Comparative Computational and Experimental Study on the Thermochemistry of the Chloropyrimidines

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The standard ($p^0 = 0.1$ MPa) molar enthalpies of formation, $\Delta_f H_M^0$, for liquid 2,4,6-trichloropyrimidine and for crystalline 2-chloropyrimidine, 2,4- and 4,6-dichloropyrimidine, and 2,4,5,6-tetrachloropyrimidine compounds were determined at $T = 298.15$ K by rotating-bomb combustion calorimetry. The standard molar enthalpies of vaporization or sublimation, $\Delta_{cr,l}^g H_M^0$, of these compounds at $T = 298.15$ K were determined by Calvet microcalorimetry. The experimental standard molar enthalpies of formation of those compounds, in the gaseous state, at $T = 298.15$ K, were thus obtained by combining these two sets of results. The latter values have been employed in the calibration of the computational procedure, which has been used to estimate the gas-phase enthalpies of formation for the other chloropyrimidines that were not possible to obtain in a pure form for the experimental study. It is found that the exchange-correlation functional based on the local spin density approximation (LSDA) seems to be a cheap choice for the estimation of enthalpies of formation for heterocycles containing nitrogen atoms; the well-known B3LYP hybrid method yields larger differences, with respect to the experimental values, for 2,4,6-tri- and 2,4,5,6-tetrachloropyrimidines.

Introduction

Nitrogen heterocycles with one or two nitrogen atoms, like pyridine or pyrimidine, are important compounds in many organic chemistry applications, being part of the chemical structures of many natural products, with a large number and variety of applications from medical to toxic effects, besides being used in the organic synthesis of many other chemicals from new pharmaceutical drugs to new pesticides.

Pyrimidine itself (Figure 1) is the building block of crucial molecules in living systems. In fact, the nucleobases cytosine, thymine, and uracil are obtained by small but important modifications of the pyrimidine ring. Despite their important role in biologically imperative components such as DNA, RNA, and coenzymes, they are also employed in the synthesis of many drugs as a starting compound. Furthermore, pyrimidine derivatives containing chlorine atoms are still crucial in many scientific areas; for example, 2-chloropyrimidine is used as an intermediate for the synthesis of pharmaceuticals, cf. sulfa drugs, and disinfectants. Recently, chloropyrimidines by themselves have been shown to be antimycotic agents against pathogenic fungi and to have significant in vitro activity against mycobacteria.[1] In spite of these noticeable uses, they also have other unattractive properties because these compounds were found to be relevant in the formation of various NO_x species during the combustion of heavy oils and coal.[2]

As stated above, the pyrimidine ring is found in a large variety of compounds, and so, accurate knowledge about the thermochemistry of pyrimidine and some of its derivatives is necessary for the calibration of computational methods used to study the diversity of structures where it is found, i.e., biomolecules, drugs, and others. In the literature, several works have been devoted
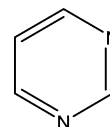

Figure 1. Pyrimidine ring.

to the determination of some thermodynamic properties of the unsubstituted pyrimidine compound in both the gas and condensed phases.[3] The gas-phase enthalpy of formation of pyrimidine is 195.8 ± 1.5 kJ mol^{-1}, a value that was determined by two different groups and using different experimental techniques. Tjebbes[4] used a static bomb calorimeter to measure the enthalpy of combustion of pyrimidine, -2292.3 ± 0.84 kJ mol^{-1}. Furthermore, this author determined the enthalpy of vaporization of this compound, 50.0 ± 0.3 kJ mol^{-1}, which was combined with the results from the combustion experiment to yield the gas-phase enthalpy of formation of pyrimidine reported above. In a latter work, Nabavian et al.[5] obtained identical results for all these quantities. The acidity of pyrimidine was experimentally determined by Meot-Ner et al.[6] as 1612 ± 10 kJ mol^{-1}. Semiempirical calculations with the AM1 method showed that the more acidic proton was that bonded to the carbon atom that is in the 4-position relative to the two nitrogen atoms in the aromatic ring. Very recently, Amunugama and Rodgers[7] reported a combined experimental and computational study to elucidate the periodic trends in the binding of metal ions to pyrimidine. They found that cation−pyrimidine bond dissociation enthalpy was explained by the populations of valence orbitals on the cation. The binding is strongest for ions with d electrons, especially when these d orbitals are full.

The rather complete knowledge about the thermodynamic properties of pyrimidine is not found for its derivatives, although the pyrimidine scaffold is found in many important compounds. For example, the enthalpy of formation in the gas phase for cytosine[3] is associated with a very large uncertainty: its value

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is reported as -59 ± 10 kJ mol^{-1}. Differences between experimental results for the enthalpy of formation in the condensed phase and for the enthalpy of phase transition determined by different groups are larger than 25 kJ mol^{-1}. Large differences between experimental enthalpies of phase transition are also found for adenine and thymine. Therefore, it seems that experimental work with these compounds derived from pyrimidine is still needed. In the present work, gas-phase enthalpies of formation for all chloropyrimidine compounds are reported; these have been obtained experimentally when compounds with high purity were available for experimental determinations and were obtained by computational methods when the chlorinated pyrimidines were not accessible. The experimental investigation includes the determination of the standard molar energies of combustion, in oxygen, at $T = 298.15$ K, of different chloropyrimidines, using a rotating-bomb combustion calorimeter, from which the values of the standard molar enthalpies of formation, in the condensed phase, were derived. The determination of the standard molar enthalpies of sublimation or vaporization, at $T = 298.15$ K, was done by Calvet microcalorimetry using the high-temperature vacuum sublimation technique. These values allowed for the derivation of the standard molar enthalpies of formation in the gaseous state of 2-chloropyrimidine [CAS 1722-12-9], 2,4-dichloropyrimidine [CAS 3934-20-1], 4,6-dichloropyrimidine [CAS 1193-21-1], 2,4,6-triclhoropyrimidine [CAS 3764-01-0], and 2,4,5,6-tetrachloropyrimidine [CAS 1780-40-1], which were compared with values estimated from the Cox scheme[8] and those obtained by computational methods. Herewith, several computational approaches have been considered, namely methods based on the density functional, on the Moller–Plesset perturbation, and on the Gaussian-N theories. The variety of methods chosen is confined to those that are available in public computer codes that are commonly used in computational thermochemistry or that can be applied to molecules of the size studied here with standard computers.

