THE HYDRATION RATE OF TRIMETHYL ETHYLENE IN DIFFERENT ACIDS

THE NITRATION OF PARA-CRESOL AND OF PARA-CRESYL CARBONATE IN THE PRESENCE OF SULFURIC ACID

THE PREPARATION OF CRYSTALLINE LACTIC ACID

Thesis by
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ABSTRACT

The hydration of trimethyl-ethylene is effected by different acids. At constant ionic strength the rate is first order with respect to both pentene concentration and the nitric acid concentration. The rate at a given acid concentration is increased on the addition of potassium nitrate. Other acids were used alone as follows: hydrochloric, perchloric, hydrobromic, dithionic, p-toluene-sulfuric, picric, sulfuric, oxalic and acetic. Strong acids give not much different rates. The dibasic acids like sulfuric and oxalic have mostly their first hydrogen ion effect on the rate of hydration. Dithionic acid shows its second hydrogen ion effect.

Nitration of p-cresol and p-cresyl carbonate have been carried out in the presence of sulfuric acid. It was found in the case of p-cresol that the ortho directive power of the hydroxyl group decreased as sulfuric acid increased, and that more and more of the entering nitro group took up a position meta to the hydroxyl. In the case of p-cresyl carbonate, increase in the amount of sulfuric acid likewise increased the meta-ortho ratio. This change in directive power is ascribed to the salt-forming property of the oxygen atom of p-cresol and p-cresyl carbonate.

Several methods have been worked out for obtaining optically active lactic acid (both isomers) from a commercial aqueous syrup. One of the methods consists of fractional distillation followed by fractional crystallization from a mixture of equal volumes of ethyl and isopropyl ethers. This process effects a good separation of the active isomer $\ell(+)$ from the $d\ell$- form. The active acids were also prepared by way of their zinc ammonium salts obtained by resolution of the commercial syrup. It

was also found that when zinc ammonium d(-) lactate was mixed with a large quantity of the double salts of the dℓ acid, the active acid could be separated out by warming up to 55°. Some of the properties of the crystalline acids were described.

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Introduction

The hydration of trimethyl-ethylene has been observed a long time ago. Miklaschewsky (Ber., 24, ref. 26a, 1891) noticed that a 5-10% solution of formic, acetic or oxalic acid brings about the hydration. Michael and Brunel (Am.Chem.J., 48, 270, 1912) found that dilute solution of hydrobromic acid less than 5 N would give only the carbinol.

In this investigation the rate of hydration of trimethyl-ethylene has been measured at 25° in aqueous solution containing variable amounts of nitric acid and potassium nitrate, and a number of other acids alone. This is one of the series of investigations on the hydration of unsaturated compounds to be carried out in this laboratory. The hydration rate of isobutene in dilute nitric acid has been measured (Lucas and Eberz, J.Am.Chem.Soc., 56, 460, 1934).

Experimental

Materials.- The trimethyl-ethylene was prepared by refluxing 500 cc. of tertiary amyl alcohol (Eastman's practical) with 200 gm. of crystalline oxalic acid (Norris, J.Am.Chem.Soc., 53, 3114, 1931). The pentene thus collected was dehydrated with calcium chloride and subjected to further fractionations, using a column 85 cm. long inserted with a water condenser at the top. The fractionations were carried out very slowly and two preparations were represented by Fig. 1.

The second preparations gave a yield of 27.6% of pure trimethylethylene, which is much higher than any previous results (Norris, J.Am.Chem.Soc., 53, 3114, 1931; Parks and Huffman, ibid., 52, 4387, 1930). The boiling point of this pentene is 38.2-38.3 (corrected).

Apparatus and Solutions.- A saturated solution of trimethylethylene in water was prepared by shaking 1-2 ml. of this pentene with 600 ml. of water in a tube Q as shown in Fig. 2, which was then placed in the thermostat at 25° until the solution is clear. The tube was evacuated slightly and the calculated amount of acid run in and the tube was turned up and down for a number of times, so that the solution became homogeneous. In those experiments in which the solution was brought to the desired ionic strength, a known amount of potassium nitrate was previously placed in the tube. The solution was then passed into the apparatus shown in Fig. 2, which had been swept out with air saturated with pentene vapor.

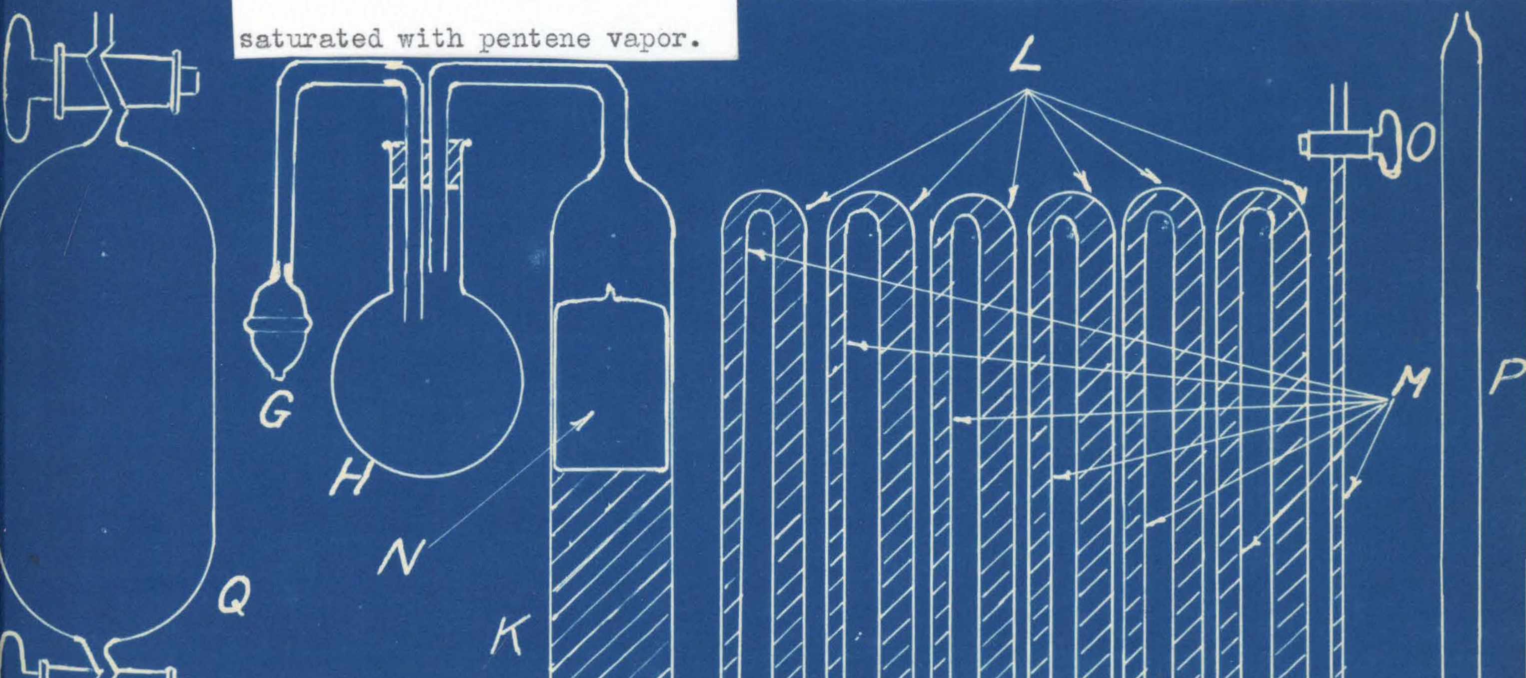

Fig. 2 Apparatus in which the hydration of trimethyl ethylene was carried out.

The liquid entered the apparatus of (capacity 500 ml., Fig. 2) at 0°, flowed down the seven small vertical tubes M (34 cm. x 5 mm. bore) and up the six large vertical tubes L (34 cm. x 15 mm.) and finally filled the large vertical tube K (34 cm. x 30 mm. bore) in which the float N fitted snugly. About 100 ml. of solution was allowed to run into the flask H (500 ml.) and an atomizer bulb G was then connected to the glass tubing leading to H. The apparatus was designed to allow withdrawals of samples of the solution without appreciable changes in composition. The float minimized the diffusion of pentene into the air space above it and the long, narrow tubes minimized diffusion of pentene into the less concentrated solution under the float. H and J were kept at 25° for all the measurements.

<u>Sampling</u>.- This was accomplished by means of the pipet P (Fig. 2) which was constricted at both ends and contains 18.59 ml. of water at 25°. This was connected by a short length of rubber tubing to the stopcock O which was kept closed while air was blown in by the atomizer bulb G. The pressure in G served to force liquid into P as soon as O was opened. A quantity of liquid was allowed to overflow in order to discard any of the solution which might have lost pentene through contact with air in the pipet P. The top of the pipet was closed with the finger, the pipet was connected with the evacuated iodine flask used in the analysis and the contents of P was washed into the flask. The error in measuring this pipet was negligible in comparison with the titration error.

Analysis.- The pentene was determined essentially according to the method of Davis, Crandall and Higbee (Ind.Eng.Chem., Anal.Ed. 3, 108, 1931) as follows: 10.00 ml. of 0.05 N bromide-bromate solution was pipetted into the flask, which was then evacuated by means of a water aspirator. Following the addition of 5 ml. of 6 N sulfuric acid, the sample was then introduced from the pipet, which was rinsed thoroughly. Still under partial vacuum, the flask was shaken frequently for five minutes in the dark, then a freshly made solution of 1 gm. of potassium iodide in a small amount of water was run in and titration was made with 0.02 N thiosulfate. A blank was run from time to time and the amount of pentene was calculated from the difference in the two values.

The concentration of the different acids was determined by titration of a sample with 0.1 N sodium hydroxide, after the hydration rate measurements were made. The values obtained were mostly close to the normalities desired.

Reaction Product.- The reaction taking place is given in equation 1.

$$(CH_3)_2C{=}CHCH_3 + H_2O \longrightarrow (CH_3)_2COHCH_2CH_3 \qquad (1)$$

The product of the reaction was shown to be tertiary alcohol as follows: 5 ml. of pentene was introduced into the shaking tube Q (Fig. 2) containing about 600 ml. of 1.0 N nitric acid and the solution was allowed to stand in the thermostat at 25° for three days, shaking from time to time. The acid was then neutralized with sodium hydroxide and the neutral solution was distilled through a 40 cm. column of glass rings. Ten ml. of distillate were collected when the temperature reached the boiling point of water. The upper phase of the distillate was pipetted out and was saturated with anhydrous potassium carbonate. This gave a non-aqueous phase of 2 ml. the boiling point of which was 101.5°. On the addition of 10 ml. of concentrated hydrochloric acid a second phase of approximately 2 ml. separated. The boiling point of this was 86°. These constants check the respective boiling points of tertiary pentanol and its chloride.

Data and Discussion

The integrated first order reaction rate expression for the hydration of trimethyl-ethylene in dilute aqueous solution according to equation (1) is shown in equation 2

$$2.303 \log_{10} C_o/C_t = kt \qquad (2)$$

where C_o is the initial molality of pentene, C_t is the molality of pentene at the time t (expressed in hours) and k is the specific reaction rate constant.

The experimental data of a typical run and the specific first order rate constants calculated as above are shown in Table I.

TABLE I

Hydration of Trimethyl-ethylene

at 25° in 0.0946 N nitric acid and 0.9000 N potassium nitrate.

