Synthesis and thermochemical study of quinoxaline-*N*-oxides: enthalpies of dissociation of the N–O bond

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The synthesis of three new quinoxaline mono-*N*-oxides derivatives, namely, 2-*tert*-butoxycarbonyl-3-methylquinoxaline-*N*-oxide, 2-phenylcarbamoyl-3-ethylquinoxaline-*N*-oxide, and 2-carbamoyl-3-methylquinoxaline-*N*-oxide, from their corresponding 1,4-di-*N*-oxides is reported. Samples of these compounds were used for a thermochemical study, which allowed derivation of their gaseous standard molar enthalpies of formation, $\Delta_f H_m^o$ (g), from their enthalpies of formation in the condensed phase, $\Delta_f H_m^o$ (cr), determined by static bomb combustion calorimetry, and from their enthalpies of sublimation, $\Delta_{cr}^g H_m^o$, determined by Calvet microcalorimetry. Finally, combining the $\Delta_f H_m^o$ (g) for the quinoxaline-*N*-oxides derived in this work with literature values for the corresponding 1,4-di-*N*-oxides and atomic oxygen, the bond dissociation enthalpies for cleavage of the first N—O bond in the di-*N*-oxides, DH_1(N–O), were obtained and compared with existing data. Copyright © 2011 John Wiley & Sons, Ltd.
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Keywords: dissociation enthalpy N–O bond; quinoxaline mono-*N*-oxides derivatives; synthesis; thermochemistry

INTRODUCTION

The interest in a large range of compounds with the *N*-oxide functional group has been expanded significantly over the past two decades because of their remarkable success in a broad variety of applications as oxidizing agents. Some of these compounds, particularly the quinoxaline derivatives, assumed relevant importance because of their selective biological activities[1–6] related with inherent pharmacological and toxicological properties.[7,8] Energetic studies on compounds containing terminal N—O bonds in different molecular environments have been developed in our research group,[9–18] with the main goal of evaluating the influence of the chemical vicinity on that bond. In this context, computational and experimental studies have been extensively developed for quinoxaline 1,4-di-*N*-oxides.[9–20] More recently, with the possibility of synthesizing very pure samples of two quinoxaline derivatives containing only a single dative N–O bond, the first experimental thermochemical study for quinoxaline-*N*-oxide derivatives has been reported.[13] The present work reports the experimental study of the energetics of three new quinoxaline mono-*N*-oxide derivatives whose structures are represented in Scheme 1, that is, 2-*tert*-butoxycarbonyl-3-methylquinoxaline-*N*-oxide (**4.1**), 2-phenylcarbamoyl-3-methylquinoxaline-*N*-oxide (**4.2**), and 2-carbamoyl-3-methylquinoxaline-*N*-oxide (**4.3**). Their syntheses have been performed from the corresponding 1,4-di-*N*-oxides (compounds **3.1–3.3**, Scheme 1) by selective reduction.

The standard ($p^o = 0.1$ MPa) massic energies of combustion in oxygen of the three compounds were measured with a high precision static bomb calorimeter, from which the values of the standard molar enthalpies of formation in the crystalline phase at $T = 298.15$ K were derived. The enthalpies of sublimation of the three compounds were determined from high temperature Calvet microcalorimetry measurements. Combining the standard molar enthalpies of formation in the crystalline phase with the enthalpies of sublimation of each compound, the corresponding standard ($p^o = 0.1$ MPa) molar enthalpies of formation in the gas phase at $T = 298.15$ K were obtained. The latter results were used to obtain the experimental values for the first N—O bond dissociation enthalpy in the parent di-*N*-oxide quinoxalines based on their standard molar enthalpies of formation in the gas phase that were previously reported in the literature.[11,12]

EXPERIMENTAL

Synthesis and purification

The quinoxaline di-*N*-dioxides (**3.1–3.3**, Scheme 1) were prepared from benzofuroxan (**1**) and the appropriate β-ketoester/amide (**2**) following the method described by Robertson and Kasubick.[21] Briefly,

