CORRECTION.

The Equilibrium between Carbon Monoxide, Carbon Dioxide, Sulfur Dioxide and Free Sulfur.—The following corrections should be made in the article appearing under this title in the November issue:[1]

P. 1630. Equations at top of page should read:

$$K_1 = \frac{P_{CO_2} P_{S_2}^{1/4}}{P_{CO} P_{SO_2}^{1/2}} \qquad K_2 = \frac{P_{CO} P_{S_2}^{1/2}}{P_{COS}}$$

P. 1630. Last line in Table I, 1st column, 41.2 should be 44.2.

P. 1640. First column in Table V, 7th formula, CO should be CO_2.

P. 1641. Experiment 7, $(CO_2 + S_2)$ should be $(CO_2 + {}^1/_4S_2)$.

P. 1642. First equation, the IT term should be positive. Line 19, equation should read: $-(1.375 - 0.0028T + 0.00000093T^2)$.

P. 1643. Middle of page, F_{298} should be ΔF_{298}.

J. B. FERGUSON.

RETARDATION BY SUGARS OF DIFFUSION OF ACIDS IN GELS.

By Evarts A. Graham and Helen Tredway Graham.

Received April 1, 1918.

The experiments described in this paper were first undertaken in order to find out, if possible, whether the protective action of carbohydrates against certain toxic agents in the body could be paralleled outside of the body. The results obtained are very interesting from this physiological point of view, but they also have some importance as data on the diffusion of electrolytes in gels, and it is from this chemical point of view that they will here be chiefly considered.

The greater part of the recent work on diffusion in gels has dealt with the phenomena of Liesegang's rings, precipitation membranes, etc., where the simple process of diffusion through the colloidal medium is complicated by the permeability of the precipitate formed during the diffusion. While it is undoubtedly true, as Bechhold and Ziegler[2] suggested, that a substance diffusing into a colloidal system actually changes the properties of the diffusion medium, it is possible, with suitable experimental conditions, to avoid any such marked changes as accompany the formation of rings or membranes of precipitate. Moreover, any process of diffusion in any medium whatsoever, necessarily brings with it some modification of the medium, as is shown empirically for instance by the inconstancy of Fick's "diffusion constant" with changing concentration;[3] there is therefore no

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[1] This Journal, 40, 1642 (1918).

[2] Bechhold and Ziegler, *Z. physik. Chem.*, 56, 105 (1906).

[3] For hydrochloric acid, for example, the "diffusion constant" varies from 1.39 to 2.31, as the concentration changes from 0.21 to 4.23 moles per liter. Landolt-Börnstein, 1912, p. 135.

a priori reason for assuming that the fundamental laws of diffusion in colloidal systems are different from those of diffusion in other media.

This conclusion is borne out by experiment: Nell,[1] while showing that the rate of diffusion of electrolytes into and out of gelatin is less than in water, shows at the same time that this decrease, due to the presence of the colloid, runs parallel with the decrease of conductivity when gelatin is added to the aqueous solution of an electrolyte, provided due allowance is made for the conductivity of the gelatin itself. The rate of diffusion and the conductivity are therefore similarly influenced by the same factors in the two systems. Dumanski[2] considers that in colloidal dispersions the decrease in conductivity and in rate of diffusion is due mainly to the fact that the presence of the colloid decreases the cross section available for the moving ions (molecules), since even in cases where the ions (molecules) penetrate the colloidal particles, they move much more slowly through them than in the external solution. Öholm[3] finds perfect parallelism between the decrease in the conductivity and in the diffusion coefficient of potassium chloride in gelatin gels, and finds further that the gelatin affects the conductivity and the diffusion in general in the same way as does an ordinary nonelectrolyte (sugar, glycerin). His conclusion that the colloid does not affect the degree of ionization of the electrolyte is confirmed by the work of Paterno and Cingolani[4] on the freezing-point constant of potassium chloride in solutions of gum arabic, dextrin and tannic acid. Pincussohn,[5] who measured the rate of diffusion of 0.1 N solutions of acids into 30% gelatin gels, states that the acids, when arranged in the order of decreasing diffusion rate, give in general the same series as when arranged in the order of decreasing degree of ionization. As a matter of fact, his experimental series follows the order of rate of diffusion in aqueous solution quite as closely as it does that of degree of ionization. Finally, the identity of the underlying laws of diffusion in colloidal and other media is demonstrated by the work of Vanzetti,[6] who has shown in an elaborate series of experiments, that when an acid (nitric, hydrochloric, hydrobromic, hydroiodic) or a salt (potassium chloride) diffuses upward through a gel, the ratio of the height reached to the square root of the time taken to reach this height ($h/\sqrt{t}$) is a constant, as well as the ratio between the height reached and the total quantity diffused

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[1] Nell, *Ann. Physik*, 18, 323 (1905).

[2] Dumanski, *Z. physik. Chem.*, 60, 553 (1907); *Z. Chem. Ind. Kolloide*, 3, 210 (1908).

[3] Öholm, *Medd. Vetenskapsakad. Nobelinst.*, 2, No. 30 (1913).

[4] Paterno and Cingolani, *Gazz. chim. ital.*, 44, [1] 36 (1914); *C. A.*, 8, 1691 (1914).

[5] Pincussohn, *Z. Exper. Path. Ther.*, 10, 308 (1912).

[6] Vanzetti, *Atti ist. Veneto*, 73, II, 1385 (1914); 74, II, 805, 1229 (1915); *Z. Elektrochem.*, 20, 570 (1914).