Bromate used by 18.59 ml. as 0.02 N $Na_2S_2O_3$

Reaction time in hours	$Na_2S_2O_3$ ml	Pentene molality	log C_o/C_t	K hrs^{-1}
0.0	4.99			
0.567	4.63	0.00268	0.03252	0.132
1.567	4.06	.00249	.08957	.132
2.567	3.56	.00218	.14665	.132
3.533	3.12	.00192	.20395	.133
5.483	2.45	.00132	.30893	.130
7.900	1.78	.00096	.44768	.130
9.450	1.56	.00081	.52201	.127
			Mean	0.131

The values obtained for k show that the reaction is first order with respect to the pentene concentration.

The different runs with different acids are shown in Table II (from run No. 1 to run No. 17).

TABLE II

Run No. 1. HNO_3 = 0.0496 *N*; KNO_3 = 0.9500 *N*.

Reaction time in hours	$Na_2S_2O_3$ ml.	$\log C_o/C_t$	k hrs^{-1}
0.0	5.10		
0.867	4.75	0.03088	0.0688
2.383	4.29	.07511	
4.900	3.67	.14290	
8.150	2.99	.23190	
18.803	1.53	.52288	

Run No. 2. HNO_3 = 0.0946 *N*; KNO_3 = 0.9000 *N*.

0.0	4.99		
0.567	4.63	0.03250	0.1310
1.567	4.06	.08957	
2.567	3.56	.14665	
3.533	3.12	.20395	
5.483	2.45	.30893	
7.900	1.78	.44768	
9.450	1.50	.52201	

Run No. 3. HNO_3 = 0.246 *N*; KNO_3 = 0.750 *N*/

0.0	4.33		
0.500	3.73	0.06478	0.3350
0.933	3.23	.12729	
1.550	2.62	.21819	
2.416	2.00	.33546	
3.100	1.62	.42697	
3.833	1.23	.54658	
4.633	1.02	.62789	

TABLE II (cont)

Reaction time in hours	$Na_2S_2O_3$ ml.	log C_o/C_t	k hrs^{-1}
Run No. 4. HNO_3 = 0.515 N; KNO_3 = 0.500 N.			
0.0	4.67		
0.283	3.87	0.08161	0.718
0.566	3.10	.17796	
0.883	2.60	.25435	
1.217	2.01	.36612	
1.617	1.59	.46792	
2.100	1.29	.55873	
Run No. 5. HNO_3 = 0.982 N.			
0.0	4.08		
0.217	3.11	0.10790	1.255
0.450	2.40	.23045	
0.667	1.90	.33191	
0.917	1.50	.43457	
1.150	1.26	.51029	
1.583	1.00	.61066	
Run No. 6. HNO_3 = 0.516 N.			
0.0	7.13		
0.333	6.00	0.07444	0.472
0.583	5.40	.12070	
0.850	4.80	.17185	
1.100	4.41	.20865	
1.466	3.77	.27675	
1.816	3.17	.35203	
2.316	2.90	.39069	
5.900	1.30	.73915	

TABLE II (cont)

Run No. 7. HNO_3 = 0.1068 N.

Reaction time in hours	$Na_2S_2O_3$ ml.	log C_o/C_t	k hrs^{-1}
0.0	5.85		
0.533	5.60	0.1897	0.0890
1.933	5.00	.06819	
3.266	4.50	.11395	
4.400	4.00	.16510	
5.950	3.60	.21086	
8.450	2.85	.31232	
11.00	2.40	.38695	
12.90	2.05	.45541	
Run No. 8. HNO_3 = 0.0532 N.			
0.0	7.20		
0.517	7.10	0.00607	0.0435
1.517	6.79	.02546	
2.717	6.42	.04979	
3.567	6.30	.05799	
6.500	5.46	.12014	
7.917	5.27	.13552	
9.283	4.99	.15923	
11.317	4.55	.19932	
Run No. 9. $HClO_4$ = 0.099 N			
0.0	6.18		
0.533	5.80	0.02756	0.0905
1.600	5.20	.07000	
2.766	4.80	.10975	
3.666	4.50	.13778	
6.100	3.70	.22279	
8.700	3.00	.31387	
11.317	2.40	.41078	

TABLE II (cont)

<u>Run No. 10.</u> HCl = 0.104 <u>N</u>.

Reaction time in hours	$Na_2S_2O_3$ ml.	log C_o/C_t	k hrs^{-1}
0.0	6.11		
0.550	5.69	0.03093	0.0955
1.217	5.41	.05284	
1.917	5.09	.07932	
2.600	4.74	.11026	
3.300	4.47	.13573	
3.967	4.21	.16176	
5.333	3.71	.21667	
8.517	2.81	.33733	
<u>Run No. 11.</u> H_2SO_4 = 0.114 <u>N</u>.			
0.0	7.05		
0.400	6.90	0.00934	0.0582
1.450	6.48	.03661	
2.450	6.08	.06429	
3.450	5.79	.08551	
4.950	5.32	.12228	
5.933	4.97	.15183	
6.933	4.82	.16514	
8.650	4.35	.20970	
<u>Run No. 12.</u> HBr = 0.103 <u>N</u>.			
0.0	7.58		
0.500	7.32	0.1516	0.865
1.233	6.98	.03583	
2.333	6.28	.08171	
3.183	5.86	.11177	
3.867	5.57	.13381	
5.017	5.08	.17381	
6.233	4.68	.20942	
7.217	4.38	.23820	

TABLE II (cont)

Run No. 13. p-Toluene sulfonic acid = 0.0948 N.

Reaction time in hours	$Na_2S_2O_3$ ml.	log C_o/C_t	k hrs^{-1}
0.0	8.21		
0.683	7.80	0.02225	0.0691
1.317	7.41	.04452	
2.017	7.01	.06862	
2.700	6.79	.08247	
3.450	6.41	.10748	
4.467	6.00	.13619	
6.283	5.41	.18114	

Run No. 14. Picric acid = 0.059 N.

Reaction time in hours	$Na_2S_2O_3$ ml.	log C_o/C_t	k hrs^{-1}
0.0	7.12		
0.633	6.92	0.01237	0.0332
1.617	6.55	.03624	
2.650	6.42	.04494	
2.983	6.40	.04630	
4.200	6.22	.05869	
6.917	5.72	.09508	
11.467	4.95	.15787	

Run No. 15. $H_2S_2O_6$ = 0.0932 N.

Reaction time in hours	$Na_2S_2O_3$ ml.	log C_o/C_t	k hrs^{-1}
0.0	7.49		
0.500	6.93	0.03375	0.0686
1.533	6.59	.05559	
2.417	6.13	.08702	
3.433	5.74	.11557	
4.383	5.39	.14289	
5.850	4.92	.18251	
9.250	3.94	.27898	

TABLE II (cont)

Run No. 16. Oxalic acid = 0.202 N.

Reaction time in hours	$Na_2S_2O_3$ ml.	log C_o/C_t	k hrs^{-1}
0.0	6.55		
1.983	5.90	0.04539	0.0418
3.200	5.62	.06650	
5.783	5.10	.10867	
7.567	4.80	.13500	
17.283	3.60	.25994	
19.467	3.30	.29673	

Run No. 17. Acetic Acid = 0.105 N.

0.0	8.07		
21.42	7.89	0.00979	0.0011
45.75	7.75	.01757	
69.63	7.52	.03065	
93.70	7.35	.04058	
119.63	7.11	.05500	
143.50	6.90	.06802	

An easier and more accurate evaluation of k is the slope of the curve obtained by plotting log C_o/C_t against time t (Fig. 3 and Fig. 4). Since in nearly all the cases these straight lines passed through the origin, the constants obtained in this way proved to be as accurate as those calculated by plotting log C_t against t as in Table III. The advantage of plotting log C_o/C_t against t lies in the fact that the different families of curves can be more conveniently compared.

Fig. 3 contains the plots of log C_o/C_t against t for the hydration reaction at 25°. The concentrations of nitric acid varied from 1.0 N to 0.05 N and the ionic strength for a set of runs is 1.0 N. The concentrations of other acids were made close to 0.10 N except in the case of oxalic and picric acids. It is to be observed that in all cases straight lines are obtained and this shows that the rate in all cases is first order with respect to the pentene concentration.

Fig. 4 contains the plots of log C_o/C_t against t for strong acids. They are made not to pass through the same origin in order to differentiate their close rates.

The constants calculated from plots of log C_t against t are listed in Table III and Table IV.

TABLE III

Hydration Constants of Trimethyl-ethylene with nitric acid at 25°

HNO_3 N	KNO_3 N	u N	k hrs^{-1}	k adjusted to 1.0 N
0.0496	0.9500	0.9996	0.0688	1.387
.0946	.9000	0.9946	0.1310	1.385
.2460	.7500	0.9960	0.3350	1.353
.5150	.5000	1.0150	0.7180	1.395
.9820	0	0.9820	1.2550	1.278
.5160	0	0.5160	0.4720	0.915
.1068	0	0.1068	0.0890	0.832
.0532	0	0.0532	0.0435	0.819

TABLE IV

Hydration constants of trimethyl-ethylene with different acids at 25°

Acids	Acidity N	k hrs^{-1}	k adjusted to 0.10 N
HCl	0.1040	0.0955	0.0918
$HClO_4$	.0990	.0905	.0915
HBr	.1030	.0865	.0840
HNO_3	.1068	.0890	.0832
$H_2S_2O_6$	.0932	.0686	.0737
p-Toluene-sulfonic acid	.0948	.0691	.0730
Picric acid	.0590	.0332	.0563
H_2SO_4	.1140	.0582	.0512
Oxalic acid	.2020	.0418	.0207
Acetic acid	.1050	.0011	.0011

It is worthy of note that at unit ionic strength of nitric acid and potassium nitrate solution the rate is almost directly proportional to the acid concentration. Strong acids like perchloric, hydrochloric, hydrobromic, dithionic, p-toluene-sulfonic and picric acids give the hydration rates not much different from one another. The dibasic acids like sulfuric and oxalic have mostly their first hydrogen ion effect on the hydration rates. Picric acid can only be made up to the saturated solution. Dithionic acid shows that its second hydrogen is highly ionized. The specific reaction rates in Tables III and IV are so adjusted to 1.0 $\underline{N}$ and 0.10 $\underline{N}$ in order to make a better comparison.

In Fig. 5 the rate constants at 25° are plotted against the concentration of nitric acid. Two curves are obtained, one at an ionic strength 1 $\underline{N}$ and the other at variable ionic strength corresponding to the nitric acid concentrations.

The straight line character of the curve at 1 $\underline{N}$ indicate that the reaction at constant ionic strength is directly proportional to the nitric acid concentration and therefore is first order with respect to it. It is evident, also, that nitric acid and potassium nitrate are equivalent in their salt effect upon the hydration rate of trimethyl-ethylene.

Summary

The hydration of trimethyl-ethylene is catalyzed by nitric acid and at constant ionic strength the rate is first order with respect to both pentene concentration and the nitric acid concentration. The rate at a given acid concentration is increased on the addition of potassium nitrate.

The hydration of trimethyl-ethylene is also catalyzed by other strong and weak acids. The apparent order of their effects on the rate of hydration is HCl and $HClO_4 >$ HBr and $HNO_3 > H_2S_2O_6$ and p-toluene-sulfonic $>$ picric $> H_2SO_4 >$ oxalic $>$ acetic.

Acknowledgement

This work was financed by a grant from the Rockefeller Foundation and was carried out under the direction of Professor H. J. Lucas, to whom the author wishes to express his sincere thanks.

