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Experimental Thermochemical Study of 6-Chloro-2,3-dimethylquinoxaline 1,4-Dioxide and DFT Evaluation of the N–O Bond Enthalpies in Related Haloquinoxalines

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The standard molar enthalpy of formation at $T = 298.15\,\mathrm{K}$ of 6-chloro-2,3-dimethylquinoxaline 1,4-dioxide in the gas-phase was derived using the values of the enthalpies of combustion for the crystalline solid, measured by using rotating-bomb combustion calorimetry, and of the enthalpies of sublimation, measured by using Calvet microcalorimetry. This value was used for calibrating the computational procedure employed to estimate the gas-phase enthalpies of formation for the deoxygenated quinoxaline derivatives and also to compute the first, second, and mean (N–O) bond dissociation enthalpies in the gas-phase. The B3LYP/6-311+G(2d,2p) calculations were also extended to the fluorine, bromine, and iodine derivatives and to the isomers with a halogen substituted at position 5. When the halogen atom enters the same position in the quinoxaline ring, it was found that the substituent had almost no influence on the computed (N–O) bond dissociation enthalpies, except for 5-fluoro-2,3-dimethylquinoxaline 1,4-dioxide.

In recent years, polyfunctionalized quinoxalines have been prepared and studied because of their industrial importance as corrosion inhibitors[1] and, mainly, their interesting biological activities and DNA interactive behaviour.[2–9] Among these heterocyclic compounds, there are several quinoxaline 1,4-dioxide (quinoxaline *N*,*N*′-dioxide) derivatives, of which their capacity to act as selective bioreductive drugs has been described.[10–12] In an effort to develop novel selective hypoxic-cytotoxins and to improve bioavailability and pharmacological and toxicological properties of quinoxaline 1,4-dioxide derivatives and to achieve synergism among metals and these type of bioreductive agents, several complexes recently have been subjected to cytotoxic evaluation in hypoxic and aerobic conditions. In fact, metal complexes may have reduction potentials in more appropriate ranges to release the ligand in vivo, i.e., the bioactive drug, by direct ligand substitution or reduction by cellular reductases.[13,14]

In the chemical and biochemical processes involving the formation/dissociation of N–O bonds, the bond dissociation energies (BDE) are relevant in order to establish the relative reactivity of species in terms of their abilities to transfer oxygen atoms.[12,15,16] For several years, we have been involved in the updating these data for several classes of *N*-oxide derivatives, as the result of experimental and theoretical thermochemical studies performed for those oxygenated compounds and, whenever necessary, for the corresponding compounds without N–O bonds.[17–20] Concerning the quinoxaline 1,4-dioxides, our previous studies have addressed mainly the energetic influence of the molecular environment in the vicinity of the N–O bonds for several compounds with different 2,3-substituents.[20–23]

The aim of the present work was to investigate the energetics of a new quinoxaline 1,4-dioxide derivative having a chloro substituent in the benzenic ring of the 2,3-dimethylquinoxaline 1,4-dioxide and to evaluate the values of BDE for the N–O bonds. The haloquinoxaline 1,4-dioxide derivatives have been reported in literature as compounds with relevant anti-mycobacterial activities,[24,25] although no energetic thermochemical studies have been reported for them.

To achieve our goals, we used results from combustion and sublimation calorimetric measurements, in combination with functional group contribution estimations and density functional theory-based computations, in order to determine the mean molar dissociation enthalpy of the (N–O) bonds, $\langle DH^{\circ}_{\mathrm{m}}(\text{N–O})\rangle$. The comparison of the N–O BDE obtained with those for 1,4-dioxide derivatives permit the evaluation of the influence of the halogen on the behavior of the molecule in terms of its oxidizing capability.

The present work reports a combined rotating bomb calorimetry and Calvet Microcalorimetry study in order to obtain data for the standard molar enthalpies of formation and sublimation of crystalline 6-chloro-2,3-dimethylquinoxaline 1,4-dioxide (**1b**), Fig. 1. Density functional theory calculations have been performed to compute the first, second, and mean enthalpies of dissociation of the N–O bonds in this compound and have been also extended to its isomer, 5-chloro-2,3-dimethylquinoxaline 1,4-dioxide (**1f**). Further, in order to check the size and electronic influence of the substituents at positions 5 or 6 in 2,3-dimethylquinoxaline 1,4-dioxide (**3a**), the computations have been carried out also for the 5- or 6-fluoro-, bromo-, and iodo-2,3-dimethylquinoxaline 1,4-dioxides.

