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Are isatin and isatoic anhydride antiaromatic and aromatic respectively? A combined experimental and theoretical investigation

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This paper reports the results of our thermochemical/calorimetric determination of the enthalpies of combustion, phase change, and formation of isatin, isatoic anhydride, and *N*-methylisatin. The density functional calculations accompanied by vibrational and thermal corrections were also performed for these compounds and *N*-methylisatoic anhydride. Through a combination of theoretical calculations and associated isodesmic reactions, we have deduced that isatin has some antiaromatic character and isatoic anhydride enjoys some aromatic stabilization.

Introduction

Isatin (indole-2,3-dione) and isatoic acid (*o*-(*N*-carboxyamino)-benzoic acid, or more properly its cyclic anhydride) enjoy a chemical provenance which dates back well into the 19th century because of their relationship to the pigment indigo. The interest has been more than just that of similarity of chemical structure. For example, the chemistry of both species has contributed to an understanding of the atmospheric blotching and loss of color of paintings.[1] Additionally, isatin and some of its relatively simple derivatives are pharmacologically relevant, *e.g.* isatin "inhibits natriuretic peptide-induced hyperthermia in rats"[2] and some of its semicarbazones show anticonvulsive activity.[3] Isatoic anhydride and its derivatives have numerous industrial uses with patented applications as diverse as cationic paper coatings[4] to adhesives for rubber to metal.[5]

Isatins have a major importance in organic chemistry as they can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines.[6] The synthetic versatility of these compounds has led to their extensive use in the pharmaceutical industry since they can be used as raw materials for drug synthesis.

In nature, isatin and substituted isatins are found in plants,[7] for example the melosatin alkaloids (methoxy phenylpentyl isatins),[8] and also in humans as they are metabolic derivatives of adrenaline.[9] Isatin is also a component of coal tar.[10]

Isatoic anhydride is also an extremely versatile compound.[11] Because of the ease of its reactions with electrophiles or nucleophiles, its analogs and derivatives have found wide application in the manufacture of agricultural chemicals, dyes, pigments, flavors, fragrances, pharmaceuticals, and miscellaneous industrial chemicals useful as UV light absorbers, blowing agents, flame-proofing agents, corrosion inhibitors, dry bleaches, disinfectants, and sanitizing agents.[11,12]

Despite the long-term, diverse interests in isatin and isatoic anhydride and their derivatives, little is known about the relationships of structure and energetics. More precisely, isatin contains the –CO–CO–NH– functional group and despite the considerable thermochemical interest in the isomeric –CO–NH–CO– group and the even simpler –CO–NH– group,[13] there are very few compounds within this group for which the enthalpies of combustion and of formation are known. One is isatin itself, one measurement dating to 1893 and the other to 1933.[14] Others include oxamic acid, oxamide and parabanic acid (imidazolidine-trione): a brief discussion documents problems in these data and interpretations. Oxamic acid was calorimetrically studied once in the late 20th century[15] and several times almost 100 years earlier[16] in surprising agreement (the discrepancy is *ca.* 15 kJ mol^{-1}). For oxamide, there is the contemporary result found in ref. 15, the more ancient one in ref. 16*b*, one more in the mid-20th century[17] and an even more recent one found in ref. 18. Distressingly, there is a 60 kJ mol^{-1} spread in values – with nearly 50 kJ mol^{-1} between the current, and presumably most credible.[15,18] For parabanic acid, there are two reports by the same author,[19] both dating to the late 19th century. How do we compare our results on isatin with the results of these species?

Isatoic anhydride contains the –CO–O–CO–NH– group that is found in only one species for which the enthalpies of combustion and formation have been determined, the cyclic anhydride of *N*-carboxyphenylalanine.[20] These two substances structurally differ greatly but in terms of number and type of bonds they differ by only four C–H bonds and one C–C bond. For solids, equating this with two methylene groups suggests[21] a difference of *ca.* 56 kJ mol^{-1}. What is found here?

The current study presents the results of contemporary calorimetric and computational chemistry to provide an understanding of the thermochemistry of isatin, isatoic anhydride, *N*-methylisatin and *N*-methylisatoic anhydride.