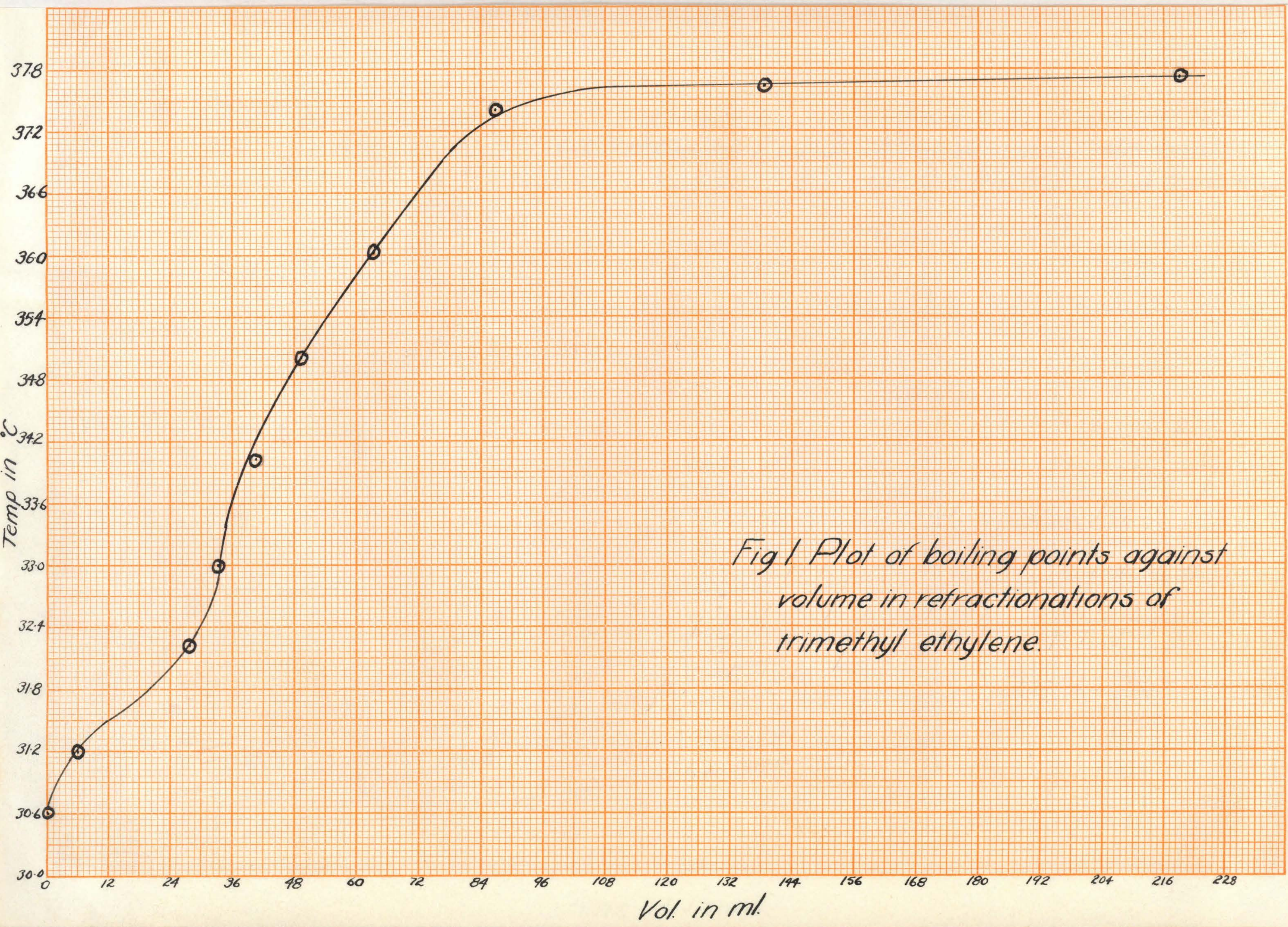

Fig I. Plot of boiling points against volume in refractionations of trimethyl ethylene.

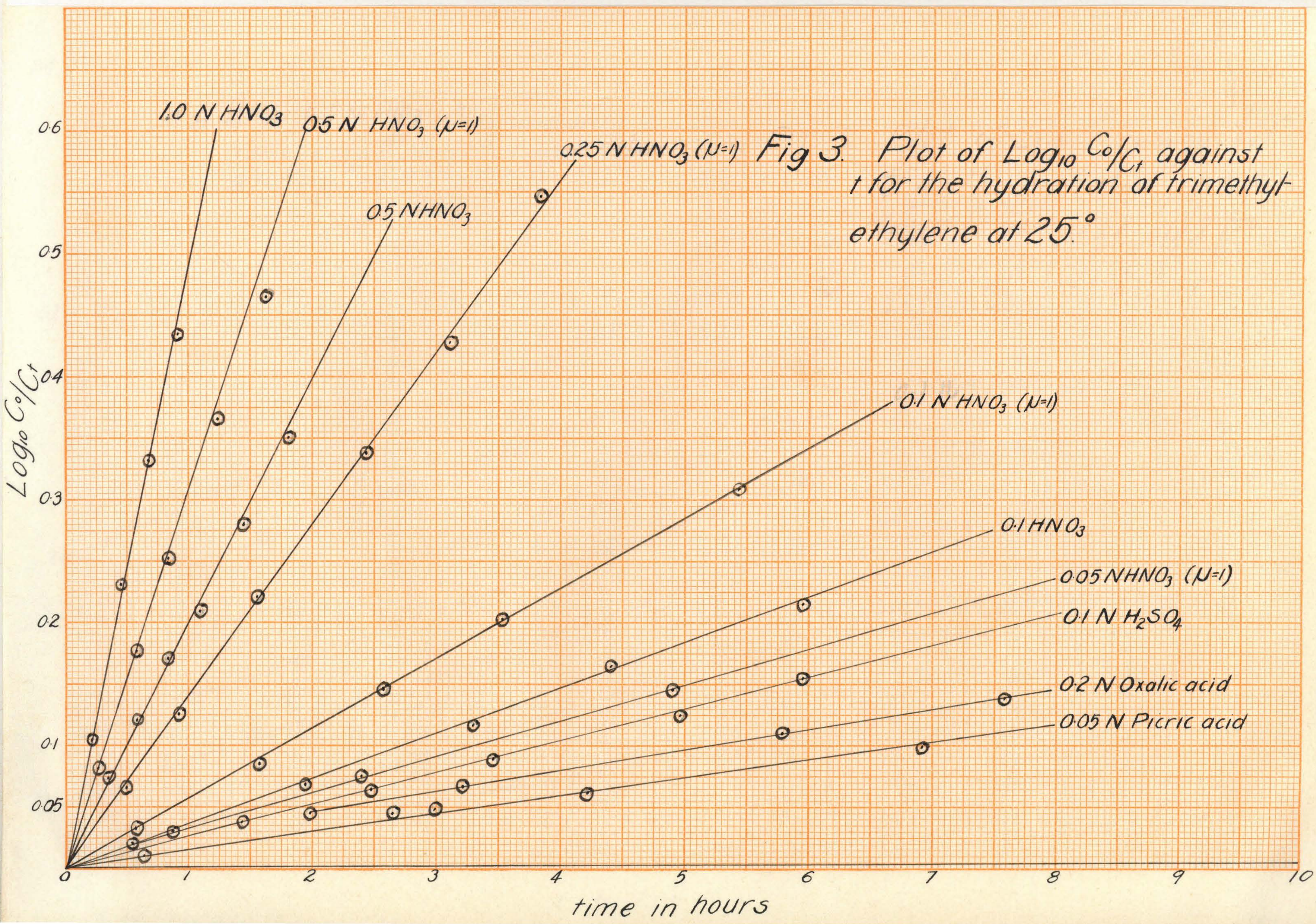

Fig 3. Plot of $\log_{10} C_0/C_t$ against t for the hydration of trimethylethylene at 25°.

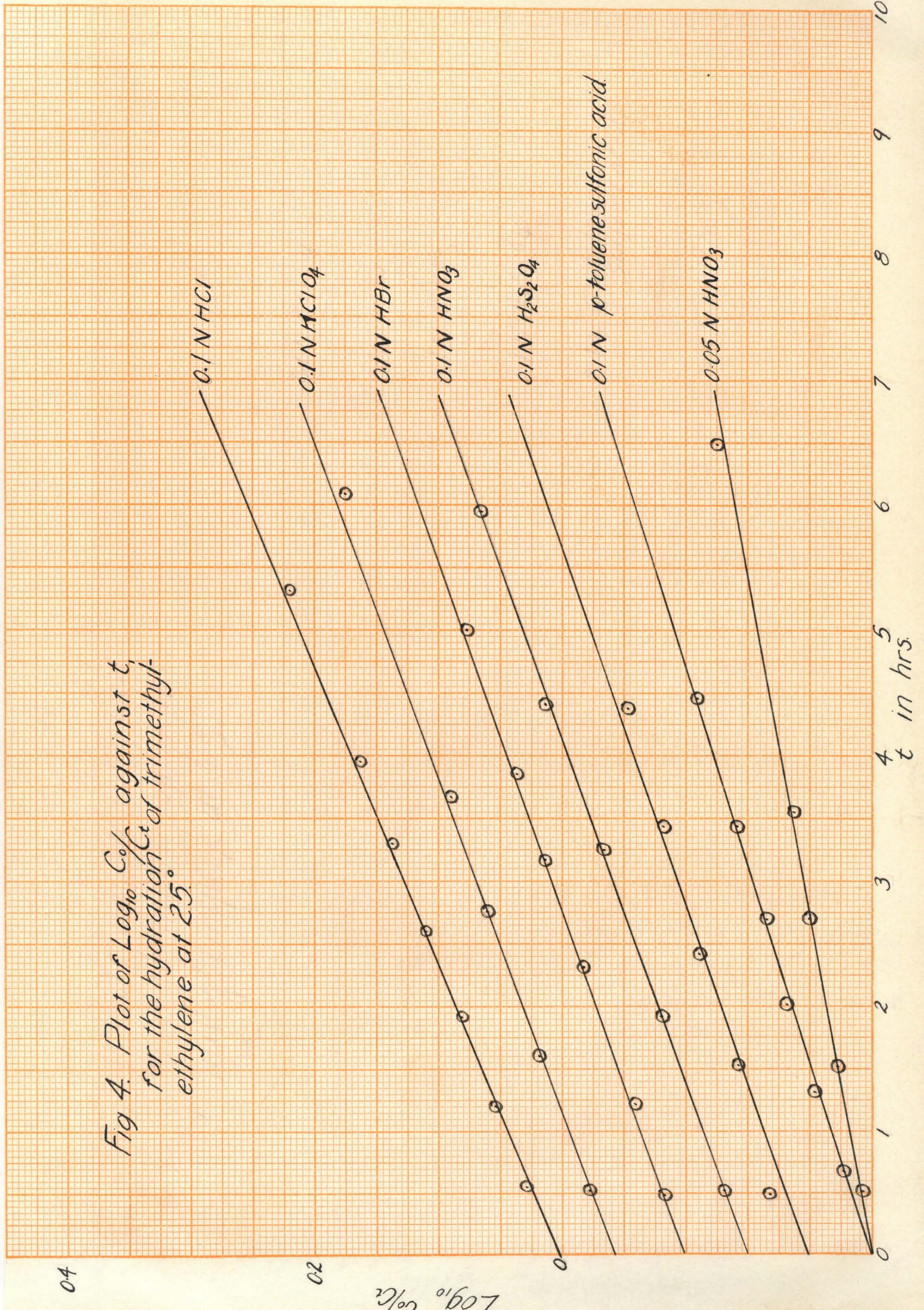

Fig 4. Plot of $\mathrm{Log}_{10}\, C_0/C_t$ against t, for the hydration of trimethylethylene at 25°.

