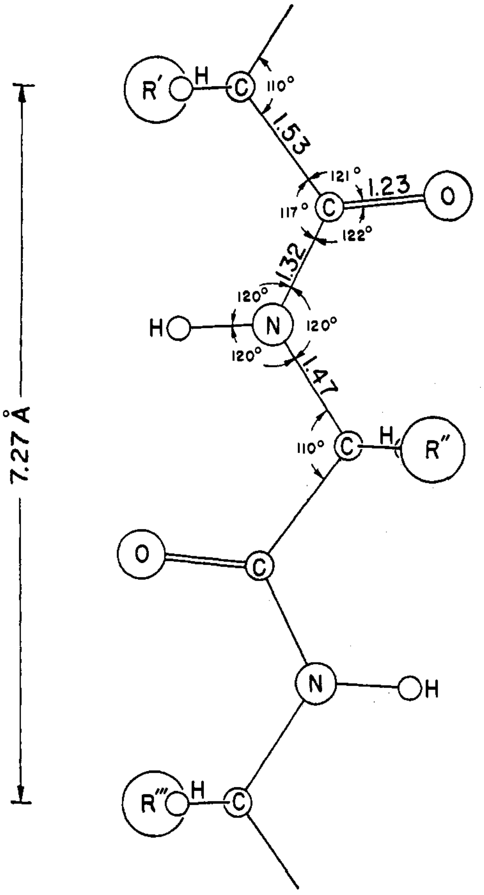

Fig. 1.—Dimensions of the fully-extended polypeptide chain as derived from recent crystal structure data.

chain of proteins as derived from the data listed in the table. With the exception of the revised αC–N distance (1.47 Å.), these distances and bond angles differ little from those previously assigned,[5,7] but the probability that they are essentially correct is greatly increased. The bonds around the nitrogen atom form angles which are close to 120°. The N–C bond which is involved in resonance is about 1.32 Å. in length. In the choice of bond angles around the carbonyl carbon atom, values intermediate between those found in N-acetylglycine and β-glycylglycine were taken, with slight weighting in favor of the N-acetylglycine structure which was based upon complete intensity data and on three-dimensional Fourier refinement of atomic parameters. The C–C distance 1.53 Å. is intended to reflect the fact that in amino acids and some other recently determined structures the C–C bond has been reported as slightly, but probably significantly, less than the classical 1.54 Å. Although the dimensions of the polypeptide chain in proteins probably depart little from those here indicated, more direct evidence based on precise determinations of atomic positions in crystals of higher linear peptides is greatly desired.

Acknowledgment.—All of the references cited in this paper refer to work which was carried out in the Gates and Crellin Laboratories. We are glad to acknowledge the support provided by the Rockefeller Foundation and by the National Foundation for Infantile Paralysis for this basic attack on the general problem of the structure of proteins.

Summary

Data from recent crystal structure studies of amino acids and peptides are used to derive values for the bond lengths and bond angles of the polypeptide chain of proteins.

PASADENA, CALIFORNIA RECEIVED DECEMBER 5, 1949

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

The Exchange Reaction between Anhydrous Deuterium Chloride and Phenol[1]

BY HAROLD HART

Deuterium–hydrogen exchange has been used as a diagnostic tool in the study of the lability of hydrogen atoms in organic compounds since heavy water first became available. In the case of aromatic compounds, this exchange has been shown to follow the common orientation rules of electrophilic substitution.[2]

It is well known that the aromatic ring of phenols is particularly susceptible to such substitution. Thus, it is possible to alkylate phenol in certain cases without the use of any of the common Friedel–Crafts catalysts.[3,4] In spite of this fact, exchange studies with phenol and anisole with heavy water in the presence of aqueous hydrochloric acid or aqueous alkali have shown the reaction to be slow, even at 100°.[5,6,7,8]

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[1] This paper was presented at the 116th meeting of the American Chemical Society, Atlantic City, September, 1949.

