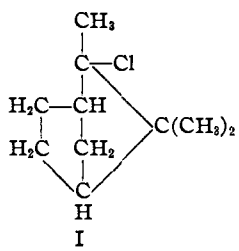
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Wagner–Meerwein Rearrangement. The Catalytic Action of Phenols in the Isomerization of Camphene Hydrochloride

BY PAUL D. BARTLETT AND JOHN D. GILL, JR.

The isomerization of camphene hydrochloride (I) into isobornyl chloride (II)



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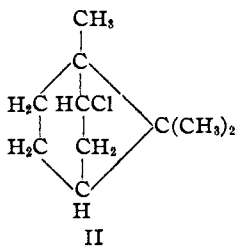

II

is attended by inversion of configuration at the carbon atom to which the chlorine migrates.[1] This fact was the basis of a suggestion that the catalyst for the rearrangement (usually hydrogen chloride) might function by the donation of a new chloride ion and simultaneous removal of the old one. Most of the catalysts which are known to promote the rearrangement contain chlorine and hence fall within the scope of this mechanism. Cresol, however, is an important exception. Unable to donate a chloride ion, it nevertheless converts camphene hydrochloride into isobornyl chloride in some manner not dependent upon the presence of hydrogen chloride. Therefore the *ability to donate a chloride ion is not a necessary condition for catalytic activity.*

If we return to the original view of Meerwein and van Emster,[2] that the rearrangement is catalyzed through complex formation which facilitates the removal of chloride ion, two conclusions follow: (1) the final recombination with a chloride ion must occur during, or with extreme promptitude after, the rearrangement of carbon–carbon links[3] and (2) cresol and hydrogen chloride must both have the power of acting as acceptors of chloride ion, and thus as electrophilic or electron-acceptor reagents. The latter conclusion has been confirmed recently for a series of phenols.[4]

Since this conclusion groups hydrogen chloride and cresol together as catalysts, it seems important to know whether cresol and other phenols enter into the reaction in the same way as hydrogen chloride, and also how the catalytic power of a phenol varies with its structure.

The catalytic efficiency of a phenol is small in comparison with that of hydrogen chloride, and since the latter catalyst is always present in a solution containing camphene hydrochloride, it is necessary to depress its concentration in order to make the phenol-catalyzed reaction predominate. This is done by using sufficient concentrations of camphene to force the dissociation equilibrium

$$\text{Camphene hydrochloride} \rightleftharpoons \text{Camphene} + \text{HCl} \quad (1)$$

strongly toward the side of camphene hydrochloride. The amount of free hydrogen chloride, and the rate of rearrangement due to it, thus become very small. We find that for the larger phenol concentrations the rate measured is practically all due to the phenol. With the smaller concentrations of phenol it becomes necessary to correct for the contribution of the hydrogen chloride to the observed rate. It is possible to do this by a method described in the Experimental Part. The constants k_1, discussed below, are in each case the unimolecular velocity constants for that part of the rate which is due to catalysis by the phenol. All the runs in this study were made at 25° in nitrobenzene solution.

A considerable improvement has been made in the technique of making the rate runs by taking advantage of the fact that the equilibrium of Equation (1) is always established more rapidly than the rearrangement occurs. This means that it is unnecessary to go through the troublesome preparation and unsatisfactory purification of camphene hydrochloride for the runs. Instead, we now make up a solution of camphene in pure nitrobenzene and pass in a measured deficient amount (about 50%) of hydrogen chloride gas by means of a gas buret. By the time of the first titration, the resulting solution is identical in composition with that which would be obtained if it were possible to add weighed amounts of pure camphene hydrochloride and camphene. The

(1) Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937); **60**, 1585 (1938).

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

(3) Compare Bartlett and Bavley, THIS JOURNAL, **60**, 2416 (1938); Bernstein and Whitmore, *ibid.*, **61**, 1324 (1939).

(4) Bartlett and Dauben, *ibid.*, **62**, 1339 (1940).

considerable amounts of isobornyl chloride always present in these solid preparations are thus avoided at the beginning of the reaction.

