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Determination of the Mechanism of γ-Lactone Hydrolysis by a Mass Spectrometric Method[1]

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Two lines of evidence suggest that both the acid and basic hydrolysis of γ-lactones should involve splitting of the acyl–oxygen bond, bond 5, in Fig. 1. One is the close similarity of the kinetics of the hydrolysis reactions to those of ordinary aliphatic esters which have been shown to involve acyl–oxygen fission.[3,4] The other is the fact that the acid-catalyzed and basic hydrolyses of β-butyrolactone have been shown to involve acyl–oxygen fission even though the neutral hydrolysis of this lactone does involve alkyl–oxygen fission.[5] However, the kinetics of the hydrolysis of the β- and γ-lactones differ considerably in strong acids[6] and since it is of some importance to be sure this difference is not tied in with a change in bond split for the two lactones, we have done experiments to determine the mechanism of the acid catalyzed and basic hydrolysis of γ-butyrolactone.

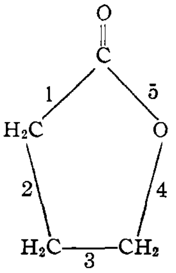

Fig. 1.—γ-Butyrolactone, numbered bonds.

The general method for determining the type of bond split is well known and consists simply of hydrolyzing the lactone in an aqueous solution containing excess H_2O^{18} and finding the location of the marked oxygen in the hydrolysis product. Initial experiments with the γ-butyrolactone were made using procedures very similar to those of Olson and Hyde. The lactone (containing oxygen of ordinary isotopic composition) was hydrolyzed in solutions of H_2O^{18}, and after neutralization and evaporation the sodium salt of the resulting γ-hydroxybutyric acid was heated to drive off water and leave the salt of the unsaturated vinylacetic acid. Unfortunately, no conditions were found where this dehydration proceeded in a simple fashion. Invariably the equivalents of unsaturates, as determined by bromine titration, were considerably less than the equivalents of water formed. After some consideration of other chemical procedures it was finally decided to use a direct mass spectrometric analysis of the γ-butyrolactone.

The procedure for the mass spectrometric determination involves two steps. The first is to insert ordinary γ-butyrolactone into a mass spectrometer, record the mass-intensity pattern and, as far as possible, correlate the various masses with particular fragments of the molecule. The second step is to take a sample of γ-lactone which has been equilibrated through the hydrolysis reaction with H_2O^{18} of known isotopic content and determine in the mass spectrometer where changes in ion intensity due to the O^{18} occur. If these isotope effects occur with fragments whose molecular origin is definitely known then it is possible to deduce the bond split in the original hydrolysis. The method involves, of course, the two usual assumptions in mass spectrometric analysis, that there are no molecular rearrangements of the carbon–oxygen chain caused by electron impact and that there is no marked isotope effect on the products resulting from electron impact. The application of this mass spectrometric method to the determination of mechanisms involving oxygen reactions is novel and one of the points of interest is that the method can give useful results even though the H_2O^{18} currently available contains only 1.6% $O.^{18}$

Experimental

Materials and Procedure.—The mass spectrometric analyses were made using a General Electric magnetic scanning recording mass spectrometer. The ion accelerating voltage was constant at 2000 volts and the electron accelerating value was 150 volts. Mass assignments were confirmed by analyzing mixtures of lactone and benzene or toluene since for these last the mass-intensity patterns are well known.[7]

The γ-butyrolactone was obtained from the Clifts-Dow Company and was distilled before use. Chemical tests showed the material to be better than 99.8% pure.

Two experiments were made on the acid catalyzed hydrolysis in H_2O^{18}. In both experiments 1 ml. of lactone (0.013 mole) was added to a solution of 0.25 ml. of 96% sulfuric acid in 5 ml. of water containing 1.6% O^{18}. In one case the mixture sat for 100 hours at 23°, a time calculated to be several-fold larger than that for the hydrolysis to reach equilibrium. In the second case the hydrolysis was still more drastic, the mixture sat for eight hours at 85° followed by fourteen hours at 23°. After these hydrolysis periods the lactone was removed by benzene extraction over a period of three hours followed by distillation to remove the benzene. (The long extraction period permitted some of the γ-hydroxy acid, which is not extracted by benzene, to revert to lactone.)

