Electrophilic Halogenation of 8-Quinolinol and Its Copper(II) Chelate[1]

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Electrophilic halogenation of 8-quinolinol and its copper(II) chelate with elemental halogen and *N*-halosuccinimide was studied. Under acidic conditions, substitution at the 5 position of 8-quinolinol was favored, during chlorination and bromination, and, in basic media, the 7 position was favored. Iodination was characterized by the reverse orientation and may take place by a different mechanism. Orientation of substituents in the monohalogenation of 8-quinolinol is influenced by its prototropic form, the halogenating agent, and the solvent employed. MO calculations consistent with the experimental results are reported.

There has been considerable interest in 8-quinolinol and its derivatives, since the reports of Hahn[2] and Berg[3] established the value of those compounds as precipitants of metal ions. Further interest has been elicited by the studies of Zentmyer,[4] Albert, *et al.*,[5] and Gershon, *et al.*,[6] who related the mechanism of fungitoxicity of the 8-quinolinols, in part, to chelation of metals.

In a comprehensive review of the literature to 1956, Hollingshead[7] concluded that on reaction of 8-quinolinol with excess elemental halogen only 5,7-dihalogeno-8-quinolinols resulted. On using equimolar quantities of reactants, substitution occurred in the 5 position, but the product was always contaminated with some 5,7-disubstituted derivative. More recent work on the halogenation of 8-quinolinol has yielded a variety of results.[8-14]

Of further interest were studies of the effect of chelation on halogenation of 8-quinolinol. Maguire and Jones[15] concluded, as a result of dihalogenation reactions on metal chelates of this ligand with elemental chlorine, bromine, and iodine, that coordination does not alter the reactive positions of 8-quinolinol toward electrophilic reagents. On the basis of competitive bromination of metal chelates of 8-quinolinol in the presence of free ligand with elemental bromine, Hix and Jones[16] stated that the rate of bromination of chelates was about 35 times greater than that of the free ligand. In attempting to generalize these concepts to electrophilic reactions of bis(8-quinolinolato)copper(II), Chawla and Jones[17] reported that benzoylation, sulfonation, nitration, thiocyanation, mercuration, and condensation with formaldehyde can be readily effected on the chelate. Iodination was achieved in poor yield and acetylation failed. The halogenation of metal chelates of 8-quinolinol with *N*-halosuccinimido was reported by Prasad, *et al.*,[18] and reinvestigated by Gershon, *et al.*[14,19] These results allowed for the following conclusions. Chelation increases the rate of halogenation and does not change the reactive positions in electrophilic substitution. This is in agreement with the work of Hix and Jones[16] and Maguire and Jones.[15] Chelation does affect orientation of substituents in electrophilic substitution with *N*-halosuccinimide.[19]

In view of the diversity of results obtained from the variety of halogenation methods, a systematic study of the halogenation of 8-quinolinol and its copper(II) bischelate using elemental chlorine, bromine, and iodine was desired. Halogenations were carried out in chloroform at ambient temperatures for 3 hr and the ratios of halogen to substrate were 1:1, 2:1, and 3:1. The rationale for this approach and the identification and quantitation of the products were previously discussed.[14,19] The results of the reactions are compiled in Table I. On chlorination of 8-quinolinol and its copper(II) chelate with elemental chlorine, it was again confirmed that the rate of chlorination is greater for the chelate than for the ligand.[16] This is apparent from the greater uptake of chlorine by the chelate as compared with the ligand during the experimental time. The outstanding difference observed in this chlorination reaction is that the ligand yielded measurable quantities of 7-chloro-8-quinolinol, whereas the chelate afforded only insignificant yields of this isomer.

The products of bromination of 8-quinolinol and its copper(II) chelate with 1 equiv of bromine per equivalent of quinolinol were not greatly different. Doubling the ratio of bromine to 8-quinolinol resulted in the formation of only 5,7-dibromo-8-quinolinol. With respect to the chelate, 2 and 3 equiv of bromine, at ambient temperatures, caused the formation of tarry products which were unsuitable for analysis. This bromination was successfully carried out by Hix and Jones[16] at 0–5°.