(h/q). The constancy of these ratios is demanded by the ordinary laws of diffusion.[1]

Vanzetti has not considered, however, the question of the influence of relatively indifferent substances on diffusion in a gel, and there seems to have been no accurate work done on this question. Yet it is a point of the greatest physiological importance, since there are always present in cells indifferent materials which may not react with the diffusing substance, but nevertheless affect the progress of the diffusion. In 1906 Bechhold and Ziegler[2] published some work on the possibility of influencing diffusion in gels by introducing into them indifferent substances. Their observations, though interesting, are far from conclusive. They found that the presence of certain salts (sodium chloride and sodium iodide) increases the rate of diffusion of methylene blue and beet-juice in gelatin and agar gels, whereas sodium sulfate lowers it. Similarly with nonelectrolytes, they found that urea favors the diffusion of both these dyes, while glucose and glycerin hinder the diffusion of beet-juice but favor the diffusion of methylene blue. The last two nonelectrolytes, as well as alcohol, interfere with the diffusion of the electrolytes tried (sodium chloride and sodium sulfate). The differences in the distances traversed by the diffusing substances in the absence and presence of indifferent substances, are not greater than a centimeter, and apparently no duplicate experiments were carried out. In view of the difficulty of controlling all the factors involved in determining the condition of a colloid, it is possible that some of Bechhold and Ziegler's results might be modified or even reversed by more careful work.

The only other work found in the literature on the effect of added substances on diffusion in gels was carried out by Böhi[3] who showed that the diffusion of electrolytes (silver nitrate, ferric chloride, sodium hydroxide and hydrochloric acid) in a gelatin gel was not affected by the presence of cadmium iodide, formanilid or various other substances used; but that certain aromatic hydroxyl compounds (tannin and gallic acid) had a marked effect in hindering diffusion, and concluded that this effect was due in part to chemical reaction.

It seemed desirable to make an accurate and, if possible, quantitative study of the effect of indifferent substances on diffusion in gels, and it was decided to carry out the experiments with sugars, primarily, as stated at the beginning of the article, because of their physiological importance; but also because they are easily obtained pure and uniform, and have well-known properties. Moreover, preliminary experiments showed that they cause a marked retardation of the diffusion of electrolytes in

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[1] See Stefan, *Ber. Wiener Akad.*, 79, II, 161 (1879); 98, II, 473 (1889).

[2] Bechhold and Ziegler, *Loc. cit.*

[3] Böhi, *Vierteljahr. Naturf. Ges. Zürich*, 56, 183 (1911).

gels; and some work by Arrhenius[1] existed to show that saccharose (and undoubtedly any sugar) has a similar effect on diffusion in water.

Experimental Method.

The sugars used in our experiments were glucose, saccharose and lactose, and the diffusion medium gelatin gel, usually 10%. The experiments here summarized were carried out with acids (hydrochloric, nitric, sulfuric, phosphoric, lactic, formic, acetic and butyric, all 0.2 *N*); but a few preliminary experiments with bases have shown that the effect on the diffusion of these substances is analogous.[2]

The experimental procedure was the following: A weighed amount of Gold Label gelatin was dialyzed in cold tap water overnight, or in 4 changes of distilled water at room temperature for 9 hours. The gelatin was then melted by warming and to it were added a few drops of lysol, litmus solution sufficient to give a decided color to the mixture and 0.2 *N* sodium hydroxide solution to neutralize. Distilled water was then added to make the gelatin solution 20 %. To 10 cc. of this gelatin in the control tubes was added an equal volume of water; in the other tubes part of the water was replaced by the appropriate volume of molar sugar solution so that the final concentration of the gelatin in every tube was 10%. The final concentration of sugar ranged from 0.025 to 0.5 molar. The contents of the tubes were thoroughly mixed by means of special pipets with large outlets, and introduced with the help of these pipets into the tubes (diameter, 14–15 mm., length 250–260 mm.) in which the diffusion was to take place. The pipets made it possible to avoid getting any of the gelatin mixture on the walls of these diffusion tubes above the part actually filled by the gelatin. The tubes were plugged with cotton, and the gelatin mixture allowed to set at room temperature, after which they were immersed to within 2 to 3 cm. of the top in a de Khotinsky thermostat at 26°. In the whole series of experiments here described, the temperature never varied more than two or three tenths from 26°. The tubes were allowed to remain in the thermostat overnight before the acid was introduced, in order that the gel, which changes rapidly immediately after heating and subsequent cooling, might be as nearly as possible an unchanging medium during the course of the duffusion.

On the following day, 0.2 *N* acid (15 cc.) was carefully introduced on top of the gel. It was necessary to remove each tube from the thermostat for this purpose and for subsequent readings, but the tube was never out of the thermostat for more than a minute at a time, and was handled very carefully, in order to avoid convection currents as far as possible. The

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[1] Arrhenius, *Z. physik. Chem.*, 10, 51 (1892).

[2] The experiments on the diffusion of bases as well as the preliminary experiments with acids were carried out by one of us (E. A. G.) with Dr. Frank Nuzum, in the Otho S. A. Sprague Memorial Institute Laboratory of Clinical Research, Chicago.

introduction of the acid caused a sharp color-change in the litmus at the surface of the gel, and the distance from the line of division between the acid shade and the neutral shade of litmus, to a permanent mark at the top of the tube, was immediately and carefully measured, and the exact time noted. Measurements of this distance were made at definite intervals (usually 12 hours) after this time and the rate of progress of the hydrogen-ion concentration sufficient to turn litmus thus found. The diffusion was allowed to continue for at least 144 hours, and in many cases longer. No attempt was made to read the distance more accurately than to half a millimeter, since duplicate tubes made up of the same gelatin, and as nearly identically as possible, often showed a difference of this amount. At best the reading error was large. Moreover, it was often difficult with the organic acids to determine the exact point of color-change. An experiment with lactic acid and phenolphthalein colored slightly pink with hydroxide, showed that the vagueness of this point was not decreased by the substitution of this indicator for litmus.

The tubes in any one series with a sugar concentration ranging from zero to 0.5 molar, were always made up from the same preparation of gelatin. The acids were within 0.005 of exactly 0.2 N, except the phosphoric acid which was 1.01 × 0.2 N. The phosphoric acid was made up as a dibasic acid, since the tertiary ionization is so slight as not to affect phenolphthalein.

Effect of Sugars on Distances of Diffusion.

