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# Intramolecular hydrogen bonding in 8-quinolinol *N*-oxides, quinaldinic acid *N*-oxides and quinoline-2-carboxyamide *N*-oxide. Deuterium isotope effects on $^{13}C$ chemical shifts

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**Abstract**

Secondary isotope effects on $^{13}C$ chemical shifts have been measured in a series quinolinols, quinaldinic acid *N*-oxides and quinoline-2-carboxyamide *N*-oxide. For 8-quinolinol *N*-oxides a good correlation was found between δOH and $^{n}\Delta C(OD)$ isotope effects. The OH and $^{13}C$ chemical shifts and $^{n}\Delta C(OD)$ show very small temperature dependences. The primary isotope effects are small, positive and temperature insensitive. Furthermore, they increase with increasing $^{n}\Delta C(OD)$. All features point towards a localised hydrogen bond in an asymmetric double well potential.

The quinaldinic acid *N*-oxides show long-range isotope effects on $^{13}C$ chemical shifts of both signs with $^{2}\Delta C{=}O(OD)$ rather small. The primary isotope effects of the quinaldinic acid *N*-oxide is of order of 0.5 ppm, whereas for its 4-ethoxy-derivative is smaller, ~0.3 ppm. The OH chemical shifts resonate at the low field ~18–20 ppm and the OH resonance is fairly broad at room temperature, especially for the 4-ethoxy-derivative. The temperature effects on the chemical shifts, primary and secondary isotope effects are small. For quinaldinic acid *N*-oxides the asymmetric broad quasi-single potential is suggested.

For quinoline-2-carboxyamide *N*-oxide the isotope effects are small, indicating rather weak hydrogen bond © 1997 Elsevier Science B.V.

*Keywords:* Strong hydrogen bonds; Secondary deuterium isotope effects on $^{13}C$ chemical shifts; Primary deuterium isotope effects; Hydrogen bond potentials; 8-Quinolinol *N*-oxides; Quinaldinic acid *N*-oxides

## 1. Introduction

The intramolecular hydrogen bonds in heterocyclic *N*-oxides, such as 8-quinolinol *N*-oxides and quinaldinic acid *N*-oxides have attracted much interest, as they are medium strength up to strong and of resonance assisted type [1–7]. Such type of hydrogen bonds influence considerably the physical, chemical and biological properties of organic compounds [8]. Proton transfer processes in medium and strong hydrogen bond have been proposed to play a special role in enzyme catalysis and other biological processes [8,9]. The dynamic properties of hydrogen bond are determined by the shape of proton potential. This potential can roughly be divided into three types (Fig. 1): the asymmetric two-well potential, where the

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Dedicated to Professor H. Ratajczak on his 65th birthday.


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Fig. 1. Typical hydrogen bond potential wells.

proton is positioned on the proton-donor atom (Fig. 1(A)); the two well potential with a low barrier, where the proton transfer is possible (Fig. 1(B)) and one-well potential (for the shortest hydrogen bridge) (Fig. 1(C)). The last two system can be symmetric or asymmetric. In the case of resonance assisted intramolecular hydrogen bond with large amplitude of proton vibration the differentiation between these systems may be difficult [8].

For 8-quinolinol *N*-oxides and quinaldic acid *N*-oxides the form of hydrogen bond potential has been discussed, however the conclusions have not been equivocal [2–7,11]. The X-ray structure of 8-quinolinol *N*-oxide (**1**) shows a short (2.48 Å) nonlinear hydrogen bond [1]. Ghuge et al. [2] have suggested the presence of asymmetrical hydrogen bond in 8-quinolinol *N*-oxide and its several 5-substituted derivatives and the nearly symmetrical one for 5,7-di-nitro- and 5,7-dichloro-derivatives in solid state. Brzeziński and Zundel [3], based on $^{1}$H NMR studies in acetonitrile solution, have proposed for **1** an equilibrium: OH...ON = $O^{-}$...$^{+}$HON, with a longer residence time of the proton at the CO group than at NO group.

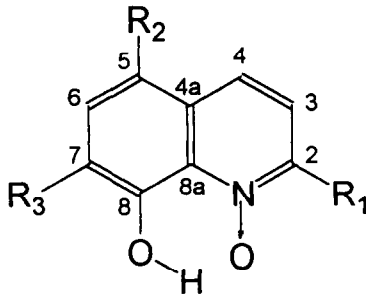
For quinaldinic acid *N*-oxide and its 4-substituted derivatives the existence of strong intramolecular hydrogen bond has been evidenced on the basis of IR [7] and $^{1}$H NMR [6] studies, and the double minimum potential implying tautomerism has been suggested. The signals of the OH proton have been observed at very low field, ~18.7 ppm for quinaldinic acid *N*-oxide and 19.6 ppm for its 4-diethylamino-derivative. For the similar compounds, picolinic acid *N*-oxides, the double well [6,10] has been suggested. However, recently Szafran et al. [11] have proposed an asymmetric quasi-single for picoline acid *N*-oxides and several 4-substituted derivatives. The picolinic acid *N*-oxide and its 6-methyl derivative have very short O...O distance in the crystal (2.39 Å [12] and 2.41 Å [13]). The short distance may result in a single well potential [11]. As can be seen, it is very difficult to find an exact answer to the problem of the type intramolecular hydrogen potential for heterocyclic *N*-oxides.

