Fig. 2.—The correlation between activation energy and log PZ of the decompositions of various substituted benzazides: upper line, O, m- and p-substituted benzazides; lower line, ◯, o-substituted benzazides.

benzene ring with the breaking bond in each parent compound. The double bond character of the breaking bonds in oximes and hydroxamic acids is negligible as compared with that of azides; hence the above resonance is less effective in oximes and hydroxamic acids than in azides. Data indicate that the rate ratios of cyclohexyl to phenyl derivatives are 12 in the Lossen,[10] 25 in the Beckmann[18] and 140 in the Curtius rearrangements. The ratios appear to correspond to the acceleration attributable mainly to the loss of the resonance stabilization of phenyl derivatives and presumably parallel to the acceleration due to the steric restriction of resonance by the o-group.

In view of these facts, the resonance stabilization would be expected to play a more important

(18) Y. Yukawa and M. Kawakami, unpublished data.

role in the Curtius rearrangement than in the others, and the steric restriction of resonance by the o-group would accelerate the reaction to a greater extent in the Curtius than the other rearrangements.

A further point of interest is found in the Arrhenius parameters obtained (given in Table I). o-Substituted compounds provide much lower energies of activation and slightly lower log PZ factors than those of the m- and p-isomers, except for the o-hydroxy compound. The more bulky the group in the o-position, the faster the rate and the lower the energy of activation. The restriction of the resonance or an increase in steric effect attributable to the o-substitution would be reflected primarily in the energy of activation and only slightly in the log PZ factor. Moreover, the activation energy parallels the log PZ factor and both are correlated linearly.[1,19] The plots of $\Delta E^* vs.$ log PZ in ortho series are ranged below the line of m- and p-substituted derivatives, as shown in Fig. 2. Only the o-hydroxy compound falls above the m-,p-correlation line. The vertical displacement of the ortho correlation line from that of m-,p-derivatives may refer mainly to the contribution of the steric restriction of resonance between the benzene ring and the azidocarbonyl residue, except the o-hydroxy derivative. It is, therefore, reasonable to consider that the difference of about 3 kcal. between both lines would be equal to the additional conjugation energy of the m-,p-substituted phenyl groups to that of the azidocarbonyl residue in the initial state. The effect reflected in the log PZ term is difficult to understand in terms of the restriction of resonance. The decrease in log PZ with the bulky group may presumably be attributed to the other terms, such as the steric restriction of solvation and the changes in the degree of the freedom of motions.

Acknowledgment.—The authors wish to express their sincere appreciation to Prof. M. Nakagawa for his invaluable suggestions in this manuscript.

(19) C. N. Hinshelwood. "Kinetics of Chemical Change," The Clarendon Press, Oxford, 1940. pp. 257–261; J. E. Leffler, J. Org. Chem., 20, 1202 (1955); M. G. Evans and M. Polanyi, Trans. Faraday Soc., 32, 1333 (1936).

SAKAI-SHI, OSAKA, JAPAN

Kinetic and Equilibrium Studies of Cyclic Ketal Formation and Hydrolysis[1,2]

BY MELVIN S. NEWMAN AND ROBERT J. HARPER, JR.[3]

The work herein reported was undertaken to obtain information about the hydrolytic stability of cyclic ketals derived from 1,3-propanediol and its 2,2-dialkylated analogs. We thought that from a study concerned with rate and equilibrium features of the reactions valuable information concerning the use and preparation of cyclic ketals as blocking agents for ketonic functions would be obtained. We also foresaw that further knowledge of the gem-dialkyl effect might be gained. For comparative purposes ketals of ethylene glycol were included since such ketals are commonly in use.

To this end ketals were prepared from cyclohexanone, cyclopentanone and 2-methylcyclopentanone and 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 pseudo first-order rate constants for the acid-catalyzed hydrolyses at 30° in 70% dioxane–water of these fifteen ketals were determined and are listed in Table I.

TABLE I

RELATIVE RATES OF KETAL HYDROLYSIS: TEMPERATURE, 30°; SOLVENT, 70–30 DIOXANE–WATER, 0.003 N HCL

| | Ketones | | 2-Methyl- |
Glycols	Cyclo-hexanone	Cyclo-pentanone	cyclo-pentanone
Ethylene glycol	1.0^a(I)^b	13.0(II)	8.02(III)
1,3-Propanediol	30.6(IV)	172(V)	259(VI)
2,2-Dimethyl-1,3-propanediol	2.01(VII)	16.5(VIII)	23.0(IX)
2,2-Diethyl-1,3-propanediol	0.888(X)	7.65(XI)	11.3(XII)
2,2-Diisopropyl-1,3-propanediol	0.335(XIII)	2.67(XIV)	3.28(XV)

^{a} Ketal derived from cyclohexanone taken as standard with a relative rate of 1.0. The rate constant is 1.16×10^{-3} min.$^{-1}$. ^{b} The Roman numerals refer to the ketals involved.

