Major Thesis in Organic Chemistry.

THE CONDENSATION OF FORMALDEHYDE BY ALKALIES
AND THE MEASUREMENT OF THE VELOCITY
CONSTANT.

Respectfully submitted to

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by

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for

The M. S. Degree in Applied Chemistry.

Wöehler, by his classical discovery in 1828, was the first to reveal "the possibility of the synthetic production of those compounds which occur naturally in the members of the animal and vegetable kingdoms." Later on Kolbe synthesized acetic acid from its elements. Berthelot soon followed by building up the fats. Thus, little by little, the chemists gave up the view that it was impossible to build in the laboratory from inorganic sources those compounds naturally in the animal and the plant. These discoveries, and the recognition of their significance, opened up to chemists a new line of investigation; and since then, synthetical organic chemistry has been found to be "a fruitful field of research". Thus, the two independent sciences, biology and chemistry, have been brought in closer relation and the new compound science called bio-chemistry has sprung there from.

Notwithstanding the fact that a great deal of work has been done in the field of this alluring and fascinating science, we are inclined to over estimate the work done. We must abandon the thought that the chemical changes that take place in the living organism are fully "understood and can be duplicated in the laboratory".[a] On this point, Professor McPherson says:[b] "While of course it is true that many of the compounds in the living organism have been synthesized and that the number of such synthesis is constantly increasing, yet we must not forget that the chemist's method has never been, in detail at least, the method of Nature. Indeed, as a rule they are widely diver-

[a] Science, Jan. 27, 1911.
[b] Ibid.

gent. We are apt to employ powerful reagents, many of which so far as is known, do not exist in the organism nor in the medium from which it draws its sustenance. The drastic treatment to which the substances are often subjected and the temperature at which the reactions are carried on are all in the greatest contrast to the conditions which prevail in the organism in which the natural synthesis is effected." He adds, that [a]"in a few cases the laboratory methods employed more nearly approach the conditions which prevail in Nature and such synthesis always have greatly added interest, at least from a theoretical standpoint."

The important role that the carbohydrates play in the economy of the vegetable kingdom has been recognized, and it is but natural that many investigators in bio-chemistry have bent their energies toward solving the problems pertaining to the synthesis of the compounds in the living organism, since their solution "will be a step in the direction of gaining some understanding of the synthesis of life itself".[b]

In 1861 the Russian chemist, A. Butlerow[c] synthesized a sugar-like substance. This was accomplished by boiling trioxymethylene, a polymer of formaldehyde, with lime water. He named it "methylenitan" and provisionally adopted the formula, $C_7H_{14}O_6$ and, supposing that the trioxymethylene condenses, or polymerizes under the influence of the alkali, represented the probable reaction by the following equation:

$$4C_2H_4O_2 = C_7H_{14}O_6 + CH_2O_2.$$

a. Science, Jan. 27, 1911.
b. Ibid.
c. Compt. rend., 53. p. 145.

Butlerow[a], at the conclusion of his brief article, states that "it is the first example of a synthetic production of a substance having certain properties of a sugar-like substance by means of the most simple methods of organic chemistry."

The above work proved to be of the greatest significance as it serves as a stepping stone toward one of the ultimate goals of the chemist - the synthetic production of the sugars. Moreover, it formed a foundation pillar upon which Baeyer later based his famous hypothesis.

Baeyer in his ingenious hypothesis, suggested in 1870, assumed that the first stage in the synthetical formation of carbohydrates by plants was, "first, the production of formaldehyde from carbonic acid, and second, the formation of sugars by the polymerization of the aldehyde."[b] The equations representing the above are usually given as follows:

$$CO_2 = CO + O$$

$$H_2O = H_2 + O$$

$$CO_2 + H_2O = CH_2O$$

$$6(CH_2O) = C_6H_{12}O_6$$

We shall not attempt to discuss the various investigations carried out to prove the validity of the first part of Baeyer's theory. Suffice it to say that their results are conflicting and that no definite conclusion has been reached.

Loew[c] in 1886 built up a sugar-like substance from formaldehyde by means of an excess of milk of lime. He called the substance "formose" and gave it the formula $C_6H_{12}O_6$. In

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a. Ibid.

b. P. Haas and T. G. Hill: "An Introduction to the Chemistry of Plant Products". p. 152.

c. J. prakt. Chem. 33, p. 321.

1905-06 E. and H. Euler[a] studied the course of the action of alkalies upon formaldehyde and the conditions affecting it.

The present work was undertaken to calculate, if possible, the velocity of the reaction between formaldehyde and the alkalies, Ca $(OH)_2$ and NaOH.

The first experiments were carried out with $Ca(OH)_2$- the method used by **Loew**. Preliminary experiments were made by mixing one liter of formaldehyde solution with an equal volume of lime water. After standing six days at ordinary temperature there was no change in the formaldehyde, but the alkalinity had changed considerably. This experiment was repeated, except that the mixture was shaken for half an hour. The same results were, however, negative.

In the next experiment, milk of lime was used instead of lime water; and the mixture filtered rapidly and allowed to stand. After a few days there was no evidence of sugar formation. The experiment was repeated and every twenty-four hours samples were taken for the determination of the formaldehyde, alkalinity and refractive index. Results:

Hours	Per cent. of Formaldehyde	Alkalinity grams. $Ca(OH)_2$	Refractive Index
0	3.18	.005747	1.3368
24	.6	.003181	1.3364
48	.03	.001806	1.3362

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[a] Ber. d. Chem. Gesell. Jan.-Mar. 1906. pp.39-45.

The determination of the index of refraction was omitted in all subsequent experiments.

In the next two experiments, which were carried out in a constant temperature bath at 25°C., the conductivity of the mixture was also determined.

