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Calculation of Five Thermodynamic Molecular Descriptors by Means of a General Computer Algorithm Based on the Group-Additivity Method: Standard Enthalpies of Vaporization, Sublimation and Solvation, and Entropy of Fusion of ordinary Organic Molecules and Total Phase-Change Entropy of Liquid Crystals

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Abstract: The calculation of the standard enthalpies of vaporization, sublimation and solvation of organic molecules is presented using a common computer algorithm on the basis of a group-additivity method. The same algorithm is also shown to enable the calculation of their entropy of fusion as well as the total phase-change entropy of liquid crystals. The present method is based on the complete break-down of the molecules into their constituting atoms and their immediate neighbourhood; the respective calculations of the contribution of the atomic groups by means of the Gauss-Seidel fitting method is based on experimental data collected from literature. The feasibility of the calculations for each of the mentioned descriptors was verified by means of a 10-fold cross-validation procedure proving the good to high quality of the predicted values for the three mentioned enthalpies and for the entropy of fusion, whereas the predictive quality for the total phase-change entropy of liquid crystals was poor. The goodness of fit (Q^2) and the standard deviation (σ) of the cross-validation calculations for the five descriptors was as follows: 0.9641 and 4.56 kJ/mol (N=3386 test molecules) for the enthalpy of vaporization, 0.8657 and 11.39 kJ/mol (N=1791) for the enthalpy of sublimation, 0.9546 and 4.34 kJ/mol (N=373) for the enthalpy of solvation, 0.8727 and 17.93 J/mol/K (N=2637) for the entropy of fusion and 0.5804 and 32.79 J/mol/K (N=2643) for the total phase-change entropy of liquid crystals. The large discrepancy between the results of the two closely related entropies is discussed in detail. Molecules, for which both the standard enthalpies of vaporization and sublimation were calculable, enabled the estimation of their standard enthalpy of fusion by simple subtraction of the former from the latter enthalpy. For 990 of them the experimental enthalpy-of-fusion values are also known, allowing their comparison with predictions, yielding a correlation coefficient R^2 of 0.6066.

Keywords: enthalpy of vaporization; enthalpy of sublimation; enthalpy of solvation; entropy of fusion; total phase-change entropy; tpc entropy; group-additivity method

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1. Introduction

The reliable prediction of certain properties/descriptors of a molecule prior to its synthetic preparation has always been the goal of theoretical and experimental scientists, be it that they wanted to focus their experimental working hours on the synthesis of worthwhile compounds, be it that they wanted to verify their experimental results by means of the predictions. Among the many approaches, from the most elaborate ones such as the time-consuming *ab initio* methods to the fastest semiempirical self-consistent field procedures, one has turned out to be the most versatile and accurate and is not even quantum-theory-related: the atomic group-additivity method. A recent paper [1] demonstrated its versatility in that it enabled the calculation of mutually totally unrelated descriptors such as heat of combustion, solubility, refractivity, polarizability and toxicity by means of one single computer algorithm. This approach marks the endpoint, so to speak, of the various earlier group-additivity methods focusing on specific fields of application such as the prediction of the $\log P_{O/W}$ values [2,3], the molar refractivity [4], the molecular polarizability [5,6], or - closer to the present goal - the "simultaneous" evaluation of the logP, the aqueous solubility and the brain/blood distribution ratio logBB using individual parameter sets [7]. It should not be kept secret, however, that the unsuccessful attempts in paper [1] to reliably predict just the latter descriptor, logBB, put a damper on the expectation of a universal applicability of the present atomic group-additivity method. Yet, the exceptionally high prediction quality for the heat of combustion values across the entire structural spectrum of compounds presented in paper [1] - showing a cross-validated correlation coefficient of better than 0.9999 for 1965 compounds - at least gave rise to the hope that this method might successfully be extended to further thermodynamic descriptors.

The standard enthalpies of vaporization and sublimation were the first targets to be examined, not only because of their importance in chemical and environmental science, but also because a great deal of groundwork had already been done by W. E. Acree Jr. and J. S. Chickos [8], who collected the large number of experimental vaporization and sublimation data of more than a century. Several attempts to estimate the standard enthalpies of vaporization and sublimation have already been published: M. V. Roux et al. [9] evaluated the standard phase-change enthalpies of molecules from their experimental phase-change enthalpies at any given temperatures using their estimated heat capacity at room temperature. In cases where the number of experimental data was insufficient, they extrapolated the data from compounds with known experimental values. This estimation method, however, was limited to the vaporization enthalpy of liquid hydrocarbons. Similarly, J. Chickos et al. [10,11] estimated the vaporization enthalpies of larger even-numbered linear n-alkanes from a series of smaller ones [12,13] using their temperature dependence of the gaschromatographic retention time. A further indication of the potential applicability of the group-additivity method to predict the heats of vaporization and sublimation was found in the high correlation of the chain length of the homologues of saturated and unsaturated fatty acids with their experimental values [14].

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Determination of the enthalpy of solvation has recently been based on the Abraham solute parameters model [15-18], the model consisting of a linear equation of five parameters relating to the molecule's excess molar refraction, the polarity/dipolarity, solute hydrogen-bond acidity and hydrogen-bond basicity, and the McGowan (i. e. molecular) volume. These parameters have been derived from the molecular structure of a series of compounds using multilinear regression analysis and artificial neural networks [19]. Earlier, S. Cabani et al. [20] described a group-contribution method for the estimation of the enthalpy, Gibbs free energy and heat capacity of liquids of non-ionic solutes in water, limiting the method for the calculation of the group contributions to compounds with not more than one heteroatom and then applying correction parameters for molecules containing more than one heteroatom.

The entropy of fusion (often - and more logically - called entropy of phase change or even better: entropy of melting) of ordinary organic molecules as well as its special manifestation with liquid crystals, called total phase-change entropy, generally mean the entropy of the transition of a molecule from its most stable crystalline form to the isotropic melt. While for ordinary molecules this transition in most cases occurs in one step or two consecutive steps upon addition of thermal energy, this process is much more complex with liquid crystals in that they know several intermediate, semicrystalline phases melting at considerably different temperatures. In the first case, occurrence of more than one melting step may be explained by polymorphism of the crystalline form, their various polymorphic forms often showing distinct differences in their fusion enthalpies. In the second, the various semicrystalline forms can be stable over a considerable temperature range, thus consuming a large amount of thermal energy prior to their next phase change. The thermodynamic consequences of the difference in the melting processes between ordinary molecules and compounds exhibiting liquid crystal properties forced J. S. Chickos et al. [21] and W. E. Acree Jr. et al. [22] to treat these two categories of compounds as separate entities in their collective volumes.

The present work, being a continuation of the principle to calculate the molecular descriptors published earlier [1], will show the extendability of the approach to reliably predict the enthalpies of vaporization, sublimation and solvation, as well as the entropy of fusion. In order to clearly distinguish the phase-change entropy of ordinary compounds from that of liquid crystals, the term "entropy of fusion" will remain reserved for the former, while for the latter the well established term "total phase-change entropy" will be used throughout..

2. General Procedure

All the calculations are based on a knowledge database at present encompassing more than 28,500 records, containing the compounds in their geometry-optimized 3D form and carrying all the required (and several more) data. The database includes - besides ordinary organic molecules - organic salts, ionic liquids, liquid crystals and metal-organic compounds.

The algorithm for the calculation of the present descriptors follows the atom-group additivity principle outlined in detail in the earlier paper [1]. Consequently, the naming and

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meaning of the atom groups in the parameters tables is the same, the tables being complemented by further atom groups, where necessary, following the rules described in table 1 of [1]. The results of the evaluation of the atom-group contributions are stored in a separate parameters list for each descriptor. The only difference to the earlier work lies in the addition of a further special group as a consequence of attempts to optimize calculations of the group contributions for the entropies of fusion, where it turned out that the difference between the experimental values of open-chained and cyclical compounds was not resolvable by the given ordinary atom groups themselves. Therefore, a special group called "Endocyclic bonds" has been introduced which counts the number of endocyclic bonds in a molecule but is restricted to single bonds to take account of their reduced freedom of mobility within a ring system (bonds of higher order are by themselves restricted). Its treatment within the calculation is identical to the one described for all the other special groups.

Once the group contributions have been evaluated as described earlier, the prediction of the descriptors follows the general equation 1, where a_i and b_j are the contributions, A_i is the number of occurrences of the ith atom group, B_j is the number of occurrences of the special groups and C is a constant.

$$Y = \sum_i a_i A_i + \sum_j b_j B_j + C \tag{1}$$

It is immediately evident that this equation excludes prediction of descriptors for molecules for which not all atom groups are present in the corresponding parameters table. Yet, a further limitation is given by the condition that only atom groups are valid for consideration that have been represented by at least three independent molecules in the parameters-evaluation process. The number of molecules representing a given atom group is listed in the rightmost column of the parameters tables shown below. The remaining atom groups represented by less than three molecules are kept in the parameters tables solely for future use in this continuing project. The calculations are generally restricted to molecules containing the elements H, B, C, N, O, P, S, Si and/or halogen.

