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Estimations of the Vaporization Enthalpies of a Series of Licit and Illicit Drugs by Synthetic Analysis and Group Additivity

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Research Article

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Estimations of the Vaporization Enthalpies of a Series of Licit and Illicit Drugs by Synthetic Analysis and Group Additivity

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Abstract: Vaporization enthalpies of a total of fifteen licit and illicit drugs are evaluated by a combination of synthetic analysis and group additivity. These include: elemicin, mescaline, myristicin, cocaine, amphetamine, methamphetamine, N-ethylamphetamine, 3,4-methylene-dioxymethamphetamine (MDMA), 5-methoxy-3,4-methylenedioxy-methamphetamine (MMDMA), N,N-dimethyltryptamine, psilocin, bufotenine, 5-methoxybufotenine, serotonin, and melatonin. All estimates lack refinements with regards to stereochemistry and potential chirality but most values evaluated by synthetic analysis with the exception of derivatives of N,N-dimethyltryptamine, include structural refinements with regards to regiochemistry. Agreement between results evaluated by synthetic analysis and group additivity is quite good with an average absolute difference of 0.9 $kJ \cdot mol^{-1}$ and a standard deviation of ± 1.5 $kJ \cdot mol^{-1}$ between the two estimates. The results are compared to experimental or estimated values from the literature when available.

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1. Introduction

While a great deal is known about the physiological properties of numerous licit and illicit drugs, much less information is available in the current literature regarding their thermochemical properties. The illicit nature of some of the substances of this study obviously limits their accessibility. This article estimates the vaporization enthalpies of a series of both liquid and solid drugs at $T = 298$ K, many of which are unavailable. Estimates for the liquid phase at $T = 298$ K are currently not available for most solids, nor are experimental values for ten of the fifteen substances evaluated. For substances that are solids at this temperature, subcooled liquid results at 298 K can be useful for the estimation of other thermodynamic properties. Two methods are used for the vaporization enthalpy estimations of the substances examined, synthetic analysis (SA) and group additivity (GA). Both methods rely on experimental data but differ significantly in their application. Group additivity relies entirely on group values and the target's structure to evaluate vaporization enthalpy while in synthetic analysis, experimental vaporization enthalpies of the synthons generally make the major contribution to the enthalpy, but still require some group values [1]. Group values used in this work are taken mainly from the work of Guthrie and Taylor [2], supplemented by some additional values generated in this and in previous reports [2,3]. Details regarding estimations by

synthetic analysis (SA) are provided below; estimations entirely by group additivity (GA) are included in the Supporting Information (SI), Section S5, (pgs. S10-S16).

Structures of the drugs evaluated are provided in Figure 1. They include elemicin, myristicin, mescaline, cocaine, amphetamine, methamphetamine, N-ethylamphetamine, 3,4-methylene-dioxymethamphetamine (MDMA), 5-methoxy-3,4-methylenedioxymethamphetamine (MMDMA), N,N-dimethyltryptamine, psilocin, bufotenine, 5-methoxybufotenine, serotonin, and melatonin. A brief description of the physiological properties of each drug is also provided. Evaluations by SA are organized in a manner to highlight similarities present in their structure and evaluation. Table 1 includes a list of the synthons used in the synthetic analysis portion of the work. Two of the synthons, N-ethyldimethylamine and methyl isovalerate, were themselves evaluated by SA, from triethylamine and ethyl isovalerate (section S4, pg. S8), respectively.

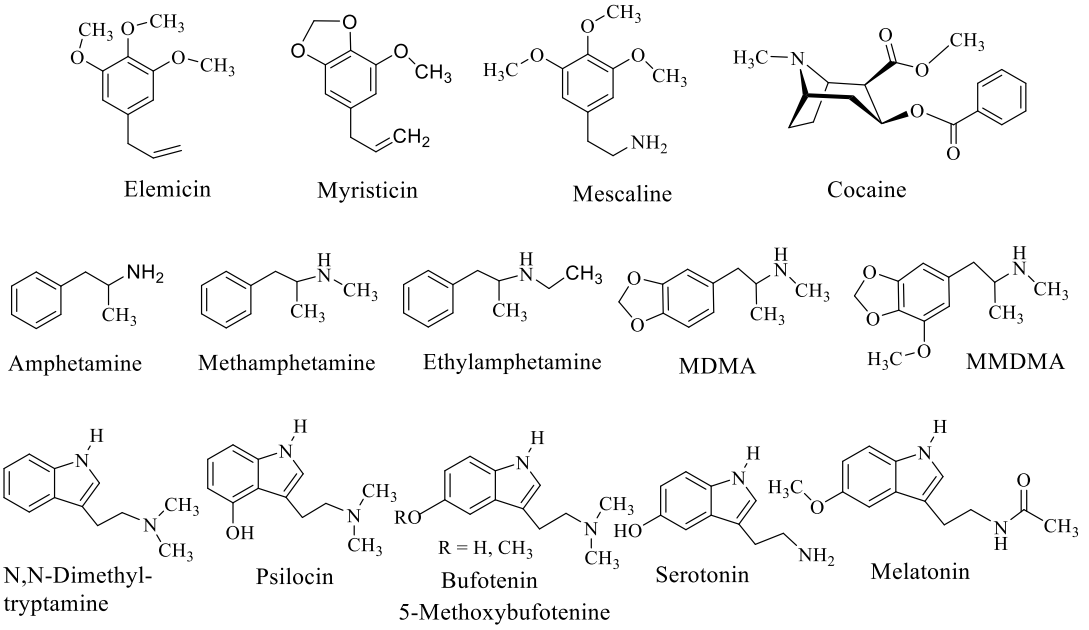


Figure 1. Structure of the drugs of this study.

Table 1. Compounds used as synthons either directly or indirectly

Syn	$\Delta_l{}^g H$(298 K)	Ref	Syn	$\Delta_l{}^g H$(298 K)	
Ethylamine {2} [a,b]	28.1±0.3		Methyl benzoate	55.6±0.1	[10,11]
Butane [b]	22.4±1.0 [c]	[4]	Methyl acetate	32.3±0.1	[12]
1-Pentene	25.5±0.1	[5]	Methyl butanoate {3} [a,b]	40.1±0.6	
Benzene [b]	33.8±0.1		Indole	65.3±0.6	[13]
n-Propylamine	31.3±0.5[c]	[6]	N-Methylpyrrolidene	34.2±0.7	[14]
Isopropyl amine	28.4±0.5[c]	[6]	N-Ethylacetamide	64.8±0.2	[15]
Methyl isopropyl amine	30.7±0.1	[7]	N-Methylpiperidine	36.8±0.6	[16]
Ethyl isopropyl amine	33.1±0.1[b]	[7]	N,N-Dimethyl-N-ethylamine	31.2±0.6 [d]	
3,4,5-Trimethoxytoluene	77.7±0.5	[8]	Triethylamine	35.4±0.2	[17]
5-Methyl-1,3-benzodioxole	54.9±1.2	[9]	Methyl isovalerate	39.8±0.3 [c,e]	

[a] An average of the number of entries. [b] See Table S3 (SI) for references. [c] Uncertainty is an estimate. [d] Evaluated from triethylamine by SA; see Table S8A, SI. [e] Evaluated from ethyl isovalerate by SA; see Table S8B, pg. S8.