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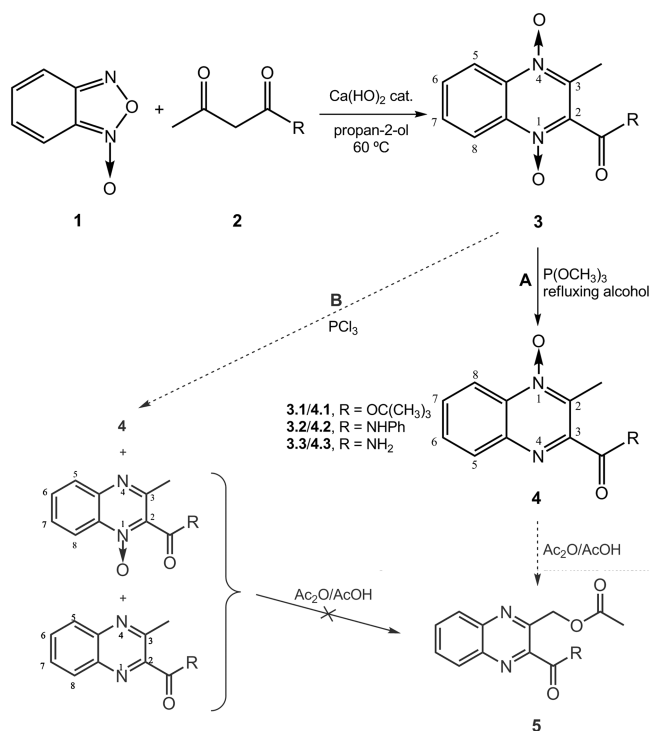
Scheme 1. Synthetic route (in black) to quinoxaline mono-N-oxides **4.1–4.3** via regioselective monodeoxygenation of **3.1–3.3** with trimethyl phosphite (**A**); smaller structures in grey (including nonregioselective reduction of **3** with phosphorus trichloride, (**B**), are included to provide pictorial support to the Discussion section

benzofuroxan (**1**, 1 mmol) was suspended in propan-2-ol and the appropriate β-ketoester/amide (**2**, 0.7 mmol) was added. The reaction was allowed to proceed at 60 °C for about 30 (**3.2**, **3.3**) to 150 (**3.1**) min on a thermostated water bath, then a catalytic amount of calcium hydroxide (0.05 mmol) was added portion-wise periodically. Di-N-oxides **3.2** and **3.3** readily precipitated from the reaction mixture and were simply isolated by suction filtration followed by thorough washing of the solid with ice-cold propan-2-ol. In turn, di-N-oxide **3.1** was significantly soluble in the reaction medium and had to be isolated by adsorption liquid chromatography on silica, using dichloromethane/methanol 40 : 1 (v/v) as eluant. All the di-N-oxides **3.1–3.3** were obtained as tan solids in 54% (**3.1**) to quantitative (**3.2**, **3.3**) yields.

The **3** compounds were then selectively monodeoxygenated with trimethyl phosphite, as described by Dirlam and McFarland.[22] In brief, the di-N-oxides (0.05 mmol) were suspended in either propan-2-ol (**3.1**) or methanol (**3.2**, **3.3**), then trimethyl phosphite (0.03 mmol) was added and the mixture refluxed for 2 h. The N-oxides, **4.1–4.3**, were precipitated from the reaction mixture upon cooling to room temperature and were isolated by suction filtration followed by thorough washing with ice-cold methanol. N-Oxides **4.1** and **4.3** were additionally submitted to purification by column chromatography on silica, using dichloromethane/methanol mixtures as eluants. After a final step of recrystallization from methanol for all **4** compounds, they were obtained as pale tan solids in 10 (**4.3**) to 50% (**4.1**, **4.2**) yields. The structures and composition of **4.1–4.3** were confirmed by electrospray ionization–ion trap mass spectrometry (ESI–IT MS), proton ([1]H-) and carbon-13 ([13]C-) nuclear magnetic resonance (NMR) and elemental analysis. All analytical and spectral data, and spectral traces and compound melting temperatures, are provided in the Supplementary Material.

Prior to the calorimetric measurements, the compounds were dried under high-vacuum conditions. The composition of both compounds were confirmed by the ratio of the mass of carbon dioxide recovered in

the combustion experiments to that calculated from the mass of the sample; the average ratios and the respective uncertainties (twice the standard deviation of the means) were 0.9997 ± 0.0005 for **4.1**, 1.0006 ± 0.0002 for **4.2**, and 1.0012 ± 0.0007 for **4.3**.

The specific densities of the different samples were assumed to be 1.0 g·cm^{-3}, estimated from the mass and volume of pellets of each compound.

The relative atomic masses used for the elements were those recommended by the IUPAC Commission in 2007.[23]

Static bomb combustion calorimetry

The energies of combustion of compounds **4.1–4.3** were measured using a static bomb calorimeter, whose bomb with an internal volume 0.290 dm^3 has a twin valve system as previously reported.[24–26]

The energy equivalent of the calorimeter ε(calor) was determined using benzoic acid ([CAS 65-85-0], Standard Reference Material (SRM 39j) supplied by the National Institute of Standards and Technology), having a massic energy of combustion, under bomb conditions, of −(26434 ± 3) J·g^{-1}. The energy equivalent of the calorimeter ε(calor) = (15546.3 ± 1.3) J·K^{-1} (the uncertainty quoted is the standard deviation of the mean), corresponding to an average mass of 2900.0 g of water added to the calorimeter, was determined from eight calibration experiments made under oxygen at $p = 3.04$ MPa and using 1.00 cm^3 of water added to the bomb.