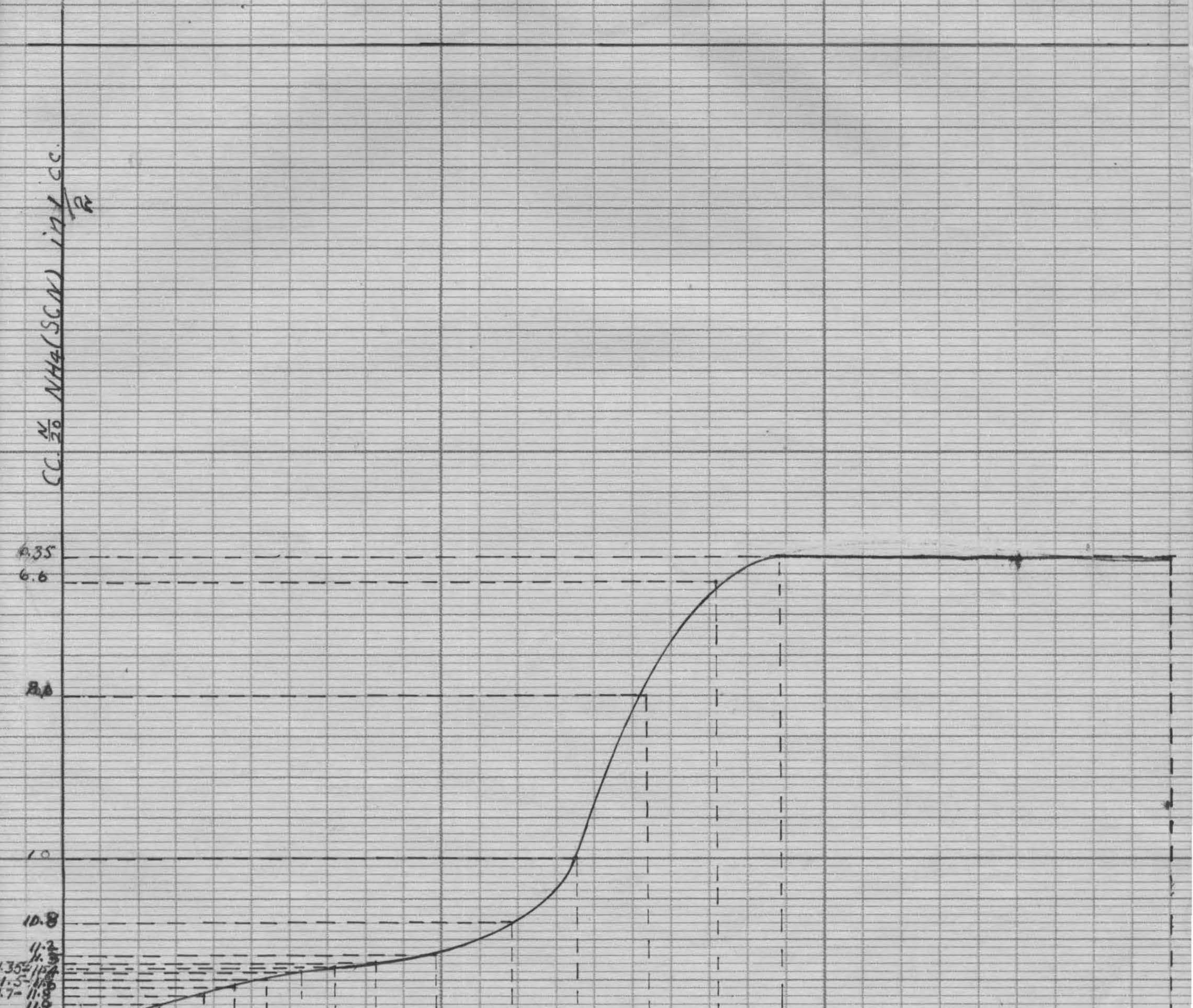
The results of these experiments are given in Tables I and II, and the corresponding curves follow them.

Table I.

Time Minutes	Formaldehyde in 1 cc. (cc.N/20 NH_4(SCN)	Alkalinity in 1 cc. (Grams $Ca(OH)_2$)	Conductivity of 10cc. H_2O	K
0	11.4	.006325	.0026182	--------
45	11.4	.006265	.0026182	--------
90	11.2	.005957	.002728	.0000854(a)
135	11.0	.005783	.002528	--------
180	10.8	.005566	.0029507	.0001305(b)
225	10.6	.005422	.0025135	--------
270	10.4	.005305	.0023095	.0001470(c)
315	10.2	.004988	.002935	--------
360	10.1	.004771	.002865	.0001381(d)
405	10.0	.004636	.0022615	--------
495	9.8	.004410	.0022197	.0001328(e)
580	9.0	.004120	.0020704	.0001770
670	7.4	.003867	.0019945	.000280
760	3.4	.003542	.001796	.000691
850	0.6	.002494	.0017262	-------
940	0.1	.002530	.0017205	-------

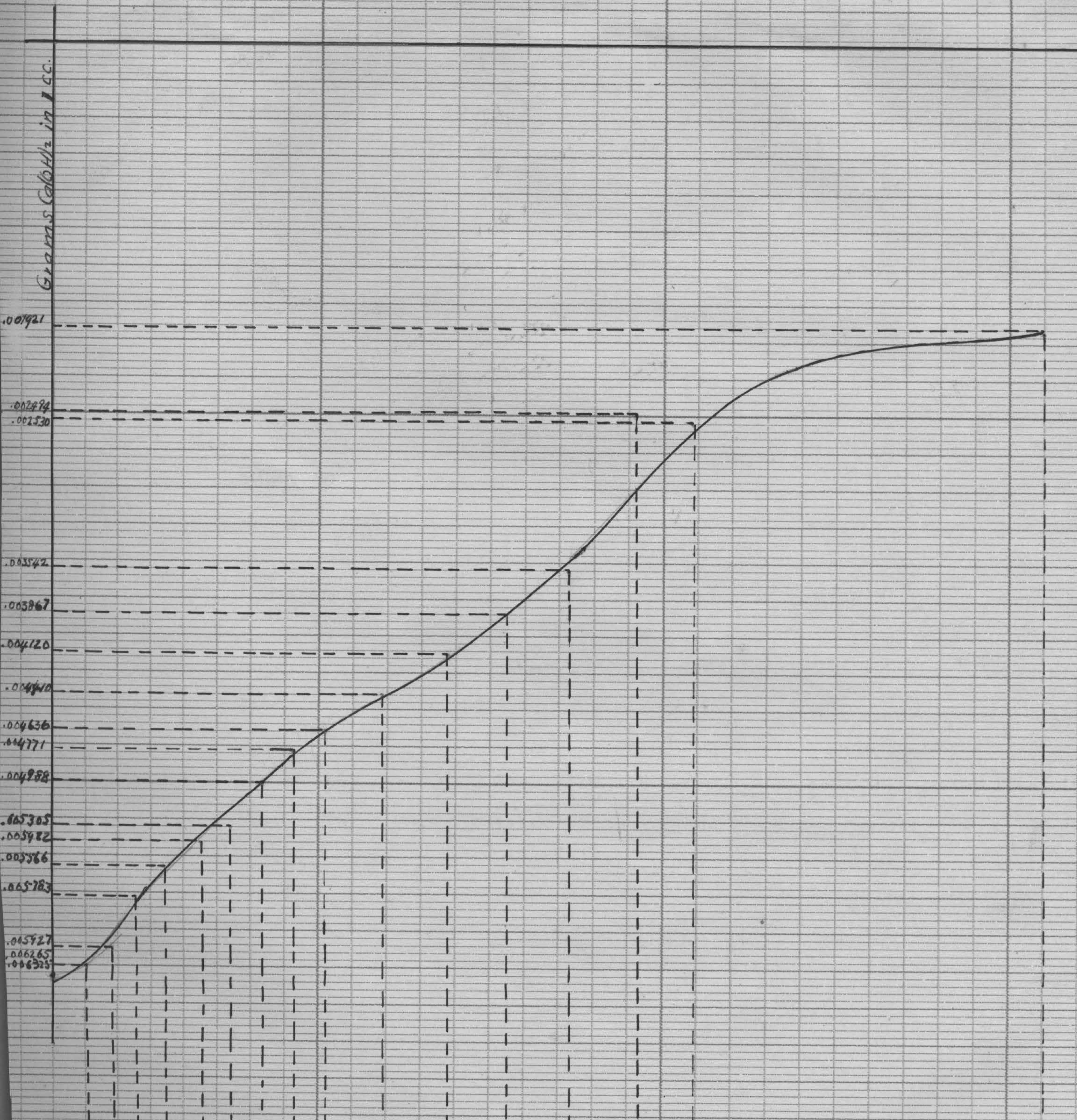
Average of (a), (b), (c), (d) and (e) = .000127

Corresponds to Table No. I



N.B.
6.30 cc $\frac{N}{20}$ $NH_4(SCN)$ (for $\frac{1}{2}$ cc solution) = 0 formaldehyde.