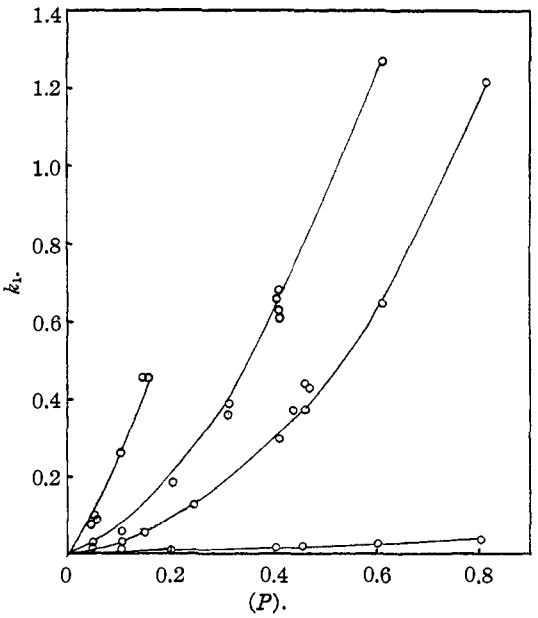

Fig. 1.—Unimolecular velocity constants k_1 at 25° for isomerization of camphene hydrochloride in nitrobenzene by (left to right) *p*-cyanophenol, phenol, *o*-cresol and picric acid, in different concentrations.

Figure 1 and the first two columns of Table I show the values of k_1 obtained with different concentrations of *p*-cyanophenol, phenol, *o*-cresol, and picric acid as catalysts. This is the order of decreasing catalytic strength, picric acid being a far weaker catalyst than the other three. Picric acid thus deviates extremely from the general parallelism which the others show between catalytic efficiency and acid strength. From the shape of the curves it is apparent that, in contrast to hydrogen chloride, the phenols are not catalytically active in strict proportion to their concentrations, but become relatively more effective as their concentrations are raised. The rate constants can be calculated from the equation

$$k_1 = a(P) + b(P)^2 \qquad (2)$$

where (P) is the concentration of the phenol. The constants a and b can be evaluated graphically by plotting the equation in the form

$$\frac{k_1}{(P)} = a + b(P) \qquad (3)$$

as is done in Fig. 2. The quantity $k_1/(P)$, plotted against (P), gives a straight line whose slope is b and whose intercept on the axis of ordinates is a.

TABLE I

UNIMOLECULAR VELOCITY CONSTANTS (k_1) FOR REARRANGEMENT OF CAMPHENE HYDROCHLORIDE BY PHENOLIC CATALYSTS. TIME IN HOURS.

p-Cyanophenol		Phenol		*o*-Cresol		Picric acid	
(P)	(k_1)	(P)	(k_1)	(P)	(k_1)	(P)	(k_1)
0.0474	0.0779	0.0511	0.024	0.051	0.014	0.101	0.0032
.0507	.0974	.102	.057	.102	.032	.202	.0067
.0507	.0900	.204	.186	.149	.053	.403	.0160
.1012	.261	.307	.364	.203	.086	.454	.0178
.1514	.454	.307	.387	.236	.113	.602	.0261
.1493	.453	.397	.659	.244	.123	.803	.0407
		.404	.635	.305	.190		
		.404	.621	.406	.292		
		.404	.682	.439	.369		
		.605	1.27	.454	.442		
				.458	.371		
				.467	.428		
				.609	.648		
				.812	1.223		

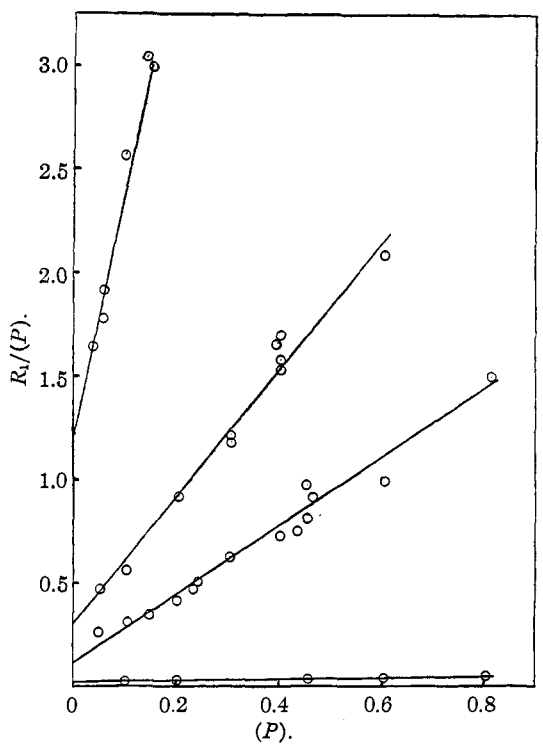

Fig. 2.—Data of Fig. 1 plotted in the form of Equation 3, to determine the values of the constants a and b.