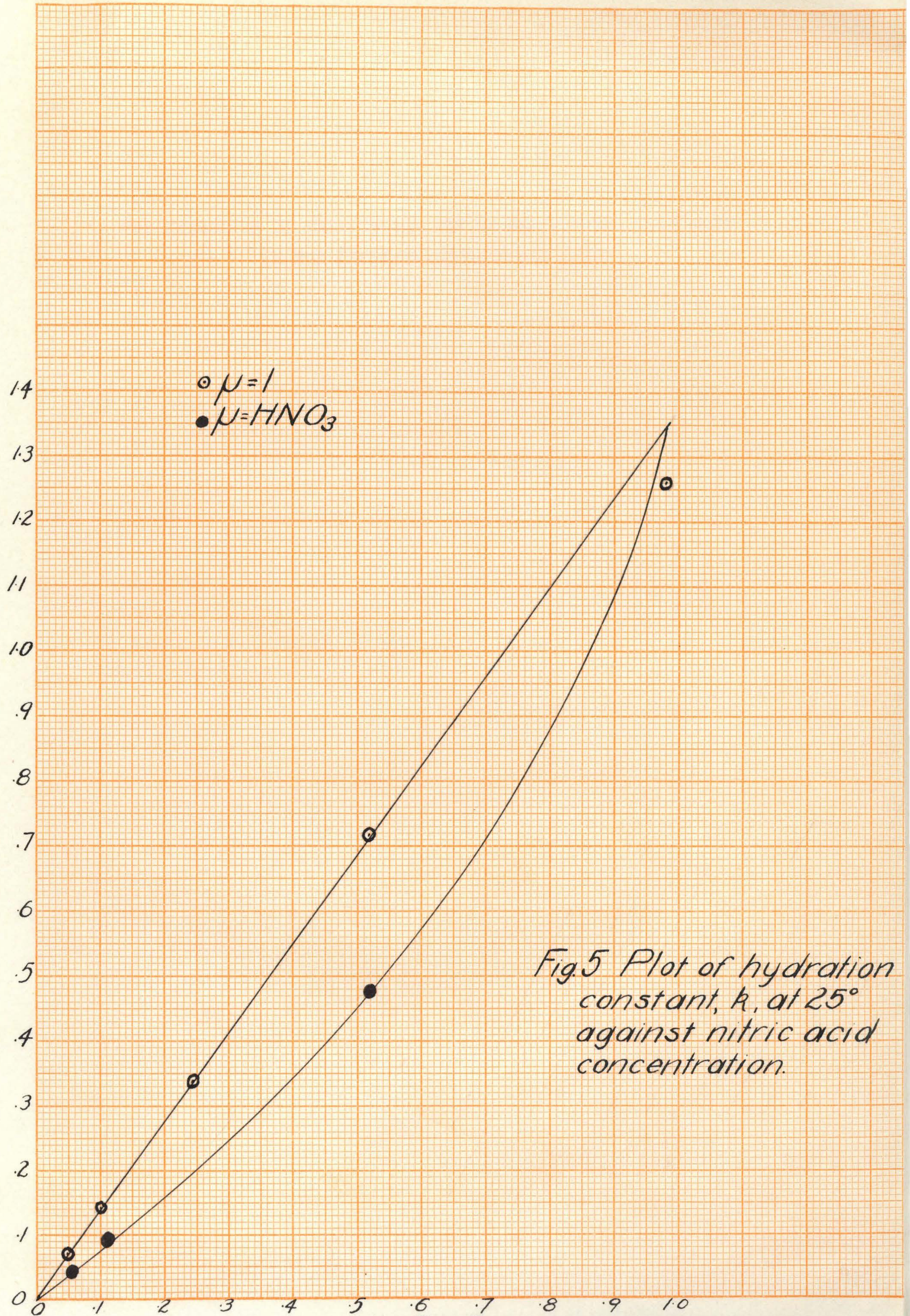

Fig.5 Plot of hydration constant, k, at 25° against nitric acid concentration.

THE NITRATION OF PARA-CRESOL AND OF PARA-CRESYL CARBONATE IN THE PRESENCE OF SULFURIC ACID

[Reprint from the Journal of the American Chemical Society, 55, 1271 (1933).

[CONTRIBUTION FROM GATES CHEMICAL LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 340]

The Nitration of Para-Cresol and of Para-Cresyl Carbonate in the Presence of Sulfuric Acid[1]

BY HOWARD J. LUCAS AND YUN-PU LIU[2]

The addition of sulfuric acid during the nitration of some aromatic compounds is known to influence the ratio of meta to ortho–para substitution. This is especially true of aromatic amines such as aniline, of which the ortho–para directing NH_2 group is converted, by salt formation, into the meta directing NH_3 group. An explanation has been advanced[3] for this behavior on two grounds, *viz.*, (1) the addition of the proton to the lone electron pair of the nitrogen atom greatly increases the electron attraction of the entire group, and (2) the blocking off of the lone pair prevents any possibility of addition formation at this point with the reagent and therefore of subsequent rearrangement to ortho and para positions on the ring.

According to Vorländer, Robinson, Ingold and others[4] the most strongly meta-directing groups are the positive poles directly attached to the benzene ring. Thus phenyltrimethylammonium nitrate is nitrated exclusively in the meta position[5] and many other compounds of similar type yield meta derivatives almost exclusively on nitration; among these may be mentioned diphenyl iodonium nitrate,[6] triphenylantimony dinitrate,[7] triphenylbismuth dinitrate[8] and diphenyllead dinitrate.[9]

The change in the ortho–para directive influence of the NH_2 group to the meta orienting influence of the NH_3X group through salt formation has been ascribed to the ionization of the salt to give a positive ion in which substituents take the meta position because of the positive charge carried by the NH_3^+ group. Flürscheim and Holmes[4d] found that the addition of ammonium sulfate to the nitrating mixture of nitric and sulfuric acid decreased the yield of the meta isomeride formed during the nitration of benzyldiethylamine while Pollard and Robinson[10] observed similar effects in the nitration of benzylpiperidine. In these cases the added salts depress the ionization of the salt undergoing nitration and thus cause a decrease in the meta directive power of the positive pole.

Since the oxygen atom resembles the nitrogen atom in the formation of

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(1) Paper presented at the Denver Meeting of the American Chemical Society, August, 1932.

(2) China Foundation Fellow.

(3) Lucas, THIS JOURNAL, **48**, 1827 (1926).

(4) (a) Vorländer, *Ber.*, **52**, 262 (1919); (b) Allan, Oxford, Robinson and Smith, *J. Chem. Soc.*, 401 (1926); (c) Goss, Ingold and Wilson, *ibid.*, 2440 (1926); (d) Flürscheim and Holmes, *ibid.*, 1562 (1926); (e) Ingold, *Annual Reports Chem. Soc.*, **23**, 130 (1926).

(5) Vorländer and Siebert, *Ber.*, **52**, 283 (1919).

(6) Vorländer and Büchner, *ibid.*, **58**, 1898 (1925).

(7) Morgan and Micklethwaite, *J. Chem. Soc.*, **99**, 2286 (1911).

(8) Vorländer and Schroedter, *Ber.*, **58**, 1900 (1928).

(9) Vorländer and Spreckels, *ibid.*, **58**, 1900 (1928).

(10) Pollard and Robinson, *J. Chem. Soc.*, 2770 (1927).

TABLE I

EFFECT OF SULFURIC ACID UPON NITRATION OF *p*-CRESOL IN GLACIAL ACETIC ACID (24 G.)

Expt.	*p*-Cresol, g.	HNO_3 1.42 g.	H_2SO_4 1.84 g.	Molal ratio H_2SO_4/*p*-Cresol	Temp., °C.	Time, min.	Products in grams *p*-Cresol	o-NO_2[a]	m-NO_2[b]	di-NO_2[c]	Percentage of yield *p*-Cr	o-NO_2[a]	m-NO_2[b]	di-NO_2[c]	Total	Ratio *m/o*
I	2.7	1.5	0	0	−15 to −20	5–10	1.1550	1.947	trace	0.0186	42.8	51.0	trace[d]	0.40	94.2	0
II	2.7	1.0	1.0	0.41	0	30	1.1840	0.3893	0.1144	.0188	43.9	10.2	3.1[e]	.40	57.6	.28
III	2.73	1.0	2.0	0.81	−15 to −20	3–5	1.9450	.3654	.1131	.0129	71.3	9.5	2.9	.30	84.0	.29
IV	2.72	1.0	3.0	1.22	−15 to −20	3–5	1.6990	.3214	.1226	.0080	62.5	8.4	3.2	.20	74.3	.36
V	2.7	1.0	4.0	1.63	−15 to −20	3–5	1.4540	.4147	.1512	.0006	53.9	10.9	4.0	.02	68.8	.36
VI	2.7	1.0	6.0	2.45	−15 to −20	30	1.1562	.3729	.1631	.0019	42.8	9.8	4.3	.04	56.9	.43
VII	2.7	1.0	7.0	2.70	−15 to −20	3–5	2.1180	.2730	.1258	.0042	78.5	7.1	3.3	.10	89.0	.45
VIII	2.7	1.5	8.0	3.27	−15 to −20	3–5	1.7655	.2737	.1263	.0049	65.4	7.2	3.3	.10	76.0	.45
IX	2.7	1.5	9.0	3.50	−15 to −20	3–5	1.8205	.2603	.1385	.0043	67.4	6.8	3.6	.10	77.9	.52
X	2.7	1.5	10.0	4.08	−15 to −20	3–5	2.2015	.2408	.1686	.0017	81.5	6.3	4.4[f]	.03	92.2	.69
XI	2.7	1.5	12.0	4.70	−15 to −20	3–5	1.8740	.2484	.1818	.0012	69.4	6.5	4.8	.02	80.7	.73
XII	2.7	1.5	25.0	9.80	−15 to −20	60	1.4041	.7520	.5880	.0010	52.1	19.7	15.4	.02	87.2	.78

[a] Nitro group ortho to the hydroxyl. [b] Nitro group meta to the hydroxyl. [c] Nitro groups ortho to the hydroxyl. [d] No benzoate of *m*-nitro-*p*-cresol obtained. [e] Benzoate of *m*-nitro-*p*-cresol obtained in 61% yield. [f] Benzoate of *m*-nitro-*p*-cresol obtained in 84% yield.

onium salts, the nitration of a phenol in the presence of varying amounts of sulfuric acid might be expected to yield different ratios of meta derivatives. It has been shown recently that the addition of sulfuric acid in the nitration of benzaldehyde and of ethyl benzoate leads to increased production of the meta derivative.[11]

For this work *p*-cresol was selected since it is known to form two addition compounds with sulfuric acid, *viz.*, $2C_7H_8O \cdot H_2SO_4$, m. p. 11.0°, and $C_7H_8O \cdot 2H_2SO_4$, m. p. 93.5°.[12] If these compounds are ionized the electronic formulas are, for the former, $2CH_3C_6H_4:\underset{\cdot\cdot}{\overset{H}{\ddot{O}}}:H^+, SO_4^=$; and for the latter, $CH_3C_6H_4:\underset{\ddot{H}}{\overset{H}{\ddot{O}}}:H^{++}, 2HSO_4^-$. The presence of a positive charge on the former would presumably increase the proportion of the meta isomer produced on nitration while the presence of a doubly positive charge on the latter would be expected to have an even greater effect. Any influence of added acid, due to salt formation alone, might be expected to carry through to the esters of *p*-cresol, and for that reason the carbonate of *p*-cresol was also nitrated under varying conditions.

The results obtained with *p*-cresol by nitrating in glacial acetic acid solution are shown in Table I, and those with *p*-cresyl carbonate and fuming nitric–sulfuric acid mixture are shown in Table II.