The action of 1 equiv of iodine on 1 equiv of 8-quinolinol resulted in the formation of 5-iodo-, 7-iodo-, and 5,7-diiodo-8-quinolinol with most of the iodine entering the 5 position. On doubling the ratio of iodine, all three products were formed in greater yield, but the results of 3 equiv of iodine were essentially the same as

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[1] This work was supported in part by the U. S. Public Health Service, Grant No. AI-05808.

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TABLE I

ACTION OF ELEMENTAL HALOGEN ON 8-QUINOLINOL AND ITS COPPER(II) COMPLEX IN CHLOROFORM AT AMBIENT TEMPERATURES

Halogenating agent	Molecular ratio or halogen to substrate	Products, % (as free ligands)[a]							
		8-Quinolinol				Bis(8-quinolinolato)copper(II)			
		Ox[b]	5-ClOx	7-ClOx	5,7-Cl$_2$Ox	Ox	5-ClOx	7-ClOx	5,7-Cl$_2$Ox
Chlorine	1	46	20	5	30	40	18	Tr[c]	42
	2	2	43	2	54	2	9	Tr	89
	3	0	0	0	100	Tr	3	Tr	97
		Ox	5-BrOx	7-BrOx	5,7-Br$_2$Ox	Ox	5-BrOx	7-BrOx	5,7-Br$_2$Ox
Bromine	1	48	4	1	47	41	14	Tr	45
	2	Tr	Tr	0	99	. . .[d]			
	3	0	0	0	100				
		Ox	5-IOx	7-IOx	5,7-I$_2$Ox	Ox	5-IOx	7-IOx	5,7-I$_2$Ox
Iodine	1	65	30	3	1	. . .[e]			
	2	47	39	8	6				
	3	43	39	9	9				

[a] All results are the average of three runs with an average deviation of ±10%. [b] Ox = 8-quinolinol. [c] Tr = trace (<1%). [d] Two and three equivalents of bromine caused the formation of tarry products which were unsuitable for analysis. [e] This reaction was complicated by the apparent reduction of Cu(II) to Cu(I) with accompanying release of unchelated 8-quinolinol.

those from 2 equiv. The iodination of bis(8-quinolinolato)copper(II) with elemental iodine was not examined becuase this reaction was complicated by the apparent reduction of copper(II) to copper(I) with accompanying release of 8-quinolinol. This will be the subject of an additional study. It appears that this reduction was not recognized by Chawla and Jones[17] who treated the copper(II) chelate of 8-quinolinol with a little more than 2 equiv of iodine. They reported that a gummy product was obtained which on decomposition yielded 6.6% of 5,7-diiodo-7-quinolinol and 6.5% of a second product which, on the basis of melting point, was claimed to be 5-iodo-8-quinolinol.

A comparison of the halogenation of 8-quinolinol and its copper(II) chelate using *N*-halosuccinimide[14,19] and elemental halogen shows that the rate of chlorination of 8-quinolinol with elemental chlorine is greater than that with *N*-chlorosuccinimide (NCS). On monohalogenation, chlorine favored the formation of 5-chloro- over 7-chloro-8-quinolinol, while with NCS the reverse was true. The same held for the copper(II) chelate except that with NCS, 5- and 7-chloro-8-quinolinols formed in about equal yields. The rates of bromination of the ligand and the chelate with elemental bromine and *N*-bromosuccinimide (NBS) were rapid and indistinguishable in all cases, under the conditions studied; however, of the monosubstitution products of the reaction of 8-quinolinol and its copper(II) chelate with bromine, the 5-bromo formed in preference to the 7-bromo analog, whereas with NBS the yield of 7-bromo exceeded that of 5-bromo-8-quinolinol, on bromination of the ligand. Only 5-bromo-8-quinolinol was obtained from the chelate. The rate of iodination of 8-quinolinol with *N*-iodosuccinimide (NIS) was much greater than that with iodine, and, in both cases, the orientation was primarily in the 5 position. With respect to the chelate, reaction with NIS resulted in the formation of primarily the 7 isomer.[14,19] Data with elemental iodine were not obtained, as was previously explained.

