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Energetic and structural characterization of 2-R-3-methylquinoxaline-1,4-dioxides (R = benzoyl or *tert*-butoxycarbonyl): experimental and computational studies

José R. B. Gomes,[1] Emanuel A. Sousa,[1] Jorge M. Gonçalves,[1] Luís Gales,[2] Ana M. Damas,[2] Paula Gomes,[1] Siddharth Pandey,[3] William E. Acree Jr[4] and Maria D. M. C. Ribeiro da Silva[1]*

[1]Centro de Investigação em Química (CIQ), Departamento de Química, Faculdade de Ciências, Universidade do Porto (UP), Rua do Campo Alegre 687, P-4169-007 Porto, Portugal
[2]Instituto de Biologia Molecular e Celular (IBMC) and Instituto de Ciências Biomédicas de Abel Salazar (ICBAS), Universidade do Porto, Portugal
[3]Department of Chemistry, Indian Institute of Technology Delhi (IIT-Delhi), Hauz Khas, New Delhi 110016, India
[4]Department of Chemistry, University of North Texas (UNT), Denton, TX 76203-5070, USA

ABSTRACT: The gaseous standard molar enthalpies of formation of two 2-R-3-methylquinoxaline-1,4-dioxides (R = benzoyl or *tert*-butoxycarbonyl), at $T = 298.15$ K, were derived using the values for the enthalpies of formation of the compounds in the condensed phase, measured by static bomb combustion calorimetry, and for the enthalpies of sublimation, measured by Knudsen effusion, using a quartz crystal oscillator. The three dimensional structure of 2-*tert*-butoxycarbonyl-3-methylquinoxaline-1,4-dioxide has been obtained by X-ray crystallography showing that the two N—O bond lengths in this compound are identical. The experimentally determined geometry in the crystal is similar to that obtained in the gas-phase after computations performed at the B3LYP/6-311 + G(2d,2p) level of theory. The experimental and computational results reported allow to extend the discussion about the influence of the molecular structure on the dissociation enthalpy of the N—O bonds for quinoxaline 1,4-dioxide derivatives. As found previously, similar N—O bond lengths in quinoxaline-1,4-dioxide compounds are not linked with N—O bonds having the same strength. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: thermochemistry, bond dissociation energies, density functional theory calculations, nitrogen—oxygen bonds

INTRODUCTION

Quinoxaline 1,4-di-*N*-oxide derivatives are key structures in a large variety of biochemical processes and this justifies the biological and industrial significance of that group of compounds. In the last two decades, they have been synthesized and evaluated with the objective of determining the influence of different substituents in positions 2 and 3 of the quinoxaline ring on their biological activity.[1–6]

In fact, the quinoxaline 1,4-dioxides are a group of synthetic antibacterial agents largely used as medicinal feed additives[7,8] and they are also used as bioreductive cytotoxic agents/species.[9–11] Several compounds derived

from quinoxaline 1,4-dioxide, which were activated under hypoxic conditions, are at different stages of development to be used as drugs. These compounds are thought to be active due to the creation of cytotoxic radicals formed after N—O bond cleavage taking place in these *N*-dioxide compounds. Accordingly, the knowledge of the energetics of the N—O bonds in this class of compounds has a fundamental importance for the characterization of their behavior. Therefore, the thermochemical study of heterobicyclic molecules derived from quinoxaline *N,N'*-dioxide has been receiving special attention,[12–16] aimed at construction of relationships between the energetic and structural properties with the reactivities of such compounds,[15,17] in order to clarify the chemical behavior of this class of molecules.

The present work reports the standard ($p^o = 0.1$ MPa) molar enthalpies of formation, in the gaseous state, at $T = 298.15$ K, for two quinoxaline 1,4-dioxides derivatives, namely, 2-benzoyl-3-methylquinoxaline-1,4-dioxide

Correspondence to: M. D. M. C. Ribeiro da Silva, Centro de Investigação em Química (CIQ), Departamento de Química, Faculdade de Ciências, Universidade do Porto (UP), Rua do Campo Alegre 687, P-4169-007 Porto, Portugal.
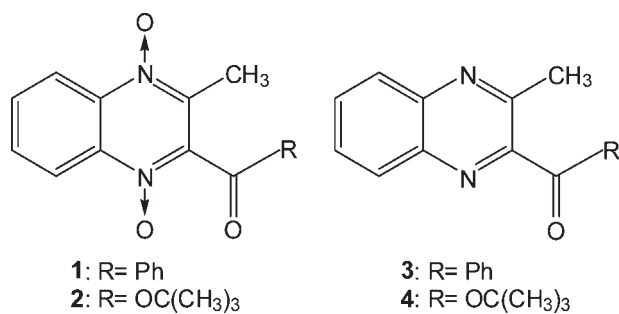E-mail: mdsilva@fc.up.pt

