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Energetics of Quinazoline-2,4(1*H*,3*H*)-dione: An Experimental and Computational Study

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Supporting Information

ABSTRACT: In this paper we report the standard ($p° = 0.1$ MPa) molar enthalpy of formation of quinazoline-2,4(1*H*,3*H*)-dione, in the gaseous phase, at $T = 298.15$ K, which was derived from a combined experimental and computational thermochemical work. The static bomb combustion calorimetry technique was used to determine the standard massic energy of combustion and consequently the standard molar enthalpy of formation, in the crystalline phase, at $T = 298.15$ K, and the Calvet microcalorimetry technique was employed to determine the standard molar enthalpy of sublimation, at $T = 298.15$ K. The obtained standard molar enthalpy of formation, in the gaseous phase, at $T = 298.15$ K, was: $\Delta_f H_m^o(g) = -(271.1 \pm 3.3)\ \mathrm{kJ \cdot mol^{-1}}$. In addition, quantum chemical calculations were performed using the G3(MP2)//B3LYP composite method to assess the relative energetic stabilities of quinazoline-2,4(1*H*,3*H*)-dione and its tautomers (4-hydroxyquinazolin-2(1*H*)-one, 2-hydroxyquinazolin-4(1*H*)-one, 2-hydroxyquinazolin-4(3*H*)-one, and quinazolin-2,4-diol). Estimates of the standard molar enthalpy of formation, in the gaseous phase, of the most stable tautomer, quinazoline-2,4(1*H*,3*H*)dione, at $T = 298.15$ K, were obtained from the G3(MP2)//B3LYP calculations using appropriate isodesmic reactions and were further compared with the obtained experimental value. The aromaticity of quinazoline-2,4(1*H*,3*H*)-dione has also been assessed through the evaluation and analysis of the Nucleus Independent Chemical Shifts (NICS) and their most significant components for the benzene and pyrimidine rings.

INTRODUCTION

The quinazoline-2,4(1*H*,3*H*)-dione molecule contains two fused six-membered rings, one a benzene ring and the other a pyrimidine ring substituted at positions 2 and 4 by a carbonyl group (see Figure 1). Quinazoline-2,4(1*H*,3*H*)-dione may be recognized as the benzo-annelated analogue of the RNA nucleobase, uracil, and so also related to the DNA nucleobase thymine with its 5-methyl group. Accordingly, both C- and N-nucleosides and nucleotide quinazolinedione derivatives have been studied by nucleic acid chemists interested in biological structure and activity. Examples of relevant studies include the possible formation of novel polynucleotide duplexes[1] and triplexes[2,3] and search for diverse antiviral activity.[4,5]

The quinazolinedione moiety is an important scaffold embedded in a variety of natural alkaloids[6−8] and many biologically active molecules including serotonergic, dopaminergic, and adrenergic receptor ligands and inhibitors of aldose reductase, lipoxygenase, cyclooxygenase, collagenase, and carbonic anhydrase.[9] As such, quinazoline-2,4(1*H*,3*H*)-dione derivatives have been widely used as key structures in the production of medicinal drugs. 7-Chloroquinazoline-2,4(1*H*,3*H*)-dione is a key intermediate for the production of two medicines: FK 366 (Zenarestat) and KF 31327. FK 366 is an aldose reductase inhibitor used in the treatment of diabetic complications (neuropathy, retinopathy, and cataracts).[10] KF 31327 was developed as a remedial drug for heart disease and as an impotence medicine.[11] 6,7-Dimethoxyquinazoline-2,4(1*H*,3*H*)-dione is a key intermediate for the production of medicines such as Alfuzosin, Prazosin, Terazosin, Doxazosin, and Iodoazidoarylprazosin (IAAP).[12−14] These drugs, which are effective α_1-adrenergic receptor blockers, are useful for antihypertensives. Ketanserin, a selective serotonin receptor antagonist with weak adrenergic receptor blocking properties, is also used as an antihypertensive agent.[15] 1,3-Substituted quinazoline-2,4(1*H*,3*H*)-diones have also been evaluated as possible peripheral vasodilators and antihypertensives as well as anti-inflammatory agents.[16] Quinazoline-2,4(1*H*,3*H*)-diones are also useful synthetic materials in heterocyclic chemistry.[17]

The crystal and molecular structure of quinazoline-2,4(1*H*,3*H*)-dione has already been studied by Liu[18] using diffractometry. Liu reported that in quinazoline-2,4(1*H*,3*H*)-dione there are intermolecular N−H···O hydrogen bonds involving the amine NH and carbonyl groups C═O that create centrosymmetric dimers between adjacent nearly coplanar molecules. These dimers are further connected by additional weak N−H···O