Plausibility tests have been carried out for each of the atom-group additivity parameters evaluations applying a 10-fold cross-validation procedure as described in [1], making sure that each compound has been used once as a test sample in the process. The results of these calculations are condensed in row A to H at the end of each parameters table. In the corresponding correlation diagrams and histograms presented below the results of the cross-validation calculations are superpositioned in red over the training data.

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3. Results

3.0. General remarks:

1) The experimental values of enthalpies and entropies are temperature-dependent. Any relationship within these properties or with other ones only make sense if they are referenced to the same temperature. The usual temperature of reference is 298.15K, and thus it was ensured in this work that experimental data from literature were only accepted if they had been either measured at or adjusted to the standard temperature of 298.15 K and standard pressure of 100 kPa.

2) All lists of molecules used in the atom-group parameters evaluations have been collected in standard SDF files, stored in the supplementary material, ready to be imported by external chemistry software. The supplementary material also provides the lists of results containing molecule names, experimental, training and cross-validation values. Beyond this, it also contains lists of experimental outliers.

3.1. Enthalpy of Vaporization

Experimental data of vaporization enthalpies have essentially been extracted for this work from the large collection of W. E. Acree Jr. and J. S. Chickos [8] and J. S. Chickos et al. [10-14], supplemented by recent data from a number of further authors publishing experimental vaporization values of several acetophenones [23], aliphatic tertiary amines [24], azidomethyl-N-nitro-oxazolidines [25], benzamides [26], benzocaine [27], bisabolol and menthol [28], crown ethers [29], N,N-dialkyl monoamides [30], fenpropidin and phencyclidine [31], flavors [32], long-chain fluorinated alcohols [33], whiskey- and metha-lactone [34], halogenated fluorenes [35], ibuprofen and naproxen [36], imidazo[1,2-a]pyrazine and phthalazine [37], insect pheromones [38], morpholines [39], organo(thio)phosphates [40], dialkyl phthalates [41], nitrogen heteroaromatics [42], phenyl-imidazoles [43], 2-acetylthiophene [44], dicarboxylic n-pentyl esters [45], and cyclic amines, ethers and alcohols [46]. The result of the atom-group parameters, resting on 3581 compounds, is summarized in Table 1. Several tentative calculations with or without inclusion of certain special groups outlined in Table 2 of the earlier paper [1] revealed a minor improvement of the goodness of fit upon inclusion of the “atom group” responsible for intramolecular acid-base bonds, named “H / H Acceptor”, as well as of those reserved for saturated and unsaturated pure hydrocarbons, called “Alkane / No of C atoms” and “Unsaturated HC / No of C atoms”, which add a correction value for each carbon atom.

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Table 1. Atom Groups and their Contributions (in kJ/mol) for Heat-of-Vaporization Calculations

Nr	Atom Type	Neighbours	Contribution	Occurrences	Molecules
1	Const		8.61	3581	3581
2	B	C3	21.55	2	2
3	B	N2Cl	33.19	1	1
4	B	NCl2	28.59	1	1
5	B	O2Cl	28.23	2	2
6	B	OCl2	25.53	1	1
7	B	S3	76.74	4	4
8	C sp3	H3C	3.07	5380	2388
9	C sp3	H3N	15.65	242	133
10	C sp3	H3N(+)	31.33	2	2
11	C sp3	H3O	16.71	372	263
12	C sp3	H3S	14.44	31	25
13	C sp3	H3P	9.04	6	4
14	C sp3	H3Si	5.87	136	53
15	C sp3	H2BC	-3.07	6	2
16	C sp3	H2C2	4.67	10588	2030
17	C sp3	H2CN	15.00	430	243
18	C sp3	H2CN(+)	29.15	10	9
19	C sp3	H2CO	15.79	1147	779
20	C sp3	H2CS	15.50	159	101
21	C sp3	H2CP	6.67	6	2
22	C sp3	H2CF	6.20	11	11
23	C sp3	H2CCl	14.13	76	65
24	C sp3	H2CBr	16.69	24	21
25	C sp3	H2CJ	20.90	29	26
26	C sp3	H2CSi	2.01	134	54
27	C sp3	H2N2	28.27	5	3
28	C sp3	H2NO	20.46	4	4
29	C sp3	H2O2	27.43	19	16
30	C sp3	H2OS	22.40	1	1
31	C sp3	H2OF	18.90	1	1
32	C sp3	H2OCl	23.06	2	2
33	C sp3	H2OSi	10.30	1	1
34	C sp3	H2S2	24.08	2	2
35	C sp3	H2SSi	6.66	9	9
36	C sp3	H2Si2	2.87	2	1
37	C sp3	HC3	3.54	939	615
38	C sp3	HC2N	12.69	75	64
39	C sp3	HC2N(+)	28.39	3	3
40	C sp3	HC2O	14.99	243	203
41	C sp3	HC2S	13.61	26	22
42	C sp3	HC2Si	7.20	6	4
43	C sp3	HC2F	5.96	7	6
44	C sp3	HC2Cl	9.66	40	38
45	C sp3	HC2Br	12.12	21	16

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46	C sp3	HC2J	18.79	4	4
47	C sp3	HCN2(+)	47.10	3	3
48	C sp3	HCO2	25.39	25	22
49	C sp3	HCOCl	20.93	1	1
50	C sp3	HCF2	7.10	15	14
51	C sp3	HCFCl	12.61	15	15
52	C sp3	HCCl2	16.96	23	22
53	C sp3	HCClBr	18.23	1	1
54	C sp3	HNO2	32.31	1	1
55	C sp3	HO3	37.33	4	4
56	C sp3	HOF2	17.06	7	7
57	C sp3	HOFCl	20.49	1	1
58	C sp3	HSiCl2	23.89	1	1
59	C sp3	C4	1.92	335	274
60	C sp3	C3N	12.60	28	23
61	C sp3	C3N(+)	26.15	4	4
62	C sp3	C3O	12.21	135	116
63	C sp3	C3S	13.69	18	16
64	C sp3	C3F	2.94	31	19
65	C sp3	C3Cl	7.77	8	6
66	C sp3	C3Br	11.95	3	3
67	C sp3	C3J	19.63	2	2
68	C sp3	C2NO	20.34	1	1
69	C sp3	C2NF	8.88	1	1
70	C sp3	C2O2	23.16	35	27
71	C sp3	C2OF	18.38	3	3
72	C sp3	C2F2	4.75	328	70
73	C sp3	C2FCl	8.73	5	5
74	C sp3	C2Cl2	13.35	5	5
75	C sp3	CN3(+)	46.89	3	3
76	C sp3	CNF2	15.25	15	6
77	C sp3	CNF2(+)	30.77	3	2
78	C sp3	CN2F(+)	28.25	4	3
79	C sp3	CO3	28.48	6	6
80	C sp3	COF2	13.65	36	30
81	C sp3	COCl2	20.61	4	4
82	C sp3	CSF2	12.70	2	1
83	C sp3	CF3	2.96	147	90
84	C sp3	CF2Cl	6.64	10	9
85	C sp3	CF2Br	9.02	5	4
86	C sp3	CFCl2	13.41	7	7
87	C sp3	CFClBr	17.37	1	1
88	C sp3	CCl3	17.43	22	21
89	C sp3	NF3	14.48	5	4
90	C sp3	NF3(+)	-1.76	2	1
91	C sp3	N3F(+)	32.36	1	1
92	C sp3	O4	38.15	2	2
93	C sp3	O2F2	24.80	14	2
94	C sp3	OF3	9.71	9	7

