AIChE

THERMODYNAMICS AND MOLECULAR-SCALE PHENOMENA

Estimation of Sublimation Enthalpies of Solids Constituted by Aromatic and/or Polycyclic Aliphatic Rings by Using a Group Contribution Method

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A group contribution (GC) method is developed to predict the sublimation enthalpy of only any compound constituted with polycyclic aromatic hydrocarbons and/or polycyclic aliphatic rings with an average absolute relative deviation of 8.98% and an average absolute error of 9.22 kJ·mol^{-1}. A statistical analysis (ANOVA table) and two validation tests are performed to show the consistency of the method. This GC method can speed up several processes in which it is required the value of the sublimation enthalpy of a solid with these characteristics (pharmaceuticals for instance). However, this method must not be used with inorganic compounds or organic solids with noncyclic structure. © 2011 American Institute of Chemical Engineers *AIChE J,* 58: 2875–2884, 2012

Keywords: sublimation enthalpies, group contribution, pharmaceuticals, polycyclic aromatic hydrocarbons

Introduction

Solid sublimation enthalpy is an important and required property for several thermodynamics applications. Its value is needed in different thermodynamic cycles to study the molecular mechanism of solvation of drug molecules.[1–4] Furthermore, if it is desired to depict a solid–vapor equilibrium diagram, the sublimation pressure must be known. This pressure can be determined by a Clausius–Clapeyron equation, but to use this equation the sublimation enthalpy must be determined.[5,6]

Although several articles in relation to these topics have been published in these last years,[1–8] and there are several database of sublimation enthalpies,[9–11] there is not a group contribution (GC) model to estimate this type of enthalpies for solids like pharmaceuticals. In addition, there are additional problems due to the transitions in the solid phase, avoiding the existence of generalized correlations.[12] Therefore, the value of the required enthalpy must be determined experimentally, although it can be determined with the fusion and vaporization enthalpies of the solid.

Theoretically, the sublimation enthalpy can be considered as the sum of the fusion and the vaporization enthalpies.[9,13] With a low variation, these values can be considered temperature independent, so that this approach is usually used to calculate the sublimation enthalpy. As there are methods to estimate fusion enthalpy,[14,15] it would be only necessary to determine the vaporization enthalpy.

However, there are not estimations for vaporization enthalpies of pharmaceuticals, although there are databases[9,16] and estimations to determine the value of this property for hydrocarbons and more organic compounds.[17] In this context, a work was recently published[18] in which this enthalpy was directly determined (with a deviation around a 10%) fitting experimental solubility data of solids in supercritical fluids (SCFs) using Bartle's semiempirical model.[19] In this equation, a term is related to the sublimation enthalpy of the solid given that the sublimation pressure appears on the development of the model. However, when it is performed a comparison between experimental sublimation enthalpies and calculated sublimation enthalpies from Bartle's model (calculated at high pressure and in the presence of a SCF), the calculated values were always around a 60–70% of the experimental value,[20,21] nearer to the value of the vaporization enthalpy of the solid.

A possible explanation might be that, at high pressures and in the presence of a SCF, this equation predicts a lower value of the sublimation enthalpy (near the vaporization enthalpy of the compound), given that at these conditions the solid might even melt at a lower temperature due to the melting point depression.[22]

The aim of this work is to develop a consistent GC method to estimate the sublimation enthalpy of pharmaceuticals, based only on the structural form of the molecule. This method might be used to speed up processes in which the sublimation enthalpy should be determined to study the solvation process of pharmaceuticals or to determine the sublimation pressure of the solid by means of a Clausius–Clapeyron equation.

It can be found in literature several GC methods to estimate properties of pure compounds.[23,24] However, there is not a GC method for estimating sublimation enthalpies of pharmaceuticals.

Although it is difficult to establish a boundary between drugs and other organic solids, drugs are usually constituted

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by aromatic hydrocarbons and/or cyclic molecules. Therefore, the GC was developed by building a set of 253 compounds of polycyclic aromatic hydrocarbons (PAHs) and different compounds constituted by PHAs and/or polycyclic aliphatic rings to define the values of the sublimation enthalpies for the most common groups in this type of compounds.

Methodology

The creation of this type of models should be first oriented on the molecular crystals with definite structures with a known value of their sublimation enthalpies with the aim of creating a first set of data.

Therefore, a set of values of sublimation enthalpies for 253 compounds was built. All of them present PAHs and/or polycyclic aliphatic rings in their molecular structures, considering that these are the groups that can be commonly found in pharmaceuticals. There are neither noncyclic molecules nor inorganic compounds in this set.