The thermochemical study of isatin and two derivatives, *N*-methylisatin and isatoic anhydride, was performed both experimentally and theoretically. The experimental approach included the determination of the standard molar enthalpies of combustion, in oxygen, at T = 298.15 K, using the static bomb combustion calorimetry (from these values the standard molar enthalpies of formation of the compounds, in the crystalline phase, were derived) and the determination of the standard enthalpies of sublimation, at T = 298.15 K, using Calvet microcalorimetry. These values allowed the derivation of the corresponding standard enthalpies of formation in the gas phase, at T = 298.15 K. While it was desirable to study both the parent and *N*-methylated isatin and isatoic anhydride, the

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Table 1 Typical combustion experiments at T = 298.15 K

	Isatin	MeIsatin	Isatoic Anh.
$m(CO_2$, total)/g	1.44362	1.65877	2.23652
m(cpd)/g	0.60073	0.67203	1.03341
m'(fuse)/g	0.00378	0.00439	0.00381
ΔT_{ad}/K	0.92702	1.12301	1.32964
ε_f/J K^{-1}	15.34	15.64	15.97
$\Delta m(H_2O)$/g	−0.2	−0.1	0.0
$-\Delta U$(IBP)/J	14850.21	17990.64	21301.86
$-\Delta U$(fuse)/J	61.39	71.29	61.87
$-\Delta U(HNO_3)$/J	28.60	31.82	39.64
$-\Delta U$(carbon)/J	0.00	0.00	0.00
ΔU(ign.)/J	1.19	1.19	1.19
$-\Delta U_\Sigma$/J	12.69	13.84	21.72
$-\Delta_c u°$/J g^{-1}	24547.37	26594.79	20492.78

Table 2 Individual values of the massic energy of combustion (combustion energy per gram), at T = 298.15 K

$-\Delta_c u°$/J g^{-1}		
Isatin	MeIsatin	Isatoic Anh.
24540.48	26573.17	20480.70
24554.49	26587.04	20491.01
24568.18	26611.86	20500.91
24530.08	26599.47	20477.27
24547.37	26603.08	20499.64
24570.08	26594.79	20492.78
24526.88	26609.37	20496.28
24529.88	26639.58	
$-\langle\Delta_c u°\rangle$/J g^{-1}		
24545.9 ± 6.1	26602.3 ± 6.9	20491.2 ± 3.4

Table 3 Derived standard ($p°$ = 0.1 MPa) molar values at T = 298.15 K (all values in kJ mol^{-1})

	$-\Delta_c U^\circ_m$(cr)	$-\Delta_c H^\circ_m$(cr)	$-\Delta_f H^\circ_m$(cr)
Isatin	3611.5 ± 2.2	3610.9 ± 2.2	251.8 ± 2.4
MeIsatin	4287.2 ± 2.6	4287.8 ± 2.6	254.2 ± 2.9
Isatoic Anh.	3342.8 ± 1.6	3340.9 ± 1.6	521.8 ± 1.9

experimental study of the *N*-methylisatoic anhydride was not performed due to the impossibility to purify adequately this compound for the calorimetric determinations.

In addition we have performed theoretical calculations, for the four compounds, based on density functional theory with the B3LYP functional and two different basis sets: 6-31G* and 6-311G**.

Results and discussion

Experimental results

The enthalpies and temperatures of fusion for isatin and *N*-methylisatin were derived from differential scanning calorimetry (d.s.c.) experiments and are respectively: isatin, $\Delta^l_{cr}H^\circ_m(T_{fus})$ = (27.82 ± 0.45) kJ mol^{-1}, at T_{fus} = (475.73 ± 0.10) K; *N*-methylisatin, $\Delta^l_{cr}H^\circ_m(T_{fus})$ = (19.50 ± 0.14) kJ mol^{-1}, at T_{fus} = (403.25 ± 0.06 K). The uncertainties assigned to the results are twice the standard deviation of the mean of at least six independent runs. The enthalpy of fusion of the isatoic anhydride could not be obtained as this compound decomposes upon fusion.

