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**Dedicated to the memory of Professor N. E. Alexandrou, Aristotelian University of Thessaloniki, Greece**

<sup>17</sup>O nmr studies, at natural abundance, of substituted quinoxaline-2(1H),3(4H)-diones demonstrate that the <sup>17</sup>O chemical shift data can provide new insights into steric and electronic interactions due to long range substituent effects on the aromatic ring. The role of considerable "keto" character and torsion angle deformation of the diamide group in solution is emphasized.

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## Introduction.

Quinoxaline-2(1H)-ones and quinoxaline-2(1H),3(4H)-diones and their derivatives have been known for many years [1]. Extensive spectroscopic investigations have been reported on quinoxalines and their derivatives but they have been focused mainly on their protolytic equilibrium [2]. This amide-iminol tautomerism involves a fast hydrogen transfer between nitrogen and oxygen. It has generally been found that compounds capable of this tautomerism usually exist predominantly in the amide form. Thus, ultraviolet and infrared spectroscopic studies indicated that the predominant tautomeric form of quinoxalin-2(1H),3(4H)-diones, both as solid and in solution, is the amide-like form, e.g. **1a** rather than the mixed form **1b** or the dihydroxy-aromatic **1c**. More recently renewed interest arises from the discovery that disubstituted derivatives, notably 6,7-dinitro and 6-cyano-7-nitro, are potent antagonists of the quisqualate and kainate receptors on neurones of the central nervous system [3]. The quinoxaline moiety is also present in peptide antibiotics [4]. Evidently their distinctive modes of action depend critically upon subtle structural changes.

<sup>17</sup>O nmr spectroscopy is becoming a powerful method for investigating structure, bonding and dynamics of oxygen containing compounds despite the low natural abundance (0.037%) and the quadrupolar properties of the <sup>17</sup>O nucleus [5]. This is due to the fact that oxygen is located at strategic molecular sites and is directly involved in inter- and intramolecular interactions and the chemical shift range for oxygen-containing organic molecules is extremely large. Recently a number of substituent chemical shift correlation studies on conjugated and non-conjugated oxygen functional

groups have appeared with particular emphasis to steric effects [5e]. However, <sup>17</sup>O nmr studies of quinoxaline-2(1H),3(4H)-diones have been limited to a single report [6].

We report here <sup>17</sup>O nmr studies of substituted quinoxaline-2(1H),3(4H)-diones which demonstrate that the <sup>17</sup>O chemical shift data can provide new insights into long range steric and electronic interactions in relation to a considerable "keto" character and an out-of-plane deformation of the diamide group in the quinoxaline-2(1H),3(4H)-dione ring system.

## Results and Discussion.

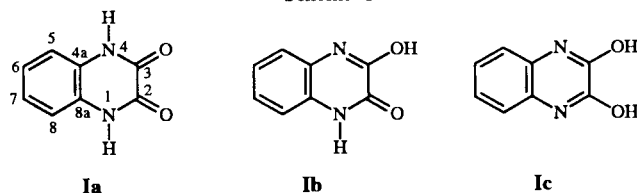
<sup>17</sup>O nmr chemical shifts are usually discussed with respect to contributions from a diamagnetic and a paramagnetic term. The diamagnetic term is considered independent of change in the chemical environment of the oxygen atom [7]. Therefore, shielding changes are essentially induced by the paramagnetic term,  $\delta^P$ . The latter is usually evaluated following the average excitation energy approximation [8]:

$$\delta^P \propto \langle r^{-3} \rangle_{2p} \frac{1}{\Delta E} \left[ Q_{AA} + \sum_{B \neq A} Q_{AB} \right] \quad (1)$$

where the expression  $\langle r^{-3} \rangle_{2p}$  is the average value of the inverse cube of the distance of the 2p electrons from the nucleus;  $\Delta E$  is the lowest excitation energy in the electronic spectrum of the compound concerned, and  $Q_{AA}$  and  $Q_{AB}$  are defined in terms of the charge density and bond order matrix and, thus, represent a measure of multiple bonding to the nucleus being studied.