The constants determined from these plots are shown in Table II. The quantity s in Table II

TABLE II

CATALYTIC EFFICIENCY OF PHENOLS IN THE REARRANGEMENT OF CAMPHENE HYDROCHLORIDE IN NITROBENZENE SOLUTION AT 25°

	Constants of Equation (2)			
Catalyst	a	b	pK_a	s
p-Cyanophenol	1.31	11.4	7.89	0.432
Phenol	.290	3.17	10.00	.036
o-Cresol	.120	1.67	10.20	.029
Picric acid	.0286	0.0256	0.80	

is the measure used by Bartlett and Dauben[4] of the acceptor activities of the phenols toward chloride ion as revealed by their enhancement of the acid strength of hydrogen chloride in dioxane solution. Unfortunately, as a result of limitations inherent in the method, no s-value for picric acid is available. The s-values of the other phenols fall in the same order as their a, b, and pK_a values. This is strong support for the view that the phenols function as catalysts by virtue of their acceptor activity toward the chloride ion.

In drawing inferences about the mechanism of this catalysis we must discard at the outset the view[5] that the dielectric constant of the medium is of prime importance in determining the rate of an ionization process in an organic halide. In the present work, as in the kinetic study of alcoholysis by Bartlett and Nebel,[6] the solvent (nitrobenzene) has a dielectric constant which equals or exceeds that of the added hydroxy-compound, so that our catalyst is promoting the removal of chloride ion while it is actually lowering the dielectric constant of the solvent.

The reaction of p-methoxybenzhydryl chloride with methanol in dilute nitrobenzene solution proceeds simultaneously by paths involving one and two molecules of methanol. This was interpreted[6] as the removal of chloride ion with one and two molecules of methanol of solvation. Bartlett and Nebel did not eliminate the less probable alternative that one of the methanol molecules was attacking the carbon atom directly, leading to the formation of methyl ether, while the second alcohol molecule, when any, was solvating the chloride ion. Now in the Wagner–Meerwein rearrangement we have an exactly similar kinetic situation, where one and two molecules of the phenol are evidently involved in independent rate-determining steps. Here, however, a direct attack by a phenol molecule upon the carbon atom holding the chlorine is out of the question, for the phenol does not enter into the product and its concentration is not changed during the reaction. The product is a chloride, not a phenyl ether, and accordingly the phenol must attack only the chlorine of camphene hydrochloride.

From the interesting work of Meerwein and Gerard[7] on the reactions occurring when camphene hydrochloride is dissolved in methanol, it would appear that, allowing for the equilibria of ether formation which set in, methanol promotes the rearrangement of camphene hydrochloride more rapidly than inert solvents of similar dielectric constant. Bartlett and Pöckel found that even acetic acid has a weak catalytic effect upon the rearrangement. From these facts it seems not unlikely that the rate-determining steps in the Wagner–Meerwein rearrangement and in the solvolysis of halides are closely similar.

The relative efficiencies of the four phenols as catalysts are in accordance with the previous observation that ortho-substituted phenols are much weaker acceptors for chloride ion than their acid strengths would lead one to expect. On this basis picric acid would be expected to be a very poor acceptor indeed, since its hydroxyl group must be so strongly chelated in the undissociated form as to be practically unavailable for outside hydrogen bonding. Not only is this borne out by the very low catalytic power of picric acid, but its b-constant of Equation (2) is low out of proportion to the other phenols, suggesting a relative hindrance to the association of two picric acid molecules in a transition complex in the rearrangement.

The mechanism of the rearrangement catalyzed by two phenol molecules can be visualized in either of two ways. From the data of Philbrick[8] we estimate that in our most concentrated phenol solution (0.603 M) about 8% of the phenol is in the double form. If the association is accomplished by the sharing of a hydrogen between the oxygens of two phenol molecules, then the O–H bond not involved in the bridge is more highly polarized than in the monomeric phenol. It would not be surprising, then, if the dimer were a stronger electrophilic reagent than the monomer and if the dimer should therefore be important as a catalyst even when present in these small amounts. Since the relation

$$k_d = b/K$$

exists between the velocity constant k_d for the catalysis by the phenol dimer, the equilibrium constant K of dimerization, and our constant b, the relative catalytic efficiencies of phenol dimer and monomer must be given by

$$\frac{k_d}{k_m} = \frac{b}{aK} = \frac{3.36}{0.265 \times 0.174} = 73$$

Here the representative value of $K = 0.174$ is taken from Philbrick's data for 0.339 M solu-

(5) See Scatchard, *J. Chem. Phys.*, **7**, 657 (1939).
(6) Bartlett and Nebel, THIS JOURNAL, **62**, 1345 (1940).
(7) Meerwein and Gerard, *Ann.*, **435**, 174 (1923).
(8) Philbrick, THIS JOURNAL, **56**, 2581 (1934).

tions of phenol in nitrobenzene, a correction being made to moles per liter.

