Thermochemistry of paracetamol

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Abstract Combustion calorimetry, Calvet-drop sublimation calorimetry, and the Knudsen effusion method were used to determine the standard ($p^o = 0.1$ MPa) molar enthalpies of formation of monoclinic (form I) and gaseous paracetamol, at $T = 298.15$ K: $\Delta_f H_m^o(C_8H_9O_2N,$ cr I$) = -(410.4 \pm 1.3)$ kJ mol^{-1} and $\Delta_f H_m^o(C_8H_9O_2N,$ g$) = -(280.5 \pm 1.9)$ kJ mol^{-1}. From the obtained $\Delta_f H_m^o$ $(C_8H_9O_2N,$ cr I$)$ value and published data, it was also possible to derive the standard molar enthalpies of formation of the two other known polymorphs of paracetamol (forms II and III), at 298.15 K: $\Delta_f H_m^o(C_8H_9O_2N,$ crII$) = -(408.4 \pm 1.3)$ kJ mol^{-1} and $\Delta_f H_m^o(C_8H_9O_2N,$ crIII$) = -(407.4 \pm 1.3)$ kJ mol^{-1}. The proposed $\Delta_f H_m^o(C_8H_9O_2N,$ g$)$ value, together with the experimental enthalpies of formation of acetophenone and 4′-hydroxyacetophenone, taken from the literature, and a re-evaluated enthalpy of formation of acetanilide, $\Delta_f H_m^o(C_8H_9ON,$ g$) = -(109.2 \pm 2.2)$ kJmol^{-1}, were used to assess the predictions of the B3LYP/cc-pVTZ and CBS-QB3 methods for the enthalpy of a isodesmic and isogyric reaction involving those species. This test supported the reliability of the theoretical methods, and indicated a good thermodynamic consistency between the $\Delta_f H_m^o(C_8H_9O_2N,$ g$)$ value obtained in this study and the remaining experimental data used in the $\Delta_r H_m^o$ calculation. It also led to the conclusion that the presently recommended enthalpy of formation of gaseous

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acetanilide in Cox and Pilcher and Pedley's compilations should be corrected by ~ 20 kJ mol^{-1}.

Introduction

Paracetamol (acetaminophen, $C_8H_9O_2N$, Fig. 1) is one of the most frequently prescribed anti-inflamatory, antipyretic, and analgesic drugs, and accounts for a substantial market share among all pharmaceutical materials in the world. Since, it is predominantly commercialized as solid dosage forms, considerable attention has been given to its solid state characterization, with particular emphasis on the study of polymorphism. Three polymorphic modifications have been reported up to now: form I (monoclinic) [1–9]; form II (orthorhombic) [6, 10, 11]; and form III, an unstable phase, which has been assigned as monoclinic [12] but whose crystal structure is still not accurately known [13]. For a long time, this phase, first mentioned in 1982 [14], could only be stabilized under special conditions (e.g., underneath a microscopy slide) [14, 15] and produced in milligram quantities [12, 14, 15]. Recently, a method for its reproducible preparation on a larger scale has been proposed [13], which opens new possibilities in terms of obtaining crystals suitable for a complete structure determination.

Considerable efforts have also been made to characterize the stability domains of the three known polymorphs of paracetamol from a thermodynamic point of view, predominantly those of forms I and II. These studies have been
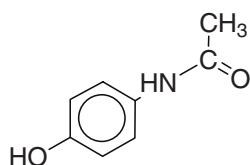
recently reviewed [16–18]. Due to inconsistencies in the reported data, the relative stability behavior of the monoclinic and orthorhombic polymorphs is still not settled, with some authors favoring an enantiotropic [14, 19–21] and others a monotropic relationship [16–18]. Nevertheless, the emerging picture seems to be that of a monotropic system, with form I being more stable than form II up to the fusion temperature [16–18]. Form III has been observed on cooling the liquid to $\sim$327 K [12, 14, 15] or on heating glassy paracetamol to the same temperature [14]. It transforms into form II at $\sim$393 K, which subsequently melts at 432 K [13, 15].

Here, we describe the determination of the enthalpy of formation of monoclinic (form I) and gaseous paracetamol, using combustion calorimetry, Calvet-drop sublimation calorimetry, and the Knudsen effusion method. From the obtained $\Delta_f H_m^o(C_8H_9O_2N, \text{cr I})$ and literature data it was also possible to derive the enthalpies of formation of polymorphs II and III of paracetamol. Finally, the recommended $\Delta_f H_m^o(C_8H_9O_2N, \text{g})$ value, in conjunction with the experimental enthalpies of formation of gaseous acetanilide, acetophenone, and 4′-hydroxyacetophenone were used to assess the predictions of the B3LYP/cc-pVTZ and CBS-QB3 methods for the enthalpy of an isodesmic reaction involving those species. This test led to the conclusion that a previously recommended enthalpy of formation of gaseous acetanilide [22, 23] should be corrected by $\sim$20 kJ mol^{-1}.