For the combustion experiments, the crystalline samples were burnt in pellet form. Because the yields on the synthesis of the compounds were low, we decided to decrease the amount of compound used in each experiment and used n-hexadecane (CAS 544-76-3, ≥ 99%, Aldrich Chemical Co. (Milwaukee, Wisconsin, USA)) as an auxiliary of the combustion measurements to achieve the adequate rise in temperature during the combustion. The measured standard massic energy of combustion of the sample of n-hexadecane used for the studies of compounds **4.1** and **4.2** was $−\Delta_c u^o$(l)= (47,150.4 ± 2.4) J·g^{-1}, while that for **4.3** was $−\Delta_c u^o$(l)= (47,193.3 ± 3.3) J·g^{-1}.

All the samples were ignited at $T = (298.150 ± 0.001)$ K in oxygen at $p = 3.04$ MPa with 1.00 cm^3 of deionized water previously added to the bomb. The electrical energy for ignition ΔU(ign.) was determined from the change in potential difference across a 1400 μF capacitor when discharged through the platinum ignition wire. For the cotton thread fuse, with empirical formula $CH_{1.686}O_{0.843}$, the massic energy of combustion is $\Delta_c u^o = -16,240$ J·g^{-1}.[27] The corrections for nitric acid formation, ΔU(HNO$_3$), were based on the value -59.7 kJ·mol^{-1},[28] 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). An estimated pressure coefficient of specific energy: $(\partial u/\partial p)_T = -0.2$ J·g^{-1}·MPa^{-1} at $T = 298.15$ K, a typical value for most organic compounds,[29] was assumed. The mass of compound, m(cpd), used in each experiment was determined from the total mass of carbon dioxide, m(CO$_2$, total), produced after an allowance for that formed from the combustion of the cotton thread fuse and the n-hexadecane. For each compound, the standard massic energy of combustion, $\Delta_c u^o$, was calculated using the procedure given by Hubbard et al.[30]

Calvet microcalorimetry

The standard molar enthalpies of sublimation of compounds **4.1–4.3** were measured by Calvet High Temperature Microcalorimetry, using the 'vacuum-sublimation drop microcalorimetric method'.[31] Samples of about 3–5 mg contained in a thin glass capillary tube were dropped at room temperature into a hot reaction vessel in a high temperature Calvet microcalorimeter (SETARAM HT 1000D (Lyon, France)) held at $T = 390$ K, $T = 443$ K, and $T = 458$ K for compounds **4.1**, **4.2**, and **4.3**, respectively, and then removed from the hot zone by vacuum sublimation. The observed enthalpies of sublimation were corrected to $T = 298.15$ K, using $\Delta_{298.15\,K}^T H_m^o$(g), estimated by a group method of enthalpic contributions based on Eqn 1 using data from Stull et al.[32]

$$\text{(1)}$$
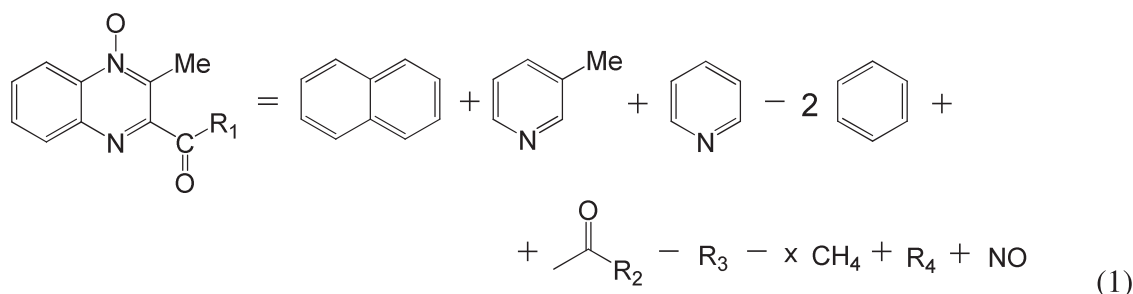
where $R_1 = OC(CH_3)_3$, $R_2 = OCH_2CH_3$, $R_3 = CH_3CH_2CH_3$, $R_4 = C(CH_3)_4$, and $x = 1$ in the case of **4.1**; $R_1 = NHPh$, $R_2 = CH_3$, $R_4 = NH_2Ph$, and $x = 2$ in the case of **4.2**; and $R_1 = NH_2$, $R_2 = CH_3$, $R_3 = CH_3CH_3$, $R_4 = CH_3NH_2$, and $x = 1$ in the case of **4.3**. The microcalorimeter was calibrated *in situ* for the working temperatures with naphthalene, $\Delta_{cr}^{g}H_m^o$(naphthalene, cr) = (72.60 ± 0.60) kJ·mol^{-1}[33] using the same procedure for the calibration experiments.

