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Studies on Hydrogen Exchange. IX.[1] Electrophilic Deuteration of 2-Pyridinol, 2-Quinolinol, and 1-Isoquinolinol

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Acid-catalyzed deuterations of 2-pyridinol, 2-quinolinol, and 1-isoquinolinol were examined and their deuteration reactivities were discussed in connection with their electrophilic substitution reactions other than deuteration.

Acid-catalyzed aromatic hydrogen exchange can be considered to involve an electrophilic attack at the initial stage of the reactions as in nitration, sulfonation, halogenation, *etc.* Studies on hydrogen exchange, which can be done by using deuterated or tritiated reactants and/or reaction medium[3], have a great advantage for fundamental studies on the reactivities of aromatic compounds toward electrophiles, because a proton or hydroxonium ion (H_3O^+) is the simplest electrophile in its special size and its electronic character. Thus, it allowed us to neglect not only the steric effect which may play an important role in other electrophilic reactions but also the electronic effect of the deuterium incorporated on a subsequent attack by another deuterium cation. The present paper describes a study on the deuteration reaction of 2-pyridinol, 2-quinolinol, and 1-isoquinolinol which may be

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regarded as pseudoaromatic compounds. The reactivities toward the electrophile of these compounds will be discussed in term mainly of the mesomeric effect of –N–CO– group in connection with nitration[4,5] and bromination[6,7] of these compounds.

Results and Discussion

Let us consider the structure of these compounds in solution. They have been already proved to have an oxo structure such as I, II, and III (in Chart 1) in either crystalline or solution state.[8,9] In strongly acid media, therefore, the basic center of these compounds where protonation occurs must be the oxygen atom. With regard to 1–isoquinolinol this was confirmed by nuclear magnetic resonance (NMR) spectroscopy. Thus, the NMR spectrum of 4–deuterio–1–isoquinolinol in conc. sulfuric acid–d_2 showed a broad peak at *ca.* 8.0 ppm lower than the reference signal of tetramethylammonium bromide and a doublet at *ca.* 4.6 ppm lower than the same reference, the former being assigned to NH proton and the latter to proton–3 which was coupled with NH proton. When this solution was diluted with deuterium oxide up to *ca.* 60% at room temperature, the broad peak at *ca.* 8.0 ppm lower than the reference disappeared and that at *ca.* 4.6 ppm lower than the reference was deformed into a singlet. This is an unequivocal evidence for the fact that protonation occurred at the oxygen atom. It is worth an emphasis that no hydrogen exchange occurred at all between NH hydrogen and acid hydrogens in conc. sulfuric acid solution. No exchange was yet observed after one day's standing of this solution at room temperature. 2–Quinolinol gave the same result as in the case of 1–isoquinolinol. It may be analogously concluded, furthermore, that protonation in 2–pyridinol, the spectrum of which gave a broad peak at *ca.* 8.5 ppm lower than the reference in sulfuric acid–d_2, occurs at the oxygen, as shown in Chart 1.

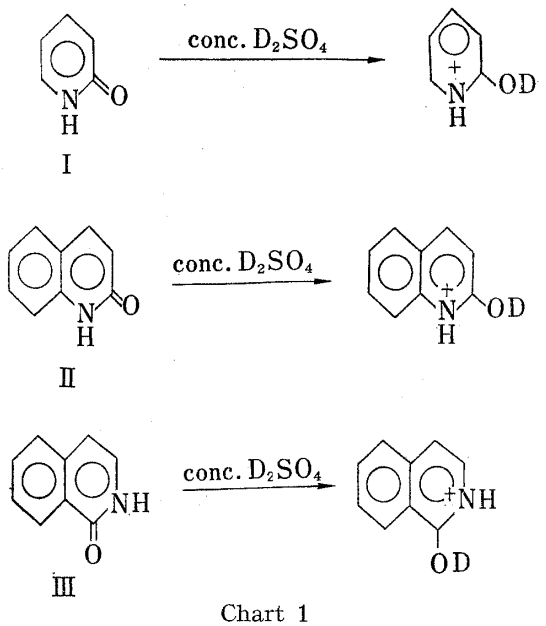

Chart 1

Let us consider the resonance structures of the conjugate acids of these compounds. According to the organic electron theory, it is expected that the strong electron–donating effect of the hydroxyl group and the electron–withdrawing effect of the cationic nitrogen function in these molecules must bring about π–electron localization as shown in Chart 2. Thus, the electrophilic