An abbreviated listing of the groups and their values used in this work is provided in Table 2. A similar table in the SI includes a more complete listing of available values. Not all group values reported in [1] are included in these tables.

Table 2. Group values from Guthrie and Taylor [**1**] unless noted otherwise ($kJ \cdot mol^{-1}$) [a]

Group	Group Value	(±)	Group	Group Value	(±)
$CH_3(X)$ [b]	5.69	±0.04	$C_B(H)$	5.61	±0.08
$CH_2(C)_2$	5.06	±0.04	$C_B(C)$	4.64	±0.21
$CH_2(C)(C_d)$	5.61	±1.17	$C_B(C_B)$ [f]	4.64	±0.21
$CH_2(C)(C_B)$	3.31	±0.75	$C_B(C_d)$ [f]	4.64	±0.21
$CH_2(C_d)(C_B)$ [c]	4.46	±1.0	$C_B(O)$	4.64	±0.21
$CH_2(C)(CO)$	1.55	±0.54	$C_B(N)$	9.58	±1.05
$CH_2(C)(O)$	3.51	±0.21	$C_dH(N)$ [g]	9.58	±1.05
$CH_2(C)(N)$	1.8	±0.54	$CO(NH)(C)_2$ (5) [h]	51.1	±0.80
$CH_2(O)_2$	0.59	±2.90	$CO(C)_2$	20.0	±0.63
$CH(C)_3$	3.05	±0.13	CO(C)(O)	18.6	±1.84
$CH(C)_2(C_B)$	1.00	±1.00	O(CO)(C)	2.68	±1.84
$CH(C)_2(CO)$	–0.75	±0.84	$O(C)_2$	8.37	±0.33
$CH(C)_2(O)$	0.0	±0.63	(CO)(O)(C)	18.6	±1.84
$CH(C)_2(N)$	–1.84	±0.79	O_pH_{Hos} (14) [i]	26.2	±1.9
$C(C)_3(C_d)$	–1.21	±1.17	$O_pH_{p/sos}$ (16) [i]	20.4	±1.4
$C(C)_3(O)$	–1.55	±1.13	OH···O (intra)	–10.3	±0.75
C_dH_2	4.18	±1.5	O_pH···O (intra)	–7.0	±2.4
$C_dH(C)$	5.15	±1.1	$N(C)_3$	12.0	±1.7
$C_dH(C_B)$ (4) [d]	5.15	±1.1	$NH(C)_2$	15.5	±1.05
$C_dH(C_d)$(6) [e] $C_dC(C_d)$ (2) [e]	6.0	±0.4	$NH(C_B)(C_d)$ [j]	14.0	±2.5
$C_d(C)_2$	4.85	±1.17	$NH(C_B)_2$, [j] $NH(C_d)_2$ [j]	14.0	±2.5
$C_d(C)C_B)$ (2) [d]	5.15	±1.17	$NH_2(C)$	18.1	±0.63

[a] New group values added to reference [**1**] are identified by the number of entries included in parenthesis or by footnotes; additional details are provided in the SI, Tables S4-S7 and the section on validation, Section 3, pp S6-S7; all other values are from [2] and references cited. [b] X = C, O, N, CO,… [c] An average of the values for $CH_2(C)(C_B)$ and $CH_2(C)(C_d)$. [d] For validation see SI, Section 3B. [e] See SI, Table 6A, 6B. [f] For validation see SI, Section 3A. [g] For validation see SI, Section 3C. [h] See Table S7. [i] O_pH_{Hos}: a phenolic hydroxide with adjacent ortho hydrogens; $O_pH_{p/sos}$: a phenolic hydroxide with a single primary or secondary alkyl substituent. [j] For validation see Section 3C, SI pg. S7.

2. Computations

All vaporization enthalpies of the synthons used were experimental values or were evaluated from experimental values. Experimental vaporization enthalpies available at temperatures other than 298 K have been adjusted to this temperature. Details describing the temperature adjustments are provided in Section 1 of the SI. References to the original data not included below are available in the SI. Uncertainties associated with this data represent one standard deviation. Uncertainties associated with both SA and GA calculations were evaluated from the square root of the sum of the squares associated with each substance and/or group value used. The general protocol followed using synthetic analysis has been to first describe the group being added and associated thermochemistry followed by a description of the group removed and its associated thermochemistry.

New group values in Section 2 of the SI were evaluated directly from experimental data using the existing group values reported by Guthrie and Taylor [2]. In section 3 of the SI, existing groups values have been used to model structurally related groups. As examples, the existing value for a $C_B(C)$ group has been used to successfully model both $C_B(C_B)$ and $C_B(C_d)$ groups. Similarly, the existing value for a $C_B(N)$ group has been used to successfully model a $C_dH(N)$ group. In these cases, comparisons of estimates to available experimental data is provided as validation for the use of an existing group value to model a structurally related one. This was necessary due to the limited amount of experimental data available for some groups. Validation was considered satisfied if the value of the predicted results using existing values for the related groups fell within the uncertainty of the experimental vaporization enthalpy value for a minimum of at least two test substances. Details regarding the values evaluated in this manner are identified in Section 3 of the Supporting Information, pp. S6-S7.

Details for estimations entirely by group additivity (GA) are included in Section 5 of the Supporting Information (pp. S10-S17 SI). As an internal check of each calculation, the molar mass of each group is included in evaluating the molecular weight of the target by GA. Comparison of the results are discussed below.

3. Estimation of $\Delta_l^g H$(298 K) for Elemicin and Myristicin by SA

Elemicin and myristicin are natural products found in many herbs and spices such as nutmeg; both exhibit hallucinogenic properties. Elemicin also exhibits some antimicrobial, antioxidant, antiviral activities and is possibly a carcinogen [18]. Figure 2 outlines a synthetic pathway to elemicin starting with 3,4,5-trimethoxytoluene (3,4,5-TMT) [8]. 3,4,5-TMT was chosen as the synthon since it permits control of the regiochemistry of the synthetic analysis. The analysis for elemicin is summarized in Table 3.

