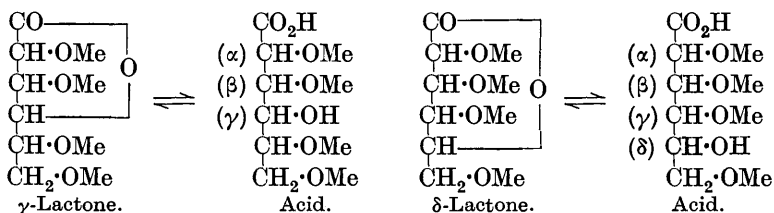


CCLXXII.—*Conductivity Measurements of the Comparative Rates of Hydrolysis of Lactones Derived from Simple Sugars.*

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A COMPARATIVE study of the rates of hydrolysis of lactones in the sugar series has revealed striking characteristics which may be used to differentiate a γ -lactone from an isomeric δ -lactone derived from the same parent sugar.



It has been established that a relationship subsists between the ease of hydrolysis or stability of a lactone and its oxide-ring structure, and since the oxide ring in the parent methylated sugar is preserved in the lactone derived from it by simple oxidation, the nature of the cyclic structure of the sugar may be ascertained with a considerable measure of certainty. This method of diagnosis of ring structure provided one of the two lines of investigation which led in the first paper of this series (Charlton, Haworth, and Peat, J., 1926, 89) to the advocacy of the new pyranose formula for glucose in its normal derivatives. On that occasion the comparative rates of hydrolysis of the lactones were measured by observing the changes of optical rotation in aqueous solution. In a subsequent paper (Drew, Goodyear, and Haworth, J., 1927, 1237) a series of curves was given expressing these speeds of hydrolysis in terms of the percentage of lactone present at any specified time.

We are now able to communicate similar evidence drawn from the study of the increasing electrical conductivity of aqueous solu-

tions of these and of a further series of lactones. We have employed this method merely as a qualitative means of distinguishing between the two classes of lactones, inasmuch as it is recognised that the determinations are not sufficiently exhaustive to be regarded as a study in chemical dynamics. The earlier results had demonstrated that the hydrolytic changes did not proceed to completion, and that a state of equilibrium was reached in the reaction



The method consisted in dissolving the lactone in water and determining the conductivity at appropriate intervals of time. Since the concentration of acid is varying and is usually unknown, a quantity λ has been introduced which has been termed the 'apparent equivalent conductivity.' This quantity is defined as the quotient of the specific conductivity divided by the concentration (in mols. per c.c.) of the total lactone, *i.e.*, lactone + undissociated acid + hydrogen ion. This is seen to differ from the 'equivalent conductivity' Λ as ordinarily defined, which is the quotient of the specific conductivity by the concentration (in mols. per c.c.) of acid, *i.e.*, undissociated acid + hydrogen ion.

The percentage p of free acid formed during the hydrolysis of the lactone has been calculated as follows.

Let $[\text{H}]_0$, m_0 , λ_0 be the hydrogen-ion concentration, total acid concentration, and apparent equivalent conductivity respectively in the solution of the free acid, and let $[\text{H}]$, m , and λ be the corresponding quantities during the reaction either at equilibrium or at any intermediate time t . Also let Λ be the true equivalent conductivity of the mixture at equilibrium or at time t , and Λ_∞ the true equivalent conductivity of the pure acid at infinite dilution. If K is the dissociation constant of the acid, we have

$$K = [\text{H}]_0^2 / (m_0 - [\text{H}]_0) = [\text{H}]^2 / (m - [\text{H}]) \quad . \quad . \quad (1)$$

$$\text{Also} \quad [\text{H}]_0 / [\text{H}] = \lambda_0 / \lambda \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$[\text{H}]_0 / m_0 = \lambda_0 / \Lambda_\infty \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\text{and} \quad [\text{H}] / m = \Lambda / \Lambda_\infty \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\text{Since} \quad m / m_0 = \lambda / \Lambda$$

$$\text{and} \quad (m - [\text{H}]) / (m_0 - [\text{H}]_0) = \lambda^2 / \lambda_0^2$$

