioxane	0.468	0.478	0.487	0.483	0.485
vs. water	0.504	0.514	0.528	0.535	0.528

Method

1. O.D. at equilibrium	0.483
2. Corrected O.D. at equilibrium	0.496

Molar Concentrations of Reactants

	<u>Ketone</u>	<u>Glycol</u>	<u>Water</u>	<u>Ketal</u>	<u>Ke</u>	<u>% Ketone</u>
Initial Conc.	0.0711	0.0776	0.0352	0		
Equil. Conc. Method 1.	0.0315	0.0380	0.0748	0.0396	2.48	44
Equil. Conc. Method 2.	0.0325	0.0390	0.0738	0.0386	2.25	46

TABLE 71
EQUILIBRIUM RUN 16

Ketal VII

Temp. - $30.0 \pm 0.1^\circ$

U.V. Readings at 287 mμ

Initial components:

0.6251 g. - ketal VII

0.0724 g. - 1 N HCl

in 49.9 ml. dioxane

Optical Density Readings

<u>Time/days</u>	<u>4</u>	<u>12</u>	<u>22</u>	<u>53</u>	<u>64</u>
vs. dioxane	0.235	0.423	0.414	0.413	0.406
vs. water	0.244	0.460	0.457		0.460

Method

1. O.D. at equilibrium	0.415
2. Corrected O.D. at equilibrium	0.449
3. Optical density of equal volumes of dilute acid and equilibrium solution measured against water	0.626

Molar Concentrations of Reactants

	<u>Ketone</u>	<u>Glycol</u>	<u>Water</u>	<u>Ketal</u>	<u>Ke</u>	<u>% Ketone</u>
Initial Conc.	0	0	0.0774	0.0679		
Equil. Conc. Method 1.	0.0271	0.0271	0.503	0.408	2.8	40
Equil. Conc. Method 2.	0.0294	0.0294	0.0480	0.0385	2.1	43
Equil. Conc.	0.0294	0.0294	0.0480	0.0385	2.1	43

TABLE 72
EQUILIBRIUM RUN 10

Ketal VIII

Initial components:

0.4051 g. - 2,2-dimethyl
1,3-propanediol

0.3525 g. - cyclopentanone

Temp. - $30.0 \pm 0.1^\circ$

0.0389 g. - 1 N HCl

U.V. Readings at 287 mu

in 49.9 ml. dioxane

Optical Density Readings

<u>Time/days</u>	<u>14</u>	<u>28</u>	<u>34</u>	<u>44</u>	<u>75</u>
vs. dioxane	1.098	1.147	1.122	1.148	1.129
vs. water	1.114	1.164	1.144	1.162	1.148

Method

1. O.D. at equilibrium	1.136
2. Corrected O.D. at equilibrium	1.138

Molar Concentrations of Reactants

	<u>Ketone</u>	<u>Glycol</u>	<u>Water</u>	<u>Ketal</u>	<u>Ke</u>	<u>% Ketone</u>
Initial Conc.	0.0837	0.0778	0.0416	0		
Equil. Conc. Method 1.	0.0688	0.0629	0.0565	0.0149	0.195	82
Equil. Conc. Method 2.	0.0690	0.0631	0.0563	0.0147	0.189	82

TABLE 73
EQUILIBRIUM RUN 14

Temp. - $30.0 \pm 0.1^\circ$

U.V. Readings at 287 mu

Initial components:

0.5578 g. - ketal VIII

2.0237 g. - 2,2-dimethyl-
1,3-propanediol

0.0674 g. - 1 N HCl

in 49.9 ml. dioxane

Optical Density Readings

<u>Time/days</u>	<u>7</u>	<u>13</u>	<u>23</u>	<u>54</u>	<u>65</u>
vs. dioxane	0.429	0.395	0.417	0.377	0.403
vs. water	0.465	0.434	0.452		0.447

Method

1. O.D. at equilibrium	0.400
2. Corrected O.D. at equilibrium	0.414
3. Optical density of equal volumes of dilute acid and equilibrium solution measured against water	0.668

Molar Concentrations of Reactants

	<u>Ketone</u>	<u>Glycol</u>	<u>Water</u>	<u>Ketal</u>	<u>Ke</u>	<u>% Ketone</u>
Initial Conc.	0	0.389	0.0721	0.0655		
Equil. Conc. Method 1.	0.0242	0.413	0.479	0.413	0.20	37
Equil. Conc. Method 2.	0.0251	0.414	0.0470	0.0404	0.183	39
Equil. Conc. Method 3.	0.0244	0.413	0.0477	0.0411	0.194	38

TABLE 74
EQUILIBRIUM RUN 15

Ketal VIII

Initial components:

0.3275 g. - cyclopentanone

2.3637 g. - 2,2-dimethyl-
1,3-propanediolTemp. - $30.0 \pm 0.1^\circ$

0.0366 g. - 1 N HCl

U.V. Readings at 287 mu

in 49.9 ml. dioxane

Optical Density Readings

<u>Time/days</u>	<u>6</u>	<u>11</u>	<u>21</u>	<u>22</u>	<u>53</u>	<u>64</u>
vs. dioxane	0.616	0.627	0.597	0.583	0.589	0.601
vs. water	0.638	0.651	0.629	0.616		0.624

Method

1. O.D. at equilibrium 0.592
2. Corrected O.D. at equilibrium 0.601
3. Optical density of equal volumes of dilute acid and equilibrium solution measured against water 0.785

Molar Concentrations of Reactants

	<u>Ketone</u>	<u>Glycol</u>	<u>Water</u>	<u>Ketal</u>	<u>Ke</u>	<u>% Ketone</u>
Initial Conc.	0.0779	0.454	0.0391	0		
Equil. Conc. Method 1.	0.359	0.412	0.811	0.420	0.23	46
Equil. Conc. Method 2.	0.0364	0.412	0.0806	0.0415	0.22	47
Equil. Conc. Method 3.	0.0355	0.412	0.0815	0.0424	0.24	46

TABLE 75
EQUILIBRIUM RUN 12

Ketal IX

Initial components:

0.2684 g. - 2-methylcyclopentanone

3.2060 g. - 2,2-dimethyl-1,3-propanediol

Temp. - $30.0 \pm 0.1^\circ$

0.0325 g. - 1 N HCl

U.V. Readings at 287 mu

in 49.9 ml. dioxane

Optical Density Readings

<u>Time/days</u>	<u>7</u>	<u>14</u>	<u>24</u>	<u>25</u>	<u>56</u>	<u>68</u>
vs. dioxane	0.635	0.615	0.595	0.617	0.585	0.586
vs. water	0.647	0.642	0.640	0.652	0.643	0.631

Method

1. O.D. at equilibrium	0.610
2. Corrected O.D. at equilibrium	0.625
3. Optical density of equal volumes of dilute acid and equilibrium solution measured against water.	0.626

Molar Concentrations of Reactants

	<u>Ketone</u>	<u>Glycol</u>	<u>Water</u>	<u>Ketal</u>	<u>Ke</u>	<u>% Ketone</u>
Initial Conc.	0.547	0.6156	0.0361	0		
Equil. Conc. Method 1.	0.0368	0.598	0.0540	0.0179	0.045	67
Equil. Conc. Method 2.	0.0377	0.599	0.0531	0.0170	0.040	69
Equil. Conc. Method 3.	0.0359	0.597	0.0549	0.0188	0.048	66

TABLE 76
EQUILIBRIUM RUN 13

Ketal IX

Initial components:

0.7309 g. - ketal IX

3.2482 g. - 2,2-dimethyl-
1,3-propanediolTemp. - $30.0 \pm 0.1^\circ$

0.0785 g. - 1 N HCl

U.V. Readings at 287 mu

in 49.9 ml. dioxane

Optical Density Readings

<u>Time/days</u>	<u>6</u>	<u>13</u>	<u>23</u>	<u>24</u>	<u>66</u>
vs. dioxane	0.830	0.810	0.783	0.754	0.794
vs. water	0.855	0.890	0.870	0.868	0.852

Method

1. O.D. at equilibrium	0.807
2. Corrected O.D. at equilibrium	0.827
3. Optical density of equal volumes of dilute acid and equilibrium solution measured against water	0.920

Molar Concentrations of Reactants

	<u>Ketone</u>	<u>Glycol</u>	<u>Water</u>	<u>Ketal</u>	<u>Ke</u>	<u>% Ketone</u>
Initial Conc.	0	0.624	0.0840	0.0793		
Equil. Conc. Method 1.	0.0486	0.673	0.0354	0.0307	0.034	61
Equil. Conc. Method 2.	0.0498	0.674	0.0342	0.0295	0.030	63
Equil. Conc. Method 3.	0.0468	0.671	0.0372	0.0325	0.0385	59

Key to Symbols for Table 77

Optical density of dioxane-water solution	$O.D._{\infty}^{unc.}$
Optical density of solution, if no contraction had occurred	$O.D._{\infty}$
Absorption correction for dioxane	corr. due
True optical density at infinity	$O.D._{\infty}^t$
Corrected optical density at equilibrium	$O.D._{eq.}$
Extinction coefficient for ketone in dioxane-water	E_{d-w}
Extinction coefficient for ketone in dioxane	E_d
Part of $O.D._{\infty}^t$ due to ketone present at equilibrium	$O.D._{\infty}^{one (eq.)}$
Part of $O.D._{\infty}^t$ due to ketone formed from the ketal present at equilibrium	$O.D._{\infty}^{al (eq.)}$
Initial concentration of ketone	C_{one}^{in}
Initial concentration of ketal	C_{al}^{in}
Equilibrium concentration of ketal	$C_{al}^{eq.}$