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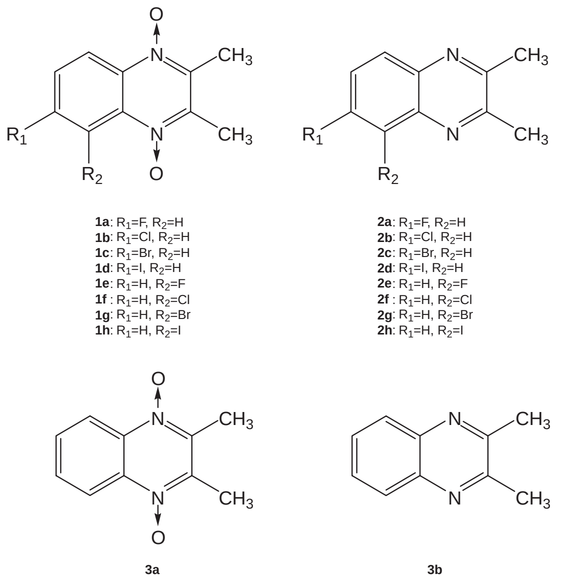


Fig. 1. Structures of the 2,3-dimethylquinoxaline and 2,3-dimethylquinoxaline 1,4-dioxide derivatives studied.

Experimental

Synthesis and Purity Control of 6-Chloro-2,3-dimethylquinoxaline 1,4-Dioxide. 6-Chloro-2,3-dimethylquinoxaline 1,4-dioxide was prepared using a modification of the experimental procedure developed by Heyns et al. for 2,3-dimethylquinoxaline.[26] The modification involved reacting 5-chlorobenzofuroxan (rather than benzofuroxan) with 2-butanone. The crude compound was collected by vacuum filtration and further purified by three crystallizations from anhydrous methanol to yield a sample having an observed melting point temperature in excellent agreement with published literature value.[27] Anal. Calcd for $C_{10}H_9O_2N_2Cl$: C, 53.47; H, 4.04; Cl, 15.78; N, 12.47%. Found: C, 53.39; H, 4.00; Cl, 15.69, N, 12.55%. The compound was sublimed under reduced pressure immediately before the calorimetric measurements.

The melting point measured in a melting point apparatus, Stuart Scientific SMP2, was 448 K, and the specific density was assumed to be $1.00\,\mathrm{g\,cm^{-3}}$. The DSC thermogram did not show any transition phases before the melting temperature.

Rotating Bomb Calorimetry. The standard molar enthalpy of combustion was measured using a rotating bomb calorimeter originally built and installed in the National Physical Laboratory, Teddington, U.K.[28] It was modified a little when it was moved to the University of Manchester, U.K.,[29] and it was finally installed in Porto University,[30] where several changes in the auxiliary equipment were made. The bomb with an internal volume 0.329 $\mathrm{dm^3}$ was internally lined with tantalum, and all the internal fittings were also made of tantalum. Water was added to the calorimeter from a weighted perspex vessel, and for each experiment, a correction was made to the energy equivalent for the deviation in the mass of water from 3965.0 g.

The electrical energy of ignition was determined from the change in potential difference across a 1281 µF capacitor after discharge through the platinum ignition wire. For each experiment, the ignition temperature was chosen so that the final temperature would be as close as possible to 298.15 K. Calorimeter temperatures were measured to $\pm 10^{-4}\,\mathrm{K}$ at time intervals of 10 s using a Hewlett-Packard (HP-2804A) quartz thermometer interfaced to a microcomputer, programmed to compute the adiabatic temperature range. In each experiment, rotation started at a time from the main period when the temperature rise was about 63% of the total expected, so the frictional work due to bomb rotation could be included in the corrections for the heat leakage and work of stirring, in accordance with procedures of Good et al.[31] In all experiments, the data acquisition and the control of the calorimeter was performed by using the LABTERMO program.[32]