Materials and methods

General

Elemental analysis (C, H, N) were made on a Fisons Instruments EA1108 apparatus. Fourier-transform infrared spectra (FT-IR) were recorded in a Jasco FT/IR 4100 spectrophotometer calibrated with polystyrene film. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained at ambient temperature, on a Bruker Ultrashield 400 MHz spectrometer. Deuterated dimethyl sulfoxide (DMSO-d$_6$) was used as solvent. The X-ray powder diffraction analysis was performed on a Bruker AXS D8 Advanced diffractometer. A Cu K$_\alpha$ radiation source ($\lambda = 1.5418$ Å) was used. The tube amperage was 30 mA and the tube voltage 40 kV. The diffractograms were recorded in the range $10° \leq 2\theta \leq 50°$, in the continuous mode, with a step size of $0.02°(2\theta)$, and

an acquisition time of 2.0 s/step. The sample was mounted on an aluminum sample holder. The indexation of the powder pattern was performed using the program Checkcell [24]. Differential scanning calorimetry (DSC) experiments were made with a temperature-modulated TA Instruments 2920 MTDSC apparatus, operated as a conventional DSC. The heating rate was $\beta = 10$ K min^{-1}. The samples with masses in the range 3.5–5.4 mg, were sealed under air in aluminum pans, and weighed to $\pm 10^{-7}$ g on a Mettler UMT2 ultra-micro balance. Helium (Air Liquide N55) at a flow rate of 0.5 cm^3 s^{-1} was used as the purging gas. The temperature and heat flow scales of the instrument were calibrated as previously described [25].

Sample preparation and characterization

All thermochemical experiments were carried out with a monoclinic paracetamol (form I) sample. It was obtained by sublimation of a commercial material (Sigma, USP grade; CAS no [103-90-2]) at 403 K and 5 Pa. Elemental analysis for C$_8$H$_9$O$_2$N (mass fraction): expected C 0.6356, H 0.0600, N 0.0927; found C 0.6349, H, 0.0628, N 0.0916. ^{1}H NMR (400 MHz, DMSO-d$_6$/TMS): δ/ppm = 1.97 (s, CH_3, 3H), 6.65–6.67 (s, CH, 2H), 7.32–7.34 (d, CH, 2H), 9.13 (s, OH, 1H), 9.64 (s, NH, 1H). ^{13}C NMR (400 MHz, DMSO-d$_6$/TMS): δ/ppm = 23.9 (CH$_3$, 1C), 115.2 (C$_b$H, 2C), 121.0 (C$_b$H, 2C), 131.2 (C$_b$–OH, 1C), 153.3 (C$_b$–NH, 1C), 167.7 (C=O, 1C). The ^{1}H and ^{13}C NMR spectra are in good agreement with those given in a reference database [26]. The ^{13}C NMR peak assignments are also in agreement with those reported by Jagannathan [27]. FT-IR (KBr, main peaks): $\tilde{v}$/cm^{-1} = 3,325(v_{N-H} stretch); 3,257–3,110 (v_{O-H} stretch); 1,655 ($v_{C=O}$ stretch); 1,612 (v_{C-C} bond stretch aromatic); 1,565 (v_{N-H} bending in plane); 1,508 (v_{C-H} bond stretch aromatic); 1,440 (v_{C-C} bond stretch aromatic); 1,369 (CH$_3$ symmetric bending); 1,327 (v_{C-N} stretch); 1,260–1,225 (v_{C-N}/v_{N-H} stretch); 1,172 (v_{C-O} stretch); 838 (v_{C-H} bend, out-of-plane). These results are in agreement with those found in the literature for form I of paracetamol [28, 29] and showed no indication of presence of water in the sample. The powder pattern was indexed as monoclinic, space group $P2_1/n$, with $a = 711.44$ pm, $b = 924.54$ pm, $c = 1180.04$ pm, $\beta = 97.58°$. These values are in good agreement with those previously reported for form I of paracetamol (monoclinic) based on single crystal X-ray diffraction experiments carried out at 295 K [5, 7]: $P2_1/n$, $a = 709.39$ pm, $b = 926.25$ pm, $c = 1165.7$ pm and $\beta = 97.67°$. No phase transitions other than fusion were observed by DSC in the range 283–450 K. The onset and the maximum temperatures of the fusion peaks were $T_{on} = (442.1 \pm 0.4)$ K and $T_{max} = (443.8 \pm 0.4)$ K, and the corresponding enthalpy of fusion was $\Delta_{fus} H_m^o = (27.2 \pm 0.5)$ kJ mol^{-1}. The uncertainties

quoted for T_{on}, T_{max}, and $\Delta_{fus}H_m^o$ correspond to twice the standard deviation of the mean of five independent determinations. These values are within the ranges of the T_{fus} and $\Delta_{fus}H_m^o$ values reported in the literature for form I of paracetamol (441–445 K and 26.3–34.1 kJ mol^{-1}, respectively) [17].

Combustion calorimetry

The standard massic energy of combustion of paracetamol (form I) was measured using an isoperibol stirred liquid combustion macrocalorimeter previously described [30]. In brief, a pellet of the compound with a mass of 0.6–0.8 g was weighed to ±0.01 mg with a Mettler AT201 balance inside a platinum crucible, which was then adjusted to the sample holder in the bomb head. The platinum ignition wire (Johnson Matthey; mass fraction: 0.9995; diameter 0.05 mm), was connected between the two discharge electrodes. A cotton thread fuse of empirical formula $CH_{1.887}O_{0.902}$ and standard massic energy of combustion $\Delta_c u^o = -(16565.9 \pm 8.6)$ J g^{-1} [30] was weighed to ±0.1 μg in a Mettler Toledo UMT2 balance. One end of the fuse was tied to the ignition wire and the other was brought into contact with the pellet. A volume of 1.0 cm^3 of distilled and deionized water from a Millipore system (conductivity, <0.1 μS cm^{-1}) was added to the bomb body by means of a volumetric pipette. The stainless-steel bomb (Parr 1108) of 340 cm^3 internal volume was assembled, and purged twice, by successively charging it with oxygen at a pressure of 1.01 MPa and venting the overpressure. After purging, the bomb was charged with oxygen at a pressure of 3.04 MPa and a few minutes were allowed for equilibration before closing the inlet valve. The bomb was placed in the calorimeter proper, inside the thermostatic bath. The combustion of the sample was initiated by discharge of a 2,990 μF capacitor, from a potential of 40 V, through the platinum wire. The discharge current heated the wire and when the temperature was increased sufficiently the thread fuse ignited, and the combustion propagated to the sample material. The nitric acid formed from combustion of the sample and traces of atmospheric N_2 remaining inside the bomb after purging, was determined by titration with aqueous sodium hydroxide (Merck titrisol, 0.01 mol dm^{-3}), using methyl red as indicator. The energy equivalent of the calorimeter, $\varepsilon^o = 18544.76 \pm 1.05$ J K^{-1}, was obtained from the combustion of a benzoic acid sample (BA; NIST SRM 39j), whose massic energy of combustion under the certificate conditions was $\Delta_c u(BA,cert) = -26,434 \pm 3$ J g^{-1}. The ε^o value refers to 3751.64 g of distilled water inside the calorimeter proper. A small residue of carbon was found in the crucible at the end of some of the experiments. The mass of this residue was gravimetrically determined as follows. The