Figure 1. Structural formulas for **1**, 2-benzoyl-3-methyl-quinoxaline-1,4-dioxide, **2**, 2-*tert*-butoxycarbonyl-3-methyl-quinoxaline-1,4-dioxide, **3**, 2-benzoyl-3-methylquinoxaline and, **4**, 2-*tert*-butoxycarbonyl-3-methylquinoxaline

and 2-*tert*-butoxycarbonyl-3-methylquinoxaline-1,4-dioxide, represented in Figure 1. Those values were calculated from the experimental values of the enthalpies of combustion of the crystalline compounds and their enthalpies of sublimation. The experimental measurements were performed using static bomb calorimetry and Knudsen effusion techniques.

Density functional theory (DFT) calculations have been performed using the same approach used in other works[13,14,16] regarding the computation of the gas-phase N—O bond dissociation enthalpies (BDEs). From the consideration of the N—O (BDEs) for **1** and **2** and also of their standard molar gas-phase enthalpies of formation, $\Delta_f H_m^o(g)$, it was also possible to estimate the $\Delta_f H_m^o(g)$ for compounds **3** and **4**.

The crystal structure of compound **2** has been obtained by X-ray crystallography and the structural data, in clear agreement with the parameters coming from the DFT computations, are interpreted jointly with the mean N—O BDEs.

EXPERIMENTAL

Synthesis and characterization of compounds

Compound **1** was prepared by slow addition of (benzoylacetone + triethylamine) solution to a warm triethylamine solution containing benzofuroxan according to the published method of Haddadin *et al.*[18] The resulting solution was stirred for 24 h at ambient room temperature. The crude product was collected by vacuum filtration and washed with chilled triethlamine. The compound was further purified by three crystallizations from anhydrous methanol. Elemental analyses were in excellent agreement with calculated values: mass fraction for $C_{16}H_{12}N_2O_3$: found C, 0.6866, H, 0.0428, N, 0.1011; calculated: C, 0.6856, H, 0.0432, N, 0.0999.

Compound **2** was prepared from benzofuroxan and *tert*-butyl acetoacetate, following the method described by Robertson and Kasubick.[2] Benzofuroxan was suspended in isopropanol in a round-bottom flask, *tert*-butyl acetoacetate was added and the suspension was heated to

333 K in a water-bath. Calcium hydroxide was added portion-wise to the warm mixture, which immediately turned into an orange solution. A condenser was adapted to the flask and the reaction proceeded for 2.5 h, with monitoring by thin-layer chromatography. The crude product precipitated as a yellow solid directly from the reaction mixture upon cooling, being collected by suction filtration, rinsed with cold isopropanol, and recrystallized from methanol. Interestingly, large and well-defined crystals of pure **2** could be additionally isolated upon slow (over 1 week) evaporation of the remnant methanolic mother-liquor. Pure compound **2** was isolated as a bright yellow solid with correct spectroscopic and analytical data, as follows: δ_H (CDCl$_3$, 300 MHz): 8.55 (dd, $J = 7.16$ Hz; $J = 2.13$ Hz, 1H), 8.51 (dd, $J = 7.13$ Hz, $J = 2.23$ Hz, 1H), 7.81 (td, $J = 7.03$ Hz, $J = 1.77$ Hz, 1H), 7.76 (td, $J = 7.03$ Hz, $J = 1.77$ Hz, 1H); 2.53 (s, 3H), 1.62 (s, 9H); δ_C (CDCl$_3$, 75 MHz): 158.68, 138.63, 137.76, 136.89, 136.14, 132.29, 131.36, 120.25, 120.10, 86.26, 29.67, 27.98, 27.29; 14.17; mass fraction for $C_{14}H_{16}N_2O_4$: found C, 0.6089; H, 0.0595; N, 0.1011; calculated: C, 0.6086, H, 0.0584, N, 0.1014.

It should be emphasized that the control of reaction time is quite important for the successful synthesis of **2**, as maximum yield is achieved within 2.5 h; in our hands, longer reaction times led to loss of the *tert*-butyl ester group, that is, conversion of **2** into 2-methyl-quinoxaline-1,4-dioxide to a significant extent, as confirmed by ^{1}H-NMR, ^{13}C-NMR and elemental analysis (data not shown) of reaction products. It is also noteworthy that, in our hands, using Ca(OH)$_2$ as the base catalyst[2] for the synthesis reaction led to significantly improved yield and purity, as compared to syntheses carried out using morpholine[3–5] or triethylamine[4–6] as base catalysts. The synthesis of **2** has been recently described by Jaso *et al.*[6] who also used benzofuroxane and *tert*-butyl acetoacetate as starting materials; their procedure was based in the addition of 4 Å molecular sieves to a methanolic solution of those reactants, after which the methanol was evaporated at 293°C and the reaction allowed to proceed at 363°C on the surface of the molecular sieves for about 1 h, without drying. However, this synthetic method gave the desired compound **2** with only a 3% yield, after purification.