Two experiments were also made on the basic hydrolysis.

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(1) Research carried out at Brookhaven National Laboratory under the auspices of the Atomic Energy Commission.

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(3) M. Polanyi and A. L. Szabo, *Trans. Faraday Soc.*, **30**, 508 (1934).

(4) S. C. Datta, J. N. Day and C. K. Ingold, *J. Chem. Soc.*, 838 (1939).

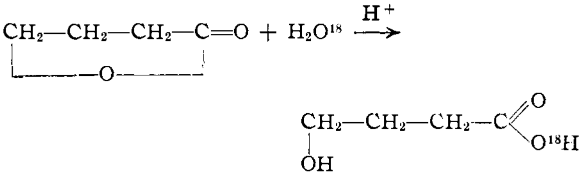
(5) A. R. Olson and J. L. Hyde, THIS JOURNAL, **63**, 2459 (1941).

(6) Unpublished work, F. A. Long, Frances Dunkle and Mary Purchase.

(7) American Petroleum Institute Research Project No. 44, N. B. S. catalog of Mass Spectral Data, Vol. 4, Pt. 1.

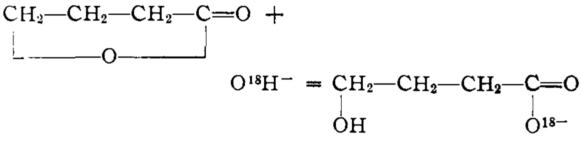
For both, 1 ml. of lactone was added to 5.5 ml. of 3 molar sodium hydroxide made by treating sodium metal with water containing 1.6% O^{18}. The hydrolysis reactions, which are very rapid under these conditions, were permitted to go to completion. Then 96% sulfuric acid was added, somewhat in excess of that needed to neutralize the base. The resulting acid solutions then sat for a comparatively long time so that the equilibrium amount of lactone would be reformed. After acidification, one of the solutions sat sixteen hours at 23° and the other for 124 hours at the same temperature. Then the lactone was extracted by benzene and recovered as before.

Mechanism Considerations.—The acid catalyzed hydrolysis of γ-butyrolactone goes to an equilibrium mixture of lactone and γ-hydroxybutyric acid containing about three parts of lactone to one part acid. Assuming acyl–oxygen fission the initial reaction in a solution containing added H_2O^{18} is



Now it is known that the oxygens of carboxylic acid exchange with oxygen of the solvent water at a rate comparable with esterification.[8] Thus if the hydrolysis of the lactone in H_2O^{18} is allowed to go for a time long compared to the time to reach the hydrolysis equilibrium both of the carboxylic oxygens will be equilibrated with the solvent. Since the oxygen of the hydroxy group does not interchange[9] with the solvent, the lactone in the equilibrium mixture will contain excess O^{18} in the carbonyl oxygen and normal oxygen in the ring. This involves the usual and highly plausible assumption that in the reverse lactone formation water is eliminated by closing the acyl–oxygen bond. This is in accord with the accepted A′-2 mechanism for esterification and ester hydrolysis.[10]

If in contrast the acid catalyzed hydrolysis reaction and its reverse involve the alkyl–oxygen bond the hydrolysis equilibrium combined with equilibration of the carboxylic oxygens will give a lactone containing excess O^{18} in both of its oxygens. Assuming acyl–oxygen fission, the equation for the basic hydrolysis is



This reaction goes to completion and on the basis of the data available the carboxyl oxygens will not undergo further equilibration.[9] However, if the solution is made acid these oxygens will be equilibrated and, of course, the equilibrium concentration of lactone will be reformed. If this acid-catalyzed reversal involves the expected acyl–oxygen bond closure, the final lactone will contain excess O^{18} only in the one carbonyl oxygen. In contrast, if the basic hydrolysis involves alkyl–oxygen fission then the final lactone will inevitably contain excess O^{18} in both oxygens.

Results and Discussion

Table I gives the mass spectrometric results for two γ-butyrolactone samples, the original lactone and O^{18} enriched lactone from the 23° acid catalyzed hydrolysis.