Results for a typical combustion experiment of each compound are given in Table 1, where $\Delta m(H_2O)$ is the deviation of the mass of water added to the calorimeter from the average mass assigned to ε_{cal}, and ΔU_Σ is the correction to the standard state, as combustion experiments were made in oxygen at p = 3.04 MPa. The remaining quantities are as previously described.[22] For the cotton-thread fuse, empirical formula $CH_{1.686}O_{0.843}$, $\Delta_c u°$ = −16250 J g^{-1}.[23] The corrections for nitric acid formation $\Delta U(HNO_3)$ were based on −59.7 kJ mol^{-1},[24] for the molar energy of formation of 0.1 mol dm^{-3} HNO_3(aq) from N_2, O_2, and H_2O(l). As samples were ignited at T = 298.15 K, $\Delta U(\text{IBP}) = -\{\varepsilon_{cal} + \Delta m(H_2O)c_p(H_2O, l) + \varepsilon_f\}\,\Delta T_{ad} + \Delta U_{ign}$ where ΔU(IBP) is the energy associated with the isothermal bomb process, ε_f is the energy of the bomb contents after ignition and ΔT_{ad} is the adiabatic temperature rise. The individual results of all combustion experiments, together with the mean value and standard deviations, are given for each compound in Table 2. Table 3 lists the derived standard molar energies and enthalpies of combustion, $\Delta_c U^\circ_m$(cr) and $\Delta_c H^\circ_m$(cr), and the standard molar enthalpies of formation for the compounds in crystalline phase $\Delta_f H^\circ_m$(cr) at 298.15 K. In accordance with customary thermochemical practice, 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[25] and in the values of auxiliary quantities. To derive $\Delta_f H^\circ_m$(cr) from $\Delta_c H^\circ_m$(cr) the standard molar enthalpies of formation of H_2O(l) and CO_2(g), at T = 298.15 K, −(285.830 ± 0.042) kJ mol^{-1}[26] and −(393.51 ± 0.13) kJ mol^{-1},[26] respectively, were used.

Measurements of the enthalpies of sublimation $\Delta^g_{cr}H^\circ_m$ are given in Table 4 with uncertainties of twice the standard deviation of the mean. The derived standard molar enthalpies of formation, in both the crystalline and gaseous phases, for the studied compounds are summarized in Table 5.

As noted earlier, the only experimentally measurement with which one can make a direct comparison is the enthalpy of formation of solid isatin, archivally[27] chosen as −(268.2 ± 3.8) kJ mol^{-1}. The two values are comparable but the discrepancy is larger than we should like.

Our experiments give a −(15.6 ± 7.1) kJ mol^{-1} difference for the enthalpies of formation of gas phase isatin and *N*-methylisatin. With what do we make a comparison? From combining the archival value for gas phase acetamide[27] and the recently measured value for *N*-methylacetamide,[28] we find a compatible difference of −(9.7 ± 5.6) kJ mol^{-1}. Likewise, using the parent carbazole and its *N*-methylated[29] derivative that share a trigonal nitrogen in a 5-membered ring with isatin and its derivative, we find a difference of −10 kJ mol^{-1}. These differences are also comparable with the one obtained from the enthalpies of formation in the gas phase of phthalimide and *N*-methylphthalimide (isomeric forms of isatin and *N*-methylisatin) −22.5 kJ mol^{-1}.[30]

Theoretical results

The optimized bond lengths and bond angles for these compounds are given in Tables 7 and 8. In Fig. 1 the numbering of the atoms is shown. We can see from the resulting equilibrium geometries that the isatins are planar molecules. The benzene ring in these compounds becomes a bit distorted with C–C bond distances between 1.39 Å and 1.41 Å and the bond angles between 117.6° and 122.0° In the *N*-methyl substituted molecules, *N*-methylisatin and *N*-methylisatoic anhydride the methyl groups orient themselves in such a way that the hydrogen atom of the methyl group which is

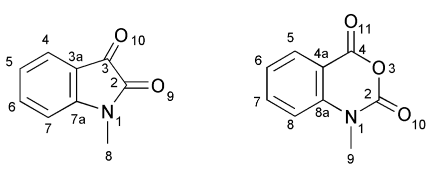

Fig. 1 Atom numbering scheme for isatin and isatoic anhydride. The positions 8 in isatin and 9 in the anhydride can be either H or CH_3.