The average ratio of the mass of carbon dioxide recovered after combustion experiments to that calculated from the mass of samples (**1**: 0.9996 ± 0.0008, and **2**: 0.9997 ± 0.0004) confirmed the composition of the samples. The thermal behavior of the compounds were studied by differential scanning calorimetry. The thermograms show that there is no transition phase before the melting temperatures: 488 K (with decomposition) and 418 K, respectively for **1** and **2**.

Structural determination of 2

Single crystals of $C_{14}H_{16}N_2O_4$ were obtained during the synthesis of the compound, mounted on top of a

fiberglass, and transferred to the diffractometer. Diffraction data were collected at 293 K with a Stoe IPDS plate equipped with MoKα radiation ($\lambda = 0.71073$ Å).

Calorimetric measurements

The energies of combustion of **1** and **2** were measured with a static bomb calorimeter, with a twin valve bomb and an internal volume of 0.290 dm^3, assembled originally in Teddington,[19,20] and now installed in Thermochemistry Laboratory, at the University of Porto.[21] The energy equivalent of the calorimeter was determined from the combustion of benzoic acid (BDH Thermochemical Standard, batch 693976/01) having a massic energy of combustion, under standard bomb conditions, of $-(26435.1 \pm 3.5)$ J·g^{-1}. The calibration results were corrected to an energy equivalent ε(calor) corresponding to an average mass of water added to the calorimeter of 2900.0 g. Seven calibration experiments were made in oxygen atmosphere at $p = 3.04$ MPa, with 1.00 cm^3 of water added to the bomb, leading to an energy equivalent of the calorimeter ε(calor) = (15551.6 ± 2.6) J·K^{-1}, where the uncertainty quoted is the standard deviation of the mean.

The samples were ignited, in pellet form, in oxygen atmosphere ($p = 3.04$ MPa) at $T = 298.15$ K, with 1.00 cm^3 of water inside the bomb. The small amount available for **2** led us to use *n*-hexadecane as an auxiliary combustion material (standard massic energy of combustion, $\Delta_c u^o = -(47160.8 \pm 4.1)$ J·g^{-1}) in the combustion experiments, in order to produce an appropriate increase of temperature. For the cotton thread fuse of empirical formula CH$_{1.686}$O$_{0.843}$, $\Delta_c u^o = -16250$ J·g^{-1}.[22] Corrections for nitric acid formation were based on -59.7 kJ·g^{-1} for the molar energy of formation of 0.1 mol·dm^3 HNO$_3$(aq) from N$_2$(g), O$_2$(g), and H$_2$O(l).[23] At $T = 298.15$ K, $(\partial u/\partial p)_T$ for the solid was assumed to be -0.2 J·g^{-1}·MPa^{-1}, a typical value for organic solids. The amount of compound burnt in each experiment was determined from the total mass of carbon dioxide produced after allowance for that resulted from the cotton thread fuse and *n*-hexadecane. For each experiment, the value of $\Delta_c u^o$ was calculated by using the procedure given by Hubbard *et al.*[24] The relative atomic masses used throughout this paper were those recommended by the IUPAC Commission in 2001.[25]

Knudsen effusion technique

For both 2-R-3-methyl-quinoxaline-1,4-dioxide derivatives, the respective standard molar enthalpies of sublimation were determined using a quartz crystal microbalance,[26,27] by the Knudsen effusion method. The effusion system was previously tested with three compounds (benzanthrone, squaric acid, and

4-hydroxy-2-methylquinoline), and there was an excellent agreement among the results obtained with those reported in the literature. The vapor effusing from the Knudsen cell was allowed to condense on a quartz crystal positioned above the effusion hole; changes in the frequency of oscillation of the quartz crystal, Δf, were proportional to the mass condensed in its surface,[28] $\Delta f = C_f \Delta m$, where C_f is a proportionality constant. From the Knudsen equation, the vapor pressure is given by Eqn (1), where $(\Delta m/\Delta t)$ is the rate of mass loss, a is the effective area of the effusion hole, and M is the molar mass of the effusing vapor.

$$p = (\Delta m/\Delta t) \cdot a^{-1} \cdot (2\pi RT/M)^{1/2} \qquad (1)$$

The measured rate of change of frequency of oscillation with time, $v = \Delta f/\Delta t$, is directly proportional to the rate of sublimed mass of the crystalline sample,[28] $v = C_f \Delta m/\Delta t$, so it is possible to establish the Eqn (2), relating directly the vapor pressure with v.

$$p = \frac{v \cdot T^{1/2} \cdot (2\pi R/M)^{1/2}}{a \cdot C_f} \qquad (2)$$

Using the integrated form of the Clausius–Clapeyron equation, the enthalpy of sublimation, $\Delta_{cr}^g H_m^o$, is derived from the slope of $\ln(v\,T^{1/2})$ against T^{-1}. From at least five independent sets of experimental measurements of the frequency of the quartz oscillator for each compound, at convenient temperature intervals, it was possible to obtain independent results for the enthalpy of sublimation of each compound, referenced to the mean temperature of the experimental range.