TABLE II

EFFECT OF SULFURIC ACID UPON THE NITRATION OF *p*-CRESYL CARBONATE

	Molal ratio				Nitration products, per cent.						
Expt.	Carbonate:	HNO_3: 2.5% N_2O_5	H_2SO_4 5% SO_3	Temp., °C.	*p*-Cresol	*o*-NO_2	di-NO_2	Total *o*-NO_2	*m*-NO_2	Total	Ratio *m*/*o*
I	1	1.9	0	−10	39.7	32.8	0.2	33.2	3.8	76.5	0.1
II	1	1.9	1.2	0 to −5	37.4	2.7	14.2	31.1	7.3	61.6	0.2
III	1	2.2	2.9	0	27.7	8.8	4.8	18.4	28.8	70.1	1.6
IV	1	2.2	3.9	0	8.9	14.2	6.7	27.6	44.5	74.3	1.6
V	1	2.2	4.4[a]	0	19.0	12.0	4.4	20.8	34.3	69.7	1.7
VI	1	2.2	5.5[b]	0	5.2	9.1	9.8	28.7	52.4	76.5	1.8
VII	1	2.1	6.2	0 to −5	5.8	6.7	11.7	30.1	65.3	89.5	2.2
VIII	1	2.1	8.2	−5 to −10	1.5	5.8	7.2	20.2	48.6	63.1	2.4
IX	1	2.1	10.3	−5 to −10	3.6	6.2	9.9	26.0	61.6	83.3	2.4

[a] 95% H_2SO_4. [b] 90% H_2SO_4.

When using fuming sulfuric and nitric acids *p*-cresol undergoes rapid decomposition and satisfactory results cannot be obtained. The addition of glacial acetic acid cuts down the undesirable side reactions so that, by working rapidly, one can obtain a fair amount of nitration products. On the other hand, the nitration of the carbonate proceeds much more smoothly and can be carried out with the nitric and sulfuric acids alone.

The results obtained in these nitration experiments are shown graphically

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(11) Baker and Moffitt, *J. Chem. Soc.*, 314 (1931); Baker and Hey, *ibid.*, 1226 (1932).

(12) Kendall and Carpenter, THIS JOURNAL, **36**, 2498 (1914).

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in the figure where the molal ratio of *m*-nitro to *o*-nitro[13] isomer is plotted against the ratios of sulfuric acid to the compound undergoing nitration. In the case of *p*-cresol, only the ortho isomer is formed when there is no sulfuric acid present, but when the sulfuric acid–cresol ratio is one-half, the meta–ortho ratio is approximately one-fourth. As more sulfuric acid is added the meta–ortho ratio rises, at first slowly, then more rapidly, and finally reaches a maximum where further addition of acid changes the meta–ortho ratio but little.

In the case of *p*-cresyl carbonate the meta–ortho ratio is 0.1 at zero concentration of sulfuric acid. It changes slowly at first as acid is added, then more rapidly, and finally approaches a maximum.

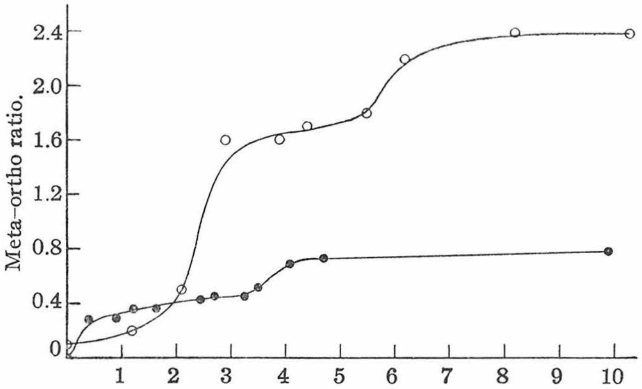

Fig. 1.—○, Nitration of *p*-cresyl carbonate; ●, nitration of *p*-cresol.

Interpretation of the Results.—Increase in the amount of the meta isomer on the addition of sulfuric acid can be accounted for on the basis of oxonium salt formation. It is to be expected that the rate of increase at first would be greater in the case of *p*-cresol since the weakly basic properties of its oxygen atom should exceed the even weaker basic properties of the carbonate. The initial rapid increase in the meta–ortho ratio during the nitration of *p*-cresol corresponds to its conversion into the addition compound, $2CH_3C_6H_4OH \cdot H_2SO_4$. Additional sulfuric acid has little effect until the second addition compound, $CH_3C_6H_4OH \cdot 2H_2SO_4$, is formed. Since the latter is partly dissociated, an excess of sulfuric acid is necessary for the complete conversion of the first into the second. The break in the curve after three moles of sulfuric acid have been added probably corresponds to this change Finally, the maximum value of 0.8 in the meta–

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[13] Since the discussion centers about the hydroxyl group the derivatives are named in reference to it, rather than to the methyl group. Thus 2-nitro-4-hydroxytoluene is here called *m*-nitro-*p*-cresol and 3-nitro-4-hydroxytoluene is called *o*-nitro-*p*-cresol.

ortho ratio indicates that even when completely converted into the disulfate compound more ortho than meta is formed.

In the case of the carbonate the rapid rise in the meta–ortho ratio comes only after approximately two moles of sulfuric acid have been added. Since the carbonate is a weaker base than the cresol the oxonium reaction on each phenolic oxygen should require a higher ratio of sulfuric acid, probably one of acid to each oxygen atom. The resulting compound, $(C_7H_7O)_2CO\cdot 2H_2SO_4$, would probably be unstable and require an excess of sulfuric acid for its complete formation. The rapid rise in the meta–ortho ratio above this point probably corresponds to the conversion of the small amount of uncombined carbonate into the oxonium complex. The second rapid rise above five moles of sulfuric acid probably corresponds to the complete transformation of the first complex into a second, *viz.*, $(C_7H_7O)_2CO\cdot 4H_2SO_4$. Further addition of sulfuric acid brings about little additional change.

The increase in the meta orienting influence of the oxygen atom through salt formation is probably due to its greater attraction for the electron pair which joins it to ring carbon, a condition associated with an increase in the residual kernel charge of the oxygen atom.[14] It is evident that this charge is greater, the greater the degree of ionization of the oxonium complex, since the hydrogen atoms act as bonds in the undissociated molecules. One would expect a progressive increase in the residual kernel charge of the oxygen atom in the following radicals: OH, OH_2X, OH_3X_2, OH_3X^+, OH_3^{++}. On the basis of the positive pole theory the last two should be exclusively meta orienting. The production of the ortho isomer, even in a large excess of sulfuric acid, seems to indicate that a part of the complex is un-ionized and that the nitration of this gives the ortho as well as the meta isomer. It is reasonable to assume, therefore, that on the addition of sulfuric acid the orienting influence of the hydroxyl group suffers modification in the same way as the amino group, but to a less extent.

Experimental

Materials.—Eastman *p*-cresol No. P 449, m. p. 33–34°, was twice distilled under reduced pressure and the portion boiling at 102–102.5° and 22 mm. was collected. It melted at 36.0°. This was converted into the carbonate by dissolving in sodium hydroxide solution and passing in carbonyl chloride.[15] After crystallizing from alcohol it melted at 113°.

3-Nitro-*p*-cresol, 3-nitro-4-hydroxytoluene (called *o*-nitro-*p*-cresol in this paper) was prepared by nitrating 108 g. (1 mole) of *p*-cresol with a mixture of 135 g. of concd. nitric acid (1.4 moles), 200 g. of concd. sulfuric acid (2 moles), and 500 ml. of water at 5–10°. The solution was extracted with ether, the ether was evaporated and the solid was twice steam distilled, m. p. 32.0–32.5°. It analyzed 99.3% pure with standard titanous sulfate and 99.0% pure with standard bromide–bromate solution.

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(14) Latimer and Porter, THIS JOURNAL, **52**, 206 (1930).

(15) Holleman and Hoeflake, *Rec. trav. chim.*, **36**, 271 (1916).

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2-Nitro-*p*-cresol, 2-nitro-4-hydroxytoluene (called *m*-nitro-*p*-cresol in this paper) was prepared by nitrating *p*-cresyl carbonate and saponifying the resulting nitrocarbonate according to the method of Copisarow.[16] The yellow, odorless needles from alcohol melted at 78.5° and analyzed 99.5% pure with standard titanous sulfate and 99.4% pure with standard bromide-bromate.

3,5-Dinitro-*p*-cresol, 3,5-dinitro-4-hydroxytoluene, was prepared by nitrating 36 g. (0.33 mole) of *p*-cresol at 30–40° with a mixture of 135 g. of concd. nitric acid (1.4 mole) and 200 g. of concd. sulfuric acid (2 moles). The reaction mixture was steam-distilled and the residue of crude product was recrystallized from alcohol several times, using norite for decolorizing, m. p. 85.0°. This was found to be 99.3% pure by analysis with standard titanous sulfate and with standard bromide–bromate.

The benzoate of 3-nitro-*p*-cresol was prepared in quantitative yield by the action of benzoyl chloride upon 3-nitro-*p*-cresol dissolved in pyridine. After one crystallization from alcohol the yield of fairly pure crystals was 90%. A second crystallization yielded colorless flakes melting at 96.0°. Reduction with standard titanous solution gave 5.4% N; theoretical for $C_{14}H_{11}O_4N$, 5.45% N.

The benzoate of 2-nitro-*p*-cresol was prepared as above, in approximately the same yield. It crystallized from alcohol in pale yellow needles melting at 90°. Reduction with standard titanous solution gave 5.42% N; theoretical for $C_{14}H_{11}O_4N$, 5.45% N.

Nitration.—The operations were carried out in a 20-cm. test-tube provided with a mercury-sealed stirrer, a dropping funnel to admit the nitrating mixture, and an exit tube carrying a calcium chloride tube to prevent moisture from entering. The test-tube was immersed in a freezing mixture of ice and hydrochloric acid at −15 to −20°. To 2.7 g. (0.025 mole) of *p*-cresol dissolved in a mixture of 18 g. of glacial acetic acid and varying amounts of C. P. concd. sulfuric acid was added a mixture of 1 to 1.5 g. of C. P. concd. nitric acid (0.01 to 0.017 mole) and 6 g. of glacial acetic acid, usually during three to five minutes. The mixture was at once poured onto ice and worked up according to the procedure described under purification. It was found that when the cresol was nitrated with a mixture of nitric and sulfuric acids alone only small amounts of nitrocresols could be obtained since considerable oxidation took place; but in glacial acetic acid the undesirable reactions were so cut down that the nitro compounds could be obtained. However, it was necessary to keep the mixture at −12 to −20° and to shorten the time of addition; otherwise there was a fairly large amount of non-phenolic material produced. Because of the deficiency of nitric acid, only a part of the *p*-cresol was nitrated. The amount of unreacted cresol could be decreased by increasing the time (see Expt. VI, Table I), but more non-phenolic compounds were formed. However, the tendency to undesirable side reactions seemed to drop off at high sulfuric acid ratios since in Expt. XII good yields of products were obtained even though the mixture stood for sixty minutes.

