The Possible Influence of Steric Effects, Field Effects and Hydrogen Bonding on the Chemical Reactivity of Certain 4,10-Disubstituted-1,7-phenanthrolines[1]

By Royal A. Cutler and Alexander R. Surrey

The preparation of some 4- and 10-anilino-1,7-phenanthroline and 4- and 10-ethoxy-1,7-phenanthroline derivatives is described. An explanation for the marked differences in activity noted for the 4-Cl and 10-Cl atoms in the 1,7-phenanthroline nucleus is discussed. It would appear that the reactivity of the 4-Cl atom depends to a large extent upon the nature of the substituent in the 10-position. The presence of an hydroxyl or anilino group in the 10-position greatly enhances the reactivity of the 4-Cl atom. This undoubtedly is due to hydrogen bonding at the 1-N atom. With 4,10-dichloro-1,7-phenanthroline (III) it has been found that the reactivity of the 4-Cl atom is decreased markedly whereas the 10-Cl atom is replaced extremely easily. This exceptional activity of the latter halogen atom has been attributed to a relief of strain in the transition state in its reaction with nucleophilic reagents. The low order of activity at the 4-position in the dichloro compound III may be explained in terms of a Field effect or/and steric inhibition of solvation.

In a previous publication[2] it was reported that the two hydroxyls in 4,10-dihydroxy-1,7-phenanthroline (I) (Chart I) showed differences in the ease with which they were replaced by chlorine when treated with phosphorus oxychloride. The more difficult replacement of the 10-hydroxyl group was ascribed to its hydrogen bonding with the 1-N atom. In the present work we have investigated the reaction of 4,10-dichloro-1,7-phenanthroline (III) with nucleophilic reagents. The results indicate that the rela-

Chart I[a]
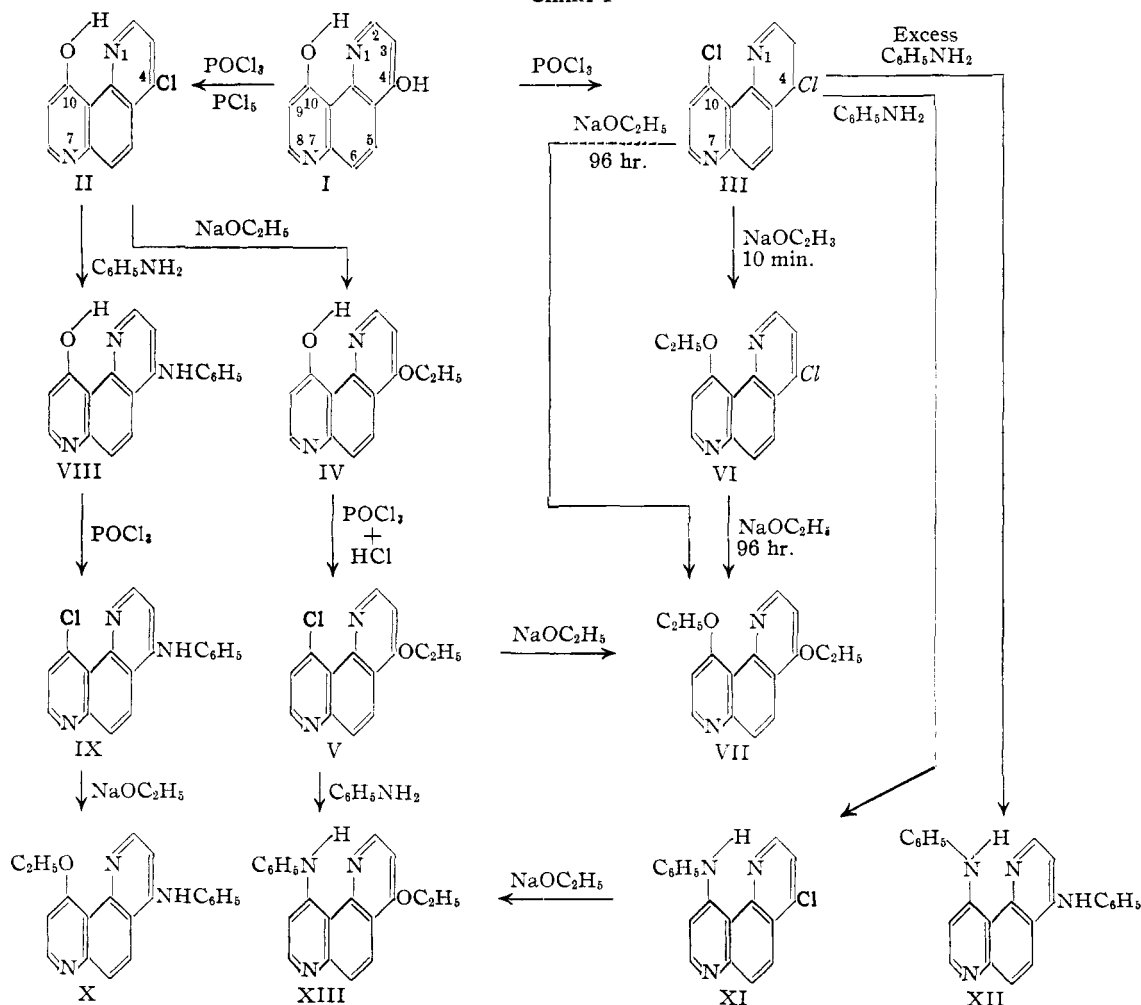
[a] The chlorine atoms in bold type appear to be considerably more reactive than the chlorine atoms in 4-chloroquinoline. The italicized chlorine atoms are much less active.

