Thermophysical Study of Several Barbituric Acid Derivatives by Differential Scanning Calorimetry (DSC)

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The present study reports a differential scanning calorimetry (DSC) study of the barbituric acid derivatives: 1,3-dimethylbarbituric acid [CAS 769-42-6], 5,5-dimethylbarbituric acid [CAS 24448-94-0], 1,3-diethylbarbituric acid [CAS 32479-73-5], 1,3,5-trimethylbarbituric acid [CAS 7358-61-4], 1,5,5-trimethylbarbituric acid [CAS 702-47-6], and tetramethylbarbituric acid [CAS 13566-66-0] in the temperature interval from $T = 268$ K to their respective melting temperatures. Temperatures, enthalpies and entropies of fusion, and the heat capacities of the solid compounds as a function of temperature are reported.

Introduction

Barbituric acid derivatives were introduced for medical use a century ago,[1] several years after the synthesis in 1864 by von Baeyer of the parent compound, barbituric acid.[2] Barbiturates act as central nervous system depressants, and by virtue of this, they produce a wide spectrum of physiological effects. They are used as sedatives, hypnotics, soporifics, anticonvulsants, or adjuncts in anesthesia.[3] Other applications of barbituric acid derivatives include their use as antivirals,[4] in photochemical nanoscience,[5] as dyes,[6] polymers,[7] dental materials,[8] water-thinned or oil-based inks,[9] and as polymerization catalysts.[10] In the context of a systematic study of the thermodynamic properties of this family of compounds, we have recently published thermochemical studies of barbituric acid[11] and its 5,5-dimethyl[12] and 5,5-diethyl (barbital)[13] derivatives. Thermophysical data existing in the literature for these types of compounds are scarce. Only experimental data concerning the C_p of barbituric acid[14,15] and the 5,5-diethyl derivative[13] are available.

Heat capacities at $T = 298.15$ K have proven quite useful in adjusting vaporization, sublimation, and fusion enthalpies with temperature. Equations for doing this have recently been reported by Chickos and co-workers.[16,17] There are several compilations of critically evaluated calorimetrically measured heat capacities,[18,19] but new data on the heat capacity of important families of compounds are still needed,[20,21] particularly for crystalline solids. There has been an effort to develop reliable and accurate group contribution schemes to improve the estimation and compensate for the scarcity of this data. The simplest schemes are based on first-order additivity and only consider the constituent groups of the molecule.[22,23] Other methods use a second-order additivity scheme that also take into account nearest-neighbor interactions in the definition of the structural units of molecules.[24] These schemes normally neglect all next-to-nearest neighbor interactions because of the limited accuracy of the available experimental heat capacity data. Estimations of the heat capacity of solids are more problematic than their liquid counterparts. This is due in part to the lack of data but also due to the anisotropic nature of the solid state. Phase transitions in solids can affect their heat capacities near these transitions. Solids that form liquid crystals, for example, seem to have larger heat capacities in certain temperature regions, and phase change entropies appear attenuated in comparison to systems that melt directly to isotropic liquids.[25] Group values for estimating the heat capacity of crystalline solids have been reported, but the estimations in many cases have been hampered by the lack of sufficient data.

During the past few years, we have been involved in the experimental determination of enthalpies of fusion, heat capacities, and the study of polymorphism of pure crystalline organic compounds.[26−32] The present work reports the temperature, enthalpy and entropy of fusion, and heat capacities of several barbituric acid derivatives measured by differential scanning calorimetry (DSC). The target compounds (see Figure 1) are 1,3-dimethylbarbituric acid (**1**), 5,5-dimethylbarbituric acid (**2**), 1,3-diethylbarbituric acid (**3**), 1,3,5-trimethylbarbituric acid (**4**), 1,5,5-trimethylbarbituric acid (**5**), and tetramethylbarbituric acid (**6**). The main objective of this work was to expand the database of available experimental heat capacities of barbituric acid derivatives and to provide reliable data to adjust and refine group contribution schemes for the estimation of this property for compounds that have not yet been investigated.

Experimental Procedures

Materials. 1,3-Dimethylbarbituric acid (**1**) [CAS 769-42-6] and 5,5-dimethylbarbituric acid (**2**) [CAS 24448-94-0] were commercially available from Fluka, and no further purification was necessary as described below.