Equilibrium constants at 30° for the reaction of the same ketones with 2,2-dimethyl-1,3-propanediol in a dioxane medium were obtained. Because of a lack of time the method for determination of the equilibrium constants was not developed to high accuracy. However, because of the possible importance to problems involving preferential blocking of ketonic functions, we are reporting our preliminary results.
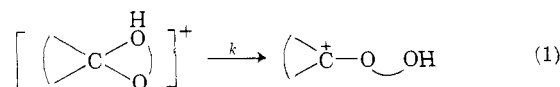
A. Comparative Reactivity of Ketals.—Ketals formed from 1,3-propanediol (1,3-dioxanes) are known to hydrolyze more rapidly than ketals formed from ethylene glycol (1,3-dioxolanes).[4] Our results with cyclohexanone (ratio of dioxane/dioxolane, 30.6), cyclopentanone (ratio, 13.2), and 2-methylcyclopentanone (ratio, 32.3) provide additional examples of this phenomenon. However, as the central hydrogens in 1,3-propanediol are replaced successively by methyl, ethyl and isopropyl groups this ratio is decreased in every case. These results are of interest in connection with the *gem*-dimethyl effect,[5] or preferably, what should be called the *gem-dialkyl effect*. The relative rates of hydrolysis for ketals of cyclohexanone with 1,3-propanediol, 2,2-dimethyl-, 2,2-diethyl- and 2,2-diisopropyl-1,3-propanediols are as 91.3:6.0:2.6:1. The largest increase in stability of the ring in the ketals comes when the two central hydrogen atoms in 1,3-propanediol are replaced with methyl groups. However, successive replacement with ethyl and isopropyl groups makes for still greater ring stability. Similar results are observed with the cyclopentanone ketals, where the comparable rates are as 64.4:6.1:2.9:1, and with the 2-methylcyclopentanone ketals, where the rates are as 79:7.0:3.4:1. The net result is that ketals formed from the readily available 2,2-dimethyl-1,3-propanediol (neopentyl glycol) are somewhat less stable to hydrolysis than ketals derived from ethylene glycol, and ketals formed from 2,2-diethyl-1,3-propanediol are slightly more stable than the corresponding ketals from

(4) For several examples see O. Ceder, *Arkiv. Kemi*, **6**, 354 (1954). However, for acetals, the order is reversed; see ref. 6 below.

(5) C. K. Ingold, *J. Chem. Soc.*, **119**, 305 (1921); G. Hammond in M. S. Newman, "Steric Effects in Organic Chemistry," J. Wiley and Sons, Inc., New York, N. Y., 1956, pp. 462–470.

ethylene glycol in the cases of cyclohexanone and cyclopentanone. In all cases studied the ketals from 2,2-diisopropyl-1,3-propanediol are more stable than those formed from ethylene glycol. However, it should be pointed out that acetals of ethylene glycol hydrolyze more rapidly than acetals of 1,3-propanediol.[4,6]

For all of the cases studied the rates of hydrolysis of ketals derived from the two cyclopentanones were greater than that for the corresponding ketal from cyclohexanone. If one assumes that the rate-determining step in hydrolysis of cyclic ketals is similar to that for acyclic ketals, namely, that step in which one of the C–O bonds of the ketal breaks to form a carbonium ion[7] as in equation 1, these results are those to be expected.[8] Reactions in

$$\left[\begin{array}{c} \overset{H}{\underset{O}{\bigvee}}C\overset{O}{\underset{O}{\diagdown}} \end{array} \right]^+ \xrightarrow{k} \overset{+}{\underset{}{\bigvee}}C-O\_OH \qquad (1)$$

which the coördination number at the ring carbon changes from four to three should go faster with cyclopentyl than with cyclohexyl derivatives.

In each case involving ketals from 1,3-propanediols the rate of hydrolysis of the ketal from 2-methylcyclopentanone is greater than that for the corresponding ketal for cyclopentanone. It should be interesting to see what effect additional and other alkyl groups will have on ketal hydrolysis rates in the cyclanone series.

B. Rate of Formation of Ketals.—Although no quantitative results were obtained in this study, qualitative observations indicated that ketals were formed slightly more rapidly from cyclohexanone and the cyclopentanones with 2,2-dimethyl-1,3-propanediol than with ethylene glycol. This behavior of 2,2-dimethyl-1,3-propanediol stands in marked contrast to that of 1,3-propanediol which reacts sluggishly with the ketones used in this work.[9] Ketals also were formed quite rapidly with both 2,2-diethyl- and 2,2-diisopropyl-1,3-propanediols although we cannot say whether the rates were slightly greater or less than the rates with ethylene glycol. From a preparative point of view all of the 2,2-di-substituted-1,3-propanediols afforded excellent yields of ketals with all three ketones and the time needed was roughly the same as when ethylene glycol was used.