it can be shown that

$$p = 100m / m_0 = 100 \left\{ \frac{\lambda^2}{\lambda_0^2} + \frac{\lambda}{\lambda_0} \left(\frac{\lambda_0 - \lambda}{\Lambda_\infty} \right) \right\} \quad . \quad . \quad (5)$$

$$\text{or approximately} \quad p = 100 \lambda^2 / \lambda_0^2 \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The values of the conductivity at infinite dilution have been taken from H. Lundén's "Affinitätsmessungen an Schwachen Säuren und Basen," 1908, Stuttgart. The acids from the lactones in Table I

contain 37, 33, 30, or 25 atoms, whence $\Lambda_{\infty} = 335, 335$ (extrapolated), 336, and 337 respectively at 18° . The tetramethyl- δ -galactonic acid (37 atoms) has an extrapolated value of 373 at 25° .

Table I gives the percentages of lactone present at equilibrium for sixteen lactones calculated by equation (5), together with an estimate of the time, t' , required to attain half the equilibrium value.

TABLE I.

Lactone.	γ -Form.		δ -Form.	
	Lactone, %, at equil.	t' , hrs.	Lactone, %, at equil.	t' , hrs.
Tetramethyl mannono- ...	89.1	624	31.9	34
„ glucono-	24.3	216	21.6	2.5
„ galactono- ...	72.3	120	10.9	2
Trimethyl rhammono-	—	—	62.6	21
„ arabono-	49.0	144	2.6	3
„ xylono-	38.5	288	46.7	52
Mannono-	81.5	264	61.1	12
Glucono-	19.6	—	10.7	2
Galactono-	75.4	292	—	—

It will be seen that, in the case of the five δ -forms of methylated glucono-, galactono-, arabono-, xylono-, and mannono-lactones, the equilibrium percentages of lactone previously determined are in satisfactory agreement with the present results. In addition, a new crystalline member of the series has been examined, *viz.*, trimethyl rhamnonolactone, prepared from trimethyl methylrhamnoside (Avery and Hirst, J., 1929, 2466). This is found to be similar in its rate of hydrolysis to tetramethyl δ -mannonolactone, to which, moreover, it is configurationally related.

Included also in these determinations are the two " β -lactones" prepared originally by Nef (*Annalen*, 1914, **403**, 204) from gluconic and mannonic acids. These unsubstituted lactones are seen to correspond closely with the fully methylated δ -lactones in respect to both extent and rate of hydrolysis, and there can be, therefore, little doubt that the views expressed by Haworth and Nicholson (J., 1926, 1899) are justified, and that the supposed " β -lactones" must be regarded as δ -gluconolactone and δ -mannonolactone.

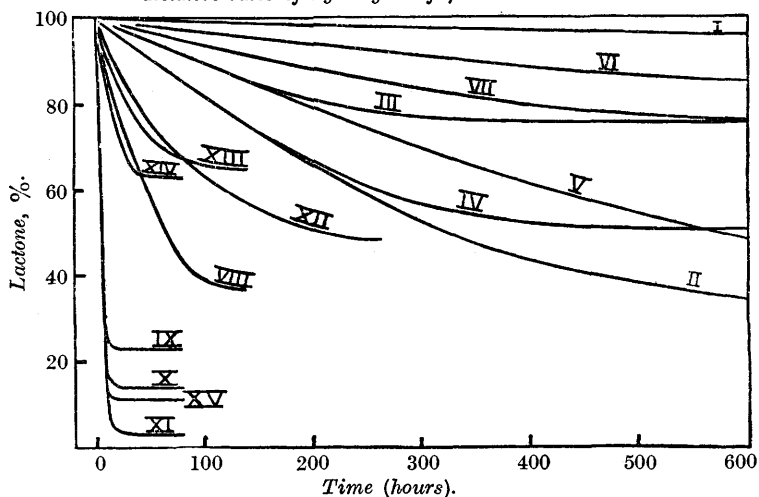
The resemblance between the corresponding methylated and unmethylated lactones extends also to the γ -series. Here the crystalline γ -gluconolactone and γ -mannonolactone, prepared by Nef (*loc. cit.*) and by earlier workers, are seen to have a close relation to the tetramethyl γ -lactones of the same series, although it is noticed that the rate of hydrolysis of γ -mannonolactone is slightly more rapid than in the case of its methylated derivative.