The most striking thing about the results obtained is the marked retardation by the sugars of the diffusion of all the acids tried. For a glucose concentration of 0.5 molar in 10% gelatin, this retardation ranges from approximately 10% for formic, acetic, butyric and lactic acids, to 20% for hydrochloric, sulfuric and phosphoric acids, and to 40% for nitric acid.[1]

As would be expected, the same concentration of disaccharides causes somewhat greater retardation (roughly, half again as much, except with nitric acid, where the increase in retardation is considerably less). The change of the retardation with the concentration of the sugar will be discussed in detail later (see page 1908) but it should be noted here that all concentrations of sugar down to and including 0.025 molar, the lowest concentrations used, have a retarding effect. This effect increases with the concentration of sugar, but not in proportion to it.

In Table I is given a typical experimental result of the diffusion of 0.2 N hydrochloric acid in 10% gelatin containing various concentrations of glucose. The distances traversed by the line of color-change, lavender to red, during the times indicated in the first column are expressed in mm.

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[1] For irregularities with nitric acid, see page 1906.

TABLE I.

Distances of Diffusion Expressed in mm. 0.2 *N* Hydrochloric Acid in 10% Gelatin at 26°.

	Molar concentration of glucose.							
Hours.	0.	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
12	16	16	15.5	15	14	13	12.5	11.5
24	22.5	22.5	22.5	22	20.5	19.5	19	17.5
36	27.5	28	27	26.5	25	24	23.5	21.5
48	32.5	32.5	31.5	31	29.5	28	27.5	25.5
60	35.5	36	35.5	35	33	31.5	30.5	28.5
72	38.5	39	38.5	38	35.5	34.5	33	31
84	42	42	41.5	41	38.5	37	35.5	33.5
96	45	45	44.5	44	41	39.5	38	35.5
108	47	47	46	45.5	43	41.5	40.5	37.5
120	50	50	49	48.5	45.5	44	42.5	40
132	51.5	51.5	51	50.5	47.5	45.5	44	41.5
144	54	54.5	53.5	53	50	48	46.5	44

Fig. 1 shows graphically the retarding effect of glucose and saccharose on the diffusion of hydrochloric and lactic acids. The diffusion distance in mm. is represented along the vertical axis and the time interval during which the diffusion has been allowed to take place along the horizontal axis. The greater retarding power of the disaccharide is clearly shown, as well as the relatively greater retarding effect on the inorganic acid. Similar curves could, of course, be constructed for all the acids and all the concentrations of sugar used, but these are sufficient for illustration.

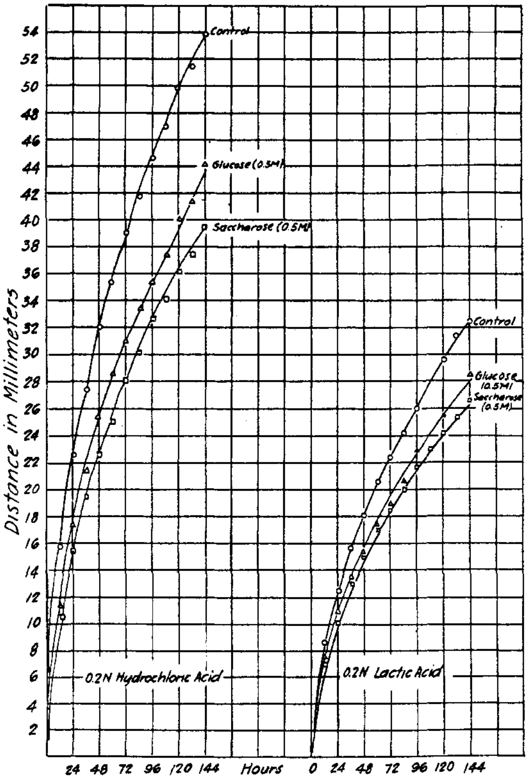

Fig. 1.—Retardation of diffusion of hydrochloric acid (0.2 *N*) and of lactic acid (0.2 *N*) in 10% gelatin by 0.5 *M* glucose and by 0.5 *M* saccharose. Temperature = 26°.

Calculation of Distance/$\sqrt{\text{time}}$ = K.

As has already been mentioned (p. 1901) Vanzetti[1] has shown that when an electrolyte diffuses upward into a gelatin gel, it follows

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[1] Vanzetti, *Loc. cit.*

the ordinary laws of diffusion, and in particular that the ratio of the distance covered to the square root of the time ($h/\sqrt{t}$) is a constant. Our experiments bear out this conclusion and show that it holds for gelatin containing sugars as well as for pure gelatin and for downward as well as upward diffusion.[1] Table II gives by way of example the values of this ratio for hydrochloric acid diffusing in gelatin with and without glucose (experimental data from Table I); the other acids and sugars give in general similar results, and the average values of the ratios are given in Table III.

The relative diffusion rates as determined by our results for the various acids, differ somewhat from those found by Pincussohn[2] and Vanzetti.[3] The most striking differences are that acetic acid diffuses relatively more rapidly than in Pincussohn's experiments, and that nitric acid diffuses more rapidly than hydrochloric, contrary to Vanzetti's results. This is true in the latter case only in the absence of sugar for, in gelatin containing sugar above a certain concentration, the relative speeds of nitric and hydrochloric acids are reversed. The cause of the differences from the earlier work is not clear. It might be advantageous to measure the rates of diffusion in specially purified gelatin. The absolute values for the speeds of diffusion are not comparable, since the temperture and the gelatin concentration differed in the 3 sets of experiments.

TABLE II.

Values of $K = \text{Distance}/\sqrt{\text{time}}$ for Diffusion of 0.2 N Hydrochloric Acid in 10% Gelatin at 26°.

(Calculated from Experimental Data Given in Table I).