It was of further interest to examine the effect of the solvent and of the prototropic form on the orientation of substituents in the halogenation of 8-quinolinol by elemental halogen and by *N*-halosuccinimide. For this study, 8-quinolinol was treated with chlorine, bromine, iodine, NCS, NBS, and NIS on a 1:1 equiv basis. The following solvents ranging in decreasing acidity were employed: 93% sulfuric acid, glacial acetic acid, pyridine, diethylamine, sodium hydroxide equivalent to the free halogen and the quinolinol, and excess 10% sodium hydroxide. In the case of iodine, iodination was also attempted with iodine dissolved in excess 47% hydriodic acid. The results are summarized in Table II. Equivalent studies on the bischelate with copper(II) were not undertaken because of the instability of the chelates in the extreme acidic and basic media. Chawla and Jones[17] reported the sulfonation of bis(8-quinolinolato)-copper(II) in concentrated sulfuric acid, whereas 8-quinolinol could not be sulfonated under these conditions. Of interest was the fact that the 5-sulfonic acid was obtained as the free ligand. In view of the stability data of Albert[20] who showed that the β_2 values for the copper(II) chelates with 8-quinolinol and 8-quinolinol-5-sulfonic acid were 23.4 and 23.1, respectively, it appears unlikely that bis(8-quinolinolato)copper(II) was sulfonated since it would not have been stable in concentrated sulfuric acid as was the bis copper(II) chelate of the sulfonic acid. The sulfonation reaction in the presence of copper(II) may have been due to a catalytic action ot the metal. Similarly, that the copper(II) chelate of 8-quinolinol was nitrated in 40% nitric acid is also subject to question because it is not likely that the complex would have been stable in such concentrated acid. Therefore, any conclusions drawn from these experiments regarding electrophilic substitution of metal chelates of ligand should be suspect. A study on the stability of bis(5,7-dichloro-8-quinolinolato)copper(II) in acid solution by Gershon, *et al.*,[21] showed that below pH 1.0 no chelate existed.

It can be seen from the data of Table II that on monohalogenation of 8-quinolinol with chlorine, NCS, bromine, or NBS in strongly acidic media the incoming halogen atom was oriented primarily to the 5 position. In strongly basic media, the halogen atom favored the 7 position. Halogenation in acidic environments which were less acidic than 93% sulfuric acid allowed for the formation of mixtures of 5-and 7-halogeno-8-quinolinols; however, the 5 isomer predominated. In basic media

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TABLE II

EFFECTS OF SOLVENTS ON ELECTROPHILIC HALOGENATION OF 8-QUINOLINOL[a]

Halogenating medium	Products, %							
	N-Chlorosuccinimide				Chlorine			
	Ox[b]	5-ClOx	7-ClOx	5,7-Cl_2Ox	Ox	5-ClOx	7-ClOx	5,7-Cl_2Ox
H_2SO_4, 93%	1	99	0	Tr[c]	Tr	96	3	1
Acetic acid, glacial	24	37	24	15	39	18	7	36
Pyridine	42	10	32	16	67	9	9	15
Diethylamine	100	0	0	0	93	1	6	0
NaOH, 3 equiv					38	5	52	5
NaOH, 10% (excess)	29	6	60	5	39	3	51	7
	N-Bromosuccinimide				Bromine			
	Ox	5-BrOx	7-BrOx	5,7-Br_2Ox	Ox	5-BrOx	7-BrOx	5,7-Br_2Ox
H_2SO_4, 93%	Tr	99	0	Tr	0	99	0	Tr
Acetic acid, glacial	28	33	13	26	34	35	0	31
Pyridine	17	16	45	22	41	13	24	22
Diethylamine	21	0	78	Tr	13	3	80	4
NaOH, 3 equiv					84	3	4	9
NaOH, 10% (excess)	74	0	16	10	89	0	8	3
	N-Iodosuccinimide				Iodine			
	Ox	5-IOx	7-IOx	5,7-I_2Ox	Ox	5-IOx	7-IOx	5,7-I_2Ox
H_2SO_4, 93%	49	1	49	1	100	0	0	0
Acetic acid, glacial	18	17	39	26	84	12	3	1
Pyridine	22	34	18	26	14	59	5	12
Diethylamine	1	88	4	7	47	32	4	17
NaOH, 3 equiv					99	Tr	Tr	0
NaOH, 10% (excess)	58	11	4	27	93	2	3	2
HI, 47%					100	0	0	0