1,3-Diethylbarbituric acid (**3**) [CAS 32479-73-5] was obtained by the condensation of malonic acid with *N*,*N*′-diethylurea

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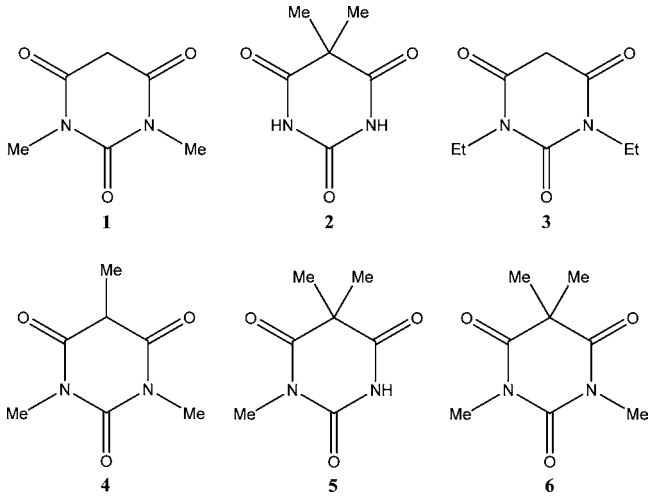

Figure 1. Molecular structures of the barbituric acid derivatives studied.

promoted by acetic anhydride according to a literature procedure.[33] The oily crude **3** slowly underwent a partial crystallization, and the crystals were filtered out with suction and were washed with a little ethanol. The crystals were recrystallized several times to a melting point (mp) of (325 to 326) K (lit.[33] mp 325 K), from mixtures of chloroform and heptane (1.4:1), in the following manner: the solution was allowed to evaporate at room temperature until 1,3-diethylbarbituric acid was a liquid layer on the bottom, and the mass was then cooled to 277 K and seeded. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 7.1$ Hz, 6 H), 3.65 (s, 2 H), 3.94 (q, $J = 7.1$ Hz, 4 H) ppm.

1,3,5-Trimethylbarbituric acid (**4**) [CAS 7358-61-4] was prepared from diethyl methylmalonate and *N*,*N*′-dimethylurea according to a literature procedure[34] and was purified as follows: The sodium barbiturate salt smoothly precipitated in the reaction mixture and was filtered out and washed with ethanol. The salt was dissolved in water, benzene was then added, and the salt was acidified adding with stirring 1 M hydrochloric acid to a pH 4. The benzene layer was separated, dried over sodium sulfate, filtered, and concentrated, giving on cooling, crystals of **3**, with an mp of 362.7 ± 0.5 K (lit.[34] mp (362.7 to 363.2) K); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.61$ (d, $J = 7.5$ Hz, 3 H), 3.31 (s, 6 H), 3.48 (q, $J = 7.5$ Hz, 1 H) ppm.

1,5,5-Trimethylbarbituric acid (**5**) [CAS 702-47-6] was obtained by condensation of diethyl dimethylmalonate with methylurea,[35] using one equivalent of sodium ethoxide in ethanol as the condensation agent. In this manner, the sodium salt of 1,5,5-trimethylbarbiturate smoothly precipitated from the reaction mixture and was filtered out, washed with ethanol, and dried in air. The salt was then acidified by quickly adding an equivalent amount of 6 M hydrochloric acid with vigorous mixing to prevent the decomposition of the salt in aqueous solution. Compound **5** was recrystallized from chloroform to the required purity, with an mp of 434.6 ± 0.2 K (lit.[36] mp (434 to 435) K); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.56$ (s, 6 H), 3.28 (s, 3 H), 8.91 (br, 1 H) ppm.

Tetramethylbarbituric acid[37] (**6**) [CAS 13566-66-0] was prepared by methylation of the sodium salt of 1,5,5-trimethylbarbituric acid in the following manner. The sodium salt (obtained as described above, 28.3 g, 0.147 mol) was reacted with methyl iodide (18.5 mL, 0.297 mol) in absolute ethanol (500 mL) at room temperature for 2.5 h. The ethanol was removed, and water (75 mL) was added, followed by extraction with petroleum ether (300 mL) and diethyl ether (300 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated to give crystals of **6**, with an mp of 382.3 ± 0.2 K (lit.[36] mp (382 to 383) K); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.54$ (s, 6 H), 3.30 (s, 6 H) ppm.