TABLE 77

VALUES OF INTERMEDIATE VARIABLES FOR THE CALCULATION
OF THE EQUILIBRIUM CONCENTRATION OF KETAL
VIA METHOD 3

Ketal	VII	VII	VIII	VIII	IX	IX
Equilibrium Run	7	16	14	15	12	13
$O.D._{\infty}^{unc.}$	0.526	0.626	0.668	0.785	0.622	0.920
$O.D._{\infty}$	0.499	0.595	0.635	0.749	0.591	0.874
corr. due	0.020	0.005	0.018	0.011	0.006	0.014
$O.D._{\infty}^t$	0.479	0.590	0.617	0.738	0.585	0.860
$O.D._{eq.}$	0.405	0.449	0.414	0.605	0.623	0.823
E_{d-w}	17.4	17.4	18.3	18.3	20.5	20.5
E_d	15.3	15.3	18.5	16.5	16.6	16.6
$O.D._{\infty}^{one} (eq.)$	0.230	0.255	0.230	0.336	0.385	0.508
$O.D._{\infty}^{al} (eq.)$	0.259	0.335	0.387	0.402	0.201	0.352
C_{one}^{in}	0.00	0.00	0.0	0.0779	0.0547	0.0
C_{al}^{in}	0.055	0.0679	0.0655	0.0	0.0	0.0793
$C_{al}^{eq.}$	0.0286	0.0385	0.0411	0.0424	0.0187	0.0325

TABLE 78
SUMMARY OF EQUILIBRIUM DATA

<u>Equilibrium Run</u>	<u>Ketal</u>	<u>Ke Values</u>			<u>Aver.</u>
		<u>1st Method</u>	<u>2nd Method</u>	<u>3rd Method</u>	
7	VII	1.72	1.55	1.57	1.62
9	VII	2.48	2.25		2.36
16	VII	2.8	2.1	2.1	2.3
10	VIII	0.195	0.189		0.192
14	VIII	0.20	0.183	0.194	0.192
15	VIII	0.23	0.22	0.24	0.23
12	IX	0.045	0.040	0.048	0.044
13	IX	0.034	0.030	0.0385	0.034

<u>Ketal</u>	<u>Ke Overall Aver.</u>
VII	2.1
VIII	0.20
IX	0.039

C. Discussion of Equilibrium Values

Unfortunately, the equilibrium work is not as broad in scope as the kinetic hydrolysis work. Certain comparisons which were made in the hydrolysis work cannot be made on the equilibrium work due to the lack of information. However, we would like to comment on the variation of equilibrium constant with change in cyclic ketone and on the use of the equilibrium data for devising a method for separation of cyclic ketones.

The accompanying reactions and the approximate equilibrium constants sum up the equilibrium work at 30°. At the onset it

<u>Reaction #</u>	<u>Reaction</u>	<u>Approx. Ke</u>
7		2.
8		0.2
9		0.04

should be admitted that the values are accurate only to plus or minus twenty percent. The experimental procedure employed does not give very good precision but perhaps modifications of procedure might remove some sources of error. The standard dioxane might be sealed in vials. Solvent entrainment from the frozen solution by the nitrogen stream might be standardized or prevented.

Finally, the effect, if any, of the free glycol on the extinction coefficients of the carbonyl compounds should be determined.

The values of the equilibrium constants, themselves, are in the order anticipated. The generalization of Brown, Brewster, and Shechter¹ predicts that the equilibrium would be further shifted to the left with cyclopentanone than with cyclohexanone. The reason for this is that, other things being equal, a double bond exocyclic to a cyclopentane ring is favored relative to a double bond exocyclic to a cyclohexane ring. A shift to the left going from cyclohexane system to cyclopentane system would be reflected in a lower equilibrium constant. The results show that the anticipated shift has occurred. It is noteworthy that the equilibrium constant decreases in the same order as the hydrolysis constant increases. Other cases of this phenomena are to be noted in the literature survey. The accompanying hydrolysis and equilibrium constants are excellent examples of the question in point.

	<u>Hydrolysis Constants^{3,4} 25°</u>	<u>Equilibrium Constants² 18°</u>
$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C}=\text{O} + \begin{array}{c} \text{HO}-\text{CH}_2 \\ \\ \text{HO}-\text{CH}_2 \end{array} \rightleftharpoons \begin{array}{c} \text{CH}_3 \\ \\ \text{C} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \end{array} + \text{H}_2\text{O} \end{array}$	8.74	0.14
$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C}=\text{O} + \begin{array}{c} \text{HO}-\text{CH}_2 \\ \\ \text{HO}-\text{CH}_2 \end{array} \rightleftharpoons \begin{array}{c} \text{CH}_3 \\ \\ \text{C} \begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array} \end{array} + \text{H}_2\text{O} \end{array}$	187.0	0.026

¹ H.C. Brown, et al., J. Am. Chem. Soc., 76, 467 (1954).

² P.H. Hermans, Z. physik. Chem., 113, 337 (1924).

³ R. Leutner, Monatsh. Chem. 66, 222 (1935).

⁴ O. Ceder, Arkiv Kemi, 6, 523 (1954).

If one neglects the change in solvent medium, it is seen

<u>Reaction #</u>	7	8	9
rel. hydrolysis constant	1	8.02	11.7
rel. equilibrium constant	1	0.1	0.02

that the values found for the hydrolysis and equilibrium constants indicate that ketal formation is faster with cyclohexanone than with 2-methylcyclopentanone. This, too, is something which Brown, Brewster, and Shechter's generalization would predict.¹ The influences, then, which contribute to greater hydrolysis rates in the ketals tend to build up larger concentrations of free ketone under equilibrium conditions.

Equilibrium constants were determined for the reaction between 2,2-dimethyl-1,3-propanediol and the ketones, cyclohexanone, cyclopentanone, and 2-methylcyclopentanone. The rates of hydrolysis for ketals derived from the above glycol and ketones were also measured. The experimental results showed that preferential blocking of the 6-membered ring ketone of a polycarbonyl compound containing a 6-membered ring ketone and a 5-membered ring ketone may be achieved by either a kinetic or equilibrium approach. In the equilibrium approach (or method), the molar ratio of glycol to polycarbonyl compound should be selected so that at equilibrium most of the 6-membered ketone will be present as a cyclic ketal and most of the 5-membered ketone will exist as the free ketone.

¹ H.C. Brown, et al., J.Am.Chem.Soc., 76, 467 (1954).

In kinetic method, hydrolysis of a diketal derived from a polycarbonyl compound containing a 6-membered ring ketone and a 5-membered ring ketone should be stopped when most of the 5-membered ring ketone is present as a free ketone and most of the 6-membered ring ketone is present as a cyclic ketal. The objective of each method is to find the conditions under which the ratio of ketal formed from the 6-membered ring ketone to the ketal formed from 5-membered ring ketone will be a maximum. The determination of these conditions and the comparative evaluation of the two methods require lengthy calculations. For this reason, the whole problem of conditions and comparative reactivity will be taken up in a later chapter of this dissertation. For the present, we will only say that there is a good base for selective ketal formation via an equilibrium approach.

In summary, the equilibrium results are consistent with what current knowledge of 5-membered and 6-membered ring ketones would predict. As a result of our work, an equilibrium method for selective ketal formation in the case of certain ketone type would seem to hold promise in the steroid field.

VI: STUDIES ON THE FORMATION OF CYCLIC KETALS

A. Introduction, Procedure, and Data

The major interests in this work were the hydrolysis and equilibrium studies. As such, a large amount of effort was not expended on the kinetics of formation. Rather, a few simple experiments were performed in which the rate of water formation was followed in the accompanying reaction. The experimental pro-

cedure employed was the standard method for ketal preparation.

Namely, ketone and glycol reacted in acid medium and the benzene azeotrope was used to remove the water formed in the reaction.

The ketals I, II, VII, and VIII were included in these studies,

I

II

VII

VIII

Early runs showed that only qualitative information was to be obtained by this approach.

The following specific procedure was employed in this work. Equal molar amounts of ketone and glycol were weighed into a 100 ml. r.b. flask. Then, 12-20 ml. of benzene, boiling chips, and the acid catalyst (solid or in solution) were added to the flask. The flask was then attached to a Dean-Stark water trap and condenser. The trap had been previously filled with benzene. Heat was applied at about the same rate in all cases. Boiling ensued in seven to ten minutes. The amount of water removed by way of azeotrope was measured at fixed time intervals. After the reaction was completed, the volume of the reaction mixture was measured.

The data reported for a given run includes concentration of reactants, relative acid concentrations, and half life time of the reaction. Inspection of these values afforded a qualitative idea of the relative ease of formation of these ketals. The inspection was based on the assumption that the rate of ketal formation is first order with respect to ketone concentration, with respect to acid concentration, and with respect to alcohol (OH group) concentration. Since the acid concentration remains constant, the following rate equation for a second order reaction should hold.¹

$$1. \frac{1}{C} - \frac{1}{C_0} = k' t$$

C = conc. of reactants
 C₀ = initial conc. of reactants
 k' = apparent rate constant
 t = time

¹ A. Frost and R. Pearson, "Kinetics and Mechanism," John Wiley and Sons, New York, N.Y., 1953, p.13.

By substituting in the values, $C = \frac{C_0}{2}$; $t = t^{1/2}$, (1/2 life time of reaction), and rearranging, we obtain equation 2.

$$2. \quad k^1 = \frac{1}{t^{1/2} C_0}$$

The relationship between the apparent rate constant (k^1) and true rate constant (k) is expressed in equation 3.

$$3. \quad k^1 = k A \quad A = \text{acid concentration}$$

Set equations 2. and 3. equal, and clear fractions to get equation 4.

$$4. \quad k = \frac{1}{t^{1/2} C_0 A}$$

Therefore, the size of the rate constant, k , is inversely proportional to the product of the half life time, the initial concentration of the reactants, and the acid concentration.