Table 4 Standard ($p^\circ = 0.1$ MPa) molar enthalpies of sublimation at $T = 298.15$ K

	No. of expts	T/K	$\Delta_{\mathrm{cr},\,298.15\,\mathrm{K}}^{\mathrm{g},\,T} H_{\mathrm{m}}^{\mathrm{o}}$ /kJ mol^{-1}	$\Delta_{298.15\,\mathrm{K}}^{T} H_{\mathrm{m}}^{\mathrm{o}}(\mathrm{g})$ /kJ mol^{-1}	$\Delta_{\mathrm{cr}}^{\mathrm{g}} H_{\mathrm{m}}^{\mathrm{o}}(298.15\ \mathrm{K})$ /kJ mol^{-1}
Isatin	8	473	146.3 ± 5.1	27.5	118.8 ± 5.1
MeIsatin	6	401	122.9 ± 3.3	17.3	105.6 ± 3.3
Isatoic Anh.	6	488	151.2 ± 2.8	68.5	82.7 ± 2.8

Table 5 Derived standard ($p^\circ = 0.1$ MPa) molar values of the enthalpies of formation in the gas phase, at $T = 298.15$ K

	$-\Delta_{\mathrm{f}} H_{\mathrm{m}}^{\mathrm{o}}(\mathrm{cr})$/kJ mol^{-1}	$\Delta_{\mathrm{cr}}^{\mathrm{g}} H_{\mathrm{m}}^{\mathrm{o}}$/kJ mol^{-1}	$-\Delta_{\mathrm{f}} H_{\mathrm{m}}^{\mathrm{o}}(\mathrm{g})$/kJ mol^{-1}
Isatin	251.8 ± 2.4	118.8 ± 5.1	133.0 ± 5.6
MeIsatin	254.2 ± 2.9	105.6 ± 3.3	148.6 ± 4.4
Isatoic Anh.	521.8 ± 1.9	82.7 ± 2.8	439.1 ± 3.4

Table 6 Calculated electronic energies (hartree), zero-point vibrational energies (kJ mol^{-1}) and thermal corrections to $T = 298.15$ K (kJ mol^{-1})

Compound	$E_{\mathrm{B3LYP/6\text{-}31G*}}$	$E_{\mathrm{ZP/B3LYP/6\text{-}31G*}}$	$E_{\mathrm{total/B3LYP/6\text{-}31G*}}$^{a}	$E_{\mathrm{B3LYP/6\text{-}311G**}}$
Isatin	−513.063455	303.22	324.26	−513.202918
MeIsatin	−552.378459	377.73	402.88	−552.525699
Isatoic Anh.	−588.323343	318.05	340.74	−588.484725
MeIsatoic Anh.	−627.633044	393.04	419.48	−627.802141

^{a} $E_{\mathrm{total}}(T = 298.15\ \mathrm{K}) = E_{\mathrm{trans}} + E_{\mathrm{rot}} + E_{\mathrm{ZP}} + \Delta_{0\,\mathrm{K}}^{298.15\,\mathrm{K}}\ E_{\mathrm{vib}}$

Table 7 Calculated B3LYP/6-311G** bond lengths (Å) and bond angles (°) of the isatins

	Isatin	MeIsatin
1–2	1.39	1.39
2–3	1.57	1.57
3–3^{a}	1.47	1.47
3^{a}–4	1.39	1.39
4–5	1.39	1.40
5–6	1.40	1.40
6–7	1.40	1.40
7–7^{a}	1.39	1.39
7^{a}–1	1.40	1.40
1–8	1.01	1.45
2–9	1.20	1.20
3–10	1.20	1.20
1–2–3	104.7	105.6
1–2–9	127.3	126.8
2–3–3^{a}	104.8	104.6
2–3–10	124.5	124.6
3–3^{a}–7^{a}	107.9	107.7
3–3^{a}–4	131.2	131.2
3^{a}–4–5	118.7	118.7
4–5–6	119.9	119.9
5–6–7	122.0	122.0
6–7–7^{a}	117.6	117.6
7–7^{a}–1	128.7	128.3
3^{a}–7^{a}–1	110.3	110.9
7^{a}–1–2	112.2	111.2
7^{a}–1–8	125.1	125.3