Table I

Mass Spectrometric Intensity Patterns for γ-Butyrolactone

Mass no.	Relative intensity Orig. lactone	Relative intensity O^{18} lactone[a]	Possible ionized fragments
88	0.134	0.39	Parent with O^{18}
87	2.10	2.07	Parent with C^{13}, parent plus proton
86	20.56	20.58	Parent
85	5.98	5.96	
58	0.218	0.51	Mass 56 with O^{18}, mass 57 with C^{13}
57	5.44	5.63	CH_2CH_2CHO
56	22.5	22.1	$CH_2CH_2{=}O$
55	5.75	5.92	$CH_2CHC{=}O$
54	0.39	0.39	
46	0.33	0.24	
45	0.54	0.51	
44	1.41	1.57	
43	4.9	5.24	
42	85.7	85.1	$CH_2C{=}O$, $CH_2CH_2CH_2$
41	41.2	40.0	$CHC{=}O$, C_3H_5
40	9.36	9.9	
39	12.4	13.0	
38	3.9	4.1	
37	2.9	3.0	
36	0.55	0.58	
32	0.26	0.19	
31	2.49	2.58	CH_3O
30	2.11	2.29	CH_2O
29	37.9	38.6	$H{-}C{=}O$, C_2H_5
28	**100.0**	**100.0**	$C{=}O$, C_2H_4
27	33.9	33.1	C_2H_3
26	15.6	15.1	C_2H_2
25	2.3	2.38	C_2H
24	0.38	0.43	C_2
20	0.42	0.52	
19	0.27	0.50	
18	6.22	16.15	H_2O
17	1.5	3.9	OH
16	0.29	0.36	O
15	4.6	4.6	CH_3
14	4.6	5.1	CH_2
13	1.4	1.4	CH
12	0.9	1.1	C

[a] 23°, acid hydrolyzed sample.

The last column of the table gives the composition of the probable ions responsible for the more significant peaks. The ion intensities are normalized in the usual fashion on the basis of 100 for the most intense peak. As might be expected with so large a molecule, the mass spectrometric pattern for the lactone is relatively complicated and unambiguous assignments of fragment composition cannot be made for many of the peaks. These difficulties are discussed in more detail below. The intensity patterns for the lactone samples obtained after hydrolysis in H_2O^{18} water containing only 1.6% O^{18} are, of course, almost identical with that for the original lactone. In fact the close agreement shown for the intensities of Table I gives an idea of the reproducibility of the spectrometer.

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[8] I. Roberts and H. C. Urey, This Journal, **61**, 2580 (1939).

[9] O. Reitz, *Z. Elektrochem.*, **45**, 100 (1939).

[10] J. N. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

To gain some added information relevant to assignment of fragment composition the mass spectrometric patterns were obtained for β-propiolactone and γ-valerolactone. The fact that the former has one less methylene group in the ring and the latter one added methyl group outside the ring as compared to the γ-butyrolactone makes their patterns of considerable assistance in interpreting the pattern from the latter. Abbreviated patterns for these two lactones are given in Table II, more detailed patterns will be reported at a later time.

Table II

Abbreviated Mass Spectrometric Patterns for β-Propio- and γ-Valerolactones

β-Propiolactone		γ-Valerolactone	
Mass	Relative intensity	Mass	Relative intensity
72(3)	0.7	100	5.45
55(3)	1.8	99	2.4
44	5.5	86	1.9
43	31.7	85	41.7
42	100.0	57	21.4
41	4.0	56	100.0
30	2.4	55	9.8
29	19.2	46	5.1
28	64.2	45	8.3
27	11.8	44	4.6
26	16.5	43	39.8
25	4.9	42	7.9
18	2.9	41	52.0
15	30.5	40	4.4
14	20.1	39	16.1
13	6.9	29	63.3
		28	94.7
		27	35.4
		26	14.9
		18	18.3
		15	11.2
		14	5.0

The most intense ion peaks from the γ-butyrolactone have masses of 28, 42, 41, 29, 27, 56 and 86 in decreasing order of intensity. For the determination of the mechanism of lactone hydrolysis the most interesting are the last two although the 27, 28, 29 group is also of some interest. The significant data are the ratios of the intensities of the intense peaks to the peaks two larger in mass. It is these ratios which can change significantly for fragments from the γ-lactone which contain added O^{18}. Table III contains several of these ratios for the original lactone and for the lactones obtained after acid and basic hydrolysis in the heavy water.