The methodology to obtain these sublimation enthalpies is the following:

1. Values of sublimation enthalpies were directly collected from literature (mainly from databases[9,10]), neglecting the unreasonable low reported values or
2. Sublimation enthalpies were considered as the sum of the fusion enthalpy and the vaporization enthalpy. If the sublimation enthalpy is calculated, then,
    - 2.1. Fusion enthalpies were collected from literature or were determined using a GC method and
    - 2.2. Vaporization enthalpies were estimated modeling experimental solubility data solid-SCFs with Bartle's semiempirical equation (SE). This model (Eq. 1) establishes a relation between the enhancement factor (ratio of the actual solubility to the ideal solubility, but changing P^{sub} for P^{ref} and adding a ρ_{ref}) of the solute and the density of the solvent. The equilibrium molar fraction of the solid in supercritical CO_2 is denoted with y_2. The value of P_{ref} is taken as 1 bar, whereas the reference density ρ_{ref} is taken as 700 kg m^{-3} (around the density value of the CO_2 at supercritical conditions) because the solvent is always supercritical CO_2. The parameters A, B, and C must be determined with a regression between experimental data and theoretical data to obtain the best fit. Initially, the value of the sublimation enthalpy is related to the parameter B, ($B = -\Delta H^{\text{sub}}/R$).[19–21]

$$\text{Ln}\left(y_2 \cdot \frac{P}{P_{\text{ref}}}\right) = A + \frac{B}{T} + C \cdot (\rho - \rho_{\text{ref}}) \qquad (1)$$

However, when it is performed a comparison between the enthalpies given by this model and the experimental enthalpies, the estimated values are always lower than the experimental values. Actually, the experimental values are always nearer than the vaporization enthalpy of the solid.[20,21] A possible explanation might be the melting point depression. In the presence of a SCF (high pressure), the solid melting temperature can decrease significantly.[22] Therefore, it might be considered that the solid can melt, and the value of the enthalpy would be the vaporization enthalpy instead of the sublimation enthalpy,[18] being thus the vaporization enthalpy ($\Delta H^{\text{vap}} = B{\cdot}R$). An example of this calculation can be found in the Appendix. It is important to take into account several limitations in this methodology to calculate sublimation enthalpies:

1. The vaporization enthalpies were obtained fitting experimental solubility data of solids in sc-CO_2 with a semiempirical model. The use of a semiempirical model can provide an important deviation if the experimental conditions reach an upper critical end point. This phenomenon might induce an error in the value of the vaporization enthalpy.[25]
2. If the fusion enthalpy is determined with a GC model, a deviation can be produced in the outcome due to the error of the method.[14,15]

To avoid the previous error sources, the values of the calculated enthalpies were evaluated, discarding the solids with a value of the fusion enthalpy more than 1/3 of the sublimation enthalpy. Although Poling et al.[12] established the previous value less or equal than 1/4, this value was increased to 1/3 because 1/4 might not be valid for all compounds.[9] Finally, the enthalpies were considered temperature independent.

With these assumptions, values of sublimation enthalpies for 253 solids were collected and were divided into functional groups, defining 41 different groups. These groups are the most common in this type of solids and were chosen because all of these molecules can be structurally defined with these functional groups. The chosen solids have a high average value of carbon atoms (around 10), and the frequency of repetition in most of the mainly groups is high.

It is important to realize that the goal is to develop a method only for solids constituted by PAHs and/or polycyclic aliphatic rings. Therefore, it is also important to highlight that this method will not be able to predict sublimation enthalpies of inorganic molecules or solids with noncyclic structures.

Table 1 depicts the chosen compounds. If the value of the sublimation enthalpy is collected from literature, the reference and the conditions (if they are available in the corresponding article) are specified.

On the other hand, if the sublimation enthalpy is calculated with the methodology previously described, the vaporization enthalpy is calculated with Bartle's SE, and the respective reference for the solubility data of this solid in supercritical CO_2 is given. Finally, the method to determine the value of the fusion enthalpy (if it is used a GC or from literature) is indicated.

In that table, it is possible to observe that the sublimation enthalpies of 225 compounds were directly taken from experimental works or from different databases. The remaining sublimation enthalpies (28 compounds) were calculated using fusion and vaporization enthalpies.

When more than two values for the same compound are presented in the correspondent databases, it was chosen the suggested value (if it is indicated[9,10]) or the value when the conditions are near to 298 K. On the other hand, when the solid vaporization enthalpy is calculated from solubility data, the solubility data are always at high pressure (more than 70 bar) and at temperatures higher than 300 K.

Finally, the multiple linear regression with a least squares method was performed with the aim of determining the values of each of the groups.

Results and Discussion

The values for the 41 groups are given in Table 2. Subscripts apr and ar denote aliphatic ring and aromatic ring,