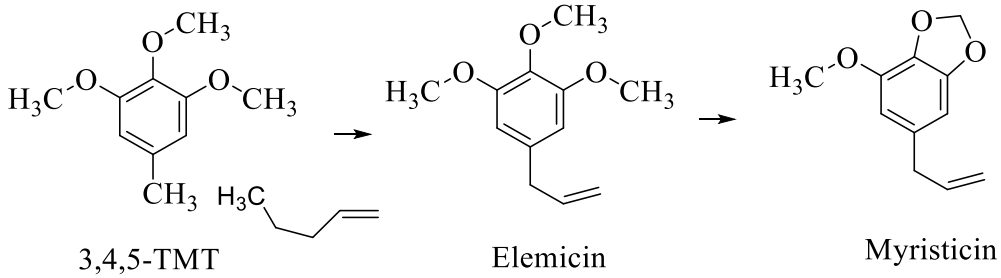


Figure 2. Synthetic pathway to Elemicin and Myristicin

Table 3. SA of Elemicin

Syn/Grp	Value	(±)	$(±)^2$
3,4,5-TMT	77.7	0.5	0.25
1-pentene	25.5	0.1	0.01
$CH_3(C)$	–5.69	0.04	0.02
$CH_2(C)_2$	–5.06	0.04	0.01
$CH_3(C)$	–5.69	0.04	0.02
$CH_2(C_d)(C_B)$	4.46	1.0	1.0
$CH_2(C)(C_d)$	–5.61	1.17	1.4
Elemicin: $\Delta_l^g H$(298 K)/kJ·mol^{-1} (85.6±1.6)			

Table 4. SA of Myristicin from Elemicin

Syn/Grp	Value	(±)	$(±)^2$
Elemicin	85.6	1.6	2. 6
$CH_2(O)_2$	0.59	2.9	8.41
$CH_3(C)$	–5.69	0.04	0.002
$CH_3(C)$	–5.69	0.04	0.002
Myristicin: $\Delta_l^g H$(298 K)/kJ·mol^{-1}			(74.8±3.3)

1-Pentene was chosen as the source of the propenyl side chain of elemicin since its vaporization enthalpy is available at T = 298 K. In the process, an ethyl group is lost in the form of a $CH_3(C)$ and $CH_2(C)_2$ group from the olefin. The former $CH_2(C)(C_d)$ of the allyl group now becomes a $CH_2(C_d)(C_B)$ group in elemicin. Additionally, the methyl group on the aromatic ring is lost and in doing so, controls the regiochemistry of the subsequent addition. Combination of the propenyl group with the aromatic ring, results in a vaporization enthalpy of (85.6±1.7) kJ·mol^{-1}. If 1-butene is used instead of 1-pentene, a value of (85.3±1.7) kJ·mol^{-1} is estimated. Estimation entirely by group additivity, which is not regiospecific, results in a value of (85.8±2.5) kJ·mol^{-1} for elemicin, SI, Table S12.

Myristicin, has proven to be an effective insecticide against many agricultural pests [19]. It has also been used as a precursor to the designer drug, 5-methoxy-3,4-methylenedioxy-methamphetamine (MMDMA) described below. As shown in Figure 2, the second step in the conversion of elemicin to myristicin involves loss of an O-methyl group and subsequent conversion of a second adjacent methyl to a cyclic methylene group and in the process forms a new five membered ring. A vaporization enthalpy of (75.0±3.8) estimated by group additivity which is non-regiospecific (Table S13, SI), compares to the value (74.8±3.3) kJ·mol^{-1} evaluated by SA at 298 K and to an experimental value of (69.4±2.4) [20]. The experimental value was adjusted to 298 K from a mean temperature of 383 K using Eq. (1) and an estimated heat capacity of 331 J·K^{-1}·mol^{-1}. Details of the temperature adjustment are provided in the SI, p. S4.

Vaporization Enthalpy/kJ·mol^{-1}**:**

$$\Delta_l^g H(298\ \text{K}) = \Delta_l^g H(T_m/\text{K}) + [10.58 + 0.26 \cdot Cp_l(298\ \text{K})] \cdot [\Delta T]/1000 \qquad (1)$$

4. Evaluation of $\Delta_l^g H$(298 K) of Mescaline by SA

Mescaline is a drug that has been used recreationally, spiritually and medicinally, going back some 6000 years. Its hallucinogenic effects have been described as similar to LSD [21, 22]. Mescaline is the major component in peyote and acts as a mimic of serotonin. It is considered a Schedule I drug by the US DEA and is therefore illegal to buy, possess, or sell unless used for religious ceremonies in the US by the Native American Church.

Synthetic analysis of mescaline shown in Figure 3 also uses the same precursor, 3,4,5-TMT. The aromatic methyl group plays a similar role in mescaline, controlling regiochemistry. It is replaced by the methyl group of ethyl amine and in the process, the methyl group is converted to a $CH_2(C)(C_B)$ group. The aromatic carbon, $C_B(C)$ remains unchanged. Details are outlined in Table 5. The value evaluated by SA of (97.7±1.0) kJ·mol^{-1} compares to a value evaluated by group additivity of (95.2±1.6) kJ·mol^{-1} at T = 298 K, Table S14, p S11 (SI).

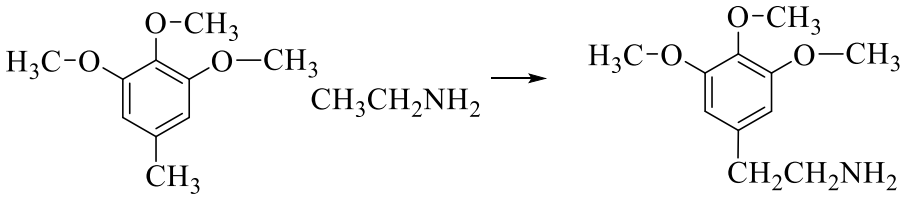


Figure 3. SA of Mescaline

Table 5. Evaluation of $\Delta_l{}^gH$(298 K) of Mescaline

Syn/Grp	$\Delta_l{}^gH$(298 K)	(±)	No.	Total	$(\pm)^2$
3,4,5-Trimethoxytoluene	77.7	0.5	1	77.7	0.25
Ethylamine	28.1	0.3	1	28.2	0.09
$CH_3(C)$	–5.69	0.04	2	–11.4	0.002
$CH_2(C)(C_B)$	3.31	0.75	1	3.31	0.56
Mescaline: $\Delta_l{}^gH$(298 K)/ kJ·mol^{-1}				(97.8±1.0)	

5. Evaluation of $\Delta_l{}^gH$(298 K) of Cocaine by SA

Cocaine was the first local anesthetic used in medicine and is the only naturally occurring one [23]. All other local anesthetics such as lidocaine, benzocaine, and novocaine among others, are synthetic. The suffix -caine has been used in medicine to identify local as opposed to general anesthetics.

