

Thermochemistry of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide. Evaluation of the mean dissociation enthalpy of the (N–O) bond†

Maria D. M. C. Ribeiro da Silva,^{a*} José R. B. Gomes,^a Jorge M. Gonçalves,^a Emanuel A. Sousa,^a Siddharth Pandey^b and William E. Acree, Jr.^b

^a Centro de Investigação em Química, Departamento de Química, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, 687, P-4169-007, Porto, Portugal.

E-mail: mdsilva@fc.up.pt; Fax: +351 226082822; Tel: +351 226082838

^b Department of Chemistry, University of North Texas, Denton, TX, 76203-5070, USA

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The standard enthalpy of formation of the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide compound in the gas-phase was derived from the enthalpies of combustion of the crystalline solid measured by static bomb combustion calorimetry and its enthalpy of sublimation determined by Knudsen mass-loss effusion at $T = 298.15$ K. This value is (383.8 ± 5.4) kJ mol⁻¹ and was subsequently combined with the experimental gas-phase enthalpy of formation of atomic oxygen and with the computed gas-phase enthalpy of formation of 2-amino-3-quinoxalinecarbonitrile, (382.0 ± 6.3) kJ mol⁻¹, in order to estimate the mean (N–O) bond dissociation enthalpy in the gas-phase of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide. The result obtained is (248.3 ± 8.3) kJ mol⁻¹, which is in excellent agreement with the B3LYP/6-311+G(2d,2p)/B3LYP/6-31G(d) computed value.

Introduction

The nitrogen oxide (NO) group has become recognized in the field of biology as an important species, having a very important role in medical areas, such as the cardiovascular system, the central neural system and also, with an increasing impact, as a therapeutic option in the field of oncology. However, as a free radical, NO cannot exist freely in a large quantity in the human body and so, to execute its functions, it has to bind to certain carrier molecules in a suitable environment, to be released to another site of the same molecule or to a different receptor to finish up a transnitrosation cycle.¹

The cytotoxic efficiency of a drug depends on several factors, such as oxygen tension, redox properties and kinetics of competitive reactions. The hypoxic cells in solid tumours, which are living in an environment more inclined towards reductive reactions than those which are well oxygenated, could transform some drugs into cytotoxic species capable of alkylating DNA.² These prodrugs as nitro derivatives, including nitroimidazoles, 9-alkyl-amino-1-nitroacridines and nitroquinolines, quinine derivatives, and agents derived from 1,2,4-benzotriazine-1,4-dioxide and quinoxaline-1,4-dioxide, would be activated through a reductive mechanism in the absence of oxygen and, for this reason, be more toxic for hypoxic cell than for well-oxygenated ones. As the products of reduction of the *N*-oxides are nontoxic, it is believed that the intermediate radicals generated by reduction are involved in the mechanism of cytotoxicity.

Therefore, in the pharmacological field, the work of synthesis and the characterization of quinoxalines *N*-oxide derivatives, has expanded during the last decade, as these compounds constitute a class of molecules which have attracted interest as biologically active materials, finding considerable application in different fields, as angiotensin II receptor antagonists, anti-inflammatory drugs, NMDA antagonists, antidepressant-tranquillizing agent and mainly as antituberculosis agents³ and antitumor drugs.⁴ For example, these heterocyclic aromatic *N*-oxides are currently being evaluated as hypoxia-selective cytotoxins in the clinical treatment of solid tumors.⁵ Further, it has been reported recently⁶ the importance of the compound Tirapazamine, 3-amino-1,2,4-benzotriazine-1,4-dioxide,

and of the related analogue 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide, as they cause light-dependent DNA damage in plasmide DNA and oligonucleotides, respectively.

These relevant aspects gave us the motivation to continue our efforts in the characterization of the thermodynamic properties of organic compounds containing terminal nitrogen–oxygen bonds. In two previous works^{7,8} we determined the mean molar dissociation enthalpy of the (N–O) bonds, $\langle DH_m^0(N-O) \rangle$, for several quinoxaline 1,4-dioxides, using combustion and sublimation measurements, sometimes in combination with functional group contribution estimations and density functional theory-based computations. These latter two methods were used to calculate the gaseous enthalpy of formation of the parent quinoxaline derivative without the (N–O) bonds whenever a direct experimental value was not available. Thermochemical data on quinoxalines continues to be scarce, mainly due to the fact that the compounds are difficult to obtain in sufficient quantity and purity for accurate thermochemical measurements.