Purity Control. All samples were carefully dried under vacuum. A determination of purity was assessed by high-performance liquid chromatography (HPLC) and DSC, using the fractional fusion technique.[38] The mole fraction of impurities in all compounds studied was less than 0.0001 as assessed by both techniques.

The standards used for DSC calibration were hexafluorobenzene, 0.999 mass fraction, supplied by Aldrich, benzoic acid National Institute of Standards and Technology (NIST) standard reference sample 39j, and high-purity indium ($w > 0.99999$) and tin supplied by Perkin-Elmer.

Apparatus and Procedure. The behavior of the samples as a function of temperature was studied by DSC. A Pyris 1 instrument from Perkin-Elmer equipped with an intracooler unit was used to monitor purity, to study the fusion process and the possible existence of phase transitions in the solid samples, and to determine heat capacities as a function of temperature. The apparatus was previously calibrated in temperature and energy with reference materials. Temperature and power scales were calibrated[39] at heating rates of (0.04 and 0.17) $K \cdot s^{-1}$. The temperature scales were calibrated by the melting temperature of the high-purity reference materials, hexafluorobenzene, tin, and indium.[40] The power scales were calibrated with high-purity indium.[40]

Table 1. Group Values (Γ) Used to Estimate Total Phase Change Entropies and Heat Capacities

components	group (Γ)	$\Gamma(\Delta_{tpce}S(T_{fus}))^a$ / J·K^{-1}·mol^{-1}	$\Gamma(C_{p,m}(cr))^a$ / J·K^{-1}·mol^{-1}
primary sp^3 carbon	CH_3—R	17.6	36.6
secondary sp^3 carbon	—CH_2—	7.1	26.9
cyclic secondary sp^3 carbon			24.6
cyclic tertiary sp^3 carbon	—CH(R)—	−14.7	11.7
aromatic tertiary sp^2 carbon	=CH—		17.5
aromatic quaternary sp^2 carbon	=CR—		8.5
cyclic quaternary sp^3 carbon	—C<(R)$_2$—	−34.6	6.1
cyclic *sec* amide	—C(=O)NH—	2.7	46.4
cyclic tertiary amide	—C(=O)NR—	−21.7	45.3[b]
N-substituted cyclic imide	—C(=O)N(R)C(=O)—	[−13.6]	[49.4][c]
cyclic imide	—C(=O)N(H)C(=O)—	[2.8]	[74.1]
cyclic urea	—NHC(=O)NH—		[63.6]
cyclic ketone			34.3

[a] Values in brackets are considered tentative assignments. [b] This value, previously assigned tentatively as [52.7], has been modified as a result of additional data. [c] New assignment.

Table 2. Temperatures and Enthalpies and Entropies of Fusion for the Compounds Studied

	T_{fus} / K	$\Delta_{fus}H(T_{fus})$ / kJ·mol^{-1}	$\Delta_{fus}S(T_{fus})_{expt}$ / J·K^{-1}·mol^{-1}	$\Delta_{tpce}S(T_{fus})_{calc}{}^a$ / J·K^{-1}·mol^{-1}
1,3-dimethylbarbituric acid	396.1 ± 0.3	17.7 ± 0.1	44.6 ± 0.3	44.4
5,5-dimethylbarbituric acid	549.3 ± 0.9	37.9 ± 0.3	69.0 ± 0.5	50.6
1,3-diethylbarbituric acid	326.8 ± 0.2	19.6 ± 0.1	60.1 ± 0.3	58.6
1,3,5-trimethylbarbituric acid	362.6 ± 0.5	13.7 ± 0.6	37.7 ± 0.5	47.3
1,5,5-trimethylbarbituric acid	434.5 ± 0.2	30.2 ± 0.1	69.6 ± 0.2	51.8, 43.8
tetramethylbarbituric acid	382.2 ± 0.2	18.5 ± 0.8	48.4 ± 2.1	45.0

[a] Values calculated according to ref 44.