The calorimetric system was calibrated using benzoic acid (NBS, Standard Reference Material 39i) with a massic energy of combustion under certificate conditions of $-(26434 \pm 3)\,\mathrm{J\,g^{-1}}$. Calibration experiments were made in oxygen at 3.04 MPa, with $1.00\,\mathrm{cm^3}$ of water added to the bomb. One set of ten calibration experiments were performed leading to the following value for the energy equivalent, $\varepsilon = (20369.0 \pm 2.3)\,\mathrm{J\,K^{-1}}$, where the uncertainty corresponds to the standard deviation of the mean. The combustion experiments of crystalline **1b** were carried out in pellet form under an oxygen atmosphere ($p = 3.04\,\mathrm{MPa}$), in the presence of $15.00\,\mathrm{cm^3}$ of an aqueous solution of As_2O_3 ($0.09667\,\mathrm{mol\,dm^{-3}}$) inside the bomb. This solution reduces all of the free chlorine produced in the combustion to hydrochloric acid. Within the precision of the analytical method, no evidence was found for oxidation of aqueous solution of As_2O_3 during a period of about 5 h in the presence of oxygen at $p = 3.04\,\mathrm{MPa}$.[33]

For the cotton thread fuse of empirical formula $CH_{1.686}O_{0.843}$, $\Delta_c u^\circ/\mathrm{J\,g^{-1}} = -16240$.[34] The amount of nitric acid formed was determined using the Devarda's alloy method,[35] and corrections for nitric acid formation were based on $-59.7\,\mathrm{kJ\,g^{-1}}$ for the molar energy of formation of $0.1\,\mathrm{mol\,dm^{-3}}$ $HNO_3(aq)$ from $N_2(g)$, $O_2(g)$, and $H_2O(l)$.[36] The extent of oxidation of $As_2O_3(aq)$ was determined by titration with a standardized iodine solution. The energy of oxidation of $As_2O_3(aq)$ to $As_2O_5(aq)$ was calculated as described by Hu et al.,[37] using the enthalpies of oxidation of $As_2O_3(aq)$ by Cl_2[38] and the thermal effects of mixing $As_2O_5(aq)$ with strong acids.[39] The amount of $H_2PtCl_6(aq)$ was determined from the loss of mass of the platinum crucible.

At $T = 298.15\,\mathrm{K}$, $(\partial u/\partial p)_T$ for the solid was assumed to be $-0.2\,\mathrm{J\,g^{-1}\,MPa^{-1}}$, which is a typical value for organic solids.[40]

For each experiment, the value of the massic energy of combustion, $\Delta_c u^\circ$, was calculated by using the procedure given by Hubbard et al.[41] for compounds containing only C, H, and N, and implemented by Hu et al.,[37] for compounds containing chlorine in their composition. The Washburn corrections, ΔU_Σ, and the heat capacities of the bomb contents, ε_i and ε_f, were calculated by the procedure given by Bjellerup,[42] using the solubility constants and energies of solution of CO_2 and O_2, as given by Hu et al.[37]

Calvet Microcalorimetry. The enthalpy of sublimation was determined in a Calvet High Temperature Microcalorimeter (SETARAM HT 1000), using a "vacuum-sublimation drop microcalorimetric method," described in the literature.[43] Samples of about 3–5 mg in a thin glass capillary tube sealed at one end were dropped at room temperature into the hot reaction vessel in the microcalorimeter, held at $T = 440\,\mathrm{K}$, and then removed from the hot zone by vacuum sublimation. The thermal corrections for the glass capillary tubes were determined and were reduced by dropping empty tubes of nearly equal mass into both calorimeter cells; $\Delta_{298.15\,\mathrm{K}}^{T} H_\mathrm{m}^\circ(\mathrm{g})$ for **1b** was derived by the group method presented in Eq. 1, based on the values of Stull et al.[44] for chlorobenzene (ClBz) and benzene (Bz) and an estimated value[45] for

Table 1. Standard Massic Energy of Combustion of 6-Chloro-2,3-dimethylquinoxaline 1,4-Dioxide