crucible containing the residue was dried for ca. 120 min in an oven at 383 K, cooled to room temperature inside a desiccator, and weighed. It was then heated in a burner flame to eliminate the residue, transferred again to the desiccator for cooling, and weighed a second time. The mass of residue formed in the experiment was taken as the mass difference between the first and second weightings.

Enthalpy of sublimation measurements

The enthalpy of sublimation of paracetamol was determined by Knudsen effusion [31–33] and Calvet-drop microcalorimetry [34, 35].

In the Knudsen effusion experiments, two cells initially charged with ~1.4 g of compound, were simultaneously used. The effusion holes were drilled in a 2.090 × 10^{-5} m thick copper foil (Cu 99%, Goodfellow Metals) soldered to the cell lids, and had areas of 2.105 × 10^{-7} m^2 (hole 1) and 2.577 × 10^{-7} m^2 (hole 2), respectively. The cells were inserted in a brass block at the bottom of the vacuum chamber. The brass block was surrounded by a tubular furnace whose temperature was controlled to better than ±0.1 K by a Eurotherm 902P thermostatic unit and a K type thermocouple. The equilibrium temperature inside each cell was assumed to be identical to the temperature of the brass block. This temperature was measured with a precision of ±0.1 K by a Tecnisis 100 Ω platinum resistance thermometer embedded in the block and connected in a four wire configuration to a Keithley 2000 multimeter. The mass loss in each run was determined to ±0.01 mg with a Mettler AT201 balance.

In the Calvet microcalorimetry experiments, a sample with a mass in the range 1.9–6.5 mg was placed into a small glass capillary and weighed with a precision of 1 μg in a Mettler M5 balance. The capillary was equilibrated for ca. 15 min at 298 K, inside a furnace placed above the entrance of the calorimetric cell, and subsequently dropped into the cell under N_2 atmosphere. The temperature of the calorimetric cell was set to 398.9 K. After dropping, an endothermic peak due to the heating of the sample from 298 K to the temperature of the calorimeter was first observed. When the signal returned to the baseline, the sample and reference cells were simultaneously evacuated to 0.13 Pa and the measuring curve associated with the sublimation of the compound was acquired. The corresponding enthalpy of sublimation was subsequently derived from the area of that curve, A, the area of the pumping background contribution, A_b, and the energy equivalent of the apparatus, ε. The value of A_b was determined in a series of independent experiments where gaseous nitrogen was pumped out of the cells and ε was obtained by electrical calibration [34]. No decomposition or unsublimed residues were found inside the calorimeter at the end of the experiments.

Density functional theory calculations

Density functional theory (DFT) [36] and complete basis set extrapolation (CBS-QB3) [37, 38] procedures were applied to predict thermochemical properties of the systems under examination. In the case of the DFT methods, full geometry optimizations and frequency calculations were carried out with the B3LYP exchange correlation functional [39, 40] and the cc-pVTZ basis set [41–43]. The total energies (E) were obtained from [36]:

$$E = V_{NN} + H^{CORE} + V_{ee} + E_X[\rho] + E_C[\rho] \tag{1}$$

where V_{NN} is the nuclear–nuclear interaction, H^{CORE} is a mono-electronic contribution to the total energy, including electron kinetic and electron–nuclear interaction energies, and V_{ee} is the coulombic interaction between the electrons. The terms $E_X[\rho]$ and $E_C[\rho]$ represent the exchange and correlation contributions, which are functionals of the electron density ρ. The corresponding molecular energies were converted to standard enthalpies at 298.15 K by using zero point energy (ZPE) and thermal energy corrections calculated at the same level of theory. The obtained vibration frequencies and ZPEs were not scaled, unless otherwise stated. The DFT and CBS-QB3 calculations were performed with the Gaussian-03 package [44].

Results and discussion

The standard atomic masses recommended by the IUPAC Commission in 2005 were used in the calculation of all molar quantities [45].