In Figure 4, three synthons are required for the synthesis of cocaine. N-Methylpyrrolidine and methyl isovalerate are included in the first step to produce intermediate I. Details of the cycloaddition are described in Table 6. A methyl group is converted to a methylene group and three methylene groups are converted to methine groups. A value of (63.8±1.9) kJ·mol^{-1} is evaluated for intermediate I. The regiochemistry is controlled by the structure of the synthons and the thermochemistry while the correct stereochemistry associated with the orientations of the two ring substituents in Figure 4 is assumed.

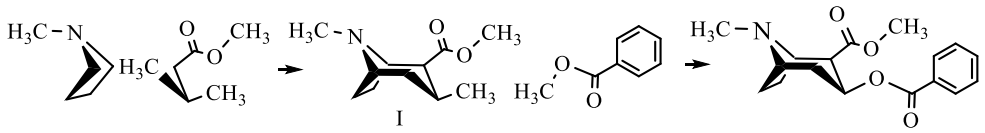


Figure 4. SA of Cocaine

Table 6. Formation of intermediate I

Syn/Grp	Value	(±)	$(±)^2$
N-Methyl pyrrolidine	34.2	0.7	0.49
Methyl isovalerate	39.8	0.3	0.09
$CH_2(C)_2$	5.06	0.04	0.002
$CH_3(C)$	–5.69	0.04	0.002
$CH(C)_2(N)$	–1.84	0.54	0.292
$CH_2(C)(N)$	–1.8	0.79	0.624
$CH(C)_2(N)$	–1.84	0.54	0.292
$CH_2(C)$ (N)	–1.8	0.79	0.624
$CH(C)_2(CO)$	–0.75	0.84	0.706
$CH_2(C)(CO)$	–1.55	0.54	0.292
(I): $\Delta_l^g H$(298 K)/kJ·mol^{-1}	63.8±1.9		

Table 7. Formation of cocaine

Syn/Grp	Value	(±)	No.	$(±)^2$
(I)	63.8	1.9	1	3.61
Methyl benzoate	55.6	0.1	1	0.01
$CH_3(C)$	–5.69	0.04	1	0.002
$CH_3(C)$	–5.69	0.04	1	0.002
$CH(C)_2(O)$	0	0.63	1	0.40
$CH(C)_3$	–3.05	0.13	1	0.002
Cocaine: $\Delta_l^g H$(298 K)/kJ·mol^{-1}	105.0±2.0			

Condensation of I with methyl benzoate in Table 7 results in a vaporization enthalpy of (105.0±2.0) kJ·mol^{-1} for cocaine. The presence of the methyl group on the ring and associated thermochemistry, directs the regiochemistry of attachment of the benzoyl group. Two epimers are possible. In the absence of the methyl group, attachment of the benzoyl group could occur at any of the other available methylene groups in intermediate I with the same thermochemistry. The value of (105.0±2.0) evaluated here compares to values of (107.5±2.0) kJ·mol^{-1} using methyl pentanoate in place of methyl isovalerate by SA, Tables S10 and S11[pg. 9, SI]. These two values compare to a value of (109.4±5.8) kJ·mol^{-1} evaluated by group additivity (Table S15–). An estimated value of (105.5±3.7) kJ·mol^{-1} is predicted by Cheméo Relay [24]. An average of (105.0±2.0) and (105.5±3.7) kJ·mol^{-1} was used in the following estimation of the fusion enthalpy of cocaine.

As noted in the introduction, vaporization enthalpies of solids can still be useful. A sublimation enthalpy of 112.6 kJ·mol^{-1} has been reported for cocaine at a mean temperature of 304 K [25]. Adjusting the sublimation enthalpy of cocaine to T_{fus} = 371. 2 K (98 ˚C), using Eq. (2) and an estimated solid heat capacity of 376.3 J·mol^{-1}·K^{-1}, results in a value of (108.8±0.8) kJ·mol^{-1}. A similar temperature adjustment of the average vaporization enthalpy estimate of (105.3±2.9) kJ·mol^{-1} evaluated using Eq. (1) and an estimated liquid heat capacity of 485.8 J·mol^{-1}·K^{-1} over the temperature range T = (298.15 to 371.2)K results in a temperature adjustment of – (10±2.0) kJ·mol^{-1} and a vaporization enthalpy of (95.0±3.8) kJ·mol^{-1}. A fusion enthalpy of approximately (13.8±2.9) kJ·mol^{-1} at 371.2 K, is estimated for cocaine obtained from the enthalpy difference between the two phases. This assumes the absence of any solid-solid phase transitions occurring

over the temperature interval, T= (298.15 to 371. 2) K. Details of these estimations are provided in the SI (pg.9).

Sublimation Enthalpy/kJ·mol^{-1}**:**

$\Delta_{cr}{}^{g}H(298\ K) = \Delta_{cr}{}^{g}H(T_m/K) + [0.75 + 0.15 \cdot Cp_{cr}(298\ K)] \cdot [\Delta T]/1000$ (2)

6. Evaluation of $\Delta_l{}^{g}H(298\ K)$ of Amphetamine, Methamphetamine and N-Ethylamphetamine by SA

Amphetamine, methamphetamine and ethylamphetamie have been included in this analysis since they are among the few compounds in this study whose vaporization enthalpies at $T = 298$ K have been reported previously [26, 27, 28]. All are synthetic central nervous system stimulants containing a chiral carbon and as a consequence, consist of two enantiomers. Amphetamine has been used recreationally, as a performance enhancer, and as an antidepressant [29]. It has also been used to treat attention deficit hyperactivity disorder, and narcolepsy. Pharmaceutical amphetamine has generally been prescribed as the racemic form since the two enantiomers have similar physiological properties. It is heavily regulated in most countries. In the US it is classified as a schedule II drug. In contrast, the two enantiomers of methamphetamine exhibit significantly different physiological properties. (+)-S Methamphetamine is a potent central nervous system stimulant and is considered a Schedule I drug by the USDEA. (-)-R Methamphetamine primarily acts as a vasoconstrictor and is typically available over the counter as a nasal decongestant [30]. N-Ethylamphetamine, formally available as an appetite suppressant in the 1950s, has also been used for recreational purposes [31]. The vaporization enthalpies of all three amines by synthetic analysis are evaluated as follows:

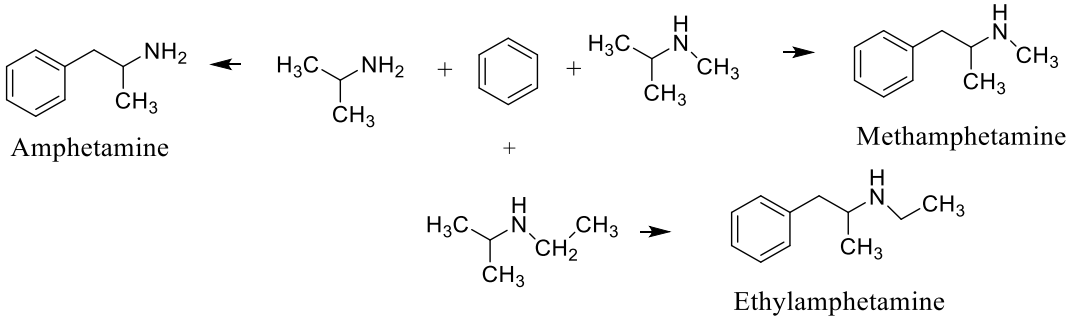


Figure 6. SA of Amphetamine, Methamphetamine and Ethylamphetamine

Table 8. Synthetic analysis of amphetamine

Syn/Grp	Value	(±)	(±)^2
Benzene	33.8	0.1	0.01
Isopropylamine	28.4	0.5	0.25
$C_B(C)$	4.64	0.21	0.0441
$C_B(H)$	–5.61	0.08	0.0064
$CH_2(C)(C_B)$	3.31	0.75	0.563
$CH_3(C)$	–5.69	0.04	0.0016
Amphetamine [a]:			

Table 9. Synthetic analysis of methamphetamine

Syn/Grp	Value	(±)	(±)^2
Benzene	33.8	0.1	0.01
Isopropyl methyl amine	30.7	0.1	0.01
$C_B(C)$	4.64	0.21	0.044
$C_B(H)$	–5.61	0.08	0.006
$CH_2(C)(C_B)$	3.31	0.75	0.56
$CH_3(C)$	–5.69	0.04	0.002
Methamphetamine [a]:			

$\Delta_l^g H_m$(298.15K)/kJ·mol^{-1} (58.9±0.9)	$\Delta_l^g H_m$(298.15K)/kJ·mol^{-1} 61.2±0.8
[a] (58.2±2.7) [26]; GA: (58.0±1.3)	[a] (58.7±4.3 [27]); GA: (61.0±1.6)

Table 10. Synthetic analysis of N-ethylamphetamine

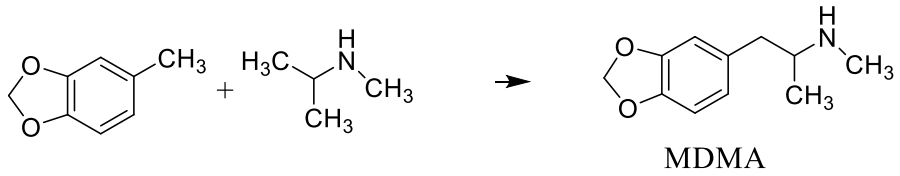
Syn/Grp	Value	(±)	(±)^2
Benzene	33.8	0.1	0.014
Isopropyl ethyl amine	33.1	0.1	0.014
C_B(C)	4.64	0.21	0.0441
C_B(H)	−5.61	0.08	0.0064
CH_2(C)(C_B)	3.31	0.75	0.5625
CH_3(C)	−5.69	0.04	0.0016
N-Ethylamphetamine [a]: $\Delta_l^g H_m$(298.15K)/kJ·mol^{-1} (63.6±0.8)			

[a](62.4±4.4 [28]); GA: (62.8±1.6)

The vaporization enthalpy of all three amphetamines can easily be evaluated by combining benzene with either isopropyl amine, methyl isopropyl amine, or ethyl isopropyl amine, respectively. Figure 6 illustrates the process and Tables 8, 9, and 10 summarize the calculations. The synthesis of all three substances requires the formation of a new C_B(C) group at the expense of C_BH group and conversion of a methyl group to a CH_2(C)(C_B). This results in vaporization enthalpies of (58.9±0.8) for amphetamine, (61.2±0.8) kJ·mol^{-1} for methamphetamine and (63.6±0.8) for ethylamphetamine as evaluated by SA. These values compare to experimental values of values of (58.2±2.7) [26], (58.7±4.3) [27] and (62.4±4.4) [28] kJ·mol^{-1}, respectively. Evaluated entirely by group additivity results in a value of (58.0±1.3) for amphetamine, (61.6±1.6) kJ·mol^{-1} for methamphetamine and (63.6±0.8) for ethylamphetamine (Tables S16, S17, S18, SI, pp. S12, S13, SI, respectively).

7. Evaluation of $\Delta_l^g H$(298 K) of MDMA and MMDMA by SA

2,4-Methylenedioxymethamphetamine, MDMA, commonly referred to as ecstasy or molly, dependent on its form, has been an extremely popular drug [32]. Its structural similarity to methamphetamine is quite evident. Unlike methamphetamine, both enantiomers of MDMA are psychoactive, although they differ in their activity [33]. Synthetic analysis of MDMA begins with 5-methylbenzodioxole using the methyl group to direct the regiochemistry of the synthesis. Condensation of 5-methylbenzodioxole with methyl isopropylamine provides a single step synthesis of the target. This is illustrated in Figure 7 and summarized in Table 11.



MDMA

Figure 7. Synthetic analysis of MDMA

Table 11. SA of MDMA

Syn/Grp	Value	(±)	No.	Value	$(\pm)^2$
5-Methyl 1,3-benzodioxole	54.9	1.2	1	54.9	1.4
Methyl isopropylamine	30.7	0.1	1	30.7	0.01
$CH_2(C)(C_B)$	3.31	0.75	1	3.31	0.56
$CH_3(C)$	−5.69	0.04	2	−11.38	0.006
MDMA: $\Delta_l{}^g H_m$(298.15K)/kJ·mol^{-1}				(77.5±1.4)	

Synthetic analysis of MDMA follows a pattern similar to the synthesis of methamphetamine. In this case, loss of the aromatic methyl group thereby directs the regiochemistry and conversion of one of the methyls of the isopropyl group to a $CH_2C)(C_B)$ group results in a value of (77.5±1.4) kJ·mol^{-1} for MDMA. Estimated by entirely by group additivity results in a value (76.4±3.4) kJ·mol^{-1} (Table S19, SI). A vaporization enthalpy of 70.7 kJ·mol^{-1} at T = 298 K is estimated by Chemeo [24].