The deuterium primary isotope effect and the secondary isotope effect on the $^{13}$C NMR spectra have shown promise in distinguishing between the hydrogen bonds with double- and single-minimum proton potential [14–20]. An important feature in this respect is to observe an array of data, e.g. both chemical shifts and deuterium isotope effects on these at different temperatures [20].

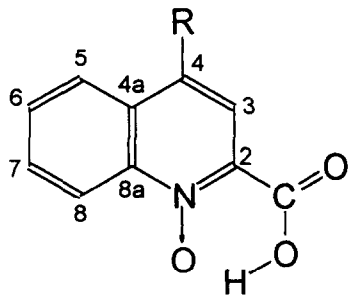
In the present study we have undertaken the investigation of the deuterium primary and secondary isotope effect for 8-quinolinol *N*-oxide and series of its 2-, 5- and 7-substituted or di-substituted derivatives as well quinaldinic acid *N*-oxide and its 4-substituted derivative. In Scheme 1 the structures of heterocyclic *N*-oxides **1–13** investigated in this study are shown. A very important feature of the present compounds is the more or less fixed distance between the heteroatoms of the hydrogen bond donor and acceptor. This is different from intermolecular complexes between phenol and amines, in which this distance can be envisaged to change with hydrogen bond strength.

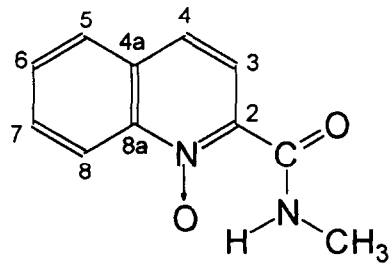
## 2. Assignments

The assignment of the $^{13}$C spectrum of 8-quinolinol *N*-oxide **1** is based on the values of 8-quinolinol [21] and effect of the *N*-oxide formation, obtained from a comparison of the $^{13}$C NMR spectra of quinoline *N*-oxide and quinoline [22], or alternatively from the chemical shifts of quinoline *N*-oxide [22] and the substituent effect of the 8-hydroxy group, as evaluated from 1-naphthol compared with the chemical shift



(1) $R_1, R_2, R_3 = H$
(2) $R_1, R_3 = H$ ; $R_2 = NO_2$
(3) $R_1 = H$ ; $R_2, R_3 = Br$
(4) $R_1, R_3 = H$ ; $R_2 = N_2$-Ph
(5) $R_1 = Me$ ; $R_2, R_3 = H$
(6) $R_1, R_3 = H$ ; $R_2 = Cl$
(7) $R_1 = CONHCH_3$ ; $R_2, R_3 = H$
(8) $R_1 = H$ ; $R_2, R_3 = I$
(9) $R_1 = H$ ; $R_2, R_3 = NO_2$





(10) R = H
(11) R = $OC_2H_5$
(12) R = $CH_3$

(13)

Scheme 1.

of naphthalene [23] (Table 1). For the substituted quinolinols (**2–9**) three different approaches are available, one starting with the substituted quinolinol [21], one starting with the substituted quinoline *N*-oxide [22] and one starting with **1** and the substituent effect [23,24]. The latter approach is seen to give the best agreement, probably as this is based on addition of the smaller perturbation. None of these methods is perfect for two reasons: the general lack of additivity as observed for substituted pyridine *N*-oxides and the fact that anisotropy effects are not taken into account in the first approach.

The quinaldinic acid *N*-oxide (**10**) are assigned based on the data for quinoline *N*-oxide and the substituent effect of the carboxylic group derived from data for naphthalene-2-carboxylic acid compared with naphthalene [23] (Table 2). The chemical shifts of C-4 and C-5 are close, but the assignments are confirmed by comparison with those of 4-methylquinaldinic acid *N*-oxide (**12**). The spectrum of quinoline-2-carboxyamide (**13**) is assigned in the same manner, based on data for the quinoline-2-carboxyamide [25] and the effect of the N–O group [22] (Table 2).

Deuteration is achieved by treatment of the compounds with a mixture of $CH_3OH$:$CH_3OD$ [26]. The procedure was not always successful and least so for compounds with low field OH resonances (see below). The assignment of resonances belonging to the protio vs. deuterio species is done by varying the ratio $CH_3OH$:$CH_3OD$.

## 3. Results

Deuterium isotope effect have been measured from one tube experiments. The primary isotope effect is

Table 1
Assignment of the $^{13}C$ NMR spectra of 8-quinolinol-*N*-oxide (**1**) (ppm)

| | 8-OH-Q [a] | ΔN → O [b] | 8-OH-Q(NO) (calculated) | Q(NO) [c] | ΔOH [d] | 8-OH-Q(NO) (calculated) | 8-OH-Q(NO) (experimental) |
|---|---|---|---|---|---|---|---|
| C-2 | 148.20 | −14.40 | 133.80 | 135.90 | −0.57 | 135.33 | 134.46 |
| C-3 | 121.90 | 0.00 | 121.90 | 121.00 | 0.57 | 121.57 | 120.41 |
| C-4 | 136.20 | −9.10 | 127.10 | 126.90 | −0.25 | 126.65 | 129.58 |
| C-5 | 117.90 | 0.50 | 118.40 | 128.20 | −7.17 | 121.03 | 116.75 |
| C-6 | 127.70 | 2.40 | 130.10 | 128.90 | −0.04 | 128.86 | 130.62 |
| C-7 | 111.50 | 1.30 | 112.80 | 130.70 | −17.09 | 113.61 | 114.91 |
| C-8 | 153.50 | −9.70 | 143.80 | 119.70 | 23.27 | 142.67 | 154.12 |
| C-8a | 138.70 | −7.00 | 131.70 | 141.30 | −9.15 | 132.15 | 132.33 |
| C-4a | 129.00 | 2.40 | 131.40 | 130.70 | 1.23 | 131.93 | 130.04 |