The results of the combustion experiments on paracetamol (form I) are shown in Table 1, where $m(C_8H_9O_2N)$, $m(fuse)$, and $m(C)$, are the mass of the compound, the mass of cotton, and the mass of soot found at the end of the combustion process, respectively; $m(n\text{-}C_{16}H_{34})$ and $m(BA)$ represent the masses of n-hexadecane or benzoic acid used as combustion aids, $n(HNO_3)$ is the amount of substance of HNO_3 formed in the bomb process and from traces of atmospheric N_2 remaining inside the bomb after purging with O_2; $\Delta m(H_2O)$ represents the difference between the mass of water inside the calorimeter proper in each experiment and the average mass of water used in the calibration experiments; ε^i and ε^f are the energy equivalents of the bomb contents in the initial and final states of the bomb process, respectively; T_i, and T_f represent the initial and final temperatures of the experiment, respectively; ΔT_c is the contribution to the observed temperature rise of the calorimeter proper, due to the heat exchanged with the surroundings, the heat of stirring, and the heat dissipated by the temperature sensor; $\Delta_{ign}U$ is the electrical energy

supplied for ignition of the sample; $\Delta_{IBP}U$ is the internal energy change associated with the bomb process under isothermal conditions, at 298.15 K; $\Delta U(HNO_3)$ is the energy change associated with the formation of nitric acid; $\Delta U(fuse)$ is the contribution of the cotton thread fuse; $\Delta U(n\text{-}C_{16}H_{34})$, $\Delta U(BA)$, and $\Delta U(C)$ are the contributions of n-hexadecane, benzoic acid, and soot; $\Delta_\Sigma U$ represents the sum of all corrections necessary to reduce $\Delta_{IBP}U$ to the standard state (Washburn corrections); $\Delta U(C_8H_9O_2N)$ is the contribution of paracetamol to the energy of the isothermal bomb process; finally, $\Delta_c u^o(C_8H_9O_2N)$ is the standard specific energy of combustion of paracetamol (phase I).

The values of T_i, T_f, and ΔT_c were calculated by using a computer program based on the Regnault–Pfaundler method [46] and $\Delta_{IBP}U$ was derived from [46, 47]:

$$\begin{aligned}\Delta_{IBP}U = &\left[\varepsilon^o + \Delta m(H_2O)c_p^o(H_2O, l)\right](T_i - T_f + \Delta T_c) \\ &+ \varepsilon_i(T_i - 298.15) + \varepsilon_f(298.15 - T_f + \Delta T_c) \\ &+ \Delta_{ign}U.\end{aligned} \tag{2}$$

The energy change associated with the ignition, $\Delta_{ign}U$, was calculated from:

$$\Delta_{ign}U = \frac{(V_i^2 - V_f^2)C}{2} \tag{3}$$

where V_i and V_f stand for the potential of the condenser of capacitance $C = 2{,}990$ μF before and after its discharge through the platinum ignition wire, respectively.

The standard state corrections, $\Delta_S U$, were derived as recommended in the literature for organic compounds containing C, H, O, and N [47], by using the following auxiliary data: $c_p^o = 1.255$ J K^{-1} g^{-1} [16], $\rho = 1.305$ g cm^{-3}, and $-(\partial u/\partial p)_T = 0.024$ J MPa^{-1} g^{-1}. The density, ρ, was calculated from the unit cell dimensions obtained in the powder pattern indexation carried out in this study. The value of $(\partial u/\partial p)_T$ was calculated as $(\partial u/\partial p)_T = -T(\partial V/\partial T)_p - p(\partial V/\partial p)_T$. The term $(\partial V/\partial T)_p = 1.236 \times 10^{-8}$ m^3 K^{-1} was obtained by combining the value of the density of paracetamol indicated above, with those derived from reported single crystal X-ray diffraction experiments at 123 K [6] and 150 K [5]. The contribution $(\partial V/\partial p)_T = -4.960 \times 10^{-15}$ m^3 Pa^{-1} was calculated from the pressure dependence of the volume of monoclinic paracetamol (form I) studied by single crystal X-ray diffraction [7, 8]. The correction $\Delta U(HNO_3)$, was based on -59.7 kJ mol^{-1} for the molar internal energy of formation of $HNO_3(aq)$ of concentration 0.1 mol dm^{-3} from $5/4O_2(g)$, $1/2N_2(g)$, and $1/2H_2O$ (l) [48]. The value of $\Delta U(C)$ was calculated from $\Delta_c u^o(C) = -33{,}000$ J g^{-1} [49], and the terms $\Delta U(fuse)$, $\Delta U(n\text{-}C_{16}H_{34})$, and $\Delta U(BA)$ were derived from the corresponding massic energies of combustion given above (see the "Materials and methods" section devoted to combustion calorimetry).

Table 1 Results of combustion experiments on paracetamol (form I) at $T = 298.15$ K