TABLE 79

DATA ON EASE OF FORMATION OF CYCLIC KETALS

<u>Run</u>	<u>Ketal</u>	<u>Molar Conc. of Reaction</u>	<u>Relative Acid Concentration</u>	<u>Half Life- time/seconds</u>
<u>First Series</u>				
3	VII	4.33	1.00	630
5	VIII	4.18	.97	1200
6	II	4.65	1.13	1920
<u>Second Series</u>				
19	VII	3.80	1.00	690
15	I	4.72	1.24	780

B. Discussion on Ease of Formation of Cyclic Ketals

In this discussion of the ease of formation of cyclic ketals we will include not only information from the data just presented, but also any useful information that can be extrapolated from other phases of this research.

Inspection of Table 79 shows the following relationships with respect to ease of formation of the cyclic ketal. This scheme

indicates that comparable ketals are formed slightly more easily by reaction of ketones with 2,2-dimethyl-1,3-propanediol than by reaction with ethylene glycol. The difference in reactivity, however, is so small that there is almost equivalence in reactivity. Also, we see indicated here that comparable ketals form more readily from cyclohexanone than from cyclopentanone. This has been predicted by the generalization concerning the relative rates of reactivity of these ketones.¹ However, the difference in reactivity is somewhat less than would be anticipated. Before passing on, we would like to reemphasize that these are only qualitative data.

¹ H.C. Brown, et al., J.Am.Chem.Soc., 76, 467 (1954).

Another approach is to calculate the relative rate of ketal formation from appropriate equilibrium and hydrolysis rate constants. This can be done for the ketals derived from 2,2-dimethyl-1,3-propanediol if one assumes that the difference in solvent medium would not effect the relative values too greatly. The equilibrium constant is related to the formation and hydrolysis rate constants in the following manner. By substituting in the accompanying equilibrium and hydrolysis constants, we obtain the

$$K_e = \frac{(\text{water}) (\text{ketal})}{(\text{ketone}) (\text{glycol})} = \frac{k_1 (\text{formation rate constant})}{k_{-1} (\text{hydrolysis rate constant})}$$

following rates of formation in Table 80, if the formation of ketal VII is taken as a standard of one.

TABLE 80

RELATIONSHIP BETWEEN EQUILIBRIUM, RELATIVE
HYDROLYSIS CONSTANTS AND RELATIVE FORMATION CONSTANTS

Reaction	VII	VIII	IX
Ketal
Equilibrium constant	2.	0.2	0.04
Relative hydrolysis rate constant	1.00	8.2	11.46
Relative formation rate constant	1.00	0.82	0.23

The result indicates that cyclohexanone forms a cyclic ketal more readily than cyclopentanone which in turn is more reactive than

2-methylcyclopentanone. This order of reactivity for ketal formation might well have been expected since it is just the reverse of the order of reactivity for ketal hydrolysis. The difference in the relative rates of ketal formation is not nearly as large as the difference in the relative rates of ketal hydrolysis. Furthermore, this information suggests that separation of these or similar ketones by selective ketal formation is not feasible.

In the synthetic work ketal formation took place readily in all cases except for those ketals derived from 1,3-propanediol. These ketals formed very slowly and in comparatively poor yields. Interestingly enough, the ketals derived from 1,3-propanediol hydrolyzed at least ten times faster than ketals derived from any other glycol.

In summary, with respect to cyclic ketal formation, cyclohexanone is more reactive than cyclopentanone, which in turn is more reactive than 2-methylcyclopentanone. Ketones undergo ketalization more readily with 2,2-dimethyl-1,3-propanediol than with ethylene glycol. However, on a practical synthetic basis, there is almost no difference in reactivity. Finally, ketal formation occurs much less readily with 1,3-propanediol than it occurs with ethylene glycol or 2,2-dialkyl-1,3-propanediols.

VII: THEORETICAL MATHEMATICAL EVALUATION OF THE KINETIC AND EQUILIBRIUM METHODS

A. Introduction

In this section we will undertake to find out and compare the theoretical product ratios obtainable by applying selective kinetic or equilibrium reaction methods to a hypothetical dicarbonyl compound and its cyclic ketal derivatives. This dicarbonyl compound contains a 6-membered ring ketone and a 5-membered ring ketone with an alpha methyl group. These ketone and ketal groups are considered to be sufficiently far apart so that each has no influence on the reactivity of the other. These calculations can also be applied to a mixture of 2-methylcyclopentanone and cyclohexanone. This mathematical analysis will cover both the kinetic and equilibrium approaches to this problem.

The hypothetical polycarbonyl compound (A) and mono and di-ketal type compounds (B, C, and D) which can arise on ketalization of compound A are the following.

R varies according to glycol used in preparing ketals

After any reaction between the polycarbonyl compound (A) and glycol, or diketal (D) and water, each of the four compounds (A, B, C, and D) will be present. The kinetic and equilibrium constants which we have determined indicate that under certain conditions most of the 6-membered ring carbonyl group will be present as a ketal and most of the 5-membered ring carbonyl will be present as the free ketone. Furthermore, ketone groups may be quickly separated from a ketal by reaction with a ketone reagent in a basic medium or by any other convenient way. Therefore, compound B can be looked upon as a desired product, compounds A and C can be classified as interfering side products, and compound D as an inert and recoverable side product. With these considerations in mind, we will now take a closer individual look at the kinetic and equilibrium approaches to selective separation of 5-membered and 6-membered ring ketones.

B. Theoretical Analysis of the Selective Hydrolysis Method

In a previous section of this dissertation, the following relative hydrolysis ratios were reported.

<u>Ratio of rates</u>	<u>Ketals derived from -</u>		
	<u>ethylene glycol</u>	<u>2,2-dimethyl-1,3-propanediol</u>	<u>2,2-diethyl 1,3-propanediol</u>
8.02	11.46	12.7

These ratios express the relationship of the relative rate of hydrolysis of ketal derived from 2-methylcyclopentanone to that of a ketal derived from cyclohexanone. These relative rate ratios should also apply to the hydrolysis of the ketals derived from the 5- and 6-membered ring ketones in the hypothetical compound D, since by definition the ketone groups are sufficiently far apart to react independently of each other.

Let us examine the hydrolysis of the diketal, compound type D, derived from ethylene glycol (D1); 2,2-dimethyl-1,3-propanediol (D2); and 2,2-diethyl-1,3-propanediol (D3). Suppose that a one molar

solution of a diketal is hydrolyzed in an acidic dioxane-water medium at 30°. Each ketal moiety derived from the 6-membered ring ketone and 5-membered ring ketone would hydrolyze at its own rate which would exhibit pseudo-first order kinetics. Therefore, plots of the logarithm of the concentration of each ketal type (derived from 6-membered ring ketone or 5-membered ring ketone) against

time would give a straight line. The concentrations of each ketal moiety could then be determined at any time, since each point on a line specifies a time and the logarithm of the concentration of the ketal moiety.

The next consideration is the method of plotting the lines. A point and a slope are sufficient to determine a line. The logarithm of the initial ketal concentration (1.00 molar) was used to specify a point for each ketal moiety. The time unit selected for the time ordinate was the time required for the hydrolysis of the ketal derived from the 6-membered ring ketone to be 90 percent completed. This corresponds to a unit change in the log ketal concentration ordinate per unit change in the time ordinate. By definition then, the line slope for the ketal moieties derived from the 6-membered ring ketone is equal to negative one. The slopes for the hydrolysis of the corresponding ketal moiety derived from the 5-membered ring ketone are the appropriate ratio values reported previously. For example, the slope for the hydrolysis of ketal derived from the 5-membered ring ketone and ethylene glycol is -8.02.

This entire approach can be justified on the following basis. One way is that it is theoretically possible to increase the catalyst concentration so that the slope of the ketal moiety derived from the 6-membered ring ketone would be actually equal to one in each case. Another way is to assume that the hydrolysis slope for the ketal derived from the 6-membered ring ketone of

compound A and ethylene glycol would be equal to the hydrolysis slope (0.00050/minutes at 30°/70-30 dioxane-water/0.003 N HCl)

found for ketal (I). Since the log (ketal concentration) value decreases

0.00050 units per minute, the log (ketal concentration) would decrease 1.00 unit in 2000 minutes. By setting the unit time at 2000 minutes, we arbitrarily fix the slope of the line equal to negative one. An analogous approach sets the unit time as 990 minutes for hydrolysis of the ketal moiety derived from the 6-membered ring ketone of compound A and 2,2-dimethyl-1,3-propanediol, and a unit time of 2248 minutes for the hydrolysis of the ketal moiety derived from the 6-membered ring ketone of compound A and 2,2-diethyl-1,3-propanediol. While the immediately preceding material would give a more concrete time basis for the unit time, a better approach is that by which the unit slope is arbitrarily defined as the time required for the hydrolysis of the ketal derived from the 6-membered ring ketone to be 90 percent complete. This approach seemed simpler and more general, and the only assumption is that the relative hydrolysis rates are the same for structurally analogous ketals.

Figure 3. shows the proper plots for the hydrolysis of ketals derived from dicarbonyl compound A and the glycols, ethylene glycol, 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol. From this graph it is possible to determine the relative amounts of the ketals derived from the 6-membered ring ketone and the

Key to Figure 3.

Time Ordinate

The time required for each ketal derived from the 6-membered ring ketone to be 90 percent hydrolyzed is from 0.0 to 1.0 on the time ordinate. From 0.0 to 0.1 on the time ordinate is equal to 200 minutes for ketal I, 99 minutes for ketal VII, and 274.8 minutes for ketal X.

Line Slopes for Ketals

<u>Ketal Moiety</u>	<u>Ketal #</u>	<u>Slope</u>
I	_____
VII
X
III	_____
IX	_____
XII	_____

Graph Points

-O- Points at which ketals derived from 5-membered ring ketones are 90 percent hydrolyzed.