Corresponds to Table No. I



Corresponds to Table No. I.

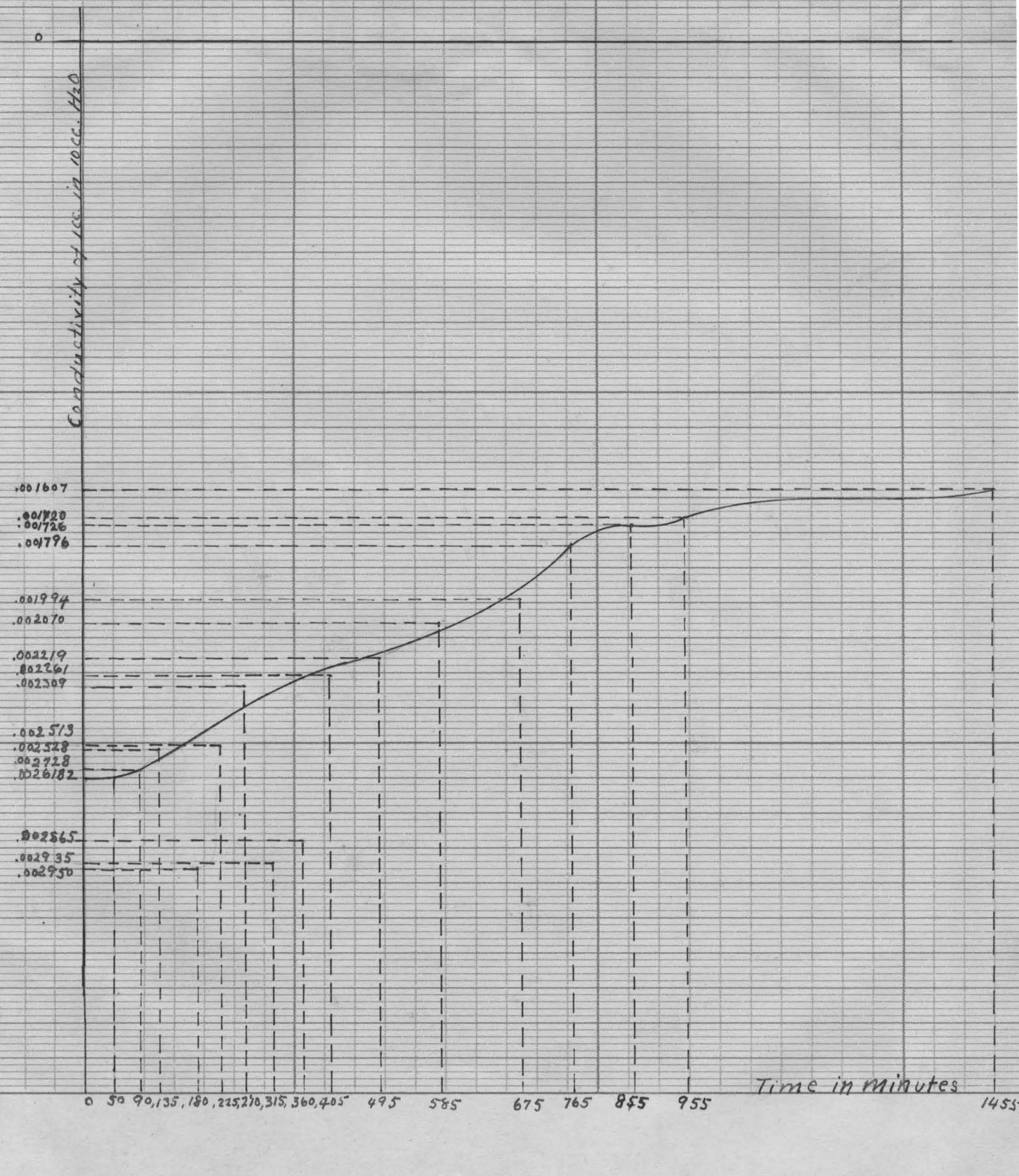
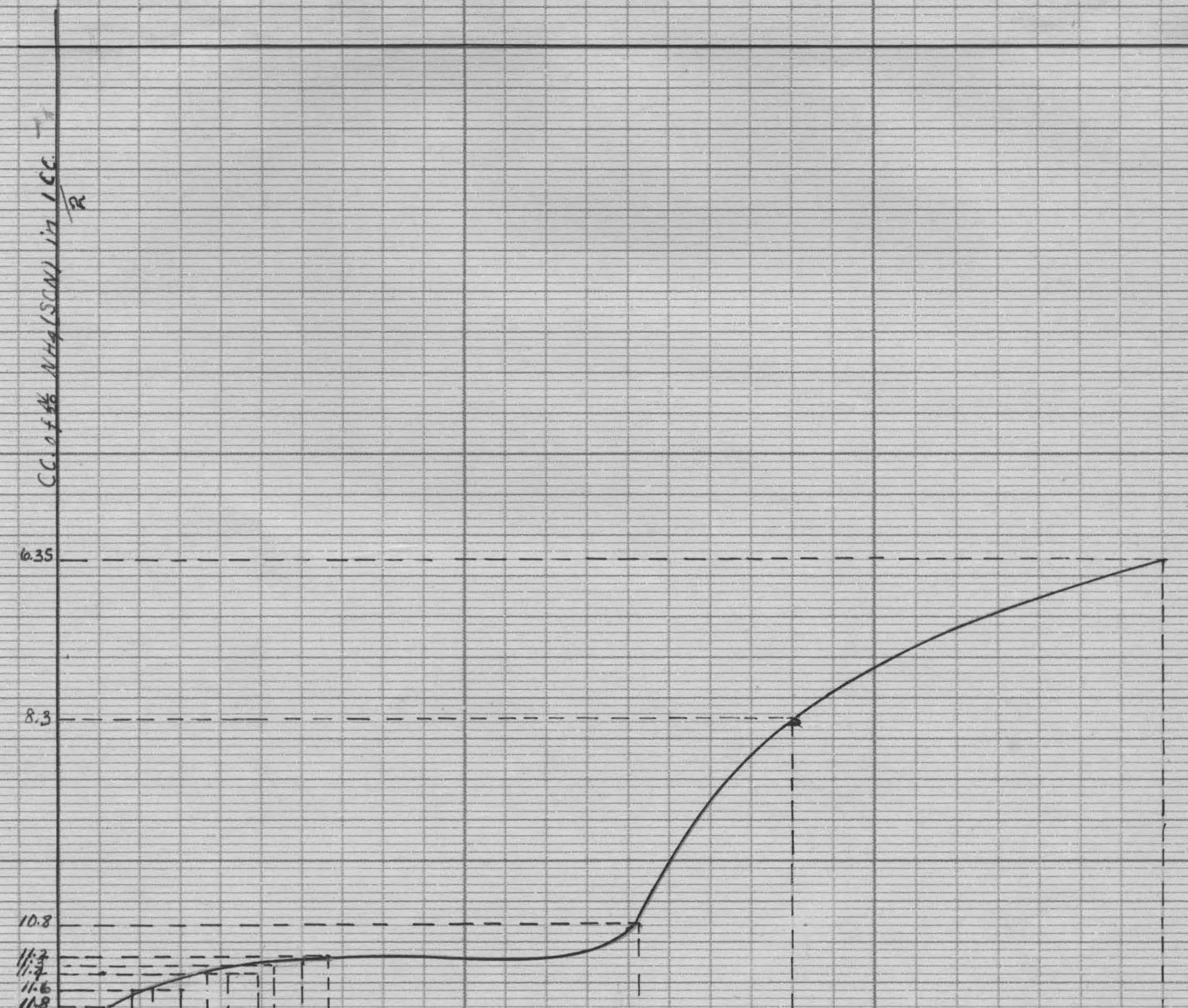


Table II.