	Molar concentration of glucose.							
Hours.	0.	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
24	4.59	4.59	4.59	4.49	4.18	3.98	3.88	3.57
36	4.58	4.67	4.50	4.42	4.17	4.00	3.92	3.58
48	4.69	4.69	4.55	4.47	4.26	4.04	3.97	3.68
60	4.58	4.65	4.58	4.52	4.26	4.07	3.94	3.68
72	4.54	4.60	4.54	4.48	4.18	4.07	3.98	3.65
84	4.58	4.58	4.53	4.47	4.20	4.04	3.87	3.66
96	4.59	4.59	4.54	4.49	4.18	4.03	3.88	3.62
108	4.52	4.52	4.43	4.38	4.14	3.99	3.90	3.61
120	4.56	4.56	4.47	4.43	4.15	4.02	3.88	3.65
132	4.48	4.48	4.44	4.40	4.13	3.96	3.83	3.61
144	4.50	4.54	4.46	4.42	4.17	4.00	3.88	3.67
Av.,	4.56	4.59	4.51	4.45	4.18	4.02	3.89	3.63

In our experiments, in contrast with the other acids and with Vanzetti's results, nitric acid diffusing in gelatin containing little or no sugar, gives for $\text{distance}/\sqrt{\text{time}}$ a value not constant, but increasing rapidly up

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[1] Cf. Procter and Law, *J. Soc. Chem. Ind.*, **28**, 297 (1909).

[2] Pincussohn, *Loc. cit.*

[3] Vanzetti, *Atti. ist Veneto*, **73**, II, 1385 (1914).

TABLE III.

Values of $K = \text{Distance}/\sqrt{\text{time}}$.

Acid.	Molar concentration of glucose.						
	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
Hydrochloric...	4.58	4.51	4.45	4.18	4.02	3.89	3.63
	4.13	4.02	3.95	3.79	3.56	3.38	3.16
Sulfuric........	3.62	3.57	3.50	3.43	3.17	2.93	2.75
	3.79	3.73	3.64	3.50	3.23	3.05	2.85
Nitric..........	5.33	4.73	4.35	3.99	3.64	3.36	3.19
Phosphoric.....	1.99	1.97	1.96	1.85	1.75	1.69	1.64
Lactic.........	2.65	2.59	2.63	2.54	2.53	2.45	2.29
	2.64	2.64	2.56	2.60	2.48	2.44	2.36
Formic.........	3.07	3.13	3.16	3.06	2.97	2.87	2.77
	3.19	3.16	3.14	3.12	3.04	3.03	2.85
Acetic.........	3.61	3.49	3.49	3.50	3.41	3.22	3.16
	3.70	3.63	3.67	3.51	3.37	3.40	3.31
Butyric........	3.32	3.20	3.19	3.18	3.10	2.97	2.89
	3.32	3.23	3.21	3.25	3.20	3.07	2.96

	Molar concentration of saccharose.						
	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
Hydrochloric...	4.39	4.22	4.08	3.75	3.48	3.35	2.94
	4.52	4.35	4.27	3.92	3.75	3.51	3.26
Sulfuric........	3.82	3.69	3.62	3.47	3.20	2.94	2.66
Nitric..........	5.78	4.91	4.37	4.08	3.73	3.43	3.20
Lactic.........	2.67	2.57	2.52	2.43	2.29	2.21	1.99
	2.65	2.57	2.55	2.49	2.46	2.32	2.18
Formic.........	3.43	3.30	3.25	3.10	3.13	2.95	2.73
Acetic.........	3.86	3.72	3.63	3.49	3.45	3.27	3.02
Butyric........	3.44	3.34	3.36	3.18	3.16	2.96	2.76

	Molar concentration of lactose.						
	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
Hydrochloric...	4.24	4.06	3.91	3.72	3.57	3.38	3.09
Sulfuric........	3.60	3.56	3.39	3.30	3.00	2.84	2.64
Nitric..........	5.28	4.44	4.28	3.88	3.71	3.27	2.84

to 72 hours, remaining practically steady for some time and then decreasing slowly. (For 0.2 N nitric acid in 10% gelatin the value of distance/$\sqrt{\text{time}}$ varies from 5.21 at 24 hours to 6.01 at 72 hours, and 5.79 at 144 hours.) All the acids used show an increase up to 24 hours,[1] and

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[1] Note, for instance, these values of the ratio distance/$\sqrt{\text{time}}$ in the experiment with hydrochloric acid and glucose for which the later values are given in Table II.

Hours.	Molar concentration of glucose.						
	0.	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
1	4.00	4.50	4.00	4.00	3.50	3.50	3.00	2.50
4	4.50	4.50	4.50	4.25	4.00	3.75	3.50	3.25
8	4.60	4.60	4.60	4.42	4.07	3.89	3.71	3.36
12	4.62	4.62	4.47	4.33	4.04	3.75	3.61	3.32
24	4.59	4.59	4.59	4.49	4.18	3.98	3.88	3.57

Vanzetti observed a slight tendency to an increase and subsequent decrease of the ratio.[1] The decrease is probably due to diminishing concentration of the diffusing liquid; in most of our experiments it is not noticeable, probably because they were not continued long enough. It was found that hydrochloric acid which gives a constant value for the ratio in 10% gelatin, gives in 3% gelatin, in which it diffuses much more rapidly, a varying value similar to that for nitric acid in 10% gelatin, while lactic acid in 3% gelatin still gives a constant value (see page 1912); and it is possible that the peculiarity may be connected with a high diffusion rate.

Relation between Retardation of Diffusion and Concentration of Sugar.

The method used in calculating the amount of retardation induced by the sugars depends on the constancy of the ratio distance/$\sqrt{\text{time}}$ for each concentration of sugar. The average value (K) of this ratio throughout the whole experiment in gelatin containing a certain sugar concentration, is subtracted from K_0, the average value of the ratio in gelatin containing no sugar. The difference (Δ) between these two values is a measure of the retardation caused by this particular sugar concentration. The calculation of the percentage retardation ($100\Delta/K_0$) makes it possible to compare the results with different acids and sugars.

The values of $100\Delta/K_0$, calculated from the experimental results in this way and recorded in part in Table IV, show that the amount of retardation produced by the sugars increases with the concentration of the sugar, as would be expected, but not in direct proportion to it. The relation between these two quantities is clearly shown by the graphic method. If there were direct proportionality between them, the $100\Delta/K_0$ concentration curve would of course be a straight line. Fig. 2 shows that this is not the case, but that the retardation is proportionately greater for the smaller concentrations of sugar. Only a few of the curves are plotted. Those with saccharose and lactose are similar to those plotted with glucose. The results with the organic acids are, in general, too inaccurate to warrant a quantitative study.