	Run number					
	1	2	3	4	5	6
m(cpd)/g	0.42422	0.40860	0.40129	0.38199	0.30950	0.49913
m' (fuse)/g	0.00237	0.00266	0.00229	0.00256	0.00248	0.00258
$(T_i/\mathrm{K}) - 273.15$	24.3493	24.4790	24.4895	24.5328	24.5229	24.3910
$(T_f/\mathrm{K}) - 273.15$	24.8736	24.9814	24.9843	25.0043	24.9139	24.9994
$\Delta T_{ad}/\mathrm{K}$	0.49081	0.47309	0.46437	0.44302	0.35920	0.57724
$\mathcal{E}_i/\mathrm{J\,K^{-1}}$	74.16	74.15	74.14	74.12	74.04	74.24
$\mathcal{E}_f/\mathrm{J\,K^{-1}}$	73.24	73.35	73.29	73.29	73.22	73.48
$\Delta m(\mathrm{H_2O})/\mathrm{g}$	−1.5	0.4	0.5	0.0	−3.1	1.6
$-\Delta U(\mathrm{IBP})/\mathrm{J}^{a)}$	10030.78	9672.28	9494.19	9056.73	7338.58	11804.55
$\Delta U(\mathrm{HNO_3})/\mathrm{J}$	25.34	28.42	22.81	24.60	21.97	29.81
$\Delta U(\mathrm{As_2O_3})/\mathrm{J}$	66.92	63.56	64.46	61.90	40.78	64.81
$\Delta U(\mathrm{ign.})/\mathrm{J}$	1.19	1.19	1.19	1.19	1.19	1.19
$\Delta U_\Sigma/\mathrm{J}$	16.03	15.42	15.21	14.48	11.82	18.77
$\Delta U(\mathrm{fuse})/\mathrm{J}$	38.49	43.20	37.19	41.57	40.28	41.90
$-\Delta_c u^o/\mathrm{J\,g^{-1}}$	23296.49	23300.18	23307.95	23332.83	23336.39	23336.88

a) ΔU(IBP) includes ΔU(ign.).

2,3-dimethylquinoxaline 1,4-dioxide (**3a**), all in the gas-phase. The microcalorimeter was calibrated in situ using the reported standard molar enthalpies of sublimation for naphthalene.[46]

$$\Delta^{T}_{298.15\,\mathrm{K}}H^{o}_{m}\ (\mathbf{1b}) = \Delta^{T}_{298.15\,\mathrm{K}}H^{o}_{m}\ (\mathbf{3a}) + \Delta^{T}_{298.15\,\mathrm{K}}H^{o}_{m}\ (\mathrm{ClBz}) - \Delta^{T}_{298.15\,\mathrm{K}}H^{o}_{m}\ (\mathrm{Bz}). \tag{1}$$

The relative atomic masses used throughout this paper were those recommended by the IUPAC Commission.[47]

Computational Details. The B3LYP method,[48] which is based on an exchange functional that mixes Hartree–Fock and Slater local-density and on the correlation functional of Lee et al.,[49,50] was used to obtain the optimized structures as well as the energies of all compounds in the gas-phase. The atomic electron density was described by using the 6-311+G(2d,2p) basis set. Vibrational frequencies were computed, without the use of any scale factor, also at the B3LYP/6-311+G(2d,2p) level of theory in order to obtain thermal corrections for $T = 298.15$ K of all compounds. All of the calculations have been performed by using the Gaussian 03 software package.[51]

Results

The individual results for the combustion experiments of compound **1b** are given in Table 1, where Δm (H$_2$O) is the deviation of the mass of water added to the calorimeter from 3965.0 g, the mass assigned for $\mathcal{E}$(cal), ΔU_Σ is the correction to the standard state, $c_p(\mathrm{H_2O, l})$ is the heat capacity of liquid water, $\mathcal{E}_i$ and $\mathcal{E}_f$ are the energy of the bomb contents after ignition, ΔT_{ad} is the temperature rise, which is corrected for heat exchange and the energy of stirring, and ΔU_{ign} is the energy associated with the ignition. The samples were ignited at a selected temperature, in order to obtain a final $T \approx 298.15$ K, and the energy associated to the isothermal bomb process, ΔU (IBP), was calculated from Eq. 2, according to Refs. 37 and 41.

