

## Powder diffraction study of the hydrogen bonds in nitroxoline and its hydrochloride

A. V. Yatsenko,<sup>a\*</sup> K. A. Paseshnichenko,<sup>a</sup> V. V. Chernyshev<sup>a</sup> and H. Schenk<sup>b</sup>

<sup>a</sup>Chemistry Department, Moscow State University, 119899 Moscow, Russia, and

<sup>b</sup>Laboratory for Crystallography, University of Amsterdam, Nieuwe Achtergracht 166, Amsterdam 1018 WV, The Netherlands

Correspondence e-mail: yatsenko@biocryst.phys.msu.su

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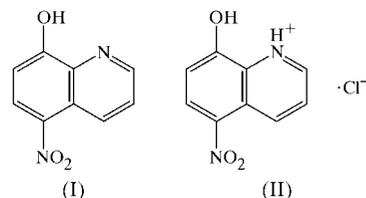
The crystal structures of 8-hydroxy-5-nitroquinoline, C<sub>9</sub>H<sub>6</sub>N<sub>2</sub>O<sub>3</sub>, (I), and 8-hydroxy-5-nitroquinolinium chloride, C<sub>9</sub>H<sub>7</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup>·Cl<sup>-</sup>, (II), have been determined from X-ray powder data. In (I), the molecules are linked *via* moderately strong hydrogen bonds to form dimers. Such a packing motif is likely to be responsible for the low solubility of (I) in water. In (II), the inversion-related cations form stacks, and anions fill the interstack channels.

### Comment

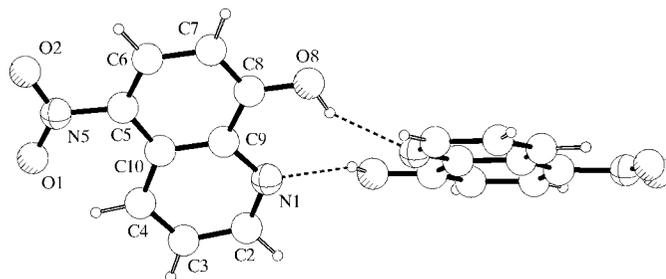
Nitroxoline, or 8-hydroxy-5-nitroquinoline, (I), also known as 5NOK, shows antibacterial and fungicidal activity. In particular, it is used for the treatment of infections of the genito-urinary system. Compound (I) has low solubility in water, but its solubility increases considerably in alkalis and acids.

To date, it has not been clear whether the molecule of (I) in the crystal exists in the neutral form, or as a zwitterion resulting from proton transfer from the hydroxy group to the quinoline N atom. DFT (density functional theory) calculations for isolated molecules predict that the zwitterionic form is 31 kJ mol<sup>-1</sup> less stable than the neutral form. This difference, while significant, is not large enough to exclude the zwitterion from consideration, since it can be overshadowed by the effects of the medium. However, visible spectroscopy, together with semi-empirical calculations on the *INDO-CISD* level (Dick & Nickel, 1983), give strong evidence for the presence of the neutral molecule. Recently, the *INDO-CISD* technique was proven to be suitable for reproducing the spectra of nitronaphthalenoles (Yatsenko *et al.*, 2001). For (I), *INDO-CISD* calculations predict that the neutral form should have its  $\pi$ - $\pi$  absorption maximum in the near-UV region, at 307 nm. Protonation of the quinoline N atom shifts this band bathochromically by 40 nm, whereas in the case of the zwitterion, this maximum is shifted to 391 nm and a new absorption band appears at 635 nm. Thus, the zwitterion should

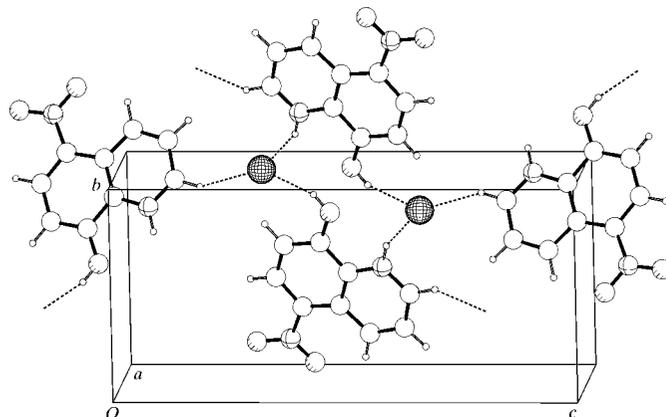
absorb light in essentially the whole of the visible region. In practice, crystals of (I) are light yellow, with no absorption maximum in the visible region, and the hydrochloride salt, (II), is deeper in colour than (I), in full agreement with the results of the calculations for the neutral form and cation, and with the spectroscopic data for solutions (Ermakov *et al.*, 1985).