<sup>17</sup>O nmr chemical shifts of several functional groups are very sensitive to solute-solvent hydrogen bonding and long range dipole-dipole interactions which are a function of the dielectric constant of the medium [9]. In order, therefore, to investigate intramolecular electronic perturbations of the amide group it is very important to use the same solution conditions. Selection of low viscosity solvents, such as acetonitrile and acetone, help to obtain narrow linewidths [10].

Scheme 1



The connection between linewidth and solution viscosity is based on the fact that the transverse relaxation rate,  $1/T_2$ , is related to molecular correlation time  $\tau_c$ . In diamagnetic solutions the  $^{17}\text{O}$  nucleus relaxes predominantly by the quadrupolar mechanism. In the extreme narrowing limit the expression for the  $^{17}\text{O}$  linewidth,  $\Delta\nu_{1/2}$ , is given by [5]

$$\Delta\nu_{1/2} = \frac{1}{\pi T_2} = \frac{3}{125} \left(1 + \frac{n^2}{3}\right) \chi^2 \tau_c \quad (2)$$

where  $\chi$  is the nuclear quadrupolar coupling constant and  $n$  the asymmetry parameter. Considering a molecule as an isotropic body of radius  $\alpha$  immersed in a medium of viscosity  $\eta$ , then

$$\tau_c = \frac{4\pi\eta\alpha^3}{3kT} \quad (3)$$

Evidently low viscosity solvents or elevated temperatures reduce correlation times and thus spectral linewidths. Unfortunately, the low solubility of quinoxaline-2(1*H*),3(4*H*)-diones in acetonitrile and acetone significantly reduces the required signal to noise ratio. Therefore, it was necessary to utilize DMSO as solvent and the effect of high viscosity was reduced by the use of elevated temperatures (Figure 1).

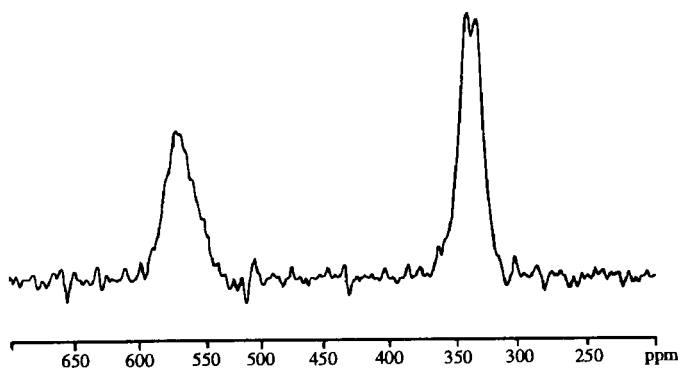


Figure 1.  $^{17}\text{O}$  nmr spectrum (54.4 MHz) in natural abundance of 6-nitroquinoxaline-2(1*H*),3(4*H*)-dione, 0.5 M in DMSO at 120°C, using a Brüker AMX-400 MHz instrument.  $T_{\text{acq}} = 10$  ms, number of scans 1000000, after multiplication of the free induction decay with a double Gaussian-exponential function (LB = -150 Hz, GB = 0.1) to increase the resolution.

The  $^{17}\text{O}$  chemical shifts of the diamide oxygens of quinoxaline-2(1*H*),3(4*H*)-diones (Table 1) fall in the region as those previously reported for the amides and peptides and, thus, are consistent with the structural formula of **1a**. There is no other tautomeric form co-existing in solution at measurable concentration. The strong deshielding of *N,N'*-diphenyloxamide and quinoxaline-2(1*H*),3(4*H*)-dione relative to *N,N'*-dimethyloxamide should be attributed to the partial keto character of the CO group due to delocalization of the nitrogen lone pair into

Table 1

$^{17}\text{O}$  Chemical Shifts of *N,N'*-substituted Oxamides and Quinoxaline-2(1*H*),3(4*H*)-diones [a]