(1) This paper was presented before the Organic Division of the XIIth International Congress of Pure and Applied Chemistry, September 10, 1951, New York, N. Y.

(2) A. R. Surrey and R. A. Cutler, This Journal, 76, 1109 (1954).

tive reactivity of the 4-Cl and 10-Cl atoms in III differ by a factor greater than five hundred.

For example, it was observed that the dichloro

compound III reacts readily with an excess of sodium ethylate in ethyl alcohol at reflux temperatures for three hours to give a monoethoxy compound, which proved to be 4-chloro-10-ethoxy-1,7-phenanthroline (VI). When this reaction was studied more carefully it was found that it was practically complete in a matter of ten minutes. On the other hand, the replacement of the 4-Cl atom by ethoxide proceeded at an extremely slow rate. Thus, if in the above experiment refluxing was continued for 96 hours, the replacement of the 4-Cl atom to give 4,10-diethoxy-1,7-phenanthroline (VII) was only 75% complete as measured by the amount of sodium chloride collected. The diethoxy compound VII was isolated without difficulty.

The marked difference in behavior of the 4-Cl and 10-Cl atoms in the dihalo compound III was also observed in its reaction with aniline. Using one mole of aniline in glacial acetic acid a good yield of 10-anilino-4-chloro-1,7-phenanthroline (XI) was obtained in 10 minutes. Only small amounts of the dianilino compound XII were formed in this reaction. However, with an excess of aniline the 4,10-dianilino-1,7-phenanthroline (XII) was the only product that could be isolated.[3]

From these results it is apparent that the activity of the 10-Cl atom in the dichloro compound III is far greater than that of the 4-Cl atom and greater than one would normally expect[4] from the activation by the 7-N atom alone.[5] In addition, the results indicate that the reactivity of the 4-Cl atom in 4,10-dichloro-1,7-phenanthroline (III) as well as in 4-chloro-10-ethoxy-1,7-phenanthroline (VI) is less than one would expect on the basis of the activation due to the 1-N atom.[4]

In an effort to explain these differences in activity a molecular model of 4,10-dichloro-1,7-phenanthroline (III) was constructed. It was observed that the 10-Cl atom is in close proximity to the 1-N atom and would appear to be sterically hindered. One might expect, therefore, that the exposed 4-Cl atom would be the first of the halogens to react. However, as shown above, the reverse is true.