[a] All results are the average of three runs with an average deviation of ±10%. [b] Ox = 8-quinolinol. [c] Tr = trace (<1%).

which were less basic than 10% sodium hydroxide, mixtures of 5- and 7-substituted 8-quinolinols were formed, but 7 substitution was favored. This is consistent with the observation of Pearson, *et al.*,[13] who reported that on bromination of phenols the presence of hydrogen bromide caused substitution to take place in the para position and, conversely, in the absence of hydrogen bromide substitution favored the ortho position.

The course of iodination seemed to be different from that of chlorination or bromination. Iodination of 8-quinolinol with NIS in strongly acidic media caused the iodo substituent to enter the 7 position, and, in strongly basic media, orientation favored the 5 position. Elemental iodine was ineffective as an iodinating agent in strong acid as well as in strong base. In the weaker bases, diethylamine and pyridine, monoiodination by both agents resulted in the formation of greater yields of 5-iodo-8-quinolinol than the 7 isomer. In acetic acid, the products formed from the different iodinatng agents did not follow the same pattern in orientation.

It thus appears that orientation of substituents in the monohalogenation of 8-quinolinol is affected by the prototropic form of the substrate, the halogenating agent, and the solvent employed.

In view of the foregoing results, the generalization of Hollingshead,[7] that on monohalogenation of 8-quinolinol only the 5-substituted product is formed, is to be questioned. The present data are also in contradiction to the report of Mychajlyszyn[11] who claimed that 5-chloro-8-quinolinol along with 5,7-dichloro-8-quinolinol was formed by chlorination of 8-quinolinol with sodium hypochlorite in sodium hydroxide. The methods of halogenation in sulfuric acid of Sukhina[9] and Aristov and Kostina[12] were herein confirmed.

In attempting to explain the reactivity of 8-quinolinol and its metal chelates toward both electrophilic and nucleophilic reagents, Burton and Davis[22] carried out Hückel LCAO calculations on the cationic, neutral, and anionic forms of the ligand. These calculations have been quoted[23] and used as the basis for further calculations[24] and in essence they state that, for electrophilic reagents, the electrophilic localization energies indicate that the preferred position for attack is the 5 position regardless of the prototropic form of the substrate. These calculations are inconsistent with the results of the present work, and it would be in order to reexamine them.

The simple Hückel calculations[22] fail to account for interelectronic repulsion in the total energy of the molecular species. A modification of the Hückel approach by Bancroft and Howe[25] allows for its refinement by including interelectronic repulsions.

In the present work, charge densities for the anion, neutral, and cation species derived from 8-quinolinol were evaluated from an eigenvalue routine on an IBM 7072 digital computer using the parameters suggested by Burton and Davis[22] for estimating the oxygen and nitrogen Coulomb integrals and the carbon–oxygen and carbon–nitrogen resonance integrals for all prototropic species concerned. In addition, π-electron charge densities were calculated for the O doubly protonated species derived from 8-quinolinol (see structure a). The rapid increase observed in absorptivity and change in shape of the absorption spectra of 8-quinolinol in solution with increasing concentrations of sulfuric acid, but below that which effects sulfonation, suggested that such a species may exist in these solutions. The Cou-

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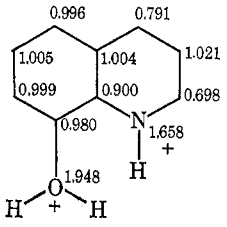
TABLE III

ELECTROPHILIC LOCALIZATION ENERGIES (ΔE_π),[a] INTERELECTRONIC REPULSION CORRECTION TERMS (ΔE_r), AND CORRECTED ELECTROPHILIC LOCALIZATION ENERGIES ($\Delta E_\pi' = \Delta E_\pi + \Delta E_r$). CORRESPONDING TO ELECTROPHILIC SUBSTITUTION AT THE 5 AND 7 POSITIONS OF THE ANION, NEUTRAL SPECIES, CATION, AND DOUBLY CHARGED CATION DERIVED FROM 8-QUINOLINOL