5-Methoxy-3,4-methylenedioxymethamphetamine (MMDMA) is one of a series of closely related designer drugs structurally related to MDMA [33, 34]. Like MDMA, MMDMA contains a chiral center. Unlike MDMA, it is not clear whether the enantiomers of MMDMA have been resolved and/or studied individually. While a simple non-regiospecific synthesis of MMDMA can simply be derived directly from MDMA by the substitution of a methoxy substituent for an aromatic hydrogen, a regiospecific synthesis of MMDMA is illustrated in Figure 8 and summarized in Tables 12 and 13.

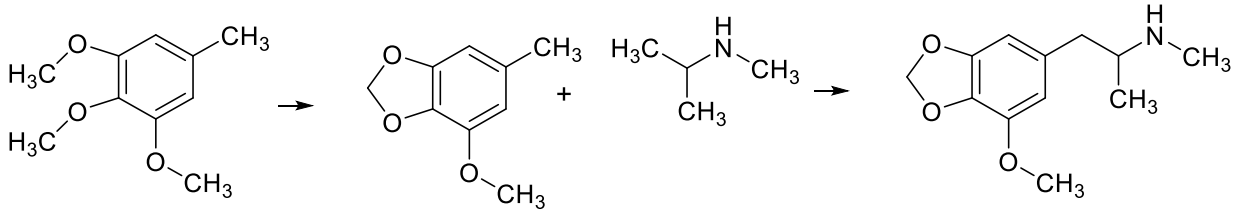


Figure 8. Synthetic analysis of MMDMA regiospecifically

Table 12. SA of III;

Syn/Grp	Value	(±)	$(\pm)^2$
3,4,5-TMT[a]	77.7	0.5	0.25
CH_2O_2	0.59	2.9	8.41
$CH_3(C)$	−5.69	0.04	0.002
$CH_3(C)$	−5.69	0.04	0.002
III: $\Delta_l{}^g H_m$(298 K)/kJ·mol^{-1}		(66.9±2.9)	

Table 13. SA of MMDMA

Syn/Grp	Value	(±)	No.	Tv	$(\pm)^2$
III	66.9	2.9	1	66.9	8.7
MIA[b]	30.7	0.1	1	30.7	0.01
$CH_3(C)$	−5.69	0.04	2	−11.4	0.006
$CH_2(C)(C_B)$	3.31	0.55	1	3.31	0.303
MMDMA: $\Delta_l{}^g H_m$(298 K)/kJ·mol^{-1}				(89.5±3.0)	

[a] 3,4,5-Trimethoxytoluene. [b] Methylisopropylamine

Starting with 3,4,5-trimethoxytoluene, formation of 5-methyl-7-methoxybenzodioxole requires the conversion of a methyl group to a $CH_2(O)_2$ together with the loss of a second adjacent methyl to form intermediate III as summarized in Table 12 and described previously in the synthesis of myristicin. Which methoxy methyl group is lost is irrelevant provided it is an adjacent methyl group that is converted to the $CH_2(O)_2$ group. A value of (66.9±2.9) kJ·mol^{-1} is calculated for III. The reaction with methyl isopropyl amine (MIA) in Table 13 follows the same course as described above for MDMA. A vaporization enthalpy of (89.5±3.0) kJ·mol^{-1} is estimated for MMDMA. Evaluated entirely by group additivity results in a value (89.5±3.5) kJ·mol^{-1} (SI, Table S20).

Conversion of MMDMA to MDMA by removal of the methoxy group, results in MDMA and a value of (76.5±3.0) kJ·mol^{-1}. This compares to the value of (77.5±1.4) kJ·mol^{-1} reported above for MDMA derived from 5-methyl-1,3-benzodioxole. Details of this retrosynthesis are reported in Section 4B of the SI (Table S9, pg. S8).

8. Evaluation of $\Delta_l^g H$(298 K) of N,N-dimethyltryptamine (N,N-DMT), psilocin, bufotenin, 5-methoxybufotenine, melatonin, and serotonin by SA

The last five drugs estimated are all structurally related substances that can be derived from indole; all also affect the central nervous system. N,N-Dimethyltryptamine is a natural product present in many plants and is known for producing brief and intense psychedelic effects in humans. Two of the four remaining substances, psilocin and bufotenine, differ from N,N-dimethyltryptamine by also containing a phenolic hydroxide. Psilocin is a psychedelic drug found in certain species of mushrooms and is responsible for their hallucinogenic effects. The phenolic group in psilocin is located at the 4 position. Bufotenine, also a psychedelic alkaloid, has the phenolic hydroxyl attached at position 5. It is also present in some species of mushrooms, plants and toads. It appears to be produced endogenously in humans and is associated with mental illness, schizophrenia and autism spectrum disorder [35, 36]. Its methyl ether, has been used for centuries in ceremonial practices by Indigenous Peoples in the Amazon and Caribbean [37]. Its effects have been described as the "Mount Everest of psychedelics" [38]. The properties of psychedelics such as bufotenine and its derivatives are currently being investigated amid a resurgence in the study of the use of psychedelics for hard to treat medical health disorders [39]. Seratonin differs from bufotenine by lacking the two methyl groups on nitrogen and melatonin differs from serotonin by methylation of the phenolic hydroxide and by acetylation of the primary amine. Due to the lack of data on appropriately substituted derivatives of indole, the effects of regiochemistry on the thermochemistry associated with the substituent's position on the aromatic ring could not be evaluated.

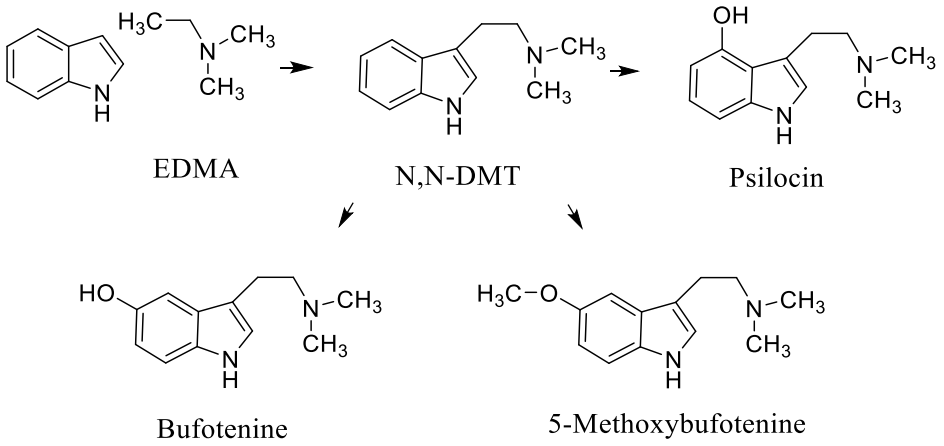


Figure 9. Synthetic analysis of N,N-Dimethyltryptamine, Psilocin, Bufotenine and 5-Methoxybufotenine