Experimental Details

The compounds, obtained commercially from Aldrich Chemical Co., were purified by repeated sublimation or fractional distillation, and the purities of the samples were checked by gas–liquid chromatography (GLC) and C, H, and N microanalysis at the Department of Chemistry, University of Aveiro, Portugal. The mass fraction w of C, H, and N were as follows: for 2-chloropyrimidine ($C_4H_3N_2Cl$), found $10^2\ w(C) = 41.7$, $10^2\ w(H) = 2.8$, $10^2\ w(N) = 24.9$, calculated $10^2\ w(C) = 41.9$, $10^2\ w(H) = 2.6$, $10^2\ w(N) = 24.5$; for 2,4-dichloropyrimidine ($C_4H_2N_2Cl_2$), found $10^2\ w(C) = 32.0$, $10^2\ w(H) = 1.5$, $10^2\ w(N) = 18.9$, calculated $10^2\ w(C) = 32.2$, $10^2\ w(H) = 1.3$, $10^2\ w(N) = 18.8$; for 4,6-dichloropyrimidine ($C_4H_2N_2Cl_2$), found $10^2\ w(C) = 32.1$, $10^2\ w(H) = 1.4$, $10^2\ w(N) = 18.9$, calculated $10^2\ w(C) = 32.2$, $10^2\ w(H) = 1.3$, $10^2\ w(N) = 18.8$; for 2,4,5,6-tetrachloropyrimidine ($C_4N_2Cl_4$), found $10^2\ w(C) = 21.9$, $10^2\ w(N) = 12.9$, calculated $10^2\ w(C) = 22.02$, $10^2\ w(N) = 12.9$.

The combustion experiments were performed with a rotating-bomb calorimeter developed by Sunner at the University of Lund, Sweden. Both the apparatus and the operating technique have been described previously,[9–11] and so, only a brief description will be given here. The bomb, with an internal volume of 0.258 dm^3, is of stainless steel lined with platinum, and the internal fittings are machined from platinum. In each experiment, the bomb is suspended from the lid of the calorimeter can to which 5222.5 g of water is added from a weighed Perspex vessel.

Calorimeter temperatures were measured to $\pm 10^{-4}$ K at time intervals of 10 s using a Hewlett-Packard (HP-2804A) quartz crystal thermometer interfaced to an Olivetti M 250E microcomputer; 100 readings are taken for the main period and for both the pre-period and the post-period. For each experiment, the ignition temperature was chosen so that the final temperature would be close to $T = 298.15$ K.

The rotating mechanism allowed simultaneous axial and end-over-end rotation of the bomb. The rotation of the bomb was started when the temperature rise in the main period reached about 63% of its total value and was continued throughout the rest of the experiment. Good et al.[12] showed that, by adopting this procedure, the frictional work due to the rotation of the bomb is automatically included in the temperature corrections for the work of water stirring and for the heat exchanged with the thermostated jacket ($T \approx 303.5$ K $\pm 10^{-4}$ K).

The energy equivalent of the calorimeter was determined by combustion of benzoic acid (Bureau of Analyzed Samples, Thermochemical Standard CRM-190r) having a massic energy of combustion under standard bomb conditions of $-26\ 432.3 \pm 3.8$ J g^{-1}. The calibration results were corrected to give the energy equivalent ϵ (calor) corresponding to the average mass of water added to the calorimeter: 5222.5 g. From six calibration experiments made in oxygen at $p = 3.04$ MPa with 1 cm^3 of water added to the bomb, ϵ (calor) = (25 172.2 $\pm$ 1.5) J K^{-1}. The uncertainty quoted is the standard deviation of the mean. The accuracy of the calorimeter was checked in our laboratory by other investigators[9] by measuring the energy of combustion of 4-chlorobenzoic acid.

The compounds were burnt in oxygen at a pressure of 3.04 MPa in the presence of aqueous As_2O_3 in order to reduce all the free chlorine produced by the combustion to hydrochloric acid. For the compounds 2-chloro- and 2,4- and 4,6-dichloropyrimidine, 25.00 cm^3 of aqueous As_2O_3 was used; 30.00 and 35.00 cm^3 were used for 2,4,6-tri- and 2,4,5,6-tetrachloropyrimidine, respectively. Within the precision of the analytical method, no evidence[11] was found for oxidation of As_2O_3(aq) during 5 h in the presence of oxygen at a pressure of 3.04 MPa. The extent of oxidation of As_2O_3(aq) was determined by titration with standardized iodine solution. For the calculation of the energetic term $\Delta U(As_2O_3)$, corresponding to the energy of oxidation of As_2O_3 to As_2O_5 in aqueous solution, we used the procedure described by Hu et al.,[13] using the enthalpies of oxidation of As_2O_3(aq) by Cl_2,[14] and the thermal effects of mixing As_2O_5(aq) with strong acids.[15]

Hexadecane (Aldrich Gold Label, mass fraction > 0.999) stored under nitrogen was used as an auxiliary combustion aid, and its massic energy of combustion was measured, $-\Delta_c u^0$(l) = (47 145.8 $\pm$ 1.3) J g^{-1}. This value is in agreement with that of Fraser and Prosen[16] for a sample of mass fraction 0.9996, $-\Delta_c u^0$(l) = (47 155.0 $\pm$ 3.8) J g^{-1}.

The crystalline compounds were burnt in pellet form, and the liquid 2,4,6-trichloropyrimidine was burnt in sealed polyester bags made of Melinex using the technique described by Skinner and Snelson,[17] who determined the massic energy of combustion of dry Melinex as $-\Delta_c u^0 = 22\ 902 \pm 5$ J g^{-1}. This value was confirmed in our laboratory. The mass of Melinex used in each experiment was corrected for the mass fraction of water ($\omega = 0.0032$), and the mass of carbon dioxide produced from it was calculated using the factor previously reported.