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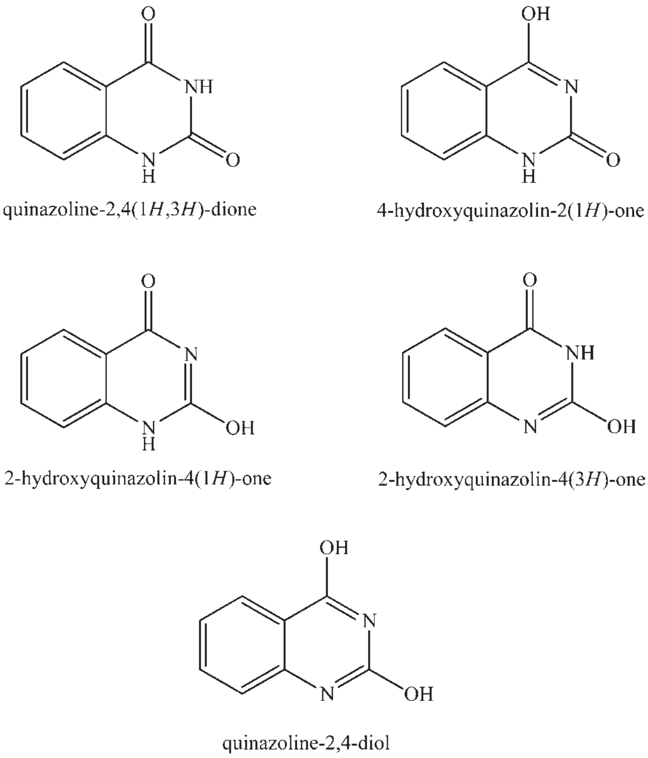


Figure 1. Molecular structure of quinazoline-2,4(1*H*,3*H*)-dione and its tautomers.

hydrogen bonds, forming a two-dimensional network. Molecules are packed in the crystal structure with adjacent benzene and pyrimidine rings approximately coplanar. A centroid—centroid separation of 0.3863 nm and a dihedral angle between the mean planes of 0.64° indicates the presence of weak intermolecular face-to-face $\pi-\pi$ stacking interactions.

Despite the important medical applications, the energetics of this compound has not yet been established. Thus, in this paper we report the standard molar enthalpy of formation of quinazoline-2,4(1*H*,3*H*)-dione obtained from a combined experimental and computational thermochemical work. In the experimental part of the work, the standard molar enthalpy of formation of the compound in the crystalline phase, at T = 298.15 K, was determined from static bomb combustion calorimetry and the standard molar enthalpy of sublimation was measured by Calvet microcalorimetry. These two thermodynamic parameters allowed the calculation of the standard molar enthalpy of formation of the compound in the gaseous phase, at T = 298.15 K. The relative energetic stability of quinazoline-2,4(1*H*,3*H*)-dione and its tautomers (see Figure 1) was assessed from quantum chemical calculations using the G3(MP2)//B3LYP composite method. The standard molar enthalpy of formation of the most stable tautomer was estimated from the computational calculations using appropriate isodesmic reactions. The aromaticity of all tautomers was assessed through the calculation of the nucleus independent chemical shifts (NICS) and compared with that of similar molecules.

■ EXPERIMENTAL SECTION

Purification of the Compound. Quinazoline-2,4(1*H*,3*H*)-dione was obtained commercially from Aldrich Chemical [CAS Registry No. 86-96-4] with the assigned purity of 0.97 in mass fraction and was further purified by repeated vacuum sublimation before the calorimetric experiments. The compositional purity of the samples and the completeness of the combustion process were confirmed through the carbon dioxide recovery ratios determined after the combustion experiments. The average ratio, together with the standard deviation of the mean, of the mass of carbon dioxide recovered to that calculated from the mass of sample was (1.0003 ± 0.0003). The purity of the sample could not be assessed by differential scanning calorimetry as this compound decomposes in the fusion process (mp > 573 K).

Static Bomb Combustion Calorimetry. The standard massic energy of combustion of quinazoline-2,4(1*H*,3*H*)-dione was measured in a static bomb combustion calorimeter equipped with a twin valve bomb (type 1108, Parr Instrument Company), made of stainless steel and with an internal volume of 0.342 dm^3. Since the apparatus and the technique have been described,[19,20] only a brief description will be given here. The energy equivalent of the calorimeter was determined from the combustion of benzoic acid, BDH Thermochemical Standard batch 69376/01, certificated in Manchester University, having a massic energy of combustion of $\Delta_c u = -(26435.1 \pm 3.5)\ J \cdot g^{-1}$, under certificate conditions. Calibration experiments were carried out in oxygen at the pressure 3.04 MPa in the presence of 1.00 cm^3 of deionized water added to the bomb. Two energy equivalents ε_{cal} were used in this study, due to some modifications done in the apparatus between the two sets of experiments performed for the compound: $\varepsilon_{cal} = (16000.8 \pm 1.4)\ J \cdot K^{-1}$, for experiments 1 to 6 and $\varepsilon_{cal} = (16005.0 \pm 2.0)\ J \cdot K^{-1}$, for experiments 7 and 8. The assigned uncertainties are the standard deviation of the mean of at least six calibration experiments.