[2] A. P. Best and C. L. Wilson, *J. Chem. Soc.*, 28 (1938).

[3] H. Hart and J. H. Simons, THIS JOURNAL, **71**, 345 (1949).

[4] G. M. Bennett and F. M. Reynolds, *J. Chem. Soc.*, 131 (1935); J. Van Alphen, *Rec. trav. chim.*, **46**, 287 (1927).

[5] C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, 1637 (1936).

[6] P. A. Small and J. H. Wolfenden, *ibid.*, 1811 (1936).

[7] T. Titani, *et al.*, *Bull. Chem. Soc. Japan*, **10**, 554 (1935); **11**, 554 (1936); **13**, 681 (1938); **14**, 353 (1939); see also *C. A.*, **30**, 2082 (1936); **31**, 97 (1937); **33**, 2399 (1939); **34**, 1902 (1940).

[8] A. I. Brodskii, *Izvest. Akad. Nauk S. S. S. R., Otdel, Khim. Nauk*, 3 (1949); *C. A.*, **43**, 5011 (1949).

Even when deuteroalcohol was used with a sulfuric acid catalyst,[9] nuclear exchange with *p*-cresol proceeded slowly, although the reaction mixture in this case was homogeneous.

Anhydrous hydrogen chloride has been shown to be a catalyst for alkylation reactions.[10] It was decided, therefore, to study the exchange reaction between deuterium chloride and phenol, when both reagents were anhydrous. It is shown in the present paper that exchange occurs and that equilibrium is extremely rapidly established under mild conditions, not only with the hydroxylic hydrogen, but also with the aromatic hydrogens in the 2, 4 and 6 positions. The possible mechanisms of this exchange are discussed.

Experimental

Materials.—The phenol samples were prepared using distilled phenol which had been dried by distillation from a benzene solution, after careful removal of the water–benzene azeotrope and the excess benzene. The phenol was then distilled *in vacuo* at about 50 mm. pressure of dry nitrogen and the sample sealed in ampoules according to the procedure described by Hart and Simons.[3]

The deuterium chloride was prepared by dropping 99.8% heavy water[11] on benzoyl chloride according to the method of Brown and Groot.[12] The deuterium chloride was condensed in a liquid-air trap, the open end of which was protected from atmospheric moisture, oxygen and carbon dioxide by means of an alkaline pyrogallol bubbler and a phosphorus pentoxide tube. After the preparation of approximately 0.3 mole of deuterium chloride, the latter was, subsequent to standard vacuum de-gassing techniques, allowed to evaporate into a previously evacuated storage system of seven 1-liter bulbs. The storage system was connected to the exchange apparatus through G (Fig. 1). It was also directly connected to the apparatus for analysis and samples were analyzed before use, according to the procedure described below.

The 2,4,6-trichlorophenol was Eastman Kodak Co. product, recrystallized from alcohol, m. p. 67–68°. Samples of pentachlorophenol were kindly furnished by the Dow Chemical Company and the Monsanto Chemical Company, and were said to contain less than 1% of less chlorinated phenols.

Mesitol was prepared by nitration of mesitylene,[13] reduction of the nitromesitylene with tin and hydrochloric acid (78.5% yield) and subsequent diazotization of the mesidine (66% yield). It was possible to shorten the nitration procedure considerably from that described in "Organic Syntheses" without diminishing the yield or purity of the product. Upon pouring the reaction mixture into 1 liter of ice water containing 40 g. of salt, yellow crystals appeared which, upon filtration and recrystallization from methanol yielded 40 g. of first crop nitromesitylene, m. p. 43–44°. A second crop of 4 to 5 g. gave an over-all yield of 81–82%.

The (thiophene-free) benzene was dried by distillation.