The electrical energy for ignition was determined from the change in potential difference across a capacitor when discharged through the platinum ignition wire. For the cotton-thread fuse (empirical formula $CH_{1.686}O_{0.843}$), $\Delta_c u^0 = -16\ 240$ J g^{-1},[18]

a value that was confirmed in our laboratory. The corrections for nitric acid formation, determined using Devarda's alloy method,[19] were based on -59.7 kJ mol^{-1} for the molar energy of formation of 0.1 mol dm^3 HNO$_3$(aq) from N$_2$, O$_2$, and H$_2$O-(l).[20] The amount of H$_2$PtCl$_6$(aq) was determined from the loss of mass of the platinum crucible and its supporting ring. An estimated pressure coefficient of specific energy was assumed: $(\partial u/\partial p)_T = -0.2$ J g^{-1} MPa^{-1} at $T = 298.15$ K, a typical value for most organic compounds.[21] For each compound, the massic energy of combustion, $\Delta_c u^0$, was calculated by a procedure similar to that developed by Hubbard et al.[18] for compounds containing just C, H, and N and implemented by Hu et al.[13] for chlorine-containing compounds.

The enthalpies of sublimation of the compounds were measured using the "vacuum sublimation" drop microcalorimetric method.[22] For the vaporization of 2,4,6-trichloropyrimidine, a method similar to the one for sublimation of solids was used, which was tested in our laboratory.[23] The samples contained in a small thin glass capillary tube sealed at one end were dropped at room temperature into the hot reaction vessel in the Calvet High-Temperature Microcalorimeter (Setaram, Lyon, France) held at a predefined temperature and then removed from the hot zone by vacuum sublimation/vaporization. The observed enthalpies of sublimation, or vaporization, were corrected to $T = 298.15$ K using $\Delta_{298.15\text{K}}^{T}H_m^0(\text{g})$ estimated by a group method (see below) on the basis of the values of Stull et al.[24]
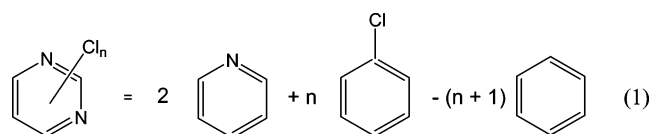

The microcalorimeter was calibrated in situ for these measurements using the reported enthalpies of sublimation of naphthalene[24] and of vaporization of *n*-decane.[25] The relative atomic masses were those recommended by the IUPAC in 2001.[26]

Computational Details

Several different computational methods, based on either the density functional theory (DFT) or on the Moller–Plesset approximation, have been used together with the 6-31G(d) basis set for the optimization of the geometry of all compounds. Vibrational frequencies have been calculated at the same level to obtain thermal corrections for $T = 298.15$ K. The exchange-correlation functionals used were as follows: the Becke's three-parameter hybrid functional using the nonlocal correlation from Lee et al., B3LYP;[27,28] the 1998 functional from Schmider and Becke, B98;[29] the Becke's 1988 exchange functional with the Perdew's 1986 correlation functional, BP86;[30,31] the Handy's family functional refined against data from 407 atomic and molecular systems, HCTH/407;[32] the 1997 hybrid functional of Perdew et al., PBE1PBE;[33] the modified Perdew–Wang exchange and Perdew–Wang 91 correlation functionals, MPW1PW91;[34] the version of the PW91 exchange functional modified by Adamo and Barone;[34] with the Becke's τ-dependent gradient-corrected correlation functional, MPWB95;[35] local spin density approximation, Slater exchange functional with the correlation functional (III) from Vosko et al., SVWN-LSDA;[36,37] the τ-dependent gradient-corrected correlation functional from van Voorhis and Scuseria, VSXC.[38] Another set of calculations has been performed with the MP2 method, i.e., Moller–Plesset

perturbation theory second-order corrections to the Hartree–Fock energy.[39] From these optimized structures, two sets of new calculations have been performed. A larger basis set, 6-311+G-(2d,2p), has been combined with the same density functional or MP2 methods to further optimize the geometry. This energy has been added to the thermal corrections calculated at the lower level of theory to obtain absolute enthalpies at $T = 298.15$ K. Another set of calculations used the B3LYP/6-31G(d) optimized geometries (and thermal corrections) and involved the computation of the energy of the molecules under study with the QCISD-(T)/6-31G(d) and MP2/GTMP2Large approaches (also named the G3MP2B3 composite approach).[40] All the calculations have been performed by means of the Gaussian03 computer code.[41] The enthalpies computed with the energies calculated with the larger basis set, 6-311+G(2d,2p), and the thermal corrections computed with the smaller basis set, 6-31G(d), or the enthalpies coming from the G3MP2B3 composite approach, have been used to compute the enthalpies of the selected reactions, all in the gas phase (shown below) where R $=$ H or Cl and *n* is the
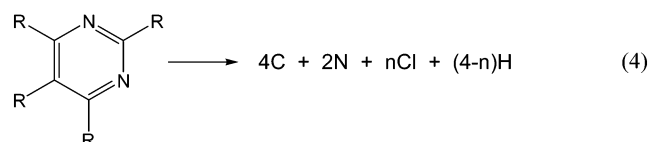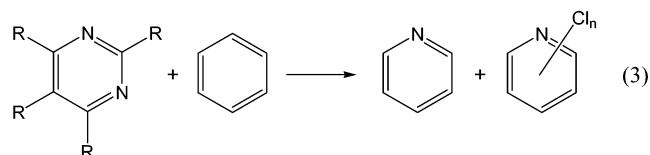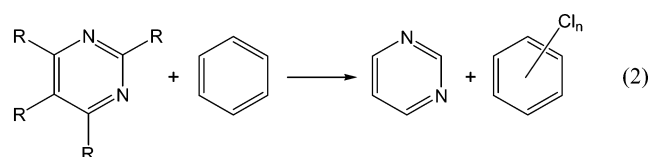
number of chlorine atoms on the pyrimidine isomer considered. The enthalpies of formation for each chloropyrimidine were estimated from the computed enthalpies of one of the reactions schematized above and the experimental enthalpies of formation in the gas phase for the other compounds there included.