The solid samples of quinazoline-2,4(1*H*,3*H*)-dione were burnt in pellet form, in oxygen, at a pressure p = 3.04 MPa, with a volume of 1.00 cm^3 of deionized water added to the bomb. *n*-Hexadecane (Aldrich Gold Label, mass fraction >0.999), stored and handled under nitrogen, was used as a combustion auxiliary due to incomplete combustions of the compound and thus avoiding the formation of a carbon soot residue. For all experiments, the temperature of the water inside the calorimeter was measured to $\pm\ (1 \cdot 10^{-4})$ K, at time intervals of 10 s, with a quartz crystal thermometer (Hewlett-Packard HP 2804A), interfaced to a PC. The ignition of the samples was made at $T = (298.150 \pm 0.001)$ K by the discharge of a 1400 μF capacitor through a platinum ignition wire. The program LABTERMO[21] was used for data acquisition: at least 100 temperature readings were taken for the initial period, and 200 readings were taken for the main and final periods. After each calorimetric experiment the carbon dioxide produced was collected in absorption tubes filled with Ascarite II. This procedure allowed us to determine the completeness of the combustion process and the compositional purity of the samples. The amount of nitric acid produced in the experiments was quantified by titration of the aqueous solution that resulted from washing the inside of the bomb.

Calvet Microcalorimetry. The standard molar enthalpy of sublimation of quinazoline-2,4(1*H*,3*H*)-dione was measured using the vacuum sublimation drop-microcalorimetric technique.[22] Samples of about (2 to 3) mg of the solid compound, contained in a small thin glass capillary tube sealed at one end, and a blank capillary were simultaneously dropped at room temperature into the hot reaction vessels in the Calvet high-temperature microcalorimeter (Setaram, Lyon, France), held at a convenient

Table 1. Combustion Experiment Results for Quinazoline-2,4(1*H*,3*H*)-dione[a]

experiment no.	1	2	3	4	5	6	7	8
$m(\mathrm{CO_2}$, total)/g		2.17738	1.56502	1.79130			2.11230	1.76245
m(cpd)/g	0.42872	0.67223	0.42836	0.51027	0.48825	0.42107	0.67867	0.51461
m(*n*-hexadecane)/g	0.25820	0.22949	0.20284	0.21840	0.19935	0.23492	0.20399	0.20605
m(cotton)/g	0.00247	0.00253	0.00256	0.00258	0.00254	0.00273	0.00241	0.00247
ΔT_{ad}/K	1.36101	1.61569	1.19799	1.35765	1.27015	1.28114	1.54920	1.32722
$\varepsilon_{\mathrm{f}}/(\mathrm{J\cdot K^{-1}})$	16.50	16.69	16.19	16.11	16.00	16.31	16.26	16.04
$\Delta m(\mathrm{H_2O})$/g	0.1	0.1	−0.1	−0.1	0.1	0.0	−0.1	0.0
$-\Delta U$(IBP)/J	21799.70	25879.68	19187.25	21744.31	20343.88	20519.82	24818.85	21262.64
ΔU(ign.)/J	0.57	0.29	0.44	0.48	0.39	0.34	0.64	0.80
$-\Delta U$(*n*-hexad.)/J	12171.90	10818.68	9562.22	10295.70	9397.49	11074.50	9620.46	9717.26
$-\Delta U$(cotton)/J	40.11	41.09	41.57	41.90	41.25	44.34	39.14	40.11
$-\Delta U(\mathrm{HNO_3})$/J	33.97	48.00	28.72	38.68	34.51	32.72	50.80	40.30
$-\Delta U$(carbon)/J	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$-\Delta U_{\Sigma}$/J	12.17	17.38	11.40	13.46	12.69	11.67	17.11	13.36
$-\Delta_{\mathrm{c}}u^{\circ}(\mathrm{cpd})/(\mathrm{J\cdot g^{-1}})$	22255.90	22246.15	22278.78	22252.08	22238.48	22220.98	22236.64	22252.99

$-\Delta_{\mathrm{c}}u^{\circ}(\mathrm{cpd})/(\mathrm{J\cdot g^{-1}}) = 22247.8 \pm 6.0$ (0.027 %)

[a] $m(\mathrm{CO_2}$, total) is the total mass of $\mathrm{CO_2}$ formed in the experiment; m (cpd) is the mass of compound burnt in the experiment; m (*n*-hexadecane) is the mass of *n*-hexadecane (auxiliary compound) used in the experiment; m(cotton) is the mass of cotton used in the experiment; ΔT_{ad} is the corrected temperature rise; ε_{f} is the energy equivalent of contents in the final state; $\Delta m(\mathrm{H_2O})$ is the deviation of the mass of water added to the calorimeter from 3119.6 g; ΔU(IBP) is the energy change for the isothermal combustion reaction under actual bomb conditions; ΔU(IBP) includes ΔU(ign.); ΔU(ign.) is the energy of combustion of the platinum wire; ΔU(*n*-hexad.) is the energy of combustion of the *n*-hexadecane; ΔU(cotton) is the energy of combustion of the cotton fuse; $\Delta U(\mathrm{HNO_3})$ is the energy correction for the nitric acid formation; ΔU(carbon) is the energy correction for carbon formation; ΔU_{Σ} is the energy correction to the standard state; $\Delta_{\mathrm{c}}u^{\circ}$ is the standard massic energy of combustion.

temperature $T = 503$ K, and were removed from the hot zone by vacuum sublimation. The thermal corrections for the glass capillary tubes were determined in separate experiments and were minimized, as far as possible, by dropping tubes of nearly equal mass, to within ± 10 μg, into each of the twin calorimeter cells. The microcalorimeter was calibrated in situ for these measurements, using the reported standard molar enthalpies of sublimation of naphthalene.[23] Accuracy tests were performed with benzoic acid and anthracene.