Table 3. Mean Experimental $C_{p,m}$(cr) Values

	$C_{p,m}$(cr)/J·K^{-1}·mol^{-1}							$C_{p,m}$(cr)/J·K^{-1}·mol^{-1}	
T/K	**1**	**2**	**3**	**4**	**5**	**6**	T/K	**2**	**5**
268.15	175.7	173.9	223.4	207.8	199.9	217.2	395.15	233.8	264.2
270.15	176.7	175.5	225.6	209.3	200.9	218.1	400.15	236.0	267.3
275.15	178.7	179.2	230.7	213.0	203.2	221.0	405.15	238.4	273.2
280.15	180.8	182.2	234.5	217.0	205.3	223.6	410.15	240.2	276.5
285.15	182.6	184.4	238.2	220.6	207.5	226.4	415.15	242.3	279.4
290.15	185.3	187.0	242.1	224.7	209.8	229.3	420.15	246.2	
295.15	187.4	188.8	246.1	228.5	212.2	232.2	425.15	247.9	
298.15	188.5	190.5	248.5	230.9	213.6	234.2	430.15	250.7	
300.15	189.5	191.4	250.3	232.6	214.6	235.4	435.15	253.7	
305.15	191.6	194.5	254.2	236.6	216.7	238.6	440.15	255.0	
310.15	193.9	196.5	259.8	241.1	218.9	243.0	445.15	258.9	
315.15	197.5	199.1		244.1	221.4	246.5	450.15	261.5	
320.15	199.9	201.5		249.4	223.9	249.6	455.15	264.4	
325.15	202.7	203.3		253.2	225.6	252.3	460.15	266.9	
330.15	204.9	205.3		258.1	227.8	255.0	465.15	270.0	
335.15	206.8	207.5		265.1	230.3	258.8	470.15	273.4	
340.15	208.9	208.9		272.4	233.0	261.8	475.15	275.8	
345.15	211.5	211.2			235.5	264.8	480.15	278.7	
350.15	214.3	214.3			237.8	268.6	485.15	282.3	
355.15	216.9	217.5			241.0	272.1	490.15	285.4	
360.15	219.7	219.2			243.0	276.3	495.15	288.2	
365.15	223.5	220.9			246.0	280.0	500.15	292.4	
370.15	227.2	222.4			249.2	285.1	505.15	296.6	
375.15		226.2			251.1		510.15	298.4	
380.15		228.2			253.4		515.15	301.5	
385.15		228.4			256.3		520.15	304.5	
390.15		232.0			259.8		525.15	308.0	

Table 4. Coefficients of the Fitted Curves

	range	A	B·10^2	C·10^3	D·10^5		rmsd[a]
	K	J·K^{-1}·mol^{-1}	J·K^{-1}·mol^{-1}	J·K^{-1}·mol^{-1}	J·K^{-1}·mol^{-1}	R^2	J·K^{-1}·mol^{-1}
1	268−370	189.0 ± 0.1	45.3 ± 0.3	0.20 ± 0.17	1.15 ± 0.22	0.9988	0.6
2	268−525	190.4 ± 0.1	48.7 ± 0.3	−0.73 ± 0.04	0.39 ± 0.01	0.9997	0.7
3	268−310	248.4 ± 0.1	82.8 ± 0.4	5.15 ± 0.50	12.00 ± 2.4	0.9997	0.1
4	268−340	230.8 ± 0.1	75.3 ± 0.7	1.31 ± 0.24	8.77 ± 0.92	0.9990	0.6
5	268−415	213.7 ± 0.1	45.1 ± 0.3	−0.40 ± 0.10	1.17 ± 0.07	0.9994	0.5
6	268−370	234.7 ± 0.1	61.5 ± 0.4	0.32 ± 0.19	1.00 ± 0.26	0.9991	0.6

[a] Root-mean-square deviation.

Thermograms of samples hermetically sealed in aluminum pans were recorded in a nitrogen atmosphere. All of the pans with the samples were weighed on a Mettler AT21 microbalance with a detection limit of 1·10^{-6} g, before and after the experiments to confirm that no product had volatilized.

After calibration, several runs with high-purity benzoic acid and indium were performed under the same conditions as the experimental determinations. The accuracies associated with measurements of temperature and enthalpy of fusion were calculated as the percentage deviation of the experimental data with respect to the values given in the literature;[40] in all cases the deviations were less than 1 K and 2.0 % for temperature and enthalpy determinations, respectively.[30]

For the determination of purity, temperature, and enthalpy of fusion, a heating rate of 0.04 K·s^{-1} was used, and five to eight samples weighing (1 to 2) mg were measured. A fresh sample was used for each run. All compounds showed thermal stability during the fusion process.