RESULTS

Target compounds were successfully obtained following the synthetic route A to target structures **4** depicted in Scheme 1. Compounds **4.1** and **4.2** were obtained in acceptable global yields (~50%), whereas compound **4.3** was synthesized in a very low yield (~10%) mainly because of the very low solubility of its dioxygenated precursor **3.3** in low molecular weight alcohols, which is suitable for carrying out the reduction step with trimethyl phosphate.[22] In any case, the compounds were isolated at high chemical purity after recrystallization with methanol, as shown by the analytical and structural data provided in the Supporting Material. The establishment of the structure of the final products as **4** mono-oxygenated isomers is discussed in the Discussion section.

The results for a typical combustion experiment for each of the compounds studied are given in Table 1: $\Delta m(H_2O)$ is the difference between the mass of water added to the calorimeter and 2900.0 g, the mass assigned for ε(calor), ΔT_{ad} is the calorimeter temperature rise corrected for the heat exchange and the work of stirring, ΔU_{Σ} is the correction to the standard state and the remaining terms are as previously defined.[30] The samples were ignited at $T = (298.150 \pm 0.001)$ K and the internal energy for the isothermal bomb process, $\Delta U(IBP)$, was calculated using Eqn (2).

$$\Delta U(\text{IBP}) = -\{\varepsilon(\text{calor}) + c_p(H_2O, l) \cdot \Delta m(H_2O) + \varepsilon_f\}\Delta T_{ad} \quad (2)$$
$$+ \Delta U(\text{ign})$$

For the combustion reaction of each compound yielding N_2 (g), CO_2 (g) and H_2O (l), the individual values of $\Delta_c u^o$, together with the mean values, $\langle \Delta_c u^o \rangle$, and their standard deviations are given in Table 2. Because the quantity available for experimental work involving compound **4.3** was very small, only five experiments were possible. In the case of **4.2**, the quantity of the compound synthesized was also small and, more importantly, it was seen to degrade during storage. In fact, because of the low yields from the syntheses, the quantities for each compound were small thus preventing a large number of experiments, and hence, preventing the reduction of the uncertainties associated with each of the experimental results.

Table 1. Typical combustion experiments at $T = 298.15$ K

	4.1	4.2	4.3
$m(CO_2,$ total)/ g	1.47614	1.31360	1.21882
m(cpd)/ g	0.34504	0.31149	0.38088
m(fuse)/ g	0.00292	0.00311	0.00258
m (*n*-hexadecane) / g	0.21053	0.16827	0.12556
ΔT_{ad}/ K	1.27472	1.09678	1.00229
ε_f / (J·K^{-1})	14.81	14.37	14.14
$\Delta m(H_2O)$/ g	0.7	1.7	−3.4
ΔU(IBP) / J	19,839.76	17,074.49	15,581.86
ΔU(fuse)/ J	47.42	50.51	41.90
ΔU(HNO$_3$)/ J	25.34	23.70	38.21
ΔU(*n*-hexadecane)/ J	9926.61	7933.92	5925.38
ΔU(ign.)/ J	0.54	0.54	0.61
ΔU_{Σ}/ J	8.93	8.56	9.19
$-\Delta_c u^o$/ (J·g^{-1})	28,491.98	29,077.27	25,133.60

$m(CO_2,$ total) is the total mass of CO_2 formed in the experiment; m (cpd) is the mass of compound burnt in the experiment; m (fuse) is the mass of fuse (cotton) used in the experiment; ΔT_{ad} is the corrected temperature rise; ε_f is the energy equivalent of contents in the final state; $\Delta m(H_2O)$ is the deviation of the mass of water added to the calorimeter from 2900.0 g; ΔU(IBP) is the energy change for the isothermal combustion reaction under actual bomb conditions; ΔU(fuse) is the energy of combustion of the fuse (cotton); ΔU(HNO$_3$) is the energy correction for the nitric acid formation; ΔU(ign.) is the electrical energy for the ignition; ΔU_{Σ} is the energy correction to the standard state; $\Delta_c u^o$ is the standard massic energy of combustion.