Results and Discussion

Results for a typical combustion experiment of each compound are given in Table 1, where Δm (H$_2$O) is the deviation of the mass of water added to the calorimeter from 5222.5 g and ΔU_Σ is the correction to the standard state. The remaining terms have been previously described.[42] The values of $\Delta_c u^0$ refer to the reaction with HCl·600H$_2$O(l) as the chlorine-containing product in the final state. The results of all combustion experiments, together with the mean value and its standard deviation, are given, for each compound, in Table 2. Details of all the combustion calorimetry experiments for each of the five chloropyrimidines studied are given as Supporting Information. Table 3 lists the derived standard molar energies, enthalpies of combustion, and standard molar enthalpies of formation for the compounds in the condensed phase at $T = 298.15$ K. In accordance with normal 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[42,43] and in values of auxiliary quantities. To derive $\Delta_f H_m^0$(cr, l) from Δ_c

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TABLE 1: Results of a Typical Combustion Experiment at $T = 298.15$ K

	2-chloro pyrimidine	2,4-dichloro pyrimidine	4,6-dichloro pyrimidine	2,4,6-trichloro pyrimidine	2,4,5,6-tetrachloro pyrimidine
m(cpd)/ g	0.97923	0.79469	0.71708	0.61068	0.86304
m'(fuse)/ g	0.00314	0.00349	0.00302	0.00257	0.00273
m''(Melinex)/ g				0.05794	
m'''(oil)/ g		0.25581	0.24907	0.25183	0.25267
ΔT_{ad}/ K	0.74005	0.91373	0.85910	0.78463	0.77157
ϵ_i/ J K^{-1}	93.95	115.20	115.12	136.19	157.04
ϵ_f/ J K^{-1}	91.05	112.02	112.17	132.34	151.01
Δm(H$_2$O)/ g	1.2	−1.2	−1.2	−2.5	−6.1
$-\Delta U$(IBP)/ J^a	18701.16	23100.09	21718.80	19848.24	19522.48
ΔU(Melinex)/ J				1327.05	
ΔU(oil)/ J		12060.22	11742.53	11872.82	11912.47
ΔU(fuse)/ J	50.99	56.68	49.04	41.74	44.34
ΔU(HNO$_3$)/ J	48.72	30.33	34.39	25.31	26.57
ΔU(As$_2$O$_3$)/ J	499.25	453.37	416.26	466.04	841.86
ΔU(ign)/ J	1.26	1.26	1.27	1.24	1.23
ΔU(H$_2$PtCl$_6$)/ J	0.87	1.07	0.9	1.44	2.00
ΔU_Σ / J	39.66	49.01	46.17	50.09	51.95
$-\Delta_c u^0$/ J g^{-1}	18444.77	13149.04	13149.87	9929.50	7697.55

^{a} ΔU(IBP) already includes the ΔU(ign).

TABLE 2: Individual Values of the Massic Energy of Combustion, $-\Delta_c u^0$, of the Compounds at $T = 298.15$ K

$-\Delta u^0$/J·g^{-1}				
2-chloro pyrimidine	2,4-dichloro pyrimidine	4,6-dichloro pyrimidine	2,4,6-trichloro pyrimidine	2,4,5,6-tetrachloro pyrimidine
18444.77	13137.23	13149.87	9929.50	7697.55
18442.14	13155.09	13158.87	9940.15	7704.01
18433.14	13149.96	13150.69	9921.82	7700.33
18447.13	13156.19	13147.39	9929.44	7699.00
18454.95	13140.13	13142.18	9937.33	7698.14
18451.56	13149.04	13150.80	9931.57	7690.31
	13151.34			
	13138.44			

$-<\Delta u^0>/$(J·g^{-1})				
2-chloro pyrimidine	2,4-dichloro pyrimidine	4,6-dichloro pyrimidine	2,4,6-trichloro pyrimidine	2,4,5,6-tetrachloro pyrimidine
18445.6 ± 3.1	13147.2 ± 2.7	13150.0 ± 2.2	9931.6 ± 2.6	7698.2 ± 1.8

TABLE 3: Derived Standard ($p^0 = 0.1$ MPa) Molar Energies of Combustion, $\Delta_c U^0_m$, Standard Molar Enthalpies of Combustion, $\Delta_c H^0_m$, and Standard Molar Enthalpies of Formation, $\Delta_f H^0_m$, for the Compounds at $T = 298.15$ K

	$-\Delta_c U^0_m$(cr,l)/ kJ mol^{-1}	$-\Delta_c H^0_m$(cr,l)/ kJ mol^{-1}	$\Delta_f H^0_m$(cr,l)/ kJ mol^{-1}
2-chloropyrimidine(cr)	2112.6 ± 0.8	2111.4 ± 0.8	85.0 ± 1.0
2,4-dichloropyrimidine(cr)	1958.7 ± 0.9	1956.2 ± 0.9	49.1 ± 1.0
4,6-dichloropyrimidine(cr)	1959.1 ± 0.7	1956.6 ± 0.7	49.5 ± 0.9
2,4,6-trichloropyrimidine(l)	1821.7 ± 1.0	1818.0 ± 1.0	30.2 ± 1.1
2,4,5,6-tetrachloropyrimidine(cr)	1677.2 ± 0.8	1672.2 ± 0.8	3.7 ± 1.0

TABLE 4: Microcalorimetric Standard ($p^0 = 0.1$ MPa) Molar Enthalpies of Sublimation, or Vaporization, at $T = 298.15$ K

	number exp	T/ K	$\Delta^{g,T}_{cr,l,298K}H^o_m$/ kJ mol^{-1}	$\Delta^{T}_{298.15K}H_m$(g)/ kJ mol^{-1}	$\Delta H^{g0}_{cr,lm}$(298.15K)/ kJ mol^{-1}
2-chloro pyrimidine(cr)	6	366	77.2 ± 1.3	7.1	70.1 ± 1.3
2,4-dichloro pyrimidine(cr)	6	365	84.6 ± 2.0	8.1	76.5 ± 2.0
2,4,6-trichloro pyrimidine(l)	5	364	64.7 ± 0.6	9.1	55.6 ± 0.6
2,4,5,6-tetrachloro pyrimidine(cr)	5	366	93.5 ± 1.8	10.5	83.0 ± 1.8

H^0_m, the following standard molar enthalpies of formation, at $T = 298.15$ K, were used: H$_2$O(l), -285.830 ± 0.042 kJ mol^{-1};[44] CO$_2$(g), -393.51 ± 0.13 kJ mol^{-1};[44] and HCl·600H$_2$O(l), -166.540 ± 0.005 kJ mol^{-1}.[20,44] Measurements of the enthalpies of sublimation or vaporization are given in Table 4 with

uncertainties of twice the standard deviation of the mean. For the 4,6-dichloropyrimidine, due to the fact that the sample ran out, only two experiments were performed, which gave the same values as the ones for 2,4-dichloropyrimidine, so this value was taken and considered as an estimate.