■ COMPUTATIONAL DETAILS

We have conducted computational calculations for quinazoline-2,4(1*H*,3*H*)-dione and its tautomers and auxiliary molecules using the G3(MP2)//B3LYP method.[24] In this method the geometries are fully optimized at the B3LYP/6-31G(d) level, and the obtained stationary points are characterized as minima through frequency calculations at the same level. Then single point energy calculations are performed at higher levels of theory: QCISD(T)/6-31G(d) and MP2/GTMP2Large. The final absolute G3(MP2)//B3LYP enthalpies, at $T = 298.15$ K, are obtained, correcting the electronic energies, by introducing the vibrational, translational, rotational, and the pV terms computed at the B3LYP/6-31G(d) level. All calculations were performed with *Gaussian 03*.[25]

NICS analysis were performed using gauge-independent atomic orbital (GIAO) method,[26−29] as implemented in the *Gaussian 03* program, with the B3LYP/6-311G(d,p) wave functions at the B3LYP/6-31G(d) optimized molecular geometries.

■ EXPERIMENTAL RESULTS

The results for a typical combustion experiment are given in Table 1. The internal energy associated with the isothermal bomb process, ΔU(IBP), was calculated through eq 1:[30]

$$\Delta U(\mathrm{IBP}) = -\{\varepsilon_{\mathrm{cal}} + c_p(\mathrm{H_2O,l})\Delta m(\mathrm{H_2O}) + \varepsilon_{\mathrm{f}}\}\Delta T_{\mathrm{ad}} + \Delta U_{\mathrm{ign}} \qquad (1)$$

where $\varepsilon_{\mathrm{cal}}$ is the energy equivalent of the calorimeter, $c_p(\mathrm{H_2O,l})$ is the specific heat capacity of liquid water, $\Delta m(\mathrm{H_2O})$ is the deviation of the mass of water added to the calorimeter from 3119.6 g, ε_{f} is the energy of the bomb contents after ignition, ΔT_{ad} is the adiabatic temperature increase calculated using the program LABTERMO,[21] and ΔU_{ign} is the energy of ignition. The remaining symbols in Table 1 have been previously described,[30] so only a brief description will be given here. The electrical energy for ignition ΔU_{ign} was determined from the change in potential difference across the capacitor when discharged through the platinum ignition wire. For the combustion of the cotton thread fuse, with an empirical formula of $\mathrm{CH_{1.686}O_{0.843}}$, the specific energy of combustion used was $\Delta_{\mathrm{c}}u^{\circ} = -16240\ \mathrm{J\cdot g^{-1}}$,[31] a value previously confirmed in our laboratory. The corrections for nitric acid formation $\Delta U(\mathrm{HNO_3})$ were based on $-59.7\ \mathrm{kJ\cdot mol^{-1}}$,[32] the molar energy of formation of $0.1\ \mathrm{mol\cdot kg^{-1}}$ $\mathrm{HNO_3(aq)}$ from $\mathrm{N_2(g)}$, $\mathrm{O_2(g)}$, and $\mathrm{H_2O(l)}$. The mass of compound, m(cpd), used in each experiment was determined from the total mass of carbon dioxide, $m(\mathrm{CO_2}$, total), produced after allowance for that formed from the cotton thread fuse and *n*-hexadecane. The standard massic energy of combustion of *n*-hexadecane was measured separately to be $-\Delta_{\mathrm{c}}u^{\circ} = (47160.8 \pm 4.1)\ \mathrm{J\cdot g^{-1}}$, where the assigned uncertainty corresponds to the standard deviation of the mean of six experiments. To calculate the standard massic energy of combustion, $\Delta_{\mathrm{c}}u^{\circ}$, corrections to the standard state were made by the procedure given by Hubbard et al.[30] An estimated pressure coefficient of specific energy: $(\partial u \partial p)_T = -0.2\ \mathrm{J\cdot g^{-1}\cdot MPa^{-1}}$ at

$T = 298.15$ K, a typical value for most solid organic compounds, was assumed.[33] The obtained mean value of the standard massic energy of combustion $\langle \Delta_c u° \rangle = -(22247.8 \pm 6.0)\ \mathrm{J \cdot g^{-1}}$, at $T = 298.15$ K, is referred to the following combustion reaction:

$$C_8H_6N_2O_2(cr) + 17/2O_2(g) \rightarrow 8CO_2(g) + 3H_2O(l) + N_2(g) \qquad (2)$$

The assigned uncertainty corresponds to the standard deviation of the eight experiments performed. The derived standard molar energy and enthalpy of combustion and the standard molar enthalpy of formation, in the crystalline phase, are respectively, $\Delta_c U_m^o(cr) = -(3607.4 \pm 2.2)\ \mathrm{kJ \cdot mol^{-1}}$, $\Delta_c H_m^o(cr) = -(3606.2 \pm 2.2)\ \mathrm{kJ \cdot mol^{-1}}$, and $\Delta_f H_m^o(cr) = -(399.4 \pm 2.4)\ \mathrm{kJ \cdot mol^{-1}}$. In accordance with normal thermochemical practice,[34] the uncertainties assigned to the standard molar enthalpies of combustion and formation are twice the overall standard deviation of the mean and include the uncertainties in calibration and in the auxiliary quantities used (level of confidence 95 %). To derive $\Delta_f H_m^o(cr)$ from $\Delta_c H_m^o(cr)$ the standard molar enthalpy of formation for $CO_2(g)$: $-(393.51 \pm 0.13)\ \mathrm{kJ \cdot mol^{-1}}$ and for $H_2O(l)$: $-(285.830 \pm 0.042)\ \mathrm{kJ \cdot mol^{-1}}$ were used.[35] The specific density, used to calculate the mass from the apparent mass in air, was estimated from the mass and the dimension of the pellets as $\rho = 1.30\ \mathrm{g \cdot cm^{-3}}$. The relative atomic masses used throughout this paper were those recommended by the IUPAC Commission.[36]