A simple alternative mechanism would be the solvation of the halide ion by two monomeric phenol molecules, each forming a hydrogen bond directly with the halogen. Our results do not distinguish between these possibilities.

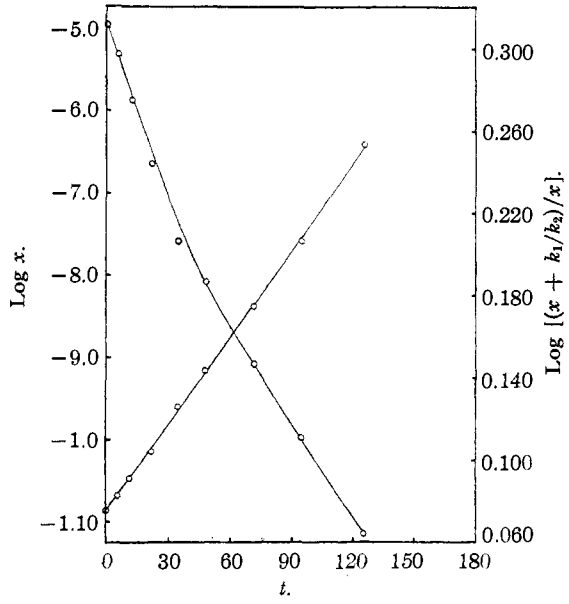

Fig. 3.—Isomerization of camphene hydrochloride by 0.101 *M* picric acid: descending curve, log *x* against time; ascending line, Equation. 7

Experimental

Materials.—Camphene was prepared by the method of Ulmann and Schmid[9] from samples of bornyl chloride melting at 126–128° and 128–130°. Samples of camphene prepared in this way melted over ranges of 1.6 to 6.4° between 40 and 50.6°. Another sample was prepared by distilling a commercial camphene from sodium, and this melted at 42.5°. By comparative kinetic runs we showed that these samples were all equivalent for the purpose of rate measurements. The optical rotations of the samples varied from $[\alpha]_D$ −0.23° for the lowest melting to −0.55° for the highest melting sample. Varying degrees of racemization might be expected to influence the melting points, but not the specific reaction rates, of different samples.

Nitrobenzene was dried over phosphorus pentoxide and distilled through a five-foot column packed with glass helices. The fractions used showed melting points in the range from 5.67 to 5.71°.

Phenol and *o*-cresol were purified by distillation. The phenol boiled at 178.4–178.8° and the *o*-cresol under 50 mm. pressure at 105.5°. The *p*-cyanophenol, crystallized from hot water, melted at 111.5–112.5°. Picric acid was fractionally crystallized from benzene, the sample used melting at 120.0–120.8°. These phenols were kindly supplied by Hyp J. Dauben, Jr., of this Laboratory.

(9) Ulmann and Schmid, *Ber.*, **43**, 3202 (1910).

Kinetic Measurements.—Some runs were made in which a supersaturated solution of hydrogen chloride in nitrobenzene was prepared and the run was started by adding a measured quantity of this to a solution containing a weighed amount of camphene and the phenolic catalyst, previously brought in a thermostat to 25°. Samples of the solution were taken with a pipet and titrated for hydrochloric acid and camphene hydrochloride as previously described.[1] Phenol, *p*-cyanophenol and cresol neutralized no base at the end-point of these titrations, but picric acid was titrated along with the hydrogen chloride. Therefore in the runs with this phenol the free hydrogen chloride was not determined, but since excess camphene was present the hydrogen chloride introduced an error not greater than 3%.

This method of introducing the hydrogen chloride proved incapable of controlling the concentrations within the desired accuracy, since in transferring the solution hydrogen chloride escaped rapidly. It was found more satisfactory to introduce pure hydrogen chloride from a gas buret into a partially exhausted flask containing the solution of camphene and the phenol. In this way, the concentrations could be controlled within a few per cent., and the actual concentrations were determined from the first titration with extrapolation when necessary.