$m(C_8H_9O_2N)/g$	0.80714	0.89538	0.63913	0.66331	0.91009	0.84242	0.70075	0.68970	0.68514
$m(\text{fuse})/\text{mg}$	2.5471	2.7564	2.3646	2.2753	2.4102	2.6396	2.3752	2.23235	2.0946
$m(C_{16}H_{34})/g$	0	0	0	0.05607	0	0	0	0	0
$m(\text{BA})/g$	0	0	0	0	0	0	0.12793	0.12559	0.13477
$m(\text{C})/\text{mg}$	0	0	0	0.5402	0.1902	0.0177	0.0371	0.6783	0
$n(\text{HNO}_3) \times 10^4/\text{mol}$	4.50	6.90	2.20	5.55	6.90	6.90	6.30	6.30	6.25
$\Delta m(\text{H}_2\text{O})/g$	−1.83	+2.80	+3.75	+5.25	+0.83	+1.06	+0.62	+0.62	+0.47
$\varepsilon^i/\text{J K}^{-1}$	15.48	15.59	15.28	15.43	15.61	15.53	15.51	15.49	15.49
$\varepsilon^f/\text{J K}^{-1}$	16.37	16.47	16.06	16.23	16.51	16.33	16.27	16.24	16.25
T_i/K	297.6983	298.1492	298.2100	298.1106	298.1044	298.1540	298.1630	298.1302	299.1596
T_f/K	299.3123	299.4949	299.2203	299.2816	299.4759	299.4333	299.3265	299.3553	299.3489
$\Delta T_c \times 10^2/\text{K}$	4.65	5.76	9.09	7.52	6.22	6.66	6.59	5.54	8.31
$\Delta_{\text{ign}}U/\text{J}$	0.67	0.62	0.64	0.60	0.61	0.66	0.66	0.67	0.56
$-\Delta_{\text{IBP}}U/\text{J}$	21561.78	23923.27	17076.92	20361.14	24304.61	22510.89	22117.31	21736.92	21880.19
$\Delta U(\text{HNO}_3)/\text{J}$	26.87	41.19	13.13	33.13	41.19	41.19	37.61	37.61	37.31
$\Delta U(\text{fuse})/\text{J}$	41.36	44.76	38.40	36.95	39.10	42.87	38.57	37.73	34.02
$\Delta U(C_{16}H_{34})/\text{J}$	0	0	0	2648.95	0	0	0	0	0
$\Delta U(\text{BA})/\text{J}$	0	0	0	0	0	0	3381.66	3319.76	3562.61
$-\Delta U(\text{C})/\text{J}$	0	0	0	17.83	6.28	0.58	1.22	22.38	0
$\Delta_\Sigma U/\text{J}$	15.64	17.48	12.12	13.36	17.80	16.32	16.09	15.80	15.90
$-\Delta U(C_8H_9O_2N)/\text{J}$	21477.91	23819.84	17013.27	17646.58	24212.80	22411.09	18644.60	18348.40	18230.35
$-\Delta_c u^o(C_8H_9O_2N)/\text{J g}^{-1}$	26609.89	26603.05	26619.42	26603.82	26604.84	26603.23	26606.64	26603.45	26608.21

Table 2 Vapor pressures of paracetamol (form I) obtained by Knudsen effusion

Hole 1 ($A = 2.105 \times 10^{-7}$ m^2, $r = 2.588 \times 10^{-4}$ m, $l = 2.09 \times 10^{-5}$ m)				Hole 2 ($A = 2.577 \times 10^{-7}$ m^2, $r = 2.864 \times 10^{-4}$ m, $l = 2.09 \times 10^{-5}$ m)			
m/mg	t/s	T/K	p/Pa	m/mg	t/s	T/K	p/Pa
3.95	56,436	394.51	0.1262	3.85	56,436	394.51	0.1002
3.43	44,123	396.35	0.1404	3.67	44,123	396.35	0.1224
4.82	45,481	398.76	0.1918	4.44	45,481	398.76	0.1440
4.61	40,982	400.10	0.2039	4.38	40,982	400.10	0.1579
7.29	44,778	403.63	0.2959	6.87	44,778	403.63	0.2273
7.12	39,034	405.11	0.3319	6.73	39,034	405.11	0.2557
11.04	47,126	408.13	0.4270	10.83	47,126	408.13	0.3415
12.96	43,671	410.99	0.5417	12.36	43,671	410.99	0.4213
15.19	44,074	412.27	0.6290	14.32	44,074	412.27	0.4838
14.66	44,982	412.40	0.5953	13.90	44,982	412.40	0.4604
17.54	44,597	414.17	0.7183	16.44	44,597	414.17	0.5494
19.26	35,145	417.01	0.9990	18.73	35,510	416.86	0.7848
20.23	33,678	418.46	1.0950	17.86	35,145	417.01	0.7567
22.65	31,275	420.05	1.3173	20.23	33,678	418.46	0.8935
38.35	43,968	422.10	1.5827	21.34	31,275	420.05	1.0144
46.27	43,651	425.11	1.9188	34.57	43,968	422.10	1.1681
53.29	43,205	427.33	2.2265	35.08	44,074	422.70	1.1830
51.92	41,053	427.33	2.2808	46.27	43,651	425.11	1.5679
				51.34	41,053	427.33	1.8446
				57.79	43,205	427.54	1.9685

The standard massic energies of combustion in Table 1 correspond to the reaction:

$$C_8H_9O_2N(cr, I) + \frac{37}{4}O_2(g) \rightarrow 8CO_2(g) + \frac{9}{2}H_2O(l)$$
$$+ \frac{1}{2}N_2(g) \quad (4)$$
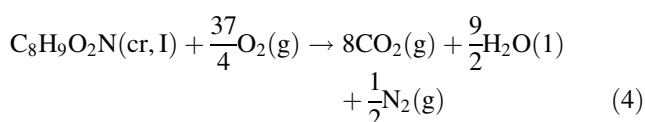
and were calculated from:

$$\Delta_c u^o = \frac{1}{m(C_8H_9O_2N)}[\Delta_{IBP}U - \Delta_\Sigma U - \Delta U(HNO_3)$$
$$- \Delta U(\text{fuse}) - \Delta U(n\text{-}C_{16}H_{34}) - \Delta U(BA)$$
$$+ \Delta U(C)] \quad (5)$$