The present paper reports experimental enthalpy of combustion and enthalpy of sublimation measurements for 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide, from which the standard molar enthalpy of formation in the gaseous state is derived. The standard molar enthalpy of formation of gaseous 2-amino-3-quinoxalinecarbonitrile is obtained from functional group contribution estimations and density functional theory-based calculations. The $\langle DH_m^0(N-O) \rangle$ in 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide is calculated, and compared with previously published values for other quinoxaline-1,4-dioxide derivatives. Such comparison allows one to better assess how neighboring functional group substituents affect the (N–O) bond strength. A better understanding of the (N–O) bond dissociation enthalpy should aid researchers in the design of new heterocyclic di-*N*-oxides having improved pharmacological properties and better oxidizing capabilities.

Results and discussion

Experimental gas-phase enthalpies of formation

The standard gas-phase enthalpy of formation, $T = 298.15$ K, of the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide compound was retrieved from a combination of the enthalpy of formation of the crystal, determined by isoperibol static bomb calorimetry, and of the

† Electronic supplementary information (ESI) available: Geometries, energies and enthalpies, at $T = 298.15$ K, for all compounds considered in this article. See <http://www.rsc.org/suppdata/ob/b4/b408250h/>

Table 1 Results of the individual experiments for the measurement of the massic energy of combustion, at $T = 298.15$ K, for the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide compound

	1	2	3	4	5	6
$m(\text{CO}_2, \text{total})/\text{g}$	1.85453	1.86702	1.34691	1.39994	1.35637	1.25366
$m(\text{cpd})/\text{g}$	0.94360	0.59615	0.57232	0.51738	0.49216	0.41590
$m(\text{hexadecane})/\text{g}$	—	0.22266	0.07057	0.12242	0.12436	0.13959
$m(\text{fuse})/\text{g}$	0.00363	0.00413	0.00383	0.00348	0.00335	0.00295
$\Delta T_{\text{ad}}/\text{K}$	1.40224	1.56552	1.06682	1.14293	1.11099	1.04422
$\varepsilon_i/(\text{J K}^{-1})$	14.78	14.69	13.89	14.10	14.09	14.10
$\Delta m(\text{H}_2\text{O})/\text{g}$	-0.20	0.50	0.50	0.30	1.40	0.50
$-\Delta U(\text{IBP})/\text{J}$	21825.63	24371.50	16606.68	17790.82	17298.79	16255.12
$\Delta U(\text{HNO}_3)/\text{J}$	77.61	67.04	59.52	56.24	53.73	45.97
$\Delta U(\text{ign})/\text{J}$	1.20	1.20	1.18	1.18	1.10	1.14
$\Delta U_{\text{Z}}/\text{J}$	22.21	16.18	13.41	12.89	12.32	10.76
$-m\Delta_c u^\circ(\text{hexadec.})/\text{J}$	—	10500.87	3328.09	5773.64	5865.24	6583.47
$-m\Delta_c u^\circ(\text{fuse})/\text{J}$	58.95	67.07	62.20	56.52	54.40	47.91
$-\Delta_c u^\circ(\text{cpd})/(\text{J g}^{-1})$	22961.80	23014.79	22965.21	22984.36	22986.57	23003.34

Table 2 Standard molar enthalpy of sublimation by Knudsen effusion method, at $T = 298.15$ K, for the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide compound

Expt.	$\langle T \rangle/\text{K}$	a/K	$\Delta_g H_m^\circ(\langle T \rangle)/\text{kJ mol}^{-1}$	$\Delta_g H_m^\circ(298.15 \text{ K})/\text{kJ mol}^{-1}$
A	426.7	16643	138.4	144.5
B	429.5	16101	133.9	140.2
C	431.1	15718	130.7	137.1
D	431.2	16374	136.1	142.5
E	432.7	15384	127.9	134.4

$\langle \Delta_g H_m^\circ(298.15 \text{ K}) \rangle / (\text{kJ mol}^{-1}) = 139.7 \pm 3.7 \text{ kJ mol}^{-1}$.

enthalpy of sublimation measured by Knudsen effusion experiments. The individual results for the combustion experiments of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide are presented in Table 1; $\Delta m(\text{H}_2\text{O})$ is the deviation of the mass of water added to the calorimeter from 2900.0 g, which is the mass assigned for $\varepsilon(\text{calor})$; ΔU_{Z} is the correction to the standard state; and the remaining terms are as previously described.⁹ The samples were ignited at $T = 298.15$ K; the energy involved in the isothermal bomb process, $\Delta U(\text{IBP})$, is derived from [eqn. (1)], where ΔT_{ad} is the calorimeter temperature change corrected for heat exchange and the work of stirring.