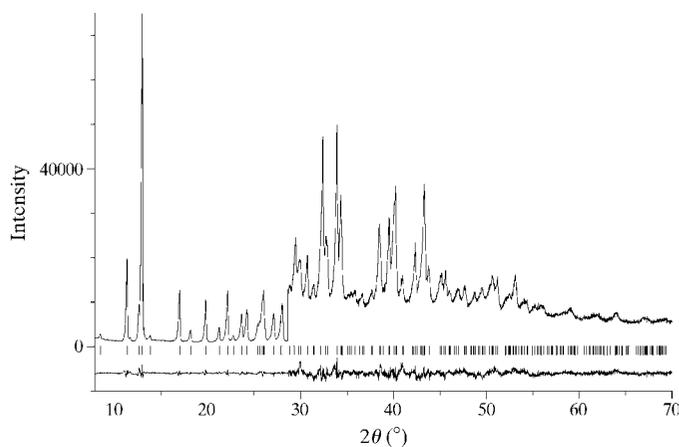
The molecule of (I) is nearly planar, the dihedral angle formed by the least-squares planes through the naphthalene and nitro moieties being only 6.3 (4)°. The dihedral angle formed by the planes through the naphthalene moieties of adjacent molecules is 44.8 (5)°. Details of the hydrogen bonds are given in Table 1. Molecules related by the 2 axis form dimers, as shown in Fig. 1. We have carried out the DFT optimization of one such dimer, starting from the crystallographic geometry. The resulting geometry does not significantly differ from the experimental geometry. After the optimization, the angle subtended by two naphthalene moieties is increased to 64° and the hydroxy group is twisted by 15° with respect to the naphthalene plane, thus facilitating the hydrogen bonding: the O8—H8...N1 angle is increased to 155°, the C9—N1...H8 angle becomes 129° (*versus* 135° in the



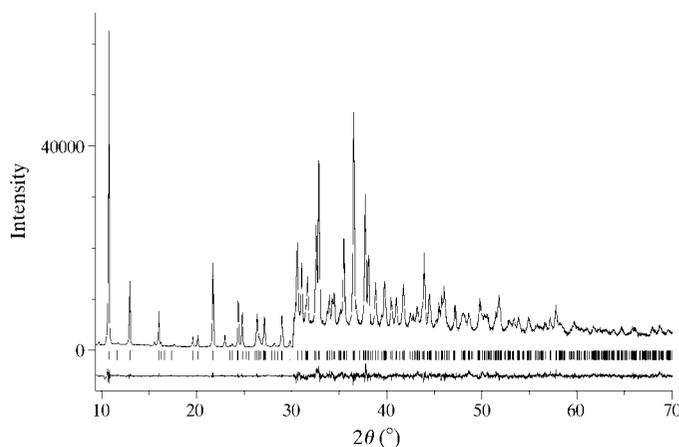
**Figure 1**  
The hydrogen-bonded dimers in (I) showing the atom-labelling scheme.



**Figure 2**  
The Cl...H contacts in (II); the atom-labelling scheme is the same as for (I) in Fig. 1.



**Figure 3**  
The Rietveld plot for (I) showing the observed and difference profiles. The reflection positions are shown above the difference profile. The high-angle area is magnified by a factor of 10.



**Figure 4**  
The Rietveld plot for (II) showing the observed and difference profiles. The reflection positions are shown above the difference profile. The high-angle area is magnified by a factor of 10.

crystal) and the O...N distance is 0.07 Å shorter than in the crystal. The DFT-calculated energy of the dimer is 19.8 kJ mol<sup>-1</sup> lower than the energy of two isolated molecules of (I). This is an exaggerated estimation for the hydrogen-bonding energy in this dimer, owing to the basis-set superposition error.