Table III

Intensity Ratios for γ-Butyrolactone

		Acid hyd. lactone		Basic hyd. lactone	
Masses	Original lactone	23° Sample	85° Sample	16-hr. sample	120-hr. sample
88/86	0.0065	0.0188	0.0164	0.0147	0.0185
58/56	.0097	.0231	.0209	.0206	.0218
31/29	.0657	.0669	....	.0665	.0679
30/28	.0211	.0229	....	.0226	.0182

It is apparent from Table III that the various ratios are essentially the same for the lactone samples recovered after both acid and basic hydrolysis in H_2O.[18] The slightly smaller values for the sixteen-hour basic hydrolysis sample may indicate that this period after acidification was not quite enough to permit the carboxyl oxygens to equilibrate with the solvent.

The data in Table III for the 88/86 ratio lead to a fairly definite conclusion on the mechanism of hydrolysis. The 88/86 ratio of 0.0065 for the original lactone is only slightly larger than the value calculated from the natural abundances of O^{18} and C^{13}. (The latter enters because there is a small contribution to mass 88 from parent ions containing two C^{13} atoms.) For the lactones obtained after hydrolysis in H_2O^{18} the 88/86 ratios vary from 0.015 to 0.019. The calculated value, corrected for the natural C^{13} effect, for one heavy oxygen in the lactone is 0.018 and for two is 0.030. Thus the experimental figures indicate conclusively that in either acid or basic hydrolysis only one of the two oxygens in the γ-lactone exchanges with the H_2O^{18}. On the basis of the earlier discussion this must be the oxygen on the carbonyl group. Hence the ring oxygen does not exchange and from this fact one concludes that both the acid and basic hydrolysis of the γ-lactone go through acyl–oxygen fission.

Confirmation of this conclusion is obtained from data on the 58/56 mass ratios although it should be emphasized that in this case, in contrast to the case for the 86 mass, the argument depends on the composition assigned to the mass 56 fragment. In Table III it can be seen that the 58/56 ratio increases from 0.009 for the original lactone to approximately 0.022 for the lactones obtained after H_2O^{18} hydrolysis. This figure indicates one heavy oxygen in the mass 56 fragment. Now a fragment of mass 56 can result from the γ-butyrolactone in three ways. One is a split of bonds 3 and 5 of Fig. 1 giving $CH_2CH_2C{=}O$. A second is a split of bonds 1 and 5 to give $CH_2CH_2CH_2{-}O$ followed by a loss of two protons. A third is splitting of bonds 1 and 3 to give $CH_2{-}O{-}C{=}O$ followed by a loss of two protons giving the rather implausible fragment $C{-}O{-}C{=}O$. For several reasons the first of these alternatives is by far the most probable. Perhaps the most obvious point is that the second and third alternatives involve breaking four bonds whereas the first involves breaking only two bonds. Another is that with β-propiolactone, where the first and second alternatives are not possible but the third one is, the 56 peak is relatively very weak whereas with the γ-valerolactone where the first alternative still exists but the second and third do not, at least without still additional bond breaks, the mass 56 peak is relatively very intense. Assuming that the mass 56 fragment is indeed $CH_2CH_2C{=}O$ from a split of bonds 3 and 5, then the presence of one heavy oxygen in this fragment from the lactone after hydrolysis in H_2O^{18} confirms the conclusion reached from 88/86 mass ratio results, *i. e.*, that the one heavy oxygen is in the carbonyl position.

Given that a split of bonds 3 and 5 is relatively probable, one would expect that the ion intensities for masses 29 or 28 would contain contributions from fragments $H-C\equiv O$ or $C=O$ resulting from the H_2C-O residue left from this bond split. The results discussed above would then lead to a prediction that the 31/29 and 30/28 intensities would show little, if any, increase for the lactones obtained after H_2O^{18} hydrolysis. Actually the results for the γ-butyrolactone, as well as comparisons with those for the β-propio and γ-valerolactones, indicate that the fragments C_2H_5 and C_2H_4 make large contributions to the ion intensities for masses 29 and 28. Even so it is of interest to note in Table III that the 31/29 and 30/28 ratios change rather little for the four lactone samples from the values for the original lactone.