$$\Delta U(\mathrm{IBP}) = -\{\mathcal{E}_{cal} + \Delta m(\mathrm{H_2O})c_p(\mathrm{H_2O, l})\}\Delta T_{ad} + \mathcal{E}_i(T_i - 298.15) + \mathcal{E}_f(298.15 - T_i - \Delta T_{ad}). \tag{2}$$

The value of the massic energy of combustion of each experiment, $\Delta_c u^o$, refers to the combustion reaction described by Eq. 3.

$$\mathrm{C_{10}H_9O_2N_2Cl(cr)} + 11\mathrm{O_2(g)} + 596\mathrm{H_2O} \rightarrow 10\mathrm{CO_2(g)} + \mathrm{HCl{\cdot}600H_2O(l)} + \mathrm{N_2(g)}. \tag{3}$$

The mean value for the standard massic energy of combustion and the standard deviation of the mean, $\langle\Delta_c u^o\rangle = -(23318.4 \pm 7.7)\,\mathrm{J\,g^{-1}}$, makes it possible to derive the standard molar energy and enthalpy of combustion, $\Delta_c U^o_m(\mathrm{cr}) = -(5238.4 \pm 3.8)\,\mathrm{kJ\,mol^{-1}}$ and $\Delta_c H^o_m(\mathrm{cr}) = -(5238.4 \pm 3.8)\,\mathrm{kJ\,mol^{-1}}$, respectively. In accordance with the normal thermochemical practice,[52] the uncertainties assigned to the standard molar enthalpies of combustion are, in each case, twice the overall standard deviation of the mean and include the uncertainties in calibration and in the values of auxiliary quantities.

At $T = 298.15$ K, the standard molar enthalpy of formation for crystalline **1b**, $\Delta_f H^o_m(\mathrm{cr}) = -(6.6 \pm 3.9)\,\mathrm{kJ\,mol^{-1}}$, was derived from its $\Delta_c H^o_m(\mathrm{cr})$ value and using the standard molar enthalpies of formation retrieved from Ref. 36, at $T = 298.15$ K, for H$_2$O(l), $\Delta_f H^o_m = -(285.830 \pm 0.042)\,\mathrm{kJ\,mol^{-1}}$, for CO$_2$(g), $-(393.51 \pm 0.13)\,\mathrm{kJ\,mol^{-1}}$, and for HCl in 600H$_2$O, $-(166.54 \pm 0.01)\,\mathrm{kJ\,mol^{-1}}$, respectively.

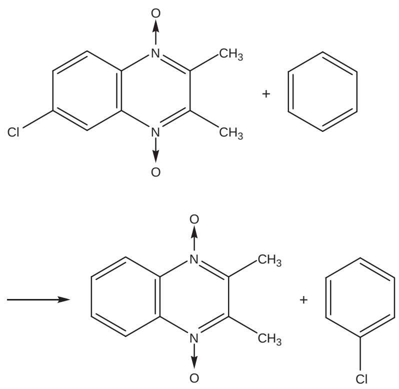
Results for measurements of $\Delta^{\mathrm{g,\,400\,K}}_{\mathrm{cr,\,298.15\,K}}H^{\mathrm{obs}}_{m}$ together with the correction to $T = 298.15$ K, $\Delta^{T}_{298.15\,\mathrm{K}}H^{o}_{m}(\mathrm{g})$, are given in Table 2. For each experiment, from both values, it is possible to derive the individual results the standard molar enthalpy of sublimation at $T = 298.15$ K as well as the corresponding mean value, $\langle\Delta^{\mathrm{g}}_{\mathrm{cr}}H^o_m\rangle = (119.4 \pm 5.4)\,\mathrm{kJ\,mol^{-1}}$, with uncertainty of twice the standard deviation of the mean. $\Delta_f H^o_m(\mathrm{g})$ for **1b** was calculated to be $(112.8 \pm 6.7)\,\mathrm{kJ\,mol^{-1}}$.