Table 2. Individual values of the massic energy of combustion, $\Delta_c u^o$, at $T = 298.15$ K. All values in J·g^{-1}

4.1	4.2	4.3
28,466.35	29,114.81	25,100.51
28,480.01	29,077.27	25,171.11
28,491.98	29,068.70	25,133.60
28,492.19	29,061.74	25,106.57
28,418.07	29,127.09	25,147.72
28,420.99	29,140.90	—
	$-\Delta_c u^o$	
28,461.6 ± 6.9	29,098.4 ± 13.6	25,131.9 ± 13.0

Table 3. Derived standard ($p^\circ = 0.1$ MPa) molar values in the condensed phases at $T = 298.15$ K. All values in kJ·mol^{-1}

Compound	$-\Delta_c U_m^o$(cr)	$-\Delta_c H_m^o$(cr)	$\Delta_f H_m^o$(cr)
4.1	7408.3 ± 6.1	7412.0 ± 6.1	-383.7 ± 6.1
4.2	8127.1 ± 10.3	8129.0 ± 10.3	-25.0 ± 10.4
4.3	5106.8 ± 7.4	5106.2 ± 7.4	-111.9 ± 7.5

Table 5. Derived standard ($p^\circ = 0.1$ MPa) standard molar enthalpies in the condensed and gaseous phases, at $T = 298.15$ K, and enthalpies of sublimation. All values in kJ·mol^{-1}

Compound	$\Delta_f H_m^o$ (cr)	$\Delta_{cr}^g H_m^o$	$\Delta_f H_m^o$ (g)
4.1	-383.7 ± 6.1	140.8 ± 3.1	-242.9 ± 6.8
4.2	-25.0 ± 10.4	145.1 ± 2.3	120 ± 11
4.3	-111.9 ± 7.5	138.0 ± 0.6	26.1 ± 7.5

Table 3 presents the derived standard molar values for the energies, $\Delta_c U_m^o$(cr), and enthalpies, $\Delta_c H_m^o$(cr), of the combustion reaction for the compounds and the standard molar enthalpies of formation, $\Delta_f H_m^o$(cr), in the crystalline phase at $T = 298.15$ K. The latter were derived from the values of $\Delta_c H_m^o$ (cr) and from the standard molar enthalpies of formation at $T = 298.15$ K of H_2O (l) ($-(285.830 \pm 0.042)$ kJ·mol^{-1}) and CO_2 (g) ($-(393.51 \pm 0.13)$ kJ·mol^{-1}).[34]

According to Rossini[35] and Olofsson,[36] the uncertainties associated with the standard molar energies and enthalpies of combustion are twice the overall standard deviation of the mean and include the uncertainties in calibration and in the values of the auxiliary quantities used.

Results of the Calvet microcalorimetric measurements yielding the standard molar enthalpies of sublimation, $\Delta_{cr}^g H_m^o$, at $T = 298.15$ K, for compounds **4.1–4.3**, are registered in Table 4, with the uncertainties being twice the standard deviation of the mean. In this table are also shown the molar enthalpies of sublimation, $\Delta_{cr, 298.15\ K}^{g,T} H_m$ and the estimated corrections to $T = 298.15$ K, $\Delta_{298.15\ K}^T H_m^o$(g) for each compound. Finally, the standard molar enthalpies of formation, $\Delta_f H_m^o$(g), derived for each compound in both the crystalline and gaseous phases are summarized in Table 5.

DISCUSSION

The identification of final compounds as pure isomers **4** was made on the basis of previous research by Dirlam and McFarland[22] and of NMR data obtained as follows. Reduction of compounds **3** was carried out using trimethyl phosphite (Scheme 1, **A**), which according to Dirlam and McFarland, allows for selective monodeoxygenation of the nitrogen farthest from the 3-methyl group in quinoxaline di-*N*-oxides like **3** (R ≠ H), having electron withdrawing substituents in carbon 2 (e.g., **3** where R = CH$_3$ or OCH$_3$; 3-methyl-2-trifluoromethylquinoxaline-1,4-dioxide).[22] These authors demonstrated, by ^{1}H-NMR, that while monodeoxygenation of structures such as **3** with trimethyl phosphite is regioselective, other reducing agents such as phosphorous trichloride or sodium dithionite lead to a mixture of the two possible monodeoxygenation products plus the fully deoxygenated quinoxaline (Scheme 1, **B**). For instance, reduction