95	C sp3	OF2Cl	17.84	2	2
96	C sp3	OCl3	27.40	2	2
97	C sp3	PF3	2.73	2	1
98	C sp2	H2=C	2.17	182	170
99	C sp2	HC=C	5.03	1314	694
100	C sp2	HC=N	8.81	15	15
101	C sp2	HC=O	11.44	122	122
102	C sp2	H=CN	17.18	103	57
103	C sp2	H=CO	10.25	35	32
104	C sp2	H=CS	8.20	49	35
105	C sp2	H=CSi	10.77	4	4
106	C sp2	H=CF	-0.09	1	1
107	C sp2	H=CCl	10.38	8	6
108	C sp2	H=CBr	13.73	1	1
109	C sp2	HN=N	30.13	39	39
110	C sp2	HN=O	34.46	6	6
111	C sp2	H=NO	14.07	1	1
112	C sp2	H=NS	18.07	2	2
113	C sp2	HO=O	18.86	14	12
114	C sp2	C2=C	5.27	220	190
115	C sp2	C2=N	8.22	15	14
116	C sp2	C2=O	13.59	149	140
117	C sp2	C=CN	15.36	14	10
118	C sp2	C=CO	12.54	39	31
119	C sp2	C2=S	71.29	2	2
120	C sp2	C=CS	9.45	29	24
121	C sp2	C=CF	2.72	11	5
122	C sp2	C=CCl	5.83	8	5
123	C sp2	C=CBr	15.79	1	1
124	C sp2	=CN2	9.12	3	2
125	C sp2	CN=N	28.80	16	16
126	C sp2	CN=N(+)	11.32	2	2
127	C sp2	CN=O	35.35	47	47
128	C sp2	C=NO	22.79	5	5
129	C sp2	CN=S	18.27	3	2
130	C sp2	C=NS	17.49	1	1
131	C sp2	C=NCl	11.93	1	1
132	C sp2	=CNCl	22.67	2	1
133	C sp2	CO=O	17.20	684	594
134	C sp2	=COS	17.48	1	1
135	C sp2	C=OS	12.33	9	9
136	C sp2	=COF	15.53	1	1
137	C sp2	C=OCl	15.41	11	9
138	C sp2	C=OBr	22.28	3	3
139	C sp2	C=OJ	25.82	2	2
140	C sp2	=CF2	-0.26	3	3
141	C sp2	=CFCl	9.81	3	2
142	C sp2	=CCl2	17.52	6	5
143	C sp2	N2=N	29.25	2	2

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144	C sp2	N2=O	35.05	3	3
145	C sp2	N=NS	13.50	5	5
146	C sp2	NO=O	33.48	3	3
147	C sp2	=NOCl	24.27	1	1
148	C sp2	NS=S	44.39	2	2
149	C sp2	O2=O	31.57	13	13
150	C sp2	O=OCl	22.73	2	2
151	C sp2	S2=S	34.03	1	1
152	C aromatic	H:C2	4.64	4749	928
153	C aromatic	H:C:N	11.74	118	70
154	C aromatic	H:C:N(+)	22.04	2	1
155	C aromatic	H:N2	15.36	7	5
156	C aromatic	:C3	6.67	233	69
157	C aromatic	C:C2	5.29	1053	618
158	C aromatic	C:C:N	9.94	38	30
159	C aromatic	:C2N	14.44	140	115
160	C aromatic	:C2N(+)	24.38	33	31
161	C aromatic	:C2:N	10.60	21	14
162	C aromatic	:C2O	8.04	443	253
163	C aromatic	:C2S	9.47	30	25
164	C aromatic	:C2Si	4.67	10	8
165	C aromatic	:C2F	4.45	143	72
166	C aromatic	:C2Cl	9.43	429	146
167	C aromatic	:C2Br	12.49	149	69
168	C aromatic	:C2J	19.48	29	26
169	C aromatic	:CN:N	16.72	2	2
170	C aromatic	:C:NO	13.67	4	3
171	C aromatic	:C:NF	14.34	1	1
172	C aromatic	:C:NCl	15.74	3	3
173	C aromatic	:C:NBr	25.24	1	1
174	C aromatic	N:N2	20.19	5	2
175	C aromatic	:N2O	16.44	2	2
176	C sp	H#C	2.42	15	14
177	C sp	C#C	6.05	62	33
178	C sp	=C2	5.50	4	4
179	C sp	C#N	17.38	72	70
180	C sp	#CCl	9.31	3	2
181	C sp	=N=O	10.44	6	5
182	C sp	=N=S	23.08	3	3
183	N sp3	H2C	2.30	78	58
184	N sp3	H2C(pi)	8.05	61	59
185	N sp3	H2N	19.23	8	7
186	N sp3	H2S	28.18	2	2
187	N sp3	HC2	-11.34	59	56
188	N sp3	HC2(pi)	-1.94	27	26
189	N sp3	HC2(2pi)	-2.43	21	21
190	N sp3	HCN	-0.76	3	2
191	N sp3	HCN(pi)	-13.33	3	3
192	N sp3	HCN(2pi)	4.97	1	1

193	N sp3	HCS(pi)	5.34	7	7
194	N sp3	HCSi	-4.02	6	6
195	N sp3	HSi2	1.94	1	1
196	N sp3	BC2	-31.30	3	2
197	N sp3	C3	-30.50	111	101
198	N sp3	C3(pi)	-25.56	37	31
199	N sp3	C3(2pi)	-22.95	52	50
200	N sp3	C3(3pi)	-27.03	13	13
201	N sp3	C2N	-19.64	4	3
202	N sp3	C2N(+)	0.00	1	1
203	N sp3	C2N(pi)	-27.16	3	2
204	N sp3	C2N(+)(pi)	3.24	4	4
205	N sp3	C2N(2pi)	-24.28	4	4
206	N sp3	C2N(3pi)	-26.84	2	2
207	N sp3	C2O	8.24	1	1
208	N sp3	C2P	-17.98	5	2
209	N sp3	C2Si	-19.79	12	8
210	N sp3	CN2(2pi)	-36.43	1	1
211	N sp3	CN2(+)(2pi)	16.44	1	1
212	N sp3	CF2	-4.56	2	2
213	N sp3	CF2(pi)	-12.61	1	1
214	N sp3	CSi2	-17.81	1	1
215	N sp3	Si3	-1.79	1	1
216	N sp2	H=C	1.29	2	2
217	N sp2	C=C	-10.46	85	82
218	N sp2	C=N	-5.89	19	10
219	N sp2	C=N(+)	-2.79	15	13
220	N sp2	=CN	18.81	9	9
221	N sp2	=CO	10.27	17	14
222	N sp2	=CF	0.00	1	1
223	N sp2	N=N	15.91	5	3
224	N sp2	O=O	0.59	7	7
225	N aromatic	:C2	-5.10	104	78
226	N aromatic	:C:N	5.35	8	4
227	N(+) sp3	C2NO(-)	0.00	1	1
228	N(+) sp2	CO=O(-)	-2.09	78	56
229	N(+) sp2	C=NO(-)	-19.89	3	3
230	N(+) sp2	NO=O(-)	0.35	6	5
231	N(+) sp2	O2=O(-)	9.02	17	11
232	N(+) aromatic	:C2O(-)	0.00	1	1
233	N(+) sp	C#C(-)	-8.48	2	2
234	N(+) sp	=N2(-)	5.96	12	10
235	O	HC	14.55	322	288
236	O	HC(pi)	20.98	174	157
237	O	HN	0.00	1	1
238	O	HN(pi)	19.03	2	2
239	O	HO	23.75	5	5
240	O	HSi	26.41	1	1
241	O	BC	-17.91	5	3

242	O	C2	-17.86	424	270
243	O	C2(pi)	-13.29	744	629
244	O	C2(2pi)	-7.15	145	120
245	O	CN(pi)	0.00	7	7
246	O	CN(+)(pi)	2.17	17	11
247	O	CN(2pi)	-2.82	9	9
248	O	CO	-8.76	54	20
249	O	CS	2.45	18	9
250	O	CP	-2.71	104	42
251	O	CP(pi)	1.25	7	5
252	O	CSi	-11.39	79	29
253	O	CSi(pi)	-14.85	37	13
254	O	N2(2pi)	-0.72	3	3
255	O	OSi	4.23	9	4
256	O	P2	16.68	1	1
257	O	Si2	-6.52	15	4
258	P3	C3	-6.83	3	3
259	P3	C2O	2.71	1	1
260	P3	N3	-7.09	1	1
261	P3	N2Cl	10.64	1	1
262	P3	O3	-4.07	1	1
263	P4	HO2=O	9.23	2	2
264	P4	CO2=O	5.40	3	3
265	P4	O3=O	-3.86	16	15
266	P4	O3=S	1.10	9	9
267	P4	O2=OS	1.77	4	4
268	P4	O2S=S	1.73	8	8
269	S2	HC	1.49	33	29
270	S2	HC(pi)	6.23	1	1
271	S2	HP	23.50	3	3
272	S2	BC	-24.53	12	4
273	S2	C2	-10.51	67	65
274	S2	C2(pi)	-2.71	23	22
275	S2	C2(2pi)	0.53	44	44
276	S2	CS	-0.35	16	8
277	S2	CS(pi)	2.39	2	1
278	S2	CP	-1.99	9	9
279	S2	Si2	-3.40	1	1
280	S4	C2=O	22.60	4	4
281	S4	C2=O2	27.80	9	9
282	S4	C2F2	-5.92	1	1
283	S4	CN=O2	1.94	9	9
284	S4	C=O2S	37.54	2	1
285	S4	O2=O	-3.83	5	5
286	S4	O2=O2	4.79	4	4
287	Si	H3C	0.00	1	1
288	Si	H2CN	2.20	1	1
289	Si	HC3	-4.21	24	24
290	Si	HC2O	2.36	2	1