The standard gas-phase enthalpy of formation of **1b** has been estimated by using the enthalpy of the reaction in Eq. 4:

Table 2. Experimental Results for the Measurement of the Enthalpy of Sublimation of 6-Chloro-2,3-dimethylquinoxaline 1,4-Dioxide

Run number	m /mg	T /K	$\Delta^{\mathrm{g},\,440\,\mathrm{K}}_{\mathrm{cr},\,298.15\,\mathrm{K}}H^{\mathrm{obs}}_{\mathrm{m}}$ /kJ mol^{-1}	$\Delta^{440\,\mathrm{K}}_{298.15\,\mathrm{K}}H^{0}_{\mathrm{m}}$ /kJ mol^{-1}	$\Delta^{\mathrm{g}}_{\mathrm{cr}}H^{\mathrm{o}}_{\mathrm{m}}$ ($T = 298.15$ K)$^{\mathrm{a)}}$ /kJ mol^{-1}
1	4.565	440	152.03	38.00	114.03
2	3.280	440	156.54	38.00	118.54
3	3.945	440	152.57	38.00	114.57
4	3.915	440	152.45	38.00	114.45
5	3.331	440	162.39	38.00	124.39
6	3.174	440	168.14	38.00	130.14

a) $\langle\Delta^{\mathrm{g}}_{\mathrm{cr}}H^{\mathrm{o}}_{\mathrm{m}}\rangle(T = 298.15\,\mathrm{K}) = 119.4 \pm 5.4\,\mathrm{kJ\,mol^{-1}}$.



(4)

calculated at the B3LYP/6-311+G(2d,2p) level of theory and the experimental enthalpies of formation of benzene, $\Delta_{\mathrm{f}}H^{\mathrm{o}}_{\mathrm{m}}(\mathrm{g}) = (82.7 \pm 0.7)\,\mathrm{kJ\,mol^{-1}}$,[53] chlorobenzene, $\Delta_{\mathrm{f}}H^{\mathrm{o}}_{\mathrm{m}}(\mathrm{g}) = (52.0 \pm 1.3)\,\mathrm{kJ\,mol^{-1}}$,[53] and 2,3-dimethylquinoxaline 1,4-dioxide, **3a**, $\Delta_{\mathrm{f}}H^{\mathrm{o}}_{\mathrm{m}}(\mathrm{g}) = (149.4 \pm 4.5)\,\mathrm{kJ\,mol^{-1}}$,[21] available in the literature. The calculated enthalpy for Eq. 4 was $-5.33\,\mathrm{kJ\,mol^{-1}}$, and when combined with the experimental values above, the gas-phase enthalpy of formation of compound **1b** was estimated to be 124.0 [±6.9] kJ mol^{-1}. The uncertainty associated with the latter result is based on the experimental uncertainties for the auxiliary species, i.e., benzene, chlorobenzene and **3a**, and on an estimate of 5.0 kJ mol^{-1} for the uncertainty associated with the calculated enthalpy for the reaction in Eq. 4. The estimated $\Delta_{\mathrm{f}}H^{\mathrm{o}}_{\mathrm{m}}(\mathrm{g})$ for compound **1b** is in good agreement with the experimental value determined in this work. The difference between the experimental and estimated values is 11.2 kJ mol^{-1}.

The first, second and mean N–O BDEs for compound **1b** were also computed at the same level of theory. The results are compiled in Fig. 2 (2nd row of numbers connecting the molecular schemes) and were, respectively, 250.2, 267.9, and 259.1 kJ mol^{-1}, following the most favorable reaction path, i.e., **1b** yielding 6-chloro-2,3-dimethylquinoxaline 1-oxide and the latter, after losing its O atoms affording compound **2b**. However, the effect of chlorine atom at position 6 is less important since the values for the path that connects **1b** to **2b** through compound 7-chloro-2,3-dimethylquinoxaline 1-oxide are almost the same, i.e., with first and second N–O bond dissociation enthalpies of 251.2 and 267.0 kJ mol^{-1}, respectively.