The dimers in (I) form stacks along [001], with an interplanar distance of 3.446 (8) Å between two neighbouring naphthalene fragments. It is likely that, under the effect of stacking interactions, the dimers flatten in the crystal, at the cost of distortion of the hydrogen-bonding geometry.

In (II), the cations form stacks along [100] (Fig. 2), with interplanar distances of 3.341 (10) and 3.447 (10) Å. The nitro group is twisted by 12.4 (5)° with respect to the naphthalene moiety. The anions make short contacts to NH, OH and CH groups, which can be considered as hydrogen bonds (Table 2).

## Experimental

Compound (I) was prepared by oxidation of 8-hydroxy-5-nitrosoquinoline by HNO<sub>3</sub>, followed by recrystallization from ethanol,

giving very thin needles. The sample obtained from aqueous solution gave an identical diffraction pattern, although of lower quality. Compound (II) was prepared by recrystallization of (I) from 5% HCl.

### Compound (I)

#### Crystal data

C<sub>9</sub>H<sub>6</sub>N<sub>2</sub>O<sub>3</sub>  
M<sub>r</sub> = 190.16  
Orthorhombic, *Fdd2*  
*a* = 28.049 (7) Å  
*b* = 31.198 (8) Å  
*c* = 3.727 (1) Å  
*V* = 3261.4 (15) Å<sup>3</sup>  
*Z* = 16  
*D<sub>x</sub>* = 1.549 Mg m<sup>-3</sup>  
Cu Kα radiation

Cell parameters from 26 reflections

$\theta$  = 4.3–16.4°

$\mu$  = 1.02 mm<sup>-1</sup>

*T* = 295 (2) K

Specimen shape: flat sheet

25 × 25 × 2.0 mm

Particle morphology: needle, light yellow

#### Data collection

DRON-3M diffractometer (Burevestnik, Russia)

Specimen mounting: pressed as a thin layer in the specimen holder

Specimen mounted in reflection mode

*h* = 0 → 20

*k* = 0 → 22

*l* = 0 → 2

2 $\theta$ <sub>min</sub> = 7.0, 2 $\theta$ <sub>max</sub> = 70.0°

Increment in 2 $\theta$  = 0.02°

#### Refinement

*R<sub>p</sub>* = 0.035

*R<sub>wp</sub>* = 0.048

*R<sub>exp</sub>* = 0.023

*S* = 2.10

2 $\theta$ <sub>min</sub> = 7.90, 2 $\theta$ <sub>max</sub> = 70.0°

Increment in 2 $\theta$  = 0.02°

Wavelength of incident radiation: 1.5418 Å

Excluded region(s): 7.00–7.88

Profile function: split-type pseudo-Voigt

224 reflections

92 parameters

H-atom parameters constrained

( $\Delta/\sigma$ )<sub>max</sub> = 0.045

Preferred orientation correction: spherical harmonics (Ahtee *et al.*, 1989)

**Table 1**

Geometry of hydrogen bonds and short C—H...O contacts (Å, °) for (I).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O8—H8...N1 <sup>i</sup>	0.90	2.05	2.811 (5)	141
C6—H6...O2 <sup>ii</sup>	1.00	2.42	3.304 (7)	147
C3—H3...O2 <sup>iii</sup>	1.00	2.59	3.472 (6)	147

Symmetry codes: (i)  $-x, 1 - y, z$ ; (ii)  $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$ ; (iii)  $x - \frac{1}{4}, \frac{3}{4} - y, z - \frac{3}{4}$ .

### Compound (II)

#### Crystal data

C<sub>9</sub>H<sub>7</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup>·Cl<sup>-</sup>  
M<sub>r</sub> = 226.62  
Monoclinic, *P2<sub>1</sub>/c*  
*a* = 7.566 (4) Å  
*b* = 7.467 (4) Å  
*c* = 16.334 (7) Å  
 $\beta$  = 92.49 (3)°  
*V* = 921.9 (8) Å<sup>3</sup>  
*Z* = 4  
*D<sub>x</sub>* = 1.633 Mg m<sup>-3</sup>

Cu Kα radiation

Cell parameters from 32 reflections

$\theta$  = 5.4–18.3°

$\mu$  = 3.61 mm<sup>-1</sup>

*T* = 295 (2) K

Specimen shape: flat sheet

25 × 25 × 2.0 mm

Particle morphology: plate, yellow

#### Data collection

DRON-3M diffractometer (Burevestnik, Russia)

Specimen mounting: pressed as a thin layer in the specimen holder

Specimen mounted in reflection mode

*h* = 0 → 5

*k* = 0 → 5

*l* = -12 → 12

2 $\theta$ <sub>min</sub> = 5.0, 2 $\theta$ <sub>max</sub> = 70.0°

Increment in 2 $\theta$  = 0.02°

**Table 2**

Geometry of hydrogen bonds and short C—H...Cl(O) contacts (Å, °) for (II).