291	Si	HC2S	0.00	2	1
292	Si	HCO2	8.33	5	1
293	Si	HN3	8.01	2	2
294	Si	C4	-0.57	21	20
295	Si	C3N	-1.80	18	14
296	Si	C3O	0.35	6	6
297	Si	C2O2	5.64	18	11
298	Si	CO3	-2.40	26	26
299	Si	O4	-16.14	6	6
300	H	H Acceptor	-12.45	16	16
301	Alkane	No of C atoms	0.09	3072	286
302	Unsaturated HC	No of C atoms	-0.07	4100	413
A	Based on	Valid groups	185		3581
B	Goodness of fit	R^2	0.9678		3460
C	Deviation	Average	2.99		3460
D	Deviation	Standard	4.30		3460
E	K-fold cv	K	10		3386
F	Goodness of fit	Q^2	0.9641		3386
G	Deviation	Average (cv)	3.14		3386
H	Deviation	Standard (cv)	4.56		3386

The total number of atom groups in Table 1, required to take account of the complete set of 3581 molecules for which experimental vaporization data are known, is 302. However, the condition to restrict their applicability to those resting on at least three independent molecules, reduces the number of “valid groups” to 187, as is shown in row A of Table 1. Accordingly, the number of compounds viable for the evaluation of the result of the complete training set and of the test sets in the 10-fold cross-validation calculation was reduced to 3460 and 3381, respectively, as listed in the right-most column. The high correlation coefficients R^2 and Q^2 of the training and the cross-validated sets (rows B and F) of better than 0.96 and the small difference between them is clear proof of the viability of the present group-additivity model for the prediction of the enthalpy of vaporization. Furthermore, the small standard deviations for the training and test sets of 4.3 and 4.56 (rows D and H) also speaks for the model’s accuracy.

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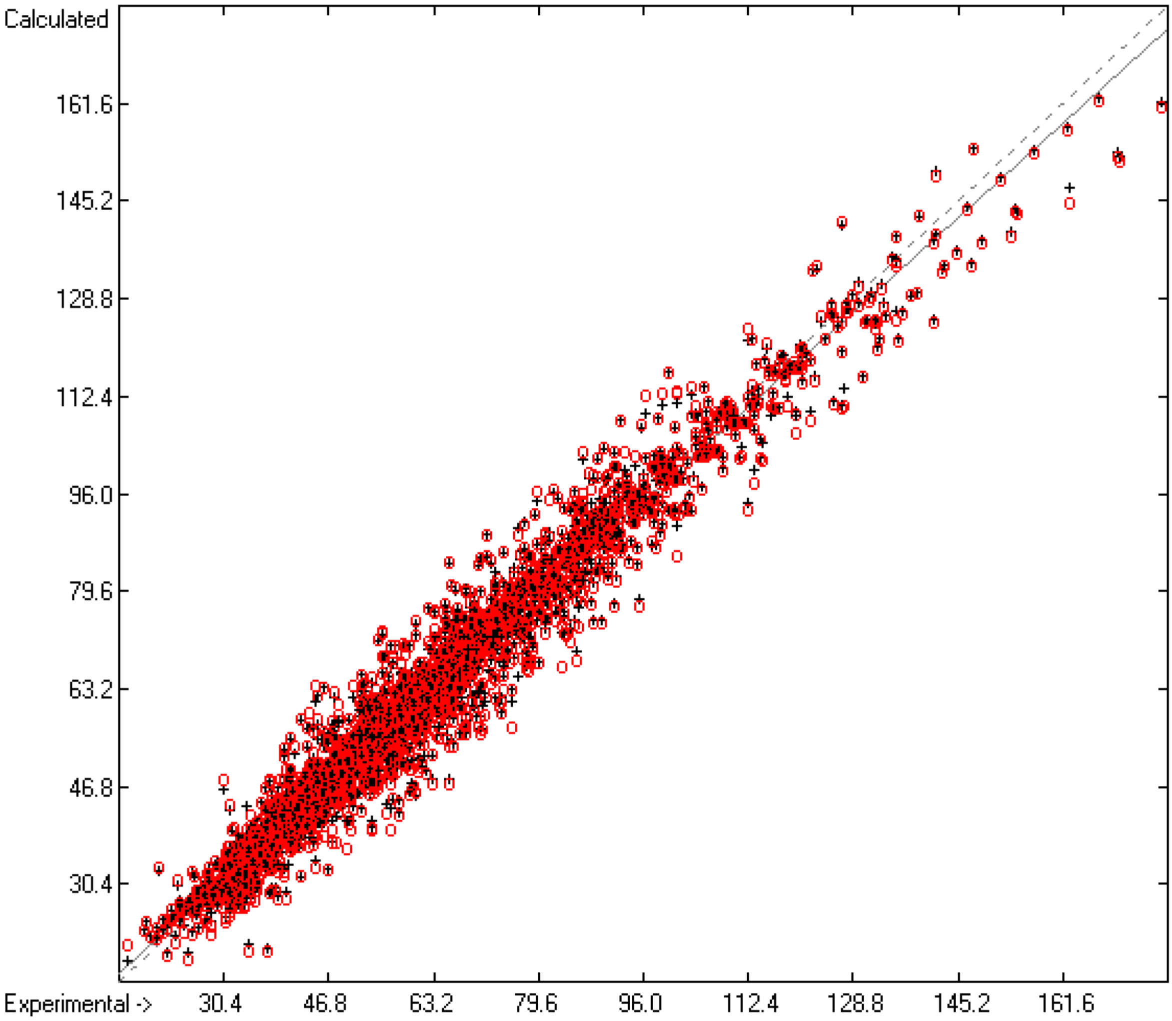

Figure 1. Correlation Diagram of the Enthalpy-of-Vaporization Data (N=3460; R^2=0.9677; Q^2=0.9640; regression line: intercept=1.9756, slope=0.9681)

The correlation diagram in Figure 1, showing a fairly even distribution of the vaporization data along the regression line, also reveals a narrow overlap of the cross-validated test data with those of the training set. The related histogram in Figure 2, exhibiting a nearly perfect Gaussian bell curve, proves the evenness of the distribution of the deviations of both test and training data about the regression line. The analysis of the distribution of the deviations yielded the following result: 79.2% of the presently 3460 tested compounds deviated by less than or equal to one cross-validated standard error of 4.56 kJ/mol, whereas 6.8% exceeded a deviation of twice that standard error. Beyond this, 32 molecules had to be viewed as outliers as their deviation surpassed by at least four times this standard error.

Despite the detailed distinction of the atom groups in Table 1, resulting in an extended list of groups of which about one third is “invalid”, the still large number of “valid” atom groups enabled the calculation of reliable enthalpy-of-vaporization data for 78.2 % of the complete set of compounds in the database..