[a] Values from Ref. [21].
[b] Values ΔN → O are calculated from the values of quinoline *N*-oxide and quinoline Ref. [22].
[c] Values for Q(NO) from Ref. [23].
[d] Values of ΔOH are calculated from values 1-hydroxynaphthalene and naphthalene [20].

defined as $^{p}\Delta = \delta H - \delta D$. The secondary isotope effects upon $^{13}C$ nuclear shieldings are defined as a $^{n}\Delta C(D) = \delta C(H) - \delta C(D)$ [17]. The observed isotopic effect for compounds **1–13** are given in Tables 4, 5, and 7. The signs of the isotope effect are obtained by the registration of the $^{13}C$ NMR spectra of compounds with different levels of deuteration. In some instances the temperature had to be lowered to obtain sharp OH resonance and to observe deuterium isotope effect at $^{13}C$ chemical shifts.

### *3.1. 8-quinolinol N-oxides*

The OH chemical shifts of the OH group of 8-quinolinol *N*-oxides (**1**) and its derivatives (**2–9**) are given in Table 3 and are seen to be at high frequency. These values depend on substituents and somewhat on solvent (Table 3). The highest frequency (20.38 ppm in $CDCl_3$) has been found for **9**; it shifts to a lower frequency in DMSO-$d_6$.

$^{13}C$ chemical shifts are given in Table 3. The

Table 2
Assigment at the $^{13}C$ NMR spectra 2-quinaldinic acid *N*-oxide (**10**) and 2-quinolinecarboxyamide *N*-oxide (**13**) in $CDCl_3$ (ppm)

| | 10 | | | | 13 | | | |
|---|---|---|---|---|---|---|---|---|
| | Q(NO) [a] | ΔCOOH [b] | 2-COOH-Q(NO) | | $QCONHCH_3$ [c] | ΔNO [d] | $Q(NO)CONHCH_3$ | |
| | | | (calculated) | (experimental) | | | (calculated) | (experimental) |
| C-2 | 135.9 | +1.68 | 137.58 | 134.71 | 150.25 | −14.40 | 134.85 | 137.48 |
| C-3 | 121.0 | −1.27 | 119.73 | 119.78 | 118.47 | 0.00 | 118.47 | 120.63 |
| C-4 | 126.9 | −0.38 | 126.52 | 130.19 | 137.60 | −9.10 | 128.50 | 126.30 |
| C-5 | 128.2 | −0.87 | 127.33 | 128.50 | 127.94 | 0.50 | 128.44 | 128.19 |
| C-6 | 128.9 | +1.69 | 130.59 | 131.03 | 127.79 | 2.40 | 130.19 | 129.68 |
| C-7 | 130.7 | +0.21 | 130.91 | 132.66 | 130.27 | 1.30 | 131.57 | 130.98 |
| C-8 | 119.7 | +0.71 | 120.43 | 122.36 | 129.07 | −9.70 | 119.37 | 122.66 |
| C-8a | 141.3 | −2.12 | 139.18 | 139.23 | 146.01 | −7.00 | 139.01 | 141.76 |
| C-4a | 130.7 | +0.64 | 131.34 | 131.25 | 128.60 | 2.40 | 131.00 | 130.72 |
| C=O | | | | 161.79 | 164.45 | – | – | 161.13 |
| $-CH_3$ | | | | | 26.02 | – | – | 26.31 |

[a] Values for Q(NO) from Ref. [22].
[b] Values ΔCOOH are calculated from the values 2-COOH-naphthalene and naphthalene as described in Ref. [23].
[c] Values for $QCONHCH_3$ from Ref. [25].
[d] Values ΔNO are calculated from values quinoline *N*-oxide and quinoline as described in Ref. [22].

Table 3
Chemical shifts of 8-quinolinol-*N*-oxides (**1–9**) (ppm)

| Compound | **1** | | | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Solvent | $CDCl_3$ | $CD_2Cl_2$ | DMSO | $CDCl_3$ | $CDCl_3$ | $CDCl_3$ | $CD_2Cl_2$ | $CDCl_3$ | $CDCl_3$ | $CD_2Cl_2$ | DMSO |
| C-2 | 134.46 | 134.93 | 135.56 | 133.98 | 135.25 | 135.12 | 145.22 | 133.92 | 132.56 | 135.67 | |
| C-3 | 120.41 | 121.05 | 121.86 | 122.86 | 121.60 | 121.69 | 123.27 | 120.24 | 122.37 | 122.72 | |
| C-4 | 129.58 | 129.84 | 130.45 | 125.81 | 129.70 | 126.20 | 128.99 | 125.59 | 129.78 | 129.07 | |
| C-5 | 116.75 | 117.10 | 117.30 | – | 107.80 | 138.36 | 116.96 | 118.04 | 117.24 | 83.85 | |
| C-6 | 130.62 | 130.85 | 130.63 | 130.42 | 137.18 | 117.79 | 129.86 | 129.70 | 131.58 | 148.48 | |
| C-7 | 114.91 | 114.81 | 114.27 | 112.15 | 108.50 | 114.74 | 114.80 | 113.69 | 116.08 | 82.21 | |
| C-8 | 154.12 | 154.60 | 153.41 | 160.77 | 151.51 | 158.10 | 154.37 | 152.37 | 154.04 | 154.92 | 162.0 |
| C-8a | 132.33 | 132.82 | 132.24 | – | 130.51 | 130.63 | – | – | – | 135.09 | |
| C-4a | 130.04 | – | 128.94 | – | 130.04 | 120.82 | – | 128.66 | – | 132.82 | |
| OH | 15.06 | 15.19 | 15.52 | 17.18 | 16.44 | 16.00 | 15.55 | 15.25 | 14.14 [b] | – | 17.81 [c] |