Time Minutes	Formaldehyde in 1 cc. (cc.N/20 $NH_4(SCN)$)	Alkalinity in 1 cc. (cc.N/20 HCL)	Conductivity of 1 cc. in 10 cc. H_2O	K
0	12.0	4.05	.001968	--------
60	11.4	3.9	.002362	.000371
120	11.0	3.45	.002346	.000316
180	10.6	3.4	.002308	.000299
240	10.6	3.4	.0022265	.000224
300	10.6	3.13	.0021988	.0001795
360	10.2	3.0	.0021076	.000197
420	10.2	2.95	.00	.000168
480	10.2	2.85	.002053	.000147
540	10.0	2.7	.002005	.000146
660	9.8	2.6	.001816	.000133
720	9.8	2.55	.001816	.000173
1440	9.0	1.85	.001735	--------
1800	4.0	1.65	-------	--------
2880	.1	1.5	-------	---------
			Average of K =	.000214

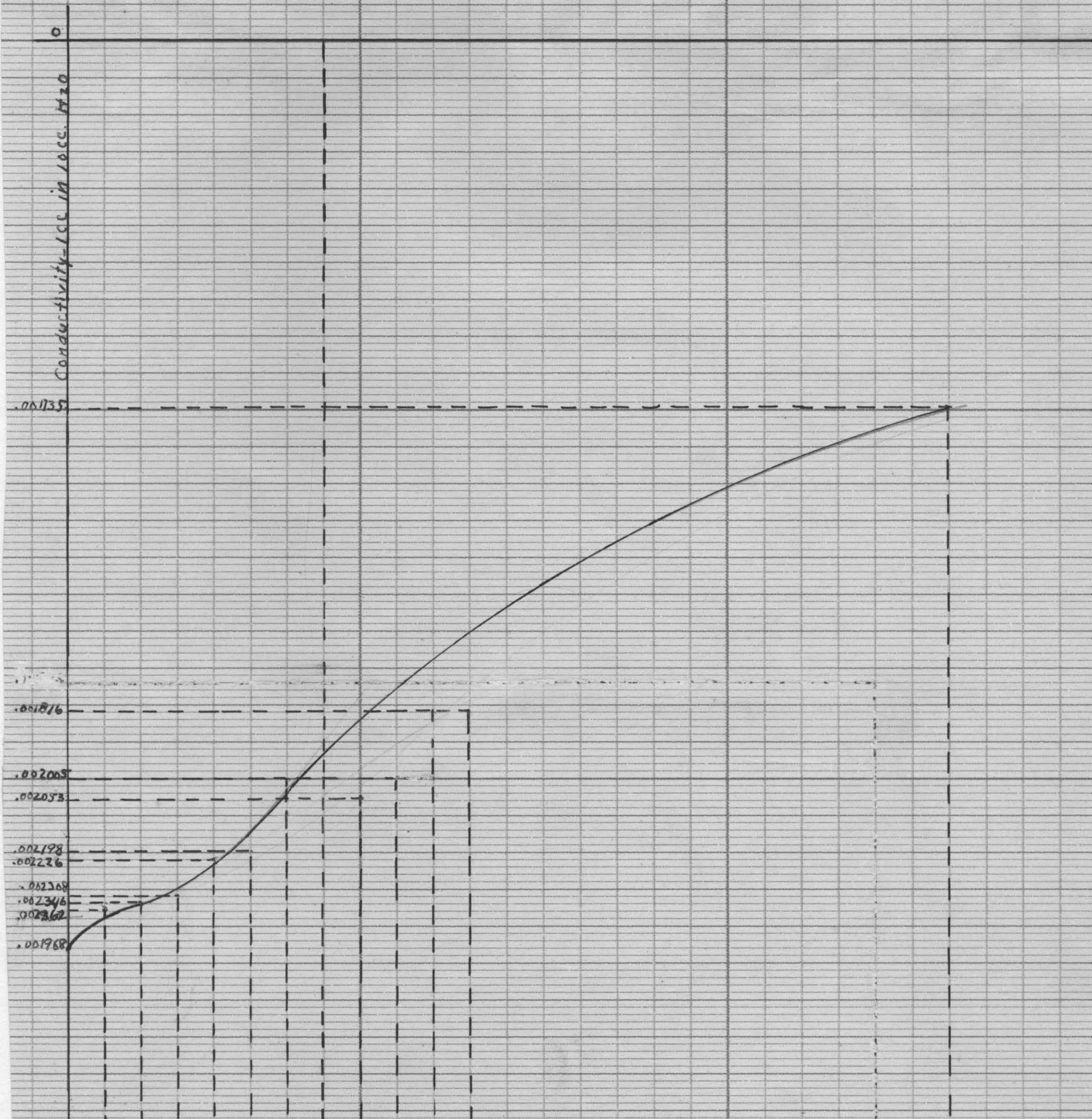
Corresponds to Table No. II.



N.B. 6.30 cc $\frac{N}{20}$ NH_4SCN (for $\frac{1}{2}$ cc solution) = 0 formaldehyde

Corresponds to table No. II.

Corresponds to Table No.II.



The experiments with NaOH are based on the conclusions of E. and H. Euler.[a] These investigators examined the general conditions of the concentration of formaldehyde and NaOH, and the boundaries for the formation of sugar. The following are their conclusions:

I. "The concentration of formaldehyde at the beginning of its change into sugar is directly dependent upon the original concentration of the formaldehyde and the soda, as the formation of sugar can always be observed only after the change of a certain amount of the formaldhyde into formate and methyl alcohol."

II. "Most favorable for condensation is a concentration of NaOH of a little less than one-half of the aldehyde concentration. An increased amount of NaOH with unchanged concentration of the formaldehyde favors the formation of formate especially noticeable in concentrated solutions."