The nitration of the *p*-cresyl carbonate was carried out in the same apparatus, as follows. To 4.83 g. (0.02 mole) of the carbonate dissolved in varying amounts of fuming sulfuric acid containing 5.0% of sulfur trioxide was added 1.9 to 2.2 g. of fuming nitric acid (0.03–0.035 mole) containing 2.5% of nitrogen pentoxide. The temperature was kept at 0 to −10° during the nitration and for three hours afterward; the mixture was then allowed to stand overnight and in the morning it was poured onto a mixture of 30 g. of chopped ice and an amount of sodium carbonate sufficient to neutralize about two-thirds of the sulfuric acid. The precipitated material was filtered onto a Gooch crucible and saponified by refluxing for two to three hours with a solution of 6 g. of sodium carbonate in 60 ml. of water.[16] The solution containing the sodium salts of *p*-cresol and its nitration products was filtered from a small amount of flocculent material, acid was added to the filtrate and this solution was worked up as described under purification

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[16] Copisarow, *J. Chem. Soc.*, 251 (1929).

below, except that the solid *o*-nitro-*p*-cresol and *m*-nitro-*p*-cresol were dried to constant weight.

Purification and Separation of Reaction Products.—The aqueous acid solutions resulting from the nitration of *p*-cresol and from the hydrolysis of the nitrated *p*-cresyl carbonate were extracted with ether several times. The ether phase was then extracted with dilute (0.5 to 1.0 *N*) sodium hydroxide. Following this extraction the ether phase was usually colored by the presence of non-phenolic compounds resulting from oxidation. This was discarded. Dilute sulfuric acid was added to the aqueous phase, another ether extraction followed, and after evaporation of the ether the residue was steam distilled, unchanged *p*-cresol and *o*-nitrocresol coming over, *m*-nitro- and dinitrocresol remaining behind. The distillate was extracted with ether, the ether phase was dried with anhydrous sodium sulfate and then evaporated. The residue was dissolved in 100 ml. of glacial acetic acid. Solutions resulting from the nitration of *p*-cresol were analyzed by titration with standard titanous sulfate solution[17] and those from the carbonate, with standard bromide–bromate solution.[17] The residue of *m*-nitro- and dinitrocresol, along with some non-phenolic material, was dissolved in ether, which was then extracted with dilute sodium hydroxide solution. This phase was filtered, dilute sulfuric acid was added, and the cresols dissolved out by ether. The ether phase, after drying with anhydrous sodium sulfate, was evaporated off and the residue was dissolved in 100 ml. of glacial acetic acid. Solutions coming from the nitration of *p*-cresol were analyzed by reduction with standard titanous solution, followed by titration with standard bromide–bromate solution. Those from the nitration of the carbonate were analyzed with bromide–bromate.

The separation by steam distillation of *p*-cresol and *o*-nitro-*p*-cresol from *m*-nitro- and di-nitro-*p*-cresol under the conditions used gave satisfactory results with a known mixture, as shown below:

	Distillate		Residue	
	p-Cresol g.	*o*-nitro-*p*-cresol, g.	*m*-nitro-*p*-cresol, g.	dinitro-*p*-cresol, g.
Weight taken	0.3001	2.0011	0.2466	0.0214
Weight recovered	.2981	1.9871	.2478	.0215

Analysis.—The determination of *p*-cresol and of *o*-nitro-*p*-cresol in a mixture of these two obtained by the steam distillation of the reaction product from the nitration of *p*-cresol was done by titrating one aliquot of the glacial acetic acid solution with standard titanous sulfate, following the procedure described by Francis and Hill[17] for the use of titanous chloride in determining nitro compounds in alcoholic solution, and by titrating a second aliquot first with an excess of titanous sulfate and second with standard bromide–bromate, following again the procedure of Francis and Hill. The use of glacial acetic acid is preferable to alcohol since the latter slowly reacts with the bromide–bromate solution.[18] From the amount of titanous solution required the amount of nitro compound can be calculated readily, and from the titanous and bromate titrations the amount of unchanged cresol is easily calculated. The data below show the results obtained with a known mixture:

ANALYSIS OF *p*-CRESOL (1.5250 G.) AND *o*-NITRO-*p*-CRESOL (0.3650 G.) DISSOLVED IN 100.0 ML. OF GLACIAL ACETIC ACID, BY REDUCTION AND BROMINATION

	$Ti_2(SO_4)_3$	$KBrO_3$	*o*-Nitro-*p*-cresol			*p*-Cresol		
Soln., ml.	(0.00528 *N*), ml.	(0.1022 *N*), ml.	Taken, g.	Found, g.	Error, %	Taken, g.	Found, g.	Error, %
2	9.01	13.73	0.00730	0.00727	−0.83	0.0305	0.03021	−1.0
2	9.04	13.78	.00730	.00729	− .50	.0305	.03028	−0.7

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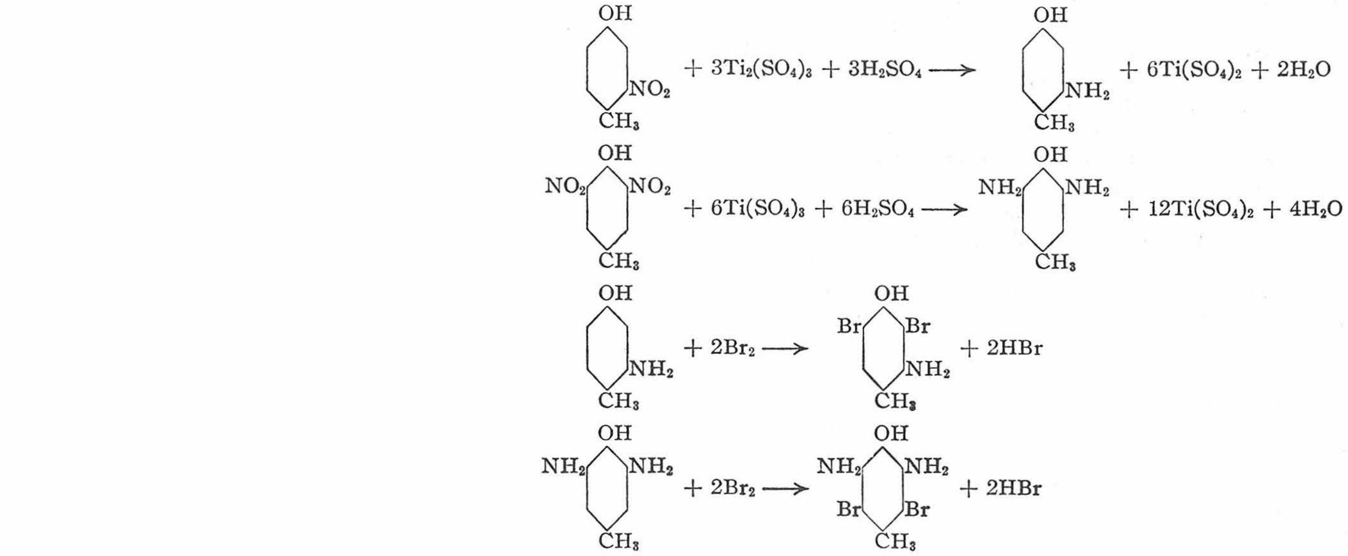
(17) Francis and Hill, THIS JOURNAL, **46**, 2498 (1924).

(18) Buxton and Lucas, *ibid.*, **50**, 249 (1928).

In the same way the mixture of *m*-nitro- and dinitro-*p*-cresol can be analyzed, the calculations being based upon the equations



When a is equivalents of titanous sulfate and b is equivalents of bromine used up, the weight of *m*-nitro- (x) and of dinitro-*p*-cresol (y) can be calculated by means of the two equations

$$x = 76.5b - 153a; \quad y = 198a - 49.5b$$

The data below show the results obtained with a known mixture.

ANALYSIS OF *m*-NITRO-*p*-CRESOL (0.2025 G.) AND DINITRO-*p*-CRESOL (0.0200 G.) DISSOLVED IN 50.0 ML. OF GLACIAL ACETIC ACID, BY REDUCTION AND BROMINATION

Soln., ml.	$Ti_2(SO_4)_3$ (0.00528 *N*) ml.	$KBrO_3$ (0.0536 *N*), ml.	*m*-Nitro-*p*-cresol Taken, g.	Found, g.	Error, %	Dinitro-*p*-cresol Taken, g.	Found, g.	Error, %
2	11.62	4.28	0.00810	0.00814	+0.5	0.00080	0.00079	−1.2
2	11.60	4.27	.00810	.00814	+ .4	.00080	.00079	−1.2

The reaction products from the nitration of *p*-cresyl carbonate were analyzed by bromination alone. In this case it was necessary to know the weight of solid material and this was obtained by complete evaporation of the ether solutions, followed by desiccation over concd. sulfuric acid for one or two days. With known mixtures bromination gave fairly satisfactory results.

ANALYSIS OF *p*-CRESOL (1.0835 G.) AND *o*-NITRO-*p*-CRESOL (2.1406 G.) DISSOLVED IN 250 ML. OF GLACIAL ACETIC ACID, BY BROMINATION ALONE

Soln., ml.	$KBrO_3$ (0.1346 *N*), ml.	*p*-Cresol Taken, g.	Found, g.	Error, %	*o*-Nitro-*p*-cresol Taken, g.	Found, g.	Error, %
10	20.15	0.04334	0.04279	−1.3	0.08562	0.08601	+0.5
10	20.18	.04334	.04290	−1.0	.08562	.08590	+ .4

The calculations above were based upon the fact that *p*-cresol reacts with two moles of bromine and the *o*-nitro derivative with only one. In the equations x is amount of *p*-cresol, y is amount of *o*-nitro-*p*-cresol, a is equivalents of bromine used and w is weight of the sample in grams.

$$x = 41.80a - 0.547w$$
$$y = 1.548w - 41.80a$$

ANALYSIS OF *m*-NITRO-*p*-CRESOL (0.3621 G.) AND DINITRO-*p*-CRESOL (0.1284 G.) IN 50 ML. OF GLACIAL ACETIC ACID; BY BROMINATION ONLY

Soln., ml.	$KBrO_3$ (0.1346 *N*), ml.	*m*-Nitro-*p*-cresol Taken, g.	Found, g.	Error, g.	Dinitro-*p*-cresol Taken, g.	Found, g.	Error, %
10	14.16	0.07242	0.07304	+0.8	0.02568	0.02506	−2.4
10	14.14	.07242	.07302	+ .8	.02568	.02508	−2.4

These calculations are based upon the fact that *m*-nitro-*p*-cresol reacts with two moles of bromine and the dinitro compound with none. The calculations are made according to the equations below in which x is weight of *m*-nitro- and y is weight of dinitro-*p*-cresol.

$$x = 38.25a$$
$$y = w - 38.25a$$

Experimental Results.—The results of the nitration of *p*-cresol in glacial acetic acid solution and of the nitration of *p*-cresyl carbonate are given in Tables I and II. It is from these data that the curves shown earlier were constructed.

In the nitration of *p*-cresol there was always a deficiency of nitric acid. The small amount of dinitro compound was assumed to be the isomer in which both nitro groups were ortho to the hydroxyl. Benzoylation of the residue non-volatile with steam from Experiment II gave an amount of the benzoate of *m*-nitro-*p*-cresol equivalent to 61% of the meta compound found by analysis and the residue from Experiment X gave 84%. None of this benzoate could be obtained from Experiment I.

Since *p*-cresyl carbonate undergoes nitration with greater difficulty, it was necessary to use a mixture of fuming nitric and fuming sulfuric acid. Here again the dinitro-*p*-cresol was assumed to be 3,5-dinitro-4-hydroxytoluene. Such an assumption probably involves an error, since the dinitro compound may in part be the 2,5- or even the 2,6- isomer. If the former is present then the meta–ortho ratio should be less than the one calculated, while if the latter is present this ratio should be greater. It is possible that the error from this source is not great since these two effects counteract each other.