FIGURE 3

RELATIVE KETAL CONCENTRATION DURING KETAL HYDROLYSIS

5-membered ring ketone. For example, when the ketal formed from the cyclopentanone moiety is 90 percent hydrolyzed [$\log (\text{ketal conc.}) = -1.00$], the ketal formed from the cyclohexanone moiety is 25.6 percent hydrolyzed [$\log (\text{ketal conc.}) = -0.13$] in the case of the ethylene glycol ketal, 19 percent hydrolyzed [$\log (\text{ketal conc.}) = -0.092$] in the case of 2,2-dimethyl-1,3-propanediol ketal, and only 17 percent hydrolyzed [$\log (\text{ketal conc.}) = -0.081$] in the case of 2,2-diethyl-1,3-propanediol ketal. Table 81, obtained from the graph, demonstrates that more selective hydrolysis occurs with ketal derived from the substituted 1,3-propanediols than with ketals derived from ethylene glycol.

Table 81 was obtained by finding the points at which the hydrolysis of the ketal derived from the 6-membered ring ketone

TABLE 81

RELATIVE % HYDROLYSIS WITH KETALS
DERIVED FROM VARIOUS GLYCOLS

<u>Ketals derived from the 6-membered ring ketone</u>	<u>Ketals derived from the 5-membered ring ketone</u>		
<u>standard for all glycols</u>	<u>ethylene glycol</u>	<u>2,2-dimethyl- 1,3-propanediol</u>	<u>2,2-diethyl- 1,3-propanediol</u>
0	0	0	0
5	34	44	49
10	54	68	71
15	73	85	88
20	82	91	93.5

was 0, 5, 10, 15, and 20 percent completed, and then finding the corresponding hydrolysis that had taken place in the ketal derived

from the 5-membered ring ketone. For example, the ketal derived from the 6-membered ring ketone and any glycol is 5 percent hydrolyzed when the ketal concentration (cyclohexanone ketal moiety) is 0.95 molar and the log of the ketal concentration is equal to -0.222. At the same time, the log of the concentration of the ketal derived from ethylene glycol and the 5-membered ring ketone is -0.18. This corresponds to a concentration of 0.66 moles and 34 percent hydrolysis for the ketal moiety derived from the 5-membered ring ketone and ethylene glycol. Analogous calculations were made to obtain the values in Table 81.

From Table 81 a simple statistical approach allows one to calculate the product composition (A, B, C, and D). This was done for the hydrolysis of the ketal derived from dicarbonyl compound A and 2,2-dimethyl-1,3-propanediol. Table 82 was formulated in the following manner. It is seen in Table 81 that when the ketal derived from the 6-membered ring ketone is 5 percent hydrolyzed, the ketal derived from the 5-membered ring ketone is 44 percent hydrolyzed. The percent of Compound A equals 5 percent X 44 percent, or 2.2

percent. Since 95 percent of the 6-membered ring ketone is still blocked, 95 percent X 44 percent, or 41.8 percent, is equal to the

percent concentration of compound B.

It is noticed that the sum of A and B is equal to 44 percent or the amount which the ketal derived from the 5-membered ring ketone is hydrolyzed. Analogous calculations yielded the results shown in Table 82.

Products A, B, C, and D.

TABLE 82

PRODUCT COMPOSITION FOR SELECTIVE HYDROLYSIS OF DIKETAL DERIVED FROM COMPOUND A AND 2,2-DIMETHYL-1,3-PROPANEDIOL

Product	Percent hydrolysis of the cyclohexanone ketal moiety			
	5%	10%	15%	20%
B2	41.8	61.2	72.2	72.8
A2	2.2	6.8	12.8	18.2
C2	2.8	3.2	2.2	1.8
D2	53.2	28.8	12.8	7.2

Table 82 shows the relative percentages of desired product (B), undesired side products (A and C), and starting diketal (inert), which would be present if the reaction of the ketal derived from 2,2-dimethyl-1,3-propanediol and compound A was stopped at various points. Similar data obtained in an analogous manner for the hydrolysis of a ketal derived from compound A and 2,2-diethyl-1,3-propanediol in Table 83. It is for the research worker to decide the point at which the reaction should be stopped. The choice is between maximum yield of the desired product (B) and a larger quantity of undesirable side products (A, C) or less than maximum yield of

TABLE 83

PRODUCT COMPOSITION FOR SELECTIVE HYDROLYSIS OF A DIKETAL DERIVED FROM COMPOUND A AND 2,2-DIETHYL-1,3-PROPANEDIOL

Product	Percent hydrolysis of the cyclohexanone ketal moiety			
	5%	10%	15%	20%
B3	46.5	63.9	74.8	74.8
A3	2.4	7.1	13.2	18.7
C3	2.6	2.9	1.8	1.3
D3	48.5	26.1	10.2	5.2

desired product and a smaller quantity of undesirable side products.

A comparison with the equilibrium method will be made shortly.

C. Theoretical Analysis of the Equilibrium Approach

The accompanying average equilibrium constants were reported

in a previous section of this dissertation. Let us imagine a molar solution of a hypothetical dicarbonyl compound

(A) which contains both a 6-membered ring ketone and a 5-membered ring ketone with an alpha methyl

group. A solution which is 1 molar both with respect to dicarbonyl compound A and 2,2-dimethyl-1,3-propanediol is allowed to go to equilibrium in an acidic dioxane medium. What are the relative amounts of blocked and unblocked 6-membered and 5-membered ring ketones present at equilibrium? Furthermore, what amount of

glycol will give the most advantageous separation of 5-membered and 6-membered ring ketones ?

Calculation Method:

	<u>Molar Concentration</u>
Initial concentration of 6-membered ring ketone	1
Initial concentration of 5-membered ring ketone	1
Initial concentration of cyclohexanone ketal	0
Initial concentration of cyclopentanone ketal	0
Initial concentration of glycol	1
Initial concentration of water	0

<u>Equilibrium Concentrations</u>	<u>Molarity</u>
cyclohexanone ketal	x
cyclopentanone ketal	y
6-membered ring ketone	1-x
5-membered ring ketone	1-y
water	x+y
glycol	1-(x+y)

$$1. \quad K_{e6} = \frac{(\text{cyclohexanone ketal}) (\text{water})}{(\text{6-membered ring ketone}) (\text{glycol})} = 2.$$

$$2. \quad K_{e5} = \frac{(\text{cyclopentanone ketal}) (\text{water})}{(\text{5-membered ring ketone}) (\text{glycol})} = 0.04$$

$$3. \quad \frac{(x) (x+y)}{(1-x) 1-(x+y)} = 2.$$

$$4. \quad \frac{(y) (x+y)}{(1-y) 1-(x+y)} = 0.04$$

By dividing equation 4. into equation 3., we obtain equation 5.

$$5. \quad y = \frac{x}{50 - 49x}$$

Solve equation 3. for y.

$$6. \quad y = \frac{x^2 - 49x + 2}{2 - x}$$

Since equations 5. and 6. are equal to the same thing, they may be set equal to each other.

$$7. \quad \frac{x}{50 - 49x} = \frac{x^2 - 4x + 2}{2 - x}$$

Simplify, and set equal to zero.

$$8. \quad 49x^3 - 247x^2 + 300x - 100 = 0$$

Divide both sides of the equation by 49.

$$9. \quad x^3 - 5.0408x^2 + 6.1224x - 2.0408 = 0$$

Cubic equation (9.) was solved by Horner's method, which is a method for approximating the real roots of an algebraic equation. For an equation such as this, which has a real root between 0 and 1, the essential steps for solving are the following.

- a. Locate the positive root between two successive tenths.
- b. Transform the equation into an equation whose roots are decreased by the smaller of these tenths.
- c. Locate the root between two successive hundredths.
- d. Transform the equation into an equation whose roots are decreased by the smaller of these hundredths.
- e. The above two-step procedure is repeated for the thousandths and ten-thousandths, or until the root has been measured to sufficient accuracy.

Synthetic division is generally used to expedite the work of substituting values for the variable. The positive root is located between the two successive tenths wherein a change in the sign of the final remainder occurs on synthetic division. Thus for equation 9. the root falls between 0.5 and 0.6.

$$9. \quad x^3 - 5.0408x^2 + 6.1224x - 2.0408 = 0$$

$$\begin{array}{r} 1 - 5.0408 + 6.1224 - 2.0408 \quad | \quad 0.5 \\ + 0.5 \quad - 2.2704 + 1.9260 \\ \hline 1 - 4.5408 + 3.8520 - 0.1148 \end{array}$$

↑

$$\begin{array}{r} 1 - 5.0408 + 6.1224 - 2.0408 \quad | \quad 0.6 \\ + 0.6 \quad - 2.6645 + 2.0747 \\ \hline 1 - 4.4408 + 3.4579 + 0.0339 \end{array}$$

↑

After the first few steps, roots can be located very quickly by solving the equation obtained by dropping the terms of higher degree than the first. The real root then is the total amount by which the roots of the original equation were reduced plus the remainder which is found by solving the equation obtained by dropping the terms of higher degree than the first from the final transformed equation.