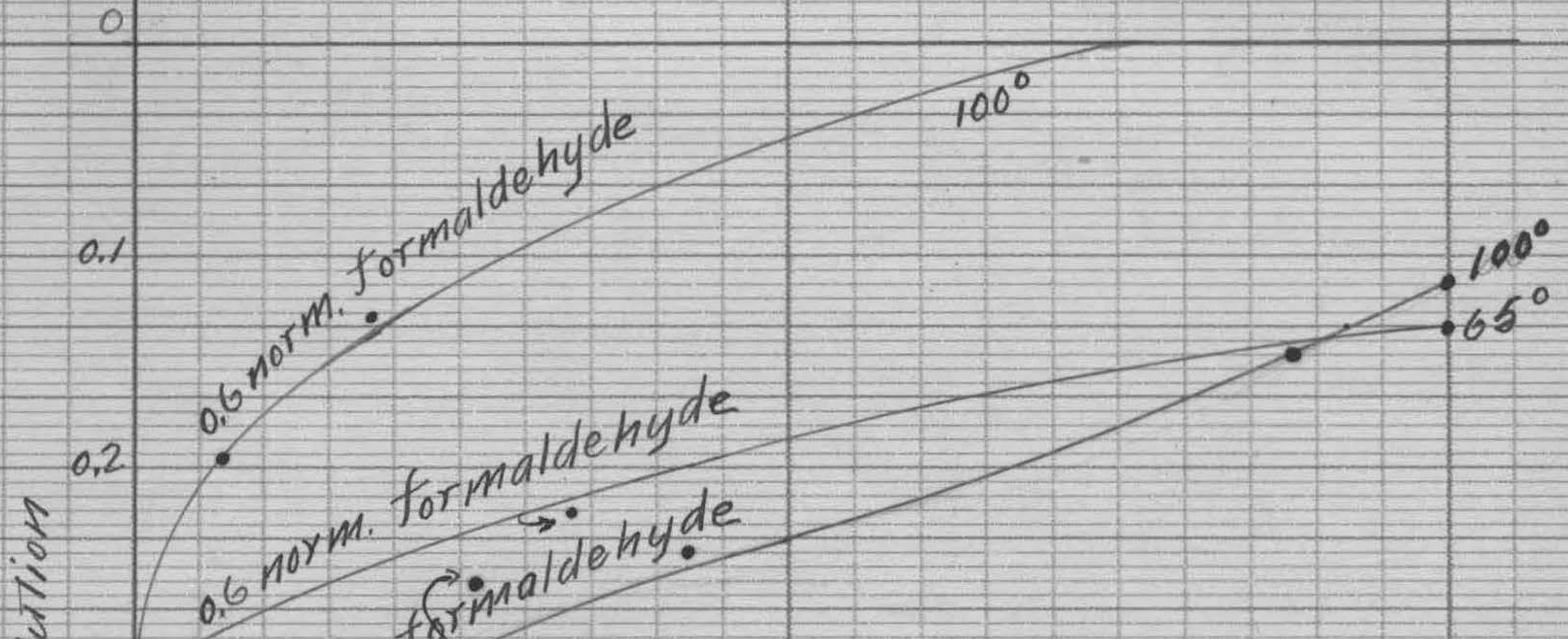
The table from which these conclusions were drawn is here given.

[a] Ber. d. Chem. Gesell. Jan.-Mar. 1906. pp. 39-45.

Formation of Formate before beginning of Sugar Formation.

Concentration of solution at beginning.		Concentration at beginning of sugar formation.		Formaldehyde used up before change into Sugar.
Normality		Normality		
Formaldehyde	NaOH	Formaldehyde	NaOH	Per cent.
2.1	3.2	0.50	2.4	76
1.2	0.6	0.40	0.20	67
0.6	0.3	0.26	0.13	57
0.45	1.1	0.19	0.97	58
0.45	0.22	0.27	0.13	40
0.30	0.90	0.18	0.84	40
0.30	0.72	0.18	0.66	40
0.30	0.12	0.20	0.07	33
0.15	0.36	0.09	0.33	40

The following table of curves is the work of the same investigators. They state that the curves show the rapidity with which NaOH, under different conditions, is used up by the formaldehyde. Thus we see how the first-third of the NaOH is used up rapidly while in the further course the NaOH content is sinking only slowly until the formation of sugar takes place, (in top curve). This holds true also when the total contents of NaOH is not sufficient for the neutralization of the formaldehyde.



The above was copied from the work of Hans and Astrid Euler. (Ber. der D. Chem. Gesel. Jan. – Mar. 1906 p. 39-45)

As suggested by these authors, the concentrations used in the following two experiments were:

Formaldehyde - - - - - - - - - - 9 grams to 1000 cc.

NaOH - - - - - - - - - - - - - - 48 grams to 1000 cc.

One liter of each solution was heated to the temperature chosen for the reaction, (68 C in the first experiment, and 70 C in the second), mixed at that temperature, and placed in a constant temperature bath. The results of these experiments are given in Tables I and II, and the corresponding curves follow them.

The constant K was calculated from the formula for monomolecular reaction or reaction of the first order:

$$K = \frac{I}{t} \log \frac{a}{a - x} .$$

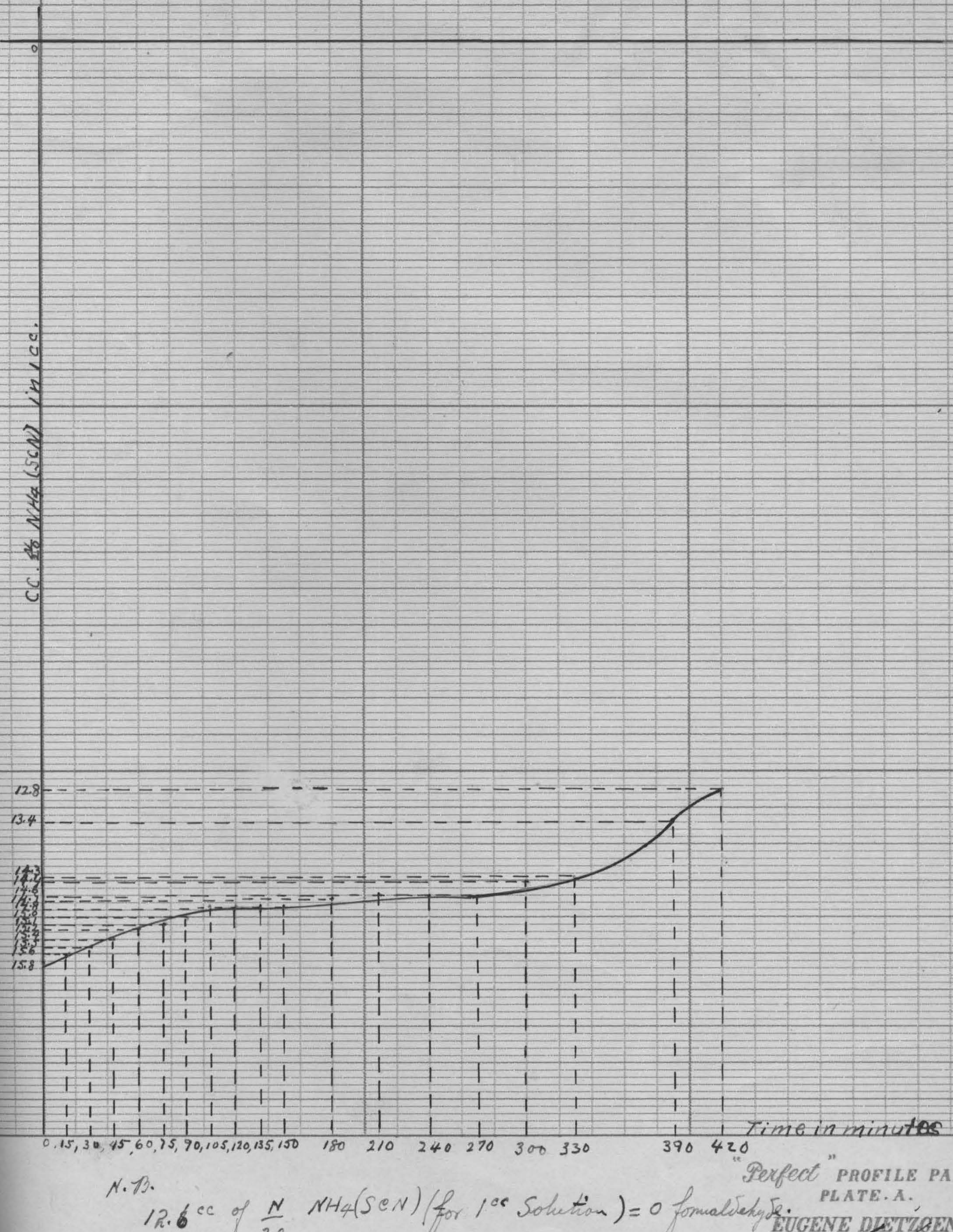
K was also calculated by means of the formula for second order and third order reactions. Both of these gave unsatisfactory results. In making up the average K, only those constants were used as indicated by the letters opposite them.

