physiological properties of hydroxyalkyl 8-quinolyl ethers having a bearing on the chemotherapy of pneumonia have been presented briefly.

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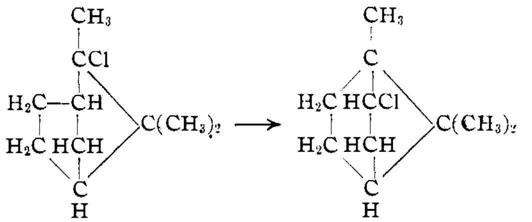
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Wagner–Meerwein Rearrangement. A Kinetic Reinvestigation of the Isomerization of Camphene Hydrochloride[1]

BY PAUL D. BARTLETT AND IRVING PÖCKEL

About a year ago we reviewed the evidence[2] that the rearrangement of camphene hydrochloride (I) into isobornyl chloride (II), and of pinene hydrochloride (III) into bornyl chloride (IV) involves complete Walden inversion at carbon atom no. 2 of the camphane ring system (the point of attachment of the chlorine in bornyl and isobornyl chlorides). Analogy with well-known cases of Walden inversion led us to propose that this rearrangement was a collision process, involving donors or acceptors of chloride ions, or both. Such a potential donor and acceptor is always present in solutions of camphene hydrochloride, since this compound dissociates rapidly and reversibly into camphene and hydrogen chloride, and this equilibrium is attained more rapidly than the rearrangement occurs.



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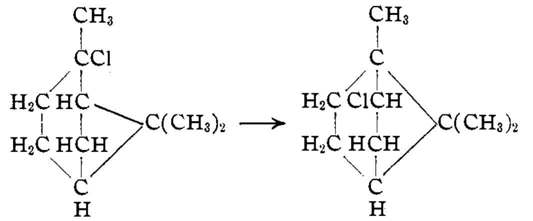

III IV

If hydrogen chloride played an essential part in the rearrangement, the reaction could not be a spontaneous, monomolecular one as reported by Meerwein and van Emster.[3] Since these authors had not considered higher orders of reaction, we recalculated their data in terms of first, second and three-halves order equations and found that in six of the nine solvents studied the data were best fitted by the formulation of the second order with respect to camphene hydrochloride, while in the remaining three solvents the three-halves order formulation was best. This left it quite uncertain in what manner hydrogen chloride entered into the rearrangement process.

We have now carried out a number of kinetic experiments designed to provide clear evidence of the order of the reaction. Nitrobenzene was chosen as a solvent because it allows the rearrangement to proceed at the most convenient rate for measurement. The results show clearly that the rearrangement involves one molecule of camphene hydrochloride and one of hydrogen chloride, and they provide a complete explanation for the apparent variation of the order of the reaction with change of solvent under the conditions of measurement used by Meerwein and van Emster and, initially, by ourselves. The dissociation equilibrium

$$\text{Camphene hydrochloride} \rightleftarrows \text{Camphene} + \text{HCl} \qquad (1)$$

lies, in the case of most of our solutions, more than 94% to the left. With pure camphene hydrochloride, the hydrogen chloride concentration in the solution will be proportional to the square root of the camphene hydrochloride concentration, and hence the rate of reaction is proportional to the $^3/_2$ power of the camphene hydrochloride concentration. However, when a large excess of camphene is present, the amount of hydrogen chloride at equilibrium is diminished and its concentration becomes proportional to that of the camphene hydrochloride. The reaction under these conditions is slowed down and becomes apparently bimolecular with respect to camphene hydrochloride. The explanation of the fact that the rearrangement seems to be sometimes second and sometimes $^3/_2$ order is that it is almost im-

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(1) Most of this material was included in a paper presented at the Organic Symposium at Richmond, Va., on December 30, 1937.

(2) Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937).

(3) Meerwein and van Emster, *Ber.*, **55B**, 2500 (1922).

possible to prepare camphene hydrochloride free from camphene. If the amount of camphene present in a particular sample is small enough, the reaction will approximate the $^3/_2$ order, but it easily may be great enough to make the second order a better approximation.