[a] Chemical shifts of carbons of the phenyl ring: C-1′ = 153.19 ppm; C-2′ = 122.98 ppm; C-3′ = 129.36 ppm; C-4′ = 131.08 ppm.
[b] The NH chemical shift is 10.50 ppm at 300 K and 10.65 ppm at 250 K, C=O = 160.00 ppm; $-CH_3$ = 26.48 ppm.
[c] The chemical shift in $CDCl_3$ = 20.38 ppm at 300 K. In $CD_2Cl_2$ = 20.87 at 250 K and 21.02 at 220 K.

predictions using substituent effects are not perfect illustrating the mutual interaction of substituents. This also means that $^{13}C$ chemical shift are less useful as gauges of tautomeric vs. non-tautomeric situations. For **9** owing to low solubility, the chemical shifts are only partly available in DMSO-$d_6$.

The deuterium isotope effect $^{13}C$ chemical shifts are given in Table 4. The two bond isotope effect $^2\Delta C(OD)$ are positive and large. The long range isotope effect at C-4 are also large. Plots of $^4\Delta$C-6(OD), $^5\Delta$C-5(OD), $^3\Delta$C-7(OD) and $^2\Delta$C-8(OD) vs. δOH are reasonably linear for these carbons (Fig. 2). For **1** pairs of values for other solvents are likewise seen fall on the same line.

The spectra were recorded at various temperatures: for **1** in the interval 300–203 K; for **7** at 250–300 K. The $^{13}C$ chemical shifts do not vary much (Table 5). The OH chemical shifts show slight increase with the lowering the temperature.

The isotope effect on $^{13}C$ chemical shift (Table 5) are seen to be invariant with temperature except for C-4, which show a slightly smaller values with the lowering of temperature despite of that fact that δOH increases from 15.19 to 15.39 ppm with the same temperature decrease.

Table 4
Primary, $^p\Delta$ and secondary, $^n\Delta C(OD)$, isotope effects of 8-quinolinol-*N*-oxides (**1–7**) at 300 K (ppm)

| Compound | **1** | | | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|---|---|---|
| Solvent | $CDCl_3$ | $CD_2Cl_2$ | DMSO | $CDCl_3$ | $CDCl_3$ | $CDCl_3$ | $CD_2Cl_2$ | $CDCl_3$ | $CDCl_3$ |
| C-2 | −0.127 | −0.118 | −0.102 | −0.217 | −0.175 | −0.156 | ≈0 | −0.112 | ±0.08(br) [b] |
| C-3 | −0.035 | −0.035 | −0.027 | ≈0 | −0.050 | −0.030 | ≈0 | ≈0 | ≈0 |
| C-4 | +0.158 | +0.181 | +0.199 | +0.412 | +0.260 | +0.273 | +0.183 | +0.171 | +0.126 |
| C-5 | −0.192 | −0.203 | −0.233 | – | −0.328 | ≈0 | −0.216 | +0.198 | −0.126 |
| C-6 | +0.066 | +0.068 | +0.060 | +0.173 | +0.051 | +0.122 | +0.052 | ≈0 | +0.043 |
| C-7 | +0.074 | +0.071 | +0.060 | +0.114 | +0.101 | +0.103 | +0.053 | ≈0 | +0.069 |
| C-8 | +0.356 | +0.374 | +0.399 | +0.642 | +0.438 | +0.487 | +0.373 | +0.364 | +0.277 |
| C-8a | +0.012 | −0.018 | −0.010 | – | – | – | – | – | +0.081 |
| C-4a | – | – | – | – | – | – | – | – | ≈0 |
| Me | | | | | | | | | (+0.133) [b] |
| −C=O | | | | | | | | | +0.096(+0.029) [b] |
| $^p\delta$ | | 0.25 [a] | | | 0.43 [a] | | | | 0.17c |

[a] Similar values at 250 and 220 K.
[b] The numbers in brackets are due to deuteration at the NH. br means broad.
[c] The $^p\delta NH = 0.01 \pm 0.01$ ppm.