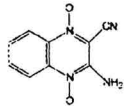
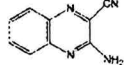
$$\Delta U(\text{IBP}) = -\{\varepsilon(\text{calor}) + c_p(\text{H}_2\text{O}, l)\Delta m(\text{H}_2\text{O}) + \varepsilon_i\}\Delta T_{\text{ad}} + \Delta U(\text{ign}) \quad (1)$$

The mean value of the massic energy of combustion of crystalline 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide, at $T = 298.15$ K, $\langle \Delta_c u^\circ \rangle = -(22985.0 \pm 8.5) \text{ J g}^{-1}$, has been used to calculate the corresponding values of the standard molar energy of combustion, $\Delta_c U_m^\circ(\text{cr}) = -(4646.9 \pm 3.8) \text{ kJ mol}^{-1}$, the standard molar enthalpy of combustion, $\Delta_c H_m^\circ(\text{cr}) = -(4643.2 \pm 3.8) \text{ kJ mol}^{-1}$. The latter value and the standard molar enthalpies of formation for $\text{H}_2\text{O}(l)$, $-(285.83 \pm 0.04) \text{ kJ mol}^{-1}$, and for $\text{CO}_2(\text{g})$, $-(393.51 \pm 0.13) \text{ kJ mol}^{-1}$, taken from the literature¹⁰ allow to derive the standard molar enthalpy of formation for crystalline 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide, which is $\Delta_f H_m^\circ(\text{cr}) = (244.1 \pm 4.0) \text{ kJ mol}^{-1}$.

The result obtained for the enthalpy of sublimation of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide, using the Knudsen effusion method is given in Table 2, together with the mean temperature of the experimental ranges and the standard molar enthalpy of sublimation at this mean temperature, $\Delta_g H_m^\circ(\langle T \rangle)$. The parameter of the Clausius–Clayperon equation corresponding to the slope was obtained using a least square fitting of the experimental data. The $\Delta_g H_m^\circ(\langle T \rangle)$ term was corrected to $T = 298.15$ K by assuming $\Delta_g C_{p,m}^\circ = -50 \text{ J K}^{-1} \text{ mol}^{-1}$.¹¹ The final number for $\Delta_g H_m^\circ$ is $(139.7 \pm 3.7) \text{ kJ mol}^{-1}$. The uncertainty assigned is twice the overall standard of the mean.

As described above, the enthalpy of formation, in gaseous state, for the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide is obtained from the corresponding standard enthalpy of formation

Table 3 Gas-phase enthalpies of formation for the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide, 3-amino-2-quinoxalinecarbonitrile and atomic oxygen species and the gas-phase (N–O) bond dissociation enthalpy for the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide compound. All values are given in kJ mol^{-1}

Compound	$\Delta_f H_m^\circ(\text{g})$	$\langle D H_m^\circ(\text{N–O}) \rangle$
	383.8 ± 5.4^a	248.3 ± 8.3^c 252.2^c
	383.9 ± 2.6^b 382.0 ± 6.3^c	
O	249.18 ± 0.10^d	

^aExperimental value. ^bCalculated by using a group additivity method. ^cB3LYP value. ^dTaken from ref. 10. ^eFrom a combination of experimental and B3LYP values, see text.

in the crystalline state and from its enthalpy of sublimation. The sum of these two quantities yields the following value, $\Delta_f H_m^\circ(\text{g}) = (383.8 \pm 5.4) \text{ kJ mol}^{-1}$, as is summarized in Table 3.

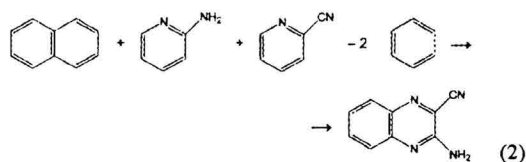
The synthesis of the compound without oxygen atoms was not possible and, therefore, the determination of the gas-phase enthalpy of formation of 2-amino-3-quinoxalinecarbonitrile was impracticable. However, that can be estimated by other techniques such as a group method or from density functional theory calculations. The estimations for the gas-phase enthalpy of formation of 2-amino-3-quinoxalinecarbonitrile coming from these approaches will be reported in the two following sub-sections.