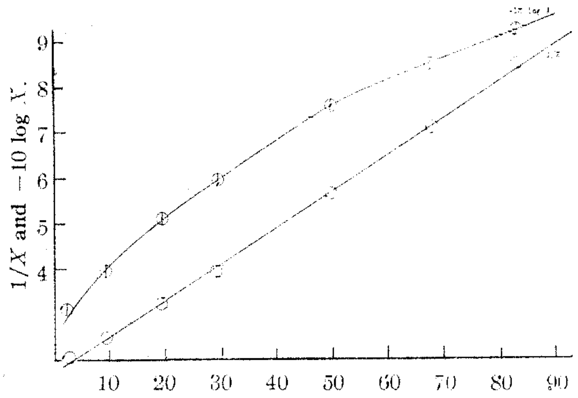

Fig. 1.—Rate of rearrangement of camphene hydrochloride to isobornyl chloride in nitrobenzene solution at 20° in the presence of excess free camphene: ○, $1/X$; ⊘, $-10 \log X$.

There are several quantitative tests, described in full below, which show that this description of the kinetics of the rearrangement is correct. First, with our purest samples of camphene hydrochloride, we were able to duplicate Meerwein's kinetic data which fit the equation of the $^3/_2$ order. Second, by the addition of excess camphene the reaction is made strictly bimolecular (Fig. 1). Third, such additions of camphene diminish the rate of the reaction to the extent predicted from the assumption that there is no spontaneous rearrangement not involving hydrogen chloride (Fig. 2). Fourth, the velocity constant for the reaction between camphene hydrochloride and hydrogen chloride is the same for the rapid reaction in which excess hydrogen chloride is present as for the slow reaction with excess camphene. Fifth, a general equation, derived on the assumption here set forth, fits the kinetic data under these conditions and in those intermediate cases where neither of the limiting formulations holds.

The supposed spontaneous rearrangement of camphene hydrochloride is therefore a process catalyzed by hydrogen chloride. Nevertheless, the balance of the evidence does not seem to be in favor of the donor hypothesis which led us to undertake this investigation. The free chloride ion, which should be the best possible donor, is without effect on the rate of the rearrangement in acetone solution, as shown by kinetic runs with and without lithium chloride. Although all the catalysts for the rearrangement reported as such by Meerwein and van Emster contain chlorine and hence are potential donors of chloride ions, we find that *o*-cresol is not only a good solvent for the rearrangement, as reported by these authors, but a specific catalyst when dissolved in nitrobenzene. Its catalytic efficiency is about one-third that of hydrogen chloride, and it takes the place of hydrogen chloride kinetically. No cresol is consumed in this reaction. Since lithium chloride, which can be a donor, is not a catalyst, and cresol, a good catalyst, cannot be a donor, this way of explaining the Walden inversion attending the rearrangement is untenable.

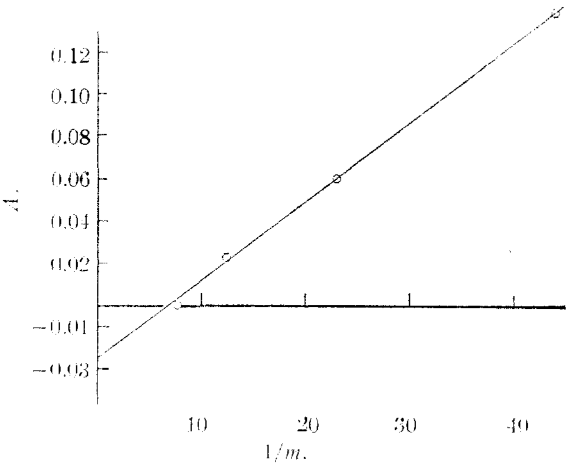

Fig. 2.—Plot of A against $1/m$: A is free camphene added; m is bimolecular rate constant.