Analytical Procedure.—The DCl–HCl mixtures were analyzed by conversion to water and determination of its density with a pycnometer. The conversion to water was accomplished by passage of the DCl–HCl mixture over cupric oxide at about 350°. Klit and Langseth[14] employed this method, but encountered some difficulty with clogging of the tube, due to the fusion of the cupric chloride which is formed. This can largely be avoided by careful control of the heating. With variac-controlled electrical heating it was possible to carry out 6 to 8 analyses before repacking of the tube became necessary.

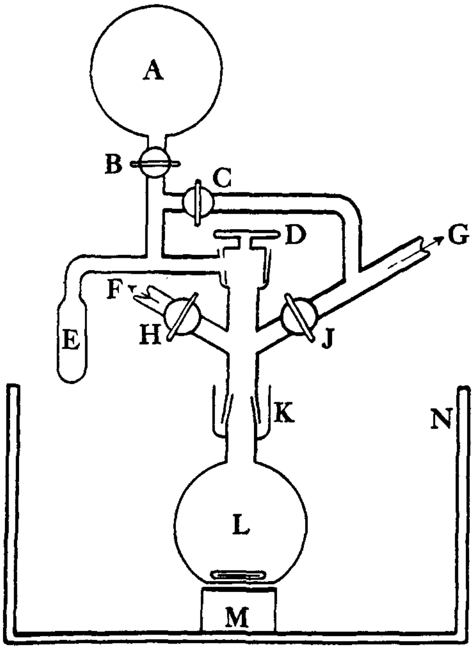

Fig. 1.—The exchange apparatus.

A system containing a 1-liter bulb, manometer, a tube (14 mm. diam.) 30 inches long packed with cupric oxide wire and containing a sealed-in thermocouple and a trap at the end of the tube for condensing the water was connected to a vacuum line, the deuterium chloride storage system and the exchange apparatus at G (Fig. 1). The tube was heated to 350° and the analytical system thoroughly evacuated. A Dry Ice–acetone-bath was placed around the condensation trap. The gas to be analyzed was then admitted to the bulb (pressure usually 650–750 mm.). The gas was then *slowly* allowed to enter the cupric oxide tube, always keeping the pressure below 75 mm. Conversion of the DCl–HCl mixture to water required about two hours.

The water frequently contained some dissolved DCl–HCl, which was converted to water by addition of a small quantity of solid barium oxide. The water was then distilled two times *in vacuo* at room temperature and the density determined at 30.000 ± 0.005° (the volume of the pycnometer was 0.24291 ± 0.00003 ml. calibrated with triply distilled water). The percentage of D_2O was calculated using density of $H_2O = 0.99567$, density of $D_2O = 1.10339$ and assuming that the density of the mixtures were linearly dependent upon the percentage composition. This is not strictly correct[15] but gave sufficient accuracy for these experiments.

Exchange Procedure.—A diagram of the apparatus used for the exchange studies is shown in Fig. 1. Line G led to the vacuum system, a manometer, the deuterium chloride storage system and to the analytical system described above. The phenol sample, contained in an evacuated ampoule, was sealed on at F, together with a magnetic hammer device for breaking the ampoule.

With stopcocks J and D closed, B and C open, the bulbs A and E were thoroughly evacuated. Deuterium chloride was condensed from one of the bulbs of the storage system into E, using liquid nitrogen. The deuterium

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[9] P. F. Tryon, W. G. Brown and M. S. Kharasch, This Journal, **70**, 2003 (1948).

[10] J. H. Simons and H. Hart, *ibid.*, **66**, 1309 (1944).

[11] We are grateful to the All College Research Committee, Michigan State College for a grant which enabled us to purchase the heavy water.

[12] H. C. Brown and C. Groot, This Journal, **64**, 2223 (1942).

[13] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., p. 449.

[14] A. Klit and A. Langseth, *Z. physik. Chem.*, **A176**, 65 (1936).

[15] A. Farkas, "Orthohydrogen, Parahydrogen and Heavy Hydrogen," Cambridge University Press, 1935, p. 137.