C. Equilibrium Studies.—As stated previously our method of determination of equilibrium constants for the reaction of the three ketones with 2,2-dimethyl-1,3-propanediol has not yet been worked out with sufficient accuracy to warrant detailed description. The results, probably accurate to ±15%, are listed below. In the equations below it

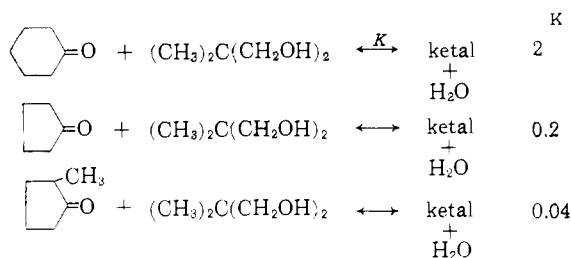(6) R. Leutner, *Monatsh.*, **60**, 317 (1932); **66**, 222 (1935).

(7) See M. Kreevoy and R. Taft, Jr., THIS JOURNAL, **77**, 3146, 5590 (1955); and C. A. MacKenzie and J. H. Stocker, *ibid.*, **77**, 3148 (1955); H. K. Garner and H. J. Lucas, *ibid.*, **72**, 5497 (1950).

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

(9) For similar observations see R. Dworzak and K. Herrman, *Monatsh.*, **52**, 83 (1929), J. Boeseken and F. Tellegen, *Rec. trav. chim.*, **57**, 133 (1938); E. Salmi, *Ber.*, **71**, 1803 (1938); E. Salmi and V. Ronnikko, *ibid.*, **72**, 600 (1939). It is also of interest that sorbitol forms 5-membered ring ketals with acetone whereas with benzaldehyde 6-membered acetals are preferred; B. C. Pressman, L. Anderson and H. A. Landy, THIS JOURNAL, **72**, 2404 (1950); L. vonVargha, *Ber.*, **68**, 18, 1377 (1935); F. Michael and K. Hesse, *ibid.*, **68**, 1582 (1935).

is assumed that the amount of hemiketal formation is small and constant, so that no effect on equilibrium is attributable to hemiketal.

				K
cyclohexanone $=O$ + $(CH_3)_2C(CH_2OH)_2$	$\xrightarrow{K}$	ketal + H_2O		2
cyclopentanone $=O$ + $(CH_3)_2C(CH_2OH)_2$	$\longleftrightarrow$	ketal + H_2O		0.2
2-methylcyclopentanone $=O$ + $(CH_3)_2C(CH_2OH)_2$	$\longleftrightarrow$	ketal + H_2O		0.04

We feel justified in reporting our preliminary results because of the calculations reported below.

The possible importance of the kinetic and equilibrium data in synthetic work may be shown by calculations involving a hypothetical compound, A, which has two ketonic functions having the same reactivities (in both free and ketalized forms) as cyclohexanone and 2-methylcyclopentanone. Furthermore, we assume that the reactivity of each function remains independent of any change in the other function. Consider A and the compounds B, C and D derived from it.
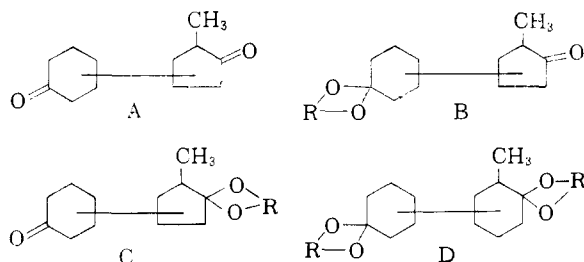
Suppose that one wishes to obtain B in the simplest way. Two approaches will be considered: one, involving a kinetic approach based on preferential hydrolysis of D; the other, involving equilibration of A and 2,2-dimethyl-1,3-propanediol. In all cases, a reaction mixture under study will contain quantities of A, B, C and D. Using the rate of hydrolysis constants (Table I) one can calculate the data shown in Tables II, III and IV.

TABLE II
PRODUCT COMPOSITION FOR SELECTIVE HYDROLYSIS OF DIKETAL D DERIVED FROM A AND ETHYLENE GLYCOL

Product	Hydrolysis of cyclohexanone ketal,[a] %			
	5	10	15	20
B	32.3	49.6	62.1	65.6
A	1.7	5.4	10.9	16.4
C	3.3	4.6	4.1	3.6
D	62.7	41.4	22.9	14.4

[a] In Tables II, III and IV the term % hydrolysis of cyclohexanone ketal means that situation when the sum of A and C totals the % indicated.