	ΔE_π		ΔE_r		$\Delta E_\pi'$	
Prototropic form	5	7	5	7	5	7
Anion	2.35×10^{-11}	2.41×10^{-11}	4.02×10^{-11}	3.73×10^{-11}	6.37×10^{-11}	6.14×10^{-11}
Neutral species	2.53×10^{-11}	2.66×10^{-11}	3.85×10^{-11}	3.80×10^{-11}	6.38×10^{-11}	6.56×10^{-11}
Cation	3.40×10^{-11}	3.58×10^{-11}	3.95×10^{-11}	4.10×10^{-11}	7.35×10^{-11}	7.68×10^{-11}
Doubly charged cation	3.02×10^{-11}	3.28×10^{-11}	4.22×10^{-11}	5.04×10^{-11}	7.24×10^{-11}	8.32×10^{-11}

[a] ΔE_π, ΔE_r, and $\Delta E_\pi'$ are expressed in ergs per molecule.

lomb integral for doubly protonated oxygen was taken to be $\alpha_c + 2.25\beta_{cc}$, where α_c is the carbon Coulomb integral and β_{cc} is the carbon–carbon resonance integral, while the resonance integral for the C–CH_2^+ bond was taken to be $0.8\beta_{cc}$. These values were selected by noting the changes in the Coulomb and resonance integrals in the treatment of Burton and Davis,[22] upon going from the anion to the neutral species and applying these changes to the singly protonated species.



a

The interelectronic repulsion terms were calculated using the carbon–carbon bond length of 1.40 Å as the length of all bonds in the π system which included the carbon–oxygen and carbon–nitrogen bonds. Errors for those approximations are expected to be very small. In order to convert the localization energies calculated from the simple Hückel theory from units of β_{cc} to the same units as those of the repulsion terms, it was necessary to evaluate β_{cc}. This was accomplished by relating the energy of the lowest π–π^* transition in units of β_{cc} to the experimentally determined quantity evaluated from the long wavelength absorption maximum of each prototropic species. The electrophilic localization energies calculated from the simple Hückel treatment, the repulsion terms, and the corrected localization energies for substitution at the 5 and 7 positions of the anion, neutral species, cation, and doubly charged cation, respectively, derived from 8-quinolinol are presented in Table III.

The values of $\Delta E_\pi'$ in Table III indicate that electrophilic halogenation should occur at the 5 position as the preferred site in all prototropic species derived from 8-quinolinol except for the anion. Electrophilic substitution should occur preferentially in the 7 position in the anion. These calculated results are in good agreement with the experimental data for chlorination and bromination of 8-quinolinol but not for iodination. This would indicate that the mechanism of iodination may be different from that of chlorination and bromination.

Experimental Section[26]

Halogenation of 8-Quinolinol and Its Bis Copper(II) Complex with Elemental Halogen in Chloroform.—To 10 ml of chloroform containing 5 mmol of elemental halogen (Cl_2, Br_2, or I_2) was added 1, 2, or 3 mequiv of 8-quinolinol or its Cu(II) complex. The mixture was stirred on a magnetic stirrer for 3 hr, after which the free ligands and the chelates were assayed according to ref 14 and 19.

Halogenation of 8-Quinolinol in Different Solvents with Elemental Halogen and *N*-Halosuccinimides.—For halogenations carried out in 93% H_2SO_4, acetic acid, pyridine, diethylamine, NaOH, and HI, the procedure was similar to that described above for the free ligands, except for chlorination with Cl_2 in 93% H_2SO_4. For this, the required amount of Cl_2 was condensed in a small calibrated test tube cooled by a Dry Ice-acetone bath. It was then poured into a solution of 8-quinolinol in 93% (w/w) H_2SO_4 in a citrate of magnesia bottle and stirred magnetically. The assay was carried out as above.

Registry No.—8-Quinolinol, 148-24-3; 8-quinolinol copper(II) chelate, 10380-28-6.

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[26] Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector to which was attached a Varian Aerograph Model 20 recorder. The column and conditions employed for the gas chromatographic separation of the chloro- and bromo-8-quinolinols were described previously[14] as were the column and conditions for the iodo-8-quinolinols.[19]