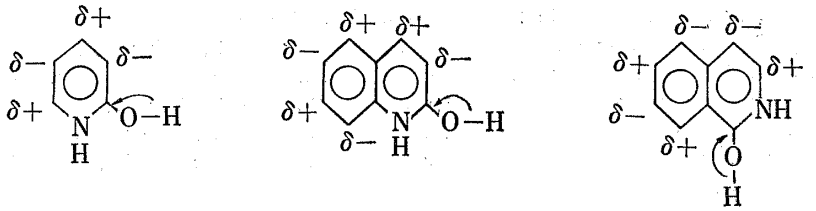

Chart 2

4) A. Binz and H.M. Bode, *Angew. Chem.*, **49**, 486 (1936).
5) A. Kaufmann and P. Peterd, *Ber.*, **50**, 336 (1917).
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substitutions can be expected to occur at the carbons marked by δ– in Chart 2, that is, 3– and 5–positions for 2–pyridinol, 3–, 6–, and 8–positions for 2–quinolinol and 4–, 5–, and 7–positions for 1–isoquinolinol. It is known, as a matter of fact, that nitration of 2–pyridinol gives 3– and 5–mononitro and 3,5–dinitro derivatives,[4] and that 2–quinolinol gives 6–nitro and 3,6,8–trinitro derivatives,[5] and 3,5,6,8–tetrabromo derivative[6] by nitration and bromination, respectively. With regard to 1–isoquinolinol, it is known that bromination occurs at 4–position[7] but its nitration has not yet been reported.[10]

The results of acid–catalyzed deuteration of 2–pyridinol, 2–quinolinol, and 1–isoquinolinol are as follows. The qualitative and quantitative analyses of the deuteration were carried out by inspection of NMR spectra in various kinds of solvents such as chloroform, dimethylsulfoxide, and alkaline or acid water with the help of NMR spectra of their nitro and/or bromo derivatives, the structure of which had already been determined.

Deuteration of 2–Pyridinol

2–pyridinol was deuterated at 120—180° in 23% D_2SO_4 solution to give 3,5–dideuterated derivative as shown in Table I. 4– And 6–positions were proved not to be deuterated below 200°. The positions deuterated were determined by inspection of 3– and 5–nitro derivatives

Table I. Deuteration of 2–Pyridinol in Aqueous 23% D_2SO_4 Solution

Ring hydrogen	Started[a]		Completed[b]	
3–H	120°	4 hr	180°	1 hr
4–H	[c]		[c]	
5–H	120°	4 hr	180°	1 hr
6–H	[c]		[c]	

a) The condition under which hydrogen exchange started.
b) The condition under which hydrogen exchange was completed.
c) The exchange was not observed to start below 200°.

which were derived by nitration of the deuterated derivatives in question. This result agrees with the fact that its nitration occurs at 3– and 5–positions to give two mononitro and 3,5–dinitro derivatives.[4] Any remarkable difference in the deuteration rate could not be observed between 3– and 5–positions. Almost the same results were obtained from the deuteration of N–methyl–2–pyridinol.

Deuteration of 2–Quinolinol

8– and 6–positions are most reactive, followed by 5– and 3–positions, and 7– and 4–hydrogens could not be replaced in 61% D_2SO_4 below 190°, as shown in Table II and Chart 3. The deuterated positions were determined with help of the spectrum of 6–nitro–2–quinolinol.

Table II. Deuteration of 2–Quinolinol in Aqueous 61% D_2SO_4 Solution

Ring hydrogen	Started[a]		Completed[b]	
3–H	140°	1 hr	180°	5 hr
4–H	[c]		[c]	
5–H	140°	1 hr	180°	5 hr
6–H	120°	4 hr	140°	8 hr
7–H	[c]		[c]	
8–H	120°	4 hr	140°	8 hr

a) The condition under which hydrogen exchange started.
b) The condition under which hydrogen exchange was completed.
c) The exchange was not observed to start even at 190°.