The transformations for solving equation 9. are now shown.

$$9. \quad x^3 - 5.0408x^2 + 6.1224x - 2.0408 = 0$$

First Transformation

$$\begin{array}{r}
 1 - 5.0408 + 6.1224 - 2.0408 \quad | \quad 0.5 \\
 + 0.5 \quad - 2.2704 + 1.9260 \\
 \hline
 1 - 4.5408 + 3.8520 - 0.1148 \\
 + 0.5 \quad - 2.0204 \\
 \hline
 1 - 4.0408 + 1.8316 \\
 + 0.5 \\
 \hline
 1 - 3.5408
 \end{array}$$

$$10. \quad x^3 - 3.5408x^2 + 1.8316x - 0.1148 = 0 \quad (\text{equation 9. with its roots reduced by 0.5})$$

Second Transformation

$$\begin{array}{r}
 1 - 3.5408 + 1.8316 - 0.1148 \quad | \quad 0.07 \\
 + 0.07 \quad - 0.2430 + 0.1112 \\
 \hline
 1 - 3.4708 + 1.5886 - 0.0036 \\
 + 0.07 \quad - 0.2380 \\
 \hline
 1 - 3.4008 + 1.3506 \\
 + 0.07 \\
 \hline
 1 - 3.3308
 \end{array}$$

$$11. \quad x^3 - 3.3308x^2 + 1.3506x - 0.0036 = 0 \quad (\text{equation 10. with its roots reduced by 0.07})$$

Third Transformation

$$\begin{array}{r}
 1 - 3.3308 + 1.3506 - 0.0036 \quad | \quad 0.002 \\
 + 0.002 \quad - 0.0067 + 0.0027 \\
 \hline
 1 - 3.3288 + 1.3439 - 0.0009 \\
 + 0.002 \quad - 0.0067 \\
 \hline
 1 - 3.3268 + 1.3372 \\
 + 0.002 \\
 \hline
 1 - 3.3248
 \end{array}$$

$$12. \quad x^3 - 3.3248x^2 + 1.3372x - 0.0009 = 0 \quad (\text{equation 11. with its roots reduced by 0.002})$$

Solve for remainder

$$1.3372x - 0.0009 = 0$$

$$x = 0.0007 \quad \text{remainder}$$

$$x = 0.5727 \quad \text{solution for equation 9.}$$

Substitute this value in equation 5., and solve for y.

$$y = 0.0261$$

Therefore, at the equilibrium concentration solution of 6-ring ketal is 0.5727 molar and the equilibrium concentration of 5-ring ketal is 0.0261 molar.

Additional calculations were made for the cases in which the initial concentration of glycol was 2, 3, and 4 molar. The only differences in the calculation were in the representation of the equilibrium concentrations of the glycol, otherwise the approach was completely analogous to the immediately preceding calculations. The results of these calculations are summed up in the accompanying Table 84. Not only is better separation achieved with higher initial concentrations of glycol, but also later calculations will

TABLE 84

EQUILIBRIUM CONCENTRATIONS OF KETALS CORRESPONDING TO
VARIOUS GLYCOL-CARBONYL COMPOUND RATIOS

<u>Initial conc. of dicarbonyl compound</u>	<u>Initial conc. of glycol</u>	<u>Equilibrium conc. of ketal formed from 6-membered ring ketone</u>	<u>Equilibrium conc. of ketal formed from 5-membered ring ketone</u>
1	1	0.5727	0.02610
1	2	0.7483	0.0561
1	3	0.8223	0.08471
1	4	0.8616	0.1107

show that greater side product contamination occurs with lower initial concentration of glycol. It should also be noticed that equation 5. describes the relation between the equilibrium

concentration (x) of the ketal formed from the 6-membered ring ketone and the equilibrium concentration (y) for the ketal formed from the 5-membered ring ketone, regardless of the initial concentration of glycol. Table 85 indicates the corresponding equilibrium concentrations of the ketals formed from the 6-membered and 5-membered

$$5. \quad y = \frac{x}{50 - 49x}$$

ring ketones, which may be obtained by starting with varying mole ratios of glycol.

The approach by which the ratio of glycol to dicarbonyl compound A is calculated will be demonstrated later. Both Tables, 84 and 85, indicate the varying degrees of selective ketalization that can be achieved by employing the equilibrium method. Furthermore, these tables indicate the preferential ketalization of the 6-membered ring ketone up to the eighty percent level before the ketalization of the 5-membered ring takes place to any considerable degree. Table 85 indicates that the point of maximum reactivity difference occurs when x and y, in equation 5., are increasing

$$5. \quad y = \frac{x}{50 - 49x}$$

at the same rate. In a plot of y as a function x, the point at which the tangent to the curve has a slope of one, i.e., $dy/dx = 1$, is the point where x and y are increasing at the same rate.

TABLE 85

CORRESPONDING EQUILIBRIUM CONCENTRATIONS OF KETALS
FORMED FROM 6- AND 5-MEMBERED RING KETONES

<u>Mole ratio of glycol to dicarbonyl compound</u>	<u>Equilibrium conc. (x) of ketal formed from 6-membered ring ketone</u>	<u>Equilibrium conc. (y) of ketal formed from 5-membered ring ketone</u>
0.0	0.00	0.0
0.108	0.10	0.002
0.231	0.20	0.005
0.374	0.30	0.008
0.551	0.40	0.013
0.78	0.50	0.020
1.101	0.60	0.029
1.612	0.70	0.044
2.622	0.80	0.074
2.96	0.82	0.084
3.39	0.84	0.095
3.58	0.85	0.102
3.95	0.86	0.110
4.30	0.87	0.118
4.70	0.88	0.1279
5.19	0.89	0.139
5.79	0.90	0.153
6.54	0.91	0.169
8.75	0.93	0.211
11.68	0.95	0.275
∞	1.00	1.000

Differentiating equation 5. yields equation 13.

$$13. \quad \frac{dy}{dx} = \frac{1(50 - 49x) - x(-49)}{(50 - 49x)^2}$$

Simplify and set equal to one.

$$14. \quad \frac{dy}{dx} = \frac{50}{(50 - 49x)^2} = 1 \qquad 15. \quad x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Solve by quadratic equation.

Therefore, $x = 0.876$

At this point the slope of the tangent is one, and maximum separation has been achieved.

Then substitute the value, 0.875, for x into equation 5., and solve for y to obtain, $y = 0.1237$.

At point of maximum separation, the equilibrium concentration of the ketal formed from the 6-membered ring ketone is 0.8760 molar and the equilibrium concentration of 5-ring ketal is 0.1237 molar.

The next problem is to determine what initial concentration of glycol is necessary to accomplish the maximum separation. This initial concentration of glycol can be determined by substituting in an appropriate equilibrium expression as shown below. The calculation will also serve as an example of how the glycol to ketone ratio was determined in Table 85.

For the ketal derived from 6-membered ring ketone

$$1.) \quad K_{e6} = 2 = \frac{(\text{ketal})(\text{water})}{(\text{ketone})(\text{glycol})}$$

Initial ketone concentration	1
Initial glycol concentration	unknown, x
Equilibrium ketal concentration	0.8760
Equilibrium water concentration	$0.8760 + 0.1237 = 0.9997$
Equilibrium ketone concentration	$1.000 - 0.8760 = 0.1240$
Equilibrium glycol concentration	$(x - 0.9997)$

Substitution in equation 1 yields equation 16.

$$16. \frac{(0.8760)(0.9997)}{(0.1240)(x - 0.9997)} = 2.$$

$$x = 4.53$$

Therefore, an initial concentration ratio of 4.53 moles of glycol for each mole of hypothetical dicarbonyl compound is required for maximum separation.

D. Comparison of Equilibrium and Kinetic Methods for Separating 5- and 6-membered Ring Ketones

As the first step in this comparison, we would like to present two tables, Table 82, which has been presented heretofore, and Table 86. Table 82 is designed to show the product composition that can be achieved by selective hydrolysis, while Table 86 is designed to show the product composition that can be achieved by the equilibrium approach. Table 86 was obtained from Table 85 in the same manner as Table 82 was obtained from Table 81.

The structure of products A, B, C, and D are shown again for the reader's convenience.

TABLE 86

PRODUCT COMPOSITION FOR SELECTIVE HYDROLYSIS OF DIKETAL DERIVED FROM COMPOUND A AND 2,2-DIMETHYL-1,3-PROPANEDIOL

Product	Percent hydrolysis of the cyclohexanone ketal moiety			
	5%	10%	15%	20%
B	41.8	61.2	72.2	72.8
A	2.2	6.8	12.8	18.2
C	2.8	3.2	2.2	1.8
D	53.2	28.8	12.8	7.2

TABLE 86a

PRODUCT COMPOSITION FOR THE EQUILIBRIUM REACTIONS BETWEEN COMPOUND A AND 2,2-DIMETHYL-1,3-PROPANEDIOL

Product	Percent hydrolysis of the cyclohexanone ketal moiety			
	5%	10%	15%	20%
B	68.9	76.2	76.3	74.1
A	3.6	8.5	13.5	18.5
C	1.4	1.5	1.5	1.5
D	26.1	13.8	8.7	5.9
(Initial glycol conc.)	12.8	5.8	3.65	2.52

Before giving any interpretations, we would like to remind the reader that product B is the desired monoketone, that ketones

A and C represent interfering side products, and that product D, the diketal, is inert and easily distinguished in reactivity from the ketonic compounds.

These tables show that while the yield of B obtained in equilibrium method is only 1.3 percent (74.1% - 72.8%) greater than that given by the hydrolysis method at the 20 percent contamination level (sum of A + C), the yields of B are:

4.1 percent greater at the 15 percent contamination level,
15.0 percent greater at the 10 percent contamination level,
and 27.1 percent greater at the 5 percent contamination level.

Or from a different viewpoint, the equilibrium method gives an equivalent yield with only about half the contaminating side products.

A more complete accounting of the two methods will now be given. Selective hydrolysis offers a good yield of B, short reaction time, and a good ratio of product (B) to interfering side products (A + C) if the reaction is run only briefly. If the unreacted diketal is recovered and recycled, an excellent overall conversion to monoketone (B) might be achieved. On the negative side, the diketal must be synthesized for the hydrolysis. Any undesirable side product ketones (A + C) must be reconverted to ketal before they can be used. Finally, the reaction must be stopped at the proper point or the separation will be made less effective by continued reaction.