TABLE 5. Standard ($p^0 = 0.1$ MPa) Molar Enthalpies of Formation, $\Delta_f H_m^0$, at $T = 298.15$ K Obtained Experimentally and Estimated with the Cox Scheme[a,b]

	$\Delta_f H_m^0(cr,l)/$ kJ mol^{-1}	$\Delta_{cr,l}^g H_m^0/$ kJ mol^{-1}	$\Delta_f H_m^0(g)/$ kJ mol^{-1}		$\Delta^b/$ kJ mol^{-1}
			exptl	Cox	
2-ClPyr(cr)	85.0 ± 1.0	70.1 ± 1.3	155.1 ± 1.6	160.0 ± 2.4	-4.9 ± 2.9
2,4-Cl$_2$Pyr(cr)	49.1 ± 1.0	76.5 ± 2.0	125.6 ± 2.2	124.1 ± 3.0	1.5 ± 3.7
4,6-Cl$_2$Pyr(cr)	49.5 ± 0.9	76.5 ± 2.0^c	126.0 ± 2.2	124.1 ± 3.0	1.9 ± 3.7
2,4,6-Cl$_3$Pyr(l)	30.2 ± 1.1	55.6 ± 0.6	85.8 ± 1.3	88.2 ± 3.6	-2.4 ± 3.8
2,4,5,6-Cl$_4$Pyr (cr)	3.7 ± 1.0	83.0 ± 1.8	86.7 ± 2.1	67.4 ± 4.0	19.3 ± 4.5

[a] The enthalpies of formation in the condensed phase and the enthalpies for phase transition are also given. [b] $\Delta_f H_m^0$ (experimental, g) $- \Delta_f H_m^0$ (Cox scheme, g). [c] Estimated, see text.

The derived standard molar enthalpies of formation in the condensed phase, standard molar enthalpies of sublimation or vaporization, and standard molar enthalpies of formation in the gaseous state are summarized in Table 5.

Cox[8] developed a scheme for the estimation of the enthalpy of formation of gaseous benzene derivatives on the basis of the transferability of group enthalpic contributions. From the literature values for the compounds that are more similar to those studied here, $\Delta_f H_m^0$ (pyridine, g) $= 140.4 \pm 0.7$ kJ mol^{-1};[25] $\Delta_f H_m^0$ (2-chloropyridine, g) $= 104.5 \pm 1.8$ kJ mol^{-1};[45] $\Delta_f H_m^0$ (3-chloropyridine, g) $= 107.6 \pm 1.7$ kJ mol^{-1},[45] the enthalpy increments for the entrance of chlorine in the ortho- and meta-positions of pyridine are -35.9 ± 1.9 and -32.8 ± 1.5 kJ mol^{-1}, respectively. So, following Cox's ideas and using these increments on the parent pyrimidine compound, $\Delta_f H_m^0$ (pyrimidine, g) $= 195.9 \pm 1.4$ kJ mol^{-1},[46] we can estimate $\Delta_f H_m^0$(g) for the different chlorinated pyrimidines. The estimated values obtained with the Cox scheme and the differences, Δ, to the experimental enthalpies of formation are also listed in Table 5. The agreement between experimental and estimated values is rather good for all isomers except for the tetrachlorinated pyrimidine. In this compound, three of the four chlorine atoms are bound to adjacent carbon atoms of the ring, and thus, the larger difference between the experimental $\Delta_f H_m^0$(g) and the value based on the Cox scheme is probably due to the interactions between neighboring chlorine atoms, suggesting that each ortho-pair of chlorine atoms leads to an enthalpy increment term larger than the 4 kJ mol^{-1} recommended by Cox for interactions of ortho-pairs of substituents with another additional correction of $+4$ kJ mol^{-1} for every set of three substituents attached to three consecutive carbon atoms of the aromatic ring. On the other hand, if one looks at the trend of the variation of the enthalpies of formation for pyrimidine and for the different chlorinated pyrimidines, it is clear that the entrance of a chlorine atom in the pyrimidine ring, yielding 2-chloropyrimidine, lowers the enthalpy by $\sim$40 kJ mol^{-1}. When a chlorine atom is introduced in the monochlorinated pyrimidine compound, the enthalpy of formation in the gas phase determined for the dichloropyrimidines is $\sim$30 kJ mol^{-1} less positive. The introduction of a third chlorine atom lowers the enthalpy of formation of the 2,4,6-trichloropyrimidine species by $\sim$40 kJ mol^{-1}. Unpredictably, on going from 2,4,6-tri- to 2,4,5,6-tetrachloropyrimidine, introduction of the fourth chlorine atoms does not change the enthalpy of formation. This fact is not supported by the trends observed and, as already stated, is not predicted by the enthalpic increments based on the Cox scheme. Obviously, one is aware of the simplicity of the Cox scheme, and therefore, a series of calculations with modern computational approaches have been performed in order to extract more information about the enthalpic effects caused by the entrance of chlorine atoms at the different positions in the pyrimidine ring. The calculations have been extended to the chlorinated pyrimidines that were

not studied experimentally due to the unavailability of high purity samples of these compounds.