Compound	CONH	NO <sub>2</sub>
<i>N,N'</i> -Dimethyloxamide	291.9	
<i>N,N'</i> -Diphenyloxamide	313.2	
Quinoxaline-2(1 <i>H</i> ),3(4 <i>H</i> )-dione	327.7	
6,7-Dinitroquinoxaline-2(1 <i>H</i> ),3(4 <i>H</i> )-dione	351.7	603.4
6-Nitroquinoxaline-2(1 <i>H</i> ),3(4 <i>H</i> )-dione	338.0	(344.5) (338.5) 569.0 (567.0)
6-Cyanoquinoxaline-2(1 <i>H</i> ),3(4 <i>H</i> )-dione	338.0	(339.6)

[a] Saturated solutions in DMSO at 90°C. The chemical shifts (ppm) were measured relative to 1,4-dioxane. Values in parenthesis were obtained at 120°C.

the adjacent aromatic system. This is in agreement with the X-ray structural data of the diamide group in **1a** giving C-O distances of 1.232 and 1.225 Å [11]. These are rather shorter than the CO distance of 1.243 Å for oxamide which is planar and in the *trans* conformation. The C-N bond lengths of 1.345 and 1.337 Å [11] are significantly longer than the C-N distance of 1.315 Å in oxamide [12]. This implies a considerably more keto character of the CO and less double bond character in the C-N bond in **1a** due to delocalization of the nitrogen lone pair in the aromatic system. However, the magnitude of the  $^{17}\text{O}$  shift differences for **1a** are significantly larger than those of *N,N'*-diphenyloxamide although the degree of delocalization of the nitrogen lone pair into the adjacent aromatic system should be less in **1a**. Thus the effect of torsion angle variation in the diamide ring should be evaluated.

Recently Boykin and collaborators [5e,13] pioneered the development of  $^{17}\text{O}$  nmr spectroscopy as a tool for investigating steric perturbations of structure in organic compounds. Steric effect studies are divided into two categories: molecular systems in which steric interactions are characterized by rotation of functional groups around single bonds to relieve van der Waals interactions and those in which steric interactions are partially accommodated by bond angle and bond length distortions. These authors suggested that deshielding is expected for an out-of-plane deformation of the amide bond which leads to greater double bond character and reduced electron density on oxygen (equation (1)). Furthermore, decreasing charge density at the oxygen is expected to lead to a contraction of the 2p orbitals and thereby a decrease in shielding.

In the crystalline form, **1a** was found to be in a very flattened boat conformation. The two diamide oxygen atoms have deviations of 0.07 and 0.004 Å and the two nitrogens of -0.040 and -0.025 Å from the least-squares plane fitted to all non-hydrogen atoms. It was suggested that this probably arises from intermolecular forces in the crystal and that a

$C_{2v}$  structure would pertain both in solution and in the free molecule. Cobb *et al.* [14] by the use of *ab initio* methods suggested that the total energies of the structures with either  $C_{2v}$  or  $C_s$  [with H(N) and O distorted slightly upwards, and N and C(O) downwards] structural constraints are effectively identical, but the  $C_{2v}$  structure is marginally lower. Our results, however, demonstrate that the observed flattened boat in the X-ray determination is probably an intrinsic property of the molecule in solution.

The  $^{17}O$  chemical shifts of the diamide group of the 6-cyano and 6-nitroquinoxaline-2(1H),3(4H)-diones are at higher frequencies compared to those of the parent compound **1a**. At  $90^\circ$  the two diamide oxygens could not be resolved. However, at  $120^\circ$  and using resolution enhancement techniques their chemical shifts could be measured for 6-nitroquinoxaline-2(1H),3(4H)-dione (Figure 1). The high frequency absorption is probably due to C(2)O amide oxygen since the lone pair of the N(1) nitrogen is considerably delocalized into the conjugated aromatic system. Surprisingly the C(3)O amide oxygen indicates a significant double bond character and reduced electron density on oxygen although the N(4) lone pair is not delocalized into the aromatic system. It is quite possible that the out-of-plane deformation of the amide bond plays a significant role.