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

Product	Hydrolysis of cyclohexanone ketal, %			
	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 IV
PRODUCT COMPOSITION FOR SELECTIVE HYDROLYSIS OF DIKETAL D DERIVED FROM A AND 2,2-DIETHYL-1,3-PROPANEDIOL

Product	Hydrolysis of cyclohexanone ketal, %			
	5	10	15	20
B	46.5	63.9	74.8	74.8
A	2.4	7.1	13.2	18.7
C	2.6	2.9	1.8	1.3
D	48.5	26.1	10.2	5.2

Evaluation of the utility of the information in Tables II, III and IV will of course vary with the objective in each specific case. If one assumes that after partial hydrolysis has occurred ketonic material (A, B and C) may be separated easily from D, it is seen that although larger amounts of B are attained after longer hydrolysis periods, the purification of B might be easier after "5%" hydrolysis since at that time the ratio of B to A + C (5%) is greater. It is noteworthy that the separations possible improve as one goes from ethylene glycol ketals to those of the dialkyl propanediol ketals. We have not calculated the results for the diisopropylpropanediol ketals but these would be slightly less favorable for the cases under discussion.

Perhaps the most interesting and significant calculations, however, stem from the equilibrium constants and are listed in Table V. Here are listed the amounts of A, B, C and D that would be present after equilibration with varying initial amounts of 2,2-dimethyl-1,3-propanediol. Note that an experimental condition such that the sum of the amounts of A and C equals 5% leads to 68.9% of B. When one recalls that in the kinetically-controlled hydrolysis experiment (see Table III) only 41.8% of B is present when the sum of A and C is 5% it is apparent that the equilibrium controlled experiment offers quite an advantage.

TABLE V
PRODUCT COMPOSITION FOR THE EQUILIBRIUM INVOLVING 2,2-DIMETHYL-1,3-PROPANEDIOL

Product	Hydrolysis of the cyclohexanone ketal, %			
	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
Init. glycol concn.[a]	12.8	5.8	3.65	2.62
Init. water concn.[b]	0.857	1.157	1.418	1.689

[a] Per mole of compound A. [b] Per mole of compound D.

It is for this reason that we deemed it important to publish our preliminary experiments on equilibria in spite of the crude nature of the equilibrium constant determinations. The simplicity of the experimental approach in an unknown case should commend itself to the laboratory worker. All that would be required would be a few small scale experiments in which varying amounts of glycol are equilibrated with the polyketonic material, followed by analysis of the products. The method of exchange dioxolanation[10] may owe its success to the fact that it apparently is controlled by favorable equilibria.

We plan to continue our investigations in this field.

(10) H. J. Dauben, Jr., B. Loken and H. J. Ringold, THIS JOURNAL, 76, 1359 (1954).

TABLE VI

YIELDS AND PHYSICAL CONSTANTS OF KETALS

Ketal	Yield %	B.p. °C.	Mm.	Refractive indices at 20°	Analyses, % Calcd. C	H	Found C	H
III	78	86.0– 88.5	57	1.4480	67.6	9.9	67.4	10.0
VI	55	100.2–100.8	33	1.4617	69.2	10.3	69.4	10.4
VII	86	110.0–110.5	19–20	1.4628	71.7	10.9	71.6	10.9
VIII	92	112.0–114.0	50	1.4546	70.6	10.6	70.6	10.7
IX	82	97.0–100.0	30	1.4543	71.7	10.9	71.8	11.0
X	84	146.0–149.0	24–25	1.4687	73.5	11.4	73.5	11.4
XI	87	135.0–137.0	30	1.4646	72.7	11.2	72.5	11.1
XII	81	110.0–111.0	7	1.4640	73.5	11.4	73.6	11.4
XIII	88	136.0–136.5	7–8	1.4751	75.0	11.7	75.0	11.7
XIV	91	125.5–127.1	6–7	1.4723	74.3	11.6	74.1	11.6
XV	75	132.0–133.0	4	1.4734	75.0	11.7	74.9	11.7

Experimental

Ethylene glycol and 1,3-propanediol were purified by distillation. 2,2-Dimethyl-1,3-propanediol,[11] m.p. 128.4–129.4°, was obtained by crystallization from benzene, and 2,2-diethyl-1,3-propanediol,[12] m.p. 61.4–61.8°, by crystallization from Skellysolve B (petroleum ether, b.p. 65–69°). 2,2-Diisopropyl-1,3-propanediol was prepared as described below.