They lead to a mean value $\Delta_c u^o(C_8H_9O_2N) = -(26606.95 \pm 1.75)$ J g^{-1}, from which $\Delta_c U_m^o(C_8H_9O_2N) = -(4022.06 \pm 0.72)$ kJ mol^{-1} and $\Delta_c H_m^o(C_8H_9O_2N) = -(4023.92 \pm 0.72)$ kJ mol^{-1} can be derived. According to normal thermochemical practice, the uncertainties assigned to $\Delta_c u^o(C_8H_9O_2N)$ are the standard deviations of the mean and those of $\Delta_c U_m^o(C_8H_9O_2N)$ and $\Delta_c H_m^o(C_8H_9O_2N)$ represent twice the overall standard deviations of the mean, including the contributions from the calibration with benzoic acid and from the combustion of n-hexadecane or benzoic acid used as combustion aids [50, 51]. The obtained $\Delta_c H_m^o(C_8H_9O_2N)$ value together with $\Delta_f H_m^o(CO_2, g) = -(393.51 \pm 0.13)$ kJ mol^{-1} [52], and $\Delta_f H_m^o(H_2O, l) =$

$-(285.830 \pm 0.040)$ kJ mol^{-1} [52] leads to $\Delta_f H_m^o(C_8H_9O_2N, cr I) = -(410.4 \pm 1.3)$ kJ mol^{-1}. Combining this result with the enthalpies of solution of monoclinic and orthorhombic paracetamol in methanol reported by Perlovich et al. [18], $\Delta_{sln}H_m^o(cr I) = (13.9 \pm 0.2)$ kJ mol^{-1} and $\Delta_{sln}H_m^o(cr II) = (11.9 \pm 0.2)$ kJ mol^{-1}, it is possible to derive the enthalpy of formation of form II paracetamol, at 298.15 K, as $\Delta_f H_m^o(C_8H_9O_2N, cr II) = \Delta_f H_m^o(C_8H_9O_2N, cr I) + \Delta_{sln}H_m^o(cr I) - \Delta_{sln}H_m^o(cr II) = -(408.4 \pm 1.3)$ kJ mol^{-1}. The enthalpy of formation of form III of paracetamol at 298.15 K can also be estimated as $\Delta_f H_m^o(C_8H_9O_2N, crIII) = \Delta_f H_m^o(C_8H_9O_2N, cr II) - \Delta_{trs}H_m^o(III \rightarrow II) = -(407.4 \pm 1.3)$ kJ mol^{-1}, based on $\Delta_{trs}H_m^o(III \rightarrow II) = -1.0$ kJ mol^{-1} at 398 K [13], and assuming that the heat capacities of forms II and III are identical in the range 298.15–398 K.

The vapor-pressures, p, of paracetamol (form I) obtained by the Knudsen method are shown in Table 2. The values of p were calculated from:

$$p = \frac{m}{At}\left(\frac{2\pi RT}{M}\right)^{1/2}\left(\frac{8r + 3l}{8r}\right)\left(\frac{2\lambda}{2\lambda + 0.48r}\right) \quad (6)$$

where m is the mass loss during the time t; A, l, and r are the area, the thickness, and the radius of the effusion hole, respectively; M is the molar mass of the compound under

study, R is the gas constant, T is the absolute temperature, and λ is the mean free path given by:

$$\lambda = \frac{kT}{\sqrt{2}\pi\sigma^2 p} \quad (7)$$

here, k represents the Boltzmann constant and σ the collision diameter. The collision diameter of paracetamol was estimated as 635 pm, from the van der Waals volume of the molecule calculated with the GEPOL93 program [53]. The obtained vapor pressure against temperature data for each hole were fitted to:

$$\ln p = a + \frac{b}{T} \quad (8)$$

where the slope b is related to the enthalpy of sublimation at the average of the highest and lowest temperatures of the range covered in each series of experiments, T_m, by $\Delta_{sub}H_m^o(T_m) = -bR$. The results for hole 1 led to $a = (36.17 \pm 0.37)$, $b = -(15098.5 \pm 153.1)$, and $\Delta_{sub}H_m^o(410.9\,K) = (125.5 \pm 2.7)$ kJ mol^{-1}; those for hole 2 yielded $a = (36.22 \pm 0.42)$, $b = -(15136.9 \pm 171.6)$, and $\Delta_{sub}H_m^o(411.0\,K) = (125.9 \pm 3.0)$ kJ mol^{-1}. The uncertainties quoted for a, b, and $\Delta_{sub}H_m^o(T_m)$ are the standard deviations of the mean multiplied by Student's factor for 95% confidence level [54]. In the case of hole 1 $t = 2.110$ (18 independent measurements), and for hole 2 $t = 2.093$ (20 independent measurements). The corresponding $\Delta_{sub}H_m^o$ values at 298.15 K, $\Delta_{sub}H_m^o(298.15\,K) = (129.3 \pm 2.7)$ kJ mol^{-1} (hole 1) and $\Delta_{sub}H_m^o(298.15\,K) = (129.6 \pm 3.0)$ kJ mol^{-1} (hole 2), were obtained from:

$$\Delta_{sub}H_m^o(298.15\,K) = \Delta_{sub}H_m^o(T) \\ + \int_T^{298.15K} \left[C_{p,m}^o(g) - C_{p,m}^o(cr) \right] dT \quad (9)$$

where $C_{p,m}^o(cr)$ and $C_{p,m}^o(g)$ are the molar heat capacities of the compounds in the crystalline and gaseous states, respectively. The temperature dependences of the heat capacities in Eq. 7 were estimated as $\left(C_{p,m}^o \text{ in J mol}^{-1}\,K^{-1} \right)$:

$$C_{p,m}^o(cr) = 0.5658T + 22.156 \quad (10)$$

$$C_{p,m}^o(g) = 0.4602T + 26.630 \quad (11)$$

Equation 10 was derived from a least squares fit to the $C_{p,m}^o(cr)$ data obtained by Boldyreva et al. [16] in the range 160–300 K, using adiabatic calorimetry. A similar fit to the $C_{p,m}^o(g)$ values calculated by statistical mechanics [55] in the range 200–400 K, using vibration frequencies obtained by the B3LYP/cc-pVTZ method and scaled by 0.965 [56] led to Eq. 11.