D—H...A	D—H	H...A	D...A	D—H...A
N1—H1...Cl1	0.90	2.11	2.945 (7)	154
O8—H8...Cl1 <sup>i</sup>	0.84	2.17	2.950 (6)	154
C2—H2...Cl1 <sup>ii</sup>	1.00	2.61	3.515 (8)	151
C4—H4...O1 <sup>iii</sup>	1.00	2.43	3.312 (10)	147
C6—H6...O2 <sup>iv</sup>	1.00	2.43	3.161 (10)	130
C3—H3...O2 <sup>v</sup>	1.00	2.58	3.170 (10)	118

Symmetry codes: (i)  $-x, 2-y, 1-z$ ; (ii)  $-x, y-\frac{1}{2}, \frac{3}{2}-z$ ; (iii)  $1-x, -y, 1-z$ ; (iv)  $1-x, \frac{1}{2}+y, \frac{1}{2}-z$ ; (v)  $x, \frac{1}{2}-y, \frac{1}{2}+z$ .

### Refinement

$R_p = 0.040$	Profile function: split-type pseudo-Voigt
$R_{wp} = 0.056$	401 reflections
$R_{exp} = 0.030$	112 parameters
$S = 1.85$	H-atom parameters constrained
$2\theta_{min} = 9.40, 2\theta_{max} = 70.0^\circ$	$(\Delta/\sigma)_{max} = 0.048$
Increment in $2\theta = 0.02^\circ$	Preferred orientation correction:
Wavelength of incident radiation: 1.5418 Å	spherical harmonics (Ahtee <i>et al.</i> , 1989)
Excluded region(s): 5.00–9.38	

The DFT and *INDO-CISD* calculations were performed using programs provided by Dr D. N. Laikov (Laikov, 1997) and Professor B. Dick (Dick & Nickel, 1983), respectively. The DFT calculations were carried out using the BLYP (Becke–Lee–Yang–Parr) exchange–correlation function (Becke, 1988; Lee *et al.*, 1988) with a triple zeta basis set, including polarization and diffuse functions for all atoms. The orthorhombic and monoclinic cell dimensions of (I) and (II) were determined with *ITO* (Visser, 1969) and *TREOR90* (Werner *et al.*, 1985), respectively, and refined to  $M_{20} = 18$  for (I) and 22 for (II), and  $F = 43$  for (I) and 39 for (II), using the first 26 and 32 peak positions, respectively. The initial molecular models were built with *MOPAC7* (Stewart, 1993) on the *PM3* level (Stewart, 1989). In (I), the position and orientation of the molecule were determined using the grid-search procedure (Chernyshev & Schenk, 1998). In (II), the position and orientation of the cation and the position of the anion were determined using the simulated annealing procedure (Zhukov *et al.*, 2001). The X-ray diffraction profiles and the difference refinements are shown in Figs. 3 and 4. The final  $R_B$  values were 0.067 for (I) and 0.076 for (II). The Cl atom was refined anisotropically; the C, N and O atoms were refined isotropically and were gathered

together into groups with a common  $U_{iso}$  parameter for each group. The H atoms were placed in geometrically calculated positions and their isotropic displacement parameters were fixed. The planarity of the naphthalene fragments and the nitro groups was restrained. The anisotropy of the diffraction-line broadening was approximated by a quartic form in *hkl* (Popa, 1998). The standard uncertainties obtained from the Rietveld refinement were corrected for serial correlation effects (Bérar & Lelann, 1991).

For both compounds, data collection: local program; cell refinement: *LSPAID* (Visser, 1986); program(s) used to solve structure: *MRIA* (Zlokazov & Chernyshev, 1992); program(s) used to refine structure: *MRIA*; molecular graphics: *PLATON* (Spek, 2001); software used to prepare material for publication: *PARST* (Nardelli, 1983).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1513). Services for accessing these data are described at the back of the journal.

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