TAUTOMERISM OF 4-HYDROXY-4(1*H*) QUINOLON

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Abstract : The tautomerism of 4-Hydroxy-4(1*H*) quinolon **I** was studied using infrared spectroscopy, ^{1}H,^{13}C NMR spectroscopy and X-ray crystallography. The keto-form of **I** is favored in the crystal form and at room temperature in polar solutions like water and dimethylsulfoxide.

Introduction

Quinolons produced by different bacteria inhibit the respiratory (1) as well as photosynthetic electron transport chains (2). They were used as lead compounds for finding new strong inhibitors. One of the most important physical and chemical properties of this class of heteroaromatic compounds is their involvement in a prototropic tautomerism (Figure 1).

In order to understand the biological activity of **I** we investigated its crystal structure and studied the tautomerism in water and DMSO solution by ^{1}H and ^{13}C NMR spectroscopy.

To further investigate the tautomerism of compound **I** in solution we synthesized the O-methylated derivate **II**, which mimics the enol-tautomeric form (Figure 1).

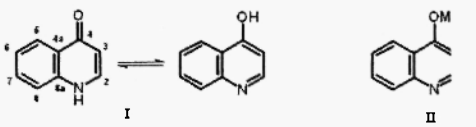

Figure-1 : Tautomerism of 4-Hydroxy-4(1*H*)quinolon **I** and the structure of 4-Methoxy 4(1*H*)quinolon **II**.

Single crystals of **I** for X-ray analysis were obtained from dichloromethane.

The crystal structure exists as a dimer. The monomers are connected by an intermolecular hydrogen bond (O...HN distance of 1.795 Å) between the imino hydrogen and the carbonyl group (Figure 2 and Figure 3). The carbon oxygen bonds length of 1.246 Å for C1A-O1A and 1.262 Å for C1-O1 are in the range of the C=O length. Also the C3N4 and C5N4 bonds of 1.352 Å and 1.383 Å indicate a nitrogen carbon single bond. This results show that the keto tautomer is favored in the crystal structure.

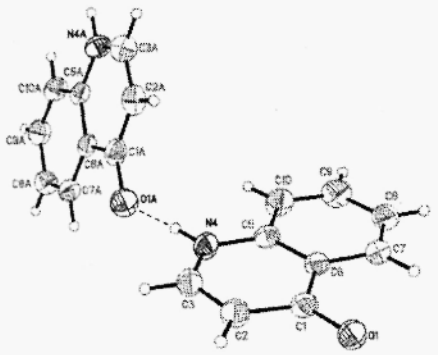

Figure-2 : Perspective view of 4-Hydroxy-4(1*H*) quinolon, **I** as a dimer.
Shown with 50% probability displacement ellipsoids.Selected bond distances (Å) and bond angles (deg): O(1a)-H(4) 1.795(20), O(1)-C(1) 1.266(1), C(1)-C(2) 1.430(2), C(2)-C(3) 1.430(2), O(1)-C(1)-C(6) 121.0(1), C(1)-C(6)-C(7) 122.97(10), C(3)-N(4)-C(5) 120.00(9).

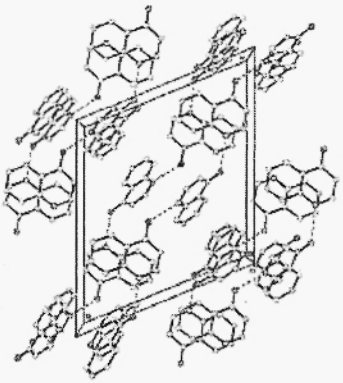

Figure-3 : Crystal packing of I shown down the *b* axis.

The ^{13}C and ^{1}H NMR spectra of compound I in dimethylsulfoxide (DMSO) and water at room temperature show a unique signal for each atom. The presence of the C4-carbonyl signal at 176.8 ppm and the comparison of chemical shift data with those of O-methyl derivate II indicates that the 4-oxo-form is the only tautomer present in DMSO. The same result was obtained from the ^{1}H NMR spectra. The assignment of the carbons and protons was obtaind from *long range COSY*, *HSQC* and *HMBC* experiments. Significant here is the chemical shift change of H3 in DMSO from 6.03 ppm in I to 7.08 ppm in II which is characteristic for the ring current of the aromatic ringsystem of II (Figure 4). In addition, H2 interacts with the imino-proton and appears as a triplett with a coupling constant of 6.5 Hz, which collapses to a doublet after addition of D_2O.

The powder FT-IR spectrum of I shows no hydroxy, but a C=O streching band at 1505 cm^{-1}. The strong hydrogen bond is indicated by the broad band at ν =2793 cm^{-1} (an identical strategy for the determination of the tautomerism for 4-hydroxyterpyridine, which exists as a mixture of both tautomers, was caried out by Branda et. al.(3)).

Our results indicates that I exist only in the keto-tautomer. They are in agreement with the fact that I binds to different quinone binding sites. This binding can only be achieved when a quinoid structure is present.

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Experimental Part

NMR spectra were recorded on Bruker spectrometers: AM250 and AMX400 (^{1}H,^{13}C). Chemical shifts are given in ppm. The assignment of the carbons and protons was obtaind from *long range COSY*, *HSQC* and *HMBC* experiments.

4-Chloro 4(1*H*)quinolon and 4-hydroxy4(1H)quinolon I were obtained from Aldrich.