The enthalpy of sublimation of paracetamol was also determined by Calvet-drop sublimation microcalorimetry, at 398.9 K, leading to $\Delta_{sub}H_m^o(398.9\,K) = (127.0 \pm 1.9)$ kJ mol^{-1} (the uncertainties quoted represent twice the standard deviation

of the mean of 12 independent results). Correction of this value to 298.15 K, using Eqs. 9–11 leads to the $\Delta_{sub}H_m^o(298.15\,K) = (130.3 \pm 1.9)$ kJ mol^{-1} in good agreement with the results from the Knudsen effusion experiments. The weighted mean [51] of the results from both techniques $\Delta_{sub}H_m^o(298.15\,K) = 129.9 \pm 1.4$ kJ mol^{-1} was selected in this study.

Based on the standard molar enthalpies of formation and sublimation of paracetamol at 298.15 K determined here, it is possible to derive $\Delta_f H_m^o(C_8H_9O_2N, g) = -(280.5 \pm 1.9)$ kJ mol^{-1}.

To the best of our knowledge, the enthalpies of formation of paracetamol in the crystalline and gaseous states have not been reported, and only two studies leading to the enthalpy of sublimation of paracetamol (form I) have been published. The vapor-pressures obtained by Perlovich et al. [18, 57] in the range 355.2–396.7 K, from transpiration experiments, give $\Delta_{sub}H_m^o(376.0\,K) = 116.5 \pm 1.6$ kJ mol^{-1}, where the uncertainty quoted includes Student's factor for 95% confidence level ($t = 2.228$, for 11 data points) [54]. Correction of this value to 298.15 K through Eqs. 9–11, leads to the $\Delta_{sub}H_m^o(298.15\,K) = (118.9 \pm 1.6)$ kJ mol^{-1}, which differs by 11.0 kJ mol^{-1} from the result recommended in this study. The enthalpy of sublimation of paracetamol (form I), $\Delta_{sub}H_m^o(330\,K) = 238.9$ kJ mol^{-1}, obtained by Williams et al. [58], from Knudsen effusion studies in the range 313–347 K, seems impossibly high.

The enthalpy of formation of gaseous paracetamol proposed in this study, in conjunction with the enthalpies of formation of gaseous acetophenone, $\Delta_f H_m^o(C_8H_8O, g) = -(86.7 \pm 1.5)$ kJ mol^{-1} [23], 4'-hydroxyacetophenone, $\Delta_f H_m^o(C_8H_8O_2, g) = -(265.4 \pm 1.4)$ kJ mol^{-1} [59], and acetanilide, $\Delta_f H_m^o(C_8H_9ON, g) = -(109.2 \pm 2.2)$ kJ mol^{-1} [57, 60], allow the derivation of the enthalpy of the isodesmic and isogiric reaction (12). The obtained result is compared in Table 3 with those predicted by the B3LYP/cc-pVTZ
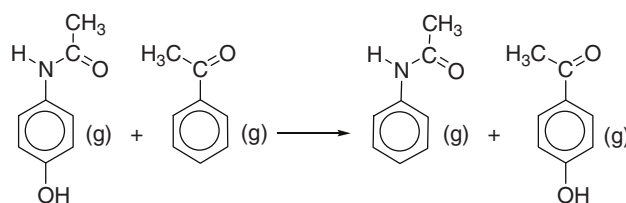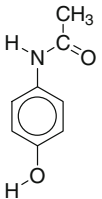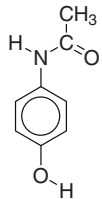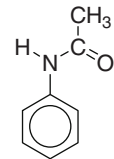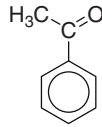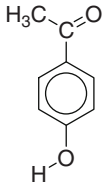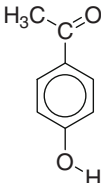

Table 3 Experimental and theoretical enthalpies of reaction (12)

	$-\Delta_r H_m^o(12)$/kJ mol^{-1}
B3LYP/cc-pVTZ	9.5
CBS-QB3	5.9
Experimental	7.4 $\pm$ 3.6 (27.1 $\pm$ 3.3)[a]

[a] Based on the enthalpies of formation of paracetamol, acetophenone, and 4'-hydroxyacetophenone selected in this study (see text), and on the enthalpy of formation of acetanilide, $\Delta_f H_m^o(C_8H_9ON, g) = -(128.9 \pm 1.7)$ kJ mol^{-1}, given in Pedley's compilation [23]

Table 4 Electronic energies (E_{el}), thermal corrections ($E_v + E_r + E_t$), zero point energies (ZPE), standard enthalpies[a] and standard Gibbs energies at 298.15 K, calculated with the B3LYP/cc-pVTZ and CBS-QB3 methods. Data in hartree[b]