Determination of k_1.—By the addition of excess camphene the phenol-catalyzed rearrangement is made to prodominate in most cases over the rearrangement catalyzed by hydrogen chloride. The results are at first plotted as a unimolecular reaction in camphene hydrochloride (log *x* against *t*) and straight lines are obtained with all but the lower catalyst concentrations. However, the reaction catalyzed by hydrogen chloride needs to be corrected for in all these runs, and this can be accomplished as follows: if *x* denotes the concentration of camphene hydrochloride, *y* that of hydrogen chloride, and *c* that of camphene, then at all times during the run practically

$$cy/x = K \text{ and } y = Kx/c$$

For the rearrangement of camphene hydrochloride catalyzed by hydrogen chloride

$$-\frac{dx}{dt} = kxy = \frac{kK}{c}x^2 \qquad (4)$$

letting

$$kK/c = k_2 \qquad (5)$$

we get for the simultaneous catalysis by hydrogen chloride and by a given concentration of phenol

$$-\frac{dx}{dt} = k_1x + k_2x^2 \qquad (6)$$

The integrated form of this is

$$\ln\frac{x + (k_1/k_2)}{x} = k_1t + \text{Const.} \qquad (7)$$

The value of k_2 can be determined from runs without phenol, and adjusted to each camphene

concentration in accordance with Equation 5. Three runs were performed without phenolic catalyst and with a sufficient excess of camphene to make its concentration substantially constant. The values of c were 0.284, 0.347 and 0.256 in these runs, which yielded values of k_2 equal to 0.0528, 0.0454 and 0.0588, respectively. These results fit rather well the equation

$$k_2 = 0.0153/c$$

Now from any run using a phenolic catalyst, the best value of k_1 can be selected by successive approximations. Two representative points are selected near the beginning and end of the run. A rough value is assumed for k_1. Using this value in the left-hand side of Equation (7), the two representative points yield a new value for k_1, leading to a better approximation. This process is repeated until the calculated k_1 checks that assumed in the calculation. The plot of Equation (7) must now be linear for the entire run, using the determined value of k_1. An example of this treatment for the most unfavorable case is provided by Run C-19, with 0.101 M picric acid as a catalyst, in which only 20% of the observed apparent first-order rate was due to the phenol and the rest to the small suppressed concentration of hydrogen chloride. The curve in Fig. 3 represents the data for this run plotted as a unimolecular reaction; the straight line is the plot of Equation (7) taking $k_2 = 0.053$ and $k_1 = 0.00326$. The units of all rate constants in this paper are moles per liter and hours.

Summary

The rearrangement of camphene hydrochloride into isobornyl chloride in nitrobenzene is catalyzed by *p*-cyanophenol, phenol, *o*-cresol, and picric acid in decreasing order of effectiveness. The unimolecular rate constant k_1 for the phenol-catalyzed rearrangement varies with the concentration of the phenol according to the equation $k_1 = a(P) + b(P)^2$ where a and b are constants for each phenol. This indicates two simultaneous mechanisms for the rearrangement, one involving the attack of a single phenol molecule, and the other involving the attack of two phenol molecules, or a phenol dimer, on the chloride. This parallels the kinetics of alcoholysis of *p*-methoxybenzhydryl chloride in nitrobenzene, previously studied. In the present case, since the product is a chloride and not a phenol ether, the attack of the phenol can be only on the chlorine of camphene hydrochloride. Its function is evidently to solvate the chloride ion through hydrogen bonding. The catalytic efficiencies of the phenols are in the order of their hydrogen bonding powers. This is also the order of their acid strengths except where ortho-substituted phenols are concerned.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Normal and Alkamine Esters of 4-Methoxyisophthalic Acid

BY L. S. FOSDICK AND O. E. FANCHER

Since Einhorn and Uhlfelder[1] first published their reports on novacain, a large number of compounds possessing local anesthetic activity has been synthesized. Although many anesthetics have been prepared whose structures bear no relation to novacain, a large number of very active compounds having similar structure have been made. It was pointed out by Shriner and Keyser[2] that the most effective anesthetics of the ester type have a carbonyl group conjugated with double bonds. This is almost invariably true with the ester type of anesthetic of which novacain is the most conspicuous member. It was thought that if one carbonyl group conjugated with a double bond was so effective, perhaps two carbonyl groups conjugated with double bonds in the same molecule might be more effective. It was found that esters of isophthalic acid would fulfill this requirement. In so far as it has been shown that various substituents in the ring[3,4] enhance anesthetic activity, it was thought that esters of 4-methoxy or 4-aminoisophthalic acid would be interesting. This paper deals with the synthesis of some esters of 4-methoxyisophthalic acid. The esters of 4-aminoisophthalic acid are now in the process of synthesis. All of the esters

(1) Einhorn and Uhlfelder, *Ann.*, **371**, 131 (1909).
(2) Shriner and Keyser, THIS JOURNAL, **60**, 286 (1938).
(3) Rohmann and Schuerle, *Arch. Pharm.*, **274**, 110 (1936).
(4) Coles and Lott, THIS JOURNAL, **58**, 1489 (1936).