From the computed values for the N–O BDEs and considering the experimental $\Delta_{\mathrm{f}}H^{\mathrm{o}}_{\mathrm{m}}(\mathrm{g})$ for compound **1b** determined here, as well as the literature value for the gas-phase enthalpy of atomic oxygen ($\Delta_{\mathrm{f}}H^{\mathrm{o}}_{\mathrm{m}}(\mathrm{g}) = (249.18 \pm 0.10)\,\mathrm{kJ\,mol^{-1}}$),[54] it is possible to estimate the gas-phase enthalpy of formation of the two chlorinated *N*-oxides appearing in Fig. 2 and also of compound **2b**. The estimates were 109.9, 110.9, and 128.6 kJ mol^{-1} for 6-chloro-2,3-dimethylquinoxaline 1-oxide, 7-chloro-2,3-dimethylquinoxaline 1-oxide, and **2b**, respectively. The gas-phase enthalpy of compound **2b** may be also estimated in a similar way to that used for compound **1b**, that is, using the reaction in Eq. 4 but with compounds **1b** and **3a** substituted by **2b** and **3b**, respectively. The experimental $\Delta_{\mathrm{f}}H^{\mathrm{o}}_{\mathrm{m}}(\mathrm{g})$ for **3b** has already been published in the literature ($(172.9 \pm 3.0)\,\mathrm{kJ\,mol^{-1}}$),[55] and the results for benzene and chlorobenzene were given already in the text. Using a similar reasoning to that employed above for compound **1b**, the enthalpy of the reaction between **2b** and benzene yielding **3b** and chlorobenzene was estimated to be $-1.88\,\mathrm{kJ\,mol^{-1}}$. This value, which is close to zero, suggests that the reactions chosen are highly isodesmic and, consequently, adequate for the present estimations. The estimated $\Delta_{\mathrm{f}}H^{\mathrm{o}}_{\mathrm{m}}(\mathrm{g})$ for compound **2b** was thus 144.1 kJ mol^{-1}. The latter value differs from that determined by using the enthalpy of the reaction **1b** yielding **2b** and atomic oxygen by 15.5 kJ mol^{-1}, which is similar to the difference of 11.2 kJ mol^{-1} found above when the experimental and estimated values for compound **1b** are compared.

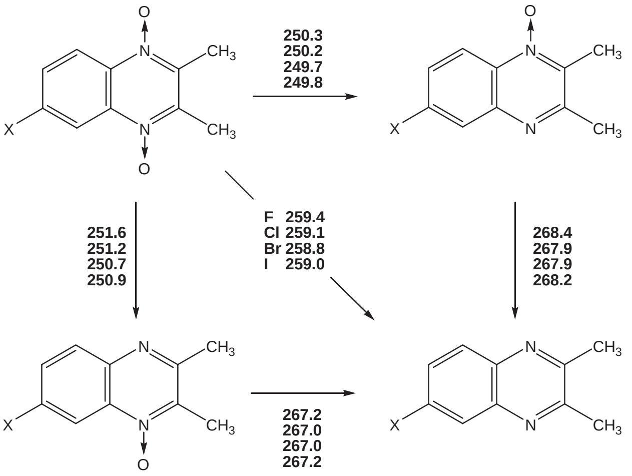


Fig. 2. First, second, and mean N–O BDEs for the 6-halogenated quinoxalines. All values in kJ mol^{-1}.

The first, second, and mean N–O BDEs for the 6-fluoro-, 6-bromo-, and 6-iodo-2,3-dimethylquinoxaline 1,4-dioxide are also given in Fig. 2. Interestingly, it was found that the enthalpic difference between the highest and the lowest mean

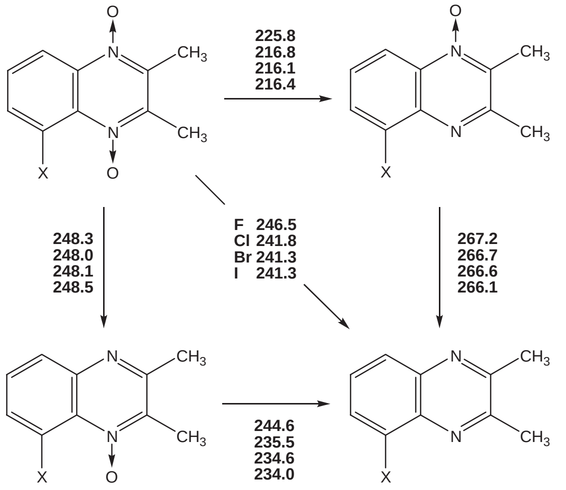


Fig. 3. First, second, and mean N–O BDEs for the 5-halogenated quinoxalines. All values in kJ mol^{-1}.