Different scans at heating rates of (0.04 and 0.17) K·s^{-1} were performed to determine the possible existence of phase transitions in the samples over the temperature range from T = 268 K to their melting temperature.

Heat capacities were determined by the "scanning method" following the experimental methodology previously described[41] with synthetic sapphire (α-aluminum oxide) as reference material.[40,41] DSC is a commonly accepted method for the quantitative determination of heat capacities, and it has been proven as a suitable technique for obtaining reliable and accurate values.[42] As a check of the experimental method, heat capacity experiments were performed with benzoic acid in the temperature interval T = (268 to 360) K.[30] The relative percentage error of our measurements in comparison with those reported in the literature was less than 2 %.[30]

The mass of sapphire used in each run was 0.030345 g. For heat capacity determinations, three to six fresh samples weighing (10 to 25) mg were scanned for each solid compound in the temperature range from T = 268 K to its melting temperature at 0.17 K·s^{-1}. The complete temperature range for determination of heat capacity was divided in intervals of approximately 40 K, overlapping by 5 K from one interval to another.

The molecular weights used to convert the specific heat capacities measured to their molar values were calculated from the atomic weights recommended by the International Union of Pure and Applied Chemistry (IUPAC) in 2005.[43]

Estimations of Total Phase Change Entropies and Heat Capacity. Total phase change entropies were calculated according to the protocol described previously.[16] Table 1 lists group values used together with the ring equation developed, eq 1, to estimate $\Delta_{tpce}S(T_{fus})_{calc}$.

$$\Delta_{tpce}S(T_{fus})_{calc} = 33.4 + 3.7(N - 3) \quad (1)$$

The estimation of a monocyclic heterocycle begins by first estimating the parent hydrocarbon of ring size N, obtained by substituting carbon for all the ring heteroatoms using eq 1.

Estimations of the heterocyclic ring is then completed by identifying the appropriate groups that modify the structure and adding their contributions. The groups are identified in columns 1 and 2 of Table 1, and their contributions are listed in column 3 of the table. The barbituric acid derivatives of this study were modeled as derivatives of cyclohexane. Modifications to the cyclohexane structure include the introduction of a cyclic amide and cyclic imide to the ring. The estimation is then completed by adding the contributions of any acyclic groups attached to the ring and modifying any ring carbons atoms that differ from the secondary sp^3 hybridized methylene groups found in the parent ring. In some cases, it is possible to model total phase change entropies in more than one manner. The estimation of 1,5,5-trimethylbarbituric acid serves as an example. In addition to the ring contribution, the molecule can either be modeled as a cyclic imide and an *N*-substituted cyclic tertiary amide or as an *N*-substituted cyclic imide and a cyclic secondary amide. Ideally both values calculated in this manner should be identical. In this case it is not possible to preferentially assign one value over the other since both the cyclic imide and the *N*-substituted cyclic imide are still tentative values. Both estimated values are included below in Table 2.

The group values for estimating $C_{p,m}(cr)$ of the compounds of this study are listed in column 4 of Table 1. The group value for a cyclic tertiary amide (old value 52.7), previously assigned as tentative, has been updated, and a new group value, that for a *N*-substituted cyclic imide, has been tentatively assigned due to the inclusion of new data. The new values were evaluated by minimizing the following function: $\sum[[C_{p,m}(cr)_{exp} - C_{p,m}(cr)_{calc}]/C_{p,m}(cr)_{exp}]^2$, using the data in Table 5.

Results and Discussion

Fusion temperatures and enthalpies and experimental entropies of fusion of the compounds measured are given in Table 2. The uncertainties were taken as the standard deviation of the mean. T_{fus} values are reported as DSC onset temperatures. Also included in the last column of the table is the estimated total phase change entropy, $\Delta_{tpce}S(T_{fus})$.[44] This term includes the total phase change entropy associated in going from $T = 0$ K to the liquid at $T = T_{fus}$. For compounds without any other phase transitions, this entropy change is identical to the fusion entropy. The uncertainty associated with predicting total phase change entropies by this method based on approximately 1000 estimations is $\pm$ 18.5 $J\cdot K^{-1}\cdot mol^{-1}$.[25] For the most part, the estimations reported in Table 2 fall well within this uncertainty, suggesting the absence of any substantial low temperature solid−solid phase transitions. To the authors' knowledge, there is no other calorimetric data in the literature for comparison with the results obtained in this study.