Ethyl Diisopropylcyanoacetate.—To a solution formed from 47 g. of sodium and 500 ml. of absolute alcohol was added 226 g. of ethyl cyanoacetate. After the precipitation of the sodio salt 374 g. of isopropyl iodide was added. On warming an exothermic reaction set in. When the refluxing moderated the mixture was heated for three hours after which a solution prepared from 51 g. of sodium in 700 ml. of absolute alcohol was added, followed by 375 g. of isopropyl iodide. After three hours of heating at reflux the mixture was left overnight. Finally, a solution formed from 5 g. of sodium in 100 ml. of alcohol was added and then 71 g. of isopropyl iodide. After two hours at reflux most of the solvent was removed under reduced pressure. The salt residue was extracted with 1:1 ether–benzene and the organic layer washed successively with water, cold 15% potassium hydroxide solution, and saturated salt solution. After filtration through anhydrous sodium sulfate the solvents were removed. Distillation yielded 313 g. (79%) of ethyl diisopropylcyanoacetate,[13] b.p. 123–125° at 18–20 mm., n^{22}D 1.4362.

Methyl Diisopropylmalonamate.—The above ester was hydrolyzed to the cyanoacid, m.p. 97–98°, essentially as described[13] and the crude cyanoacid, from 312 g. of ester, was heated at 80° with 770 ml. of 80% sulfuric acid for 13 hours and at 100° for 8 hours. The resulting solution was cooled and poured on ice. A basic solution of the amidoacid was decolorized with charcoal (Darco G-60), and acidified to yield 273 g. (92%) of air and oven-dried diisopropylmalonamic acid, m.p. 162.5–164.0° dec. Recrystallization of a small amount from formic acid afforded an acid m.p. 165–166° dec. (reported[13] m.p. 168°). To a solution of 180 g. of the crude amidoacid in 700 ml. of water containing 120 g. of potassium hydroxide was added slowly 200 ml. of dimethyl sulfate. Occasionally sufficient potassium hydroxide solution was added to maintain strong basicity. After three hours, stirring was stopped and the mixture left overnight. The crystalline methyl diisopropylmalonamate,[13] m.p. 104–105°, 133 g. (69%), which had separated was collected. Acidification of the filtrate afforded 27 g. (15%) of diisopropylmalonamic acid.

Methyl Acid Diisopropylmalonate.—Dry hydrogen chloride was bubbled into a solution of 95 g. (0.47 mole) of methyl diisopropylmalonamate in 600 ml. of dry ether for 15 minutes. On dropwise addition of 100 ml. of butyl nitrite a deep red complex formed and evolution of nitrogen began. At intervals 25-ml. portions of dry ether saturated with hydrogen chloride and 10–15 ml. portions of butyl nitrite were added until the evolution of nitrogen ceased. In all 175 ml.

of butyl nitrite (1.6 moles) was used and the total reaction time was 5 hours. Alkaline aqueous extraction removed the acidic product. After acidification, ether extraction, and crystallization from Skellysolve B, there was obtained 57.2 g. (60%) of methyl hydrogen diisopropylmalonate, m.p. 108–110°. From the neutral products, 10 g. of amido ester was recovered.[14]

2,2-Diisopropyl-1,3-propanediol.—The lithium aluminum hydride reduction of the above acid ester in ether solution for 12 hours at room temperature afforded 34.5 g. (83%) of good diol, b.p. 104.5–107.8° at 1 mm. The analytical sample, n^{25}D 1.4714, was taken from a redistilled mid-cut, b.p. 120.0–120.5° at 2 mm.

Anal. Calcd. for $C_9H_{20}O_2$: C, 67.4; H, 12.6. Found[15]: C, 67.4; H, 12.6.

The bis-3,5-dinitrobenzoate, m.p. 157.3–157.7°, was prepared by heating the diol in refluxing toluene with 3,5-dinitrobenzoyl chloride for one hour and was recrystallized from carbon tetrachloride to constant m.p.

Anal. Calcd. 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.

Ketal Formation.—In most cases, a mixture of ketone, glycol, benzene and p-toluenesulfonic acid (0.1 g.) was refluxed into a phase-separating head arranged for removal of the water formed. Often more than one equivalent of water was formed so that a certain amount of trial and error was needed before larger runs were made. Additions of 0.5 g. of catalyst were required in ketalizations in which 1,3-propanediol was a component because much greater reaction times were needed. In the preparation of ketal XIV a twofold excess of cyclopentanone was used. In most experiments, the benzene layer was washed with potassium carbonate solution before distillation. However, in the preparations of I, II, III, VI and XIII, the ketal was distilled directly. In the case of XIII, the product was passed over a small column of alumina to remove small amounts of unreacted glycol. Attempts to use an excess of cyclohexanone in order to use up as much 2,2-diisopropyl-1,3-propanediol as possible failed due to the extensive self condensation of cyclohexanone. When ketals from ethylene glycol or 1,3-propanediol were being made, the total volume of benzene was held to 25–35% by volume of the reaction mixture. Distillation of most of the ketals was troublesome because of vigorous foaming. The properties of all new ketals prepared are listed in Table VI. The ketals from cyclohexanone and cyclopentanone with ethylene glycol and 1,3-propanediol, I, II, IV and V, have been prepared previously and agreed in b.p. and refractive index with published values.[16]

Kinetic Procedure.—The rate of ketal hydrolysis was measured by following the increasing carbonyl peak in the ultraviolet with a Beckman DU spectrophotometer. In each kinetic run 3 ml. of 0.01 N hydrochloric acid and sufficient dioxane[17] to give a total volume of 10 ml. were added

(11) We thank the Tennessee Eastman Corp. for a generous gift of this diol.