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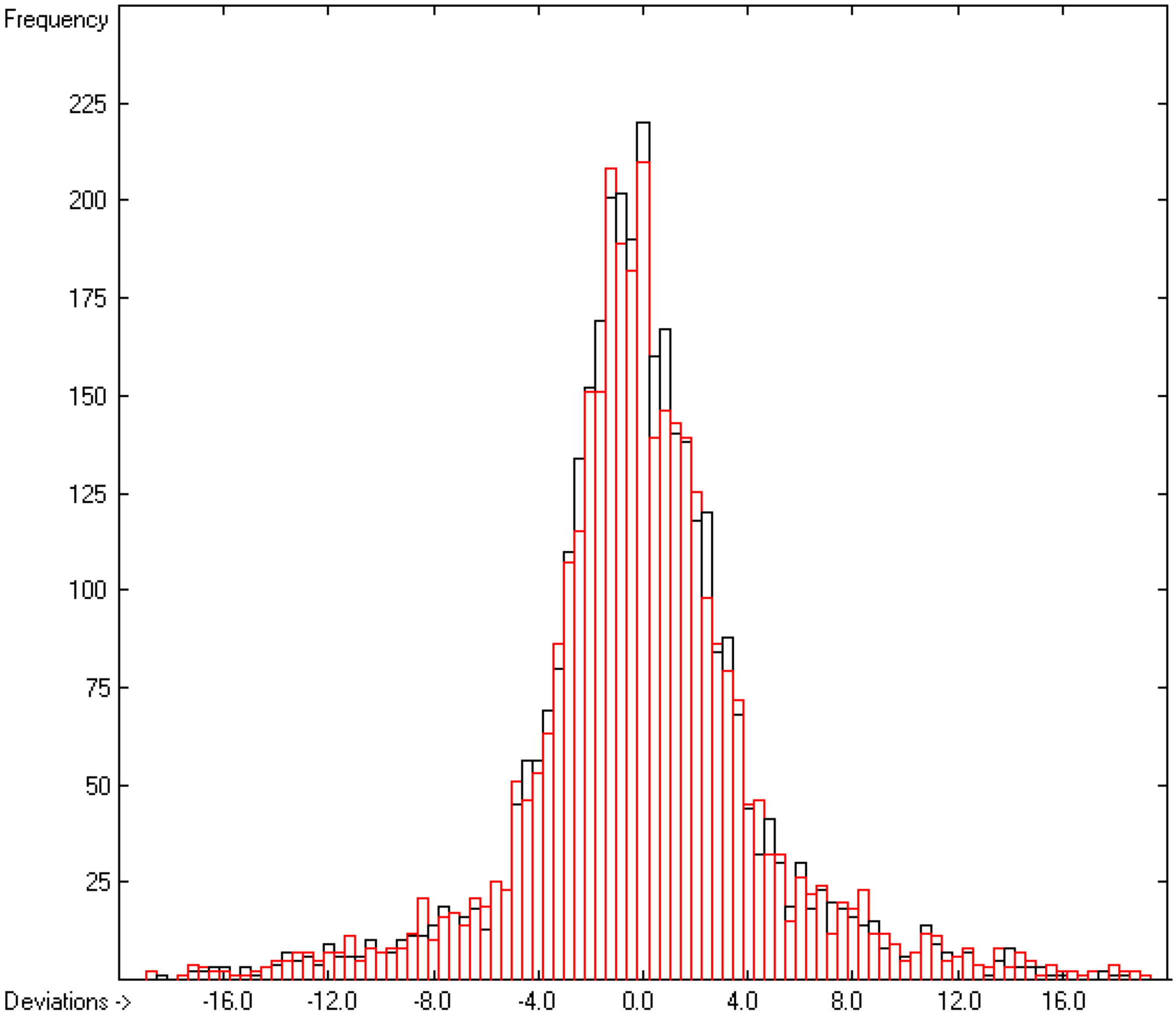

Figure 2. Histogram of the Enthalpy-of-Vaporization Data (S=4.56 kJ/mol; Exp. values range: 15.6<–>177.2 kJ/mol)

The entire set of experimental and calculated data of the heat-of-vaporization calculations is available as a separate document in the supplementary material under the name of "Experimental and Calculated Heat-of-Vaporization Data Table.doc"; the corresponding list of compounds is added as an SD file named "Compounds List for Heat-of-Vaporization Calculations.sdf" and the outliers list as an Excel file under the name "Compounds List of Heat-of-Vaporization Outliers.xls".

3.2. Enthalpy of Sublimation

The enthalpy of sublimation is the sum of the enthalpies of vaporization and fusion, provided that all of them are referenced to the same temperature. This precondition has been thoroughly followed when selecting experimental data from literature. Again, as in the previous chapter, the main contribution of experimental sublimation values has been provided by the compendium of W. E. Acree Jr. et al. [8], supplemented by a number of later publications, referencing the heat of sublimation of acetophenones [23], substituted benzamides [26], crown ethers [29], long-chain fluorinated alcohols [33], halogenated

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fluorenes [35], tricyclic nitrogen heteroaromatics [42], polyphenylbenzenes [47], adamantylideneadamantane [48], cyclic N,N'-thioureas [49], indole-3-carboxylic acids [50], vanillyl alcohol [51], alkanoylphenols [52], adamantanes [53], six-membered ring aliphatics [54], fluoroquinolones [55], oxazolidinones [56], nitrogen-containing substituted adamantanes [57], 2,7-di-t-butylfluorene [58] and nitroimidazoles [58].

Table 2. Atom Groups and their Contributions (in kJ/mol) for Heat-of-Sublimation Calculations

Nr	Atom Type	Neighbours	Contribution	Occurrences	Molecules
1	Const		21.03	1960	1960
2	B	C3	65.82	2	2
3	C sp3	H3C	5.99	1322	623
4	C sp3	H3N	26.96	143	87
5	C sp3	H3N(+)	98.98	1	1
6	C sp3	H3O	28.51	181	122
7	C sp3	H3S	30.06	7	6
8	C sp3	H2C2	6.88	2602	508
9	C sp3	H2CN	21.98	224	116
10	C sp3	H2CN(+)	27.46	13	11
11	C sp3	H2CO	29.62	242	134
12	C sp3	H2CS	23.29	50	31
13	C sp3	H2CF	15.91	1	1
14	C sp3	H2CCl	17.59	3	3
15	C sp3	H2CBr	22.76	5	4
16	C sp3	H2CJ	21.83	3	2
17	C sp3	H2N2	43.95	18	6
18	C sp3	H2NCl	36.29	1	1
19	C sp3	H2O2	53.35	25	13
20	C sp3	H2OS	54.78	1	1
21	C sp3	H2S2	47.45	6	4
22	C sp3	HBC2	-36.17	3	1
23	C sp3	HC3	2.28	509	190
24	C sp3	HC2N	14.28	34	30
25	C sp3	HC2N(+)	21.01	9	9
26	C sp3	HC2O	24.27	82	47
27	C sp3	HC2S	17.59	14	11
28	C sp3	HC2F	5.18	1	1
29	C sp3	HC2Cl	11.49	7	2
30	C sp3	HC2Br	-0.95	1	1
31	C sp3	HCN2	39.48	8	2
32	C sp3	HCN2(+)	39.93	2	2
33	C sp3	HCNO	34.73	2	1
34	C sp3	HCNS	20.56	2	1
35	C sp3	HCO2	39.96	3	3
36	C sp3	HCF2	-0.19	1	1
37	C sp3	HCCl2	15.78	1	1
38	C sp3	HN3(+)	37.31	1	1

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39	C sp3	HO3	72.23	3	3
40	C sp3	C4	-4.25	209	137
41	C sp3	C3N	5.87	18	13
42	C sp3	C3N(+)	18.44	14	11
43	C sp3	C3O	15.18	40	31
44	C sp3	C3S	6.40	5	5
45	C sp3	C3F	1.89	3	3
46	C sp3	C3Cl	-8.06	1	1
47	C sp3	C3Br	2.34	1	1
48	C sp3	C2N2(+)	34.78	7	6
49	C sp3	C2O2	39.73	8	8
50	C sp3	C2S2	37.28	4	1
51	C sp3	C2F2	7.07	62	8
52	C sp3	CN3(+)	43.89	19	12
53	C sp3	CN2F(+)	25.98	1	1
54	C sp3	CO3	57.42	2	2
55	C sp3	CF3	-4.71	27	23
56	C sp3	CCl3	16.10	3	2
57	C sp3	N3F(+)	44.00	1	1
58	C sp3	O4	73.43	1	1
59	C sp2	H2=C	7.97	12	12
60	C sp2	HC=C	5.10	452	213
61	C sp2	HC=N	35.49	21	19
62	C sp2	HC=N(+)	72.64	7	7
63	C sp2	H=CN	32.79	83	69
64	C sp2	HC=O	20.74	15	15
65	C sp2	H=CO	16.89	16	14
66	C sp2	H=CS	15.22	49	36
67	C sp2	HN=N	55.52	19	18
68	C sp2	HN=O	35.41	4	3
69	C sp2	H=NO	40.91	1	1
70	C sp2	H=NS	33.85	2	2
71	C sp2	C2=C	3.91	78	61
72	C sp2	C2=N	30.47	35	26
73	C sp2	C2=N(+)	13.76	5	5
74	C sp2	C=CN	26.81	57	48
75	C sp2	C=CN(+)	41.65	7	7
76	C sp2	C2=O	15.10	200	161
77	C sp2	C=CO	22.08	40	31
78	C sp2	C2=S	18.21	3	3
79	C sp2	C=CS	15.64	36	27
80	C sp2	C=CF	16.81	2	2
81	C sp2	C=CCl	11.02	9	5
82	C sp2	C=CBr	34.06	2	2
83	C sp2	C=CJ	32.46	1	1
84	C sp2	=CN2	64.94	6	6
85	C sp2	=CN2(+)	60.65	4	4
86	C sp2	CN=N	54.51	27	25
87	C sp2	CN=N(+)	44.16	3	3