nearest to the oxygen atom lies in the plane of the ring. This fact can be explained by the formation of a C–H ··· O intramolecular interaction, which further stabilizes this molecular conformation. The H ··· O distance of 2.47 Å and 2.23 Å, respectively for, *N*-methylisatin and *N*-methylisatoic anhydride is lower than the sum of the oxygen (1.52 Å) and hydrogen (1.2 Å) van der Waals radii and provides further support to the idea of the existence of a stabilizing intramolecular interaction (the intramolecular C–H ··· O bond angles are 103.1° and 106.6°, respectively, for *N*-methylisatin and *N*-methylisatoic anhydride).

The enthalpy of formation of gas phase isatin can be understood in terms of isodesmic reactions. A logical isodesmic reaction to begin with is

$$\text{isatin} + \text{naphthalene} \longrightarrow \text{indole} + \text{1,2-naphthoquinone} \quad (1)$$

Table 8 Calculated B3LYP/6-311G** bond lengths (Å) and bond angles (°) of the isatoic anhydrides

	Isatoic Anh.	MeIsatoic Anh.
1–2	1.38	1.39
2–3	1.37	1.37
3–4	1.40	1.39
4–4^{a}	1.47	1.46
4^{a}–5	1.40	1.40
5–6	1.39	1.38
6–7	1.40	1.40
7–8	1.39	1.39
8–8^{a}	1.40	1.40
8^{a}–1	1.39	1.40
1–9	1.01	1.47
2–10	1.20	1.20
4–11	1.19	1.20
1–2–3	115.2	116.5
1–2–10	123.9	124.3
2–3–4	126.0	126.4
3–4–4^{a}	115.6	115.1
3–4–11	117.8	118.1
4–4^{a}–8^{a}	119.6	119.9
4–4^{a}–5	120.5	119.5
4^{a}–5–6	120.2	120.4
5–6–7	119.5	119.0
6–7–8	121.1	121.3
7–8–8^{a}	119.3	119.9
8–8^{a}–4^{a}	120.0	118.7
8–8^{a}–1	121.7	121.8
8^{a}–1–9	120.2	120.3

However, there are no enthalpy of formation measurements for gas phase 1,2-naphthoquinone nor any gas phase isomerization enthalpies connecting 1,2- and 1,4-naphthoquinone,[31] *i.e.*

$$\text{1,2-naphthoquinone} \longrightarrow \text{1,4-naphthoquinone} \quad (2)$$

In that this last isomerization reaction is isodesmic, we may use the sum of these two reactions:

$$\text{isatin} + \text{naphthalene} \longrightarrow \text{indole} + \text{1,4-naphthoquinone} \quad (3)$$

as a suitable reaction to compare theory and experiment. The results are presented in Table 9. The 20 kJ mol^{-1} discrepancy is quite disconcerting given the value of enthalpy of formation of gas phase 1,4-naphthoquinone taken from the contemporary

Table 9 Values of enthalpy of reactions (1), (2) and (3) from two density functionals at $T = 0$ K and $T = 298.15$ K and for reaction 3 at $T = 298.15$ K using experimentally measured enthalpies of formation (kJ mol^{-1})

	$\Delta_r E_{T = 0\ \mathrm{K}}$		$\Delta_r H^\circ_T = 298.15$ K		
	B3LYP/6-31G*	B3LYP/6-311G**	B3LYP/6-31G*	B3LYP/6-311G**	Experimental
Reaction 1	92.5	93.2	91.7	92.4	–
Reaction 2	−30.7	−31.5	−30.1	−31.0	–
Reaction 3	61.9	61.7	61.6	61.4	41.7

Table 10 Calculated reaction energies at 0 K and enthalpies at 298.15 K (kJ mol^{-1})

	$\Delta_r E_{T = 0\ \mathrm{K}}$		$\Delta_r H^\circ_{T = 298.15\ \mathrm{K}}$		
	B3LYP		B3LYP		
	6-31G*	6-311G**	6-31G*	6-311G**	Experimental[a]
Reaction 4	−78.3	−80.6	−76.6	−78.9	−78.4
Reaction 5	−79.7	−81.7	−78.1	−80.2	−(85.5 ± 5.1)

[a] See ref. 30.

ref. 32. The early value of the 1,4-naphthoquinone[31] is within 3 kJ mol^{-1} of that most currently reported[32] and so we have some confidence in using the literature value for the enthalpy of formation of the 1,2-isomer.[33] Despite some hesitation in assuming the same enthalpy of sublimation for the two isomers, we derived an enthalpy of reaction (2) of −23.4 kJ mol^{-1} in satisfactory agreement with the results from our calculations.