Table 14. SA of Compound N,N-DMT

Syn/Grp	Value	(±)	$(±)^2$
Indole	65.3	0.6	0.36
EDMA	31.2	0.6	0.36
$CH_2(C)(C_d)$	5.61	1.17	1.37
$CH_3(C)$	–5.69	0.04	0.002
$C_d(C)(C_B)$	4.85	1.17	1.44
$C_d(H)(C_B)$	–5.15	1.17	1.44
N,N-DMT $\Delta_l{}^g H_m$(298 K)/kJ·mol^{-1}: (96.1±2.2)			

The synthetic analysis of N,N-dimethyltryptamine was achieved by combining indole with N-ethyl-N,N-dimethylamine illustrated in Figure 9 and described in Table 14. In the process a methyl group is converted to a $CH_2(C)(C_d)$ and $C_d(H)(C_B)$ is converted to a $C_d(C)(C_B)$ group. The value for N,N-DMT evaluated by synthetic analysis compares to a value of (96.4±3.8) kJ·mol^{-1}evaluated by group additivity (SI, Table S21)

Table 15. SA of Psilocin/Bufotenine

Syn/Grp	Value	(±)	$(±)^2$
N,N-DMT	96.1	2.2	5.0
O_pH_{HOS}	26.2	1.9	3.61
$C_B(O)$	4.64	0.21	0.044
$C_B(H)$	–5.6	0.08	0.006
Psilocin/ Bufotenine: $\Delta_l{}^g H_m$(298 K)/kJ·mol^{-1}: ≈ (121.4±2.9)			

Table 16. SA of Methoxybufotenine

Syn/Grp	Value	(±)	$(±)^2$
N,N-DMT	96.1	2.2	4.8
CH_3C)	5.69	0.04	0.0016
$O(C)_2$	8.37	0.33	0.1089
$C_B(O)$	4.64	0.21	0.0441
$C_B(H)$	–5.61	0.08	0.0064
5-Methoxybufotenine: $\Delta_l{}^g H_m$(298 K)/kJ·mol^{-1} ≈ (109.2±2.8)			

Since both psilocin and bufotenine are regioisomers that differ from each other by the location of a phenolic hydroxide, the calculation in Table 15 should be considered as a generic value. In psilocin the phenolic hydroxide is located at the 4 position and in bufotenine at the 5-position. It is quite likely that the vaporization enthalpies of the two differ somewhat due to differences in the magnitude of intermolecular hydrogen bonding. An approximate value of (121.4±2.9) kJ·mol^{-1} is estimated for both by SA and (122.0±4.2) kJ·mol^{-1} for both by GA, Table S22 (SI).

The addition of a methoxy group to N,N-dimethyltrypamine in Table 16 produces an approximate vaporization enthalpy of (109.2±2.8) kJ·mol^{-1} for the psychedelic 5-methoxybufotenine. Evaluation of same by group additivity results in an approximate value of (109.8±3.8) kJ·mol^{-1}, Table S22 (SI).

The last two derivatives of indole studied are serotonin and melatonin. Serotonin, which is also hydroxylated at position 5 like bufotenine, regulates appetite, sleep and mood in addition to performing many other functions both in humans and in plants and animals. In humans it is distributed widely throughout the body, including the central nervous system. [40] Its structure is remarkably similar to bufotenine differing only at nitrogen. Control of the location of hydroxylation is not currently possible as noted above.

Hydroxylation of indole at the 5 position is illustrated in Figure 10 and an approximate value is estimated in Table 17 for 5-hydroxyindole. A value of approximately (≈90.4±2.0) kJ·mol^{-1} is estimated which when condensed with ethylamine as summarized in Table 18, results in an approximate value of (≈118.1±2.8) kJ·mol^{-1} for serotonin. A similar approximate value of (≈116.1±3.9) kJ·mol^{-1} is estimated by group additivity, Table S23 (pg. 16, SI).

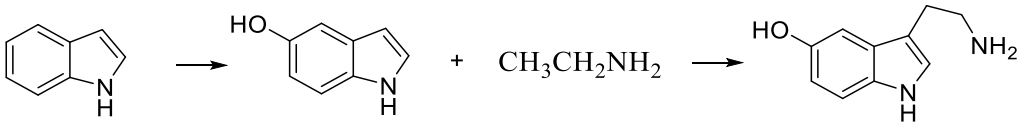


Table 17. SA of Hydroxyindole

Syn/Grp	Value	(±)	(±)^2
Indole	65.3	0.6	0.36
O_pH_{HOS}	26.2	1.9	3.6
$C_B(O)$	4.64	0.21	0.04
C_BH	–5.61	0.04	0.01
Hydroxyindole: (≈90.4±2.0) kJ·mol^{-1}			

Table 18. SA of Seratonin

Syn/Grp	Value	(±)	(±)^2
Hydroxyindole	90.4	2.0	4.0
N-Ethylamine	28.1	0.30	0.09
$CH_2(C)(C_d)$	5.61	1.17	1.4
$CH_3(C)$	–5.69	0.04	0.001
$C_d(C)(C_B)$	4.85	1.1	1.21
$C_d(H)(C_B)$	–5.15	1.1	1.21
Seratonin:	(≈118.1±2.8) kJ·mol^{-1}		

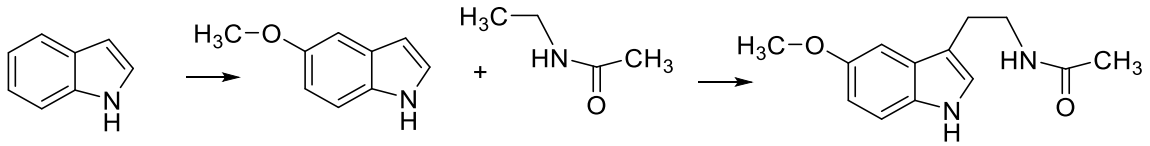


Table 19. $\Delta_l^g H_m$(298 K) of 5-methoxyindole

Syn/Grp	Value	(±)	$(±)^2$
Indole	65.3	0.6	0.36
$CH_3(C)$	5.69	0.04	0.002
$O(C)_2$	8.37	0.33	0.11
$C_B(O)$	4.64	0.21	0.044
$C_B(H)$	–5.61	0.08	0.006
5-Methoxyindole: ≈78.4±0.7) kJ·mol^{-1}			

Table 20. $\Delta_l^g H_m$(298 K) of melatonin

Syn/Grp	Value	(±)	$(±)^2$
5-Methoxyindole	≈78.4	0.7	0.49
N-Ethylacetamide	64.8	0.2	0.04
$CH_2(C)(C_d)$	5.61	1.17	1.37
$CH_3(C)$	–5.69	0.04	0.002
$C_d(C)(C_B)$	4.85	1.17	1.21
$C_d(H)(C_B)$	–5.15	1.1	1.21
Melatonin:	(≈142.8±2.1) kJ·mol^{-1}		