TABLE I

EXCHANGE DATA AT 50°

1 Expt.	2 DCl pressure, mm.	3 Phenol, moles	4 Reaction time, min.	5 Mole % DCl Initial	6 Final	7 DCl_0, mole	8 DCl, mole	9 HCl, mole	10 n
1	652	0.0554[a]	10	94.3	9.4	0.0375	0.0037	0.0360	3.7
2	666	.0551	65.5	94.3	9.2	.0382	.0037	.0367	4.0
3	658	.0552	63	96.5	9.4	.0387	.0038	.0343	3.7
4	761	.0550	130	97.4	10.0	.0452	.0046	.0417	4.2
5	617	.0552	360	94.3	7.0	.0355	.0026	.0350	4.7
6	633	.0552[b]	60	96.5	91.0	.0372	.0351	.0035	0.042
7	681	.0191[c]	60	96.5	58.1	.0400	.0241	.0174	1.3
8	585	.0410[d]	60	96.5	34.3	.0344	.0122	.0234	1.3
9	690	.0372[e]	65	96.5	46.0	.0406	.0193	.0227	1.1
10	685	.0379[f]	67	96.5	38.1	.0403	.0159	.0258	1.2

[a] Experiments 1–5 were run in the absence of any solvent. [b] Benzene. [c] 2,4,6-Trichlorophenol dissolved in 2.78 g. of benzene. [d] 2,4,6-Trichlorophenol dissolved in 6.41 g. of benzene. [e] 2,4,6-Trimethylphenol dissolved in 4 g. of benzene. [f] Pentachlorophenol dissolved in 32 g. of benzene.

chloride was then allowed to expand into 1-liter bulb A, and the pressure observed. (The volume of this system was determined as described below.) With C closed, J was opened and the remainder of the system evacuated. With J then closed, the phenol ampoule was broken and the sample allowed to run through stopcock H into 1-liter bulb L. H was then closed and the magnetic stirrer M started. M was an A. H. Thomas Co. No. 9235-R magnetic stirrer which had been wrapped carefully with the rubber tape and coated with collodion so as to keep the enclosed motor free from water. This stirrer has proven very useful for stirring operations in constant temperature baths and has given good service for over a year.

After fifteen minutes to allow the phenol to come to temperature, the deuterium chloride was condensed in E, B was closed, D was opened and the deuterium chloride was allowed to expand into L. When this was accomplished, D was closed and the exchange was allowed to proceed for a given time interval. While this was going on, B and C were opened and the pressure of deuterium chloride *not* admitted to the exchange vessel observed and subtracted from the original total pressure. The residual deuterium chloride was then transferred back to the storage system and discarded. A and E were thoroughly re-evacuated.

When the exchange was completed, the DCl–HCl mixture was condensed from L into E and D was closed. The gas was then transferred to the analytical system and analyzed as described above. When benzene was used in the exchange experiments (Expt. 6 to 10, Table I), the benzene was removed from the DCl–HCl mixtures before analysis by several distillations, using a Dry Ice–acetone-bath around the stillpot and liquid nitrogen about the receiver.

The volume of A and the rest of the system (which was needed in order to calculate the number of moles of deuterium chloride used in each experiment) was determined by filling the system with hydrogen chloride to a known pressure, then evacuating the hydrogen chloride through a sodium carbonate tube and determining the chloride by the Volhard method. The volume of the system which corresponds to the pressure values in column 2 of Table I was 1140 ml. at 300°K.

Results

The pertinent data from several of the exchange experiments are shown in Table I. These experiments are listed in an order convenient for discussion, and were not performed consecutively as listed. The quantities in columns 2 to 6 were obtained directly from the experiments. From the pressure in column 2 and the volume of the system (1140 ml.) measured at 27° and with the aid of the perfect gas equation, one can calculate the number of moles of gas initially present. When this value is multiplied by the percentages in columns 5 and 6, one obtains the number of moles of deuterium chloride present initially (DCl_0 in column 7) and the number of moles remaining after the time interval in column 4 respectively (DCl in column 8). The number of moles of hydrogen chloride present after exchange has occurred (HCl in column 9) was obtained by subtracting the values in column 8 from the total number of moles of gas originally admitted.