The standard molar enthalpy of sublimation, at $T = 298.15$ K, $\Delta_{cr}^{g} H_m^o(298.15\ \mathrm{K}) = (128.3 \pm 2.2)\ \mathrm{kJ \cdot mol^{-1}}$, was determined from six independent microcalorimetric experiments, and the uncertainty is twice the standard deviation of the mean (level of confidence 95 %). In each experiment, the observed enthalpy, $\Delta_{cr,298.15K}^{g,T} H_m^o$, $(167.2 \pm 2.2)\ \mathrm{kJ \cdot mol^{-1}}$, was corrected to $T = 298.15$ K using the equation:

$$\Delta_{298.15K}^{T} H_m^o(g) = \int_{298.15K}^{T} C_{p,m}^o(g)\,dT \qquad (3)$$

where T is the temperature of the hot reaction vessel (T was set at 503 K) and $C_{p,m}^o(g)$ is the molar heat capacity of the compound in the gaseous phase. The heat capacity and its temperature dependence

$$C_{p,m}^o(g)/(\mathrm{J \cdot mol^{-1} \cdot K^{-1}}) = -0.000386(T/\mathrm{K})^2 + 0.718(T/\mathrm{K}) - 34.176 \qquad (4)$$

were derived from statistical thermodynamics using the vibrational frequencies obtained from the differential functional theory calculations with the B3LYP functional and the 6-31G(d) basis set after scaling by an appropriate factor, 0.9613.[37]

The standard molar enthalpy of formation, in the crystalline phase, at $T = 298.15$ K, $\Delta_f H_m^o(cr) = -(399.4 \pm 2.4)\ \mathrm{kJ \cdot mol^{-1}}$, together with the standard molar enthalpy of sublimation, at $T = 298.15$ K, $\Delta_{cr}^{g} H_m^o(298.15\ \mathrm{K}) = (128.3 \pm 2.2)\ \mathrm{kJ \cdot mol^{-1}}$, yields the standard molar enthalpy of formation in the gaseous phase, at $T = 298.15$ K, $\Delta_f H_m^o(g) = -(271.1 \pm 3.3)\ \mathrm{kJ \cdot mol^{-1}}$.

■ COMPUTATIONAL RESULTS AND DISCUSSION

We have performed G3(MP2)//B3LYP calculations for quinazoline-2,4(1*H*,3*H*)-dione and its tautomers. In Table 2 we show the obtained absolute enthalpies, at $T = 298.15$ K, for all tautomers. From these values we have found that quinazoline-2,4(1*H*,3*H*)-dione, the *diketo* tautomer, is the most stable tautomer. In Table 2 we also present relative enthalpy values (difference between the enthalpy of the tautomer and that of the most stable one). The obtained relative order of energetic stabilities was: quinazoline-2,4(1*H*,3*H*)-dione > 2-hydroxyquinazolin-4(3*H*)-one > 4-hydroxyquinazolin-2(1*H*)-one > quinazolin-2,4-diol > 2-hydroxyquinazolin-4(1*H*)-one. In the G3(MP2)//B3LYP method the geometry of the molecules are optimized at the B3LYP/6-31G(d) level, but we have further optimized the molecular structure of the most stable tautomer using the 6-311++G(d,p) basis set. The bond lengths and angles obtained with the two basis sets do not differ significantly. The most relevant geometric parameters obtained with the more extended basis set are presented in Figure 2 and compared with the experimental values by Liu[18] in Table S1 of the Supporting Information. The calculated geometric parameters are in generally good agreement with the experimental data. The bond lengths obtained from our calculations differ at most by 0.0033 nm from the experimental ones while for the bond angles and dihedral angles differences of at most 2.1° and 3.1°, respectively, are observed. In agreement with the experiment, the calculated most stable molecular structure of quinazoline-2,4(1*H*,3*H*)-dione is planar. This planar structure favors the occurrence of electronic delocalization involving the two fused rings, thus stabilizing this molecule. In the pyrimidine ring the C−N−C bond angles (125.1° and 128.2°) are larger than the C−C−C bond angles due to the presence of a nonbonding

Table 2. Calculated G3(MP2)//B3LYP Absolute Enthalpies and Relative Enthalpy Values, at $T = 298.15$ K

	H	ΔH^a
tautomer	hartree	$\mathrm{kJ \cdot mol^{-1}}$
quinazoline-2,4(1*H*,3*H*)-dione	−567.667747	0.0
2-hydroxyquinazolin-4(3*H*)-one	−567.651940	41.5
4-hydroxyquinazolin-2(1*H*)-one	−567.647311	53.6
quinazoline-2,4-diol	−567.643697	63.1
2-hydroxyquinazolin-4(1*H*)-one	−567.641056	70.1

[a] Enthalpy values relative to the lowest enthalpy tautomer. One hartree = 2625.50184 $\mathrm{kJ \cdot mol^{-1}}$.