No solid−solid phase transitions were observed over the temperature interval from $T = 268$ K to the corresponding melting points for any of the compounds.

The measured molar heat capacities as a function of temperature for all compounds are collected in Table 3. The values given in Table 3 are averages of three to six independent runs. The standard deviation of all of the data associated with multiple measurements is less than 2 $J\cdot K^{-1}\cdot mol^{-1}$.

The experimental results for the compounds were fit to a third-order polynomial in temperature of the type:

$$C_{p,m}(cr) = A + B(T/K - 298.15) + C(T/K - 298.15)^2 + D(T/K - 298.15)^3 \quad (2)$$

Table 5. Heat Capacity of Compounds Used to Update Group Values for a Cyclic Tertiary Amide and N-Substituted Urea

compound	$C_{p,m}$(cr, 298.15 K) exp. / $J\cdot K^{-1}\cdot mol^{-1}$	$C_{p,m}$(cr, 298.15 K) calc. / $J\cdot K^{-1}\cdot mol^{-1}$	$\Delta C_{p,m}$[a] / $J\cdot K^{-1}\cdot mol^{-1}$	ref
imidazolidin-2-one	107.7	112.8	−5.1	45
N,N′-trimethyleneurea	129.5	137.4	−7.9	45
parabanic acid	168.9[b]	120.5	48.4	46
barbituric acid	141.1	145.1	−4	14, 15
1,3-dimethylbarbituric acid	188.5	192.5	−4.0	this work
1,3-diethylbarbituric acid	248.5	246.3	2.2	this work
5,5-dimethylbarbituric acid	190.5	199.8	−9.3	this work
5,5-diethylbarbituric acid	228.7	253.6	−24.9	13
1,3,5-trimethylbarbituric acid	230.9	216.2	14.7	this work
1,5,5-trimethylbarbituric acid	213.6	210.6	3.0	this work
tetramethylbarbituric acid	234.2	247.2	−13.0	this work
uracil	131.8	124.6	7.2	47
1-methyluracil	156.9	160.1	−3.2	47
3-methyluracil	157	160.1	−3.1	47
5-methyluracil	163	150	13	47
6-methyluracil	162.5	150	12.5	47
1,3-dimethyluracil	182.5	195.6	−13.1	47
3,6-dimethyluracil	187.4	185.5	1.9	47
1,6-dimethyluracil	188.1	185.5	2.6	47
1,5-dimethyluracil	187.6	185.5	2.1	47
5,6-dimethyluracil	191.1	175.4	15.7	47
1,3,6-trimethyluracil	212.6	221.0	−8.4	47
1,3,5,6-tetramethyluracil	244.5	246.4	−1.9	47
1,3-dimethyl-5-ethyluracil	241.1	247.9	−6.8	47
1,3-dimethyl-5-propyluracil	302.7	274.8	27.9	47
1,3-dimethyl-5-butyluracil	358.1[b]	301.7	56.4	47
1,3-dimethyl-6-ethyluracil	241.8	247.9	−6.1	47
1,3-dimethyl-6-propyluracil	287.2	274.8	12.4	47
1,3-dimethyl-6-butyluracil	296.4	301.7	−5.3	47
1,3-dimethyl-5,6-trimethyleneuracil	252.9	247.0	5.9	47
1,3-dimethyl-5,6-tetrarmethyleneuracil	282.9	271.6	11.3	47
1,3-dimethyl-5,6-pentamethyleneuracil	314.5	296.2	18.3	47
6-chlorouracil	139.4	142.1	−2.7	47
5-fluorouracil	138.3	138.2	0.1	47
5-chlorouracil	136.7	142.1	−5.4	47
5-bromouracil	144.7	145.8	−1.1	47
5-iodoracil	150.9	141.3	9.6	47
5-trifluoromethyuracil	182.2	182.8	−0.6	47
5-nitrouracil	167.2	169.5	−2.3	47
5-aminouracil	145	135	10	48
6-aminouracil	147	135	12	48
6-amino-1-methyluracil	166.2	170.5	−4.3	48
6-amino-1,3-dimethyluracil	189	206.0	−17.0	48
caffeine	231.8	204.2	27.6	49
succinamide	131.4	123.3	8.1	49
antipyrine	268.2	266.6	1.7	49
4-aminoantipyrene	294.6	277.0	17.6	49

[a] $C_{p,m}$(cr, 298.15 K, expt.) − $C_{p,m}$(cr, 298.15 K). [b] Not used in generating the group value for a cyclic tertiary amide.