Nevertheless, from the occurrence of the Walden inversion in the rearrangement, it seems clear to us that either the carbonium ion has spatial properties quite different from those that have been currently attributed to it, or else the mechanism of Meerwein requires important modification. We are continuing our work and hope to be able to choose between these alternatives. Further discussion of the mechanism is therefore postponed to a later paper.

The fact that hydrogen chloride is necessary to the otherwise uncatalyzed rearrangement explains the anomalous position of ether among the solvents of Meerwein and van Emster. Ether, though not possessing the lowest dielectric constant of the series of solvents which these authors studied, was unique for the slowness with which the rearrangement proceeded in it. A glance at their list of solvents shows that ether is the only one with definitely basic properties. Hydrogen chloride in this solvent must exist largely as diethyloxonium chloride, in which form it is incapable of assisting the removal of chloride ion from the camphene hydrochloride molecule. In harmony with this conclusion, we have found that acetone, which also possesses a basic oxygen atom, also allows the rearrangement to proceed much more slowly than corresponds to its position in the dielectric constant series. Meerwein and van Emster[3] (p. 2511) correlated the effect of ether with its basicity, although the connection could not be clear when the rearrangement was regarded as largely uncatalyzed.

Derivation of the Kinetic Equations

Wynne-Jones has shown[4] that hydrogen chloride behaves as a normal, undissociated and unassociated solute in nitrobenzene. Let x, y, and z denote the concentrations of camphene hydrochloride, hydrogen chloride, and isobornyl chloride, respectively. During any run there is a constant difference between the concentrations of hydrogen chloride and camphene, and the latter accordingly can be designated by $y + c$. By the conditions of equilibrium 1

$$K = \frac{y(y + c)}{x} \qquad (2)$$

so that

$$y = \sqrt{Kx + \frac{c^2}{4}} - \frac{c}{2}$$

The general rate equation is

$$\frac{\mathrm{d}z}{\mathrm{d}t} = -\frac{\mathrm{d}x}{\mathrm{d}t} - \frac{\mathrm{d}y}{\mathrm{d}t} = kx\left(\sqrt{Kx + \frac{c^2}{4}} - \frac{c}{2}\right)$$

For the purpose of integration we make the substitution

$$v = \sqrt{Kx + \frac{c^2}{4}}$$

Then

$$-\mathrm{d}v - \frac{2v\mathrm{d}v}{K} = \frac{k}{K}\left(v^2 - \frac{c^2}{4}\right)\left(v - \frac{c}{2}\right)\mathrm{d}t$$

The integrated form is

$$\frac{c - K}{c^2}\ln\frac{v + c/2}{v - c/2} + \left(1 + \frac{K}{c}\right)\frac{1}{v - c/2} = kt + \text{Constant} \qquad (3)$$

This integral is a linear function of time for all our runs, whether c be large or small, positive or negative. The use of this equation requires a knowledge of the values of c and K. When c is small its value is uncertain by reason of the great difficulty of obtaining samples of camphene hydrochloride which contain an excess of neither camphene nor hydrogen chloride. We have not found any titration method for camphene suitable in the presence of camphene hydrochloride, and hence to obtain the best estimate of K we have made use of the following considerations.

When c is large compared to y, we may replace $(y + c)$ in Equation (2) with c. This leads to the expression

$$y = Kx/c$$

whence, if K is small enough so that x is much greater than y

$$\frac{\mathrm{d}z}{\mathrm{d}t} = -\frac{\mathrm{d}x}{\mathrm{d}t} = k\frac{K}{c}x^2$$

and

$$\frac{1}{x} = \frac{kK}{c}t + \text{Constant} \qquad (4)$$

The reaction under these conditions is therefore of the second order with respect to camphene hydrochloride, and the second order rate constant is equal to kK/c.