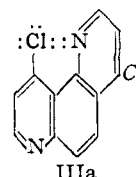The activation of the 4-Cl atom, under normal

(3) The reaction with aniline is not strictly comparable to the sodium ethoxide experiment since acetic acid was used as the solvent. It is well known that protonization of the ring nitrogen in heterocyclic compounds has a catalytic effect on the replacement of halogen in the 2- and 4-positions. In addition, the presence of an anilino group in the 10-position would also enhance the reactivity of the 4-Cl. This will be considered more fully later in the Discussion.

(4) In 4,7-dichloroquinoline, for example, the reaction with an excess of sodium ethylate in ethyl alcohol requires 90 minutes to give a 90% yield of the 4-ethoxy compound; unpublished work.

(5) (a) The normal activation toward nucleophilic reagents that occurs at the 2- and 4-positions of the pyridine nucleus has been ascribed to the tautomeric displacement of electrons toward the nitrogen atom due to the latter's greater electronegativity with respect to carbon. This would lead to partial positive charges $\delta\dagger$ at the 2- and 4-carbon atoms, and thereby facilitate the approach of a nucleophilic reagent at these positions. See "Electronic Interpretations of Organic Chemistry," A. E. Remick, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 105; cf. "The Electronic Theory of Organic Chemistry," M. J. S. Dewar, Oxford, Clarendon Press, 1949, p. 185. (b) An additional factor that should be considered in the activation toward nucleophilic reagents is the effect of solvation of the ring nitrogen. This effect would have a tendency to withdraw electrons from the nitrogen, thus increasing the magnitude of the positive charges in the ring at carbons 2 and 4.
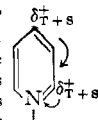
conditions, may be pictured as resulting from a tendency of the 1-N atom to pull electrons from the ring.[5a] However, this effect might be inhibited by the presence of a 10-Cl (III), or 10-OC$_2$H$_5$(VI), which would place a high electron density in close proximity to the 1-N atom (IIIa). The partial positive charge at the 4-carbon which would ordinarily facilitate the approach of a nucleophilic group would therefore not be favored. These appear to be good examples of the phenomenon which has been termed the Field or Direct (D) effect.[6]


IIIa

An additional factor to be considered in the activation or deactivation of the 4-Cl atom is solvation of the 1-N atom.[5b] If this solvation is sterically hindered by the presence of a 10-Cl (III) or 10-OC$_2$H$_5$ (VI), the positive charge at C-4 would be diminished (IIIb). A decrease in activity, therefore, of the 4-Cl atom would be anticipated.
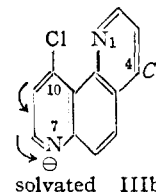

solvated IIIb

Steric effects may be used to rationalize the exceptional activity of the 10-Cl atom. It seems entirely possible that the latter, because of its close proximity to the 1-N, is subjected to a certain amount of strain in the ground state of the molecule IIIc. In passing to the transition state IIId the chlorine atom would move out of the plane of the molecule. This relief of strain which would favor the reaction might well be the major factor contributing toward the unexpected activity of the 10-Cl atom.

IIIc   solvated IIId
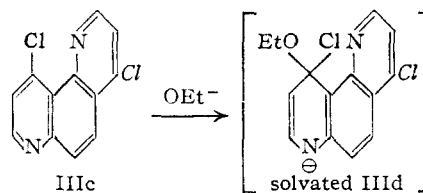
(6) The concept of the Field or Direct (D) effect, wherein the electrical field of two atoms interact owing to the transmission of electrical influence directly through empty space, has been employed by a number of workers in the past to explain the behavior of various types of organic compounds. However, in most cases it has been difficult to evaluate the magnitude of the effect because of the co-existence of the Inductive (I) effect or other complicating factors also present in the molecule. A. E. Remick ("Electronic Interpretations of Organic Chemistry," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 93) has reviewed adequately the pertinent literature on this point and has concluded, on the basis of evidence then available, "that the Field effect from dipoles is rarely, if ever, of much qualitative importance or, if it is, it is for some reason qualitatively indistinguishable from the Inductive (I) effect." More recently, however, in a study of the "Ortho Effect," J. Miller and V. A. Williams (J. Chem. Soc., 1475 (1953)) have concluded that Field effects are more important than geometrical effects.