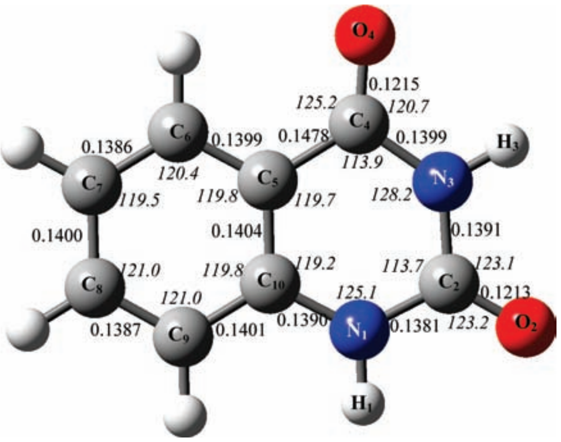
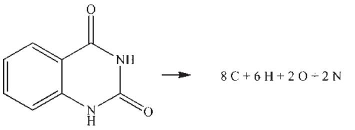


Figure 2. B3LYP/6-311++G(d,p) molecular structure of quinazoline-2,4(1*H*,3*H*)-dione. Bond lengths are in nanometers, and angles (*given in italic*) in degrees.

electron pair in the nitrogen atom. The $C_4{=}O_4$ bond is slightly tilted in the direction of the N−H fragment due most probably to a stabilizing intramolecular O···H interaction. In the case of the $C_2{=}O_2$ bond, being between two N−H bonds, the $N{-}C_2{=}O_2$ bond angles are approximately equal.

We have considered eqs 5 to 9 for the computational estimation of the standard molar enthalpy of formation, in the gaseous phase, at T = 298.15 K, of quinazoline-2,4(1H,3H)-dione:



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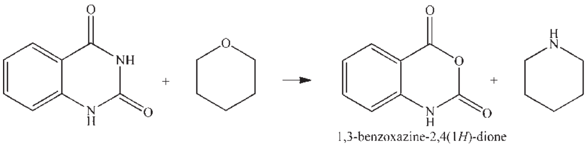

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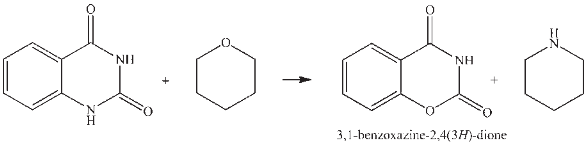

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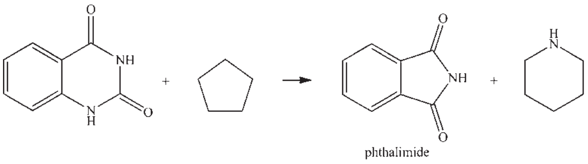

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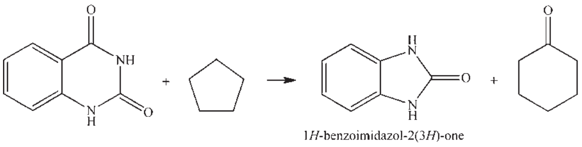

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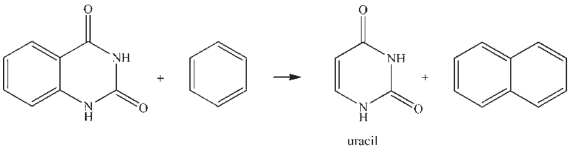

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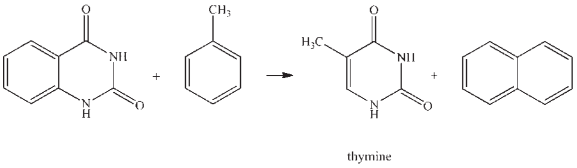
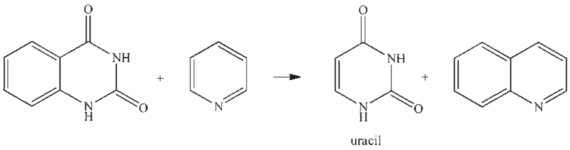


(11)



(12)

These reactions were chosen on the basis of available experimental thermochemical data for the compounds involved, and except for the atomization reactions, all of the other reactions were chosen to be isodesmic thus presumably leading to cancellation of most of the correlation energy errors inherent to the quantum chemical calculations. The computed reaction enthalpies were combined with the experimental standard molar enthalpies of formation of all of the intervening atoms or molecules, except for the compound whose enthalpy of formation we want to estimate, quinazoline-2,4(1H,3H)-dione. The calculated absolute G3(MP2)//B3LYP enthalpies, at T = 298.15 K, for quinazoline-2,4(1H,3H)-dione and for all the auxiliary atoms or molecules, as well as their experimental standard molar enthalpies of formation, at T = 298.15 K, are given in Table S2 in the Supporting Information. All of the experimental standard molar enthalpies of formation in the gaseous phase, at T = 298.15 K, were taken from Pedley's compendium[38] except for the atoms,[39] 2H-1,3-benzoxazine-2,4-(3H)dione,[40] 2H-3,1-benzoxazine-2,4(1H)dione,[40] phthalimide,[41] and 1H-benzimidazol-2(3H)-one.[42]