The values of n in column 10 represent the total number of hydrogens in the phenolic compound which have exchanged during the given time interval (column 4). The *equivalent equilibrium constant* has been defined[5] as

$$K = \frac{(\%\ \mathrm{D_{org.}})(\%\ \mathrm{H_{reagent}})}{(\%\ \mathrm{H_{org.}})(\%\ \mathrm{D_{reagent}})}$$

whence one obtains, for the case in hand

$$\frac{\%\ \mathrm{D_{org.}}}{100} = \frac{K}{(\mathrm{HCl})/(\mathrm{DCl}) + K}$$

The value of K may differ for the O–H and the C–H linkages. Thus, in the final equilibrium mixture

$$\mathrm{DCl_0} = \mathrm{DCl} + (\mathrm{PhOH_0})\frac{K'}{(\mathrm{HCl})/(\mathrm{DCl}) + K'} + m(\mathrm{PhOH_0})\frac{K''}{(\mathrm{HCl})/(\mathrm{DCl}) + K''} \quad (1)$$

where ($PhOH_0$) represents the original number of moles of phenol (column 3 of Table I), m is the number of nuclear hydrogens which have exchanged, and K' and K'' represent, respectively, the equilibrium constants for exchange at the O–H and C–H linkages of phenol. The value n in column 10 corresponds to $m + 1$.

The value of K' has been established by several workers[5,6,7] as approximately 1.10 when the reagent is heavy water, either neutral or in the presence of acidic or basic catalysts. The value of K'' is not known. As a first approximation one may assume the statistical value of 1.0, but when used with the present data this gives values of m larger than theoretically possible. Small and Wolfenden[6] also encountered this difficulty when working with phenol. Thus, in two experiments they found 4.2 to 4.4 nuclear hydrogens exchanging if K'' were 1.0, whereas 2,4,6-trichlorophenol did not show nuclear exchange under identical conditions. They offered either of two explanations, (1) that the meta hydrogens actually did exchange in the case of phenol, but that this was inhibited by the chlorine substituents in 2,4,6-trichlorophenol or (2) that the value of K was considerably greater than 1.0 (about 1.4). The latter is probably correct, since Best and Wilson have shown[2] that the exchange involves the 2, 4 and 6 positions. Also, in the present experiments 2,4,6-trimethylphenol was also studied, and gave the same results as the 2,4,6-trichloro compound. In the trimethyl compound, the meta positions should have been more susceptible to exchange than in the trichloro compound.

In the present work a value of 3.0 was assumed for m in experiment 2 of Table I.. This experiment was selected, since a check run (experiment 3) was available. The value of K'' necessary to give this value was 2.18, and this was used in calculating all of the remaining values of m. Although this value of K'' seems inordinately high, if lower values were used, even higher values of n were obtained than those given in Table I, and this was considered unreasonable. The same value of K'' was used in all of the remaining experiments.

It should be pointed out that the data in experiment 10 were corrected for the small but significant exchange with the solvent benzene, as observed in experiment 6. This correction involved the addition of an extra term to equation 1 above, and using the value of n for benzene in that time interval as the experimentally determined 0.042.

The approximate reproducibility of the results is shown by experiments 2 and 3, which were in actual fact not carried out successively, but several runs apart. Experiments 7 and 8 represent runs for equal time periods on 2,4,6-trichlorophenol in benzene, but with different quantities of starting materials, and these results are also in good agreement.