of methyl 3-methyl-2-quinoxalinecarboxylate 1,4-dioxide (structure **3** where R = OCH$_3$) with phosphorous trichloride yields a mixture that, according to ^{1}H-NMR analysis, is composed of 57% methyl 3-methyl-2-quinoxinecarboxylate 1-oxide, 16% methyl 2-methyl-3-quinoxaline carboxylate 1-oxide and 27% methyl 3-methyl-2-quinoxalinecarboxylate. Detection of such mixtures by ^{1}H-NMR is straightforward because the presence/absence of an N–O bond significantly affects the chemical shifts of neighboring protons, namely, those of the aromatic proton H-8 and of vicinal protons in the C-2 substituent (see Scheme 1 for atom numbering). Thus, the δ value for the methyl substituent differs between each of the two possible monodeoxygenation products and also between these and the fully deoxygenated quinoxaline.[22] Also, the latter usually presents all aromatic protons (H-5 to H-8) clustered in an unresolved multiplet at ~7.7–8.0 ppm, whereas peaks from protons H-5 and H-8 shift to higher δ values in monodeoxygenated derivatives, appearing at ~8.5 and ~8.2 ppm, respectively.[22] The same authors have also unequivocally shown that the selective monodeoxygenation of compounds like **3** with trimethyl phosphite occurred on the nitrogen farthest apart from the methyl group, as the subsequent reaction of the sole monodeoxygenation product obtained with acetic anhydride/acetic acid gives the corresponding 3-acetoxymethylquinoxaline **5** (Scheme 1). The formation of **5** can only take place if the remaining N–O bond is on the nitrogen closest to the methyl group.[22]

A simple inspection of the ^{1}H-NMR spectra of our monodeoxygenation products (Supporting Material) clearly shows that the compounds are pure isomers. This is further reinforced by the very sharp melting point intervals observed, which are strong indicators of high purity, and by the fact that no peak duplication was observed in the corresponding ^{13}C-NMR spectra, as would be expected if mixtures had been obtained. Furthermore, the multiplicity pattern obtained for the aromatic protons 5-H to 8-H in **4.1–4.3** corresponds to three multiplets of 1:1:2 relative intensities, as previously observed by Abadelah *et al.* for analogous amino acid and ester quinoxaline-4-oxides, whereas their 1-oxide isomers exhibited two multiplets with 1:3 relative intensities.[37] Chemical shifts observed both in the proton and carbon-13 NMR spectra of **4.1–4.3** were also in agreement with previously reported data on similar quinoxaline-4-oxides.[37–39]

Table 4. Microcalorimetric standard ($p^o = 0.1$ MPa) molar enthalpies of sublimation, at $T = 298.15$ K

Compound	No. of experiments	T / K	$\dfrac{\Delta_{cr,298.15\ K}^{g,T} H_m}{\text{kJ·mol}^{-1}}$	$\dfrac{\Delta_{298.15K}^T H_m^o(g)}{\text{kJ·mol}^{-1}}$	$\dfrac{\Delta_{cr}^g H_m^o (T=298.15K)}{\text{kJ·mol}^{-1}}$
4.1	6	390	160.5 ± 3.1	19.7	140.8 ± 3.1
4.2	6	443	195.0 ± 2.3	49.9	145.1 ± 2.3
4.3	6	458	177.6 ± 0.6	39.6	138.0 ± 0.6

Therefore, in view of all the above, we can unequivocally identify our final products as **4.1–4.3**.

The experimental standard molar enthalpies of formation reported in this work were used to derive the values for the first N–O bond dissociation enthalpies, DH_1(N–O), in the parent di-*N*-oxide quinoxalines (compounds **3**), that is, the energy associated with the following gaseous reaction:


R=OC(CH$_3$)$_3$ or NHPh or NH$_2$
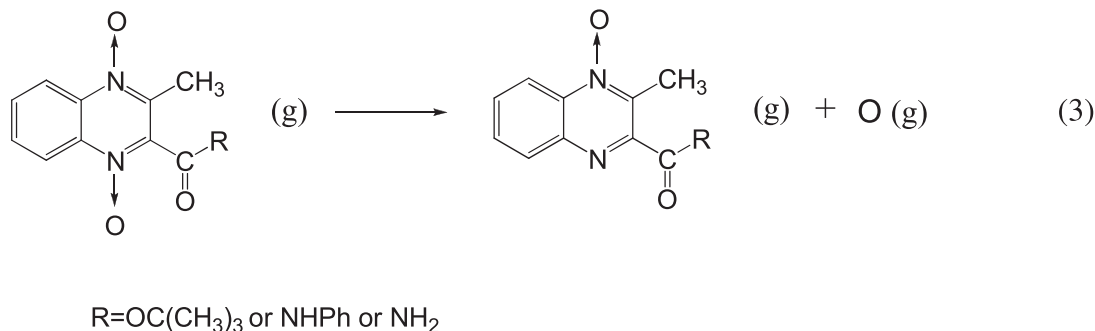
using the standard molar enthalpies of formation in the gas phase previously reported in the literature for compounds **3.1**, **3.2**, and **3.3**[11,12] and for atomic oxygen, $\Delta_f H_m^o(g) = (249.18 \pm 0.10\ \text{kJ·mol}^{-1})$.[34] The DH_1(N–O) values determined for compounds **3.1**, **3.2**, and **3.3** are given in Table 6 and are also compared with those reported in literature for 3-methoxycarbonyl-2-methylquinoxaline-*N,N'*-dioxide, **3.4** (Scheme 1, R = OCH$_3$), and 3-ethoxycarbonyl-2-methylquinoxaline-*N,N'*-dioxide, **3.5** (Scheme 1, R = OCH$_2$CH$_3$).[13]