4-hydroxy-4(1H)quinolon I
^{1}H-NMR(400.13 MHz, DMSO-d_6) δ [ppm]: 11.78 (s,br, 1H, NH, disappear by adding of D_2O), 8.1 (d, J = 8.2 Hz, 1H, H5), 7.9 (t, J = 6.5 Hz, 1H, H2), 7.6 (t, J = 7.5 Hz, 1H, H6), 7.5 (d, J = 7.8 Hz, 1H, H8), 7.3 (t, J = 7.5 Hz, 1H, H7), 6.0 (d, J = 7.5 Hz, 1H, H3). (Figure-4)

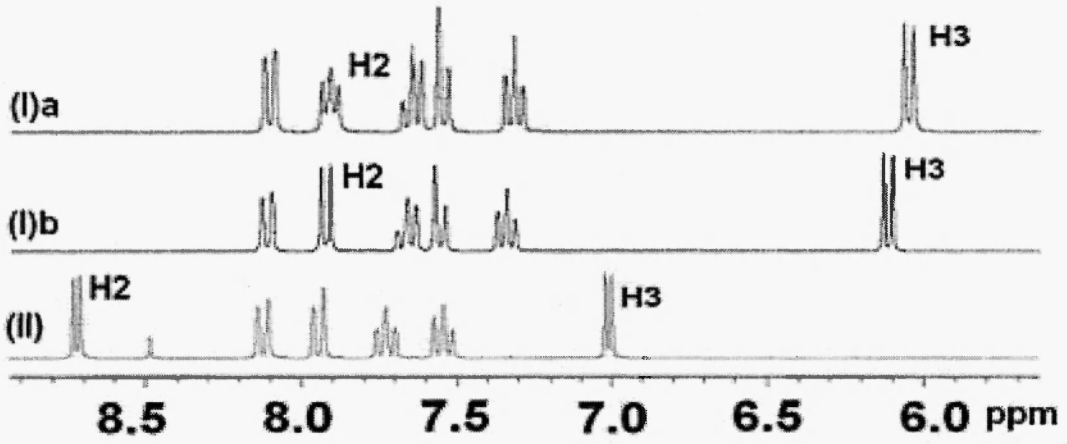

Figure-4 : ^{1}H NMR spectra of **I** a) in DMSO and b) after adding of D_2O and **II** in DMSO.

^{13}C-NMR (62.9 MHz, DMSO-d_6) δ [ppm]:

176.8(C4),140.0(C4a),139.3(C2),131.5(C6),125.7(C8a),124.9(C5),123.0(C7), 118.2(C8),108.6(C3).

^{1}H-NMR(400.13 MHz, D_2O) δ [ppm]: 7.74 (d, J = 8.2 Hz, 1H, H5), 7.67 (d, J = 7.1 Hz, 1H, H2), 7.41 (t, J = 7.8 Hz, 1H, H7), 7.20-7.12 (m, 2H, H8/H6), 6.10 (d, J = 7.1 Hz, 1H, H3).

^{13}C-NMR (62.9 MHz, D_2O) δ [ppm]: 179.0(C4),140.4(C2),138.8(C4a),132.3(C7), 124.5(C6/C8),123.9(C8a),123.7(C5), 118.1(C8/C6),108.0(C3).

4-Methoxy-4(1H)quinolon **II** was synthesized by heating of 0.5 g (3 mmol) 4-chloro 4(1*H*)quinolon and 0.65g (12mmol) sodium methoxide in 8 ml of 0.5 M sodium methoxide in methanol over night. After cooling to the room temperature, the solid was isolated by filtration in 86 % yield as the pure produkt.
Rf = 0.12 (Hexane: Ethylacetate 1:1)

^{1}H-NMR(250.13 MHz, DMSO-d_6) δ [ppm]: 8.77 (d, J = 5.1 Hz, 1H, H2), 8.18 (d, J = 8.3 Hz, 1H, H5), 8.01 (d, J = 7.7 Hz, 1H, H8), 7.79 (t, J = 5.1 Hz, 1H, H6), 7.60 (t, J = 7.4 Hz, 1H, H7), 7.07 (d, J = 5.2 Hz, 1H, H3), 4.03 (s, 3H, CH_3).

^{13}C-NMR (62.9 MHz, DMSO-d_6) δ [ppm]: 161.4(C4),151.5(C2),148.4(C4a),129.9(C6), 128.4(C8),125.6(C7),121.3(C5), 120.5(C8a),100.9(C3),56.0(CH_3).

Crystal data and structure refinement.

Empirical formula	C9 H7 N O	
Formula weight	145.16	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 13.7761(10) Å	α = 90°.
	b = 7.3709(6) Å	β = 112.594(5)°.
	c = 15.5330(11) Å	γ = 90°.
Volume	1456.20(19) $Å^3$	
Z	8	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	608	
Crystal size	0.48 x 0.43 x 0.32 mm^3	
Theta range for data collection	3.74 to 27.58°.	
Index ranges	-17<=h<=17, -9<=k<=9, -20<=l<=20	
Reflections collected	20985	
Independent reflections	3337 [R(int) = 0.0441]	
Completeness to theta = 25.00°	99.5 %	
Absorption correction	None	
Max. and min. transmission	0.9724 and 0.9590	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3337 / 0 / 208	
Goodness-of-fit on F^2	1.072	
Final R indices [I>2sigma(I)]	R1 = 0.0396, wR2 = 0.1057	
R indices (all data)	R1 = 0.0452, wR2 = 0.1095	
Extinction coefficient	0.028(4)	
Largest diff. peak and hole	0.203 and -0.160 $e.Å^{-3}$	

Table-1 : Hydrogen bonds for hs7 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(4)-H(4)...O(1A)	0.967(17)	1.786(18)	2.7497(13)	174.4(16)
N(4A)-H(4A)...O(1)#1	0.939(18)	1.876(18)	2.8131(13)	176.1(16)

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+1/2,z+1/2

References

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3. N. Branda, B. Norsten, and E. Murguly, *J.Chem.Soc.,Perkin Trans.2.* 2789-2794 (1999).

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