Group method estimate of enthalpies of formation

The estimation of standard molar enthalpies of gaseous benzene derivatives was suggested by Cox based on the assumption that each group when substituted into a benzene ring produces an increment in $\Delta_f H_m^\circ(\text{g})$ that is characteristic of the group introduced.¹² This method is known to provide good approximations for the enthalpies of formation of benzene derivatives. As an example, the Cox scheme yields a gas-phase enthalpy of formation for 2-chloro-4-nitroaniline and 2-chloro-5-nitroaniline isomers of $(28.6 \pm 2.3) \text{ kJ mol}^{-1}$ and $(35.9 \pm 2.3) \text{ kJ mol}^{-1}$, respectively.¹³ These values are in good agreement with the experimental data reported in the same work, more precisely, $(27.7 \pm 2.1) \text{ kJ mol}^{-1}$ and $(30.0 \pm 2.2) \text{ kJ mol}^{-1}$, respectively. Another approach that is used to predict gas-phase enthalpies of formation is based on the Benson's group additivity method.¹⁴ Some interesting examples of the effectiveness of the Benson's method are compiled in ref. 15. Similar schemes are reported in the literature for heteroaromatic nitrogen derivatives,^{16,17}

namely, substituted pyridine and quinoline compounds based on well established experimental values for key compounds. Thus, this latter scheme, which considers heteroaromatic nitrogen derivatives, seems appropriate for a primary estimation of the enthalpy of formation of 2-amino-3-quinoxalinecarbonitrile. The empirical determination of the $\Delta_f H_m^\circ$ (g) for 2-amino-3-quinoxalinecarbonitrile was accomplished by using experimental enthalpies of formation for molecules that show some similar structural features to those found in this compound. It is hoped that this scheme provides a good evaluation of the enthalpic increment caused by the introduction of amino or cyano groups in a position that is also adjacent to nitrogen atoms in an aromatic ring. Based on both the Cox and Benson's methods and playing with what was exposed above and also with available experimental enthalpies of formation in the literature, the reaction scheme shown below seems to be the best selection for the estimation of the enthalpy of formation of the 2-amino-3-quinoxalinecarbonitrile species.

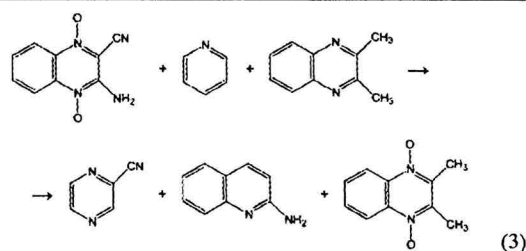
Considering eqn. (2) and the following experimental values taken from the literature, $\Delta_f H_m^\circ$ (naphthalene, g) = (150.3 ± 1.5) kJ mol⁻¹,¹⁸ $\Delta_f H_m^\circ$ (benzene, g) = (82.6 ± 0.7) kJ mol⁻¹,¹⁸ $\Delta_f H_m^\circ$ (2-aminopyridine, g) = (118.1 ± 1.1) kJ mol⁻¹,¹⁹ and $\Delta_f H_m^\circ$ (2-cyanopyridine, g) = (280.7 ± 1.5) kJ mol⁻¹,¹⁹ a value of (383.9 ± 2.6) kJ mol⁻¹ was calculated for $\Delta_f H_m^\circ$ of the gaseous 2-amino-3-quinoxalinecarbonitrile.



Computational results

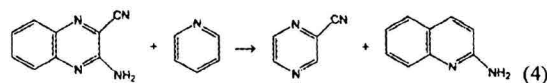
In the present work, DFT calculations at the B3LYP level of theory have been performed for a large number of compounds and, thus, to avoid a huge number of tables with structural and energy data, only the most important features of the quinoxaline derivatives are discussed here. The full account of results concerning geometries, energies and corrections to $T = 298.15$ K is given as supplementary information.† Starting with the calculated geometry of the 2-amino-3-quinoxalinecarbonitrile compound, the B3LYP/6-311+G(2d,2p) bond lengths are similar to those reported in a previous publication for 2,3-dimethylquinoxaline.⁸ The variations are smaller than 0.01 Å, except for the carbon–R distances due to the substitution of a methyl group in 2,3-dimethylquinoxaline by an amino or cyano substituent in 2-amino-3-quinoxalinecarbonitrile. The latter compound is almost planar with the exception of the amino group due to the nitrogen's electron lone pair. The HNCH dihedral angle is 155.8°, noticeable larger than the same angle in aniline, *c.f.* ~130°. This may be interpreted as a sign of some electron donation from the amino's nitrogen electron lone pair to the neighboring cyano group. Electron charge is also donated to the nearest oxygen atom in the case of the compounds with N–O bonds. The HNCH dihedral angle is the same if an oxygen atom is connected to the nitrogen closer to the cyano group while it is increased to 158–159° if an oxygen atom is bonded to the nitrogen closest to the amino group. Other important modifications in the geometrical parameters upon addition of oxygen atoms to the quinoxaline nitrogen atoms are the decrease in the carbon–R distances (R = amino, cyano) and the corresponding increases in the N–C bond lengths of the quinoxaline ring in the proximity of the N–O bond. It is worth to point out that in the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide species, the N–O distances are 1.298 and 1.266 Å for the N–O bond closer to the amino group and for the N–O bond nearer to the cyano group, respectively.