The important points to be observed from the data in Table I are (1) Experiments 1–5 show that equilibrium is established very rapidly for the exchange of four hydrogens. There seems to be a gradual increase in n as the time interval becomes long (six hours), but there is very little difference in the experiments carried out for ten minutes, or one or two hours. (2) The fact that when the 2, 4 and 6 positions of the aromatic ring are blocked with halogen or methyl groups, only one hydrogen is exchangeable in one hour (presumably the hydroxylic hydrogen). This demonstrates that the large decrease in % DCl was due to nuclear exchange, and not an unusual distribution coefficient between DCl and the hydroxylic hydrogen, and also confirms the orientation established by Best and Wilson[2] for the nuclear deuteration process. (3) Benzene exchanges but slightly under the same conditions as the rapid exchange with phenol. These factors are discussed below in connection with possible mechanisms for the rapid exchange with phenol.

Discussion

Exchange reactions involving phenol and its derivatives have been studied by several workers. Equilibrium with the hydroxylic hydrogen is established essentially instantaneously with heavy water[6] or deuteroalcohol.[9]

The nuclear hydrogens, however, did not exchange with heavy water after twenty days at 25°,[5] and even after fourteen days at 50–60° (approximately the temperature used in the present study) in the presence of alkali, had not yet reached equilibrium. Nuclear exchange is more rapid at higher temperatures; thus, *o*- and *p*-cresol reach equilibrium in twenty hours at 170° in alkaline solution.[8] Ingold, Raisin and Wilson[5] have postulated that nuclear deuteration in alkaline solution proceeds largely *via* the reaction

$$C_6H_5OD + C_6H_5O^- \longrightarrow C_6H_5OH + C_6H_4DO^-$$

Titani[7] determined the activation energy for this process between 90 and 120° as 24.8 kcal./mole. In various concentrations of aqueous hydrochloric acid, the reaction is said[7] to proceed with an activation energy of 27.3 kcal./mole according to the equation

$$C_6H_5OH + DH_2O^+ \longrightarrow C_6H_4DOH + H_3O^+$$

and to be 1.26 order with respect to H^+.

The present reaction, studied under anhydrous conditions, proceeded at a rate too rapid to measure at 50°[16] but followed the same orientation rules as with aqueous exchange. As the rate of exchange was so rapid, it is highly probable that the activation energy for exchange with anhydrous deuterium chloride is considerably lower than the values determined by Titani for aqueous exchange. The extremely rapid rate of this reaction is even more striking when one considers the fact that only about three to four per cent. of the deuterium chloride was dissolved in the phenol at any instant.[17] This suggests that the reaction does not involve the formation of any high energy intermediates, but must follow a path that is energetically favorable.

There are at least two mechanisms which one might suggest for the rapid nuclear exchange between deuterium chloride and phenol. As

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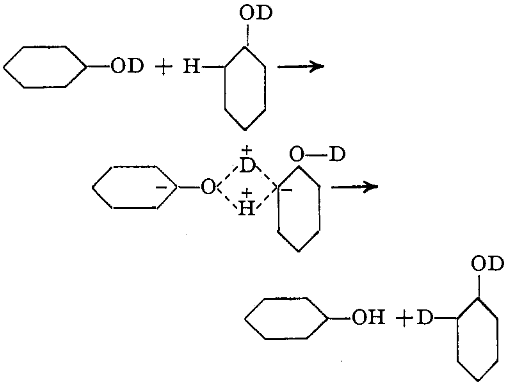
(16) Lower temperatures were not used in order to stay above the melting point of phenol. It is possible that the use of an inert solvent to slow up the reaction may enable one to study the kinetics of the exchange. This point is now under investigation.