Initially, the B3LYP method together with two different basis sets has been used to compute the enthalpy of the reactions shown by eqs 2 and 3. Then, using the experimental values available for the molecules included, the enthalpy of formation in the gas phase at $T = 298.15$ K was estimated for the chloropyrimidines compounds. The experimental enthalpies of formation used for the anchor species were as follows: benzene, $\Delta_f H_m^0 = 82.6 \pm 0.7$ kJ mol^{-1};[25] pyridine, $\Delta_f H_m^0 = 140.4 \pm 0.7$ kJ mol^{-1};[25] chlorobenzene, $\Delta_f H_m^0 = 52.0 \pm 1.3$ kJ mol^{-1};[25] pyrimidine, $\Delta_f H_m^0 = 195.9 \pm 1.4$ kJ mol^{-1};[46] 2-chloropyridine, $\Delta_f H_m^0 = 104.5 \pm 1.8$ kJ mol^{-1};[45] 3-chloropyridine, $\Delta_f H_m^0 = 107.6 \pm 1.7$ kJ mol^{-1};[45] 2,3-dichloropyridine, $\Delta_f H_m^0 = 89.5 \pm 3.4$ kJ mol^{-1};[45] 2,5-dichloropyridine, $\Delta_f H_m^0 = 71.5 \pm 2.2$) kJ mol^{-1};[45] and 2,6-dichloropyridine, $\Delta_f H_m^0 = 71.4 \pm 1.9$ kJ mol^{-1}.[45] A similar strategy has been employed in some recent studies involving chlorinated and non-chlorinated compounds with very good results.[47−49]

The enthalpy of formation of pyrimidine has been estimated from the consideration of the following reaction, and the

$$\text{(5)}$$

experimental gas-phase enthalpies of formation of benzene and of pyridine are given above. The enthalpy of formation estimated from the B3LYP calculations is 190.6 kJ mol^{-1} (Table 6), a value that differs by 5.3 kJ mol^{-1} from the experimental result given above.

For the chlorinated pyrimidines, the B3LYP estimated values are compiled in Tables 6 and 7, with the differences to the experimental results compiled in Table 5 given in parenthesis. The results computed with the B3LYP method show that reaction 3, registered in Table 7, yields the best estimates and that is due to the use of chloropyridines and pyridine in reaction 3 instead of the chlorobenzene and pyrimidine compounds as the anchor species in reaction 2. This suggests that the balance of bond type and atomic interactions between reactants and products is much better accounted for in reaction 3 than in reaction 2. The agreement between estimated and experimental results is excellent for the mono- and disubstituted pyrimidines, but large differences are found for 2,4,6-tri- and for 2,4,5,6-tetrachloropyrimidine compounds, the differences between theoretical and experimental results being larger than 10 kJ mol^{-1}. Interestingly, despite the larger differences found for these two compounds, this DFT approach also suggests that the enthalpies of formation for the 2,4,6-tri- and 2,4,5,6-tetrachlo-

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TABLE 6: Enthalpies of Formation for Pyrimidine and for All Chloropyrimidines Estimated with Several Different Computational Methods Considering Reaction 2[a]

compound	B3LYP	G3MP2B3	B98	BP86	HCTH	MP2	MPW1PW91	MPWB95	PBE1PBE	SVWN	VSXC
pyrimidine (Pyr)	190.6	189.5	190.0	191.3	191.2	191.6	189.7	191.8	189.7	191.7	191.1
	(+5.3)	(+6.4)	(+5.9)	(+4.6)	(+4.7)	(+4.3)	(+6.2)	(+4.1)	(+6.2)	(+4.2)	(+4.8)
2-ClPyr	163.3	165.9	163.4	161.7	160.4	166.8	162.5	161.4	162.4	159.8	162.6
	(−8.2)	(−10.8)	(−8.3)	(−6.6)	(−5.3)	(−11.7)	(−7.4)	(−6.3)	(−7.3)	(−4.7)	(−7.5)
4-ClPyr	159.5	161.7	159.6	157.8	156.7	162.0	159.1	157.6	159.0	156.6	159.0
5-ClPyr	173.2	173.2	173.4	171.5	170.9	175.3	173.4	171.3	173.4	172.0	173.5
2,4-Cl$_2$Pyr	130.3	134.2	130.8	126.9	124.6	135.5	129.0	126.3	128.8	123.5	129.8
	(−4.7)	(−8.6)	(−5.2)	(−1.3)	(+1.0)	(−9.9)	(−3.4)	(−0.7)	(−3.2)	(+2.1)	(−4.2)
2,5-Cl$_2$Pyr	144.7	146.5	145.2	141.7	139.8	149.7	144.0	141.3	143.8	140.3	145.5
4,5-Cl$_2$Pyr	147.5	145.1	147.5	142.8	143.0	149.0	146.3	141.5	145.9	138.3	139.2
4,6-Cl$_2$Pyr	127.0	130.2	127.2	123.7	121.6	131.0	126.0	123.3	125.7	121.1	126.5
	(−1.0)	(−4.2)	(−1.2)	(+2.3)	(+4.4)	(−5.0)	(0.0)	(+2.7)	(+0.3)	(+4.9)	(−0.5)
2,4,5-Cl$_3$Pyr	121.3	120.0	121.7	115.2	114.1	125.0	119.1	113.6	118.6	108.7	113.7
2,4,6-Cl$_3$Pyr	100.7	104.7	101.4	95.6	92.2	106.7	98.7	94.8	98.4	90.5	100.5
	(−14.9)	(−18.9)	(−15.6)	(−9.8)	(−6.4)	(−20.9)	(−12.9)	(−9.0)	(−12.6)	(−4.7)	(−14.7)
2,4,5,6-Cl$_4$Pyr	101.7	95.6	101.9	92.4	92.9	102.8	97.8	89.6	96.9	80.4	84.9
	(−15.0)	(−8.9)	(−15.2)	(−5.7)	(−6.2)	(−16.1)	(−11.1)	(−2.9)	(−10.2)	(+6.3)	(+1.8)
mean deviation (Δ)	8.2	9.6	8.6	5.1	4.7	11.3	6.8	4.3	6.6	4.5	5.6

a All values in kJ mol^{-1}. Values in parenthesis refer to the enthalpic differences with respect to the experimental results.