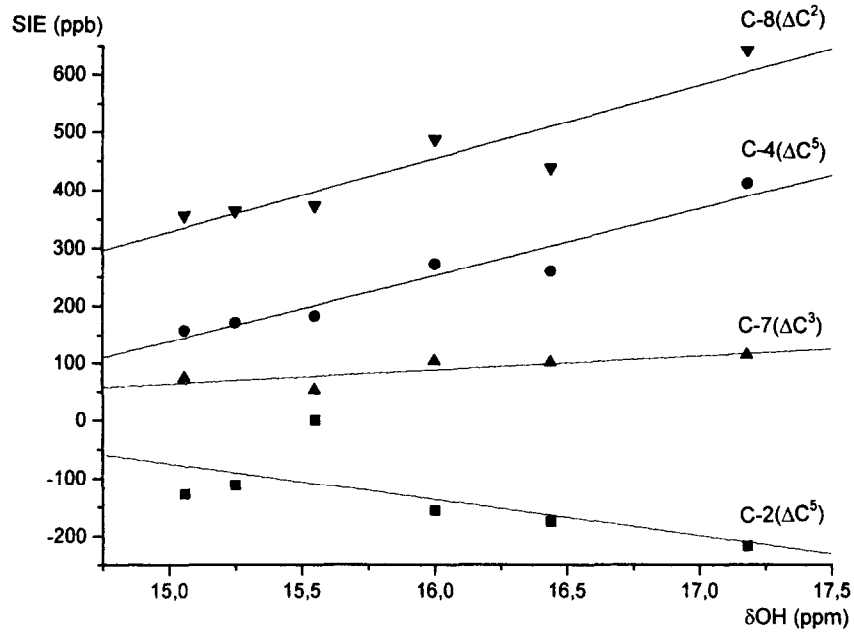



Fig. 2. Plot of $^{n}\Delta C(OD)$ vs. δOH for 8-quinolinol *N*-oxide.

For **7** an isotope effect of −0.019 ppm is seen at the OH resonance owing to deuteration at NH. The reverse effect is not resolved as the NH resonance is broad.

The primary isotope effect have been measured for **1**, **3** and **7**. They are small, ~0.2–0.4 ppm, and largely temperature independent (Table 4). A plot of $^{p}\Delta$ vs. δOH shows a linear relationship. This correlation line is shifted towards lower $^{p}\Delta$ values as compared with that obtained for β-diketones [14,16] (Fig. 3).

### 3.2. *Quinaldinic acid N*-oxides

The proton chemical shifts of the OH group are to very high frequency 18–20 ppm (Table 6). The compounds had to be cooled to obtain sharp OH resonance and to be able to measure the deuterium isotope effects on $^{13}C$ chemical shifts. They showed some temperature and solvent dependence. The $^{13}C$ chemical shifts of **10** show weak but consistent solvent dependence most clearly at C-2, C-3, C-4 and C=O carbons (Table 6).

Table 5
Temperature effects on $^{n}\Delta C(OD)$ isotope effects (ppm) and chemical shifts (ppm $K^{-1}$) of **1** and **7** in $CD_2Cl_2$

| | **1** | | | | | | **7** | | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{n}\delta C(OD)$ | | | | | $\Delta\sigma/\Delta T \times 10^{-3}$ | $^{n}\delta C(OD)$ | | $\Delta\sigma/\Delta T \times 10^{-3}$ |
| Temperature | 300 K | 270 K | 250 K | 230 K | 203 K | | 300 K | 250 K | |
| C-2 | −0.118 | −0.126 | −0.123 | −0.119 | −0.121 | 3.6 | ≈0 | | 5.0 |
| C-3 | −0.035 | −0.034 | −0.034 | −0.031 | −0.033 | 4.6 | – | – | – |
| C-4 | +0.181 | +0.174 | +0.170 | +0.168 | +0.165 | – | +0.126 | +0.099 | 6.4 |
| C-5 | −0.203 | −0.202 | −0.200 | −0.200 | −0.204 | 5.2 | −0.126 | −0.121 | 3.0 |
| C-6 | +0.068 | +0.065 | +0.067 | +0.062 | +0.062 | – | +0.043 | +0.039 | 0 |
| C-7 | +0.071 | +0.071 | +0.074 | +0.076 | +0.077 | 8.7 | +0.069 | +0.074 | 1.2 |
| C-8 | +0.374 | +0.373 | +0.372 | +0.370 | +0.374 | 15.0 | +0.277 | +0.277 | 10 |
| C-8a | −0.018 | – | −0.019 | – | – | 12.1 | +0.081 | +0.066 | 9.6 |
| C-4a | – | – | – | – | – | 14.7 | ≈0 | ≈0 | 7.8 |
| OH | 15.19 | 15.26 | 15.31 | 15.35 | 15.39 | | 14.15 | 14.28 | |