Table 1. Set of Compounds

Compounds	Temp. Range (K)	Fusion Enthalpy (kJ mol^{-1})	Vaporization Enthalpy (kJ mol^{-1})	Sublimation Enthalpy (kJ mol^{-1})	References
[4-(Benzyloxy)phenyl] acetic acid	–	–	–	106.4	26
1-(3-Nitrophenyl)-1*H*-pyrrole-2,5-dione	(350–370)	–	–	115.7	10
1,1,1,2-Tetraphenylethane	298	–	–	132.6	10
1,1,1-Triphenylethane	298	–	–	108.6	10
1,1′-Diphenyl-1,1′-bicyclopentyl	–	–	–	141.4	10
1,2,3,4,4a,7,8,9,10,11,12,12a-Dodecahydrochrysene	(293–313)	–	–	115.4	10
1,2,3,6,7,8-Hexahydropyrene	398	–	–	92.3	10
1,2:4,5-Dibenzopyrene	298	–	–	155.2	9
1,2:5,6-Dibenzanthracene	298	–	–	149.0	9
1,2-Benzodiphenylene sulfide	349	–	–	111.9	10
1,2-Dimethylbenzene	248	–	–	60.1	10
1,2-Dimethylnaphthalene	–	–	–	84.0	7
1,3,5-Triazine	298	–	–	54.2	10
1,3,5-Triethiane	298	–	–	93.2	10
1,3,5-Triphenylbenzene	298	–	–	149.8	9
1,3,5-Tri-*tert*-butylbenzene	298	–	–	81.2	10
1,3-Diamino-2,4,6-trinitrobenzene	298	–	–	143.5	10
1,3-Dimethyl-5-ethyluracil	(312–321)	–	–	98.7	10
1,3-Dithiolan-2-one	–	–	–	80.3	10
1,4-Benzenedicarboxamide	(373–498)	–	–	57.3	10
1,4-Bromoiodobenzene	(279–355)	–	–	78.5	10
1,4-Chloroiodobenzene	(259–320)	–	–	71.9	10
1,4-Diaminobenzene	298	–	–	92.2	10
1,4-Di-*tert*-butylbenzene	298	–	–	82.8	10
1,5-Diphenyltetrazole	343	–	–	119.7	10
1,*N*-Dimethylcytosine	(401–426)	–	–	132.8	10
1-Amino-4-hydroxy-2-phenoxy-9,10-anthraquinone	(359–366)	–	–	152.2	10
1-Amino-cyclopentanecarboxylic acid	298	–	–	77.6	10
1-Hydroxypyrene	382	–	–	129.0	10
1-Naphthalenamine	–	–	–	90.0	10
1-Naphthol	–	–	–	91.2	7
1-Naphtholic acid	–	–	–	110.4	7
1-Nitroanthraquinone	396	–	–	115.5	10
1-Phenyldodecane	298	–	–	135.1	10
2,2,4,4-Tetramethyl-1,3-cyclobutanedione	–	–	–	70.3	10
2,2′-Bipyridine	298	–	–	81.8	10
2,2′-Biquinoline	298	–	–	134.7	10
2,3-Benzofluorene	298	–	–	122.0	9
2,3-Benzothiophene	(273–403)	–	–	65.7	10
2,3-Dichloropyridine	298	–	–	73.5	10
2,3-Dimethyl-2,3-diphenylbutane	320	–	–	96.7	10
2,3-Diphenylbutane	326	–	–	96.7	10
2,4,5,7-Tetramethylphenanthrene	–	–	–	114.2	10
2,4,6-Triisopropylbenzophenone	298	–	–	116.0	10
2,4,6-Tri-*tert*-butylaniline	298	–	–	92.5	10
2,4,6-Tri-*tert*-butylnitrosobenzene	298	–	–	96.4	10
2,5-Dihydroxybenzoic acid	–	–	–	109.0	10
2,5-Dinitrophenol	306	–	–	93.4	10
2,6-Dibromopyridine	298	–	–	85.6	10
2,6-Di-*tert*-butylphenol	298	–	–	92.9	10
2,6-Methoxybenzoic acid	298	–	–	129.8	10
2-Acetylnaphthalene	305	–	–	84.0	7
2-Amino-3-methylbenzoic acid	298	–	–	107.3	10
2-Aminoanthraquinone	–	–	–	136.8	10
2-Aminophenol	298	–	–	98.8	10
2-Aminotropone	(273–333)	–	–	71.1	10
2-Bromonaphthalene	298	–	–	81.2	10
2-Chlorobenzoic acid	298	–	–	100.9	10
2-Ethylimidazole	298	–	–	89.6	10
2-Fluorobenzoic acid	298	–	–	94.4	10
2-Hydroxybenzoic acid	–	–	–	95.5	2
2-Imidazolidinone	298	–	–	103.2	10
2-Iodobenzoic acid	298	–	–	92.6	10
2-Methylphenol	288	–	–	76.0	10
2-Methylthio-4-ethylamino-6-isopropylamino-1,3,5-triazine	338	–	–	100.9	10
2-Nitroaniline	(310–319)	–	–	90.0	10
2-Phenylquinoline	298	–	–	105.4	10

(*Continued*)

Table 1. (Continued)