Melatonin is a naturally occurring hormone produced in the brain and involved in sleep-wake cycles. It is used as medication for treatment of disrupted sleep patterns such as in jet lag [41]. Synthetic analysis of melatonin also begins with the evaluation of 5-methoxyindole. This is described in Table 19. The introduction of a methoxy group at the 5 position of indole is estimated to produce a material with a vaporization enthalpy of ≈ 78.4 kJ·mol^{-1}. The correct regiochemistry here is assumed. Condensation of N-ethylacetamide at the terminal methyl of the ethyl group of the amide to carbon 3 of 5-methoxyindole results in a vaporization enthalpy of ≈ (142.8±2.1) kJ·mol^{-1} for melatonin (and its regioisomers). Similarly by group additivity, using the group value for a secondary amide, (51.1±0.8) kJ·mol^{-1}, a value of (143.2±3.5) kJ·mol^{-1} is evaluated for melatonin (Table S24, p. S16). While melatonin is a commercially available solid with a melting temperature of 390 K, evaluation of its vaporization enthalpy experimentally at T= 298 K would be a challenging objective.

Discussion

The vaporization enthalpies of a series of licit and illicit drugs have been estimated by a combination of synthetic analysis and group additivity. Table 21 summarizes all estimates. Values by both methods appear to agree within the uncertainties reported. The average absolute error between SA and GA values was 1.0 kJ·mol^{-1} and ± 1.6 kJ·mol^{-1} represents the standard deviation between the two estimates.

Table 21. A summary of the vaporization enthalpies estimated by SA and GA (kJ·mol^{-1})

Drugs	SA	GA	Drugs	SA	GA
Elemicin	85.6±1.6	85.8±2.4	MDMA[b]	76.4±3.0	76.4±3.4
Myristicin	74.8±3.3	75.0±3.8	MMDMA	89.5±3.0	89.5±3.5
Mescaline	97.8±1.0	95.2±1.6	N,N-DMT	96.1±2.2	96.4±3.8
Cocaine	105.0±2.0	109.4±5.8	Psilocin	≈121.4±2.9	≈121.7±4.2

Amphetamine	58.9±0.9	58.0±1.3	Bufotenine	≈121.4±2.9	≈121.7±4.2
Methamphetamine	61.2±0.8	61.0±1.6	5-Methoxybufotenine	≈109.2±2.8	≈109.5±3.8
Ethylamphetamine	63.6±0.8	62.8±1.7	Seratonin	≈118.2±2.8	≈115.8±3.9
MDMA[a]	77.5±1.4	76.4±3.4	Melatonin	≈142.8±2.2	≈142.9Cd(±3.5

[a] From 5-methyl-1,3-benzodioxole. [b] From 3,4,5-trimethoxytoluene.

The use of the same group values in both SA and GA estimations and the good agreement obtained between the two methods, may introduce some concern regarding their independence. In an effort to address this concern, the sum of the enthalpy contributed by the synthons and by the group values were segregated and are reported separately in Table 20 for each drug. Columns 2 and 5 of the table identify the total enthalpy and associated uncertainty contributed by the synthons; similarly in columns 3, and 6, the corresponding total contributions by the group values are displayed. The net contributions made by the group values are in most instances small and range from negative to positive values depending on the compound and synthetic pathway chosen.

Table 22. Individual contributions provided by the synthons and group values to the total $\Delta_l^g H_m$(298 K)/(kJ·mol^{-1}) evaluated by SA

	Synthons	Group Values		Synthons	Group Values
Elemicin	103.2±0.5	-17.6±1.5	N,N-DMT[a]	96.5±0.8	-0.38±2.0
Myristicin	103.2±0.7	-28.4±3.3	MDMA[b]	85.6±2.2	-8.1±0.8
Mescaline	105.8±0.6	-8.1±0.8	MDMA[c]	108.4±0.5	-32.0±3.0
Cocaine	129.6±0.8	-24.6±1.8	MMDMA	108.4±0.5	-18.9±3.0
Amphetamine	62.2±0.05	-3.4±0.8	Psilocin	96.1±0.8	24.9±2.8
Methamphetamine	64.5±0.14	-3.4±0.8	Bufotenine	96.1±0.8	24.9±2.8
Ethylamphetamine	66.9±0.14	-3.4±0.8	Seratonin	93.4±0.7	24.9±2.8
5-MeO-Bufotenine	96.1±0.8	13.1±2.8	Melatonin	130.1±0.8	12.7±2.0

[a]N,N-Dimethyltryptamine [b] From 5-methylbenzodioxole; [c] From 3,4,5-TMT via MMDMA.

Perhaps the strongest support that the two estimations are independent support that the two estimations are independent comes from the observations that for dimethyl tryptamine, contributions by the group values cancel, and from the two values results evaluated for MDMA, where two independent synthetic routes requiring significantly different group value contributions result in enthalpies that are in good agreement.

Only one synthesis by SA has generally been reported in this work. A number of compounds however, have been evaluated using alternative synthetic pathways and synthons. Results have generally been reproduced within the uncertainties cited. The results reported here are those that provided the best reproduction of regiochemistry. It is somewhat surprising that in the cases examined by multiple pathways, the results did not seem particularly sensitive to regiochemistry given the typical uncertainties associated with these estimations. Mescaline as an example, estimated by SA from 2-phenethylamine and three methoxy groups with a total disregard of

regiochemistry, results in a vaporization enthalpy of (96.9±1.9) kJ·mol^{-1} compared to (97.8±1.0) kJ·mol^{-1} evaluated for the regiospecific isomer (SI pg.17). It should also be noted, that differences due to stereochemistry are not addressed in this work and that this is another factor that can certainly influence the values reported.

The combination of SA and GA appears to be a promising approach for evaluating physical properties that exhibit group behavior [42]. This approach seems useful for substances that may be difficult to evaluate experimentally either because of size, availability or stability. SA may also be useful for identifying experimental measurements that may be unreliable provided alternative synthetic pathways can be devised for evaluation of the material in question. As measurements of potential synthons become available, it should be possible to refine the estimates of materials that currently have roadblocks for their evaluation.

Declarations
Ethical Approval. Not applicable

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Availability of data and materials: All relevant data is provided in the Supporting Information

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5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a tryptamine with psychedelic properties. It is found in a wide variety of plant species, and a single psychoactive toad species, the Colorado River toad. This drug, as well as dimethyltryptamine and bufotenin, have been registered to be used in South America in religious and spiritual rituals. https://go.drugbank.com/drugs/DB14010

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