88	C sp2	CN=O	39.66	234	194
89	C sp2	C=NO	42.74	2	2
90	C sp2	CN=S	39.85	8	7
91	C sp2	C=NS	34.89	1	1
92	C sp2	=CNS(+)	41.29	2	2
93	C sp2	=CNCl	38.14	4	3
94	C sp2	CO=O	34.06	424	345
95	C sp2	CO=O(-)	80.89	22	22
96	C sp2	C=OCl	29.03	1	1
97	C sp2	CS=S	56.97	3	3
98	C sp2	N2=N	80.72	4	4
99	C sp2	N2=N(+)	65.95	6	5
100	C sp2	N2=O	59.57	76	70
101	C sp2	N2=S	66.62	29	29
102	C sp2	N=NS	51.62	22	22
103	C sp2	NO=O	52.79	8	8
104	C sp2	=NO2	61.12	1	1
105	C sp2	N=OS	48.27	1	1
106	C sp2	NO=S	58.04	11	11
107	C sp2	=NOS	52.75	1	1
108	C sp2	NS=S	60.83	5	3
109	C sp2	=NS2	64.37	1	1
110	C sp2	O2=O	41.40	7	7
111	C sp2	=OS2	41.22	2	2
112	C sp2	OS=S	73.06	1	1
113	C sp2	S2=S	49.39	5	5
114	C aromatic	H:C2	5.36	7115	1269
115	C aromatic	H:C:N	18.20	150	96
116	C aromatic	H:C:N(+)	28.26	48	28
117	C aromatic	H:N2	23.27	7	5
118	C aromatic	B:C2	-25.04	3	1
119	C aromatic	:C3	5.51	454	155
120	C aromatic	C:C2	3.12	1684	835
121	C aromatic	C:C:N	11.10	80	48
122	C aromatic	C:C:N(+)	16.04	33	21
123	C aromatic	:C2N	22.21	354	258
124	C aromatic	:C2N(+)	28.67	169	134
125	C aromatic	:C2:N	17.03	79	61
126	C aromatic	:C2:N(+)	18.05	35	20
127	C aromatic	:C2O	20.46	617	387
128	C aromatic	:C2P	-1.63	12	4
129	C aromatic	:C2S	16.31	80	64
130	C aromatic	:C2F	4.45	77	42
131	C aromatic	:C2Cl	12.48	424	166
132	C aromatic	:C2Br	14.66	63	43
133	C aromatic	:C2J	20.68	31	27
134	C aromatic	:C2Si	4.80	10	2
135	C aromatic	C:N2	28.80	4	2
136	C aromatic	:CN:N	29.72	11	9

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137	C aromatic	:CN:N(+)	33.74	3	2
138	C aromatic	:C:NO	41.44	13	12
139	C aromatic	:C:NO(+)	33.50	5	5
140	C aromatic	:C:NCl	21.70	18	13
141	C aromatic	:C:NBr	31.31	3	2
142	C aromatic	N:N2	43.11	13	8
143	C aromatic	:N2O	39.92	3	1
144	C aromatic	:N2S	36.08	3	3
145	C aromatic	:N2Cl	35.90	3	3
146	C sp	=C2	6.39	3	2
147	C sp	C#C	3.24	14	7
148	C sp	C#N	16.49	96	67
149	C sp	C#N(+)	11.33	4	3
150	C sp	#CS	28.03	2	2
151	C sp	N#N	47.80	1	1
152	C sp	#NP	12.53	3	1
153	N sp3	H2C	5.03	23	12
154	N sp3	H2C(pi)	6.38	223	199
155	N sp3	H2N	17.97	10	8
156	N sp3	H2S	41.98	1	1
157	N sp3	HC2	-23.83	14	13
158	N sp3	HC2(pi)	-13.51	72	55
159	N sp3	HC2(2pi)	-20.10	200	165
160	N sp3	HCN	-0.15	2	1
161	N sp3	HCN(pi)	6.71	14	9
162	N sp3	HCN(2pi)	-6.84	25	25
163	N sp3	HCS(pi)	-15.10	20	20
164	N sp3	C3	-51.07	16	11
165	N sp3	C3(pi)	-53.90	59	49
166	N sp3	C3(2pi)	-60.80	72	54
167	N sp3	C3(3pi)	-61.26	18	14
168	N sp3	C2N(pi)	-7.05	6	3
169	N sp3	C2N(+)(pi)	-5.52	24	9
170	N sp3	C2N(2pi)	-36.36	4	4
171	N sp3	C2N(+)(2pi)	-20.13	1	1
172	N sp3	C2N(3pi)	-54.74	3	3
173	N sp3	C2S	-49.13	4	2
174	N sp3	C2F(2pi)	-64.78	1	1
175	N sp3	CN2(pi)	30.74	4	3
176	N sp3	CN2(2pi)	-49.40	3	3
177	N sp3	CN2(+)(2pi)	3.72	1	1
178	N sp3	CNF(2pi)	-34.74	5	4
179	N sp2	C=C	-32.77	79	74
180	N sp2	C=N	-4.54	13	9
181	N sp2	C=N(+)	-15.43	5	5
182	N sp2	=CN	-4.63	38	36
183	N sp2	=CN(+)	36.68	1	1
184	N sp2	C=O	-12.04	9	9
185	N sp2	C=P	-49.18	1	1

186	N sp2	=CO	-16.24	18	13
187	N sp2	=CS	-26.78	10	8
188	N sp2	N=N	12.19	21	13
189	N sp2	N=O	0.00	10	6
190	N sp2	=NO	-6.67	2	1
191	N aromatic	:C2	-14.01	208	145
192	N aromatic	:C:N	-4.98	4	2
193	N(+) sp3	H3C	2.77	13	13
194	N(+) sp3	H2C2	-82.36	3	3
195	N(+) sp2	C=CO(-)	-68.61	7	7
196	N(+) sp2	C=NO	-26.37	10	5
197	N(+) sp2	C=NO(-)	-11.30	3	3
198	N(+) sp2	CO=O(-)	-4.38	270	163
199	N(+) sp2	=CO2(-)	2.17	5	5
200	N(+) sp2	NO=O(-)	0.15	28	12
201	N(+) sp2	O2=O(-)	6.00	14	6
202	N(+) aromatic	H:C2	-46.79	6	6
203	N(+) aromatic	:C2O(-)	-7.10	56	40
204	N(+) sp	C#C(-)	-14.36	3	3
205	N(+) sp	#CO(-)	0.00	4	3
206	N(+) sp	=N2(-)	19.14	2	2
207	O	HC	4.49	143	92
208	O	HC(pi)	8.19	560	470
209	O	HN(pi)	2.28	4	3
210	O	HO	29.95	4	4
211	O	C2	-39.23	94	37
212	O	C2(pi)	-31.33	292	201
213	O	C2(2pi)	-24.06	147	121
214	O	CN(pi)	0.00	2	1
215	O	CN(+)(pi)	0.00	14	6
216	O	CN(2pi)	4.91	1	1
217	O	CO(pi)	-27.16	8	6
218	O	CP(pi)	-16.12	3	1
219	O	N2(2pi)	5.87	4	4
220	O	N2(+)(2pi)	6.27	5	5
221	P3	C3	16.70	2	2
222	P3	S3	-66.68	1	1
223	P4	C3=N	0.00	1	1
224	P4	C3=O	-30.50	1	1
225	P4	C3=S	46.30	1	1
226	P4	O3=O	0.00	1	1
227	S2	HC	-2.58	1	1
228	S2	HC(pi)	18.47	2	2
229	S2	C2	-22.69	19	12
230	S2	C2(pi)	-15.86	34	29
231	S2	C2(2pi)	-7.94	59	49
232	S2	CN(pi)	25.96	1	1
233	S2	CN(2pi)	-6.82	6	6
234	S2	CS(pi)	-6.16	8	4

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235	S2	CP(pi)	0.00	3	1
236	S2	N2	-2.00	1	1
237	S2	N2(2pi)	21.36	2	2
238	S2	NS	1.00	2	1
239	S4	C2=O	-5.89	2	2
240	S4	C2=O2	-4.26	27	27
241	S4	CN=O2	9.20	20	20
242	Si	C4	2.02	1	1
243	Si	C3Si	-0.67	2	1
244	H	H Acceptor	-8.63	107	89
245	Alkane	No of C atoms	-0.53	849	59
246	Unsaturated HC	No of C atoms	-0.10	2679	148
A	Based on	Valid groups	154		1960
B	Goodness of fit	R^2	0.8887		1866
C	Deviation	Average	7.81		1866
D	Deviation	Standard	10.33		1866
E	K-fold cv	K	10		1791
F	Goodness of fit	Q^2	0.8657		1791
G	Deviation	Average (cv)	8.56		1791
H	Deviation	Standard (cv)	11.39		1791

The correlation coefficients R^2 and Q^2 (row B and F at the bottom of Table 2) exhibit a higher scatter of the experimental data in comparison with the heat-of-vaporization data. The increased uncertainty might be partly ascribed to the fact that in many cases molecules form several crystal structures at different temperatures, having different enthalpies of fusion, and that, therefore, the starting point of the measurements is not clearly defined. In other cases the molecules may not be completely crystalline due to impurities. Another reason may be that while many of the compounds in the enthalpy of the vaporization dataset of the previous chapter are liquid at ambient room temperature and the vaporization measurements have been performed at temperatures not too far removed from 298.15 K, requiring only a small correction back to this reference temperature, the enthalpy of sublimation measurements, on the other hand, are often carried out at higher temperatures where the compounds are more volatile. In these cases, the uncertainty in the correction term needed to extrapolate the experimental value back to the reference temperature is higher and increases with the difference between the experimental and the reference temperature.