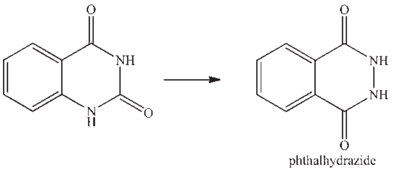
Table 3. Computed G3(MP2)//B3LYP Standard Molar Enthalpy of Formation, $\Delta_f H^o_m(g)_{comp.}$, of Quinazoline-2,4(1*H*,3*H*)-dione, in the Gaseous Phase, at *T* = 298.15 K (kJ·mol^{-1})

		Δ^a
reaction	$\Delta_f H^o_m(g)_{comp.}$	kJ·mol^{-1}
5	−266.0	−5.1
6	−265.8	−5.3
7	−257.1	−14.0
8	−259.6	−11.5
9	−262.3	−8.8
10	−266.4	−4.7
11	−254.3	−16.8
12	−269.5	−1.6

[a] Δ represents the enthalpic difference between the experimental and computed value ($\Delta = \Delta_f H^o_m(g)_{exp.} - \Delta_f H^o_m(g)_{comp.}$)

The obtained estimates for the standard enthalpy of formation of quinazoline-2,4(1H,3H)-dione are presented in Table 3. The estimates obtained from the atomization reaction and the isodesmic reactions 6, 10, and 12 are in very good agreement with the experimental value. The differences between computational estimates and experimental value are larger for reactions 7, 8, 9, and 11. However, the maximum deviation is only 16.8 kJ·mol^{-1}.

There is reported in the literature the standard molar enthalpy of formation of an isomer of quinazoline-2,4(1H,3H)-dione, 2,3-dihydrophthalazine-1,4-dione (phthalhydrazide), $\Delta_f H^o_m(g) = -(107.4 \pm 2.4)$ kJ·mol^{-1}.[43] The experimental enthalpy for the isomerization reaction:



(13)

(163.7 ± 4.1) kJ·mol^{-1} is in very good agreement with the value obtained from computational calculations at the G3(MP2)//B3LYP level: 168.2 kJ·mol^{-1}.

All considered molecules consist of two fused six-membered rings, one a benzene ring and the other a substituted pyrimidine ring. From the viewpoint of Hückel aromaticity each ring can be considered as aromatic with a number of π-electrons, 6, thus satisfying the Hückel $4n + 2$ rule for the emergence of aromatic character. The calculated NICS values, tabulated in Table 4, do indeed indicate the expected behavior. The benzene ring of all of

Table 4. Isotropic (σ_{iso}) and Out-of-Plane (σ_{ZZ}) Components of the Chemical Shielding Tensor Measured at the Center (0) and 0.10 nm above the Center (+1) of the Benzene and the Heterocyclic Rings (All Values in ppm)

	benzene ring				heterocyclic ring			
	0		+1		0		+1	
compound	σ_{iso}	σ_{ZZ}	σ_{iso}	σ_{ZZ}	σ_{iso}	σ_{ZZ}	σ_{iso}	σ_{ZZ}
benzene	−8.90	−14.52	−11.13	−29.32				
pyrimidine					−6.04	−11.06	−10.53	−27.48
uracil					−1.73	+14.92	−2.12	−2.42
quinazoline	−9.40	−14.23	−11.58	−29.35	−6.70	−9.90	−10.72	−27.00
quinazoline-2,4(1*H*,3*H*)-dione	−8.83	−9.08	−10.28	−24.93	−0.99	+18.79	−1.86	−0.38
quinazoline-2,4-diol	−8.52	−10.53	−10.62	−26.34	−6.29	+0.08	−8.19	−17.99
2-hydroxyquinazolin-4(3*H*)-one	−8.81	−10.80	−10.68	−26.33	−2.15	+14.00	−3.71	−5.76
4-hydroxyquinazolin-2(1*H*)-one	−8.73	−8.11	−9.99	−24.16	−1.81	+15.16	−3.55	−4.79
2-hydroxyquinazolin-4(1*H*)-one	−9.46	−11.02	−10.86	−26.61	−0.74	+16.86	−2.88	−3.50

the considered systems evidence NICS components both at the ring center and 0.10 nm above which are very similar to those observed for the benzene ring. As to the pyrimidine ring, we observe a considerable attenuation of aromatic character, with almost all systems being compatible with nonaromatic character. The exception is the pyrimidine ring of quinazoline-2,4-diol which evidence an aromatic character as important as that observed for quinazoline. We can further observe that the presence of carbonyl substituents at the pyrimidine ring has the effect of attenuating its aromatic behavior.