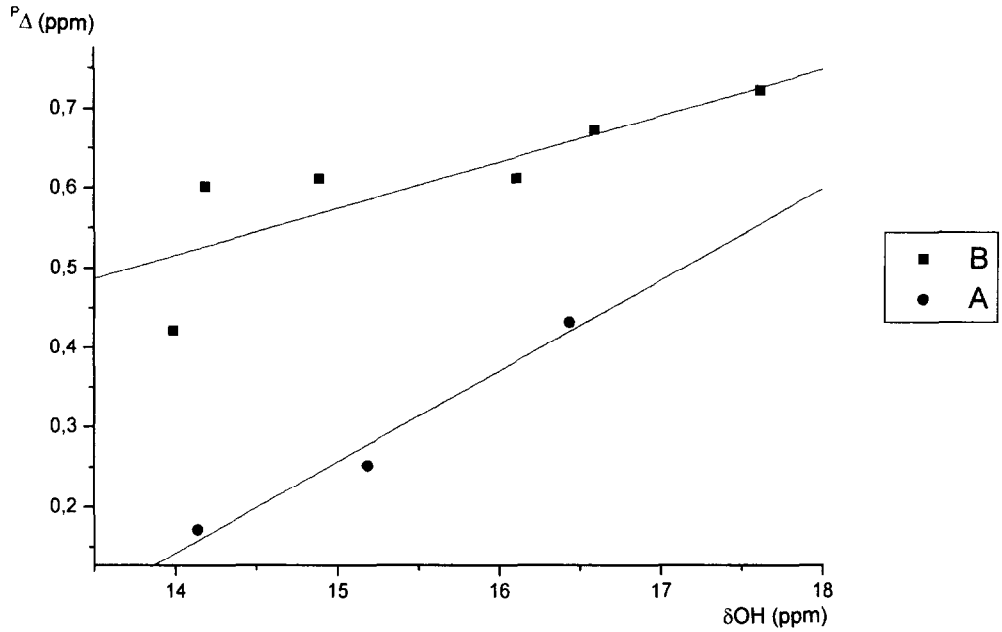



Fig. 3. Plot of primary isotope effects vs.δOH, β-diketones from Refs. [14,16] (■), 8-quinolinol *N*-oxides (●).

The deuterium isotope effect on the $^{13}C$ chemical shifts are given in Table 7. The pattern of isotope shifts is clearly different from that of 8-quinolinol *N*-oxides. The most important is observed at C-4; the isotope effect at the carboxyl carbon is remarkably small (0.12 ppm) compared with simple carboxylic acids (0.2 ppm) [17].

The primary isotopic effect of **10** and **12** are ~0.45 ppm, whereas that for **11** is 0.32 at 230 K. It is to be noted that the OH chemical shifts of the latter

Table 6
$^{13}C$ chemical shifts of quinaldinic acid *N*-oxides (**10–12**) (ppm)

| | **10** | | | | | | **11** | **12** |
|---|---|---|---|---|---|---|---|---|
| Solvent | $CD_2Cl_2$ | | | $CDCl_3$ | | | $CD_2Cl_2$ | $CDCl_3$ [b] |
| Temperature | 300 K | 250 K | 230 K | 300 K | 250 K | 230 K | 230 K | 250 K |
| C-2 | 135.15 | 134.80 | 134.67 | 134.71 | – | 134.02 | 136.41 | 133.24 |
| C-3 | 119.82 | 119.68 | 119.49 | 119.78 | 119.48 | 119.37 | 101.10 | 119.71 |
| C-4 | 130.91 | 131.44 | 131.59 | 131.19 | 130.80 | 131.06 | 158.39 | 140.65 |
| C-5 | 129.00 | 129.05 | 129.08 | 128.50 | 128.52 | 128.55 | 123.44 | 124.97 |
| C-6 | 131.37 | 131.44 | 131.48 | 131.03 | 131.14 | 131.19 | 130.27 | 130.68 |
| C-7 | 133.11 | 133.29 | 133.37 | 132.66 | 132.88 | 132.99 | 133.41 | 132.27 |
| C-8 | 122.52 | 122.38 | 122.31 | 122.36 | 122.12 | 122.03 | 119.02 | 122.14 |
| C-8a | 139.57 | 139.46 | 139.31 | 139.23 | – | 138.47 | 138.22 | 137.67 |
| C-4a | 131.71 | – | – | 131.25 | – | – | 123.21 | 130.41 |
| CO | 162.04 | 162.26 | 162.35 | 161.79 | – | – | 162.78 | 162.24 |
| others | | | | | | | 66.82 | 18.92 |
| δOH | – | 18.64 | 18.73 | 18.31 | 18.80 | – | 20.44 [a] | 19.25 [c] |

[a] Observed at 19.6 ppm in $CDCl_3$ at 300 K.
[b] Chemical shifts in $CD_2Cl_2$ are very similar to those given.
[c] 19.15 ppm in $CD_2Cl_2$.

Table 7
Primary and secondary isotope effects of quinaldinic acid *N*-oxides (**10–12**) and 2-quinolineamide *N*-oxide (**13**) (ppm)

| Compound | **10** | | **11** | **12** | **13** |
|---|---|---|---|---|---|
| Solvent | $CD_2Cl_2$ | $CD_2Cl_2$ | $CD_2Cl_2$ | $CD_2Cl_2$ | $CDCl_3$ |
| Temperature | 230 K | 250 K | 230 K | 250 K | 300 K |
| C-2 | 0.30 | 0.21 [b] | [d] | br. [e] | 0.03 |
| C-3 | –0.108 | –0.09 | | –0.10 | 0.01 |
| C-4 | 0.54 | ≈0.57 [c] | | 0.67 | 0.05(5) |
| C-5 | 0 | 0 | | 0 | |
| C-6 | 0 | [c] | | 0 | |
| C-7 | 0.13(5) | 0.12 | | 0.101 | |
| C-8 | –0.04 | n.r. [g] | | | |
| C-8a | 0.34 | 0.33(5) | | 0.39 | |
| C-4a | – | n.r. | | n.m. | |
| C=O | 0.12(5) | 0.11 | | br. | 0.11 |
| $ch_3$ | – | – | | | 0.13 |
| $^p\delta$ | 0.44 | 0.45 [f] | 0.33 | | n.m. |

[a] For chemical shifts see Table 2 and Table 6.
[b] Broad.
[c] Some overlap prevents a precise determination.
[d] Could not be measured due to insolubility a low temperature.
[e] br. means broad.
[f] 0.47 ppm at 270 K.
[g] n.m. not measured and n.r. not resolved.

is larger that those of **10** and **12**. The primary isotopic effect of **10** shows little temperature dependence.