Theoretical details

The Gaussian 03 suite of program[29] has been used to compute, at the B3LYP level of theory,[30] structural and energetic details for all compounds considered here. The density functional theory based B3LYP method uses the exchange functional introduced by Becke in 1988 together with the LYP correlation functional of Lee *et al.*[31,32]

The atomic electron density of hydrogen, carbon, nitrogen, and oxygen atoms has been described with two different basis sets. The 6-31G*(d) basis set has been used to fully-optimize the geometry of all compounds and to compute the vibrational frequencies. The absence of negative frequencies ensured that all structures were minima on the potential energy surface. These calculations permitted us to extract the thermal corrections for $T = 298.15$ K as well as to obtain structural guesses for the calculations performed with a larger basis set. The larger basis set was the 6-311 + G(2d,2p) basis set, which was used only for the full-optimization of the structures of all compounds. Finally, the enthalpies of all compounds were obtained by combining the energy coming from the

calculations completed at the highest level of theory and the thermal corrections retrieved from the scaled vibrational frequency (factor = 0.98) calculations performed at the B3LYP/6-31G(d) level. For the open-shell species, namely the gas-phase oxygen atom, the unrestricted UB3LYP approach has been employed both for the calculation of the total energy and corresponding thermal corrections.

RESULTS AND DISCUSSION

Crystal structure determination of $C_{14}H_{16}N_2O_4$

The crystal structure of $C_{14}H_{16}N_2O_4$ was solved using SHELXS[33] and refined using SHELXL[34] program. C5 to C8-bound hydrogen atoms were refined freely with isotropic displacement parameters while all of the hydrogen's from the methyl groups were positioned with idealized geometry and refined riding on their parent C atoms at distances of 0.93 Å, with U_{iso} (H) = 1.2 U_{eq} (C). Tables containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are deposited with the Cambridge Crystallographic Data Centre (CCDC reference number 633371). Briefly, the most important details for this crystallographic structure are: $M = 276.29$, monoclinic, $a = 5.9167(18)$ Å, $b = 9.708(5)$ Å, $c = 12.051(4)$ Å, $U = 690.7$ Å^3, $T = 290$ K, space group $P2_1$ (no. 4), $Z = 2$, μ(Mo-Kα) = 0.099 mm^{-1}, 8018 reflections measured, 1737 unique ($R_{int} = 9.84$) which were used in all calculations. The final $R(F_2)$ was 0.056 and the final $wR(F_2)$ was 0.152 (all data).

A perspective view of the compound, obtained using ORTEP[35] and showing the atomic numbering scheme is presented in Figure 2. The N1—O1 and the N2—O2 bond lengths are 1.286(2) Å and 1.288(2) Å, respectively, which are in the upper limit of the data retrieved for 158 N—O groups, with N belonging to a ring system (the N—O distance ranges between 1.22–1.31 Å) from the crystal structures deposited in the Cambridge Crystallographic Data Base. Moreover, these N—O distances are in good
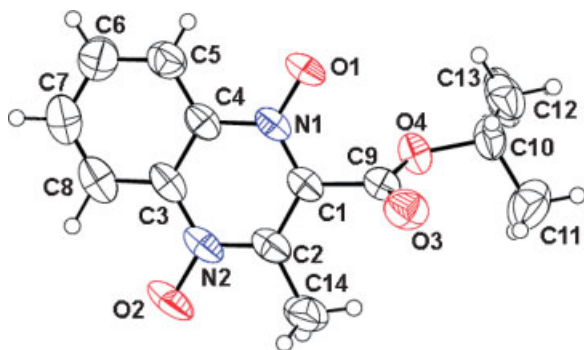
agreement with those of other quinoxaline-1,4-dioxide derivatives;[36–42] a total of 10 crystal structures are available in the Cambridge Crystallographic Data Base and the N—O distances range between 1.28–1.31 Å. In three of these compounds,[36–38] the crystallographic packing leads to hydrogen bonds involving the oxygen atom of the N—O group, which may contribute to the elongation of this bond. This is the case for 2-(N-(2-hydroxyethyl)carboxamide)-3-methylquinoxaline 1,4-dioxide,[36] very similar to **2**, that displays N—O distances of 1.286 and 1.304 Å. However, the N—O group with a bond length of 1.304 Å is involved in an intermolecular hydrogen bond with the N—H bond of the N-(2-hydroxyethyl)carboxamide. In compound **2**, there is no evidence for intermolecular hydrogen bonding involving the oxygen atoms. Another synthesized heteroaromatic N-oxide with high similarity to **2** is 2-methyl-3-carboethoxyquinoxaline.[39] The crystal structure of this compound shows that there are no hydrogen bonds in the crystal packing and that the N—O bond lengths are slightly longer (1.292 and 1.303 Å) than the N—O bond lengths in **2**.