10) It was reported that 1–ethoxyisoquinolin gave 5–nitro derivative by an usual nitration procedure.[5]

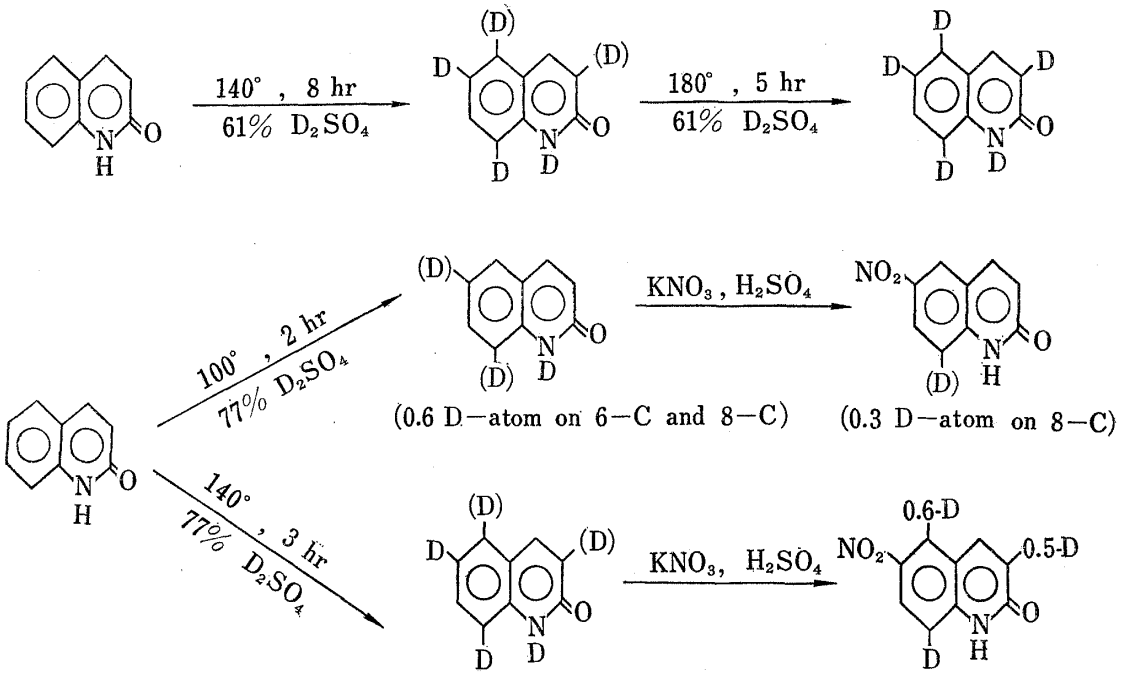

Chart 3

In order to compare the reactivity of these positions with each other in more detail, another experiment was carried out in 77% D_2SO_4. Thus, 2–quinolinol was partly deuterated and the total amount of the deuterium substituted was determined by integration of signals on the NMR spectrum.[11] The partly deuterated 2–quinolinol thus prepared was then nitrated to partly deuterated 6–nitro–2–quinolinol, on the spectrum of which each signal intensity was quantitatively determined. It was revealed that 5–H underwent deuteration slightly faster than 3–H, while no remarkable difference was found between 8–H and 6–H. It can be summarized that the reactivity decreased in the following order of positions:

$$8 \approx 6 > 5 \gtrsim 3 > 7 \approx 4$$

Deuteration of 1–Isoquinolinol

Hydrogen at 4–position of 1–isoquinolinol was preferentially replaced in 61% D_2SO_4 at 100° before all the other hydrogens. This was proved by the fact that the higher doublet of AB type spectrum (due to 3–H and 4–H) disappeared and the other part (due to 3–H) of AB signals, which was further spin–coupled with NH proton, became decoupled. This was supported also by the spectrum of 4–bromo derivative which was prepared from the deuterated 1–isoquinolinol in question with acetic acid and bromine. This fact coincided well with the result of its ready bromination.[7] Then, 1–isoquinolinol was heated in 61% D_2SO_4 at 165° for 3 hr and partly deuterated derivative thus obtained was nitrated with potassium nitrate in 80% H_2SO_4 under ice–cooling to a mixture of mononitro–1–isoquinolinols, from which 5–nitro and another mononitro derivative (mp 253—254°) were isolated by silica–gel column chromatography. The NMR spectrum of 5–nitro derivative showed that 7–H, which gave a triplet signal, was partly deuterated and that 6–H and 8–H were not replaced at all since the signal pattern of the 7–H that remained was unchanged. The signal integration of this compound confirmed the above assignment and also revealed that 1.6 atoms of hydrogen remained in 7– and 2–positions. With regard to the other nitro derivative, two structures of 6–nitro– and 7–nitro–1–isoquinolinols can fit its NMR spectrum which is reproduced in Fig. 1. The signals A, B,

11) As signals due to 5–, 6–, 7–, and 8–protons were overlapped with each other, areal intensity of each signal could not be determined directly.