(12) We thank the Union Carbide and Carbon Co. for a generous gift of this diol.

(13) This procedure is essentially that of F. Marshall, *J. Chem. Soc.*, 2754 (1930).

(14) This procedure was based on the similar procedure of N. Sperber, D. Papa and E. Schwenk, THIS JOURNAL, **70**, 3091 (1948).

(15) All microanalyses by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(16) E. Salmi, *Ber.*, **71**, 1803 (1938).

(17) Purified as described in L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 369, except that the final distillation was over calcium hydride.

to 5 ml. of stock solution of ketal in dioxane. All of the components were brought to 30° before mixing. Part of the reaction mixture was then transferred to a quartz cell and placed in a water-jacketed cell compartment for the course of the reaction. Water was pumped through the jackets from a bath held at 30.00 ± 0.05°. With this method, the over-all reaction temperature control was 30.0 ± 0.15°. The optical density was determined at convenient intervals. Usually 20 to 25 readings were made. With the slower reactions, the optical density at infinite time was obtained by running the same reaction at a higher acid concentration. From 3 to 9 kinetic runs were made with each ketal. Rate constants for the hydrolysis of cyclic ketals were evaluated by substantially the same method used[18] in calculating rate constants for the hydrolysis of acyclic acetals and ketals with two exceptions.[19] Under the conditions studied, both the above authors and ourselves observed typical pseudo first-order kinetics for the ketals studied. In this work, the rate constant for a given run was always within 2% of the average rate constant for a given cyclic ketal, although in most cases agreement was within 1% of the average.

TABLE VII

HYDROLYSIS OF 1,4-DIOXASPIRO[4,4]NONANE (II) AT 30 ± 0.15° IN 70–30 DIOXANE–WATER[a]

slope = 1.12 × 10⁻⁴ sec.⁻¹; −6.70 × 10⁻³ min.⁻¹. k = 2.66 × 10⁻⁴ sec.⁻¹; 1.54 × 10⁻² min.⁻¹.

Time, sec.	O.D.[b]	Time, sec.	O.D.
222	0.047	2592	0.349
359	.073	2751	.366
546	.099	2970	.384
699	.127	3217	.403
873	.149	3401	.417
1013	.168	3815	.447
1182	.192	4277	.483
1439	.226	4522	.498
1639	.246	5086	.527
1908	.279	5413	.544
2040	.292	6100	.575
		6387	.583
			.710

[a] Initial ketal concentration, 0.039 M.   [b] Optical density at 287 mμ, slit 0.150.

Equilibrium Measurements.—In a typical experiment 0.6251 g. of 3,3-dimethyl-1,5-dioxaspiro[5,5]undecane (VII) and 0.0724 g. of 1 N hydrochloric acid were placed in a 50-ml. calibrated volumetric flask. There was added sufficient dioxane to give 50 ml. of solution at 30.0 ± 0.1°. The initial molar concentration of ketal was 0.0679 and of water 0.0774. Aliquots of this solution 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 solution for a short while and the vials were sealed. The sealed vials were put in brown bottles, which were placed in a bath held at 30.0 ± 0.1°. Vials were opened at intervals and the optical density of the solution at a chosen point, 287 mμ, was measured against water. The time elapsed since the vials were sealed and the optical density of the solution were as follows: 4 days, 0.244; 12 days, 0.460; 22 days, 0.457; 64 days, 0.460. From the relative constancy of the last three readings, it was assumed that equilibrium had been reached. The optical density due to dioxane (0.010) was subtracted from the equilibrium reading and the equilibrium ketone concentration was calculated to be 0.0294 M by use of an extinction coefficient (E = 15.3) obtained from standard solutions. From the above value for the ketone concentration, the initial reactant concentrations and the stoichiometry of the reaction, equilibrium concentrations of 0.0385 M for ketal, 0.0480 M for water and 0.0294 M for glycol were calculated. The overall equilibrium constant obtained for this run was 2.1, where

(18) M. Kreevoy and R. Taft, THIS JOURNAL, 77, 3146 (1955).