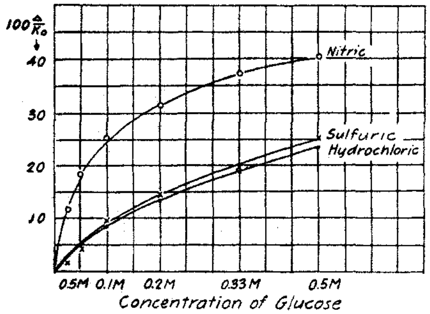

Fig. 2.—Relation between the concentration of glucose and the percentage retardation of diffusion. The values of the percentage retardation ($100\Delta/K_0$) from Table IV.

These results are in general analogous to known physiological facts concerning the condition of "acidosis," which occurs during fasting, diabetes, and in poisoning with

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[1] Vanzetti, *Z. Elektrochem.*, **20**, 575 (1914).

TABLE IV.

Percentage Retardation ($100\ \Delta/K_0$).

Molar concentration of glucose.

Acid.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
Hydrochloric	1.5	2.8	8.7	12.2	15.1	20.7
	2.7	4.4	8.2	13.3	18.2	23.5
Sulfuric	1.4	3.3	5.3	12.4	19.1	24.0
	1.6	4.0	9.6	14.8	19.5	24.8
Nitric	11.3	18.4	25.1	31.7	37.0	40.2
Phosphoric	1.0	1.5	7.0	12.1	15.1	17.6
Lactic	2.3	0.8	4.2	4.5	7.6	13.6
	0.0	3.0	1.5	6.1	7.6	10.6
Formic	..	..	0.3	3.3	6.5	9.8
	0.9	1.6	2.2	4.7	5.0	10.7
Acetic	3.3	3.3	3.1	5.5	10.8	12.5
	1.9	0.8	5.1	8.9	8.1	10.5
Butyric	3.6	3.9	4.2	6.6	10.5	13.0
	2.7	3.3	2.1	3.6	7.5	10.8

Molar concentration of saccharose.

	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
Hydrochloric	3.9	7.1	14.6	20.7	23.7	33.0
	3.8	5.5	13.3	17.0	22.4	27.9
Sulfuric	3.4	5.2	9.2	16.2	23.0	30.4
Nitric	15.1	24.4	29.4	35.5	40.7	44.6
Lactic	3.8	5.6	9.0	14.2	17.2	25.5
	3.0	3.8	6.0	7.2	12.5	17.7
Formic	3.8	5.3	9.6	8.8	14.0	20.4
Acetic	3.6	3.6	9.6	10.6	15.3	21.8
Butyric	2.9	2.3	7.6	8.1	14.0	19.8

Molar concentration of lactose.

	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
Hydrochloric	4.3	7.8	12.3	15.8	20.3	27.1
Sulfuric	1.1	5.8	8.3	16.7	21.1	26.7
Nitric	15.9	18.9	26.5	29.8	38.1	46.2

substances like chloroform, phosphorus, etc. In this condition, various organic acids, together with acetone, are formed in abnormal amounts in the body. The administration of comparatively small amounts of alcohol, sugars and other substances possessing alcohol groups, is accompanied by a marked diminution in the output of these acids, and by a marked improvement in the individual's symptoms. The administration of from only 75 to 80 g. of carbohydrate in 24 hours to an average-sized adult, is usually sufficient to produce a marked improvement. In the case of chloroform poisoning, we have a very interesting example of the protective action of glucose against an inorganic acid. In a former article[1] by one of us, it has been shown that the late manifestations of chloroform poisoning, such as edema, necrosis of the liver, fatty degenerative changes and a tendency to hemorrhage, are chiefly if not entirely ascribable to the action of hydrochloric acid which is formed within the body as a dissociation product of chloroform, probably according to the well-known views of Nef on methylene dissociation. In another article[2] it has also been shown that the administration of sufficient amounts of sugar to dogs protects them from the degenerative changes already mentioned produced in the tissues by chloroform. Likewise, the peculiar insusceptibility of normal newborn pups to these late poisonous effects of chloroform is to be ascribed to the fact that their livers are richly supplied with glycogen (polymerized glucose), which is very largely depolymerized into glucose by hydrochloric acid liberated from the chloroform molecule. It would therefore seem that there is a direct protective action of glucose against hydrochloric acid effects in the cell. But, as bearing on the point brought out in the preceding paragraph, it is still more interesting that this protective action in the body is not proportional to the concentration of the glycogen (or glucose). If the liver is made experimentally to become poor in glycogen, the production of severe effects is very easily accomplished by the administration of acids. Increasing amounts of glycogen afford increasing protection up to a point where almost a maximum of protection is obtained, so that concentrations beyond this point have very little, if any, additional effect. For example, a dog whose liver contains 9% of glycogen of its total wet weight seems to be as unsusceptible to the results of chloroform poisoning as one whose liver contains 18 or more % of glycogen.

The fact that smaller concentrations of sugar cause a relatively greater retardation of diffusion of acids in gelatin is comparable to the findings of Arrhenius concerning the diffusion of electrolytes in water containing saccharose. Arrhenius[3] worked with the change in the diffusion constant, and found that this change is not a linear function of the saccharose concentration, but rather that the diffusion constant suffers a larger decrease for the first additions of saccharose to the water than for subsequent equal increments of the saccharose concentration.

The retardation of diffusion is then not a linear function of the sugar concentration; it is therefore desirable to find out if possible what the relation is between these two quantities. The typical form of the retardation-concentration curves, as shown in Fig. 2, at once suggests that they are parabolas; and if this is so, it should be possible by substituting values

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[1] E. A. Graham, *J. Exp. Med.*, **22**, 48 (1915).

[2] *Ibid.*, 21, 185 (1915).