Compounds	Temp. Range (K)	Fusion Enthalpy (kJ mol^{-1})	Vaporization Enthalpy (kJ mol^{-1})	Sublimation Enthalpy (kJ mol^{-1})	References
2-Pyridinecarboxamide	298	–	–	93.0	10
2-Pyridinecarboxylic acid	298	–	–	91.0	10
2-Thiouracil	–	–	–	129.3	10
3,4:9,10-Dibenzopyrene-5,8-quinone	–	–	–	112.5	10
3,5-Dichlorophenol	298	–	–	82.8	10
3,5-Dimethylpyrazole	298	–	–	83.4	10
3,5-Di-*tert*-butylbenzoic acid	348	–	–	108.4	10
3-Bromobenzoic acid	298	–	–	99.2	10
3-Cyanopyridine	–	–	–	72.1	10
3-Methylcholanthrene	413	–	–	127.2	10
3-Nitrobenzoic acid	298	–	–	110.0	10
4-Aminopyridine	–	–	–	87.1	10
4-Benzylphenol	(313–335)	–	–	97.4	10
4-Bromophenol	(260–302)	–	–	87.3	10
4-Chlorobenzoic acid	298	–	–	107.9	10
4-Diacetylbenzene diethyl ketal	316.5	–	–	112.5	10
4-Dimethylaminoantipyrine	–	GC[14,15]	SE[27]	80.2	–
4-Ethylphenol	(278–317)	–	–	84.0	10
4-Isopropylaminodiphenylamine	335	–	–	120.7	10
4-Methylthiopyridine	365	–	–	75.3	10
4-Phenylpyridine	298	–	–	81.4	10
4-*tert*-Butyl phenol	298	–	–	85.9	10
5,12-Dihydrotetracene	298	–	–	118.9	9
5,12-Tetracenequinone	–	–	–	108.8	10
5,6-Dimethylchrysene	394	–	–	135.0	10
5,7-Dichloro-8-hydroxyquinoline	298	–	–	109.3	10
5-Aminotetrazole	(383–443)	–	–	112.6	10
5-Bromouracil	–	–	–	128.4	10
5-Iodo-7-chloro-8-hydroxyquinoline	(383–414)	–	–	131.0	10
6,13-Pentacenequinone	298	–	–	116.3	10
6-Azauracil	–	–	–	141.0	10
8-Azaadenine	(418–463)	–	–	128.4	10
9,10-Anthraquinone	298	–	–	107.9	10
9,10-Diphenylanthracene	298	–	–	170.0	9
9,9-Bifluorenyl	298	–	–	134.0	9
9,9′-Biphenanthryl	–	–	–	151.5	10
9-Amidoanthracene	461	–	–	134.8	10
9-Aminoacridone	–	–	–	115.0	10
9-Ethylhypoxanthine	–	–	–	108.8	10
9-Methyl carbazole	298	–	–	95.5	10
9-Methyl fluorene	298	–	–	82.8	10
9-Methylanthracene	–	–	–	98.9	10
9-Phenylanthracene	298	–	–	120.5	9
Acenaphthacene	298	–	–	84.8	9
Acenaphthylene	298	–	–	72.5	9
Acetaminophen	–	–	–	117.9	8
Acetanilide	(317–336)	–	–	99.8	10
Acridine	298	–	–	92.0	10
Acridone	–	–	–	136.2	10
Alfa-terpineol	(283–328)	–	–	80.3	10
Alfatocopherol	–	GC[14,15]	SE[28]	102.2	–
Aminobenzoic acid	298	–	–	111.6	10
Anastrozole	–	GC[14,15]	SE[29]	129.4	–
Anthanthrone	465	–	–	152.2	10
Anthracene	298	–	–	101.9	9
Anthranthrene	479	–	–	135.0	10
Anthrone	298	–	–	106.1	10
Aspirin	–	–	–	109.7	30
Astaxanthina	–	GC[14,15]	SE[31]	138.2	–
Atorvastatin	–	GC[14,15]	SE[32]	167.4	–
Barbituric acid	(294–438)	–	–	111.3	10
Benzanilide	360	–	–	99.2	10
Benzanthrone	298	–	–	126.6	10
Benzene	298	–	–	44.7	9
Benzenemethanol	298	–	–	105.7	10
Benzil	329	–	–	98.4	10
Benzimidazole	(340–359)	–	–	102.2	10
Benzofurazan	298	–	–	64.4	10
Benzoic acid	298	–	–	88.3	10
Benzo[*e*]pyrene	298	–	–	122.5	9

(*Continued*)

Table 1. (Continued)