(19) (a) Instead of natural logarithms, log₁₀ were used and a constant to correct for this was introduced in converting the slopes to rate constants. (b) The best straight line slope was drawn visually through the points on the graph.

the equilibrium

$$K_e = \frac{[\text{ketal}][\text{water}]}{[\text{ketone}][\text{glycol}]}$$

expression is as indicated.

The K_e for equilibria involving 2,2-dimethyl-1,3-propanediol and cyclohexanone, cyclopentanone and 2-methylcyclopentanone were determined but different runs gave values only in rough agreement. The K_e for cyclohexanone was determined to be roughly 2.0 ± 0.4, that for cyclopentanone 0.2 ± 0.02, and that for 2-methylcyclopentanone 0.04 ± 0.006. For the purposes of the calculations listed in Table V, the values of K_e were taken as 2, 0.2 and 0.04.

Product Composition Calculation for Tables II, III and IV.—To illustrate the method used for calculations of the values listed in these tables, the calculation of the first column in Table II will be given. It was assumed that the individual ketal moieties in the diketal D would hydrolyze at relative rates identical to those of the individual ketals I and III (Table I), and that the rate of hydrolysis of each ketal moiety would be unaffected by the other function in the hypothetical compound being considered. Assuming the initial concentration of D is one molar, substitution into the equation 1 for hydrolysis of I the value of x = 0.05 (corresponding to 5% hydrolysis) leads to a time, t, of 44.2 min. Substitution of this value of t into equation 2 for hydrolysis of III leads to a value of x of 0.34 (corresponding to 34% hydrolysis).

$$\frac{2.303}{t} \log \frac{a}{a-x} = 1.16 \times 10^{-3} \tag{1}$$

$$\frac{2.303}{t} \log \frac{a}{a-x} = 8.02 \times 1.16 \times 10^{-3} \tag{2}$$

From these values, the percentage of A, B, C and D present at this time are calculated as

A = 0.05 × 34, or 1.7%
B = 0.95 × 34, or 32.3%
C = 0.05 × 66, or 3.3%
D = 0.95 × 66, or 62.7%

The other points in Tables II, III and IV are similarly calculated.

Calculations for Table V.—Assume that one prepares a solution in dioxane one molar with respect to A and to 2,2-dimethyl-1,3-propanediol, and that these equilibrium constants hold

$$K_e = \frac{[\text{cyclohexanone ketal}][\text{water}]}{[\text{cyclohexanone moiety}][\text{glycol}]} = 2.0 \tag{3}$$

$$K_e = \frac{[\text{2-methylcyclopentanone ketal}][\text{water}]}{[\text{2-methylcyclopentanone moiety}][\text{glycol}]} = 0.04 \tag{4}$$

We would like to know the relative amounts of blocked and unblocked 6-membered and 5-membered ring ketones present at equilibrium. Furthermore, we would like to know what amount of glycol would give the most advantageous preferential blocking of 6-membered ring ketone compared to 5-membered ring ketone. If we assume that one mole of glycol is present at the start to one mole of diketone A, then at equilibrium these molar concentrations will be present

cyclohexanone ketal	x
2-methylcyclopentanone ketal	y
cyclohexanone moiety	$1 - x$
2-methylcyclopentanone moiety	$1 - y$
water	$x + y$
glycol	$1 - x - y$

Equation 3 becomes

$$\frac{x(x+y)}{(1-x)(1-x-y)} = 2.0 \tag{5}$$

and equation 4 becomes

$$\frac{y(x+y)}{(1-y)(1-x-y)} = 0.04 \tag{6}$$

Dividing (5) by (6) we get

$$y = x/(50 - 49x) \tag{7}$$

TABLE VIII

EQUILIBRIUM CONCENTRATIONS OF KETALS WITH VARIOUS
2,2-DIMETHYL-1,3-PROPANEDIOL–KETONE RATIOS

Init. concn. of dicarbonyl cpd.	Init. concn. of glycol	Equil. concn. of cyclohexanone ketal	Equil. concn. of 2-methylcyclo-pentanone ketal
1	1	0.57	0.03
1	2	.75	.06
1	3	.82	.09
1	4	.86	.11
1	4.5	.88	.12

Substituting for y in (5) and solving for x, we get

$$x^3 - 5.041x^2 + 6.122x - 2.041 = 0 \qquad (8)$$

This equation was solved by Horner's method[20] to yield a value $x = 0.573$, which leads to a value of 0.026 for y. In a similar way calculations can be made for other initial glycol concentrations. In Table VIII a few of these results are listed.

(20) I. S. and E. S. Sokolnikoff, "Higher Mathematics for Engineers and Physicists," McGraw-Hill Book Co., Inc., New York, N. Y., 1934, pp. 27–32.

By differentiating equation 7, simplifying, and setting equal to 1 (because maximum separation can be obtained when $dy/dx = 1$) we get

$$\frac{dy}{dx} = 1 = \frac{50}{(50 - 49x)^2} \qquad (9)$$

On solving, we find that $x = 0.88$ and $y = 0.12$.