Isatin is isomeric to phthalimide and, of course, *N*-methylisatin is isomeric to *N*-methylphthalimide. Therefore, we have considered the following isomerization reactions, respectively:

$$\text{isatin} \longrightarrow \text{phthalimide} \qquad (4)$$

$$N\text{-methylisatin} \longrightarrow N\text{-methylphthalimide} \qquad (5)$$

The energies of phthalimide and *N*-methylphthalimide have been obtained using the same calculation procedure described for the isatins. The resulting reaction energies at $T = 0$ K, $\Delta_r E_{T = 0\ \mathrm{K}}$, and reaction enthalpies at $T = 298.15$ K are presented together with the corresponding experimentally observed values of Table 10. We can see from the results in Table 10 that the calculated energetics of the isomerization reactions are in very good quantitative agreement with the experimentally derived values and that the isomerization enthalpies are very nearly the same for isatin and *N*-methylisatin.

A brief discussion of aromaticity and antiaromaticity

Aromatic character is a multifaceted feature of both organic and inorganic species, of neutrals and ions, of carbocyclic and heterocyclic molecules, of single and multi-ring systems and of cages.[34] Let us admittedly briefly discuss the key compounds of the current study, isatin and isatoic anhydride, and for these, only some of their thermochemical aspects.[35] Let us start with a comparison of isatin and 3-indazolone, both of which are heterocyclic analogs of indene and indane with CO and NH groups. We recognize isatin as π-isoelectronic to indenone and 3-indazolone to indole, and so related by loss of an annelated benzene ring to the unequivocally antiaromatic cyclopentadienone and pyrrole respectively.

The following isodesmic reaction may be used to compare the relative aromaticity of these two species.

$$\text{isatin} + \text{PhNHNHPh} + \text{PhCOPh} \longrightarrow \text{3-indazolone} + \text{PhCOCOPh} + \text{PhNHPh} \qquad (6)$$

Using data from the solid phase because we have only enthalpy of formation and not enthalpy of sublimation data for 3-indazolone in this phase,[36] we find this reaction to be exothermic by *ca.* 109 ± 20 kJ mol^{-1}. Although this does not allow us to disentangle the antiaromaticity of isatin from the aromaticity of 3-indazolone it strongly suggests destabilization of the former species and stabilization of the latter. This conclusion is further supported by the values of the bond separation energies calculated from the B3LYP/6-311G** energies for isatin (538.0 kJ mol^{-1}) and for the indazolone (627.5 kJ mol^{-1}).

By related simple electron counting, we recognize isatoic anhydride as π-isoelectronic to 2-quinolone, and so related to the aromatic 2-pyridone. The following isodesmic reaction compares these species

$$\text{isatoic anhydride} + \text{PhCHCHCOPh} \longrightarrow \text{2-quinolone} + \text{PhCOOCOPh} \qquad (7)$$

Again using data from the solid phase because we have only enthalpy of formation and not enthalpy of sublimation data for chalcone (PhCHCHCOPh),[37] (we have both for 2-quinolone[38] and benzoic acid anhydride[39]), we find this reaction to be exothermic by merely 14 kJ mol^{-1}. This suggests that isatoic anhydride is rather aromatic.

We now return to the aforementioned phenylalanine-*N*-carboxylic acid cyclic anhydride. From ref. 20 we find its enthalpy of formation, as solid, is −553.5 kJ mol^{-1}, some 32 kJ mol^{-1} more negative than the 521.8 kJ mol^{-1} we report for isatoic anhydride. We expected a difference of some 56 kJ mol^{-1}. This implies again some stabilization for isatoic anhydride – dare we say, once again, aromaticity? We defer to a later study a more thorough investigation of the plausible aromaticity of isatoic anhydride and plausible antiaromaticity of isatin.