The gas-phase enthalpy of formation for the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide species was estimated from the enthalpy of following isodesmic reaction:



calculated with the B3LYP/6-311+G(2d,2p) energies of each species, corrected for $T = 298.15$ K, and the experimental gas-phase enthalpies of formation of pyridine, $\Delta_f H_m^\circ$ (g) = (140.4 ± 0.7) kJ mol⁻¹,¹⁸ of 2,3-dimethylquinoxaline, $\Delta_f H_m^\circ$ (g) = (172.9 ± 3.0) kJ mol⁻¹,²⁰ of cyanopyrazine, $\Delta_f H_m^\circ$ (g) = (356.8 ± 2.0) kJ mol⁻¹,²¹ of 2-aminoquinoline, $\Delta_f H_m^\circ$ (g) = (182.3 ± 2.9) kJ mol⁻¹,¹⁶ and finally of 2,3-dimethylquinoxaline-1,4-dioxide, $\Delta_f H_m^\circ$ (g) = (149.4 ± 4.5) kJ mol⁻¹.⁸ The B3LYP/6-311+G(2d,2p)/B3LYP/6-31G(d) enthalpy of reaction (3) is -0.4 kJ mol⁻¹ which yields an estimated gas-phase enthalpy of formation for 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide of (375.6 ± 8.2) kJ mol⁻¹. The error associated with this value was calculated by assuming an error of 5 kJ mol⁻¹ for the enthalpy calculated for reaction (3). The estimated gas-phase enthalpy for the dioxide compound is in rather good agreement with the experimental result reported in a previous sub-section and in Table 3. Accordingly, a similar scheme was followed to estimate the enthalpy of formation of 2-amino-3-quinoxalinecarbonitrile. This estimation was performed by considering the enthalpy computed for the isodesmic reaction shown below, together with the experimental enthalpies of formation for pyridine, cyanopyrazine and 2-aminoquinoline species.

At the B3LYP/6-311+G(2d,2p)/B3LYP/6-31G(d) level of theory, the computed enthalpy for reaction (4) is 16.7 kJ mol⁻¹. When combined with the experimental gas-phase enthalpies of formation of all species in reaction (3) except 2-amino-3-quinoxalinecarbonitrile the estimated enthalpy of formation for this compound in the gas-phase is (382.0 ± 6.3) kJ mol⁻¹. This result is in agreement with the estimated number coming from the group method.



(N–O) bond dissociation enthalpy

The mean (N–O) bond dissociation enthalpy, $\langle DH_m^\circ(\text{N–O}) \rangle$, for 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide corresponds to one-half of the enthalpy of the gaseous reaction, 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide → 2-amino-3-quinoxalinecarbonitrile + 2 oxygen. Using the above reported enthalpies of formation for these two quinoxaline derivatives, Table 3, and the enthalpy of formation of atomic oxygen, $\Delta_f H_m^\circ$ (g) = (249.18 ± 0.10) kJ mol⁻¹,¹⁰ the $\langle DH_m^\circ(\text{N–O}) \rangle$ is (248.3 ± 8.3) kJ mol⁻¹.