Figures 3 demonstrates the larger scatter of the data about the regression line, leading to a cross-validated standard deviation of 11.39 (see row H in Table 2), i. e. 2.5 times larger than for the heat of vaporization. Figure 4 visualizes the error distribution, showing that, according to an analysis, 74% of the molecules' predicted values differ by less one cv-standard deviation and only 5.6% by more than twice that amount. Only 16 compunds had to be declared as outliers because their experimental value exceeded four times the cv-standard deviation. One compound, norcamphor, had to be excluded from calculation because its experimental

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enthalpy of sublimation was lower than its experimental enthalpy of vaporization, an obviously impossible finding.

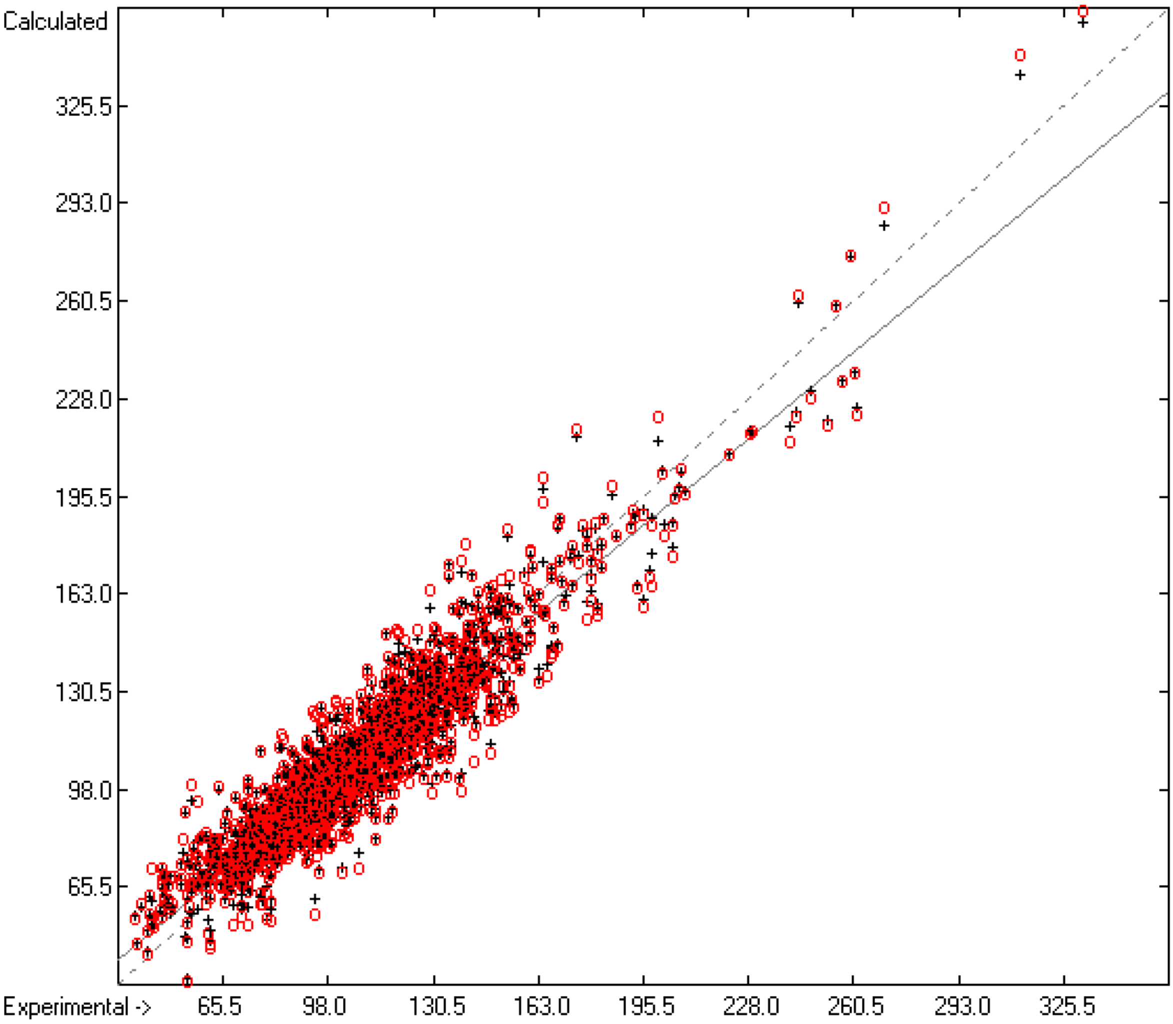

Figure 3. Correlation Diagram of the Enthalpy-of-Sublimation Data (N=1866; R^2=0.8887; Q^2=0.8657; regression line: intercept =12.0233, slope=0.8884)

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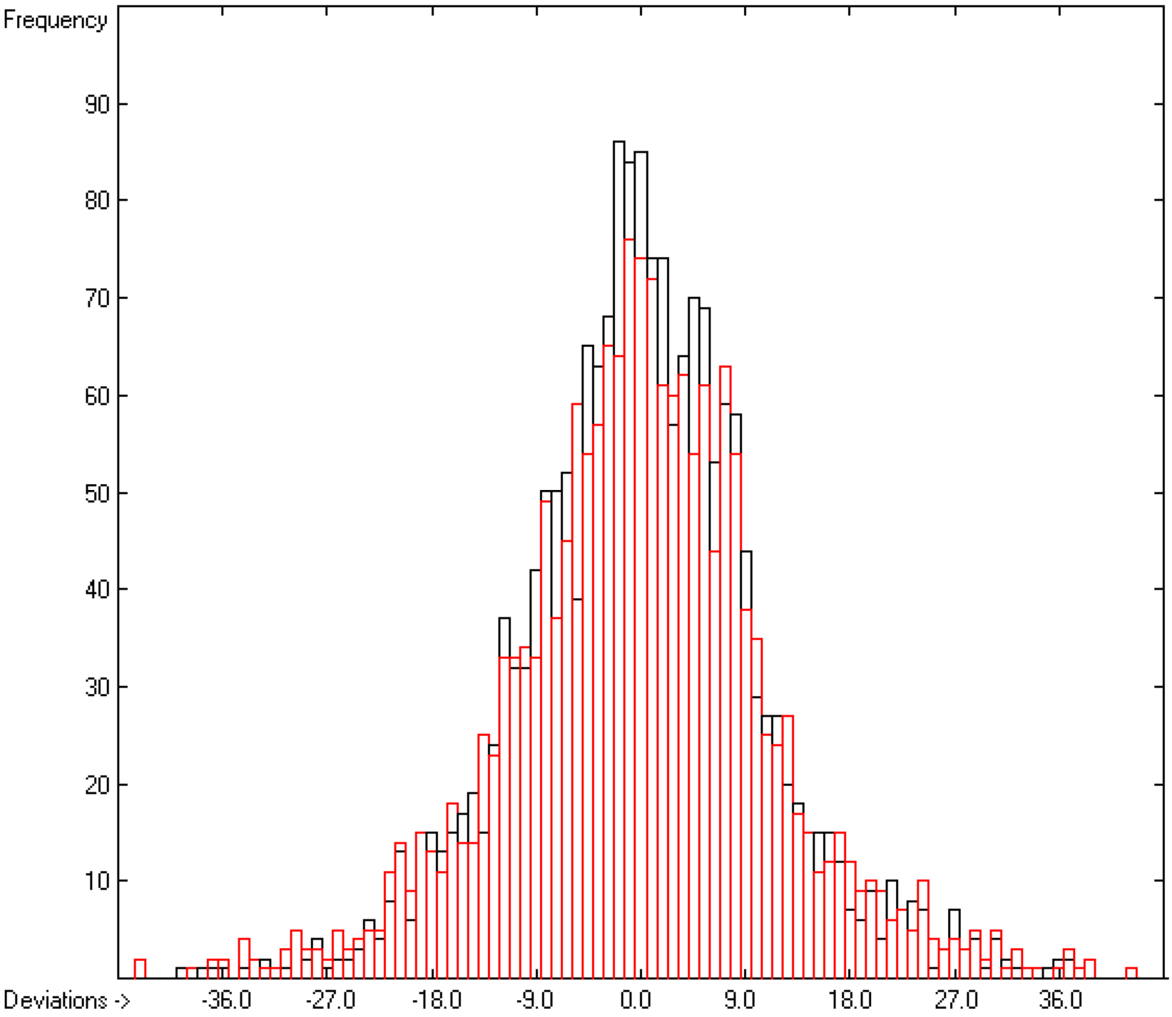

Figure 4. Histogram of the Enthalpy-of-Sublimation Data (S=11.39 kJ/mol; Exp. values range: 38.7<–>331.88 kJ/mol)

The lower number of "valid" atom groups of 154, as shown in row A of Table 2, led to the slightly reduced amount of 75.9% of the molecules in the representative database for which the heat of sublimation was calculable.