Compounds	Temp. Range (K)	Fusion Enthalpy (kJ mol^{-1})	Vaporization Enthalpy (kJ mol^{-1})	Sublimation Enthalpy (kJ mol^{-1})	References
Benzo[*ghi*]perylene	298	–	–	132.9	9
Benzophenone	298	–	–	93.1	10
Benzoxazole	–	–	–	69.5	10
Beta-carotene	–	–[33]	SE[28]	128.7	–
Binaphthalene	383	–	–	138.3	10
Biphenyl	298	–	–	82.1	9
Biphenylene	298	–	–	83.8	9
Butylparaben	–	–	–	108.4	3
Caffeine	(413–463)	–	–	105.1	10
ε-Caprolactam	298	–	–	87.3	10
Cholesterol	–	–[34]	SE[34]	114.6	–
Chromone	298	–	–	81.3	10
Coronene	298	–	–	143.0	9
Coumarin	(293–353)	–	–	83.1	10
Cyanuric acid	298	–	–	131.0	10
Cyclotetradecane	298	–	–	134.8	10
Cytosine	298	–	–	147.2	10
Desoxybenzoin	–	–	–	99.3	10
Dibenzofuran	298	–	–	84.4	10
Dibenzosuberone	298	–	–	109.3	10
Dibenzoylmethane	298	–	–	115.7	10
Dibenzyl	298	–	–	84.0	26
Dibenzyl sulfide	–	–	–	93.3	10
Dibenzyl sulfone	–	–	–	125.5	10
Dibenzylideneazine	298	–	–	93.3	10
Diflunisal	–	–	–	120.1	21
Dimethylparaben	–	–	–	100.9	3
Diphenyl oxalate	–	–	–	102.5	10
Diphenylfulvene	–	–	–	104.6	10
Diphenylmethane	298	–	–	87.2	26
Eflucimibe	–	GC[14,15]	SE[35]	157.9	–
Examestane	–	GC[14,15]	SE[29]	122.8	–
Fluorene	298	–	–	86.5	9
Flurboprifen	–	–	–	104.9	21
Fluvastatin	–	GC[14,15]	SE[32]	136.1	–
Formanilide	(298–318)	–	–	77.8	10
Fuflenamic acid	–	–	–	119.4	4
Glutarimide	298	–	–	94.1	10
Hexacyclopropylethane	–	–	–	109.0	10
Hexaethylbenzene	340	–	–	95.0	10
Hexamethoxycarbonylbenzene	298	–	–	154.3	10
Ibuprofen	–	–	–	115.8	36
Imidazole	(292–309)	–	–	83.4	10
Indane	298	–	–	55.4	9
Indene	298	–	–	61.8	9
Iodobenzene	(243–255)	–	–	43.1	10
Irgacure	–	GC[14,15]	SE[37]	110.2	–
Ketoprofen	–	–	–	112.0	21
Letrozole	–	GC[14,15]	SE[29]	129.9	–
Lidocaine	–	GC[14,15]	SE[38]	104.8	–
Lovastatin	–	GC[14,15]	SE[32]	90.6	–
Medroxyprogesterone acetate	–	–[40]	SE[39]	92.1	–
Methimazole	–	–[40]	SE[41]	87.2	–
Methyl benzyl sulfone	–	–	–	99.2	10
Methyl-2-aminobenzoate	292.5	–	–	78.4	10
Methylbiphenyl	298	–	–	80.2	10
Methyparaben	–	–	–	98.8	3
N-Phenyl benzephenone imine	298	–	–	115.5	10
N,*N*′-Bis-(2-methoxyphenyl)terphthalamide	–	–	–	197.5	10
N,*N*-Diphenylacetamide	358	–	–	122.7	10
Naphthacene	298	–	–	135.9	9
Naphthalene	298	–	–	72.6	9
Naproxen	–	–	–	128.3	7
Niflumic acid	–	–	–	130.2	4
Nimesulide	–	–[40]	SE[42]	82.2	–
Nitrendipine	–	–[40]	SE[43]	94.8	–
N-Methylsuccinimide	298	–	–	80.1	10
N-Phenylbenzylamine	303	–	–	103.6	10
Penicillin G	–	–[40]	SE[44]	122.2	–
Pentafluorobenzoic acid	(335–359)	–	–	91.6	10

(*Continued*)

Table 1. (Continued)

Compounds	Temp. Range (K)	Fusion Enthalpy (kJ mol^{-1})	Vaporization Enthalpy (kJ mol^{-1})	Sublimation Enthalpy (kJ mol^{-1})	References
Pentafluorophenol	(273–299)	–	–	67.4	10
Phenanthridine	298	–	–	98.6	10
Phenazine	298	–	–	91.8	10
Phenazopyridine	–	–[40]	SE[41]	93.0	–
Phenyl benzoate	298	–	–	99.0	10
Phenyl salicylate	294	–	–	109.1	10
Phenyl vinyl sulfone	–	–	–	82.0	10
Phthalimide	(378–418)	–	–	85.8	10
Phthalazine	298	–	–	81.1	10
Phthalic acid	298	–	–	129.8	10
Picene	298	–	–	149.4	9
Piperazine	(413–450)	–	–	103.8	10
Progesterone	–	–[34]	SE[34]	93.9	–
Propylparaben	–	–	–	123.7	3
Protocate acid	–	–[40]	SE[45]	120.1	–
Protocatechu	–	–[40]	SE[45]	127.6	–
p-Phenacetin	(312–387)	–	–	121.8	10
p-Terphenyl	(353–383)	–	–	125.6	10
p-Toluidine	298	–	–	78.8	10
Pyracene	298	–	–	89.6	9
Pyracyclene	298	–	–	83.2	9
Pyrene	298	–	–	100.3	9
Quinone	–	–	–	68.0	10
Resorcinol dibenzoate	338	–	–	165.8	10
Rosuvastatin	–	GC[14,15]	SE[32]	122.2	–
Salicylamide	–	–[46]	SE[47]	89.76	–
Simvastatin	–	–[40]	SE[32]	109.4	–
Succinic acid	(292–320)	–	–	73.6	10
Succinimide	(317–340)	–	–	83.1	10
Sulfanilic acid	–	–	–	66.9	10
Sulfonamide I	–	–	–	114.0	48
Sulfonamide II	–	–	–	124.9	48
Testosterone	–	–[34]	SE[34]	110.5	–
Tetrabenzonaphthalene	298	–	–	151.0	9
Tetrahydro-4*H*-thiopyran-4-one	298	–	–	72.6	10
Tetramethyl pyrazine	298	–	–	94.6	10
Tetrathiofulvalene	351	–	–	92.0	10
Tetrazole	(333–363)	–	–	97.5	10
Theophylline	–	–[40]	SE[49]	126.0	–
Thiophene	(192–213)	–	–	49.0	10
Thymol	(283–323)	–	–	89.1	10
Toluene	298	–	–	48.0	9
Tricyclohexylmethane	298	–	–	117.4	10
Triphenylmethane	298	–	–	108.4	9
Triphenylmethanol	298	–	–	121.8	10
Uracil	(394–494)	–	–	127.0	10