TABLE I
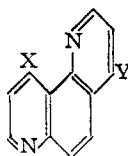
No.	X	Y	Yield, %	Recrystn. solvent	M.p., °C.	Formula	Analyses, % Calcd.	Found	Prepared from
IV	-OH	-OC2H5	90	Dioxane	142.5-143	$C_{14}H_{12}N_2O_2$	C, 69.99	70.08	II
							H, 5.02	5.49	
							N, 11.66	11.61	
V	-Cl	-OC2H5	90	Methanol	121.5-122.5	$C_{14}H_{11}ClN_2O$	Cl, 13.71	13.51	IV
							N, 10.83	10.70	
VI	-OC2H5	-Cl	60	Skelly C	147.5-148.5	$C_{14}H_{11}ClN_2O$	Cl, 13.71	13.42	III
							N, 10.83	10.86	
VII	-OC2H5	-OC2H5	90	Skelly C	156-157	$C_{16}H_{16}N_2O_2$	C, 71.62	71.64	V[a]
							H, 6.01	5.86	
							N, 10.44	10.65	
VIII	-OH	-NHC6H5	94	Ethanol	221-222	$C_{18}H_{13}N_3O$	N, 14.63	14.70	II
IX	-Cl	-NHC6H5	90	Benzene	190-190.5	$C_{18}H_{12}ClN_3$	N, 13.72	13.53	VIII
X	-OC2H5	-NHC6H5	55	Benzene	219.5-220.5	$C_{20}H_{17}N_3O$	N, 13.33	13.21	IX
XI	-NHC6H5	-Cl	80	Ethanol	164-165	$C_{18}H_{12}ClN_3$	Cl, 11.57	11.40	III
XII	-NHC6H5	-NHC6H5	70	Pyridine-ethanol	269-270	$C_{24}H_{18}N_4$	N, 15.46	15.26	III
XIII	-NHC6H5	-OC2H5	60	Skelly C	124-125	$C_{20}H_{17}N_3O$	N, 13.33	13.15	V[b]

[a] Also prepared in about 20% yields from III or VI by refluxing with alcoholic sodium ethoxide for 96 hours. [b] Also prepared in about 30% yield from XI by refluxing for seven hours with alcoholic sodium ethoxide.

As was indicated above, the 4-Cl atom in 4-chloro-10-ethoxy-1,7-phenanthroline (VI) reacted very slowly with sodium ethoxide. On the other hand, the 4-Cl atom in 4-chloro-10-hydroxy-1,7-phenanthroline (II) reacted readily with sodium ethoxide.[7] The more reactive nature of the 4-Cl atom in the latter compound is undoubtedly attributable to chelate bonding at the 1-N atom (IIa). The effect of this "intramolecular solvation" would be

IIa
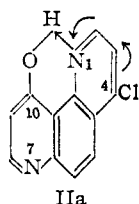
to draw electrons from the 4-position and therefore facilitate approach of a nucleophilic agent at this point. A similar situation exists with 10-anilino-4-chloro-1,7-phenanthroline (XI).

The proofs of structures in the present work were carried out in the following manner (see Chart I). We have shown previously[2] that the chlorohydroxy compound obtained from 4,10-dihydroxy-1,7-phenanthroline (I) by treatment with phosphorus oxychloride and phosphorus pentachloride is 4-chloro-10-hydroxy-1,7-phenanthroline (II). This chlorocompound II reacts with sodium ethoxide and aniline to give the corresponding 4-ethoxy IV and 4-anilino VIII derivatives, respectively. Replacement of the 10-hydroxy group by chlorine in these two compounds gave rise to the 10-chloro-4-ethoxy-(V) and 4-anilino-10-chloro-(IX) phenanthrolines. The isomeric compounds obtained by treatment of the dichloro derivative III with sodium ethoxide

(7) The 4-Cl atom in XI is also readily replaced by ethoxyl.

and aniline were not identical with V and IX and therefore must be 4-chloro-10-ethoxy-1,7-phenanthroline (VI) and 10-anilino-4-chloro-1,7-phenanthroline (XI).

