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Proton and Carbon-13 Nuclear Magnetic Resonance Chemical Shift Data for Nitroquinolines and Their *N*-Oxides[1]

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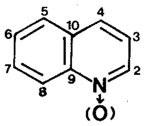
Proton and carbon-13 nuclear magnetic resonance (NMR) spectra of seven positional isomers of nitroquinoline and the corresponding *N*-oxides were taken in $CDCl_3$ and analyzed. The results are presented, and the effect of the *N*-oxide is briefly discussed.

Keywords——nitroquinoline; nitroquinoline 1-oxide; *N*-oxide; NMR; chemical shift; carbon-13; proton

Nitroquinolines and their *N*-oxides are suspected to have genotoxic potency. In fact, 4-nitroquinoline 1-oxide is well known to be a potent carcinogen toward a wide variety of experimental animals and a mutagen in many microorganisms.[2]

Figure 1 shows the structures of quinoline and its *N*-oxide with the atomic numbering. In this paper, we present the chemical shift data for protons and carbons of nitroquinolines and their *N*-oxides in $CDCl_3$. Most of the spectra were taken with a nuclear magnetic resonance (NMR) spectrometer operating at 100 MHz. Assignments of the signals were made with the aid of homonuclear (H↔H) and heteronuclear (H↔C) decoupled spectra. The chemical shifts of nitroquinolines were evaluated by visual inspection of the spectra. Chemical shift evaluation of quinoline, its *N*-oxide, and 3-nitroquinoline *N*-oxide, the spectra of which showed poor resolution, was done with the aid of spectra taken with a 400 MHz spectrometer. The spectra of the series of *N*-oxides were subjected to a computer-assisted simulation but no appreciable differences were found between the visually determined and the simulated values. As regards the accuracy of the data, the chemical shifts of quinoline, its *N*-oxide, and all the nitroquinoline *N*-oxides involve errors of less than 1 Hz, whereas those of the parent nitroquinolines may involve errors of ± 2 Hz. Some of the proton chemical shift data previously reported[3] were revised in the present study.

The list of the chemical shift of the series of nitroquinolines and their *N*-oxides described here may be useful in the fields of quinoline chemistry and NMR spectroscopy. Proton and carbon chemical shift data for a series of amino,[4] alkyl,[5,6] and halogeno[6] derivatives of pyridine, quinoline, and their *N*-oxides[7,8] have already been reported.



Experimental

Materials——All the compounds examined were preparations previously synthesized in our laboratory,[2] except for quinoline and 5-, 6-, and 8-nitroquinolines, which were purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo). No impurities in the preparations were detectable in the NMR spectra.

NMR Spectra——The spectra were obtained at ambient temperature (*ca.* 25 °C) on a JNM MH-100 or a JNM FX-100 spectrometer operating at 100 MHz and some were taken on a JNM GX-400 spectrometer operating at 400 MHz. The solutions examined were *ca.* 5% solutions in $CDCl_3$.

Results and Discussion

Proton Chemical Shifts

Proton chemical shifts of nitroquinolines and their *N*-oxides are shown in Table I. Differences in chemical shifts of protons of the *N*-oxides from those of the corresponding parent nitroquinolines are also given in the same table. A negative sign of the substituent chemical shift (SCS) indicates that an up-field shift is induced. As can be seen in Table I, the SCS values induced by the *N*-oxygenation correspond to large up-field shifts for the 2-H and 4-H resonances, reflecting electron-donating effect of the *N*-oxide group, whereas down-field shifts in 8-H were seen, probably due to the magnetic anisotropy effect. One of the irregular features found in SCS of the *N*-oxide is a shielding effect on 7-H in the 8-nitro isomer, *i.e.*, an up-field shift of 0.26 was observed. This may be due to a severe twist of the 8-nitro group induced by electrostatic repulsion between the $O=N^+\text{–}O^-$ and $N^+\text{–}O^-$ groups. This speculation is supported by the irregular substituent effects at 7-H induced by nitro-substitution at the 8-positions of quinoline and its *N*-oxide, as shown in Table III. Thus, although the down-field shift of the *ortho* protons produced by nitro-substitution ranges from 0.99 to 0.58 ppm in all the other cases, a rather smaller down-field shift of 0.30 ppm was observed for 7-H of 8-nitroquinoline, and, moreover, no appreciable shift was observed for