### *3.3. Quinoline-2-carboxyamide N*-oxide

The $^{13}C$ chemical shifts for quinoline-2-carboxyamide *N*-oxide (**13**) are given in Table 2. The δNH chemical shift equals 11.42 ppm. The deuterium isotope effect due to deuteration at NH position are small and very local (Table 7). The $^2\Delta CO(NH)$ vs. δNH value fits reasonable well with the plot of other hydrogen bonded amides [27].

## 4. Discussion

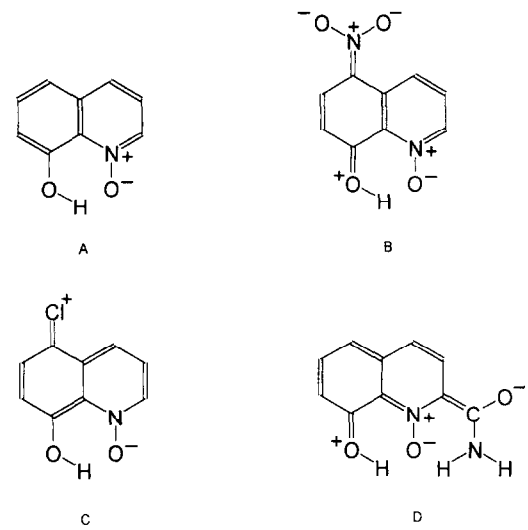
Considering that the different types of hydrogen bond potentials have been inferred for 8-quinolinol *N*-oxides and quinaldinic acid *N*-oxides it is appropriate briefly to give some of the key points for primary and secondary isotope effects for different types of the hydrogen bond potentials (Fig. 1). For system 1A both primary and secondary isotope effects are small to medium and $^2\Delta C(OD)$ is proportional to δOH. The effects are normally also local (only seen for carbon close to the site of deuteration) except in conjugated systems [20]. For symmetrical double minimum potential well (1B) with low potential barrier only the intrinsic part of the isotope effect is observable [26]. Both effects are large and proportional to δOH. For unsymmetrical double-well system an equilibrium contribution to both primary and secondary isotope effect is found. These contributions depend on the chemical shift difference of the nucleus in the two tautomers and on the change in chemical equilibrium upon deuteration [17,20]. Effects may be seen on all nucleus irrespective on their position relative to the site of deuteration and the signs may be both positive and negative. The equilibrium isotope effects normally vary with temperature [28]. For the strongest hydrogen bond with one well symmetrical potential (1C) small negative primary effects are expected [14–16].

### *4.1. 8-Quinolinol N*-oxides

The 8-quinolinol *N*-oxide (Table 4) show isotope effects even at carbons far away from the centre of deuteration. This may indicate a tautomeric equilibrium, as has been suggested by Brzeziński and Zundel

[3,4]. However, long range isotope effect may be also observed in conjugated systems [29]. The intramolecular hydrogen bond in 8-quinolinol *N*-oxides is of resonance assisted type, so the second possibility has to be taken into account. The slight variation of the OH shift for compound **1** with temperature is not consistent with an equilibrium situation. A similar conclusion can be drawn for compound **7**. The small positive values of the primary isotope effect is likewise against a tautomeric equilibrium. Then, the hydrogen bond picture is the asymmetric double-well potential with the hydrogen atom localised at the minimum corresponding to the phenolic oxygen atom. Such types of intramolecular hydrogen bond are known not be very sensitive to solvent effects. A small solvent effect on the chemical shift and secondary isotopic effect of **1** is observed (Tables 3 and 4). It is interesting that the data points for **1** on different solvent fall closely to the data for the substituted compounds in $CDCl_3$. A large effect was observed only for 3,5-dinitro-8-quinolinol **9** (17.81 ppm in DMSO, in comparison with 20.38 ppm in $CDCl_3$). It may indicate the existence of tautomeric equilibrium or other partial disruption of the intramolecular hydrogen bond in **9**.

The system under study was found to be very sensitive to changes in hydrogen bond energy induced by the substituent effects. The behaviour of 8-quinolinol *N*-oxides with respect to substituents are quite different from that of the *o*-hydroxyacyl aromatics [29]. In the latter case substitutents in position *para* to the OH group had very little effect on $^2\Delta C(OD)$, but a clear-cut effect on δOH. For series of 8-quinolinol *N*-oxides substitution at position 5 (*para* to the OH group) has a similar effect at both parameters, as can be seen from the plot in the Fig. 2. An electron withdrawing substituent in positions 5 and 7, such as nitro- and phenyllazo- groups (**2** and **4**), decreased electron density on the phenolic oxygen atom (resonance structure B, Scheme 2), increased acidity of the OH group, and—as a consequence—the hydrogen bond energy. The strongest hydrogen bond has been found for 5,7-dinitro-8-quinolinol *N*-oxide (**9**) as judged from a $\delta(OH) = 20.38$ ppm in $CDCl_3$. The 5- and 7-substituted halogens also increased the hydrogen bond strength, despite the fact that they are mesomerically electron donating substituents. The small effect observed for 5-chloro-8-quinolinol *N*-oxide may be explained by