The equilibrium approach offers better product yields, less contaminants, versatility in that either diketone or diketal can be used as starting components and ready utilization of contaminating side products since they may be fed back directly in the system. In fact, if side products (A, C, and D) are recovered and fed back into the equilibrium, almost complete conversion to the desired monoketone (B) could be achieved. On the negative side, long reaction times could be encountered since this is an equilibrium process. Also possible complications could arise in the equilibrium approach due to the large excess of glycol required for the best results.

In summary, the equilibrium approach is superior to selective ketal hydrolysis for differentiating by reactivity the 5-membered ring ketone from the 6-membered ring ketone. From a theoretical viewpoint, both methods are basically sound and should be widely applicable.

VIII: EXPERIMENTAL SYNTHETIC WORK

A. Introduction

The description of the experimental synthetic work will be given in two parts. The first deals with ketal synthesis and consists of a sample ketal preparation, a discussion of the modifications of this basic method employed, and summary tables describing the ketals prepared by this method.

The second part describes the synthesis of the intermediates which were not otherwise available. The unavailable intermediates were 2-methylcyclopentanone and 2,2-diisopropyl-1,3-propanediol. The methylcyclopentanone and the glycol were prepared according to the accompanying schemes:

2-methylcyclopentanone

The synthesis of the ketone was accomplished by a standard Dieckmann, methylation, and decarboxylation. However, we are indebted to F. Marshall¹ for a description of the intermediate compounds in the glycol synthesis as well as for reaction steps 2, 3, and 4. The hydrolysis of the hindered amide, which occurred in this sequence, was accomplished with butyl nitrite and hydrogen chloride according to method of Papa and Schwenk.² A sample reaction is given for each step in the previously mentioned reaction scheme.

B. Synthesis of Ketals

1. Preparation of 3,3-diethyl-1,5-dioxaspiro [5,4] decane

In a 1 l. r.b. flask, there were introduced 63.1 g. (0.75 moles) of cyclopentanone, 99.2 g. (0.75 moles) of 2,2-diethyl-1,3-propanediol, 0.1 g. of *p*-toluenesulfonic acid, and 500 ml. of benzene. The flask was attached to a small column with a phase-separating head and heat was applied. The theoretical amount of water was removed by distilling in approximately three hours. During this time the vapor phase temperature rose from that of the benzene-water azeotrope (69°) to the temperature of boiling benzene. The reaction was continued for two additional hours.

¹ F. Marshall, J.Chem.Soc., 2754 (1930).

² N. Sperber, et al, J.Am.Chem.Soc., 70, 3091 (1948).

The top organic layer was washed with sodium carbonate solution, water, and saturated salt solution. The benzene solution was then filtered through anhydrous sodium sulfate and the benzene was removed by distillation under reduced pressure. An initial distillation yielded a product, b.p. 136-139° at 32-34 mm. A final distillation yielded 130.2 g. (87.3%) of ketal, b.p. 128-130° at 21 mm. The analytical sample, $n_{D}^{20.6} = 1.4643$, was taken from a mid-cut, b.p. 129.0-129.1° at 20 mm.

Anal. Calc'd for $C_{12}H_{22}O_2$: C, 72.7; H, 11.2.

Found: C, 72.5; H, 11.1.

2. Comment on Ketal Preparation

The basic procedure employed in ketal formation is exemplified by the preceding example. Information on all the ketals prepared in this work is summarized in Tables 87 and 88. Comments on various minor procedural steps and modifications of the above procedure for preparation of the ketals are given below.

a. Starting Materials

The starting materials were purified prior to use. Liquids were purified by distillation. 2,2-Dimethyl-1,3-propanediol (m.p. 128.4-129.4°) was recrystallized from benzene and the 2,2-diethyl-1,3-propanediol (m.p. 61.4-61.8°) was recrystallized from petroleum ether, b.p. 65-69° (Skellysolve B). The catalyst, *p*-toluenesulfonic acid, was not purified. Benzene was purified according

to the standard procedure.¹ All starting materials were available except 2-methylcyclopentanone and 2,2-diisopropyl-1,3-propanediol whose syntheses are described subsequently.

b. Apparatus

For ketals, VII through XII, a small column and a phase separating head were used. For ketals, I through VI, and XIII through XV, a Dean-Stark water separator and a condenser were used.

c. Reaction Modifications

While benzene served as a true solvent in most cases, its low miscibility with ethylene glycol and trimethylene glycol necessitated its use as a minor diluent (25-35% by volume) when ketals derived from either ethylene glycol or 1,3-propanediol were being prepared. Normally, about 0.1 g. of p-toluenesulfonic was used as a catalyst. However, in the preparation of ketals derived from 1,3-propanediol, 0.5 g. of p-toluenesulfonic acid was added initially. The reaction was stopped periodically and additional 0.5 g. portions of catalyst were added. In order to drive the reaction to completion and prevent any 2,2-diisopropyl-1,2-propanediol from contaminating the product, we used a two-fold excess of cyclopentanone in the synthesis of ketal, XIV, 3,3-diisopropyl-1,5-dioxaspiro[5,4]decane. The base (carbonate) treatment was

¹ L. Fieser, "Experiments in Organic Chemistry," D.C.Heath and Co., New York (1941), p.363.

eliminated and the ketal was directly distilled in reactions I, II, III, VI, and XIII. Finally, in the preparation of ketal XIII, the product was passed through a small alumina column in order to eliminate any unreacted glycol.

d. Reaction Time and Yields

Usually, the reactions were completed within a few hours time. The ketals derived from 1,3-propanediol were formed much more slowly and were produced in smaller yields than the other ketals prepared in this research. Of the ketones, 2-methylcyclopentanone seemed a little less reactive. Length of a reaction is a function of catalyst and reactant concentrations and the rate constant of the reaction. Unless rate differences are very large, they cannot be spotted in synthetic operations without careful control of catalyst and reactant concentrations.

e. Experimental Difficulties

An excess of cyclohexanone was used in an attempt to drive ketalization of the glycol to completion in one instance. This approach failed, however, because the excess ketone underwent aldol condensation. Cyclohexenylcyclohexanone (I)¹ was introduced into the reaction as a bothersome contaminant.

Experience indicates that more than the theore-

tical amount of water is produced in the reaction of ketones and

¹ G. Kon and J. Nutland, J.Chem.Soc., 3101 (1926).

ethylene glycol. Lower yields than were necessary were experienced in some cases because the reaction was stopped after the theoretical amount of water had been removed by azeotrope.

Almost all of the ketals foamed vigorously and caused difficulty during distillation.

f. Products

All the ketals formed in this research were liquids with the exception of IV, 1,5-dioxaspiro [5,5] undecane, whose approximate melting point is 34° .¹ The properties of the ketals are listed in Tables 87 and 88. All new compounds were analyzed by Galbraith Microanalytical Laboratories, P.O.Box 32, Knoxville, Tenn.

C. Synthesis of Intermediates

1. Preparation of 2-methyl-2-carbethoxycyclopentanone

In a 5 l. r.b. flask equipped with a stirrer and reflux condenser, 53 g. (2.3 moles) of sodium was dispersed in 500 ml. of toluene. With the addition of 404 g. (2 moles) of diethyl adipate, approximately 3 l. of benzene, and 5 ml. of ethanol to the dispersion in the flask, reaction was initiated. Additional ethanol was added in 5 ml. portions during the next several hours until the total volume of ethanol added was 25 ml. The mixture was stirred and refluxed for one day. A take-off condenser was attached and a benzene-alcohol mixture (approx. 300 ml.) was removed until the

¹ J. Boeseken and F. Tellegen, Rec.trav.chim., 57, 133 (1938).

TABLE 87

NAMES AND ANALYSIS OF KETALS

Ketal	Ketal #	Calc'd		Found	
		C	H	C	H
1,4-dioxaspiro [4,5] decane	I				
1,4-dioxaspiro [4,4] nonane	II				
6-methyl-1,4-dioxaspiro [4,4] nonane	III	67.6	9.9	67.4	10.0
1,5-dioxaspiro [5,5] undecane	IV				
1,5-dioxaspiro [5,4] decane	V				
7-methyl-1,5-dioxaspiro [5,4] decane	VI	69.2	10.3	69.4	10.4
3,3-dimethyl-1,5-dioxaspiro [5,5] undecane	VII	71.7	10.9	71.6	10.9
3,3-dimethyl-1,5-dioxaspiro [5,4] decane	VIII	70.6	10.6	70.6	10.7
3,3,7-trimethyl-1,5-dioxaspiro [5,4] decane	IX	71.7	10.9	71.8	11.0
3,3-diethyl-1,5-dioxaspiro [5,5] undecane	X	73.5	11.4	73.5	11.4
3,3-diethyl-1,5-dioxaspiro [5,4] decane	XI	72.7	11.2	72.5	11.1
7-methyl-3,3-diethyl-1,5- dioxaspiro [5,4] decane	XII	73.5	11.4	73.6	11.4
3,3-diisopropyl-1,5-dioxaspiro [5,5] undecane	XIII	75.0	11.7	75.0	11.7
3,3-diisopropyl-1,5-dioxaspiro [5,4] decane	XIV	74.3	11.6	74.1	11.6
7-methyl-3,3-diisopropyl-1,5 dioxaspiro [5,4] decane	XV	75.0	11.7	74.9	11.7

TABLE 88
YIELDS AND PHYSICAL CONSTANTS OF KETALS

<u>Ketal</u>	<u>Mole ratio of reao.</u>	<u>Percent yield</u>	<u>Boiling point °C.</u>	<u>Pressure mm.</u>	<u>Refractive indices at 20°</u>
I	0.7	86	89-90	40	1.4585 lit., 1.4583 ^a
II	0.34	69	88.0-89.3	80	1.4483 lit., 1.4481 ^a
III	0.25	78	86-88.5	57	1.4480
IV	0.8	64	84-85 80-81	9-10 7-8	1.4691 lit., 1.4692 ^a
V	0.8	52	79.7-80.7	18	1.4617 lit., 1.4616 ^a
VI	0.38	55	100.2-100.8	33	1.4617
VII	1.0	86	110-110.5	19-20	1.4628
VIII	1.0	92	112-114	50	1.4546
IX	0.37	82	97-100	30	1.4543
X	1.0	84	116-119	24-25	1.4687
XI	1.0	87	135-137	30	1.4646
XII	0.367	81	110-111	7	1.4640
XIII	0.138	88	136-136.5	7-8	1.4751
XIV	0.125	91	125.5-127.1	6-7	1.4723
XV	0.1	75	132-133	4	1.4734

^a E. Salmi, Ber., 71B, 1803 (1938).

vapor temperature was 72° , which was 4° above the boiling point of the benzene-alcohol azeotrope.