Table I. Proton Chemical Shifts (ppm from TMS) of Nitroquinolines and Their *N*-Oxides and the Effect of N-Oxygenation on the Proton Chemical Shifts of Each Nitroquinoline[a]

Compound	2-H	3-H	4-H	5-H	6-H	7-H	8-H
Quinoline	8.91	7.37	8.13	7.80	7.53	7.71	8.12
2-Nitro-	—	8.25	8.50	?	7.6—8.1	?	8.28
3-Nitro-	9.63	—	9.01	8.04	7.77	7.98	8.24
4-Nitro-	9.10	7.95	—	8.39	7.77	*ca.* 7.7	8.23
5-Nitro-	9.03	7.63	8.96	—	8.35	7.78	8.39
6-Nitro-	9.11	7.59	8.36	8.79	—	8.47	8.23
7-Nitro-	9.07	7.60	8.30	7.93	8.30	—	9.03
8-Nitro-	9.01	7.53	8.24	8.01	7.59	8.01	—
Quinoline *N*-oxide	8.54	7.30	7.75	7.87	7.64	7.76	8.75
3-Nitro-	9.26	—	8.63	8.14	7.86	8.00	8.79
4-Nitro-	8.50	8.18	—	8.69	7.84	7.84	8.77
5-Nitro-	8.62	7.55	8.46	—	8.45	7.86	9.12
6-Nitro-	8.66	7.48	7.92	8.83	—	8.48	8.94
7-Nitro-	8.63	7.55	7.86	8.09	8.43	—	9.59
8-Nitro-	8.48	7.45	7.82	8.05	7.70	7.75	—
Effect of N-oxygenation[b]							
Quinoline	(−0.37)	(−0.07)	(−0.38)	(+0.07)	(+0.11)	(+0.05)	(+0.63)
3-Nitro-	(−0.37)	—	(−0.38)	(+0.10)	(+0.09)	(+0.02)	(+0.55)
4-Nitro-	(−0.60)	(+0.23)	—	(+0.30)	(+0.07)	?	(+0.54)
5-Nitro-	(−0.41)	(−0.08)	(−0.50)	—	(+0.10)	(+0.08)	(+0.73)
6-Nitro-	(−0.45)	(−0.11)	(−0.44)	(+0.04)	—	(+0.01)	(+0.71)
7-Nitro-	(−0.44)	(−0.05)	(−0.44)	(+0.16)	(+0.13)	—	(+0.56)
8-Nitro-	(−0.53)	(−0.08)	(−0.42)	(+0.04)	(+0.11)	(+0.26)	—

a) Measured in *ca.* 5% $CDCl_3$ solution at room temperature (*ca.* 25 °C). *b)* The value in parentheses is the difference in chemical shift of the proton of the *N*-oxide from that of the corresponding nitroquinoline. The sign — indicates that an up-field shift was induced by N-oxygenation.

TABLE II. Carbon-13 Chemical Shifts (ppm from TMS) of Nitroquinolines and Their *N*-Oxides and the Effect of N-Oxygenation on the Carbon Chemical Shifts of Each Nitroquinoline[a)]