Again, the unsubstituted γ -galactonolactone, obtained as the monohydrate, had a slower rate of hydrolysis than the tetramethyl

γ -galactonolactone, the rate of hydration of which appears to be among the most rapid in the γ -series. It may be said, therefore, that the present results confirm, apart from some minor variations, the general and significant classification of the two series of lactones.

In Fig. 1 the comparative rates of hydrolysis are expressed by graphs, the percentage hydrolysis having been calculated by the approximate formula (6). This approximation leads to an error which depends both on the initial concentration of the free acid and on the stage which the reaction has reached. It can be shown that

FIG. 1.
Relative rates of hydrolysis of γ - and δ -lactones.



- | | |
|--|---|
| I. Tetramethyl γ -mannonolactone. | VIII. Tetramethyl δ -mannonolactone. |
| II. " γ -gluconolactone. | IX. " δ -gluconolactone. |
| III. " γ -galactonolactone. | X. " δ -galactonolactone. |
| IV. Trimethyl γ -arabonolactone. | XI. Trimethyl δ -arabonolactone. |
| V. " γ -xylonolactone. | XII. " δ -xylonolactone. |
| VI. γ -Mannonolactone. | XIII. " δ -rhamnonolactone. |
| VII. γ -Galactonolactone. | XIV. δ -Mannonolactone. |
| | XV. δ -Gluconolactone. |

the maximum error occurs when the ratio of unhydrolysed lactone to free acid is 75 : 25, and the average of this maximum error for the 16 lactones is 2.3%.

The δ -lactones are divisible into two series, *viz.*, the moderately rapidly (Curves VIII, XII, XIII, XIV) and the extremely rapidly hydrolysing (Curves IX, X, XI, XV), but even the lowest rate found among the δ -lactones is several times as great as the highest among the γ -series.

Although the free acids cannot be isolated in the pure state, their affinities can be judged approximately from their equivalent con-

ductivities, measured as soon as possible after their liberation by mineral acids from their barium salts. In the case of ten methylated acids in which the concentrations lay between 0.0605*N* and 0.0343*N*, the equivalent conductivity lay between 41.67 and 23.10 mhos.

In the earlier investigation, where the progress of the hydrolysis was followed by means of polarimetric measurements, it was pointed out that the variation of concentration and the presence of increasing amounts of free acid in the lactone solutions in the course of hydrolysis, would render the observations slightly inaccurate; nevertheless, it was considered that the values afforded a close approximation. The slight error caused by the presence of sodium sulphate in the solutions of the optically active acids has been obviated in these experiments by liberating the free acids from their barium salts. We have endeavoured to work with the same concentration of a lactone and its related acid, but in some instances this has not been possible owing to scarcity of material.

EXPERIMENTAL.

The solutions of the different lactones were made by rapidly dissolving *ca.* 0.1 g. in 10 c.c. of water, giving a solution about 0.05*N*. The electrical conductivity was measured by the usual Kohlrausch method, readings being taken immediately after dissolution and again at suitable intervals of time. The water used had a specific conductivity of 3×10^{-6} mho, and measurements were made at 18°. The lactone was also converted into the free acid by treatment with 0.1*N*-baryta at 60° in order to form the barium salt of the corresponding acid, and, after cooling, the addition of the exact equivalent of sulphuric acid liberated the free acid, the conductivity of which was observed immediately and again at intervals. It was ascertained from separate experiments that the conductivity of the barium sulphate produced under these conditions was negligible.

In many cases we were handicapped by the rarity of certain of the substances, which are difficult to prepare and to preserve in an anhydrous condition. The success with which we were able to liberate the free acids from the barium salts by the addition of an exact equivalent amount of sulphuric acid may be judged by a comparison of the values of the apparent equivalent conductivities of the equilibrium mixtures produced first from the lactone and secondly from the free acid. The two values should be in complete agreement,* except in the case of the unmethylated lactones where the free acid is capable of generating a mixture of γ - and δ -lactones.

* Where the equilibrium value, as deduced by measurements on the free acid, differs from the measurements on the lactone, the former has been used in Table I, except in the case of tetramethyl δ -galactonolactone, for which the mean of the two has been given.

In the above manner the hydrolysis of the lactone to the equilibrium mixture of free acid and lactone, as well as the reverse change from free acid to equilibrium mixture, could be followed, although in this investigation greater importance has been attached to the former reaction.