C, D, and E in the figure can be assigned in two ways; 5–H, 7–H, 8–H, 3–H, and 4–H for 6–nitro–1–isoquinolinol and alternatively, 8–H, 6–H, 5–H, 3–H, and 4–H for 7–nitro one. A–real intensities of signals A, B, C, D, and E of the deuterated derivative were evaluated as 1:1:0.5:1:0 by integration of each signal. Since the NMR spectrum of 5–nitro derivative of this partly deuterated 1–isoquinolinol had already revealed that 8–H remained intact, the former possibility could be excluded. It can, therefore, be concluded that the latter nitro derivative was 7–nitro–1–isoquinolinol and that 50% of 5–H had been replaced with deuterium. Furthermore, since 3–H was proved intact from the spectrum of 7–nitro derivative, it turned out that 60% of the signal due to 7–H remained in the spectrum of 5–nitro derivative, overlapped with that of 3–H.

Then, the 1–isoquinolinol so far deuterated was heated in 61% D_2SO_4 at 180° for 4 hr. The product was proved to be 4,5,7–trideuterio–1–isoquinolinol, its NMR spectrum consisting of three singlets due to 3–, 6–, and 8–hydrogens. Finally, when this trideuterio derivative was heated at 200° for 1 hr in the same acidic medium, 8–H was found to have undergone deuteration and then, 3–H began to be deuterated when heated for 4 hr under the same condition. Qualitative comparison in the deuteration reactivity can now be made of each position in 1–isoquinolinol as follows:

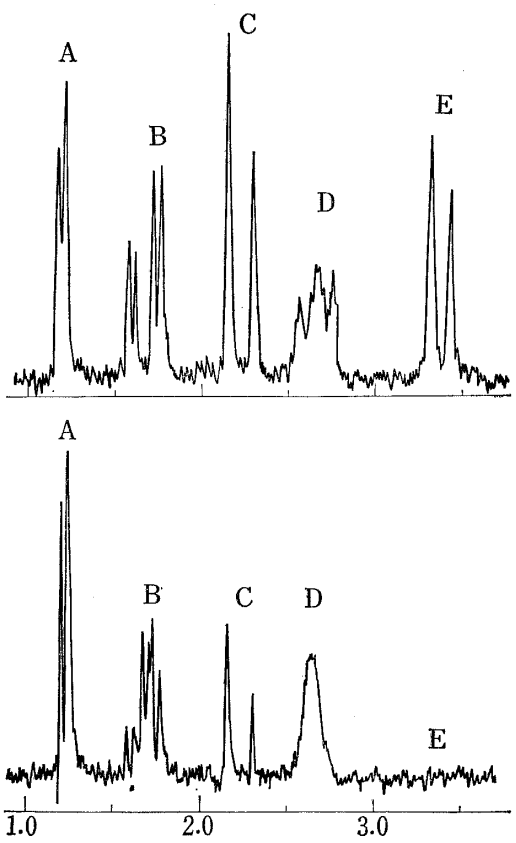

Fig. 1. NMR Spectra of 7–Nitro–1–isoquinolinol and Its Partly Deuterated Derivative measured in DMSO at 23°

Singnal A: 8–H; signal B: 6–H, singal C: 5–H; signal D: 3–H which was furhter coupled with NH proton; signal E: 4–H.
Chemical shift is represented as τ–values calibrated with the internal tetramethylsilane.

$$4>5\gtrsim7>8>3<6$$

Although 4–nitro derivative, in addition to 5– and 7–nitro ones, is expected from the above results to be formed by nitration of 1–isoquinolinol, it has not yet been isolated from