Calorimetric studies

The standard enthalpies of formation in condensed phase, at $T = 298.15$ K, for the two quinoxaline 1,4-dioxide derivatives were calculated from the respective massic energies of combustion, $\Delta_c u^o$, determined by static bomb calorimetry. Typical results for one combustion experiment of each compound are presented in Table 1. The energy involved in the isothermal bomb process, ΔU(IBP), after ignition of the samples at $T = 298.15$ K, is derived from Eqn (3), where ΔT_{ad} is the calorimeter temperature change corrected for heat exchange and the work of stirring, $\Delta m(H_2O)$ is deviation of the mass of water added to the calorimeter from 2900.0 g (the mass assigned for

Figure 2. View of the molecular structure of $C_{14}H_{16}N_2O_4$, showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are represented by circles of arbitrary size

Table 1. Typical combustion experiments for **1** and **2**, at $T = 298.15$ K

	1	**2**
$m(CO_2, \text{total})$/g	1.17997	1.61510
$m(\text{cpd})$/g	0.46797	0.44734
$m(\text{hexadecane})$/g	—	0.19711
$m'(\text{fuse})$/g	0.00265	0.00282
ΔT_{ad}/K	0.86723	1.37144
ε_f/(J K^{-1})	13.71	14.94
$\Delta m(H_2O)$/g	−0.10	1.20
$-\Delta U$(IBP)/J^a	13497.77	21354.93
ΔU(HNO$_3$)/J	31.04	32.24
ΔU(ign)/J	0.61	0.60
ΔU_Σ/J	9.65	10.57
ΔU(hexadecane)/J	—	9296.06
ΔU(fuse)/J	43.10	45.80
$-\Delta_c u^o$/J g^{-1}	28664.19	26758.75

^{a} ΔU(IBP) already includes the ΔU(ign).

ε(calor)), ΔU_Σ is the correction to the standard state and the remaining terms were previously described.[24]

$$\Delta U(\text{IBP}) = -\left\{\varepsilon(\text{calor}) + c_p(\text{H}_2\text{O, l}) \cdot \Delta m(\text{H}_2\text{O}) + \varepsilon_f\right\}$$
$$\Delta T_{ad} + \Delta U(\text{ign})$$

(3)

The corresponding values of the standard molar energy, of combustion, $\Delta_c U_m^0(\text{cr})$, and the standard molar enthalpy of combustion, $\Delta_c H_m^0(\text{cr})$ were calculated using the mean values of massic energy of combustion, $\langle\Delta_c u^o\rangle$, of the crystalline compounds, at $T = 298.15$ K. The value of the standard molar enthalpy of formation in the crystalline state for each of the compounds, $\Delta_f H_m^o(\text{cr})$, was calculated using the corresponding value for $\Delta_c H_m^o(\text{cr})$ and the values for the standard molar enthalpies of formation for $\text{H}_2\text{O(l)}$ and for $\text{CO}_2\text{(g)}$ taken from the literature,[43] $-(285.83 \pm 0.04)$ kJ $\cdot$ mol^{-1} and $-(393.51 \pm 0.13)$ kJ $\cdot$ mol^{-1}, respectively. Table 2 presents a resume of the final results of these parameters derived for the two compounds.

Knudsen effusion measurements

The results for the determination of the standard molar enthalpies of sublimation of **1** and **2**, obtained by the Knudsen method, are summarized in Tables 3 and 4, respectively, together with the mean temperatures of the experimental ranges and the standard molar enthalpies of sublimation at these mean temperatures, $\Delta_{cr}^g H_m^o(\langle T \rangle)$; the parameter of the Clausius–Clapeyron equation corresponding to the slope was obtained using a least square fitting of the experimental data. The value of $\Delta_{cr}^g H_m^o(\langle T \rangle)$ was corrected to $T = 298.15$ K assuming $\Delta_{cr}^g C_{p,m}^o = -50$ J $\cdot$ K^{-1} $\cdot$ mol^{-1},[26] yielding the final $\Delta_{cr}^g H_m^o$. The uncertainties assigned are twice the overall standard deviations of the mean.