At this stage a thick pale yellow pudding-like mixture consisting of a suspension of the sodium salt of carbethoxycyclopentanone was present. A dry ice condenser was attached, and 600 g. (4.2 moles) of methyl iodide was added over a period of four hours. The mixture was stirred at room temperature for fifteen hours. Much grainy crystalline sodium iodide had precipitated but some viscous organic salt remained. After the reaction was heated for one hour, additional methyl iodide (100 g., 0.7 moles) was introduced and heat was continued for three hours.

Water was added, and the organic layer was treated successively with 15 percent potassium hydroxide and saturated salt solution. After removal of solvents at normal and reduced pressure, distillation from a modified Claisen flask yielded 248.2 g. (72.8%) of 2-methyl-2-carbethoxycyclopentanone, (b.p. $108-115^{\circ}$ at 10 mm.) and 64.6 g. of diethyl adipate (b.p. $115-118^{\circ}$ at 4-5 mm.). If allowance is made for the recovered diethyl adipate, the yield is 86.3 percent. 2-Methyl-2-carbethoxycyclopentanone (b.p. $103-106^{\circ}$ at 9 mm., $n_D^{20} = 1.4450$) was obtained in corresponding yields of 75.4 percent and 83.4 percent in a similar run.

2. Preparation of 2-Methylcyclopentanone

In a 500 ml. r.b. flask there were introduced 74.5 g. of a mixture of ethyl and isopropyl esters of 2-methyl-2-carboxycyclopentanone, 200 ml. of glacial acetic acid, and 1 drop of

85 percent phosphoric acid. The flask was attached to a small column. The top of the condenser was sealed so that any exit gases would have to bubble through lime water. Heat was applied but no action was indicated by the lime water. Thereupon, several ml. of phosphoric acid, 1 drop of sulfuric, and 50 ml. of water were added. Heat was reapplied and evolution of carbon dioxide was indicated by lime water. From time to time additional phosphoric acid (1 ml. portions) and water (10 ml. portions) were added. The methylcyclopentanone was steam distilled. The organic layer was washed with saturated salt solution and was filtered through anhydrous magnesium sulfate. The crude ketone was fractionated to yield 30.8 ml. of 2-methylcyclopentanone (b.p. 137-139°, $n_{D}^{20} = 1.4347$). The pot contents were strained to give an additional 3.5 ml. of ketone. The total yield, 34.3 ml., (31.3 g.) was 72.7 percent based upon 2-methyl-2-carbethoxycyclopentanone.

3. Preparation of Ethyl Diisopropylcyanoacetate

To a solution formed from 47 g. (2.04 moles) of sodium and 500 ml. of ethanol in a 3 l., 3-necked flask equipped with stirrer, dropping funnel, and condenser and blanketed under nitrogen, was added 226 g. (2 moles) of ethyl cyanoacetate. The sodium derivative of ethyl cyanoacetate precipitated. Then 374 g. (2.2 moles) of isopropyl iodide was added. With the addition of heat, spontaneous refluxing began. When this moderated, the mixture was allowed to stand for an hour prior to being refluxed for two hours. Then, a solution prepared from 51 g. (2.22 moles) of sodium in

700 ml. of ethanol was added, followed by 374.9 (2.2 moles) of isopropyl iodide. After refluxing for three hours, the reaction mixture was permitted to stand overnight. A further solution of 5 g. of sodium in 100 ml. of ethanol and 71 g. (0.42 moles) of isopropyl iodide were introduced and the reaction was heated for 2 additional hours. The solvent was removed at reduced pressure. The organic products were dissolved in approximately 1 l. of ether-benzene (1:1) and the organic solution was treated successively with water, 15 percent potassium hydroxide solution and saturated salt solution. The ether-benzene solution was filtered through anhydrous sodium sulfate and the solvent was removed. A distillation yielded 313.3 g. (79.2%) of product, b.p. 123-125° at 18-20 mm., and 118-120° at 15 mm., $n_{D}^{22.4} = 1.4360$.

4. Preparation of Diisopropylcyanoacetic Acid

In a 2 l. r.b. flask with an attached take-off condenser, there was introduced 312 g. (1.58 moles) of diisopropyl ethylcyanoacetate, 390 ml. of 35 percent potassium hydroxide, and 100 ml. of ethanol. The mixture was refluxed for sixteen hours during which the original two phases changed into a homogeneous solution. The basic solution was poured into a large beaker filled with cracked ice. Dilute hydrochloric acid was added to the reaction mixture until the solution was acid to congo red, then the beaker was placed in a refrigerator. The colorless crystalline acid precipitated was collected and dried. The mother layer was subjected to continuous ether extraction. The ether was removed and the acid was collected.

Recrystallization of a small sample from petroleum ether, b.p. 65-69° (Skellysolve B) gave diisopropylcyanoacetic acid,¹ m.p. 97-98°.

5. Preparation of Diisopropylmalonamic Acid

The product from the previous reaction was introduced in a 2 l. r.b. flask equipped with a stirrer, together with 770 ml. of 80 percent sulfuric acid. This mixture was heated at approximately 80° for thirteen hours, 100° for eight hours, and was poured on ice. The amide-acid was collected, redissolved in base, treated with charcoal and reprecipitated with acid. The product was air and oven dried. There was obtained 272.7 g. (92.1% from ethyl diisopropylcyanoacetate) of diisopropylmalonamic acid, m.p. 162.5-164.0° decomp. Recrystallization of a small amount from concentrated formic acid raised the melting point to 165-166° (reported¹ as m.p. 168°).

6. Preparation of Methyl Diisopropylmalonamate

In a 2 l. r.b. flask equipped with a stirrer and a dropping funnel, there were introduced 179.9 g. (0.96 moles) of diisopropylmalonamic acid, 120 g. (1.8 moles) potassium hydroxide and 700 l. of water. To this solution 200 ml. (2.11 moles) of dimethyl sulfate was added dropwise. From time to time sufficient potassium hydroxide was added to keep the reaction mixture strongly basic. Stirring was

¹ F. Marshall, J.Chem.Soc., 2754 (1930).

continued for approximately three hours. After the mixture stood overnight, 133 g. (69%) of colorless crystalline methyl diisopropylmalonamate, m.p. $104-105^{\circ}$ was removed by filtration and the unreacted acid was recovered by acidification of the filtrate and filtration. Since 26.8 g. of diisopropylmalonamic acid was recovered, the yield of ester was increased to 81 percent.

7. Preparation of Methyl Diisopropylmalonate

In a 1 l. r.b. flask equipped with stirrer, condenser, and dropping funnel, there was introduced a solution of 94.8 g. (0.47 moles) of methyl diisopropylmalonamate in 600 ml. of anhydrous ether. Anhydrous hydrogen chloride was bubbled through this solution for 15 minutes. On dropwise addition of 100 ml. (0.9 moles) of butyl nitrite, a deep red complex formed and evolution of nitrogen began. From time to time small volumes (25 ml.) of ether saturated with hydrogen chloride and of butyl nitrite (10-15 ml.) were added until the evolution of nitrogen stopped. In all, 175 ml. (1.6 moles) of butyl nitrite was used. The overall reaction time was 5 hours.

The reaction mixture was extracted with base so that the aqueous layer contained the acidic product and the organic layer contained the unreacted starting material. The aqueous layer was acidified and immediately extracted with ether. The ether was replaced by petroleum ether, b.p. $65-69^{\circ}$ (Skellysolve B) from which 57.2 g. (60%) of methyl diisopropylmalonate, m.p. $108-110^{\circ}$, was obtained. Since 10 g. of methyl diisopropylmalonamate was recovered from the original organic layer, the yield was increased to 69 percent.

8. Preparation of 2,2-diisopropyl-1,3-propanediol

To 23 g. (0.61 moles) of lithium aluminum hydride and 700 ml. of anhydrous ether in a 3 l., 3-necked r.b. flask equipped with stirrer and condenser, there was added 52.5 g. (0.26 moles) of methyl diisopropylmalonate dissolved in 400 ml. of ether. The mixture was stirred for twelve hours at room temperature and then allowed to stand overnight. The excess lithium aluminum hydride was destroyed by the dropwise addition of moist ether and water. The ether solution was removed, extracted with 10 percent potassium carbonate, saturated salt solution and filtered through anhydrous magnesium sulfate. Aluminum oxide wastes were subjected to constant ether extraction for 20 hours. After removal of solvent, distillation yielded 34.45 g. (83%) of a viscous liquid, which was 2,2-diisopropyl-1,3-propanediol, b.p. 104.5-107.8° at 1 mm. The analytical sample, $n_D^{25} = 1.4714$, was taken from a mid-cut, b.p. 120.0-120.5° at 2 mm.

Anal. Calc'd for $C_9H_{20}O_2$: C, 67.4; H, 12.6.

Found: C, 67.4; H, 12.6.