We now make up a series of runs by adding different known amounts A of camphene to portions of a stock solution of a single sample of camphene hydrochloride containing an unknown excess c_0 of camphene. In these runs

$$c = c_0 + A$$

Denoting the observed bimolecular rate constants for these runs by m, we get the relationship

$$m = kK/(c_0 + A)$$

which can be transformed to

$$A = (kK/m) - c_0 \qquad (5)$$

According to this, if the known values of A be plotted as ordinates against the observed $1/m$ values as abscissas, the plot should be a straight line of slope kK and of intercept $-c_0$ on the axis of ordinates. Figure 2 shows this plot for a series of runs made on the stock solution without added camphene and with three known concentrations of camphene added. The bimolecular formulation is not valid for the run without added camphene, since the value of c in this case is not high enough to make the assumptions valid. This point has nevertheless been put on the graph for comparison. It can be seen that the three points for which Equation (4) is valid fall on a good straight line and allow an extrapolation to be made which gives a value of 0.0253 for c_0 and of 3.72×10^{-3} for kK. Knowing the true values of c for all the runs, we can now calculate a value of K for each point of the kinetic run where we

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[4] Wynne-Jones, *J. Chem. Soc.*, 1064 (1930).

have values of both x and y. Among all the determined quantities, y is the least certain, since hydrogen chloride has a great tendency to escape during the sealing and opening of the ampoules. However, the average values of K for the several runs are in good agreement, and we take the general average of 1.8×10^{-3} as the most probable value. This K is used wherever Equation (3) has been applied. The use of Equation (3) on the run of the present series to which no camphene was added yields a k of 2.45 in as good agreement with the value 2.07 determined from the slope of the line in Fig. 2 as the uncertainty of K would lead us to expect.

When c becomes zero, Equation (2) becomes

$$K = y^2/x$$

and the kinetic equations are

$$\frac{\mathrm{d}z}{\mathrm{d}t} = -\frac{\mathrm{d}x}{\mathrm{d}t} - \frac{\sqrt{K}}{2\sqrt{x}}\frac{\mathrm{d}x}{\mathrm{d}t} = k\sqrt{K}\,x^{3/2}$$

and

$$\frac{2}{\sqrt{Kx}} + \frac{1}{2x} = kt + \text{Constant} \qquad (6)$$

In the concentration range actually used, only the first term of the integral is of importance, and the reaction should therefore be of the $^3/_2$ order. In only a few of our runs, and of Meerwein's, was the camphene hydrochloride pure enough to approach this behavior; for even the small amount of camphene present in the run of Fig. 1 causes the run to be more nearly second than $^3/_2$ order.

In the presence of a large excess of hydrogen chloride, y is practically equal to $-c$, and only then will the reaction be kinetically of the first order with respect to camphene hydrochloride.

Equation (3) can be shown, by the usual methods of evaluating limits, to approach these special cases under appropriate conditions.

Materials and Experimental Procedure

The nitrobenzene used as solvent was purified by distillation through a nine-foot (2.75-meter) column. It boiled at 98° at 19 mm. and melted at 5.3°.

The camphene was prepared by the methods of Ullmann and Schmid[5] and Bertram and Walbaum.[6] All samples of camphene melted above 49°.

Camphene hydrochloride was prepared at first by the method of Meerwein and van Emster. This method of preparation involves keeping for some time in a vacuum desiccator over alkali, which in our experience always results in a preparation containing excess camphene. Our samples of the hydrochloride most free from camphene were obtained by keeping the product, after drying, in an atmosphere of hydrogen chloride for one hour. This resulted in preparations containing as much as 20% of isobornyl chloride. Run 3.5, which shows $^3/_2$ order kinetics, was carried out with a sample prepared in this manner. In the run with acetone as a solvent, it was found necessary to allow the samples to stand with sodium methoxide for two hours instead of one, to ensure complete decomposition of the camphene hydrochloride.

The technique of Meerwein and van Emster was used in the kinetic runs, except for the substitution of methyl red for iodoeosin as indicator. For comparison with the results of Meerwein, the temperature of 20° was chosen and used throughout. The temperature was controlled by a thermostat within less than 0.1°.

Most of the runs were carried beyond 70% completion, to make possible a clear differentiation between orders of reaction.