Summary

Nitrations of *p*-cresol and of *p*-cresyl carbonate have been carried out in the presence of sulfuric acid in amounts varying from 0 to 10 moles of acid per mole of organic compound. It was found in the case of *p*-cresol that the ortho directive power of the hydroxyl group decreased as sulfuric acid

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increased, and that more and more of the entering nitro group took up a position meta to the hydroxyl. However, a maximum value of about 0.8 was reached for the meta–ortho ratio. This change in directive power is ascribed to the salt-forming property of the oxygen atom of *p*-cresol. The predominating tendency toward ortho substitution, even when a large excess of acid is present, probably arises from the fact that the oxonium salt is in part un-ionized.

In the case of *p*-cresyl carbonate, increase in the amount of sulfuric acid likewise increased the meta–ortho ratio. It is assumed that here also oxonium salt formation is responsible for the change.

These changes in orientation are entirely analogous to the modification in the orientation of amino and substituted amino groups by the addition of sulfuric acid.

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THE PREPARATION OF CRYSTALLINE LACTIC ACID

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THE PREPARATION OF CRYSTALLINE LACTIC ACID

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On account of its importance in intermediary metabolism, lactic acid was among the first compounds chosen in our plan, which we have described in a previous communication (1), to augment the available data on the free energies of formation of substances significant in biological chemistry. It was necessary for this purpose to obtain pure crystalline lactic acid, free of water, anhydride, and lactide. The only description in the literature of the preparation of crystalline lactic acid is that of Krafft and Dÿes (2). Table I shows that the product obtained by their method contains relatively large quantities of anhydro impurities. The subject of the present communication is the description of a method which yields the active isomers of lactic acid in a crystalline state, free of water, anhydride, and lactide, supplemented by the description of two methods of separating the active forms from the commercial syrup.[1] Lactic acid commercially available at present either is in the form of the U.S.P. syrup, which usually exhibits a low optical activity corresponding to the excess it happens to contain, which is variable, of one or the other optical isomer, or is the expensive zinc sarcolactate. The methods described below now make it possible to obtain easily and quickly and at low cost large quantities of both active isomers in a relatively high degree of purity.

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[1] In this communication the form of lactic acid commonly named sarcolactic or *d*-lactic acid is designated as *l*(+)- or *l*-lactic acid. The salts of this form are levo- and the free acid dextrorotatory. The opposite form is correspondingly designated as *d*(−)- or *d*-lactic acid. Optically inactive lactic acid is referred to as the *dl* form without any implication regarding its constitution; *i.e.*, whether it is a simple mixture of equal quantities of the two active forms, or a definite compound.

The summary in Table III of some of the physical properties of the free acids prepared by these methods shows that they probably have not been obtained in as pure a state out of solution hitherto. For example, the melting points of the active forms are more than 25° higher than the values given in standard reference works (3, 4). They are also less hygroscopic than they are commonly described.

We shall describe first the preparation of the crystalline free acids from the commercial syrup (which contains as a rule about 50 per cent lactic acid, 30 per cent anhydride and lactide, and 15 per cent water). Briefly, the method consists of fractional distillation followed by fractional crystallization from a mixture of equal volumes of ethyl and isopropyl ethers. The typical procedure was as follows: 200 cc. of syrup were distilled from a 1 liter Claisen flask, first with a water pump at about 60° until most of the water had been driven off, and then, with the outside bath temperature raised to 105°, with an oil pump through two liquid air traps at a pressure of about 0.1 mm. A middle fraction of about 75 cc. was collected and redistilled with the oil pump. The middle fraction from the second distillation, usually about 60 cc., was then set away in ice-salt to crystallize. Even when a large quantity of lactic acid is required, it is preferable to carry out the distillation a number of times with small portions because with large quantities greater losses are incurred during the longer heating required at 105°.

In order to minimize anhydride formation in the syrup and in the vapor through overheating, the side arm of the distilling flask, internal diameter about 2 cm., was fused into the neck about 1 cm. above the bulb and was shielded from the heat of the paraffin bath by asbestos board. For the same reason the filter flask in which the distillate was received was kept at room temperature in a water bath during the collection of the middle fractions.

In about 2 hours the first nuclei of crystals appeared in the second middle fraction set away in ice-salt. Removed then to the temperature of ice and shaken vigorously, the syrup soon became a solid crystalline mass. The product at this stage corresponds to that obtained by Krafft and Dÿes. The degree of anhydro impurity present is shown in Table I.

The crystalline lactic acid was now dissolved in an equal volume of a mixture of equal parts of ethyl and isopropyl ethers (dried over sodium), complete solution requiring about ½ hour at 37°. After some hours at the temperature of ice-salt, crystallization set in. After another hour, when the contents had become a nearly solid mass of crystals, they were filtered quickly with suction. The crystallization was repeated three times. After the first crystallization, crystallization began in the subsequent ethereal solutions

TABLE I

Titration of Twice Distilled Lactic Acid (Krafft and Dÿes (2))

Weight	First titration, N/14 NaOH	Back titration, N/14 NaOH	Total titration, N/14 NaOH	Calculated value for pure lactic acid, N/14 NaOH	Free lactic acid calculated on basis of sole impurity as	
					Anhydride	Lactide
gm.	*cc.*	*cc.*	*cc.*	*cc.*	*per cent*	*per cent*
1.0447	162.0	1.5	163.5	162.4	93.7	97.2
1.0260	159.2	1.4	160.6	159.5	93.7	97.2
1.0513	163.0	1.5	164.5	163.5	93.7	97.2

TABLE II

Titration of Crystalline Lactic Acid

Specimen	Weight	First titration, N/14 NaOH	Back titration, N/14 NaOH	Total titration, N/14 NaOH	Calculated titration value for pure lactic acid, N/14 NaOH
	gm.	*cc.*	*cc.*	*cc.*	*cc.*
l(+)-Lactic acid prepared by recrystallization of distillate three times from the mixed ethers	0.5004 0.6836 0.7083	77.84 106.30 110.09	0.06 0.04 0.04	77.90 106.34 110.13	77.86 106.37 110.21
Same after melting and heating to 56° and crystallizing again	0.9963 0.7343	154.62 114.10	0.16 0.28	154.78 114.38	154.87 114.15
l(+)-Lactic acid from zinc ammonium salt, recrystallized three times from the mixed ethers	0.4182 0.4319	65.06 67.05	0.05 0.05	65.11 67.10	65.00 67.08
d(−)-Lactic acid from zinc ammonium salt, recrystallized three times from the mixed ethers	0.5498 0.3990	85.40 61.95	0.00 0.00	85.40 61.95	85.46 62.02

immediately on cooling under the tap. After the final recrystallization, the fine white crystals were dried at room temperature in a vacuum desiccator. Titration of this product showed that it contained less than 0.1 per cent of impurities such as water, anhydride, or lactide (Table II).

The fractional crystallization from the mixed ethers effects also a separation of the active isomer, which was in excess in the original syrup (here the *l*(+) form), from the main bulk of inactive material. This was shown by the optical activity of the ethereal mother liquor, which was nearly zero (indicating that no resolution, but only a separation of the excess of active isomer from the inactive form, had occurred), and by the melting point of a mixture of the *l*(+) acid obtained by this method and some *l*(+) acid prepared from the zinc ammonium *l*(+) salt. Separately the melting point of each form was 52.7–52.8°. The mixed melting point was 52.7°. On the other hand, the melting point of an equimolar mixture of the acid obtained by fractional crystallization of the distillate from the crude syrup with that prepared from zinc ammonium *d*(−)-lactate was 16.8° (Table III).

We have not had occasion as yet to try the separation by this method of the *d*(−) acid from a preponderance of the *dl* form because all the commercial syrups we secured contained an excess of the *l*(+) isomer. Nevertheless, we feel confident in recommending the method because the solubility in the mixed ethers of the two active acids prepared from their respective zinc ammonium salts was the same, both being much lower than that of the *dl* form. *dl*-Lactic acid can also be crystallized from the mixed ethers, but the temperature of solid CO_2 is necessary for a good yield, while for the active acids 0° is sufficiently low.

The active acids were also prepared by way of their zinc ammonium salts obtained by resolution of the commercial syrup. The method of resolution employed was essentially that described by Purdie and Walker (5). 1000 cc. of lactic acid syrup were made alkaline to litmus with concentrated ammonia, and then boiled until acid again. This was repeated several times until long boiling was necessary to restore a faint acidity. 560 gm. of zinc *dl*-lactate (air-dried) were now added. The solution was again boiled until all the salt had dissolved, and while still boiling the volume was made up to 2 liters. It was filtered rapidly with suction while still hot, and then transferred to a clean and dry 4 liter beaker. The beaker was placed in a bath of ice water and stirred. When cool it was seeded with about 0.1 gm. of finely powdered zinc ammonium *l*(+)-lactate. Within a short time after the seed had been thoroughly stirred in, the crystals of the optically active zinc ammonium salt began to cloud the solution. The process was controlled by microscopical examination of the crystals from time to time. The optically active double salt forms short, relatively wide, single, rectangular or square prisms; the inactive salt forms long narrow rods frequently arranged in radiating clusters. The inactive form appeared when the solution was too dilute, or when it was set away at 0–2°. When the syrup was too concentrated, crystallization was very slow, and after 24 hours only a poor yield of active crystals contaminated with the inactive form was obtained. If the solution was too dilute, it was boiled again until a definite quantity of water (determined by weight) was driven off; if too concentrated, it was also boiled, then brought to a definite weight with water, and, after cooling, seeded again. When the conditions were suitable, an abundant quantity of optically active crystals appeared in an hour throughout the solution. The beaker was left to stand overnight at room temperature (15–20°). When microscopical examination showed the copious deposit at the bottom of the beaker to be not more than slightly contaminated with inactive crystals, the supernatant liquor was decanted off and centrifuged. The precipitates in the centrifuge cups and in the beaker were washed three times with 95 per cent alcohol, and, after drying in air, the optical activity of an 8 per cent aqueous solution was measured. The amount of solid remaining undissolved in making the 8 per cent solution was a good measure of the degree of contamination with inactive salt.

After the first batch of active crystals had been separated from the syrup, there was dissolved in it a quantity of zinc *dl*-lactate, equal to the weight of the active double salt obtained, and then it was seeded with the opposite active form. Purdie and Walker and others have reported obtaining large quantities of both active forms by this method of repeated crystallization after seeding alternately with one and then the other active form. In spite of many attempts this method always failed us. Repeatedly on seeding with zinc ammonium *d*(−)-lactate we obtained either the *dl* form, or large quantities of the *l*(+) double salt. From one batch of syrup in three successive crystallizations we obtained over a kilo of the *l*(+) double salt, although the last two seedings were with *d*(−) double salt. The probable reason for our failure is that the syrup contained too great an excess of the *l*(+) isomer. We did succeed in obtaining a small quantity of the *d*(−) double salt each time on seeding a virgin syrup with *d*(−) seed, although it contained an excess of the *l*(+) form.

We found also that when zinc ammonium *d*(−)-lactate was mixed with a large quantity of the double salt of the *dl* acid, the active salt could be separated out by warming to 55° for about an hour and then setting aside at room temperature overnight. We did not succeed in obtaining the double salt of the *l*(+) acid by this method, probably because of the excess of the *d*(−) in the crude syrup. This experience suggests that large yields of either form of active zinc ammonium lactate (3 to 4 times that separated by Purdie and Walker) can be obtained by their method of seeding a supersaturated solution if the initial lactic acid syrup contains an excess of the same active form as the seed added. The opposite form can also be obtained by seeding a virgin syrup, as in our case, but the yields are small. If the crude syrup contains a 20 per cent or greater excess of one active form, the preferable method for obtaining a large quantity of the pure isomer, which is in excess, is distillation and crystallization from the mixed ethers as described above, without previous precipitation of the active zinc ammonium salt.