N–O BDEs was only 0.6 kJ mol^{-1}, suggesting that substitutions at positions 6 or 7 do not influence the strength of the N–O bonds. In fact, among the four halogens chosen here, the size and electron-withdrawing effect of these ligands are appreciably different, which suggests that the positions analyzed here are too far from the N–O bonds, and so, the effects on the N–O bond strengths are negligible. However, by comparison of the BDEs compiled in Fig. 2 with the first, second, and mean BDEs reported previously for compound **3a**,[21] it was found that the difference between the mean BDEs for the halogenated derivatives (R = F, Cl, Br, or I) and that for **3a** (R = H) varies in the range of 1.8–2.4 kJ mol^{-1}, which is 3–4 times larger than that verified between the halogenated compounds. This shows that the effects are almost negligible although that their influence on the stability of the N–O bonds is noticed.

In the case of halogen substitution at position 5 in compound **3a**, i.e., compounds **1e**–**1h** in Fig. 1, the greater proximity between the halogen substituent and the N–O bond significantly changes the computed N–O BDEs, as shown in Fig. 3. The first, second, and mean BDEs are smaller than those computed for the compounds with halogens at position 6, showing that the proximity between the halogen atom and one of the N–O bonds destabilizes the bond. In the case of R = F, the effect is smaller than that introduced by any of the other three halogens studied here. In fact, in the case of the heavier halogens, the BDEs are almost the same; the enthalpic differences are smaller than 1 kJ mol^{-1}. As shown in Fig. 3, the first BDE when the N–O bond that is cleaved is near the halogen substituent is almost the same as that for compounds **1f**–**1h**, whereas for compound **1e**, it is more than 9 kJ mol^{-1} larger.

The analysis made above for the N–O bond strength variation with substitution at positions 5 and 6 of the quinoxaline 1,4-dioxide ring shows that it is possible to control the ability by which quinoxaline 1,4-dioxides act as bioreductive drugs by variation of the stereoelectronic properties of the substituents. However, by comparison of the BDEs computed here for compounds **1e**–**1h** (substitution at position 5 of the quinoxaline 1,4-dioxide ring) with that reported previously for 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide, it seems that the N–O bond near the substituent is strongly destabilized. In other words, the compounds formed by inclusion of substituents at position 5 are not stable and, therefore, not adequate to act as bioreductive drugs.

Conclusion

A combination of rotating-bomb calorimetry and Calvet microcalorimetry experiments were performed in order to determine the standard molar enthalpies of formation in the condensed- and in the gas-phases as well as the enthalpy of phase transition of 6-chloro-2,3-dimethylquinoxaline 1,4-dioxide. The experimental values were $-(6.6 \pm 3.9)$, (112.8 ± 6.7), and (119.4 ± 5.4) kJ mol^{-1}, respectively.

The enthalpy of formation in the gas-phase of that quinoxaline 1,4-dioxide derivative was also determined by computational methods, more precisely at the B3LYP/6-311+G(2d,2p) level of theory, and the estimated value was 124.0 [$\pm$6.9] kJ mol^{-1}, which is in satisfactory agreement with the experimental result. The same computational approach was employed to estimate the enthalpy of formation of the 6-chloro-2,3-dimethylquinoxaline compound. Two different reactions were chosen, and the values obtained were 128.6 or 144.1 kJ mol^{-1}. Finally, the computations were extended to the determination of the N–O BDEs of the 5- or 6-fluoro-, chloro-, bromo-, and iodo-2,3-dimethylquinoxaline 1,4-dioxides. The computed BDEs show that the influence on the N–O bonds is strong in the case of 5-substitution and negligible but present in the case of 6-substitution. Interestingly, the enthalpic differences between the computed BDEs for the three heaviest halogens considered were smaller than 1.5 kJ mol^{-1}.

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