In order to find out what initial glycol concentration would be required to obtain maximum separation, substitute the following values in equation 3

initial ketone concentration	1
initial glycol concentration	z
cyclohexanone ketal concn. at equil.	0.88
water concn. at equilibrium	$0.88 + 0.12 = 1.00$
cyclohexanone concn. at equil.	$1.00 - 0.88 = 0.12$
glycol concn. at equilibrium	$z - 1$

On solving we find that $z = 4.5$ and hence maximum preferential blocking can be obtained when 4.5 moles of 2,2-dimethyl-1,3-propanediol is equilibrated with one mole of the hypothetic diketone A.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BRITISH COLUMBIA]

The Protonation of the Carbonyl Group. I. The Basicity of Substituted Acetophenones[1]

BY ROSS STEWART AND K. YATES[2]

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The basicities of twenty m- and p-substituted acetophenones have been determined by a spectrophotometric method in sulfuric acid media. With the exception of hydroxy and alkoxy groups which, it is believed, hydrogen bond strongly to the solvent, a very good correlation exists between pK_{BH^+} and σ^+. A good correlation also exists between pK_{BH^+} and $\nu_{C=O}$, the carbonyl stretching frequencies in the ketones. The conjugate acid of 2-acetylfluorene is considerably more stable than that for p-phenylacetophenone and the theoretical consequences of this are discussed.

In connection with a study of the position of protonation of the carboxyl group, which will be reported later, we found it necessary to use compounds containing the carbonyl group as models. The protonation of the carboxyl group might occur at either the "carbonyl" or "ether" oxygen but there is one oxygen atom only available for protonation in a carbonyl compound. We have accordingly determined the effect of m- and p-substituents on the basicity of acetophenones and this information later will be correlated with the data obtained with substituted benzoic acids.

Hammett[3a,b,c] in his classical investigation of the strength of very weak bases determined the basicity of acetophenone and its p-CH_3 and p-Br derivatives by a spectrophotometric method in sulfuric acid solution. This approach, which we have followed, utilizes the concept of the H_0 acidity function and has the advantage of producing absolute values of basicities, i.e., absolute insofar as they are based on dilute aqueous solution as the standard state. Pratt and Matsuda[4] determined relative basicities of some acetophenones in benzene solution by a dis-

(1) Presented at the San Francisco Meeting of the American Chemical Society, April 7–11, 1958.

(2) Holder of a National Research Council of Canada Studentship, 1957–1958.

(3) (a) L. A. Flexser, L. P. Hammett and A. Dingwall, THIS JOURNAL, 57, 2103 (1935); (b) L. A. Flexser and L. P. Hammett, ibid., 60, 885 (1938); (c) L. P. Hammett and A. J. Deyrup, ibid., 54, 2721 (1932).

(4) E. F. Pratt and K. Matsuda, ibid., 75, 3739 (1953).

tillation method. They observed as we do, that p-OMe and p-OEt have anomalously high basicities.

Experimental

Acetophenones.—Commercially available acetophenones were purified either by vacuum distillation or by several recrystallizations.

m-Methylacetophenone was prepared from m-bromotoluene by the method of Gilman and Nelson.[5] m-Chloro- and m-bromo-acetophenones were obtained by diazotization of m-aminoacetophenone followed by the standard Sandmeyer procedure. p-Fluoroacetophenone and 2-acetylfluorene were prepared by the standard Friedel–Crafts acylation of fluorobenzene and fluorene, respectively. The physical constants of the purified compounds are reported in Table I.

Sulfuric Acids.—Sulfuric acid–water solutions ranging from 44.0 to 95.5% acid were prepared by dilution of Fisher C.P. Reagent grade sulfuric acid (95.0% min.). Concentrations were determined by titration with standard base. The H_0 values of these were obtained by interpolation from a standard curve constructed using the values given by Paul and Long.[6] Further solutions up to 99.9% acid were prepared from 30% fuming sulfuric acid (Baker and Adamson reagent) and H_0 values of these determined by indicator methods.[3c] All H_0 values of solutions were checked periodically.

Measurement of pK_{BH^+}.—A sample of each ketone weighed on a microbalance was dissolved in acetone to make a 5×10^{-3} M stock solution from which 0.1-ml. aliquots were pipetted into standardized 10-ml. volumetric flasks. After the acetone had been removed at the pump, the flasks were made up to volume with the sulfuric acid–water mixtures, the resulting concentration of ketone being 5×10^{-5}

(5) H. Gilman and J. F. Nelson, Rec. trav. chim., 55, 520 (1936).

(6) M. A. Paul and F. A. Long, Chem. Revs., 57, 1 (1957).