Experimental gaseous standard molar enthalpies of formation

The experimental results for the standard molar enthalpies of formation and sublimation of crystalline

Table 2. Derived standard ($p^o = 0.1$ MPa) molar energies of combustion, $\Delta_c U_m^o$, standard molar enthalpies of combustion, $\Delta_c H_m^o$, and standard molar enthalpies of formation, $\Delta_f H_m^o$, for crystalline **1** and **2** compounds at $T = 298.15$ K

Compound	$\dfrac{-\Delta_c u^o}{\text{J} \cdot \text{g}^{-1}}$	$\dfrac{-\Delta_c U_m^o(\text{cr})}{\text{kJ} \cdot \text{mol}^{-1}}$	$\dfrac{-\Delta_c H_m^o(\text{cr})}{\text{kJ} \cdot \text{mol}^{-1}}$	$\dfrac{\Delta_f H_m^o(\text{cr})}{\text{kJ} \cdot \text{mol}^{-1}}$
1	28666.5 ± 5.6	8034.7 ± 4.3	8035.9 ± 4.3	24.8 ± 4.3
2	26758.5 ± 8.2	7393.1 ± 5.3	7395.6 ± 5.3	-400.2 ± 5.6

Table 3. Parameters of Clausius–Clapeyron equation and standard enthalpies of sublimation for **1**: $\Delta_{cr}^g H_m^o(298.15 \text{ K}) = 153.8 \pm 1.8$ kJ $\cdot$ mol^{-1}

Exp.	T/K	$\langle T \rangle$/K	a	$-b$/K^{-1}	r	$\dfrac{\Delta_{cr}^g H_m^o(\langle T \rangle)}{\text{kJ} \cdot \text{mol}^{-1}}$	$\dfrac{\Delta_{cr}^g H_m^o(298.15 \text{ K})}{\text{kJ} \cdot \text{mol}^{-1}}$
1	393.1–408.1	400.7	46.57 ± 0.29	18039 ± 115	0.9999	150.0	155.1
2	394.6–403.5	399.2	46.47 ± 0.55	17993 ± 220	0.9998	149.6	154.6
3	383.1–398.1	390.7	45.75 ± 0.93	17754 ± 363	0.9992	147.6	152.2
4	385.7–400.6	393.2	46.19 ± 0.16	17945 ± 67	0.9999	149.2	153.9
5	381.6–396.8	389.2	45.14 ± 0.52	17539 ± 203	0.9997	145.8	150.4
6	386.5–401.7	394.2	46.96 ± 0.43	18252 ± 168	0.9998	151.7	156.5

Table 4. Parameters of Clausius–Clapeyron equation and standard enthalpies of sublimation for **2**: $\Delta_{cr}^g H_m^o(298.15 \text{ K}) = 164.1 \pm 1.8$ kJ mol^{-1}

Exp.	T/K	$\langle T \rangle$/K	a	$-b$/K^{-1}	r	$\dfrac{\Delta_{cr}^g H_m^o(\langle T \rangle)}{\text{kJ} \cdot \text{mol}^{-1}}$	$\dfrac{\Delta_{cr}^g H_m^o(298.15 \text{K})}{\text{kJ} \cdot \text{mol}^{-1}}$
1	363.2–372.3	367.8	53.94 ± 1.82	19252 ± 667	0.9988	160.1	163.6
2	359.2–371.1	365.3	54.20 ± 1.45	19146 ± 533	0.9992	159.2	162.5
3	362.2–370.1	366.2	55.63 ± 1.08	19701 ± 393	0.9994	163.8	167.2
4	357.3–369.7	363.4	54.05 ± 1.09	19110 ± 397	0.9991	158.9	162.1
5	356.7–369.2	363.3	54.97 ± 2.66	19444 ± 968	0.9963	161.7	164.9

Table 5. Derived standard ($p^o = 0.1$ MPa) molar enthalpies of formation, $\Delta_f H^o_m$, and standard molar enthalpies of sublimation, $\Delta^g_{cr} H^o_m$, for compounds **1** and **2** at $T = 298.15$ K

Compound	$\dfrac{\Delta_f H^o_m(\text{cr})}{\text{kJ} \cdot \text{mol}^{-1}}$	$\dfrac{\Delta^g_{cr} H^o_m}{\text{kJ} \cdot \text{mol}^{-1}}$	$\dfrac{\Delta_f H^o_m(\text{g})}{\text{kJ} \cdot \text{mol}^{-1}}$
1	24.8 ± 4.3	153.8 ± 1.8	178.6 ± 4.7
2	-400.2 ± 5.6	164.1 ± 1.8	-236.1 ± 5.9

1 and **2** allow us to calculate the gaseous enthalpies of formation, at $T = 298.15$ K, for these quinoxaline 1,4-dioxides derivatives. The final standard molar enthalpies of formation, $\Delta_f H^o_m$, in both crystalline and gaseous states, as well as the standard molar enthalpies of sublimation, $\Delta^g_{cr} H^o_m$, at $T = 298.15$ K, for the two compounds are summarized in Table 5.

