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^{17}O and ^{14}N NMR Studies of Quinoxaline-2(1H),3(4H)-diones and N,N'-Substituted Oxamides: The First Experimental Evidence of Torsion Angle Deformation Resulting from an Unprecedented Through Six-bond Substituent Effect on the Diamide Group of Quinoxaline-2(1H),3(4H)-diones

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Abstract: ^{17}O and ^{14}N NMR studies of quinoxaline-2(1H),3(4H)-diones demonstrate a significant torsion angle deformation of the diamide group in solution due to an unprecedented through six bond substituent effect.

Quinoxaline-2(1H)-ones and quinoxaline-2(1H),3(4H)-diones and their derivatives have been known for many years[1]. 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[2]. The quinoxaline moiety is also present in peptide antibiotics.[3] Evidently their distinctive modes of action depend critically upon subtle structural changes. Extensive spectroscopic investigations have been reported on quinoxalines and their derivatives but they have been focused mainly on their protolytic equilibria[4]. In this communication we report ^{17}O and ^{14}N NMR studies of quinoxaline-2(1H),3(4H)-diones and, for comparative reasons, of N,N'-substituted oxamides. We present the first observation of an out-of-plane deformation of the diamide group in the quinoxaline-2(1H),3(4H)-dione ring system resulting from an unprecedented through six bond substituent effect.

In DMSO solution, N,N'-dimethyl and N,N'-diethyl oxamide have nearly identical ^{17}O chemical shifts (Table 1). This agrees with the general observation that the effect of N-alkyl substitution of amides on $\delta(^{17}O)$ is rather small and practically independent of the solvent[5]. The situation is different for N,N'-diphenyloxamide and quinoxaline-2(1H),3(4H)-diones. Thus for quinoxaline-2(1H),3(4H)-dione (**4**) a deshielding of ≈ 36 ppm is observed relative to that of N,N'-dimethyl oxamide. A further shift of ≈24 ppm for 6,7-dinitroquinoxaline-2(1H),3(4H)-dione (**5**) is observed which is, probably, the largest six bond substituent shift observed to date. There are considerable substituent effects on $\delta(^{14}N)$ which result in a strong deshielding along the series Ph>Et>Me (Table 1).

^{17}O and ^{14}N 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 and nitrogen atoms[6]. Therefore, shielding changes are essentially induced by the paramagnetic term, δ^p. The latter is usually evaluated following the average excitation energy approximation[7]

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

Table 1. ^{17}O and ^{14}N chemical shifts[a] of N,N'-substituted oxamides and quinoxaline-2(1H),3(4H)-diones, saturated solutions in DMSO at 90°C[8].

Compound	$\delta(^{17}O)$ CONH	$\delta(^{17}O)$ NO_2	$\delta(^{14}N)$ CONH	$\delta(^{14}N)$ NO_2
N,N'- dimethyloxamide (**1**)	291.9		-280.6	
N,N'- diethyloxamide (**2**)	290.4		-264.7	
N,N'- diphenyloxamide (**3**)	313.2		-253.8	
Quinoxaline-2(1H),3(4H)-dione (**4**)	327.7		-232.7	
6,7-dinitroquinoxaline-2(1H),3(4H)-dione (**5**)	351.7	603.4	-232.9	-16.1

[a]The chemical shifts (ppm) were measured relative to 1,4-dioxane (^{17}O NMR) and nitromethane (^{14}N NMR).

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; ΔE 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.

The strong ^{17}O deshielding of N,N'-diphenyloxamide and quinoxaline-2(1H), 3(4H)-dione relative to N,N'-dimethyl and N,N'-diethyloxamide should be attributed to the partial keto character of the CO group due to delocalization of the nitrogen lone pair into the adjacent aromatic system. This is also in agreement with the ^{14}N chemical shift data which show increased deshielding along the series Ph>Et>Me. This may be reasonably explained by electronic changes involving an increase in π-bonding of the nitrogen atom through its lone electron pair when either an electron donor is introduced or the lone electron pair is delocalized into an adjacent aromatic system[9]. This is in agreement with the X-ray structural data of the diamide group in **4** giving C-O distances of 1.232 and 1.225 Å[10]. 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 are

significantly longer than the C-N distance of 1.315 Å in oxamide[11]. This implies a considerably greater keto character of the CO and less double bond character in the C-N bond in **4** due to delocalization of the nitrogen lone pair into the aromatic system. However, the magnitude of the ^{17}O and ^{14}N shift differences for **4** 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 **4**. Thus the effect of torsion angle variation in the diamide ring should be evaluated.

Recently Boykin and collaborators[12] pioneered the development of ^{17}O NMR spectroscopy as a tool for investigating steric perturbations of structure in organic compounds. 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. Furthermore, decreasing charge density at the oxygen is expected to lead to a contraction of the 2p orbitals and thereby a decrease in shielding (Eq. 1).

In the crystalline form, **4** 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.[13] have endeavoured to answer the matter by optimizing the ab initio structure with either C_{2V} or C_S (with H(N) and O distorted slightly upwards, and N and C(O) downwards) structural constraints. The total energies were found to be effectively identical, but for the C_{2V} structure was marginally lower. Our results, however, demonstrate that the flattened boat observed in the X-ray determination is probably an intrinsic property of the molecule in solution.

The strong deshielding of **5** by ≈24 ppm compared to **4** is probably the largest through six bond substituent effect so far observed. This cannot be attributed to a significant delocalization of the nitrogen lone pair into the aromatic ring and, subsequently, to the nitro group since the ^{14}N chemical shifts of **4** and **5** are identical. Furthermore, $\delta(^{17}O)$ of the nitro group (δ ≈603.4 ppm) is very similar to that of the o-dinitrobenzene (≈609 ppm). Thus a torsion angle of 36° is expected for the orientation of the nitro group 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[12(b)]. 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[14]. Thus, the reduction in shielding of the diamide oxygen should be attributed to 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 structure determinations and complications arising from an interplay of 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[12(c)], 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 an out-of-plane deformation of the CO group particularly for the 6,7-dinitro derivative. This combination of long range electronic and stereochemical effects may be important in explaining the chemical and biological reactivity of quinoxaline-2(1H),3(4H)-diones and their derivatives.

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