As can be seen, the DH_1(N–O) values derived from the experimental enthalpies of formation span a range of $40 \pm 17\ \text{kJ·mol}^{-1}$; the less positive value, corresponding to a more labile bond, is found for **3.1**, $242.4 \pm 9.0\ \text{kJ·mol}^{-1}$, while the most positive value is found for compound **3.2**, $282 \pm 14\ \text{kJ·mol}^{-1}$. The latter may be considered only as qualitative because of the larger uncertainties associated with the experimental $\Delta_f H_m^o(g)$ determined before for compounds **3.2** and **4.2**. The value derived for compound **3.3**, $255.6 \pm 7.4\ \text{kJ·mol}^{-1}$, is within the associated uncertainty identical to those reported before for compounds **3.4** and **3.5** (Table 6).[13] First, it is possible to conclude that the *tert*-butoxycarbonyl, the phenylcarbamoyl, and the carbamoyl groups have a larger destabilization effect than the methyl group and hence the dative N→O bonds adjacent to the former groups are cleaved first (Scheme 1). Then, from the numerical data reported above for DH_1(N–O), it can be concluded that the *tert*-butoxycarbonyl group causes a larger destabilization

compared with the phenylcarbamoyl substituent. For a better understanding of the quality of the results above, we will now take into account previously reported N–O bond dissociation enthalpies for some other quinoxaline derivatives. Previously, some of us were able to obtain reasonable quantities of highly pure samples of the compounds quinoxaline-*N,N'*-dioxide, pyrazine-*N,N'*-dioxide and 2,3-dimethylquinoxaline-*N,N'*-dioxide, which allowed the determination of their $\Delta_f H_m^o(g)$ by isoperibol static bomb calorimetry and Calvet microcalorimetry.[19,40] The mean values reported for the cleavage of both dative N→O bonds, DH_M(N–O), in the 1,4-di-*N*-oxides listed above are $255.8 \pm 2.0\ \text{kJ·mol}^{-1}$,[19] $254.0 \pm 2.3\ \text{kJ·mol}^{-1}$,[19] and $260.9 \pm 2.7\ \text{kJ·mol}^{-1}$,[40] respectively, for quinoxaline-*N,N'*-dioxide, pirazine-*N,N'*-dioxide and 2,3-dimethylquinoxaline-*N,N'*-dioxide. These values were calculated as half of the enthalpy associated with the following chemical process:

$$X1,4 - \text{di} - N - \text{oxide}(g) \rightarrow X(g) + 2O(g) \qquad (4)$$
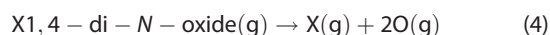
where X is quinoxaline or pyrazine or derivatives of these compounds obtained by replacing H with other chemical groups, whose gaseous enthalpies of formation are also reported in literature.[9] In the case of the dimethyl derivative of quinoxaline, the Becke, three-parameter, Lee–Yang–Parr (B3LYP)/6-311 + G(2 d,2p), DH_M(N–O) = 260.8 kJ·mol^{-1}, and B3LYP/6-311 + G (2 d,2p)//B3LYP/6-31 G(d), DH_M(N–O) = 260.6 kJ·mol^{-1}, calculated values were found to be in excellent agreement with the experimental result providing further support for the quality of the DH_M(N–O) derived for these 1,4-di-*N*-oxides.[40] The DH_M(N–O) obtained for 2,3-dimethylquinoxaline 1,4-di-*N*-oxide clearly suggests that the DH_1(N–O) for cleavage of a N→O bond in an adjacent position to the methyl groups in 2,3-dimethylquinoxaline 1,4-di-*N*-oxide, that is, methyl groups attached to positions 2 or 3 of the ring, is $\leq 260.9 \pm 2.7\ \text{kJ·mol}^{-1}$. In principle, this limiting

Table 6. Derived standard ($p^o = 0.1$ MPa) molar enthalpies of formation, $\Delta_f H_m^o$ (g), and enthalpies of N–O bond dissociation, DH_1(N–O), at $T = 298.15$ K. The uncertainties are twice the overall standard deviation of the mean. All values in kJ·mol^{-1}