Additional proof of structure was obtained by the reaction of 10-chloro-4-ethoxy-1,7-phenanthroline (V) with aniline and the reaction of 10-anilino-4-chloro-1,7-phenanthroline (XI) with sodium ethoxide. The same compound 10-anilino-4-ethoxy-1,7-phenanthroline (XIII) was obtained in both cases. This was not identical with the anilino-ethoxy derivative (X) formed from 4-anilino-10-chloro-1,7-phenanthroline by treatment with sodium ethoxide. The formation of the same compound, 4,10-diethoxy-1,8-phenanthroline (VII) from either 10-chloro-4-ethoxy-(V) or 4-chloro-10-ethoxy-1,7-phenanthroline (VI) by treatment with sodium ethoxide furnished further corroboration for the structures assigned.

Acknowledgment.—The authors are indebted to Dr.'s S. Archer, J. F. Brown, Jr., W. S. Johnson and C. F. Koelsch for helpful discussions and comments, and to Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analyses recorded.

Experimental[8]

Preparation of IV, VI, VII and X (Table I).—A general procedure for the preparation of the above ethoxy compounds is given below.

One part of the chloro compound (see Table I) was dissolved in thirty parts of absolute alcohol and refluxed for about three hours[9] on a steam-bath with slightly more than equivalent amounts of either potassium hydroxide or sodium ethylate. After removing the potassium or sodium chloride

which had separated, alcoholic hydrogen chloride solution was added. After standing overnight in the refrigerator, the hydrochloride was filtered off, dissolved in water and the solution filtered with charcoal. The free base was liberated with ammonium hydroxide and extracted with chloroform. The residue from the chloroform solution was purified by recrystallization (see Table I).

In the preparation of VII from III or VI, refluxing with sodium ethoxide was carried out for 96 hours. Even after this time the reaction had gone to an extent of only 75% of completion as indicated by the amount of sodium chloride collected. An excess of alcoholic hydrogen chloride was added to the reaction mixtures, the resulting hydrochloride filtered off, dissolved in water and the base liberated with alkali in the presence of a layer of ether. On standing, VII separated in practically pure form from the ether solution.

Preparation of VIII, XI, XIII and XII (Table I).—The anilino compounds were prepared from the corresponding chloro derivatives by heating with one volume of aniline (two volumes for XII). At about 70° an exothermic reaction occurred in the case of III and V, the temperature rising rapidly to about 150–160°. With II no exothermal reaction occurred until the temperature reached 115°. After the initial reaction the mixtures were heated in the following manner: for VIII, 150° for 15 minutes; XI, 90° for 5 minutes; XIII, 120° for 15 minutes; XII, 180° for 40 minutes. The mixtures were dissolved in five volumes of acetic acid, poured into water and the hydrochlorides of the anilino compounds collected by filtration. These were in turn suspended in water and converted to the free bases by the addition of ammonium hydroxide solution with warming. The hydrochloride of XI was soluble in water and was not isolated.

Preparation of XI by the above method gave a product which was contaminated with considerable amounts of the dianilino compound XII because of the initial temperature rise. When the reaction was run in five volumes of glacial acetic acid at 100° for 10 minutes, only a small amount of the dianilino derivative XII was formed. The latter was separated from the main product by virtue of its insolubility in chloroform.

Preparation of V and IX (Table I).—The hydrochloride IV was treated with six volumes of phosphorus oxychloride. An exothermic reaction occurred immediately and a clear yellow solution resulted within a few minutes. When the free base was used solution had not occurred after ten minutes. However, after the addition of a tenth of a volume (based on the amount of IV) of water, a clear solution was obtained in about two minutes.[10]

Refluxing VIII with three volumes of phosphorus oxychloride for ten minutes gave a clear orange solution. The above two reaction mixtures were worked up as in the preparation of III as previously reported.[2]

(10) Similar observations were reported in the analogous chlorination of 4-chloro-10-hydroxy-1,7-phenanthroline (II).[2] It was postulated that the acid (or water) was necessary to break up the hydrogen bond between the 10-Cl and 1-N atoms by furnishing protons to engage the 1-N in salt formation.