Kinetic Results

Our conditions were so chosen that the order of reaction in most cases can be seen clearly from a plot of the function of concentration of camphene hydrochloride which should vary linearly with time. Figure 1 shows such a plot for one of the runs with excess camphene. In this case the reaction should be second order if hydrogen chloride is essentially involved in it, and first order if it is a spontaneous reaction of the camphene hydrochloride. The figure shows that it is second order.

The problem of calculating the rate constant from a given run is essentially that of finding the slope of the best straight line through the experimental points. One can determine this quantity by the method of least squares, but for runs with relatively few points there is no better way than plotting the points and drawing the line by inspection, determining its slope graphically. This is the method which we have employed. It has the further advantage of providing a visible check for each run that the kinetic formulation employed is that which actually gives a straight line without trend.

The most stringent test of the correctness of our formulation of the reaction is provided by the comparison, in Table I, of the values of the rate constant, referred to camphene hydrochloride and hydrogen chloride concentrations, obtained from runs with excess camphene, excess hydrogen chloride, and the purest available camphene hydrochloride, using in each case the suitable equation for the interpretation of the data.

In spite of the benefit which we have gained from the publication in full of the original data of Meerwein and van Emster, we are reporting here only sample data for each type of run, in ac-

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(5) Ullmann and Schmid, *Ber.*, **43**, 3206 (1910).

(6) Bertram and Walbaum, *J. prakt. Chem.*, **49**, 8 (1894).

TABLE I

VELOCITY CONSTANTS IN NITROBENZENE AT 20°, CALCULATED FOR REACTION BETWEEN CAMPHENE HYDROCHLORIDE AND HYDROGEN CHLORIDE

Run	Initial x	Excess camphene	Excess HCl	k (moles/l., hrs.)	Equation used
3.9	0.432	--	0.0438	2.69	-
M	.396	Small	—	2.28	6
3.5	.189	Small	—	2.19	6
3.6	.144	0.548	—	2.50	4
3.8	.480	.109	—	2.07	3
4.2	.550	.033 (cal.)	—	2.00	3
4.5	.577	.055 (cal.)	—	2.01	3
5.3	.472	.0253	—	2.45	3
5.5	.489	.0479	—	2.10	4
5.6	.514	.0856	—	2.08	4
5.7	.525	.1642	—	2.07	4

Run M is the one by Meerwein and van Emster.

cordance with the usual policy of THIS JOURNAL. The variation in the determined concentrations of hydrogen chloride is due not to any lack of sharpness of the titration method, but to the ease with which hydrogen chloride escapes from solution during the sealing and opening of the ampoules.

TABLE II

RATE OF CONVERSION OF CAMPHENE HYDROCHLORIDE INTO ISOBORNYL CHLORIDE IN NITROBENZENE SOLUTION AT 20° IN THE PRESENCE OF 0.0479 MOLE/LITER EXCESS CAMPHENE (See Fig. 1)

Sample run: Experiment 5.5. A = 0.0226 Mole/Liter

Time, hours	Cc. 0.1 N methylate consumed by the free HCl	Cc. 0.1 N methylate consumed by the camphene hydrochloride	X camphene hydrochloride moles/liter	Y free HCl moles/liter
2.33	—	24.21	0.489	—
9.47	0.56	19.90	.402	0.0119
19.28	.47	15.30	.309	.0095
29.17	.41	12.64	.255	.0083
49.78	.29	8.60	.174	.0059
67.88	.27	6.97	.141	.0055
82.90	.23	5.80	.117	.0046

TABLE III

RATE OF CONVERSION OF CAMPHENE HYDROCHLORIDE INTO ISOBORNYL CHLORIDE IN NITROBENZENE SOLUTION AT 20° IN THE PRESENCE OF EXCESS HYDROGEN CHLORIDE