Table I.

Time Minutes	(cc.N/20 NH_4(SCN) for 1 cc. Sol.	(cc.N/20 HCL)for 1 cc. Solution.	K
0	15.8	1.3	---------
15	15.6	1.15	.00187 (a)
30	15.5	1.09	.00143 (b)
45	15.4	1.09	.00128 (c)
60	15.2	1.00	.00150 (d)
75	15.1	.93	.00143 (e)
90	15.0	.87	.00139 (f)
105	14.8	.83	.00155 (g)
120	14.8	.83	.00135 (h)
135	14.8	.7	.00120 (i)
150	14.8	.7	.00108
180	14.7	.66	.00102
210	14.6	.66	.00097
240	14.6	.63	.00085
270	14.6	..6	.00075
300	14.4	.43	.000832
330	14.3	.40	.00083
360	----	..33	------
390	13.4	.33	.00154
420	12.8	.30	.00386

Average of (a), (b), (c), (d), (e), (f), (g), (h), and (i) = .001444.

Corresponds to Table No. I.



N.B.
12.6 cc of $\frac{N}{20}$ $NH_4(SCN)$ (for 1cc Solution) = 0 formaldehyde.

Corresponds to Table No. I.

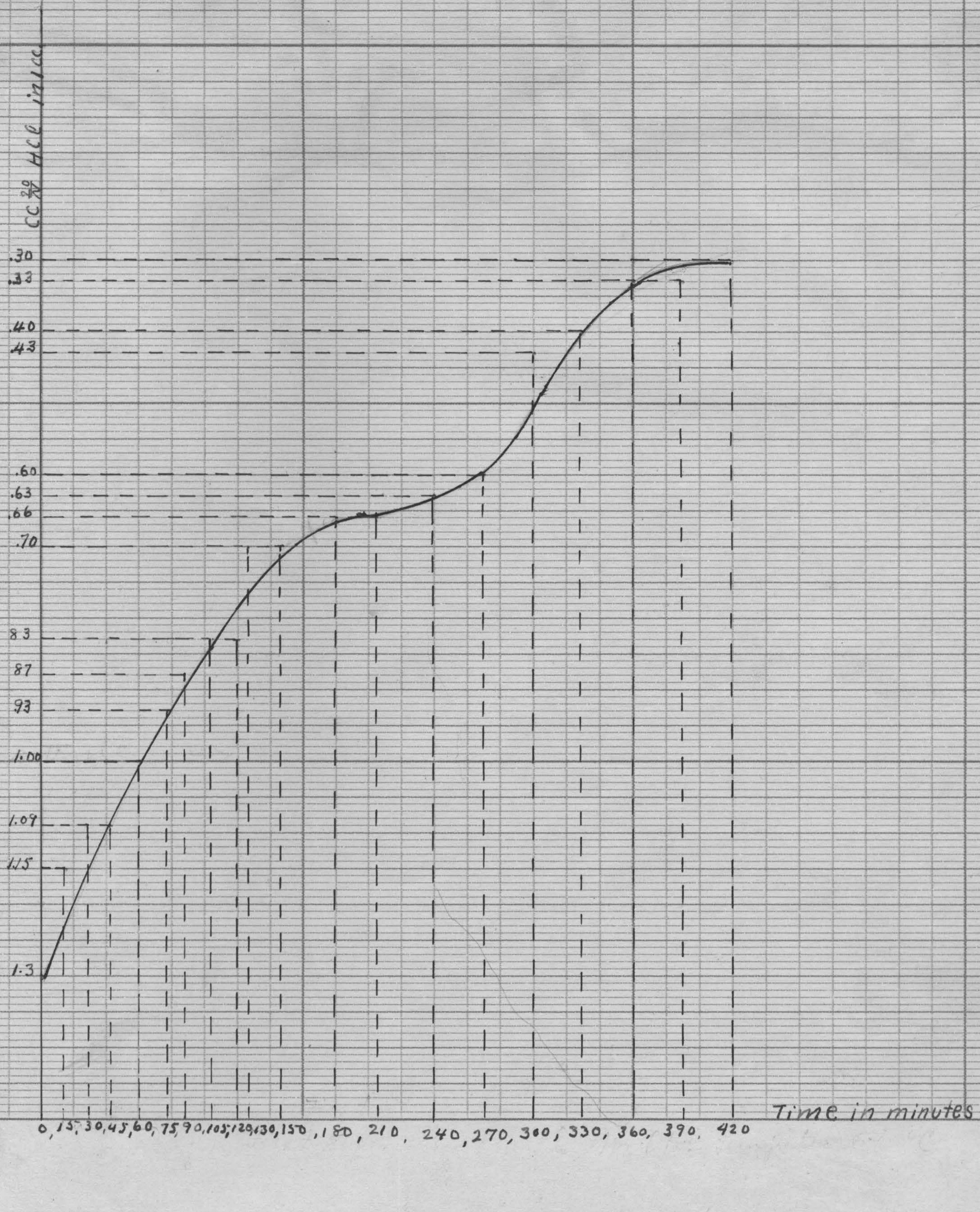
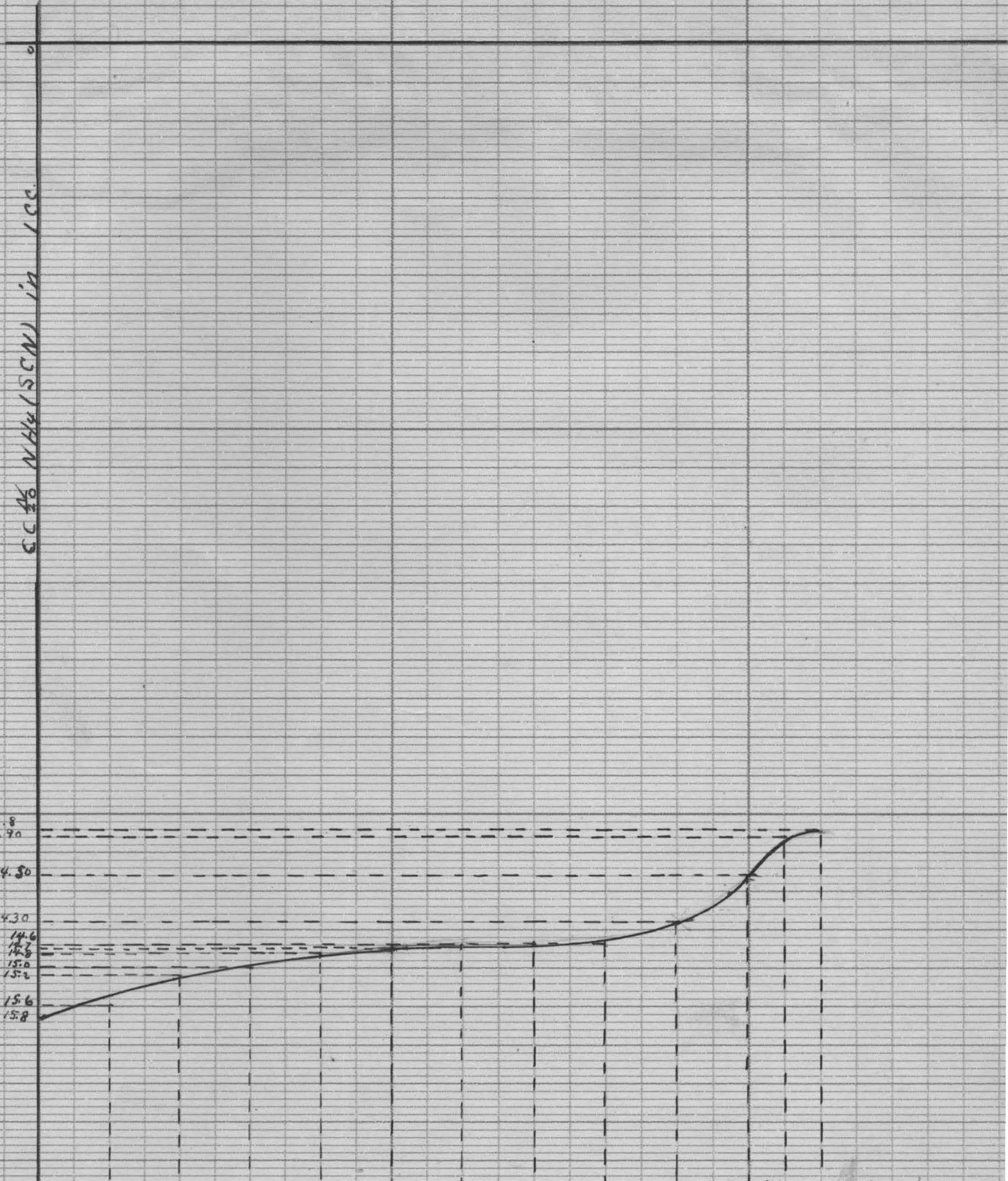