We may also briefly discuss the stability and aromaticity of quinazoline-2,4(1*H*,3*H*)-dione in terms of language derived from a recent model[44] for the aromaticity of derivatives of indane and indene, species with benzenes fused to five-membered rings. For these species we suggested the use of the reaction

$$\mathrm{C_6H_4XYZ + 2C_2H_6 \rightarrow \mathit{o}\text{-}C_6H_4(CH_3)_2 + CH_3XYZCH_3} \tag{14}$$

By analogy, as recently and qualitatively extended to the tautomeric 1,2,3-benzotriazin-4-ones[45] with their fused six-membered rings, we now write

$$\mathrm{C_6H_4WXYZ + 2C_2H_6 \rightarrow \mathit{o}\text{-}C_6H_4(CH_3)_2 + CH_3WXYZCH_3} \tag{15}$$

To the extent that thermochemical data for species of the $\mathrm{CH_3XYZCH_3}$ are often absent, we are a fortiori thwarted for many cases where $\mathrm{CH_3WXYZCH_3}$ is to be discussed should we seek quantitation. Nonetheless, we recognize the appropriate current acyclic fragment corresponding to quinazoline-2,4(1*H*,3*H*)-dione as $\mathrm{CH_3CONHCONHCH_3}$, that is, N^1-acetyl-N^3-methylurea with a not surprisingly unmeasured enthalpy of formation. We may still provide a meaningful, if still estimated, enthalpy for the relevant reaction 16 (−WXYZ− = −CONHCONH−)

$$\text{quinazoline-2, 4}(1H, 3H)\text{-dione} + \mathrm{2C_2H_6 \rightarrow \mathit{o}\text{-}C_6H_4(CH_3)_2 + CH_3CONHCONHCH_3} \tag{16}$$

However, the enthalpy of formation of the related *N*-acetylurea is available from the archival literature,[38] assuming that reaction 17 is thermoneutral (making use of the estimation philosophy in ref 44 and the enthalpy of formation of *N*-methylurea from ref 46),

$$\mathrm{CH_3CONHCONH_2 + NH_2CONHCH_3 \rightarrow CH_3CONHCONHCH_3 + NH_2CONH_2} \tag{17}$$

So the desired enthalpy of formation equals −431.1 $\mathrm{kJ \cdot mol^{-1}}$. Accordingly, reaction 16 is endothermic by 27 $\mathrm{kJ \cdot mol^{-1}}$. Following from a preliminary analysis[47] of reaction 15, comparison is made with the carbocycles 1,2,3,4-tetrahydronaphthalene and naphthalene (−WXYZ− = $\mathrm{-CH_2CH_2CH_2CH_2-}$ and −CH=CH−CH=CH−, respectively) and their associated reactions 18 and 19 (the enthalpy of formation of 2,4-hexadiene is from ref 48, all other data from ref 38)

$$\text{1, 2, 3, 4-tetrahydronaphthalene} + \mathrm{2C_2H_6 \rightarrow \mathit{o}\text{-}C_6H_4(CH_3)_2 + CH_3(CH_2)_4CH_3} \tag{18}$$

$$\text{naphthalene} + \mathrm{2C_2H_6 \rightarrow \mathit{o}\text{-}C_6H_4(CH_3)_2 + (E, E)\text{-}CH_3CH{=}CHCH{=}CHCH_3} \tag{19}$$

After all, these last carbocyclic species represent archetypal nonaromatic and aromatic species, or more precisely species with no aromatic and expected aromatic enhancement over the benzene ring of the reference species, *o*-xylene. Reaction 18 is endothermic by −6 $\mathrm{kJ \cdot mol^{-1}}$ (exothermic by 6 $\mathrm{kJ \cdot mol^{-1}}$), while reaction 19 is endothermic by 80 $\mathrm{kJ \cdot mol^{-1}}$. We thus conclude that the aromaticity of quinazoline-2,4(1*H*,3*H*)-dione lies between that of our archetypes for nonaromatic and aromatic species with two fused six-membered rings, corroborating our earlier conclusion in this paper that the aromaticity of the pyrimidine ring has been attenuated. We are encouraged.

The final comparison[42] involving the enthalpy of formation of quinazoline-2,4(1*H*,3*H*)-dione is that of the parent heterocycle quinazoline in which the two −C(O)NH− amide groups have been replaced by a corresponding −CH=N− imine group. We choose to use the more recent, and more precise, values for this quantity by the current paper's corresponding author[49] over that measured earlier by others,[50] namely, (166.5 ± 2.3) $\mathrm{kJ \cdot mol^{-1}}$ and (243.1 ± 2.7) $\mathrm{kJ \cdot mol^{-1}}$, as opposed to (180.3 ± 8.8) $\mathrm{kJ \cdot mol^{-1}}$ and (258.6 ± 8.8) $\mathrm{kJ \cdot mol^{-1}}$. This corresponds to a difference of 565.9 $\mathrm{kJ \cdot mol^{-1}}$ and 514.2 $\mathrm{kJ \cdot mol^{-1}}$ or 283 $\mathrm{kJ \cdot mol^{-1}}$ and 257 $\mathrm{kJ \cdot mol^{-1}}$ for each of the two independent amide groups replaced by imines. The current findings are in accord with the earlier suggested[42] differences of (275 ± 20) $\text{kJ}\cdot\text{mol}^{-1}$ and (242 ± 20) $\text{kJ}\cdot\text{mol}^{-1}$ for gaseous and solid amides.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Optimized bond lengths, bond angles, and dihedral angles (Table S1) and calculated and experimental enthalpies of formation (Table S2) for quinazoline-2,4(1*H*,3*H*)-dione. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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