In the present work, the B3LYP method was also used to compute $\langle DH_m^\circ(\text{N–O}) \rangle$ for 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide as well as the first and second (N–O) bond dissociation enthalpies. In these calculations, the triplet ground state was considered to compute the energy of atomic oxygen. The full results concerning the computed bond dissociation enthalpies are schematically reported in Fig. 1. In this Figure, the arrows mean loss of atomic oxygen in the species that appears on the left. The $\langle DH_m^\circ(\text{N–O}) \rangle$ is 252.2 kJ mol⁻¹, which is close to the value obtained by considering the experimental enthalpies of formation for the oxygen atom and for the 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide species and the theoretically estimated enthalpy of formation of the 2-amino-3-quinoxalinecarbonitrile compound, *c.f.* Table 3. The computed first (N–O) bond dissociation enthalpy is almost the same if the oxygen atom removed belongs to the aromatic nitrogen atom adjacent to the cyano group or to the nitrogen atom nearest to the amino group. At first sight, this result seems somewhat surprising since

the cyano and amino groups are known to have opposite effects in terms of electron donation as given by the different signs in their Hammett constants. This can be explained if one considers a conjugation of factors. First, a cancellation of their electronic effects may exist due to the proximity of these substituents and also due to possible delocalization through the aromatic ring. Second, resonance between the N–O groups and the attached cyano and amino substituents is also expected. This may occur as $\text{N}\equiv\text{C}-\text{C}=\text{N}^+\text{O}^- \leftrightarrow ^-\text{N}=\text{C}-\text{C}=\text{N}^+=\text{O}$ for the former interaction and $\text{H}_2\text{N}-\text{C}=\text{N}^+\text{O}^- \leftrightarrow \text{H}_2\text{N}^+=\text{C}-\text{N}^-\text{O}^-$ for the interaction between adjacent NO and NH₂ groups. Third, the most important factor is the hydrogen bond found between NO and NH₂. The use of the Atoms in Molecules (AIM)²² approach shows a (3, -1) critical point for the N–O...H–NH interaction with $\rho = 0.024$ and $\nabla^2 = 0.112$; these values were found to be characteristic of a weak interaction.²³ This is consistent with a similar N–O bond enthalpy of dissociation computed for N–O near CN or near NH₂ substituents despite the different N–O distances reported in the preceding section. Thus, the removal of the oxygen atoms breaks with this stabilizing interaction and, therefore, N–O bond enthalpy of dissociation increases. The comparison of the present data with data reported recently for 2-methyl-3-R-quinoxaline-1,4-dioxide, R = H, methyl, methoxycarbonyl, ethoxycarbonyl and benzyl derivatives^{7,8} shows that the effect of the amino substituent in the computed (N–O) bond dissociation enthalpy is identical to that coming from the ethoxycarbonyl group. The amino and ethoxycarbonyl substituents are those that reduce more the (N–O) bond enthalpy of dissociation. If we neglect the effects caused by the other group attached to the quinoxaline ring, the oxidizing power varies in the following decreasing order: methoxycarbonyl \gg amino > ethoxycarbonyl > cyano > methyl \geq H = benzyl.

Conclusions

In the present work, a combined experimental and computational study has been entailed to obtain the (N–O) bond enthalpy of dissociation for 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide compound in the gas-phase. The experimental value was obtained from the experimental enthalpies of formation in the gas-phase of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide and atomic oxygen and from a estimated result for the enthalpy of formation of the 2-amino-3-quinoxalinecarbonitrile species since it was not possible for us to synthesize this compound. The result obtained compares excellently with the N–O bond dissociation enthalpy computed at the B3LYP/6-311+G(2d,2p)/B3LYP/6-31G(d) level of theory. The experimental/estimated result is $248.3 \pm 8.3 \text{ kJ mol}^{-1}$ while the fully computed result is $252.2 \text{ kJ mol}^{-1}$. The oxygen atom that is first removed is the one that is nearer to the amino group ($242.5 \text{ kJ mol}^{-1}$) while a larger energy, $261.9 \text{ kJ mol}^{-1}$, is needed to remove the second oxygen atom.

The design of new heterocyclic di-N-oxides is dependent on the energetics of their (N–O) bonds which have particular interest in the development of the pharmacological properties of these compounds. They have the potential to act as oxidizing agents, and thus, it is desirable to place them in increasing order in terms of their capacity to transfer oxygen atoms in chemical and biochemical conversions. The 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide compound has an oxidizing capacity larger than those previously reported for 2-methyl-3-R-quinoxaline-1,4-dioxide derivatives (R = H, CH₃, C(O)OC₂H₅, CH₂C₆H₅), identical to that reported for 2-acetyl-3-methylquinoxaline-1,4-dioxide and lower than that reported for 2-methyl-3-methoxycarbonylquinoxaline-1,4-dioxide and 2-phenyl-3-benzoylquinoxaline-1,4-dioxide.^{7,8}