[3] Arrhenius, *Z. physik. Chem.*, **10**, 51 (1892).

of the relative retardation (Δ/K_0) for y, and of the concentration (c) for x, in the general mathematical expression for a parabola,

$$y^n = ax$$

to obtain a constant value for n. The most convenient method of carrying out the calculation is by taking the logarithms of both sides of the equation. We then have

$$n \times \log \Delta/K_0 = \log c + \log a,$$

an equation which may easily be tested. Since it is a linear expression with two variables, $\log \Delta/K_0$ and $\log c$, we should obtain a straight line by plotting these two logarithms, the slope of the line being determined by the constant n. When due allowance is made for the experimental error, the results, as plotted in Fig. 3 for glucose, indicate that the relationship between sugar concentration and retardation of diffusion probably may be expressed approximately by the equation

$$(\Delta/K_0)^n = ac.$$

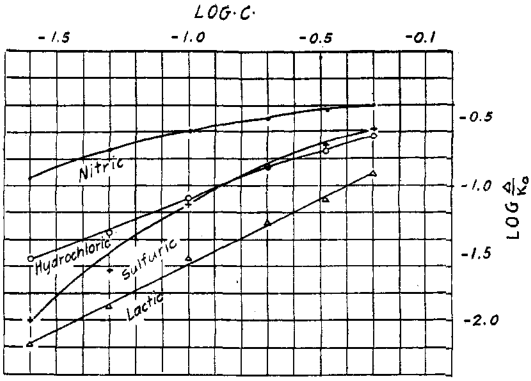

Fig. 3.—Relation between the logarithms of the glucose concentration and the logarithms of the relative retardation of diffusion of the acids indicated.

The curves for lactose and saccharose are very similar to those for glucose and therefore are not given. Table V gives by way of illustration, the numerical results from which the glucose-hydrochloric acid curve in Fig. 3 was plotted, as well as the numerical value of n calculated as indicated from these results and Fig. 3.

TABLE V.

Hydrochloric Acid and Glucose.

Glucose conc. in mols (c).	Log c.	Δ/K_0.	Log Δ/K_0.	Log a from Fig. 3.	$n = \frac{\log c + \log a}{\log \Delta/K_0}$.
0.025	—1.602	0.027	—1.569	—0.40	1.276
0.050	—1.301	0.044	—1.357		1.253
0.100	—1.000	0.082	—1.086		1.289
0.200	—0.699	0.138	—0.860		1.278
0.333	—0.477	0.182	—0.740		1.185
0.500	—0.301	0.235	—0.629		1.115
				Average,	1.233

Results in 3% Gelatin.

In an attempt to obtain greater diffusion distances and therefore smaller experimental error, the diffusion was carried out in 3% gelatin gel with hydrochloric and lactic acids, and glucose. As has already been mentioned, it was found that in this dilute gelatin, the ratio of the distance of diffusion to the square root of the time was no longer constant for the diffusion of hydrochloric acid, except where there was a good deal of sugar present, and the speed of diffusion was consequently decidedly decreased. This is similar to the peculiarity observed with nitric acid in 10% gelatin (see page 1907). Lactic acid diffusing in 3% gelatin, however, gives as constant a value of the ratio as in 10% gelatin, although the constant is of course larger in the less concentrated gelatin (4.35 in control gelatin, 3.84 in gelatin containing 0.5 M glucose). The experimental results with hydrochloric acid are given in Table VI; and in Fig. 4 are plotted the distances of diffusion of the acid 36 hours after its introduction into tubes containing varying amounts of glucose. The proportionately greater retardation produced by the smaller concentrations of sugar is strikingly shown here.

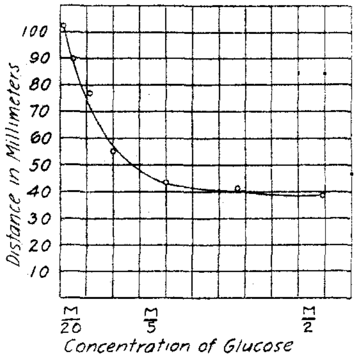

Fig. 4. Distances of diffusion of 0.2 N hydrochloric acid in 3% gelatin, after 36 hours, in the presence of glucose in various concentrations.

TABLE VI.

Distances of Diffusion Expressed in mm. 0.2 N Hydrochloric Acid in 3% Gelatin at 26°.

	Molar concentration of glucose.							
Hours.	0.	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
12	46.4	45	41	35	26.5	24	22.5	22
24	79	77	69.5	59.5	42.5	35.5	33	32
36	103.5	101.5	91	77.5	54.5	43.5	40.5	39
48[1]	...	...	112	96.5	66	50.5	47	45
60	...	...	...	..	75.5	56.5	52.5	50.5
72	...	...	...	..	86	63.5	58.5	56
84	...	...	...	..	92.5	68	62.5	59.5
96	...	...	...	..	101.5	73	67	64
108	...	...	...	..	108	77.5	71	68
120	....	...	...	..	116	82	75	71.5

Since the experimental error did not seem to be materially reduced with lactic acid in the more dilute medium and since the ratio distance/$\sqrt{\text{time}}$

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[1] No further readings could be made in the control tubes, as the acid had reached the bottoms of the tubes; similarly after this reading for the two tubes containing the most dilute glucose solution.

proved to be inconstant with hydrochloric acid, the dilute gelatin was abandoned for the present.

Effect of Salts on Diffusion.

It was thought possible that the diffusion of acids into gels might run parallel with the swelling of gels in acid solution. In this case retardation of diffusion by the sugars might be interpreted as being essentially a reduction of the swelling of the gel. Fischer[1] has shown that nonelectrolytes (including various sugars) are much less effective than electrolytes in reducing the swelling of colloids in acid or alkaline solutions. In our first experiments on the relative effects of electrolytes and nonelectrolytes on diffusion, a sodium chloride solution only half so concentrated as the sugar solution was used, in order to allow for the ionization of the electrolyte. It was found, however, that the salt was markedly less effective than the sugar in retarding diffusion, and solutions of sugar and of salt of equal concentration were therefore compared. Even under

Table VII.