R	1,4-di-*N*-oxides	$\Delta_f H_m^o$ (g)	mono-*N*-oxide	$\Delta_f H_m^o$ (g)	DH_1(N–O)
OC(CH$_3$)$_3$	**3.1**	-236.1 ± 5.9[12]	**4.1**	-242.9 ± 6.8[1]	242.4 ± 9.0
NHPh	**3.2**	87.5 ± 9.5[11]	**4.2**	120 ± 11[1]	282 ± 14
NH$_2$	**3.3**	19.7 ± 5.5[11]	**4.3**	26.1 ± 7.5[1]	255.6 ± 7.4
OCH$_3$	**3.4**	-148.7 ± 3.2[19]	**4.4**	-144.3 ± 5.3[13]	253.6 ± 6.2[13]
OCH$_2$CH$_3$	**3.5**	-178.0 ± 4.3[40]	**4.5**	-174 ± 8[13]	253 ± 9[13]

[1]This work.

value can be used with enhanced confidence because the DH_1 (N–O) calculated for 2,3-dimethylquinoxaline-*N,N'*-dioxide using the same density functional theory approach and basis sets was ~252 kJ·mol^{-1}.[40] The 260.9 ± 2.7 kJ·mol^{-1} value was also found to be valid for the DH_1(N–O) values calculated for **3.5** and also for 3-benzyl-2-methyl-quinoxaline 1,4-di-*N*-oxide.[40] Therefore, the DH_1(N–O) for compound **3.2** is probably not accurate and must be used with caution. In the cases of compounds **3.1** and **3.3**, the DH_1(N–O) values seem to be accurate even though they are associated with large uncertainties. Why is that so? On one hand, the DH_1(N–O) values derived for these compounds, respectively, 242.4 ± 9.0 kJ·mol^{-1} and 255.6 ± 7.4 kJ·mol^{-1}, are lower than the 260.9 ± 2.7 kJ·mol^{-1} value introduced above and, on the other hand, these values are in quite good agreement with either the experimentally derived DH_1 (N–O) results for **3.4** and **3.5** (DH_1(N–O) = ~253 kJ·mol^{-1}, c.f. Table 6) and the B3LYP/6-311 + G(2 d,2p)//B3LYP/6-31 G(d) calculated data for **3.1** and **3.3** (DH_1(N–O) = ~242–245 kJ·mol^{-1}).[11–13]

CONCLUSIONS

Experimental thermochemical work involving static bomb calorimetry and Calvet microcalorimetry has been performed for three quinoxaline derivatives containing a single dative N→O bond, namely 2-*tert*-butoxycarbonyl-3-methylquinoxaline-*N*-oxide, 2-phenylcarbamoyl-3-methylquinoxaline-*N*-oxide, and 2-carbamoyl-3-methylquinoxaline-*N*-oxide. The two calorimetric techniques were used to measure their energies of combustion and the enthalpies of sublimation from which their standard molar enthalpies of combustion and of formation (crystalline and gaseous states) were derived at $T = 298.15$ K.

The gas phase standard molar enthalpies of formation for the mono-*N*-oxides were combined with existing literature values for the corresponding di-*N*-oxides and for atomic oxygen allowing the determination of the first standard molar enthalpies of dissociation of the N→O bond next to an electron-withdrawing group in the quinoxaline di-*N*-oxides. The values obtained for 2-*tert*-butoxycarbonyl-3-methylquinoxaline-*N*-oxide and 2-carbamoyl-3-methylquinoxaline-*N*-oxide were 242.4 ± 9.0 kJ·mol^{-1} and 255.6 ± 7.4 kJ·mol^{-1}, respectively. These results are in good agreement with the same quantities calculated using a hybrid density functional theory approach and are also in agreement with the experimental values reported for 3-methoxycarbonyl-2-methylquinoxaline-*N,N'*-dioxide and 3-ethoxycarbonyl-2-methylquinoxaline-*N,N'*-dioxide compounds, the only two experimental DH_1(N–O) values existing in the literature for quinoxaline derivatives. In the case of the third *N*-oxide compound studied here, 2-phenylcarbamoyl-3-methylquinoxaline-*N*-oxide, the derived DH_1(N–O) was 282 ± 14 kJ·mol^{-1}, which is too high compared with the values determined for the other quinoxaline-*N*-oxides studied so far and is above the upper limit for the DH_1(N–O) estimated for 2-X-3-methylquinoxaline-*N, N'*-dioxide based on previous experimental work performed for 2,3-dimethylquinoxaline-*N,N'*-dioxide, that is, 260.9 ± 2.7 kJ·mol^{-1}.

SUPPLEMENTARY MATERIAL

Analytical and structural data on compounds **4.1**, **4.2** and **4.3** (melting points, elemental analyses, MS/NMR data and spectra).

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