Experiment 3.9

Time, hours	Cc. 0.1 N methylate consumed by the free HCl	Cc. 0.1 N methylate consumed by the camphene hydrochloride	Camphene hydrochloride moles/liter	Free HCl moles/liter
0.5	2.35	21.34	0.4324	0.0476
1.0	2.83	20.02	.4057	.0574
3.0	2.48	16.07	.3256	.0503
5.5	2.34	10.65	.2158	.0474
7.0	2.11	9.57	.1939	.0428
8.5	2.19	7.79	.1579	.0444
10.5	1.75	6.73	.1364	.0355
12.5	1.63	5.62	.1139	.0330
15.0	1.77	4.45	.0902	.0359
			Average	.0438

TABLE IV

RATE OF CONVERSION OF CAMPHENE HYDROCHLORIDE INTO ISOBORNYL CHLORIDE IN NITROBENZENE SOLUTION AT 20° IN THE PRESENCE OF A SMALL EXCESS OF CAMPHENE

Experiment 5.3. Excess camphene 0.0253 mole/liter

Time, hours	Cc. 0.1 N methylate consumed by the free HCl	Cc. 0.1 N methylate consumed by the camphene hydrochloride	Camphene hydrochloride moles/liter	Free HCl moles/liter	Value of left-hand member of Eq. 3
2.05	—	23.38	0.472	—	85.5
9.18	0.70	17.50	.353	0.0141	102.2
19.00	.53	12.95	.261	.0107	124.1
28.92	.47	9.66	.195	.0095	149.9
49.5	.39	6.33	.128	.0079	199.3
67.67	.35	4.61	.093	.0071	249.2
82.67	.31	3.96	.080	.0063	278.8
93.83	.23	3.70	.075	.0047	294.0

TABLE V

RATE OF REARRANGEMENT OF OUR PUREST SAMPLE OF CAMPHENE HYDROCHLORIDE INTO ISOBORNYL CHLORIDE IN NITROBENZENE SOLUTION AT 20°

(The low value of K_e indicates a small excess of camphene.)

Time, hours	Cc. 0.1 N methylate consumed by the free HCl	Cc. 0.1 N methylate consumed by the camphene hydrochloride	Free HCl Y moles/liter	Camphene HCl X moles/liter	$K_e \times 10^3$ Y^2/X
0.5	0.78	9.38	0.0158	0.1893	1.3
7.0	.79	8.69	.0159	.1755	1.4
26	.63	5.63	.0128	.1136	1.4
48	.45	3.77	.0091	.0760	1.1
77.5	.49	2.53	.0098	.0511	1.9
				Average	1.4

In all experiments the samples analyzed were 4.954 cc. each.

For a test of the effect of chloride ion on the rate of the rearrangement we were obliged to go to acetone as a solvent, since this solvent dissolves lithium chloride in amount sufficient for the test. Figure 3 shows the rates of reaction with and without 0.02 M lithium chloride. Although these runs are plotted according to Equation (4), the reaction appears to be of higher order than this. This may be due to the fact that over the long period of duration of the run, acetone is condensing with itself under the influence of the hydrogen chloride, and the nature of the solvent is thus undergoing change. There is also the possibility, which we have not investigated, that the equilibrium between isobornyl chloride and camphene hydrochloride may be more in favor of the latter in this solvent, so that the reaction cannot so well be treated as irreversible. The coincidence of the two curves in this case is good evidence that lithium chloride has no appreciable catalytic influence upon the reaction.

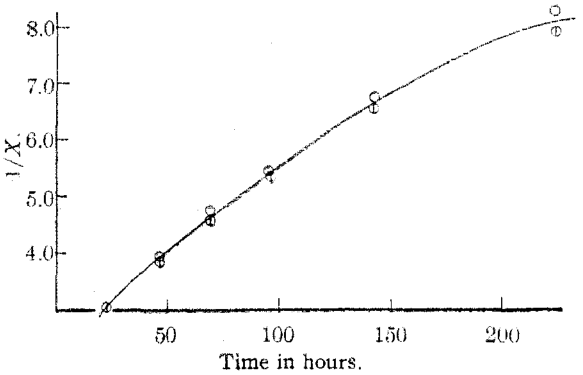

Fig. 3.—Rate of rearrangement of camphene hydrochloride into isobornyl chloride in acetone solution at 20° both in the presence of 0.02 mole/liter of LiCl and without the presence of LiCl: X = concn. camphene hydrochloride in moles/liter: ⦶, lithium chloride present; ○, lithium chloride not present.