Distances of Diffusion Expressed in mm. 0.2 *N* Hydrochloric Acid in 10% Gelatin at 26°

	Molar concentration of salt.							
Hours.	0.	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
12	14	14	14.5	13.5	12.5	13	12.5	12.5
24	21	21.5	21.5	21	19	19	19	19
36	26	26	26	25.5	23.5	23.5	23	23
48	30.5	30.5	30.5	30	27.5	27.5	27	27
60	34	34	33.5	33	30.5	31	30	30
72	37.5	37.5	37.5	37	34.5	35	34	33.5
84	40.5	40	40.5	39	36.5	37.5	36	36
96	43.5	43	43	42.5	40	41	39	39
108	46	45.5	45	44.5	41.5	43.5	41	41
120	49	48	48	47	44.5	46	44	44
132	50.5	50	50	49	46.5	48	46	46
144	53	52	52	51	48	50.5	48	47.5

	Molar concentration of saccharose.							
Hours.	0.	0.	0.025.	0.05.	0.1.	0.2.	0.33.	0.5.
12	14	14	14	13.5	12	11	11	9
24	21	21.5	20.5	20	18	16.5	16.5	13.5
36	26	26	25	24	21.5	20	19.5	16.5
48	30.5	30.5	29	28.5	25.5	24	23	20
60	34	34	32.5	31.5	28.5	27	25.5	22.5
72	37.5	37.5	36	35	32	30	29	24.5
84	40.5	40	39	37.5	34.5	32	30.5	27
96	43.5	43	41.5	40	37	35	33	29.5
108	46	45.5	44	42.5	39.5	36	35	31.5
120	49	48	46.5	44.5	42	38.5	37	33.5
132	50.5	50	48.5	47	44	40.5	38.5	35
144	53	52	50.5	49	46	42.5	40.5	37

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[1] Martin Fischer, "Oedema and Nephritis," John Wiley and Sons, N. Y., 1915, pp. 66–81.

these conditions of equal concentration, the salt had a much smaller retarding effect, as shown by the typical experiment recorded in Table VII. At 144 hours, for instance, the retardation of diffusion of 0.2 *N* hydrochloric acid by 0.5 *M* saccharose is 29.5%; by 0.5 *M* sodium chloride, 9.5%. These two series were carried out simultaneously with the same preparation of gelatin, and are therefore strictly comparable. Reference to Table I shows that the retardation by glucose of the diffusion of hydrochloric acid is approximately 20%, so that the effect of the salt is decidedly less than that of the monosaccharide also. A careful series of experiments on the retarding action of salts was not carried out, but rough experiments have shown that nitric and acetic acids are, like hydrochloric acid, retarded decidedly more by sugars than by sodium chloride. Indeed, 0.5 *M* sodium chloride has no appreciable retarding effect on the diffusion of acetic acid even after 72 hours, while 0.5 *M* glucose produces about 10% retardation.

The Mechanism of the Retardation of Diffusion.

There is not at the present time sufficient experimental evidence at hand to warrant the formulation of a hypothesis for the retardation of diffusion by sugars, but certain considerations bearing on this point are suggested by the above facts.

1. The degree of retardation seems to bear no relation to the rate of diffusion of the acid, since as a rule phosphoric acid is retarded more than the faster acetic acid.[1]

2. In general the "stronger" acids are retarded more than the "weaker," though this cannot be followed out in detail; for example, lactic acid which is ionized more than acetic acid, is retarded no more than the latter.

3. Since saccharose and lactose produce practically the same degree of retardation, it seems probable that all disaccharides have approximately the same retarding power; and it may be inferred that all monosaccharides also have equal retarding power, but smaller than that of the disaccharides. It is hoped to test this point by using other sugars in later experiments.

4. A consideration of the results with salt is particularly suggestive, especially in comparison with the effects of salt and sugar on the swelling of gelatin in acid. It should be remembered in comparing these two sets of experiments that there is a fundamental difference between them, since in the swelling experiments the salt (or sugar) is not in the gelatin but in the acid solution; while in the diffusion experiments it is in the gelatin. In Table VIII is given the percentage decrease of swelling produced by sodium chloride and by the most effective of the non-electrolytes, sac-

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[1] See Table IV. The exceptions occur only with the two lowest concentrations of glucose where the percentage of reading error is necessarily greatest.

charose (calculated from Fischer's Tables XXV and XXIX).[1] Fischer measures the swelling by the gain in parts by weight of a gelatin disc immersed in hydrochloric acid solution containing salt or sugar in various concentrations (0–1.0 M). Taking as a basis the gain in hydrochloric acid solution alone, the percentage decrease in this gain produced by the addition of salt or sugar has been calculated from his results.

TABLE VIII.

Percentage Decrease of Swelling.

		Molar concentration of saccharose.				
Conc. of hydrochloric acid.	Hours.	0.1.	0.3.	0.5.	0.6.	1.0.
0.005 *N*..............	18.45	24.6	..	..	43.9	65.7
	26.30	12.3	..	..	32.9	63.7
		Molar concentration of salt.				
		0.1.	0.3.	0.5.		
0.050 *N*..............	14.00	29.6	50.7	60.6	..	..
	27.35	28.7	49.4	58.6	..	..

It is unfortunate that there are no available data using the same concentration of acid with the two substances.[2] However, it may be said that under the conditions of the experiment the salt is in general more effective than the sugar in reducing swelling, just the reverse of the effect on diffusion.

Since the substances arranged in the order of their power to decrease acid swelling give, in general, the well-known lyotrope series,[3] the results on the retardation of diffusion seem to deviate from a more or less general law. But the apparent dissimilarity between the swelling and diffusion phenomena is modified by the difference in the experimental conditions mentioned above, particularly in view of Procter's results on the acid swelling of gelatin.[4] According to Proctor, the swelling of gelatin in acid solution is due to the fact that the anion of a highly ionizable salt formed from the acid and the gelatin (a diacid base) tends to diffuse outward. The amount of swelling is dependent upon "the excess of concentration of diffusible ions of the jelly over that of the external solution." The addition of salts to the acid solution in Fischer's swelling experiments increases the concentration of diffusible ions in the external solution, while the addition of salts to the gelatin in our diffusion experiments relatively decreases the concentration of diffusible ions in the external solution. Considered solely from this point of view, therefore, the two sets of ex-

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[1] Fischer, *Loc. cit.*

[2] In a personal communication, Dr. Fischer states that he has since found that in acid solutions of equal concentration, salt is much more effective than sugar in decreasing the swelling of gelatin.