Scheme 2. Resonance structures of 8-quinolinol *N*-oxides.

increasing the charge density on the oxygen atom of the NO group (resonance structure C, Scheme 2) and the basicity of the *N*-oxide group. In the case of 5,7-dibromo- and 5,7-diiodo-derivatives (**3** and **8**) the steric effect of the halogen in position *ortho* to OH group is mainly responsible for the increasing the hydrogen bond energy. In the case of the carboxyamido substituent in position 2 (**7**) a weakening of the hydrogen bond OH...ON is observed. It can be ascribed to the formation the bifurcated hydrogen bond between the NH group and the NO moiety (D, Scheme 2). Such a scheme is also found for 1,8-dihydroxyantraquinone [31]. The finding that the NO group is an acceptor of two hydrogen bonds is supported by the finding of a ΔOH(NH) isotope effect. The corresponding ΔNH(OH) isotope effect cannot be seen as the NH resonance is somewhat broad. However, for cases such as *o*-hydroxydibenzoylmethane a very large effect was observed for the OH resonance due to deuteration of the tautomeric β-diketone system [20], indicating that in the compound **9** there is no tautomeric equilibrium. The long-range isotope effect is also seen at the carbonyl carbon (Table 4).

### 4.2. *Quinaldinic acid N*-oxides

The substituents $-OC_2H_5$ and $-CH_3$ in **11** and **12** respectively, are not in conjugation with the carboxylic group. The changes in the chemical shift of the carboxylic acid proton and carbon going from

**10** to **12** may result from the change in the hydrogen bond energy or proton transfer equilibrium due to the higher basicity of the N–O moiety. As can be seen from the Table 6, the difference in chemical shifts between compounds **10–12** are small. The deuterium isotope effect at $^{13}C$ chemical shifts of the carboxylic group are unusually small (Table 6). The long-range isotopic effect of both signs are observed, the largest being for carbon in positions *ortho* (C-8a) and *para* (C-4) to the NO group (Table 6). It may indicate the transmission pathway of the isotope effect including the NO group is favoured. The primary isotope effect is medium size and diminishes with increasing δ(OH). Small changes of primary and secondary isotope effects with the temperature are observed. These findings indicate that in the quinaldinic acid *N*-oxides no tautomeric equilibrium takes place. Taking into account the large values δ(OH) and the values of the primary and the secondary isotope effect one can suggest the presence of a broad asymmetric single potential, similar to that found for picolinic acid *N*-oxides.

### 4.3. *Quinoline-2-carboxyamide N*-oxide

The intramolecular hydrogen bond in quinoline-2-carboxyamide is much weaker than in the parent acid **10**, as can be seen from the NH chemical shift (δNH = 11.42 ppm). The value of $^{2}\Delta CO(ND)$ fits the plot $^{2}\Delta C(ND)$ vs. δNH found for amides [27]. Recently, the correlation between $^{2}\Delta C(ND)$ and δNH have been demonstrated for enamines [30]. The values of long range isotope effects (Table 7) indicate the presence of strongly asymmetric hydrogen bond (Type 1A, Fig. 1) with the proton localised at the nitrogen atom in **13**.

## 5. Experimental

### 5.1. Compounds

8-quinolinol *N*-oxide (**1**) was obtained by *N*-oxidation of 8-quinolinol [32]. Derivatives of 8-quinolinols *N*-oxide: **2** [33], **3** [34], **4** [35], **8** [36] and **9** [33] were prepared from **1** by reported methods. 2-methyl-8-quinolinol *N*-oxide (**5**) was prepared by *N*-oxidation of 2-methyl-8-quinolinol with perphthalic acid in ether [32]; m.p. 98–100°C. 5-chloro-8-quinolinol *N*-oxide (**6**) was prepared by *N*-oxidation of 5-chloro-8-quinolinol with perphthalic acid in chloroform/ether; m.p. 168–170°C. Quinaldinic acid *N*-oxides (**10–12**) [37] and 2-quinoline-2-carboxyamide *N*-oxide (**13**) [38] have been obtained as described previously.

8-hydroxy-2-quinolinecarboxyamide *N*-oxide (**7**) was obtained following the procedure described for **13** [38] by direct homolytic amidation in *N,N*-dimethyformamide, using the substrate: *t*-BuOOH + $FeSO_4$ molar ratio 1:2. The product was extracted from reaction mixture with chloroform; m.p. 192°C (Analysis C,H,N = 60.24, 4.50 and 12.84 vs. calculated 60.55, 4.58 and 12.84). 8-Quinolinol was purchased from POCH, Poland and 2-methyl-8-quinolonol and 5-chloroquinolinol from Aldrich, Weinheim, Germany.

### 5.2. NMR

The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC250 NMR spectrometer operating at 250.13 and 62.89 MHz, respectively. The digital resolution was 0.55 Hz per point. The temperature was normally 300 K. TMS was used as internal reference. Low temperature spectra were measured in $CDCl_3$ or in $CD_2Cl_2$.

The $^{2}H$ spectra were recorded at 38.397 MHz in 10 mm NMR tubes using $CHCl_3/CDCl_3$ as internal reference.

Deuteration was achieved by dissolving the compounds in mixtures of $CH_3OH$ and $CH_3OD$ and subsequent rotary evaporation. The experiments were done as one tube experiments with varying degrees of deuteration.

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