The following tables record the experimental results obtained. The apparent equivalent conductivity λ of the lactone solution is given at time intervals t during the course of the hydrolysis. The equivalent conductivity λ_0 , or apparent equivalent conductivity λ , is then recorded for the free acid immediately after its liberation from the barium salt, and also, whenever possible, the apparent equivalent conductivity λ at different times t until the attainment of equilibrium.

Tetramethyl γ -mannonolactone, 0.0427N.

t (days)	9	14	19	34	39	45	46	52
λ	4.37	6.01	7.35	10.23	10.84	11.87	11.87	12.02 (const.)

Free acid: 0.0427N. Initial λ , 41.67.

γ -Mannonolactone, 0.0337N.

t (days)	2	3	5	7	10	27	30
λ	2.06	3.56	4.95	5.47	6.85	10.93	11.07 (const.)

Free acid, 0.0388N.

t (days)	0	2	3	6	27
λ	27.15	22.58	22.55	21.64	18.41

Tetramethyl γ -galactonolactone, 0.0664N.*

t (days) ...	0	2	4	7	8	9
λ	0.80	5.07	7.69	10.20	10.81	11.22
(days) ...	10	12	15	21	23	25
λ	11.59	11.80	11.90	12.05	12.07	12.07 (const.)

Free acid, 0.0605N.

t (days) ...	0	0.33	1	3	4	5
λ	24.8	22.15	19.64	16.30	15.29	14.30
t (days) ...	6	8	11	17	19	21
λ	13.69	13.20	12.90	12.80	12.65	12.65 (const.)

γ -Galactonolactone, 0.0562N.

t (days) ...	0.25	2	4	7	23	27
λ	0.69	2.32	3.18	4.27	7.11	7.15 (const.)

Free acid, 0.0562N.

t (days) ...	0	5 (mins.)	35 (mins.)	0.75
λ	14.75	14.39	14.08	13.43
t (days) ...	2	6	23	27
λ	12.77	12.56	9.25	8.95 (const.)

Trimethyl γ -xylonolactone, 0.0601N.

t (days) ...	2	3	5	7	10	26	30	34	37
λ	4.81	6.18	8.40	10.10	13.24	19.20	20.20	20.32	20.60 (const.)

* These values were determined by Dr. D. I. Jones on a specially purified specimen of lactone. The temperature was 25°.

Free acid, 0.0553*N*.

<i>t</i> (days)	0	2	3	6	26	34
λ	26.44	26.00	25.88	25.22	22.68	20.50 (const.)

Trimethyl γ -arabonolactone, 0.0481*N*.

<i>t</i> (days)	2	3	5	7	10	26
λ	6.79	8.54	11.62	13.41	15.82	17.99 (const.)

Free acid, 0.0489*N*.

<i>t</i> (hrs.)	0	48	72	144	26 days
λ	25.40	23.97	22.58	20.39	17.85 (const.)

Tetramethyl γ -gluconolactone, 0.0427*N*.

<i>t</i> (days)	0.9	1.5	7	9	10	11	12	14
λ	6.04	7.19	17.53	19.66	20.81	21.01	21.92	22.97
<i>t</i> (days)	15	16	18	19	21	24	28	42
λ	24.00	24.60	25.25	25.80	26.07	26.50	26.75	28.40 (const.)

Free acid, 0.0427*N*. Initial λ , 32.90. *γ -Gluconolactone*, 0.0208*N*.

(The specimen had been exposed to the atmosphere and apparently had already undergone partial conversion to the free gluconic acid.)

<i>t</i> (days)	0	2	4	6	21
λ	15.56	17.30	19.90	21.81	34.20 (const.)

Free acid, 0.0208*N*.

<i>t</i>	0	2 hrs.	17 days	21 days
λ	38.41	32.80	28.82	28.60 (const.)

Tetramethyl δ -mannonolactone, 0.0430*N*.

<i>t</i> (hrs.)	0.2	3	18	24	42	70	91	115
λ	1.13	7.00	13.45	15.60	19.67	22.75	24.38	24.84

Free acid, 0.0430*N*.