Experimental

Materials

2-Amino-3-quinoxalinecarbonitrile-1,4-dioxide was prepared by slow addition of triethylamine to a *N,N*-dimethylformamide solution containing dissolved benzofuroxan and malonodinitrile reactants according to the published method of Ley *et al.*²⁴ The ensuing chemical reaction is very exothermic; hence the reaction mixture was maintained at 20 °C by placement in a cold-water bath. After the addition of triethylamine was complete, the solution was stirred an additional 90 minutes at ambient room temperature. The crude product was collected by vacuum filtration, washed with methanol and further purified by three crystallizations from hot *N,N*-dimethylformamide. Elemental analysis was in agreement with calculated value: mass fractions for C₉H₆N₄O₂: found C, 0.5355; H, 0.0291; N, 0.2765; calculated: C, 0.5347; H, 0.0299; N, 0.2771.

As the compound is sensitive to moisture, before the combustion measurements, the sample was kept in an oven ($T = 373 \text{ K}$) for several hours, and cooled in a desiccator with a dried atmosphere. The purity of the compound was confirmed by the average ratio of the mass of carbon dioxide recovered after combustion experiments to that calculated from the mass of sample: (0.9934 ± 0.0006), where the uncertainty is the standard deviation of the mean. The relatively low value for carbon dioxide recovery corresponds to the presence of a small amount of water in the sample, as it has been checked by Karl Fisher analysis.

The thermal behaviour of the compound has been studied by DSC. The thermogram shows that there is not transition phase before the melting temperature (514 K, with decomposition).

Combustion calorimetry

The energy of combustion of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide was measured in a isoperibol static bomb calorimeter, with a twin valve bomb, of internal volume of 0.290 dm³, formerly installed in England, as is described in the literature.^{19,25} The

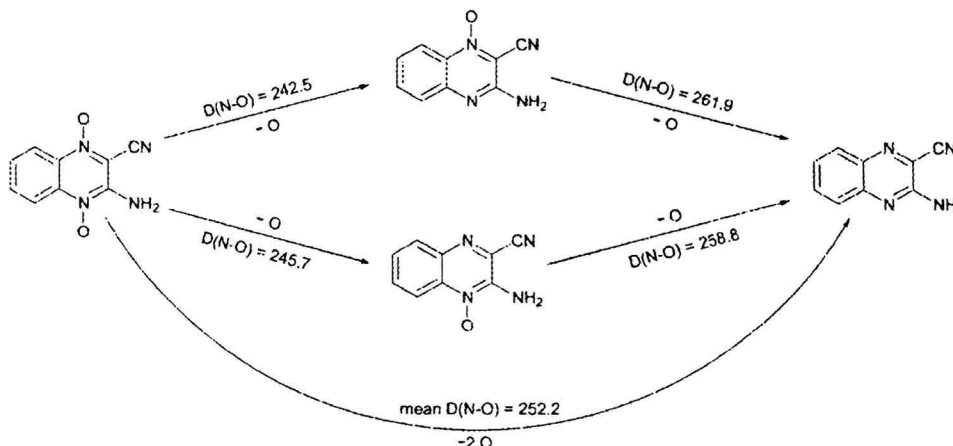


Fig. 1 Computed first, second, and mean (N–O) bond dissociation enthalpy for 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide. Results computed at the B3LYP/6-311+G(2d,2p)/B3LYP/6-31G(d) level of theory. All values are given in kJ mol^{-1} .

apparatus, after installation in our laboratory, had some modifications whose detailed description has been made previously.²⁶ 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 $-(26435.1 \pm 3.5) \text{ J g}^{-1}$. The calibration results were corrected to give the energy equivalent $\epsilon(\text{cal})$ corresponding to an average mass of water added to the calorimeter of 2900.0 g. One set of seven calibration experiments was made in oxygen atmosphere at $p = 3.04 \text{ MPa}$, with 1.00 cm^3 of water added to the bomb, leading to an energy equivalent of the calorimeter $\epsilon(\text{calor}) = (15551.6 \pm 2.6) \text{ J K}^{-1}$, where the uncertainty quoted is the standard deviation of the mean.