TABLE 7: Enthalpies of Formation for All Chloropyrimidines Estimated with Several Different Computational Methods Considering Reaction 3

compound	B3LYP	G3MP2B3	B98	BP86	HCTH	MP2	MPW1PW91	MPWB95	PBE1PBE	SVWN	VSXC
2-ClPyr	158.7	158.4	158.4	159.1	158.4	161.3	157.5	159.4	157.3	158.8	159.2
	(−3.6)	(−3.3)	(−3.3)	(−4.0)	(−3.3)	(−6.2)	(−2.4)	(−4.3)	(−2.2)	(−3.7)	(−4.1)
4-ClPyr	154.9	154.2	154.6	155.2	154.7	156.5	154.1	155.7	154.0	155.6	155.6
5-ClPyr	161.5	160.6	161.2	161.6	161.1	163.6	160.9	162.0	160.8	162.2	162.3
2,4-Cl$_2$Pyr	125.1	125.0	124.8	124.9	124.0	128.1	123.8	125.2	123.6	124.5	125.5
	(+0.5)	(+0.6)	(+0.8)	(+0.7)	(+1.6)	(−2.5)	(+1.8)	(+0.4)	(+2.0)	(+1.1)	(+0.1)
2,5-Cl$_2$Pyr	129.9	129.2	129.6	129.5	128.5	133.2	128.6	129.7	128.5	129.4	130.7
4,5-Cl$_2$Pyr	142.1	141.5	141.8	141.9	141.0	144.7	141.4	142.4	141.3	142.6	142.9
4,6-Cl$_2$Pyr	123.5	121.5	123.1	123.1	122.3	124.3	122.1	123.5	122.0	123.2	124.6
	(+2.5)	(+4.5)	(+2.9)	(+2.9)	(+3.7)	(+1.7)	(+3.9)	(+2.5)	(+4.0)	(+2.8)	(+1.4)
2,4,5-Cl$_3$Pyr	117.0	115.3	116.9	116.3	114.7	119.4	115.4	116.7	115.3	116.1	118.8
2,4,6-Cl$_3$Pyr	96.6	94.4	96.3	95.6	94.3	98.1	94.6	95.8	94.4	94.7	97.6
	(−10.8)	(−8.6)	(−10.5)	(−9.8)	(−8.5)	(−12.3)	(−8.8)	(−10.0)	(−8.6)	(−8.9)	(−11.8)
2,4,5,6-Cl$_4$Pyr	96.7	89.3	96.2	94.1	95.1	95.4	93.9	93.4	92.4	89.9	89.1
	(−10.0)	(−2.6)	(−9.5)	(−7.4)	(−8.4)	(−8.7)	(−7.2)	(−6.7)	(−6.7)	(−3.2)	(−2.4)
mean deviation (Δ)	5.5	3.9	5.4	5.0	5.1	6.3	4.8	4.8	4.7	3.9	4.0

a All values in kJ mol^{-1}. Values in parenthesis refer to the enthalpic differences with respect to the experimental results.

ropyrimidines are identical, which is in agreement with the present experimental results and contradicts the suggestions coming from application of the Cox scheme to this class of compounds.

Because the B3LYP estimates are consistently more positive than the experimental results for the strongly chlorine-substituted pyrimidines, G3MP2B3 calculations have also been carried out. In this situation, besides consideration of reactions 2 and 3 with results reported in Tables 6 and 7, respectively, the reaction of atomization 4 has also been used together with the experimental enthalpies of formation of the constituting atoms, $\Delta_f H_m^o$(H, g) = 218.00 kJ mol^{-1}, $\Delta_f H_m^o$(C, g) = 716.67 kJ mol^{-1}, $\Delta_f H_m^o$ (N, g) = 472.68 kJ mol^{-1}, and $\Delta_f H_m^o$ (Cl, g) = 121.30 kJ mol^{-1}.[50] The use of the atomization reaction combined with a composite method is known to yield rather good estimates of gas-phase enthalpies of formation for molecular sizes equivalent to those studied here and has been used for comparison purposes. The results computed with the atomization reaction together with the G3MP2B3 composite method are compiled in Table 8. The most important conclusion retrieved now is that the estimated values for the 2,4,6-tri- and 2,4,5,6-tetrachloropyrimidines are not identical. If reactions 2 and 4 are considered, the difference between the enthalpies for these compounds is larger than 9 kJ

TABLE 8: Enthalpies of Formation for Pyrimidine and All Chloropyrimidines Estimated with the G3MP2B3 Considering the Reaction of Atomization 4[a]

compound	$\Delta_f H_m^0$(g)	compound	$\Delta_f H_m^0$(g)
pyrimidine	186.5	4,5-Cl$_2$Pyr	128.7
	(+9.4)		
2-ClPyr	153.5	4,6-Cl$_2$Pyr	113.9
	(+2.0)		(+12.1)
4-ClPyr	148.9	2,4,5-Cl$_3$Pyr	100.2
5-ClPyr	160.3	2,4,6-Cl$_3$Pyr	84.9
			(+0.9)
2,4-Cl$_2$Pyr	117.9	2,4,5,6-Cl$_4$Pyr	72.3
	(+7.7)		(+14.4)
2,5-Cl$_2$Pyr	130.1	mean deviation (Δ)	7.8

a All values in kJ mol^{-1}. Values in parenthesis refer to the enthalpic differences with respect to the experimental results.

mol^{-1}. Furthermore, the use of reaction 2 together with the G3MP2B3 composite approach gives an estimate for the 2,4,6-trichloropyrimidine molecule, which is 18.9 kJ mol^{-1} more positive than the experimental value, cf. Table 6. On the other hand, the estimate for this same compound resulting from the use of the atomization reaction almost matches the experimental result, cf. Table 8. However, the enthalpy of formation estimated

for the tetrachlorinated compound is now 14.4 kJ mol^{-1} less positive than the experimental result. Again, the consideration of reaction 3 gives the best estimates with a mean deviation between computed and available experimental results of only 3.9 kJ mol^{-1}. In all cases, the estimated values for 2,4,5,6-tetrachloropyrimidine are always less positive than the results obtained for 2,4,6-trichloropyrimidine in accordance with the Cox scheme's values; however, in the case of reactions 2 and 3, the enthalpies of formation estimated for 2,4,5,6-tetrachloropyrimidine, when the composite method is used, differ from the result estimated with the Cox scheme. On the other hand and when compared with the experimental results, the B3LYP method was found to give the correct tendency for these compounds; i.e., the enthalpy of formation for the tetrachlorinated molecule is negligibly more positive than that for 2,4,6-trichloropyrimidine. The two latter sentences still do not resolve the problem and therefore the following question: are the enthalpies of formation for 2,4,6-tri- and 2,4,5,6-tetrachloropyrimidines identical or not? This question is still unanswered.