The *l*(+) seed was prepared as follows: A quantity of zinc *l*(+)-lactate was converted to the ammonium salt by treatment with H_2S, followed by ammonia, and was then added to twice the equivalent quantity of lactate in the form of the zinc salt. The combined solutions were concentrated on the water bath to a syrup, and then cooled. The short rectangular prisms of the active double salt obtained were separated from the syrup by suction filtration, washed with 95 per cent alcohol, and air-dried. The *d*(−) seed was obtained by means of the morphine salt by Patterson and Forsyth's modification (6) of the method of Irvine (7).

The following was the typical method of preparation of the active acid from its double salt. 500 gm. of zinc ammonium *d*(−)-lactate were dissolved in 1200 cc. of cold water and filtered immediately. The clear filtrate was set away overnight at about 2°. The next morning the precipitate of zinc lactate was separated by suction filtration and washed with distilled water until the washings no longer gave a positive test with Nessler's reagent. The salt was air-dried to constant weight and its water of crystallization determined by heating at 100° to constant weight. The theoretical value for the optically active form is 12.9 per cent, corresponding to 2 molecules of water of crystallization. The *dl* form contains 3 molecules of water of crystallization. When the water of crystallization was greater than 12.9 per cent, the salt was recrystallized until the theoretical value was obtained. If the zinc salt was pure from the outset, the collected filtrate and washings of ammonium lactate were boiled with $Ca(OH)_2$ to drive off the ammonia, and the free acid was obtained by precipitating the calcium with oxalic or sulfuric acid. If the zinc salt was impure, this free acid was converted to the zinc salt by boiling with zinc oxide, and then recrystallized until the theoretical percentage of water of crystallization was obtained. The free acid was liberated from the zinc salts by treatment with H_2S.[2] The combined aqueous solutions of the free acid were now concentrated at 60° with a water pump to a syrup, then distilled, and crystallized from the mixture of ethyl and isopropyl ethers as described above. In this manner about 120 gm. of free acid were obtained from about 500 gm. of each active double salt.

The purity of the free acids prepared, *i.e.* their freedom from anhydride, lactide, and water, was determined by titration with N/14 NaOH and phenolphthalein as indicator. The following standardized technique was employed. Between 0.4 and 1.0 gm. of the acid was transferred quickly to a tared weighing bottle, which was then covered, weighed, and inserted with tongs into a wide necked flask containing 100 cc. of CO_2-free distilled water.

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[2] Free lactic acid is adsorbed in large quantities by such precipitates as zinc sulfide, calcium sulfate, and calcium oxalate, and boiling several times with large quantities of distilled water was necessary in order to avoid large losses. The precipitates were washed until the washings gave a negative reaction in the following test described by Denigès (8). 0.2 cc. of solution and 2 cc. of concentrated H_2SO_4 are heated in a boiling water bath for 2 minutes. After cooling under the tap, a drop of an alcoholic solution of guaiacol is added. A fuchsin red color develops with 0.01 mg. of lactic acid.

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The stopper was then shaken off the weighing bottle, and the titration begun with a stream of CO_2-free nitrogen bubbling continuously through the solution. When the apparent end-point was reached, the weighing bottle and lid were removed with tongs and rinsed with CO_2-free water, the rinsings being collected in the flask containing the lactic acid. The solution was now brought to a boil and again titrated to the first appearance of pink. The total alkali added to this point was designated as the first titration value. 5 cc. of N/14 NaOH were now added and the solution again boiled for 3 minutes, after which the remaining excess of alkali was back titrated with N/14 HCl. The addition of excess alkali, boiling, and back titration were repeated until the difference between the acid used and the alkali added in one back titration was not more than 0.2 cc. The difference between the total excess alkali added and the amount of N/14 HCl used in the back titration was noted as the back titration value. If lactide and anhydride are present (in the absence of a significant amount of water), the sum of the initial titration figure and the total acid liberated by boiling in excess of alkali is greater than the titration figure calculated on the assumption that the lactic acid weighed out was free of water, anhydride, or lactide. If T cc. of N/14 NaOH is the total titration figure observed per gm. of material weighed out, the percentage of free lactic acid is given by the formula $\frac{172.7 - T}{17.3} \times 100$, on the assumption that the only impurity is anhydride, and by the formula $\frac{194.4 - T}{39} \times 100$ if the impurity is assumed to be solely lactide. Typical titration results with pure and impure lactic acids are given in Tables I and II.

Table III summarizes the melting points, dissociation constants, and hygroscopic properties of the pure acids. The melting point determinations were made on 10 to 12 gm. samples in a wide test-tube stirred constantly with dry nitrogen. The inside temperature was read with an Anschütz thermometer. The temperature of the water bath outside was kept about 1° higher than the inside during the melting, and 1° lower during the subsequent crystallization. The temperatures are the equilibrium temperatures observed during the melting when both phases were present. The crystallization temperatures were 1° lower. The melting points of the pure active forms observed are much higher than the values of 25–27° given in Landolt-Börnstein (3) or the "International critical tables" (4), which are based on the work of Jungfleisch and Godchot (9). The low values found by these authors are probably to be attributed to incomplete resolution. This surmise is supported not only by the difference in the melting points, but also by the failure of other workers (7) and ourselves to obtain a satisfactory resolution by the method described by Jungfleisch and Godchot. The melting point of *dl*-lactic acid prepared by melting together and then crystallizing equal quantities of the pure *l*(+) and *d*(−) acids was found to be 16.8°, nearly 1° lower than the melting point given by Krafft and Dÿes for their *dl*-lactic acid. The probable explanation for this difference is that, apart from contamination with water or anhydro compounds, the product obtained by Krafft and Dÿes was a mixture of the *dl* and one of the active forms. Such mixtures we have found melt at temperatures higher than 16.8°, according to the degree of excess of one of the active forms. The general experience has been that commercial lactic acid syrup, from which Krafft and Dÿes obtained their product, contains nearly always an excess of one of

TABLE III

Summary of Some of the Properties of the Optically Active Lactic Acids

Specimen	Melting point	Water absorbed from the air at room temperature; fraction of original weight	Dissociation constant at 25°
	°*C.*		*pK*
d(−)-Lactic acid from recrystallization of distillate (Specimen A)	52.7	0 in 4 hrs.; 2% in 20 hrs.	3.81 ± 0.01
d(−)-Lactic acid from zinc ammonium salt (Specimen B)	52.8	0 in 4 hrs.; 2% in 20 hrs.	3.83 ± 0.01
2 parts Specimen A + 1 part Specimen B	52.7		
l(+)-Lactic acid from zinc ammonium salt	52.8	1% in 4 hrs.; 3% in 20 hrs.	3.79 ± 0.01
Equal weights of Specimen A and *l*(+)-lactic acid	16.8	In liquid state 3% in 3 hrs.; 10% in 15 hrs.	3.81 ± 0.01

the active forms; and this mixed composition is carried over into the distillates.

The dissociation constants were determined in the usual manner by electrometric titration with Moloney hydrogen electrodes (10) in duplicate, against a saturated calomel half-cell. In the computation of the dissociation constants we have assumed the activity coefficient of the undissociated acid to be 1, which is justified by the freezing point data given in the "International critical tables." The activity of the lactate ions was estimated by the simplified form of the Debye-Hückel equation. The values obtained, therefore, approximate thermodynamic dissociation constants, pK (as distinguished from titration constants, usually designated as pK').

TABLE IV

Optical Rotations of Lactic Acid and Its Salts When λ = 5461 Å., at 21–22°

	Concentration	α	$[\alpha]_{\mathrm{Hg}}^{21-22}$	$[\mathrm{M}]_{\mathrm{Hg}}^{21-22}$
	gm. per cent	*degrees*		
d(−)-Lactic acid	8.00	+0.41	+2.6	+2.3
“ “	4.00	+0.18	+2.3	+2.1
l(+)-Lactic “	8.00	−0.41	−2.6	−2.3
“ “	4.00	−0.16	−2.0	−1.8
Zinc ammonium *l*(+)-lactate	8.00	−1.10	−6.9	−8.9
“ “ *d*(−)-lactate	8.00	+1.10	+6.9	+8.9
Sodium *l*(+)-lactate	4.20	−1.15	−13.7	−15.8
“ *d*(−)-lactate	7.05	+1.70	+12.1	+13.5

The avidity of the free acids for water was determined approximately by exposing a weighed quantity of the acid to the air at room temperature in an open weighing bottle. Table III shows that the pure optically active acids are only slightly hygroscopic. This also runs counter to the description usually given, which is derived from the papers of Jungfleisch and Godchot. As in the case of the difference in the melting points, the discrepancy probably is to be ascribed to incomplete resolution, and possibly also to contamination of the product obtained by these authors by water and anhydride, since the free acids were prepared from their

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quinine salts by the distillation method of Krafft and Dÿes, and were not purified further.

The pure optically active acids are relatively quite stable. Kept in a desiccator at room temperature, both forms remained unchanged for more than a month; after 6 months, only a small amount of anhydride formation was found to have occurred. The second group of figures in Table II shows that only a small amount of anhydride formation occurs during the melting of the crystals.

The rotations of the free acids and their salts are given in Table IV. The measurements were made at 21–22° in a 2 dm. tube, with the mercury green line (λ 5461 Å.). The difference in the specific rotations of the two sodium salts is the usual effect of changing the concentration.

The biological activity of the two optically active forms was tested with lactic acid dehydrogenase prepared from muscle by the method of von Szent-Györgyi (11). When the *l*(+) form was added to the enzyme and methylene blue in an evacuated Thunberg vessel, the dye was quickly decolorized. The *d*(−) form, on the other hand, was quite inactive, giving a longer decoloration time than the enzyme alone. We are indebted to the kindness of Mr. H. F. Schott for this examination of the two forms of lactic acid prepared, and for his active interest and many helpful suggestions throughout the course of this work.

SUMMARY

1. Two methods are described for obtaining optically active lactic acid (both isomers) from a commercial aqueous syrup.

2. A method is described of preparing the active isomers in a crystalline state, free of water, anhydride, and lactide.

3. Some of the properties of the crystalline acids are described. The following physical constants are given: melting points, *l*(+)-lactic acid, 52.8°; *d*(−)-lactic acid, 52.8°; *dl*-lactic acid, 16.8°; the acid dissociation constant of the three forms at 25° is pK = 3.81 ± 0.02.

BIBLIOGRAPHY

1. Borsook, H., and Huffman, H. M., *J. Biol. Chem.*, **99**, 663 (1932–33).
2. Krafft, F., and Dÿes, W. A., *Ber. chem. Ges.*, **28**, 2589 (1895).
3. Roth, W. A., and Scheel, K., Landolt-Börnstein physikalisch-chemische Tabellen, Berlin, 5th edition, **1** (1923).

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4. International critical tables of numerical data, physics, chemistry and technology, New York and London, **4** (1928).
5. Purdie, T., and Walker, J. W., *J. Chem. Soc.*, **62,** 754 (1892); **67,** 616 (1895). Purdie, T., *J. Chem. Soc.*, **63,** 1143 (1893).
6. Patterson, T. S., and Forsyth, W. C., *J. Chem. Soc.*, **103,** 2263 (1913).
7. Irvine, T., *J. Chem. Soc.*, **89,** 935 (1906).
8. Denigès, G., *Bull. Soc. chim.*, series 4, **5,** 647 (1909).
9. Jungfleisch, E., and Godchot, M., *Compt. rend. Acad.*, **140,** 719 (1905); **142,** 55 (1906).
10. Moloney, P. S., *J. Physic. Chem.*, **25,** 758 (1921).
11. von Szent-Györgyi, A., *Biochem. Z.*, **157,** 50 (1925).