Compound	2-C	3-C	4-C	5-C	6-C	7-C	8-C	9-C	10-C
Quinoline	150.3	121.0	136.0	127.7	126.5	129.4	129.4	148.3	128.3
3-Nitro-	144.0	141.0	132.2	130.0	128.8	133.4	130.0	150.1	126.0
4-Nitro-	150.3	115.1	152.3	122.7	129.8	130.2	130.9	150.0	118.5
5-Nitro-	151.6	123.9	131.8	145.4	124.6	127.4	136.5	148.2	121.1
6-Nitro-	153.8	122.8	137.8	124.6	145.5	122.8	131.3	150.2	127.0
7-Nitro-	152.7	124.0	135.9	129.5	120.0	147.1	125.7	148.0	131.4
8-Nitro-	152.5	122.8	136.2	132.1	125.3	123.6	148.2	139.3	129.0
Quinoline *N*-oxide	135.9	121.0	126.9	128.2	128.9	130.7	119.7	141.3	130.7
3-Nitro-	130.0	144.0	120.7	130.6	130.8	133.9	120.3	142.0	127.7
4-Nitro-	134.0	119.2	140.0	124.6	131.3	131.8	120.1	142.9	122.4
5-Nitro-	136.2	124.1	120.8	146.0	126.6	128.4	126.3	142.4	123.8
6-Nitro-	138.0	123.3	126.4	124.6	147.4	123.5	122.5	143.6	130.0
7-Nitro-	136.9	124.5	124.8	130.3	122.4	148.5	116.9	141.3	133.5
8-Nitro-	137.5	123.0	124.9	131.1	128.0	125.3	143.1	132.1	132.1
Effect of N-oxygenation[b)]									
Quinoline	(−14.4)	(+0.0)	(−9.1)	(+0.5)	(+2.4)	(+1.3)	(−9.7)	(−7.0)	(+2.4)
3-Nitro-	(−14.0)	(+3.0)	(−11.5)	(+0.6)	(+2.0)	(+0.5)	(−9.7)	(−8.1)	(+1.7)
4-Nitro-	(−16.3)	(+4.1)	(−12.3)	(+1.9)	(+1.5)	(+1.6)	(−10.8)	(−7.1)	(+3.9)
5-Nitro-	(−15.4)	(+0.2)	(−11.0)	(+0.6)	(+2.0)	(+1.0)	(−10.2)	(−5.8)	(+2.7)
6-Nitro-	(−15.8)	(+0.5)	(−11.4)	(+0.0)	(+1.9)	(+0.7)	(−8.8)	(−6.6)	(+3.0)
7-Nitro-	(−15.8)	(+0.5)	(−11.1)	(+0.8)	(+2.4)	(+1.4)	(−8.8)	(−6.7)	(+2.1)
8-Nitro-	(−15.0)	(+0.2)	(−11.3)	(+1.0)	(+2.7)	(+1.7)	(−5.1)	(−7.2)	(+3.1)

a) Measured in *ca.* 5% $CDCl_3$ solution at room temperature (*ca.* 25 °C). *b*) The value in parentheses is the difference in chemical shift of the carbon of the *N*-oxide from that of the corresponding nitroquinoline. The sign — indicates that an up-field shift was induced by N-oxygenation.

TABLE III. The Substituent Chemical Shift (SCS) of the Nitro Group on Proton Chemical Shifts in Each Derivative (a Positive Value Indicates a Down-Field Shift)

Substituent	2-H	3-H	4-H	5-H	6-H	7-H	8-H
Quinoline	0.00 (δ=8.91)	0.00 (δ=7.37)	0.00 (δ=8.13)	0.00 (δ=7.80)	0.00 (δ=7.53)	0.00 (δ=7.71)	0.00 (δ=8.12)
2-Nitro	—	+0.88	+0.37	?	?	?	+0.16
3-Nitro	+0.72	—	+0.88	+0.24	+0.24	+0.27	+0.12
4-Nitro	+0.19	+0.58	—	+0.59	+0.24	?	+0.11
5-Nitro	+0.12	+0.26	+0.83	—	+0.82	+0.07	+0.27
6-Nitro	+0.20	+0.22	+0.23	+0.99	—	+0.76	+0.11
7-Nitro	+0.16	+0.23	+0.17	+0.13	+0.77	—	+0.91
8-Nitro	+0.10	+0.16	+0.11	+0.21	+0.06	+0.30	—
Quinoline *N*-oxide	0.00 (δ=8.54)	0.00 (δ=7.30)	0.00 (δ=7.75)	0.00 (δ=7.87)	0.00 (δ=7.64)	0.00 (δ=7.76)	0.00 (δ=8.75)
3-Nitro	+0.72	—	+0.88	+0.27	+0.22	+0.24	+0.04
4-Nitro	−0.04	+0.88	—	+0.82	+0.20	+0.08	+0.02
5-Nitro	+0.08	+0.25	+0.71	—	+0.81	+0.10	+0.37
6-Nitro	+0.12	+0.18	+0.17	+0.96	—	+0.72	+0.19
7-Nitro	+0.09	+0.25	+0.11	+0.22	+0.79	—	+0.84
8-Nitro	−0.06	+0.15	+0.07	+0.18	+0.06	−0.01	—

TABLE IV. The Substituent Chemical Shift of the Nitro Group on Carbon Chemical Shifts in Each Derivative (a Positive Value Indicates a Down-Field Shift)