Conclusion

Through a combination of calorimetric measurements, quantum chemical calculations and isodesmic reactions, we have deduced that isatin has some antiaromatic character and isatoic anhydride enjoys some aromatic stabilization.

Experimental

Materials

Isatin [91–56–5], *N*-methylisatin [2058–74–4] and isatoic anhydride [118–48–9] are all commercial products (Aldrich

Chemical Co.). The compounds were purified by vacuum sublimation until the combustion results were consistent and the carbon dioxide recovery ratios were satisfactory. The average ratios, together with the standard deviation of the mean, of the mass of carbon dioxide recovered to that calculated from the mass of sample were: isatin, (100.09 ± 0.06); *N*-methylisatin, (100.04 ± 0.02) and isatoic anhydride, (99.95 ± 0.01). The density of the compounds was estimated as $\rho = 1.0$ g cm^{-3}.

Each compound was also studied by differential scanning calorimetry over the temperature range T = 298 K to the respective temperature of fusion. Measurements were performed with a Setaram DSC 141 apparatus using a heating rate of 1.67×10^{-2} K s^{-1}. The samples were contained in hermetically sealed stainless steel crucibles. The recorded thermograms did not show any phase transitions between T = 298 K and the melting temperatures of the samples: isatin, T_{fus} = (475.73 ± 0.10) K; *N*-methylisatin, T_{fus} = (403.25 ± 0.06 K). Isatoic anhydride decomposes in the fusion.

Combustion calorimetry

The enthalpies of combustion were measured using a static bomb calorimeter. The apparatus and technique have been described elsewhere.[40] The energy equivalent of the calorimeter was determined using the combustion of benzoic acid (Bureau of Analysed Samples, Thermochemical Standard, BCS-CRM-190 n) for which the massic energy of combustion (combustion energy per gram) is $-\Delta u_{\mathrm{c}}$ = (26432.3 ± 3.8) J g^{-1}, under certificate conditions. The calibration results were corrected to give the energy equivalent $\varepsilon_{\mathrm{cal}}$ corresponding to the average mass of water added to the calorimeter, 3119.6 g. From six calibration experiments performed $\varepsilon_{\mathrm{cal}}$ = (16004.8 ± 1.6) J K^{-1}, where the uncertainty quoted is the standard deviation of the mean.

Calvet microcalorimetry

The enthalpies of sublimation of the compounds were measured using the "*vacuum sublimation*" drop microcalorimetric method.[41] Samples, about 3–5 mg, of each solid compound contained in a thin glass capillary tube sealed at one end, were dropped, at room temperature, into the hot reaction vessel, in a high temperature Calvet microcalorimeter held at a convenient temperature T, and then removed from the hot zone by vacuum sublimation. The observed enthalpies of sublimation were then corrected to T = 298.15 K using the value of $\Delta_{298.15\,\mathrm{K}}^{T} H_{\mathrm{m}}^{\circ}$(g) estimated by a group method based on the values of Stull *et al.*[42] The microcalorimeter was calibrated *in situ* for these measurements using the reported enthalpies of sublimation of naphthalene.[42]

Computational details

The most stable conformations of isatin, *N*-methylisatin, isatoic anhydride and *N*-methylisatoic anhydride were obtained using the density functional theory (DFT) with the Becke 3-parameter hybrid exchange[43] and Lee-Yang-Parr[44] correlation density functional (B3LYP) and two different basis sets: 6-31G*[45,46] and 6-311G**.[47,48] Harmonic vibrational frequencies were calculated through construction and diagonalization of the Hessian matrices at the optimum B3LYP/6-31G* molecular geometries obtained using the same basis set. This procedure allowed characterizing these equilibrium geometries as true minima and to obtain the corrections needed to derive energies at the temperature of 298.15 K. All calculations were performed using the UK version of GAMESS.[49,50] Total energies, identified by the subscripts B3LYP/6-31G* and B3LYP/6-311G**, as well as zero-point vibrational energies and total internal energy corrections are reported in Table 6 for the studied compounds.

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