Computed geometries and N—O bond dissociation enthalpies

The present DFT approach was previously found to be suitable for the optimization of the structures of these kinds of compounds.[13] Views of the B3LYP/6-311 + G(2d,2p) fully-optimized geometries of **1** and **2** are depicted in Figure 3 where selected bond lengths and angles are also included. The bond lengths and angles are very similar for both compounds suggesting that the influence of the R group (see Figure 1) is almost the same in both cases. The largest differences are found for the C=O and C(=O)—C bond lengths but, even in these two cases, they are lower than 0.01 Å. The comparison between the experimental and computational geometries for **2** reveals that the DFT method yields bond lengths that almost match the experimental results. Again, the largest difference in bond lengths is found for the C=O group. The X-ray result is 1.191 Å while the B3LYP/6-311 + G(2d,2p) value is 1.204 Å. The experimental NCCO dihedral angle, white dotted line in Figure 3, is 109.3° while the computed value is only 101.4° which is a consequence of the different physical state of the molecule in experimental and computational investigations. In the X-ray experiments, the lateral intermolecular interactions in the packed crystalline state are
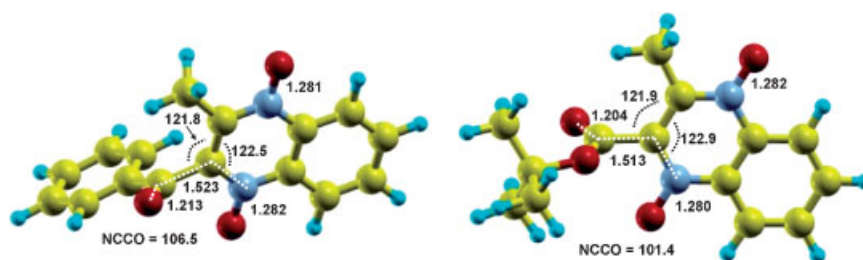

Figure 4. First, second, and total (N–O) bond dissociation enthalpies for (a) compound **1** and (b) compound **2**. All values are in $\text{kJ} \cdot \text{mol}^{-1}$

probably the cause for a COR moiety that is less normal with respect to the quinoxaline ring. Interestingly, the N—O bonds lengths seem to be unaffected if the bond is adjacent to a —CH$_3$ or to a —COR group.

The B3LYP/6-311 + G(2d,2p)//B3LYP/6-31G(d) values for the first, second, total, and mean N—O bond dissociation enthalpies for compounds **1** and **2**, and corresponding derivatives, are given in Figure 4. The gas-phase calculations suggest that, in principle, both compounds will have a similar behavior regarding their promptness to form active cytotoxic radicals. In fact, these two bulky R groups have been chosen in order to see if at least one of the N—O bonds was weakened, lowering the energy required to cleave the bond and, in principle, leading to easy formation of active cytotoxic radicals. However, the enthalpies of dissociation are nearly the same as those computed previously for 2-ethoxy-carbonyl-3-methylquinoxaline-1,4-dioxide (R group in Figure 1 is —OCH$_2$CH$_3$); first is 242.9 kJ · mol^{-1}, second is 267.0 kJ · mol^{-1} and total is 510.0 kJ · mol^{-1}.[13] Therefore, it is concluded that attaching these three different R groups to the carbonyl substituent in position 2 of the quinoxaline ring has little influence on the strength of the N—O bonds. A possible explanation for this may be due to the ability of the carbonyl group to attract and

Figure 3. B3LYP/6-311+G(2d,2p) optimized structures of compounds **1** (left) and **2** (right). Selected bond lengths and angles are in Å and in degrees, respectively

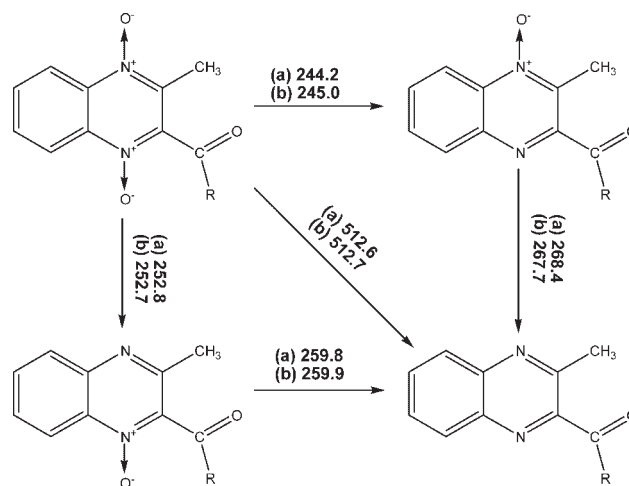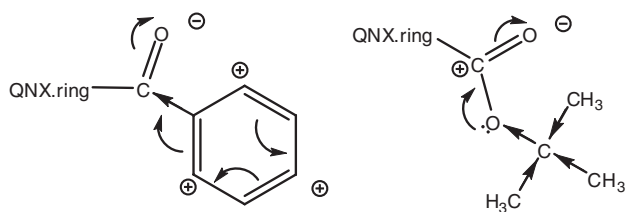**Scheme 1**

attenuate the electron density coming from the different R groups due to mesomeric or inductive effects. Consequently, the carbonyl 'absorbs' the electronic character of the different R groups, blocking any effect that these might exert on the quinoxaline ring, cf. Scheme 1.