Substituent	2-C	3-C	4-C	5-C	6-C	7-C	8-C	9-C	10-C
Quinoline	0.0 ($\delta=150.3$)	0.0 ($\delta=121.0$)	0.0 ($\delta=136.0$)	0.0 ($\delta=127.7$)	0.0 ($\delta=126.5$)	0.0 ($\delta=129.4$)	0.0 ($\delta=129.4$)	0.0 ($\delta=148.3$)	0.0 ($\delta=128.3$)
3-Nitro	−6.0	+20.0	−3.8	+2.3	+2.3	+4.0	+0.6	+1.8	−2.3
4-Nitro	0.0	−6.0	+16.3	−5.0	+3.3	+0.8	+1.5	+1.7	−9.8
5-Nitro	+1.6	+2.9	−4.2	+17.7	−1.9	−2.0	+7.1	−0.1	−7.2
6-Nitro	+3.8	+1.8	+1.8	−3.1	+19.0	−6.6	+1.9	+1.9	−1.3
7-Nitro	+2.7	+3.0	−0.1	+1.8	−6.5	+17.7	−3.7	−0.3	+3.1
8-Nitro	+2.5	+1.8	−0.2	+4.4	−1.2	−5.8	+18.8	−9.0	+0.7
Quinoline *N*-oxide	0.0 ($\delta=135.9$)	0.0 ($\delta=121.0$)	0.0 ($\delta=126.9$)	0.0 ($\delta=128.2$)	0.0 ($\delta=128.9$)	0.0 ($\delta=130.7$)	0.0 ($\delta=119.7$)	0.0 ($\delta=141.3$)	0.0 ($\delta=130.7$)
3-Nitro	−5.9	+23.0	−6.2	+2.4	+1.9	+3.2	+0.6	+0.7	−3.0
4-Nitro	−1.9	−1.8	+13.1	−3.6	+2.4	+1.1	+0.4	+1.6	−8.3
5-Nitro	+0.3	+3.1	−6.1	+17.8	−2.3	−2.3	+6.6	+1.1	−6.9
6-Nitro	+2.1	+2.3	−0.5	−3.6	+18.5	−7.2	+2.8	+2.3	−0.7
7-Nitro	+1.0	+3.5	−2.1	+2.1	−6.5	+17.8	−2.8	0.0	+2.8
8-Nitro	+1.6	+2.0	−2.0	+2.9	−0.9	−5.4	+23.4	−9.2	+1.4

that of 8-nitroquinoline *N*-oxide. This may mean that the electron-withdrawing effect and anisotropy effect of the 8-nitro group are reduced by twisting out of the aromatic plane due to repulsion between the $O=N^+–O^-$ and ring-N lone pair electrons in 8-nitroquinoline and between the $O=N^+–O^-$ and $N^+–O^-$ groups in its *N*-oxide.

Carbon-13 Chemical Shifts

Chemical shifts data are shown in Table II, which also lists the SCS induced by the *N*-oxygenation of nitroquinolines. The *N*-oxygenation produces large up-field shifts in 2-C, 4-C, and also in 8-C and 9-C. The up-field shift of 8-C may be rationalized by assuming that the negatively charged *N*-oxide group produces a shielding effect on 8-C through its electron-repulsive effect toward 8-hydrogen. As has been already reported,[7,8] the conversion to the *N*-oxide results in an up-field shift for the carbons *ortho* and *para* to the nitrogen and the sum of the shifts for these carbons is known to be about 30 ppm for the derivatives previously examined, *i.e.*, alkyl and chloro derivatives of pyridine, quinoline, and isoquinoline. As can be seen in Table II, the sums of the shifts induced in the 2-, 4-, and 9-carbons are 30.5 ppm for quinoline, 32.2—33.8 ppm for 3-, 5-, 6-, 7-, and 8-nitroquinolines, and 35.7 ppm for the 4-nitro isomer. The slightly larger shifts thus induced in the nitro derivatives suggest that the electron-withdrawing nature of the nitro group may enhance the electron-donating resonance effect of the *N*-oxide group; the nitro group at the 4-position showed the greatest effect among all the nitro isomers.

The substituent effects of the nitro group are shown in Table IV. Profound down-field shifts were produced in the *ipso* carbons to the nitro group and medium sized up-field shifts were produced in the *ortho* carbons.

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