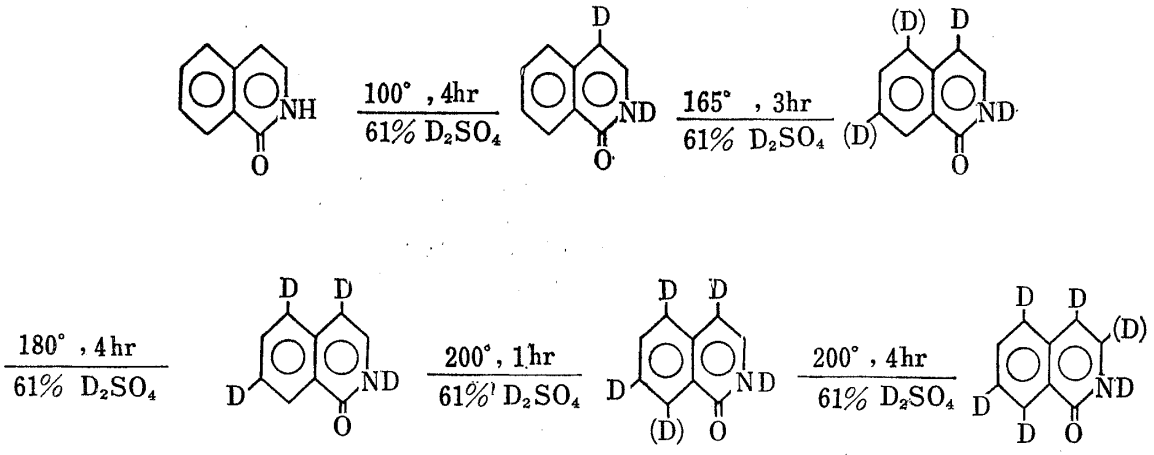

Chart 4

the reaction mixture. It was clearly seen by thin-layer chromatography, however, that the crude product obtaind from the nitration contained another nitro compound in an appreciable amount. This is now under investigation.

It became evident from the above results that the acid-catalyzed deuteration reactions proceed just as predicted by the organic electron theory. Thus, the orientation of deuteration seems to be ruled by π-electron localization as shown in Chart 2 and by the naphthoidal reactivity of α-position of the naphthoid system. These orientations, furthermore, will be discussed from consideration by the molecular orbital calculation in a forthcoming paper.

Experimental

Reagents——Deuterium oxide and conc. D_2SO_4 were purchased from Showa Denko Co., Ltd., the D-atom contents of these reagents being 99.7 and 99.9%, respectively.

Compounds——2-Quinolinol was prepared according to the description by Ochiai, *et al.*[12] and 1-isoquinolinol was obtained by hydrolysis of 1-chloroisoquinolin by 6 hr's heating in 48% H_2SO_4 solution. 2-Pyridinol was purchased from Tokyo Kasei Co., Ltd. Their melting points were 194°, 211°, and 106°, respectively. 3- and 5-nitro-2-pyridinols were prepared with KNO_3 and H_2SO_4,[13] and 6-nitro-2-quinolinol was obtained by the usual nitration at room temperature.[5]

Nitration of 1-Isoquinolinol——One gram of 1-isoquinolinol was dissolved in 6 ml of conc. H_2SO_4 under ice-cooling. To this solution was added 0.84 g of KNO_3 in small portions. After the reaction mixture was kept standing in an ice bath for 2 hr and then left at room temperature overnight, it was poured in ice water. The resulting precipitates were extracted with $CHCl_3$ and the solvent was evaporated under reduced pressure. The residue was put on a silica-gel column and eluted with benzene-AcOEt (1:1) and then AcOEt. After an unknown nitro compound (mp 234—236°) came out first, 500 mg of 5-nitro-1-isoquinolinol was eluted out, which was identified with the authentic sample.[11] Then, 480 mg of 7-nitro-1-isoquinolinol came out, which was recrystallized from acetone. mp 253—254°. *Anal.* Calcd. for $C_9H_6O_3N_2$: C, 56.84; H, 3.17; N, 14.73. Found: C, 56.86; H, 3.43; N, 14.68.

NMR Measurements——The spectra were measured with a JNM-3H-60 spectrometer (Japan Electron Optics Lab. Co.), operating at 60 Mcps at 23°. Sample concentrations for the NMR measurements ranged from 20 mg to 30 mg/0.5 ml of the solvent.

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