	Paracetamol (Conformation I)	Paracetamol (Conformation II)	Acetanilide	Acetophenone	4′-hydroxyacetophenone (Conformation I)	4′-hydroxyacetophenone (Conformation II)
B3LYP/cc-pVTZ						
E_{el}	−515.679387	−515.679979	−440.429046	−385.035143	−460.289465	−460.289730
ZPE	0.158855	0.158932	0.154920	0.137675	0.141887	0.141901
$E_v + E_r + E_t$	0.010410	0.010368	0.009151	0.007807	0.008957	0.008949
H^o(298.15 K)	−515.509178	−515.509735	−440.264031	−384.888717	−460.137677	−460.137936
G^o(298.15 K)	−515.557538	−515.557916	−440.309794	−384.930208	−460.181684	−460.181920
Boltzmann weight[c]	0.401	0.599			0.438	0.562
CBS-QB3						
E_{el}	−514.806059	−514.806731	−439.653838	−384.346613	−459.501525	−459.501805
ZPE	0.157059	0.157074	0.153151	0.136094	0.140240	0.140246
$E_v + E_r + E_t$	0.010516	0.010520	0.009243	0.007878	0.009058	0.009053
H^o(298.15 K)	−514.637540	−514.638193	−439.490500	−384.201697	−459.351283	−459.351562
G^o(298.15 K)	−514.685982	−514.686820	−439.536432	−384.243271	−459.395434	−459.395695
Boltzmann weight[c]	0.292	0.708			0.431	0.569

[a] H^o(298.15 K) = E_{el} + ZPE + E_v + E_r + E_t + RT, where E_v, E_r, and E_t represent the vibrational, rotational, and translational contributions; [b]1 hartree = 2625.499963 kJ mol^{-1}; [c]Based on the computed G^o(298.15 K) values for the different molecular conformations

and CBS-QB3 methods, which were computed from the data in Table 4. Note that the enthalpies of paracetamol and 4′-hydroxyacetophenone used in the theoretical calculations of $\Delta_r H_m^o$ (12) correspond to Boltzmann averages of the values obtained for the conformations I and II illustrated in Table 4 [61].

It can be concluded from Table 3 that the theoretically predicted enthalpies of reaction (12) are within the uncertainty interval of the corresponding experimental value and that there is no significant difference between the B3LYP/cc-pVTZ and CBS-QB3 results. This supports the reliability of those methods and indicates a good thermodynamic consistency between the enthalpy of formation data used to derive the experimental value of $\Delta_r H_m^o$ (12) in Table 4. It also substantiates the accuracy of the enthalpies of formation and sublimation of monoclinic paracetamol (form I) recommended in this study.

Finally, our selection of the enthalpy of formation of gaseous acetanilide deserves a comment. The value $\Delta_f H_m^o (C_8H_9ON, \ g) = -(109.2 \pm 2.2)$ kJ mol^{-1} indicated above was derived as follows. First, $\Delta_f H_m^o (C_8H_9ON, \ cr) = -(209.5 \pm 1.4)$ kJ mol^{-1} was calculated from the enthalpy of combustion of solid acetanilide given by Johnson [60], which has been recommended as reference for testing the accuracy of combustion calorimeters [62]. The vapor-pressures of acetanilide reported by Perlovich et al. [57] in the range 309–330 K lead to $\Delta_{sub} H_m^o (319.7 \ K) = (99.5 \pm 1.7)$ kJ mol^{-1}, where the uncertainty quoted is the standard deviation of the mean multiplied by Student's factor for 95% confidence and 18 independent measurements ($t = 2.110$) [54]. This value was corrected to 298.15 K by using Eq. 9 and the temperature dependences of the heat capacities of solid and gaseous acetanilide $\left(C_{p,m}^o \text{ in J mol}^{-1} \text{ K}^{-1} \right)$ given by:

$$C_{p,m}^o(cr) = 0.4950T + 31.725 \qquad (13)$$

$$C_{p,m}^o(g) = 0.4350T + 15.213 \qquad (14)$$

Eq. 13 was derived from $C_{p,m}^o(C_8H_9ON, \ cr, 298.15 \ K) = 179.3$ J K^{-1} mol^{-1} [63, 64] and $C_{p,m}^o(C_8H_9ON, \ cr, 323 \ K) = 191.6$ J K^{-1} mol^{-1} [64, 65], and Eq. 14 was obtained from a least squares fit to $C_{p,m}^o(g)$ values in the range 200–400 K, calculated by statistical mechanics [55], using vibration frequencies predicted by the B3LYP/cc-pVTZ method and scaled by 0.965 [56]. Hence $\Delta_{sub} H_m^o$ (298.15 K) $= (100.3 \pm 1.7)$ kJ mol^{-1} was derived, which combined with the $\Delta_f H_m^o (C_8H_9ON, \ cr)$ value indicated above leads to the selected $\Delta_f H_m^o (C_8H_9ON, \ g) = -(109.2 \pm 2.2)$ kJ mol^{-1}. This value differs by 19.7 kJ mol^{-1} from that indicated in Cox and Pilcher and Pedley's compilations, $\Delta_f H_m^o (C_8H_9ON, \ g) = -(128.9 \pm 1.7)$ kJ mol^{-1} [22, 23]. If our $\Delta_f H_m^o (C_8H_9ON, \ g)$ selection is replaced by Cox and

Pilcher and Pedley's in the calculation of the enthalpy of reaction (12) then, as indicated in Table 3, $\Delta_r H_m^o (12) = -(27.3 \pm 3.3)$ kJ mol^{-1} is obtained, in very poor agreement with the corresponding theoretical estimates. Since the enthalpy of formation of crystalline acetanilide given by Cox and Pilcher and Pedley, $\Delta_f H_m^o (C_8H_9ON, \ cr) = -(209.5 \pm 1.5)$ kJ mol^{-1}, is essentially identical to that selected in this study, the origin of the discrepancy lies on the enthalpy of sublimation included in the compilation. This exercise clearly illustrates the usefulness of combining experimental and high level quantum chemistry calculation results in the assessment of thermochemical data.

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