respectively. To obtain the sublimation enthalpy ΔH_{sub} of the solid, the compound should be divided in groups, applying subsequently the Eq. 2. In Eq. 2, n_i is the number of times a group i appears in the solid, and X_i is the contribution of group i to the values of the sublimation enthalpy. It is important to point out that when a carbon atom belongs at the same time to an aromatic and cyclic ring, the value of that carbon atom should be taken as the value of the carbon atom of the aromatic ring. An example can be found in the Appendix.

$$\Delta H^{\text{sub}}(\text{kJ mol}^{-1}) = \sum n_i \cdot X_i \tag{2}$$

The average absolute relative deviation (AARD) in percent and the average absolute error (AAE) in kJ mol^{-1} were calculated with Eqs. 3 and 4, respectively. Subscript exp denotes experimental value or the calculated value from experimental solubility data solid-SCFs. On the other hand, subscript pre denotes the predicted values with our method. Finally, N is the number of compounds

$$\text{AARD} = \left(100/N\right) \cdot \sum_{i=1}^{N} \frac{\left|\Delta H_{\text{pre}} - \Delta H_{\text{exp}}\right|}{\Delta H_{\text{exp}}} \tag{3}$$

$$\text{AAE} = \frac{\sum \left|\Delta H_{\text{exp}} - \Delta H_{\text{pre}}\right|}{N} \tag{4}$$

Our method predicts experimental values with an AARD of 8.98% and an AAE of 9.22 kJ mol^{-1}. These values are low, taking into account that the usual value of the sublimation enthalpy of this type of compounds is around 80–110 kJ mol^{-1}.

Figure 1 depicts a plot that shows the predicted sublimation enthalpies vs. the experimental sublimation enthalpies of the 253 solids. On the other hand, Figure 2 depicts the Bland–Altman plot. In this case, the dashed lines depict the

Table 2. Group Contribution Values (kJ mol^{-1})

Molecular Fragment	X (kJ mol^{-1})	Molecular Fragment	X (kJ mol^{-1})
Nonring C Increments			
—CH$_3$	11.57	=CH$_2$	40.54
—CH$_2$—	3.38	=CH—	3.43
>CH—	−11.26	=C<	−9.40
>C<	−16.46		
Aliphatic Ring Increments			
—CH$_2$— (apr)	10.38	—O— (apr)*	−9.28
>CH— (apr)	−4.75	—N< (apr)	15.37
>C< (apr)	−7.25	—NH— (apr)	34.34
=CH— (apr)	11.78	—N= (apr)	19.08
=C< (apr)	−13.04	—S— (apr)	17.19
Halogen Increments			
—F	3.92	—Cl	18.43
—Br	21.85	—I	17.49
Oxygen and Carboxyl Increments			
—OH (phenol)	26.17	>C=O (no ring)	6.47
—OH	16.79	>C=O (ring)	13.01
—CHO	30.36	—O— (no ring)	5.89
—COOH	40.37	—C(=O)O—	12.09
Aromatic Ring Increments			
CHar	8.10	Nar	11.15
Car	2.60		
Nitrogen and Sulfur Increments			
—CN*	1.16	=N—*	−10.12
—NO$_2$	23.17	C=S	29.66
—NH$_2$	25.21	SO$_2$	−4.39
—NH—	17.08	—S—*	−5.82
>N—*	−17.59		

limits of agreement (average difference (1.30 kJ mol^{-1}) ± 1.96·standard deviation) and the solid line depicts the value of the average of the differences between the experimental and predicted value (our result is 1.30 kJ mol^{-1}). It can be observed in these figures the accuracy of our estimations.

These errors can be considered low, given that bigger differences can sometimes be found for the same solid depending on the experimental work,[10] and the values of sublimation enthalpies usually range from 90 to 120 kJ mol^{-1}. For instance (see NIST webbook http://webbook.nist.gov/chemistry/), the value of the sublimation enthalpy for the anthracene ranges from 84 to 104 kJ mol^{-1} (a difference around 20%), and something similar occurs for the naphthalene, finding a difference between the different experimental works around 15%.