Samples of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide, in pellet form, were ignited at $T = 298.15 \text{ K}$, also in oxygen at the pressure 3.04 MPa and with 1.00 cm^3 of water added to the bomb. As the amount of compound available was small, *n*-hexadecane, $\Delta_c u^\circ = -(47161.9 \pm 3.2) \text{ J g}^{-1}$, has been used as an auxiliary in five of the six combustion experiments, in order to perform a convenient increase of temperature. Corrections for the cotton thread fuse, carbon formation and nitric acid were made as previously described.²⁷ At $T = 298.15 \text{ K}$, $(\partial u/\partial p)_T$ for this solid was assumed to be $-0.2 \text{ J g}^{-1} \text{ MPa}^{-1}$, a typical value for organic solids.

For each experiment, the value of $\Delta_c u^\circ$ was calculated by using the procedure given by Hubbard *et al.*⁹ The relative atomic masses used throughout this paper were those recommended by the IUPAC Commission in 1999.²⁸ The amount of substance used in each experiment was determined from the total mass of carbon dioxide produced after allowance for that from the cotton thread fuse and *n*-hexadecane.

Knudsen effusion technique

The enthalpy of sublimation of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide was derived from measurements using a Knudsen effusion method with quartz crystal microbalance. This system has been described firstly by Burkinshaw and Mortimer¹¹ and more recently by Ribeiro da Silva and Gonçalves.²⁹

The vapour effusing from the Knudsen cell condenses on a quartz crystal resonator positioned above the effusion hole. For a small mass deposited, the change in the resonance frequency of the quartz crystal, Δf , is directly proportional to the mass deposited on its surface,³⁰ $\Delta f = C_f \Delta m$, where C_f is a proportionality constant.

During an effusion experiment, the rate of change of the resonance frequency, $\nu = \Delta f/t$, is proportional to the effusion rate of the compound from the cell, $\Delta m/t$, which can be related to the vapour pressure, p , accordingly to the Knudsen eqn. (5), where A_o is the hole area and w_o is the Clausing factor.

$$\Delta m/t = p A_o w_o (M/2\pi RT)^{1/2} \quad (5)$$

Then, the rate of change of the resonance frequency can be expressed by [eqn. (6)], which after a rearranging leads to [eqn. (7)].

$$\nu = \Delta f/t = C_f \Delta m/t = C_f p A_o w_o (M/2\pi RT)^{1/2} \quad (6)$$

$$p = \nu T^{1/2} [(2\pi R/M)/(C_f A_o w_o)] \quad (7)$$

The integrated form of the Clausius–Clapeyron eqn. (8) was used to derive the standard molar enthalpy of sublimation at the mean temperature of the experimental range, $\Delta_g H_m^\circ(<T>)$. A plot of $\ln(\nu T^{1/2})$ against $1/T$ should give a straight line of slope $a = \Delta_g H_m^\circ(<T>)/R$ and ordinate b .

$$\ln(\nu T^{1/2}) = -(a/T) + b \quad (8)$$

From five independent sets of experimental measurements of the frequency of the quartz oscillator for the compound studied, at convenient temperature intervals, it was possible to obtain five independent results for the enthalpy of sublimation of the compound, referred to the mean temperature of the experimental range.

Computational details

Density functional theory, DFT, calculations have been performed with the B3LYP three-parameter hybrid method³¹ based on a mixture of non-local HF and Becke's gradient-corrected exchange³² and with the correlation functional due to Lee *et al.*³³ The calculations have been performed by following an identical approach to that used in previous works devoted also to the calculation of thermodynamic parameters.^{8,34–37} Accordingly, the 6-31G(d) basis set was used for a preliminary optimization of the coordinates of the systems under study. Then, calculation of frequencies has been performed also at the B3LYP/6-31G(d) to ensure that these states were local minima and to obtain zero-point energies as well as translational, rotational and vibrational contributions to the enthalpy at $T = 298.15 \text{ K}$. As suggested by Scott and Radom,³⁸ a factor of 0.980 was used to scale the frequencies. These corrections were introduced in the energies computed by a final optimization at the B3LYP/6-311+G(2d,2p) level of theory. All these calculations have been performed by means of the GAMESS-US³⁹ and Gaussian98⁴⁰ packages.

These B3LYP/6-311+G(2d,2p)/B3LYP/6-31G(d) enthalpies were then used to estimate the enthalpy of formation of the 2-amino-3-quinoxalinecarbonitrile species and also to calculate the first, second and mean (N–O) bond dissociation enthalpies of the corresponding dioxide derivative, namely, 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide.

The Atoms in Molecules analysis was performed considering the wavefunction coming from the B3LYP/6-311+G(2d,2p) geometry optimization of 2-amino-3-quinoxalinecarbonitrile-1,4-dioxide and the Xaim⁴¹ program.

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