The range studied for each compound, the coefficients of the fitted third-order equation in temperature, and the root-mean-square deviation (rmsd) for all the compounds are collected in Table 4. To our knowledge, there are no $C_{p,m}$ data in the literature for comparison with our results.

Estimations of heat capacities at $T = 298.15$ K are relatively straightforward. The estimation requires an identification of the correct groups and evaluating their sum. As noted in the Experimental Section, one group value previously assigned as tentative has been updated, and one additional value, an *N*-substituted cyclic imide, has been added. The compounds and data used for this purpose are included in Table 5, which includes experimental values from this work as well as from the recent literature. All of the compounds in Table 5, except for parabanic acid and 1,3-dimethyl-5-butyluracil, were used in generating the new group values. These two compounds resulted in errors greater than three standard deviations when included in the correlations and were therefore excluded. The heat capacity of 1,3-dimethyl-5-butyluracil (351.8 $J\cdot K^{-1}\cdot mol^{-1}$) is particularly surprising since the value for the isomer, 1,3-dimethyl-6-butyluracil (296.4 $J\cdot K^{-1}\cdot mol^{-1}$), is considerably lower. The two isomers differ only in the location of the butyl group on the heterocyclic ring. The standard deviation associated

with the estimations listed in Table 5 was ± 11.0 $J \cdot K^{-1} \cdot mol^{-1}$. This increases to ± 14.9 $J \cdot K^{-1} \cdot mol^{-1}$ if the uncertainties associated with the two outliers are included.

Some flexibility also exists in the estimation of $C_{p,m}$(cr). As described above, 1,5,5-trimethylbarbituric acid (**5**) can be estimated as either a cyclic imide attached to a cyclic tertiary amide, 235.3 $J \cdot K^{-1} \cdot mol^{-1}$, or as an *N*-substituted cyclic imide attached to a cyclic secondary amide, 210.6 $J \cdot K^{-1} \cdot mol^{-1}$. In principle, both estimations should produce identical results. In general, the use of different groups in an appropriate manner usually results in $C_{p,m}$(cr) values that do not vary a great deal from each other. In this case the later value is preferred because the former calculation uses a value that is still tentatively assigned, [74.1] $J \cdot K^{-1} \cdot mol^{-1}$. 5,5-Dimethylbarbituric acid (**2**) has been estimated as the sum of a cyclic urea and cyclic secondary amide in Table 5, 199.8 $J \cdot K^{-1} \cdot mol^{-1}$. An alternative method, perhaps less indicative of the properties of the molecule, is to estimate $C_{p,m}$(cr, 298.15 K) as the sum of a cyclic urea and two cyclic ketones. This results in the value 211.5 $J \cdot K^{-1} \cdot mol^{-1}$, not terribly different from the experimental value of 190.5 $J \cdot K^{-1} \cdot mol^{-1}$.

The uracils in Table 5 were previously estimated by Zielenkiewicz et al.[47,48] using this group method. Uracil was estimated as the sum of two cyclic secondary amides and two tertiary aromatic sp^2 C, 127.8 $J \cdot K^{-1} \cdot mol^{-1}$. If this protocol is applied using the older group value previously available for a cyclic tertiary amide, 52.7 $J \cdot K^{-1} \cdot mol^{-1}$,[22] a value for 1-methyluracil of 170.7 $J \cdot K^{-1} \cdot mol^{-1}$ is calculated, which differs from the value of 153.5 $J \cdot K^{-1} \cdot mol^{-1}$ reported in Table 2 of ref 47. It is not clear exactly how these authors arrived at some of their estimated values. The use of the group value for a tertiary aromatic sp^2 C was intended for aromatic compounds and would probably be a more appropriate choice to use if uracil was being modeled as a dihydroxypyrimidine. Otherwise, the use of the group value for a cyclic tertiary sp^2 carbon is recommended for cyclic unsaturated compounds of this sort.

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