<i>t</i> (hrs.)	0	3	17.5	24	42	70	91
λ	31.54	30.98	29.12	27.90	26.85	26.29	25.75 (const.)

 δ -Mannonolactone, 0.0562*N*.

<i>t</i> (hrs.)	0.15	0.3	0.5	1	1.3	2.5
λ	1.81	1.88	2.46	3.26	3.77	5.16
<i>t</i> (hrs.)	3.5	4.5	6.5	20	28	43
λ	6.05	7.15	7.68	14.00	15.16	15.66 (const.)

Free acid, 0.0387*N*.

<i>t</i> (days)	0	2	3	6	20	26
λ	25.70	21.07	20.95	20.13	18.34	17.47 (const.)

Trimethyl δ -xylonolactone, 0.0132*N*.

<i>t</i> (hrs.)	1	4.5	6	23	26	29
λ	2.80	8.50	9.90	21.63	22.95	24.45
<i>t</i> (hrs.)	31.5	47	95	119	20 (days)	
λ	26.00	30.80	39.95	42.68	46.64 (const.)	

Free acid, 0.0132*N*.

<i>t</i> (hrs.)	0	0.15	0.3	4	24	30
λ	65.10	59.80	59.15	57.00	53.85	52.15
<i>t</i> (days)	2	5	21	25	29	
λ	51.20	50.80	48.14	47.60	45.67 (const.)	

Tetramethyl δ-gluconolactone, 0.0361N.

<i>t</i> (mins.)	5	10	15	25	30	35
λ	4.08	6.48	8.16	11.03	12.38	13.24
<i>t</i> (mins.)	55	75	100	120	170	24 (hrs.)
λ	16.41	19.53	22.76	24.15	27.50	33.60 (const.)

Free acid, 0.0347N.

<i>t</i> (hrs.)	0	44	68	99
λ	37.98	38.23	33.52	33.37

δ-Gluconolactone, 0.0562N.

<i>t</i> (mins.)	4	6	10	20	30	40
λ	1.46	1.97	2.72	4.41	5.45	6.56
<i>t</i> (mins.)	60	120	180	240	290	19 (hrs.)
λ	8.68	12.79	15.24	16.58	17.45	18.35 (const.)

Free acid, 0.0562N.

<i>t</i> (hrs.)	0	1.25	3.25	19	26
λ	19.45	19.20	18.71	17.75	17.75
<i>t</i> (hrs.)	44	47	116	32 (days)	
λ	17.60	17.60	16.94	16.10 (const.)	

Tetramethyl δ-galactonolactone, 0.0457N.

<i>t</i> (mins.)	3	5	10	15	20	30
λ	8.24	8.66	9.55	10.29	10.80	11.90
<i>t</i> (mins.)	45	60	80	100	120	150
λ	14.04	15.40	17.40	19.02	20.42	21.70
<i>t</i> (mins.)	180	210	240	260	17 (hrs.)	
λ	23.35	24.29	25.21	25.60	28.40 (const.)	

Free acid, 0.0461N.

<i>t</i> (hrs.)	0	60	84
λ	30.60	29.22	29.20 (const.)

Trimethyl δ-arabonolactone, 0.0526N.

<i>t</i> (mins.)	3	5	9	12	16	22	27	39
λ	2.005	2.435	3.155	3.575	4.280	5.16	5.89	7.50
<i>t</i> (mins.)	50	60	70	80	90	100	110	120
λ	8.96	10.13	11.05	12.08	12.95	14.10	14.98	15.74
<i>t</i> (mins.)	130	140	150	180	210	18 (hrs.)		
λ	16.50	17.24	18.15	19.57	20.42	25.98 (const.)		

Free acid, 0.0524N.

Initial λ , 26.34; after 6 days, 26.08 (const.).*Trimethyl δ-rhamnonolactone, 0.0343N.*

<i>t</i> (hrs.)	0.2	0.5	1	2	3.3	4
λ	1.40	1.75	2.37	3.24	4.67	5.41
<i>t</i> (hrs.)	20	27	47	70	120	
λ	13.20	14.31	17.89	19.45	19.90 (const.)	

Free acid, 0.0343N.

<i>t</i> (hrs.)	0	0.1	1	18	66	114
λ	33.65	32.40	31.13	25.00	20.75	19.90 (const.)

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