Table II.

Time Minutes	cc. N/20 $NH_4(SCN)$ for 1 cc. Sol.	cc. N/20 HCL for 1 cc. Solution.	K
0	15.8	1.2	------
30	15.6	1.083	.00093 (a)
60	15.2	.983	.00150 (b)
90	15.0	.866	.00138 (c)
120	14.8	.786	.00135 (d)
150	14.7	.7	.00122 (e)
180	14.6	.666	.00113 (f)
210	14.6	.6	.00098 (g)
240	14.6	.566	.00085 (h)
270	14.30	.533	.00102 (i)
300	13.50	.483	.00195
315	12.90	.38	.00358
330	12.8	.33	.00364

Average of (a), (b), (c), (d), (e), (f), (g), (h) & (i) = .000118.

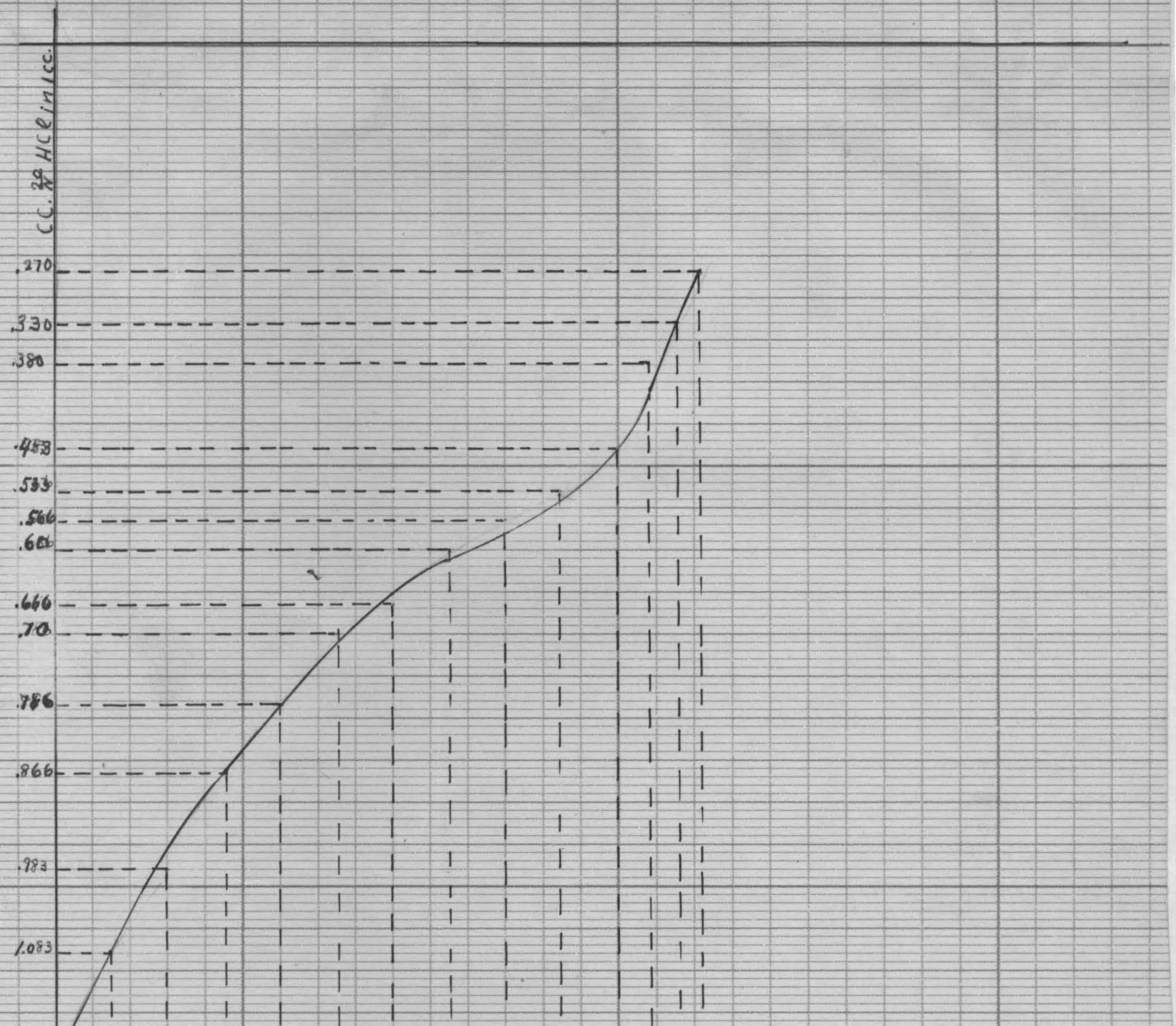
Corresponds to Table No. II.