[3] See, for instance, Fischer, *Loc. cit.*, Fig. 8, p. 64.

[4] Procter, *J. Chem. Soc.*, 105, 313 (1914); Procter and Wilson, *Ibid.*, 109, 307 (1916).

periments should give reversed results, if the swelling and diffusion phenomena are fundamentally identical; that is, the addition of salt to the gelatin should favor diffusion. To test the question of the underlying parallelism between the swelling and diffusion phenomena, it might be profitable to carry out diffusion experiments in which the salt was added to the acid and not to the gelatin.

5. Since, however, salt, as well as sugar, added to the gelatin, actually retards diffusion, there must be other factors involved which are opposed to the hypothetical ionic increase of diffusion just discussed. It is not possible at this time to say what these factors are. With sugar, the retardation of diffusion may be due in part to some chemical action between the acid and the sugar,[1] or perhaps to the increased viscosity of the gel. Neither of these possibilities would account for the retardation by salt, however. There can be no question of chemical action between hydrochloric acid and sodium chloride, and the addition of salt to a gelatin gel lowers the viscosity,[2] and so would tend to increase diffusion.

6. In order, therefore, to account for the retardation of diffusion by salt, and probably also for the retardation by sugar, it would seem necessary to have recourse to some "colloidal chemical" hypothesis. Similarly, the decrease of swelling by sugar cannot be accounted for by Procter's ion concentration theory, but must be explained in some other way. It is conceivable that the retardation is in part merely a mechanical process, the result of the filling up of the interstices in the gelatin gel by the added substance, salt or sugar. Likewise, it may be due to adsorption, or to "dehydration" of the colloid by the added substance, or it may be a surface phenomenon of some other sort. It is impossible in the present

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[1] Such as the formation of oxonium salts. The suggestion of this possibility we owe to the kindness of Dr. Julius Stieglitz.

[2] It is of course not possible to measure the viscosity of a gel by means of a viscosimeter, but it may be obtained indirectly. Two kinds of evidence may be mentioned here to show that gelatin containing salt has a lower viscosity than gelatin alone. In the first place (Fraas, *Wied. Ann. Physik. Chem.*, 53, 1074 (1894)) has shown that sodium chloride greatly diminishes the modulus of elasticity of a gel; the viscosity must there-also be diminished, since viscosity = modulus of elasticity × relaxation time. In the second place, the presence of sodium chloride decreases the rate of gelation of gelatin, and therefore after a certain short time, decreases the viscosity below that of pure gelatin. Rate of gelation is rate of change of viscosity, and the effect of salts on this quantity is of course independent of the effect on viscosity itself. It has been shown that above gelation temperature, salts affect the viscosity of aqueous gelatin solutions just as they do that of water; but at and below this temperature, this effect is complicated by the effect on rate of gelation. For the action of salts on the viscosity and the gelation of gelatin see among others von Schroeder, *Z. physik. Chem.*, 45, 75 (1903); Levites, *Z. Chem. Ind. Kolloide*, 2, 161, 208, 237 (1907–8); *Beibl. Ann. Physik*, 28, 1120 (1904); Griffiths, *Mem. Proc. Manchester Lit. Philos. Soc.*, 41, p. ix (1896); Pascheles, *Arch. ges. Physiol. (Pflüger's)*, 71, 333 (1898); Gokun, *Z. Chem. Ind. Kolloide*, 3, 84 (1908).

stage of our knowledge to say what factors actually are involved in the decrease of swelling and the retardation of diffusion. It may not be superfluous to point out here that the similarity between the equation developed on page 1911 to express the relationship between relative retardation and sugar concentration, and the adsorption equation, is purely formal, since the concentration involved in the latter is the concentration of the adsorbed substance after equilibrium has been reached.

Summary.

1. The diffusion of hydrogen ion from various organic and inorganic acids into gelatin containing sugar (glucose, saccharose or lactose) has been studied and found to be markedly retarded by the presence of the sugar.

2. In agreement with the diffusion law, the ratio of the distance of diffusion to the square root of the time has been found in general to be a constant in gelatin with, as well as without, sugar.

3. The decrease in this ratio with increasing sugar concentration has been found to be not proportional to the concentration of the sugar, but relatively greater for the smaller concentrations. The experimental relation may be approximately expressed by the equation

$$(\Delta/K_0)^n = ac$$

where Δ/K_0 represents the relative retardation, a and n are constants, and c is the concentration of the sugar.

4. Sodium chloride added to the gelatin also retards the diffusion of acids, but the retardation is less than that caused by sugar in equal concentration. This is the reverse of their effect in reducing the acid swelling of gelatin, in which sodium chloride is more effective than sugar.

5. The mechanism of the retardation is briefly discussed.

CHICAGO, ILL.

[CONTRIBUTION FROM THE LABORATORY OF THE DODGE AND OLCOTT CO.]

THE ISOMERIC LACTONES, CARYOPHYLLIN AND URSON.

BY FRANCIS D. DODGE.

Received August 3, 1918.

Caryophyllin, a crystalline compound occurring in clove buds, was first isolated by Baget and Lodibert, in 1825.[1] The empirical formula was found to be $C_{10}H_{16}O$, and the substance was regarded as an isomeride of camphor. It was subsequently studied by Dumas,[2] Bonastre,[3] and Mylius,[4] the latter of whom suggested the formula $C_{20}H_{32}O_2$ as agreeing

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[1] *J. physik. Chem.*, 11, 101 (1825).

[2] *Ann. chim. phys.*, [3] 53, 166 (1858).

[3] *J. Phys. Chem.*, 20, 565 (1834).

[4] *Ber.*, 6, 1053 (1873).