Analysis of the ion intensities for masses in the region 40 to 45 does not permit of any conclusion about the hydrolysis mechanism. The relatively large size of the 43 and 44 peaks makes detection of isotope effects difficult as also does the uncertainty about the magnitude of the carbon dioxide background for the mass 44 peak. Furthermore it is difficult to assess the contribution made to the 41 and 42 peaks by the various possible fragments. However it can be said that none of the effects in this region are inconsistent with the conclusions reached above.

Qualitatively, the experimental results all indicate acyl-oxygen fission for both the acid-catalyzed and basic hydrolysis of γ-butyrolactone but it is not possible to give a quantitative figure to the percentage of reaction by this path. Although the data are best fitted by the assumption that all of the hydrolysis goes by the acyl-oxygen split, the variation in the intensity ratios is such that as much as 10 or 15% might actually go by the path of alkyl-oxygen fission. This uncertainty is probably unavoidable when water with only 1.6% O^{18} is used.

Summary

Samples of γ-butyrolactone have been hydrolyzed in aqueous solutions containing 1.6% H_2O^{18} and either three molar sodium hydroxide or 0.8 molar sulfuric acid and the lactone reformed from the hydrolysis product. These lactone samples have been subjected to mass spectrometric analysis and the ion intensity patterns compared with that obtained from ordinary γ-butyrolactone. On the basis of changes in the ion intensity ratios for masses 88/86 and 58/56 it is concluded that both the acid-catalyzed and basic hydrolysis of this lactone goes by an acyl-oxygen bond split in accord with predictions based on the results for hydrolysis of aliphatic esters and β-lactones.

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Condensations Effected by Boron Fluoride Complexes. III. The Acylation of Certain Substituted Thiophenes and Furans[1]

By Martin W. Farrar and Robert Levine

In earlier communications[1,2] from this Laboratory, it was reported that catalytic amounts of the diethyl ether and acetic acid complexes of boron fluoride may be used as condensing agents to give high yields of 2-acylfurans and 2-acylthiophenes when furan and thiophene are acylated with anhydrides. A possible mechanism for these acylations was also presented.

In the present paper, we report the extension of our earlier work to the acylation of a number of substituted furan and thiophene compounds with acetic, propionic and *n*-butyric anhydrides in the presence of boron fluoride etherate as the condensing agent. The ketones which have been prepared in the present study are listed in Table I.

The acylation of 2-methylfuran with acetic anhydride has resulted in a 42% yield of 5-methyl-2-acetylfuran. This yield is considerably higher than that reported by Reichstein[3] who prepared it by the interaction of 2-methylfuran with acetyl chloride in the presence of stannic chloride as the condensing agent. The higher homologs, 5-methyl-2-propionyl and 5-methyl-2-*n*-butyrylfuran, which were prepared in yields of 52% and 62%, respectively, are apparently new compounds. The acylation of 2-methylthiophene in 81% yield compares very favorably with that reported earlier[4] when orthophosphoric acid was used as the condensing agent. Propionylation and *n*-butyrylation of 2-methylthiophene gave 82% and 97% yields of 5-methyl-2-propionyl and 5-methyl-2-*n*-butyrylthiophene, respectively. These ketones have apparently not been reported previously.

The benzoylation of 3-methylthiophene using aluminum chloride as the catalyst has resulted in the formation of two isomeric ketones, 3-methyl-2-benzoylthiophene and 4-methyl-2-benzoylthiophene.[5] The acetylation of this alkylated thiophene using aluminum chloride as the condensing

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[1] For paper II in this series, see Levine, Heid and Farrar, This Journal, **71**, 1207 (1949).

[2] Heid and Levine, *J. Org. Chem.*, **13**, 409 (1948).

[3] Reichstein, *Helv. Chim. Acta*, **13**, 356 (1930).

[4] Hartough and Kosak, This Journal, **69**, 3093 (1947).

[5] Steinkopf and Jacob, *Ann.*, **515**, 273 (1935).