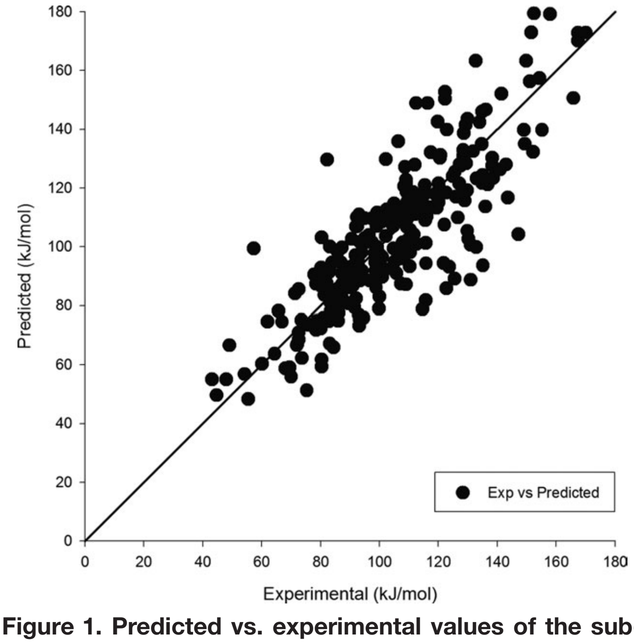

Figure 1. Predicted vs. experimental values of the sublimation enthalpy for the compounds.

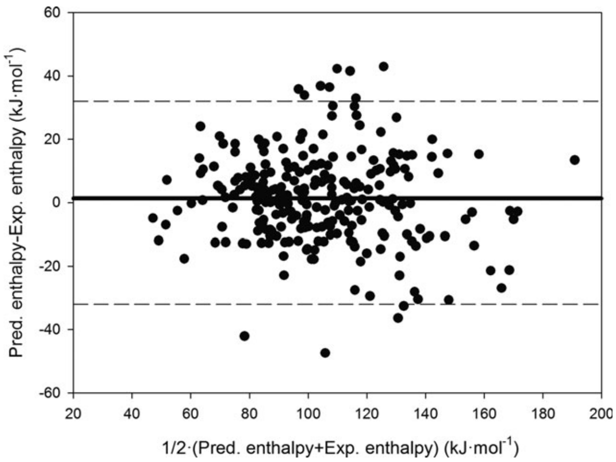

Figure 2. Bland–Altman plot.

A statistical analysis was performed. The multiple regression gave an R^2 value of 0.988, a standard deviation of 14.77, and a coefficient variation of 0.155. Table 3 shows the ANOVA table, whereas in Table 2 the * shows the functional groups with statistical insignificance (confidence level $\alpha < 0.05$).

The prediction ability of the method was validated by randomizing the database with 253 compounds. Forty compounds were chosen at random in order to use them as a test set, using the remaining data (213 solids) as a data set to generate the values of the functional groups. This validation was performed two times. The AAE and the AARD were calculated for each data and test set.

Table 4 shows these results. Although the AARD and the AAE of the test sets are higher than the deviations of their correspondent sets of compounds, these differences are not significant. Indeed, these values are near to the AARD and AAE of the set of 253 compounds, and in addition both test sets give similar deviations.

These facts indicate that this method is suitable for any solid constituted by aromatic and/or polycyclic aliphatic rings. However, this GC method presents two limitations: (1) it is impossible to distinguish between isomers and (2) the number of groups.

Only 41 groups were defined, and although there are not drawbacks with solids with a molecular structure similar to pharmaceuticals because these groups are the most common, it is possible to find solids constituted with groups that were not considered in the calculations. This fact might hinder to extend the values of the groups to other type of solids like inorganic compounds.

Table 3. ANOVA Table

Model	Squares Sum (SS)	Mean Squares (MS)	Freedom Deg. (fd)
Regression	2863870.80	69850.80	41
Residuals	56129.20	264.76	212
Total	$2.92 \cdot 10^6$		253

Table 4. AARD and AAE for the Respective Validation Tests

Set Type	AARD (%)	AAE (kJ mol^{-1})
Set of compounds 1	8.75	9.18
Set of compounds 2	8.32	9.15
Test set 1	9.63	10.93
Test set 2	9.37	10.70

About the drawbacks related to isomers, although the sublimation enthalpy of a solid varies depending on the geometric properties as occurs with other properties (e.g., fusion enthalpy), it should be specified that this variation is not usually high taking into account the big values of the sublimation enthalpies. For instance, for the three isomers of the methylbenzoic acid (MBA), the difference between their sublimation enthalpies is only 2.90 kJ mol^{-1} (95.90 kJ mol^{-1} for 2-MBA, 97.00 kJ mol^{-1} for 3-MBA, and 98.80 kJ mol^{-1} for 4-MBA). Therefore, the relative error of the estimation would not suffer a great increase. The values for these compounds can be found in the NIST webbook.