In order to test this hypothesis, the dissociation enthalpy of the two N—O bonds of 2-p-nitrobenzoyl-3-methylquinoxaline-1,4-dioxide have also been calculated at the same B3LYP/6311 + G(2d,2p)//B3LYP/6-31G(d) level of theory. This compound was considered since it is expected that the nitro group would also attract electron charge from the aromatic ring and, therefore, it is supposed to lead to a different electronic —C(=O)R environment that would affect the computed N—O bond dissociation enthalpy. The computed total enthalpy for the cleavage of the two bonds is $510.2 \, \text{kJ} \cdot \text{mol}^{-1}$, which yields a mean bond dissociation enthalpy for the two N—O bonds of $255.1 \, \text{kJ} \cdot \text{mol}^{-1}$. This value is identical to those reported above, though somewhat smaller ($5 \, \text{kJ} \cdot \text{mol}^{-1}$) than that reported for 2-benzyl-3-methylquinoxaline-1,4-dioxide.[13] Thus, it seems that all —C(=O)R substituents bonded directly to the quinoxaline-1,4-dioxide ring in positions 2 or 3 will have a similar effect on the strength of the N—O bonds leading to identical enthalpies to cleave these bonds in this class of compounds.

Finally, the similar lengths calculated for the N—O bonds in the two title compounds, and also for other differently substituted quinoxalines-1,4-dioxides,[13,14] do not necessarily imply that all N—O dative bonds will have the same energy.

Estimated enthalpies of formation

The enthalpies of formation of compounds **3** and **4** have been estimated after the consideration of the enthalpy of the following reaction:

$$\textbf{1} \text{ or } \textbf{2} \text{ (g)} \rightarrow \textbf{3} \text{ or } \textbf{4} \text{ (g)} + 2 \, {}^3\text{O (g)} \qquad (4)$$
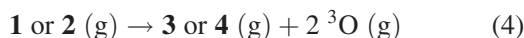
which is the same as after consideration of the total N—O BDEs shown in Figure 4, for the loss of both oxygen atoms in **1** or **2**, and the $\Delta_f H^o_m$ listed in Table 5 for compounds **1** and **2** and for atomic oxygen available in the literature.[43] This strategy was found to be an adequate approach for the estimation of the enthalpy of formation of a very similar compound, namely, 2,3-dimethylquinoxaline,[13] and so, supposedly it should be also a good

approach in this case. The $\Delta_f H^o_m$ values computed for **3** and **4** are $192.9 \, \text{kJ} \cdot \text{mol}^{-1}$ and $-221.7 \, \text{kJ} \cdot \text{mol}^{-1}$, respectively. The reader should be aware of the uncertainties associated with both the experimental $\Delta_f H^o_m$ (g) for **1** and **2** and the computed N—O BDEs. Therefore, the estimated $\Delta_f H^o_m$ values for the compounds **3** and **4** are associated with an uncertainty of $\sim 10 \, \text{kJ} \cdot \text{mol}^{-1}$.

CONCLUSIONS

Complementary experimental and computational studies on both structural and energetic aspects of two quinoxaline-1,4-dioxide derivatives have been performed. The two compounds studied differ from other studied previously by the presence of two bulky substituents attached to the quinoxalinic ring at position 2. Experimental and computational techniques yield the same answer about the N—O bond lengths, that is, they have almost the same size. However, previous work on an analogue of Tirapazamine, 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide,[14] the similar bond lengths are not necessarily connected with bonds having the same strength and, thus, require different energy for their cleavage. Also interesting is the fact that the N—O BDEs are affected only by the type of atoms attached directly to the quinoxalinic ring. As shown above, the difference between the N—O BDEs calculated for several 2-R-3-methylquinoxaline-1,4-dioxides, with R = —COR', is almost negligible, even if R' changes from an ethyl group to a tert-butyl or phenyl group.

The combination of experimental and computational techniques allowed also to determine the standard molar gas-phase enthalpies of formation of 2-benzoyl-3-methylquinoxaline and 2-tert-butoxycarbonyl-3-methylquinoxaline, and of their corresponding 1,4-dioxide derivatives.

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