The strong deshielding of 6,7-dinitroquinoxaline-2(1H),3(4H)-dione by  $\approx 24$  ppm compared to **1a** could be attributed to a significant delocalization of the lone pair of the diamide nitrogen into the aromatic ring and, subsequently, to the nitro group and/or to a significant out-of-plane deformation of the CO group.  $\delta(^{17}O)$  of the nitro group ( $\delta \approx 603.4$  ppm) is very similar to that of the *o*-dinitrobenzene ( $\approx 609$  ppm) but very different from that of *p*- and *m*-dinitrobenzene (584 and 579 ppm respectively). The data for the aromatic nitro compounds yielded a quantitative relationship between the  $^{17}O$  chemical shift of the nitro group and the torsional angle between the aromatic ring and the nitro group [15]. At  $0^\circ$ , the charge density on conjugated nitro group oxygens is greater than those of the  $90^\circ$  rotamer (non-conjugated nitro group). By simple considering charge density effects on chemical shift (Q term, equation (1)), the non-conjugated nitro group is expected to be deshielded relative to a conjugated one. Increasing nitro group-aromatic ring orbital overlap would be expected to result in increasing single bond character of the nitro function and should be reflected by a shielding trend. Thus a torsion angle of  $\approx 36^\circ$  is expected for the orientation of the nitro group of 6,7-dinitroquinoxaline-2(1H),3(4H)-dione with respect to the plane of the aromatic ring according to the well documented quantitative relationship between  $\delta(^{17}O)$  and torsion angle on aromatic nitro groups [15]. This torsion angle inhibits a significant delocalization of the diamide nitrogen lone pair into the nitro group. Apparently, this significant out-of-plane torsion angle deformation and additional compressional effect

arising from direct interaction of the nitro groups results from distortion of planarity of the quinoxaline groups [16]. Thus, the reduction in shielding of the diamide oxygen should be attributed to a combination of electronic effects and a significant out-of-plane deformation of the CO moiety.

At present it is premature to attempt to quantify the expected correlation between torsion angle and  $\delta(^{17}O)$  due a lack of sufficient number of X-ray structural data and complications arising from an interplay of long range electronic effects, torsion angle and in-plane distortion of the diamide CO group. However, since linear regression analysis of the calculated torsion angles (MM2) and experimental  $\delta(^{17}O)$  of aryl ketones, aryl carboxylate esters (C=O) and aryl amides resulted in slopes [ $\delta(^{17}O)$ ] vs [angle degree] of 0.86 to 0.6 [13(b)], it is evident that the out-of-plane deformation is quite significant.

The present data clearly show that in quinoxaline-2(1H),3(4H)-diones there is a considerable double bond (keto) character at the carbonyl oxygen which is due to long range electronic effects and an out-of-plane deformation of the CO group, especially, for the 6,7-dinitro derivative. This combination of long range electronic and stereochemical effects may be important in explaining chemical and biological reactivity of quinoxaline-2(1H),3(4H)-diones and their derivatives.

## EXPERIMENTAL

Quinoxaline-2(1H),3(4H)-dione was prepared according to [17], 6-nitro- and 6,7-dinitroquinoxaline-2(1H),3(4H)-diones according to [18] and 6-cyanoquinoxaline-2(1H),3(4H)-dione according to [3a,b].

$^{17}O$  nmr spectra were recorded on a Bruker AMX-400 spectrometer operating at 54.48 MHz. The spectrometer was equipped with a high resolution probe accepting 10-mm sample tubes. The field was optimized using deuterium oxide. No field lock was used during data acquisition. The chemical shifts (ppm) were determined relative to external 1,4-dioxane (+0.2 ppm relative to water at 303 K) determined in a separate replacement experiment. Their errors were estimated to  $\pm 1.5$  ppm. Acoustic ringing effects [5f] were alleviated using a preacquisition delay time of  $\approx 50$ -200  $\mu$ s.

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