9. Preparation of the bis-3,5-Dinitrobenzoate Derivative of 2,2-Diisopropyl-1,3-propanediol

In a 200 ml. r.b. flask, 3,5-dinitrobenzoyl chloride (4.6 g., 0.02 moles), and 2,2-diisopropyl-1,3-propanediol (1.6 g., 0.01 moles) were refluxed in toluene (100 ml.) for one hour. With the removal of heat, the diester crystallized from the toluene

solution in nearly quantitative yield. The product was collected by filtration and washed with 20 ml. of 1 N sodium hydroxide. Repeated recrystallization from carbon tetrachloride yielded an ester, m.p. 157.3-157.7°.

Anal. Calc'd for $C_{23}H_{24}N_4O_{12}$: C, 50.4; H, 4.4; N, 10.2.

Found: C, 50.2; H, 4.4; N, 10.2.

IX: SUMMARY AND POSSIBLE FUTURE WORK

At this point we would like to sum up the principal results and conclusions of this work as well as to indicate possible future outgrowths of the same. This recapitulation will follow the chapter sequence used in the dissertation.

For theoretical and practical reasons, we studied the rates of hydrolysis and formation of cyclic ketals and the equilibrium of the same reactions. From a theoretical viewpoint, we wanted to see whether the effect of gem-dimethyl grouping in promoting ring formation could be extended to larger alkyl groups, particularly the ethyl and isopropyl groups. From a practical viewpoint, we were interested in the preferential blocking and regeneration of ketonic groups in polyfunctional compounds which contained 5- and 6-membered ring ketones. The fifteen cyclic ketals derived from the ketones, cyclohexanone, cyclopentanone, and 2-methylcyclopentanone, and the glycols, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, 2,2-diethyl-1,3-propanediol, 2,2-diisopropyl-1,3-propanediol, and ethylene glycol were prepared and hydrolyzed under kinetic and equilibrium conditions for the previously mentioned theoretical and practical reasons.

For ketals derived from cyclic ketones and 1,3-propanediols, the relative rates of hydrolysis in a dioxane-water medium at 30° increase in the order indicated.

Ketals derived from 1,3-glycols

For ketals derived from cyclic ketones and ethylene glycol, the relative rates of hydrolysis increase in the accompanying order.

The ratio of the hydrolysis rate of a ketal derived from 2-methylcyclopentanone and a glycol to the hydrolysis rate of a ketal derived from cyclohexanone and the same glycol is larger for ketals derived from 2,2-diethyl-1,3-propanediol (ratio 12.7) and 2,2-dimethyl-1,3-propanediol (ratio 11.5) than it is for ketals derived from ethylene glycol (ratio 8.0).

Ketal hydrolysis has also provided a study of the effect of gem-dialkyl groups in promoting ring stability in three series of ketals. For ketals derived from a cyclic ketone and 1,3-propanediol, the rate of hydrolysis decreases with every increase in the size of the groups at the C₂ position. This relationship is valid for the dihydrogen, dimethyl, diethyl, and diisopropyl groups. However, a proportionately greater amount of decrease takes place in the hydrolysis rate on substituting the dimethyl group for the dihydrogen

than takes place for replacing any dialkyl group with its next larger counterpart, as the relative rates of hydrolysis of type I ketals indicate.

Relative rates of hydrolysis of type I ketals

R H; CH₃; C₂H₅; ipr

$$\frac{\text{H}}{1} > \frac{\text{CH}_3}{.066-.096} > \frac{\text{C}_2\text{H}_5}{.029-.045} > \frac{\text{ipr}}{.011-.016}$$

Finally, ketal hydrolysis has shown that ketals derived from 1,3-propanediol are more prone to undergo ketal hydrolysis than ketals derived from ethylene glycol.

The equilibrium work has shown that in the type reaction
cyclic ketone + 2,2-dimethyl-1,3-propanediol $\rightleftharpoons$ cyclic ketal + water
the equilibrium shifts to the left as the ketone involved is changed from cyclohexanone (Ke = 2.) to cyclopentanone (Ke = 0.2) to 2-methylcyclopentanone (Ke = 0.04). The values for the equilibrium constants are subject to a 25 percent error because of inaccuracies in the analytical method.

$$K_e = \frac{(\text{ketal}) (\text{water})}{(\text{ketone}) (\text{glycol})}$$

Comparative studies indicate that the rates of formation of cyclic ketals are in the same order of magnitude for ketals derived from either ethylene glycol or 2,2-dimethyl-1,3-propanediol and from either cyclohexanone or cyclopentanone. The limited and somewhat erratic data seem to show that 2,2-dimethyl-1,3-propanediol is slightly more reactive than ethylene glycol and that cyclohexanone

is slightly more reactive than cyclopentanone. Since the hydro-

lysis constants ($K-1$) and the equilibrium constants (K_e) were determined for the cyclohexanone, cyclopentanone, and 2-methylcyclopentanone cases of reaction 1, the formation constants (k_1) for the same reactions can be calculated by substituting the appropriate experimental values in equation 2.

$$2. K_e = \frac{k_1}{k-1}$$

The formation constants determined in this manner have the accompanying relationship for the cyclohexanone, cyclopentanone, and 2-methylcyclopentanone cases of reaction I.

Relative Formation Constants of Reaction I

$$\frac{\text{cyclohexanone}}{1} > \frac{\text{cyclopentanone}}{0.8} > \frac{\text{2-methylcyclopentanone}}{0.23}$$

It should be mentioned, however, that the hydrolysis and equilibrium constants used in these calculations applied to somewhat different solvent media and that the assumption was made that the variation in solvent medium did not greatly effect the relative rate and equilibrium values.

Finally, preparative studies indicate that ketals may be readily prepared from the glycols, ethylene glycol, 2,2-dimethyl-1,3-propanediol, 2,2-diethyl-1,3-propanediol, and 2,2-diisopropyl-1,3-propanediol, but not from 1,3-propanediol.

In the theoretical mathematical section we have shown that in the hydrolysis of a diketal (D), the ketones (A, B, and C) will

be formed. In this analysis B was viewed as the desired monoketone product and A and C were looked upon as side products. The analysis showed that a larger yield of B with fewer side products (A and C) can be achieved via partial hydrolysis of ketals derived from 2,2-dimethyl-1,3-propanediol and 2,2-diethyl-1,3-propanediol than from partial hydrolysis of ketals derived from ethylene glycol. Additional calculations showed that the reaction must be stopped by the time the hydrolysis of the ketal derived from the 6-membered ring ketone is 15 percent completed, for continued reaction leads to a decrease in the yield of B and increase in the yield of A. That is, much of the product selectivity is lost by continued reaction.

The calculations based upon the equilibrium studies indicate that in the reaction between dicarbonyl compound (A) and 2,2-dimethyl-1,3-propanediol the greatest yield of B and smallest yield of A and C is achieved via the equilibrium method when the mole ratio of glycol to dicarbonyl compound A is 4.5 to 6.0. Furthermore,

the equilibrium approach gives better yields of the desired compound B with fewer side products (A and C) than the method of selective ketal hydrolysis in the same general reaction system. It should be pointed out, however, that selective ketal formation of the 6-membered ring ketone over a 5-membered ring ketone can also be accomplished via transketalization in good yield and with few side reactions.¹ However, since ethylene glycol itself reacts with the 5-membered carbonyl ring, accidental traces of the glycol present in the transketalization reaction prevent selective ketal formation from occurring. As yet, the method has not been used much by steroid chemists. In any case, one would conclude that there are probably now better means available for blocking steroidal ketones than steroid chemists are currently using. Furthermore, the number and variety of steroid compounds indicated a need for additional ways of selectively blocking and regenerating carbonyl groups.

In this work synthesis was subordinate in nature. However, eleven new cyclic ketals and the interesting highly substituted glycol, 2,2-diisopropyl-1,3-propanediol, were prepared.

This research has suggested other work which might be done in this area of chemistry. The ketals prepared in this work seem ideally suited for testing one of the more plausible theories explaining the so-called gem-dimethyl effect in promoting ring stability. The determination of the activation energies and entropy

¹ H. Dauben, et al., J. Am. Chem. Soc., 76, 1359 (1954).

values for the hydrolysis of these ketals would be required. These activation energies and probability factors should also deepen the understanding of the relationships in the relative rate constants reported. Samples of many of the ketals are available to anyone interested.

The equilibrium work might be refined and extended to include all fifteen ketals. Ketals derived from unsaturated cyclic ketones might be subjected to similar kinetic and thermodynamic studies. Ketals derived from steroidal ketones might be exposed to controlled hydrolysis or equilibrium conditions to find out the degree of selective ketone and ketal formation which can be obtained with the various types of polycarbonyl ketals or ketones, respectively. Transketalization using ketals derived from simple ketones and 2,2-dialkyl-1,3-propanediol might be investigated, since the same reaction using ketals derived from simple ketones and ethylene glycol has looked so promising in the ketal field. Finally, we would like to see the 2,2-dialkyl-1,3-propanediols or their derivatives used in the selective or nonselective blocking and freeing of steroidal ketones.

AUTOBIOGRAPHY

I, Robert John Harper, Jr., was born in Savannah, Georgia, on August 16, 1930. I received my secondary school education at Benedictine Military School in Savannah, Georgia. My undergraduate training was at Fordham University, which granted me the Bachelor of Science degree, magna cum laude, in 1952. In September, 1952, I entered the graduate school of Ohio State University. I worked as a teaching assistant in general and organic chemistry for two years, as a research assistant for Dr. Newman's Office Ordinance Research contract for one year, and during my final year I was granted the Standard Oil of Indiana Fellowship. In September, 1956, I was called to active duty as a 1st Lieutenant, U.S.A.F. While on active duty, I completed the remaining requirements for the degree Doctor of Philosophy.