Conclusions

This work presents a consistent GC method to estimate the sublimation enthalpy of only any solid constituted by aromatic and/or polycyclic aliphatic rings (for instance pharmaceuticals). An AARD of 8.98% and an AAE of 9.22 kJ mol^{-1} were obtained predicting values of sublimation enthalpies for 253 solids. The main limitation is that only 41 groups were defined, hindering the prediction for other types of solids.

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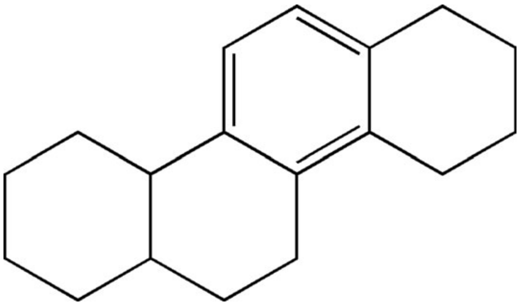
Appendix: Examples

Using Bartle's model to determine vaporization enthalpies of several solids

Experimental solubility data (around 45 points at different conditions of pressure and temperature) of naphthalene in supercritical CO_2 between 308 and 338 K were determined by McHugh and Paulaitis[50] and were modeled with Bartle's model. The parameters A, B, and C from Eq. 1 are given in Table A1. If the parameter $-B$ is multiplied by the gas constant (R), the estimated enthalpy is 58.65 kJ mol^{-1}. This result is obviously nearer to the vaporization enthalpy (55.4 kJ mol^{-1})[9] than the sublimation enthalpy (72.60 kJ mol^{-1}).[9] The same can be observed for other solids such as acetaminophen or 2-hydroxybenzoic acid (2-HBA). Table A1 shows the results and the comparison with experimental data. In these last two cases, the experimental vaporization enthalpies were obtained as the difference between the experimental values of the sublimation enthalpies (acetaminophen[8] and 2-HBA[2]) and the respective fusion enthalpies.[51] It should also be indicated that the relative deviation in the sublimation enthalpies will be lower, taking into account the bigger value of this enthalpy compared to the vaporization enthalpies.

Sublimation enthalpy of 1,2,3,4,4a,7,8,9,10,11,12,12a-dodecahydrochrysene ($C_{18}H_{24}$)



This solid is constituted with a benzene ring and several aliphatic rings. In this case, four carbon atoms belong to an aromatic and to different cyclic rings. When a similar case occurs, the values of those four carbon atoms should be taken as the values of the carbon atoms of the benzene ring. Then:

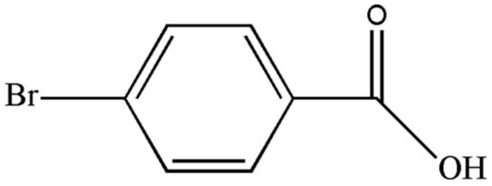
$$\Delta H^{\text{sub}}(\text{predict.}) = \sum n_i \cdot X_i = 2 \cdot (X_{\text{CHar}}) + 4 \cdot (X_{\text{Car}}) + 10 \cdot (X_{-\text{CH2}-(\text{apr})}) + 2 \cdot (X_{>\text{CH}-(\text{apr})}) = 2 \cdot (8.10) + 4 \cdot (2.60) + 10 \cdot (10.38) - 2 \cdot (4.75) = 120.90\ \text{kJmol}^{-1}.$$

The experimental value of the sublimation enthalpy of this compound[10] is 115.40 kJ mol^{-1}. The difference between the predicted and the experimental value is 5.50 kJ mol^{-1}.

Table A1. Estimated Vaporization Enthalpies Using Bartle's Model and the Comparison with the Experimental Values

Compound	Parameter A	Parameter B	Parameter C	ΔH_{vap} Estim. (kJ mol^{-1})	ΔH_{vap} Exp. (kJ mol^{-1})
Naphthalene	23.26	−7057.48	0.09	58.65	55.40[9]
Acetaminophen	19.11	−8917.97	0.008	74.11	89.40
2-HBA	19.49	−7244.96	0.007	60.20	66.70

Sublimation enthalpy of 3-bromobenzoic acid ($C_7H_5BrO_2$)



$$\Delta H^{\mathrm{sub}}(\mathrm{predict.}) = \sum n_i \cdot X_i = 4 \cdot (X_{\mathrm{CHar}}) + 2 \cdot (X_{\mathrm{Car}}) + 1 \cdot (X_{-\mathrm{Br}}) + 1 \cdot (X_{-\mathrm{COOH}}) = 4 \cdot (8.10) + 2 \cdot (2.60) + 1 \cdot (21.85) + 1 \cdot (40.37) = 99.82\,\mathrm{kJ\,mol^{-1}}.$$

The experimental value of the sublimation enthalpy of this compound[10] is 99.20 kJ mol^{-1}. The difference between the predicted and the experimental value is less than 1.00 kJ mol^{-1}.

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