N. B.

12.6 cc of $\frac{N}{20}$ $NH_4(SCN)$ (for 1cc Solution) = 0 formaldehyde.

Corresponds to table No. II.



The chief conclusions deduced from this work may be summarized as follows:

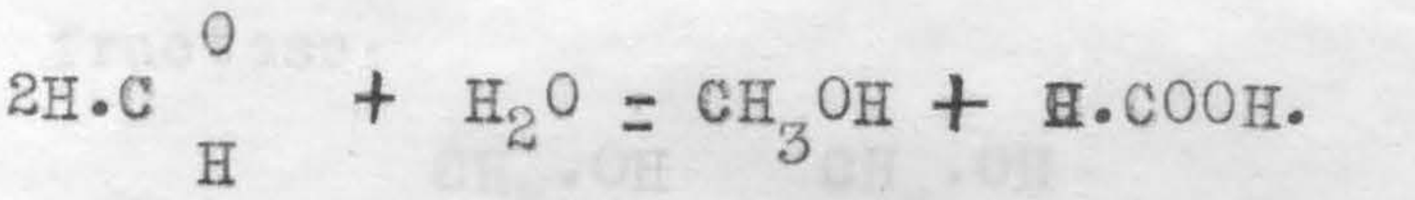
I. When the concentration of the $Ca(OH)_2$ is small, condensation of formaldehyde to sugar apparently does not take place. The same thing is true when the concentration of the formaldehyde is large. In both cases, however, the $Ca(OH)_2$ is converted to the formate and the greater part of the formaldehyde is condensed into formic acid and methyl alcohol.

II. With excess of milk of lime at 25°C the condensation to sugar takes place comparatively slowly, particularly when the concentration of formaldehyde is considerable.

III. The figures for K show that the reaction, as a whole, is not one of the first order, but that the first stage of the reaction is probably of this order. The last stages are more complicated and no satisfactory results could be obtained for K.

IV. The formula, $6CH_2O = C_6H_{12}O_6$ or, $6H.C^{O}_{H} = CH_2.OH.CH(OH).CH(OH).CH(OH).CH(OH).C^{O}_{H}$ (a mixture of compounds, $C_6H_{12}O_6$) usually given to represent the polymerization, or "aldol condensation", that formaldehyde undergoes in the presence of an alkali, does not sufficiently represent what actually takes place.

The behavior of formaldehyde under the conditions in these experiments shows that the change is far more complicated than the reaction suggested above would seem to indicate. Probably a portion of the formaldehyde always undergoes the following change:



$$2H.\underset{H}{\overset{O}{C}} + H_2O = CH_3OH + H.COOH.$$

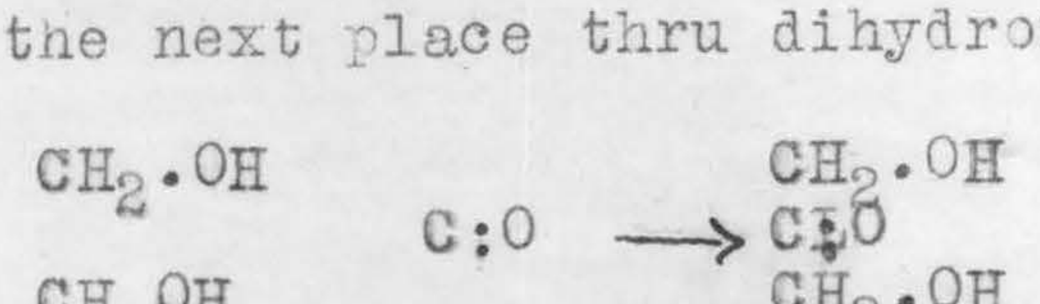
This is also indicated by the results of E. and H. Euler[a]. Evidently, the reaction takes place in different stages. In regard to this, Meldola, in his "Presidential Address," (Journal of the Chemical Society of London, Volume 89, Part I, 1906, pp. 745-770), says, "With respect to the intermediate stages between formaldehyde and the sugars, where we had nothing but hypothesis to guide us, it may be useful to call attention to the later discoveries and theoretical suggestions which chemists have given plant physiologists either for confirmation or refutation . . . . . "

"Emil Fischer suggested looking for the trios, 'glycerose' in the green plants. Glycerose is known to be a mixture of glyceric aldehyde and dihydroxyacetone, and in 1897 Piloty indicated certain possible stages in the development of fructose from glycerose, thus:

In the first place thru glycolic aldehyde to glyceric aldehyde:

$$\begin{matrix}CH_2OH\\CH_2OH\end{matrix} \longrightarrow \begin{matrix}CH_2OH\\CHO\end{matrix} + H.CHO \longrightarrow \begin{matrix}CH_2.OH\\CH.OH\\CHO\end{matrix}$$

In the next place thru dihydroxyacetone:



$$\begin{matrix}CH_2.OH\\CH_2OH\end{matrix} \quad C{:}O \longrightarrow \begin{matrix}CH_2.OH\\C{:}O\\CH_2.OH\end{matrix}$$

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a. Ber. d. Chem. Gesell., Jan.-Mar. 1906. pp.39-45

The aldehyde and ketone are then supposed to condense to fructose:

$$\begin{array}{llll} CH_2.OH & CH_2.OH & & \\ CH.OH & + \; C{:}O & \longrightarrow & CH_2(OH).(CH(OH))_3.CO.CH_2OH \\ CHO & CH_2.OH & & \end{array}$$

To this view there is much chemical, but this far no biological, evidence."

Lastly, it is eminently fitting to quote the words of Meldola given at the conclusion of his address. He says, "A general survey of the state of knowledge at which we have arrived concerning what is unquestionably the most fundamental of all bio-chemical processes going on in the living world, I imagine, leave on the minds of chemists the impression that the facts which have hitherto been wrested from Nature are but fragments of the whole structure and that our observations are really records of the state of perfection of certain chemical or microchemical methods of detecting and estimating particular compounds or groups of compounds, rather than a complete story of the chemical processes going on in the green leaf."

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E. Frankland Armstrong: "The Simple Carbohydrates and the Glucosides". pp. 62-76.

H. E. Michael; "Studies in Plant Chemistry". p. 321.

R. Meldola: "The Chemical Synthesis of Vital Products". pp. 1-20.

Methods of Analysis Used.

For the analysis of the formaldehyde the "cyanide method" given on p. 33 A. O. A. C. 1908 was used.

The alkalinity was measured by the use of N/50 and N/20 HCL, using methyl orange as an indicator.

The conductivity was measured by the Wheatstone Bridge method as given in Findley's "Practical Chemistry". pp. 144-151.