For investigating the catalytic effect of *o*-cresol on the rearrangement, we chose to use an excess of camphene, in order that the hydrogen chloride-catalyzed reaction might be repressed to a minimum. Under these conditions the reaction in the absence of cresol would be strictly second order with respect to camphene hydrochloride, in accordance with Equation (4). The reaction actually observed in the presence of *o*-cresol is faster than this, and is first order over 70% of the total reaction, as shown in Fig. 4. From the known values of the rate constants we calculate that the reaction due to hydrogen chloride is less than 5% of the total reaction observed under these conditions. The order of the reaction shows (1) that hydrogen chloride is not involved in the cresol-catalyzed rearrangement, and (2) that cresol is not consumed and is thus a true catalyst. The velocity constant for reaction between camphene hydrochloride and cresol is 0.88. Cresol is thus about one-third as effective a catalyst for the reaction as hydrogen chloride.

A similar experiment using acetic acid instead of cresol showed that this compound too has a feeble catalytic activity in the Wagner–Meerwein rearrangement. The velocity constant here is 0.063. This constant, however, is not directly comparable to that for cresol, since acetic acid in nitrobenzene solution exists in the form of double molecules[7] in which the acid hydrogen is probably bound up in the formation of a chelate ring. The small catalytic activity observed may be that of the small fraction present as monomeric acetic acid. This uncertainty does not apply to the case of cresol.

Summary

1. The rearrangement of pure camphene hydrochloride into isobornyl chloride in solution requires the participation of hydrogen chloride. Since this hydrogen chloride is in equilibrium with camphene and camphene hydrochloride, the reaction rate varies with the camphene hydrochloride concentration in a manner which depends upon whether hydrogen chloride, or camphene, or neither, is present in excess.

2. A number of kinetic experiments under these various conditions support the quantitative implications of the essentially catalytic nature of the reaction.

3. The chloride ion is not a catalyst for the reaction. *o*-Cresol is a strong catalyst and acetic acid is a weak one.

4. The importance of hydrogen chloride in the reaction explains the slowness of the reaction in the basic solvents, ether and acetone.

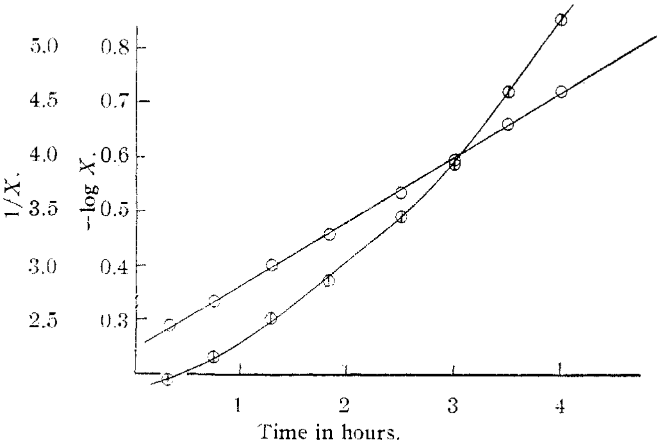

Fig. 4.—The rate of rearrangement of camphene hydrochloride to isobornyl chloride in nitrobenzene solution at 20° in the presence of 0.300 mole/liter of excess camphene and 0.311 mole/liter of *o*-cresol: ○, $-\log X$; ⦶, $1/X$.

5. Further work is being done on the mechanism of the rearrangement.

CAMBRIDGE, MASS.

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[7] Waentig and Pescheck, *Z. physik. Chem.*, **93**, 541 (1919).