(17) This is approximately the solubility of hydrogen chloride in phenol at 50° (H. Hart, unpublished results).

exchange at the hydroxylic hydrogen is instantaneous,[6,9] one might postulate a bimolecular reaction between O-deuterated phenol and another molecule of phenol according to the scheme

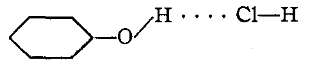


(I)

This reaction is obviously slow in aqueous solution, or aqueous exchange would be more rapid than it is. It is conceivable that when phenol was the solvent, this might be an easy reaction energetically.[18]

A reaction path which seems more favorable to us involves the direct ring deuteration with deuterium chloride as well as, of course, the instantaneous deuteration of the hydroxyl. The rate of direct deuteration would be markedly enhanced by the fact that phenol molecules are good coördinators of halogen.

Bartlett and Dauben[19] have shown that when various phenols were added to solutions of hydrogen chloride in dioxane, the acidity of the solution was markedly enhanced. This was attributed to the formation of complexes between phenol and hydrogen chloride of the type

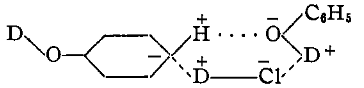


(II)

Similar complexes between phenol and halogen have also been postulated by Swain[20] to account for the kinetics of the reaction between trityl chloride, phenol and methanol.

Although phenol apparently coördinates halogen very well, hydrogen chloride is not ionized by this solvent to any great extent. In evidence of this, one may sight the work of Dolby and Robertson[21] who found that the conductivity of phenol was only slightly enhanced by anhydrous hydrogen chloride. It is also known[3] that hydrogen chloride obeys Henry's law in phenol. Even in dioxane, which is a considerably stronger base than phenol, ionization due to coördination of dioxane with the hydrogen is only said to be "incipient."[22]

In addition to being a good coördinator of halogen, phenol may also act as a base, being a good proton acceptor. Thus we suggest that the rapid rate of nuclear exchange is due to the fact that phenol may act in both these capacities. The exchange may be represented by the scheme



(III)

The quasi six-membered ring is drawn for convenience only; *i.e.*, the phenol molecules which coördinate the halogen of the deuterium chloride and the ring hydrogen need not be the same molecule. Indeed, the reaction may be polymolecular in phenol, several molecules being involved in both processes.[3] Whether the reaction occurs in a stepwise fashion, the first step being the formation of a complex such as II followed by III cannot be determined. The salient point is that the reaction involves simultaneous making and breaking of bonds, thus requiring little activation energy (but possibly a high entropy factor[20]). The exchange in aqueous solution proceeds considerably more slowly, even in the presence of hydrochloric acid, because water is probably a much poorer coördinator of halogen than phenol. In other words, the proper combination of acidity and basicity, in the general sense, is necessary for the reaction to proceed most efficiently.

Summary

It has been shown that anhydrous deuterium chloride exchanges rapidly with phenol, equilibrium being established in several minutes at 50°, and that the exchange involves not only the hydroxylic hydrogen, but the hydrogens of the 2, 4 and 6 positions as well.

Possible mechanisms for the reaction, and the difference in rate between anhydrous and aqueous exchange are discussed.

EAST LANSING, MICH. RECEIVED OCTOBER 22, 1949

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[18] In the abstract of Brodskii's paper (see ref. 8), the original of which is as yet unavailable to us, reference is made to Mikhulins' "hydrogen rearrangement," consisting in a migration of the deuterium atom of PhOD into ortho and para positions in the ring. This reaction is said to be completed in 50 hours at 200°, but the other conditions, such as solvent and method of analysis, etc., are not given. Other experiments of shorter duration at lower temperatures are not mentioned. The rate of this reaction is now under investigation in this laboratory.

[19] P. D. Bartlett and H. J. Dauben, THIS JOURNAL, **62**, 1339 (1940).

[20] C. G. Swain, *ibid.*, **70**, 1119 (1948).

[21] R. M. Dolby and P. W. Robertson, *J. Chem. Soc.*, 1711 (1930).

[22] A. J. Weith, Jr., M. E. Hobbs and P. M. Gross, THIS JOURNAL, **70**, 805 (1948).