Several different exchange-correlation functionals, some older and some newer than the B3LYP method, were used together with reactions 2 and 3 in the estimation of the gas-phase enthalpies of formation of the different chlorinated pyrimidines. Furthermore, MP2 calculations have been also carried out for comparison purposes. The results estimated with a series of DFT methods and with the MP2 approach are also listed in Tables 6 or 7. A rapid analysis of all results reported in these tables shows that the majority of the methods go in the same direction; even the absolute values are not the same as those estimated with the B3LYP method; i.e., we get identical results for 2,4,6-tri- and for 2,4,5,6-tetrachloropyrimidine compounds, and some other approaches predict the tetrachlorinated compound as having a less positive enthalpy of formation. In addition, the mean deviations between the computational results and the available experimental data show that, among the approaches considered here, the SVWN and the MPWB95 functionals give the smaller errors for this class of compounds. The larger mean deviations are found for the B98 functional and for the MP2 method. The good behavior found with the SVWN functional seems to suggest that this functional is an important choice when dealing with heterocycles containing nitrogen atoms, because very recently we have found among a series of exchange-correlation functionals that the SVWN method was the best DFT approach for the estimation of the gas-phase enthalpies of formation of piperidine and methylpiperidines.[51] However, in that work, the MP2 method was also found to yield accurate estimates for piperidine and methylated piperidine. However, this method requires more computational resources than the DFT approaches. In the present study, the differences between the estimates obtained with the MP2 method and experimental results are somewhat larger than those found for the piperidines.[51]

The analysis of the enthalpies estimated for the monochloropyrimidines shows that the insertion of a chlorine atom at position 5 is the least stable; a small enthalpic difference is found for insertion at positions 2 or 4, but the latter is more stable by 3−4 kJ mol^{-1}. These findings are in agreement with that observed for the dichloropyrimidines where the 4,6-dichloropyrimidine isomer is the most stable, reflecting a double insertion at position 4 in the nonsubstituted pyrimidine. Therefore, the two dichloro isomers with a chlorine atom at position 5 are the less stable ones. The mean enthalpic difference between the dichloropyrimidines without chlorine atoms and those with chlorine atoms at position 5 is 17−18 kJ mol^{-1}. A similar but larger enthalpic variation is computed for the isomerization of 2,4,6- to 2,4,5-trichloropyrimidine. Importantly, if one looks at the chloropyrimidines with a chlorine atom at the least stable position (i.e., position 5, namely, 5-chloropyrimidine, 2,5-tri- or 4,5-dichloropyrimidines, 2,4,5-trichloropyrimidine, and 2,4,5,6-tetrachloropyrimidine), an almost constant diminishing of the gas-phase enthalpy of formation is found on going from 5-chloro- to 2,4,5,6-tetrachloropyrimidine. For example, in the case of the G3MP2B3 composite method combined with reaction 2, Table 6, the variation is of about −25 kJ mol^{-1} per chlorine atom inserted. A slightly larger variation of ∼ −30 kJ mol^{-1} is calculated for the VSXC functional; for the other functionals, variations between 20 and 30 kJ mol^{-1} are calculated.

Conclusions

A joint experimental and computational study has been carried out to investigate the gas-phase thermochemistry of all chloropyrimidines in terms of their standard molar gas-phase enthalpies of formation at $T = 298.15$ K. The experimental work involved the determination of the enthalpies of combustion of the chloropyrimidines available in a high-purity state, i.e., 2-chloropyrimidine, 2,4- and 4,6-dichloropyrimidine, 2,4,6-trichloropyrimidine, and 2,4,5,6-tetrachloropyrimidine compounds, by rotating-bomb combustion calorimetry. The standard molar enthalpies for phase transition—all compounds are solids except the trichlorinated derivative—have been determined by Calvet microcalorimetry. From these experiments, the standard molar enthalpies of formation in the gas phase at $T = 298.15$ K have been obtained. The experimental results for these five compounds show that the enthalpy of formation diminishes by insertion of chlorine atoms by 30−40 kJ mol^{-1} except for the tetrachloropyrimidine compound. The experimental result obtained for the latter is identical to that obtained for 2,4,6-trichloropyrimidine, contradicting the decrease found on going from pyrimidine to the trichlorinated derivative and also the estimations based on the Cox scheme.

Several different computational approaches were combined with four selected reactions for the estimation of the enthalpies of formation of pyrimidine and of all the ten possible chloropyrimidines. In the case of the chloropyrimidines, all computational approaches were used together with a working reaction, where the chloropyrimidine is combined with benzene yielding pyridine and chloropyridine, resulting in excellent estimates for the less substituted pyrimidines. For the tri- and tetrachloropyrimidines, the majority of the computational approaches used yield too positive enthalpies of formation. The approaches considered best for the class of compounds studied in the present work are the G3MP2B3 composite method and the SVWN-LSDA functional. As found previously, the later exchange-correlation functional yields very good estimates of enthalpies of formation for piperidine and methylpiperidines, which are also heterocycles containing a nitrogen atom in the ring. However, the MP2 method was found to yield very good estimates of enthalpies of formation of piperidine and methylated derivatives, and that behavior was not found in the case of the chlorinated pyrimidines. Using the working reaction described above, we find that all methods seem to predict similar enthalpies of formation for 2,4,6-tri- and 2,4,5,6-tetrachloropyrimidine, in agreement with the experimental findings. Finally, a global analysis including all possible chlorinated pyrimidines shows that there is in fact a decrease of the enthalpy of formation with the introduction of a chlorine atom into the ring if we consider the less stable 5-chlorinated isomer as reference. On

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going from 5-pyrimidine to 2,4,5,6-tetrachloropyrimidine, the enthalpy of formation is less positive by $20-30$ kJ mol^{-1} per chlorine atom inserted, depending on the computational approach.

Supporting Information Available: Tables S1−S5 contain the details of the combustion experiments of each of the five chloropyrimidines studied. This material is available free of charge via the Internet from http://pubs.acs.org.

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