RENSSELAER, NEW YORK

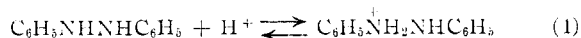[A CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Mechanism of the Benzidine Rearrangement. III. The Rearrangement of p,p'-Dideuterohydrazobenzene

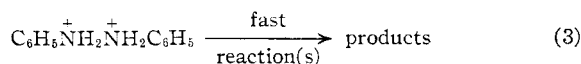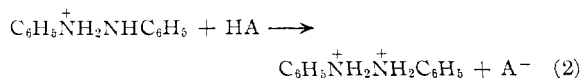BY GEORGE S. HAMMOND AND WINSTON GRUNDEMEIER

The rate of rearrangement of p,p'-dideuterohydrazobenzene in absolute ethanol containing hydrogen chloride is found to be, at most, 10% slower than that of the undeuterated compound. Furthermore, the ratio of benzidene to diphenyline in the product mixture is identical within experimental error with the deuterated and undeuterated substrates. These results imply that the rate-determining step of the reactions is the formation of the second conjugate acid of hydrazobenzene and that the subsequent product-determining reactions are not implemented by proton removal from the nuclear positions undergoing substitution.
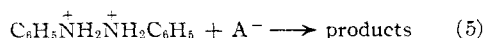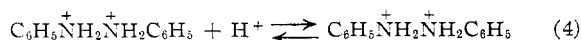
It has been demonstrated recently that the rate of rearrangement of hydrazobenzene to a mixture of benzidine and diphenyline[1] is proportional to the square of the hydrogen ion concentration in the medium[1,2] and is, furthermore, subject to linear general acid catalysis.[3] These data are in accord with the following mechanisms each of which involves the equilibration of hydrazobenzene with its first conjugate acid.

$$C_6H_5NHNHC_6H_5 + H^+ \rightleftarrows C_6H_5\overset{+}{N}H_2NHC_6H_5 \quad (1)$$

Mechanism A

$$C_6H_5\overset{+}{N}H_2NHC_6H_5 + HA \longrightarrow$$
$$C_6H_5\overset{+}{N}H_2\overset{+}{N}H_2C_6H_5 + A^- \quad (2)$$

$$C_6H_5\overset{+}{N}H_2\overset{+}{N}H_2C_6H_5 \xrightarrow[\text{reaction(s)}]{\text{fast}} \text{products} \quad (3)$$

Mechanism B

$$C_6H_5\overset{+}{N}H_2\overset{+}{N}H_2C_6H_5 + H^+ \rightleftarrows C_6H_5\overset{+}{N}H_2\overset{+}{N}H_2C_6H_5 \quad (4)$$

$$C_6H_5\overset{+}{N}H_2\overset{+}{N}H_2C_6H_5 + A^- \longrightarrow \text{products} \quad (5)$$

(1) R. B. Carlin, R. G. Nelb and R. C. Odioso, THIS JOURNAL, **73**, 1002 (1951).

(2) G. S. Hammond and H. Shine, ibid., **72**, 220 (1950).

(3) M. D. Cohen and G. S. Hammond, ibid., **75**, 880 (1953).

Mechanism C

$$C_6H_5\overset{+}{N}H_2NHC_6H_5 + HA \longrightarrow \text{products} \quad (6)$$

On intuitive grounds mechanism A was preferred over either of the other two despite the fact that it would involve an unprecedented rate-determining transfer of a proton from oxygen to nitrogen. This prejudice was shown to be in accord with the observation that the solid compound, hydrazobenzene dihydroiodide, underwent rearrangement at a rate about four times the rate of its reversion to hydrazobenzene when it was dissolved in an alcohol–water solvent.[3]

In mechanism B the general acid catalysis would be due to the participation of the anion of the weak acid in removing a proton from one of the positions to which rearrangement is occurring. If this were the mechanism, it would follow that the rate should show a kinetic isotope effect if a *para* hydrogen were replaced by deuterium. The same might be true of the completely concerted mechanism C although this would not necessarily be the case. It would be quite conceivable that in a transition state such as I (where S represents solvent molecules), bond breaking at the *para* position might not have made enough progress to show an isotope effect.