The list of compounds, their experimental and calculated data and 3D structures are available in the supplementary material under the names of "Experimental and Calculated Heat-of-Sublimation Data Table.doc" and "Compounds List for Heat-of-Sublimation Calculations.sdf". A list of the outliers has been added under the name of "Compounds List of Heat-of-Sublimation Outliers.xls".

3.3. Enthalpy of Fusion

It seems obvious to try to apply the atom-group additivity method as described in the preceding chapters for the prediction of the enthalpy of fusion, all the more as several authors [21, 60] have already used this principle very successfully. However, since the presented predictions of the enthalpies of sublimation and vaporization rest exclusively on experimental values at 298K, it is legitimate to refer to the simple Equation 2 which defines a molecule's enthalpy of fusion at standard conditions as the difference between its enthalpy of sublimation and its enthalpy of vaporization.

$$\Delta H^0_{fus}(298K)\ \text{calc.} = \Delta H^0_{sub}(298K)\ \text{calc.} - \Delta H^0_{vap}(298K)\ \text{calc.} \qquad (2)$$

Accordingly, the standard deviation of the thus evaluated enthalpy of fusion can be calculated by means of the error-propagation equation for the sum of two cross-validation standard errors $Q^2(\Delta H^0_{sub})$ (=11.39kJ/mol) and $Q^2(\Delta H^0_{vap})$ (=4.56kJ/mol), resulting in a standard deviation σ for the calculated enthalpy of fusion of 12.27 kJ/mol. Evidently, this deviation is largely dominated by the uncertainty of the experimental heats of sublimation and, thus would gain the most upon the provision of more accurate sublimation data.

How well do the predictions of equation 2 compare to experimental heat-of-fusion data? In order to answer this question more than 1200 experimental values have been inserted into the database, originating from Acree's compendium publication [8], complemented by recent values for crown ethers [29], fluorinated alcohols [33], adamantanes [53], 2-chloro-3-(trifluoromethyl)pyridine [61], cyanatophenyl derivatives [62], diphenylamines [63], fatty acids [64], pyridinecarbothioamides [65], isoniazid [66] and phenylthiazole-thione [67]. Figure 5 shows the correlation of the experimental with the predicted values, calculated by means of Formula 2. After removal of the worst 28 outliers the correlation coefficient R^2 for the remaining 990 samples (for which both the experimental and predicted values were available) was calculated to 0.60. This rather low value is at least in part explicable by findings outlined in several papers revealing that for certain compounds experimental values originating from different authors often scatter over a large range. For instance, K.-A. Eckert et al. [64] graphically demonstrated for various fatty acids that the value of their enthalpy of fusion varied drastically over a period of up to 80 years of repeated examination. Some examples: the enthalpy of fusion for palmitic acid randomly varied over the years between ca. 41 and 60 kJ/mol, and for stearic acid the range, varying between ca. 45 and 74 kJ/mol, was even wider. Analogous observations were made by J. Leitner and S. Jurik [68], who discovered similar discrepancies by different authors also for small molecules, exemplified by paracetamol and aspirin, for which the published values varied between 26 and 34.1, and between 29.89 and 32.92 kJ/mol, respectively. Figure 5, also demonstrating that the overwhelming number of experimental data is concentrated in the narrow range of below 40 kJ/mol, provides another explanation for the difficulty to enable exact predictions. The related histogram in Figure 6 nevertheless proves a satisfyingly even distribution of the deviations about the regression line drawn in Figure 5. Thanks to the broad applicability of the "valid" number of atom-group parameters for both the heat of sublimation as well as the heat of vaporization, Equation 2 enabled the estimation of the heat of fusion of 68% of the database's molecules.

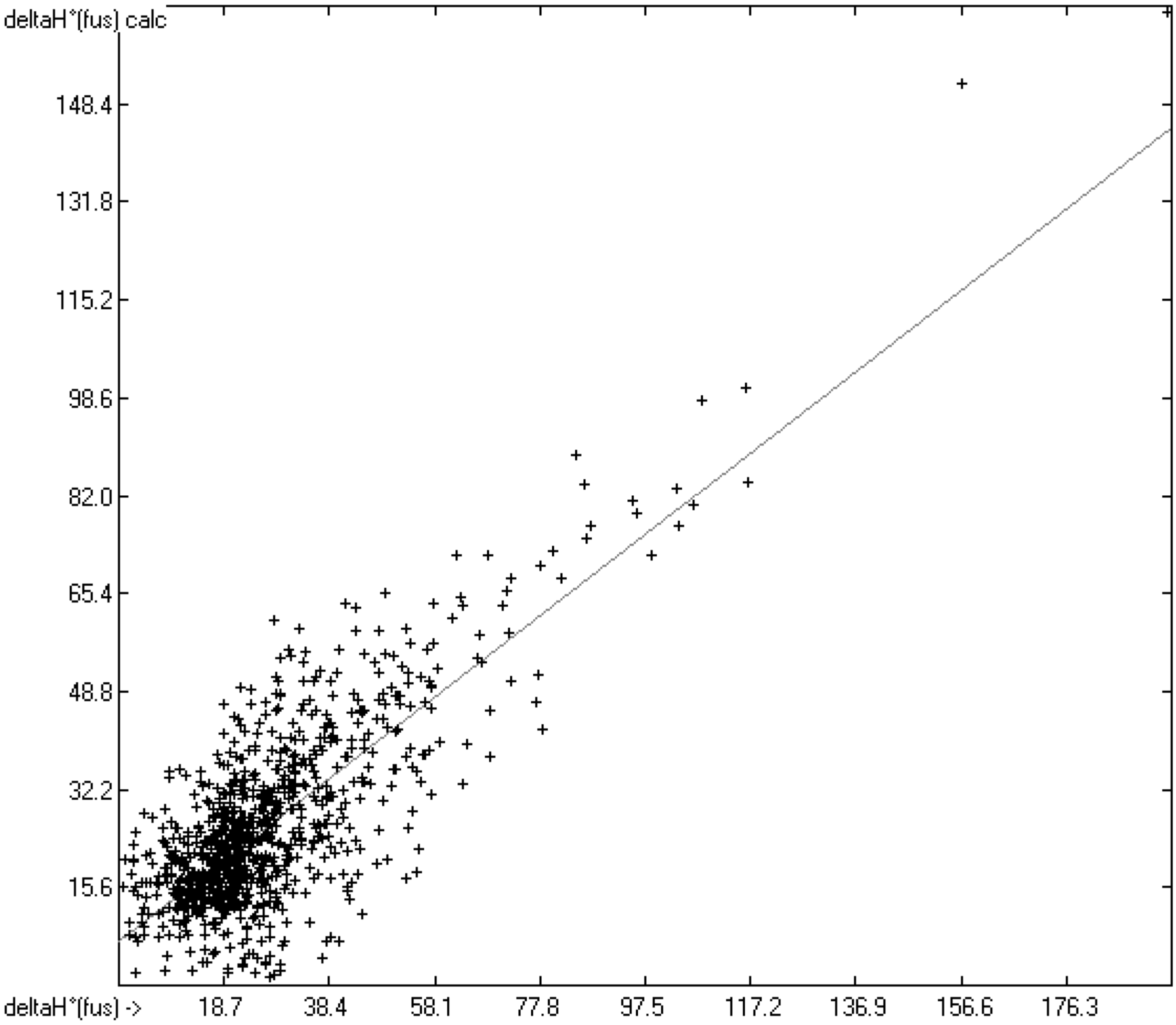

Figure 5. Correlation Diagram of the Enthalpy-of-Fusion Data (N=990; R^2=0.6066; calculated values evaluated by means of Formula 2)

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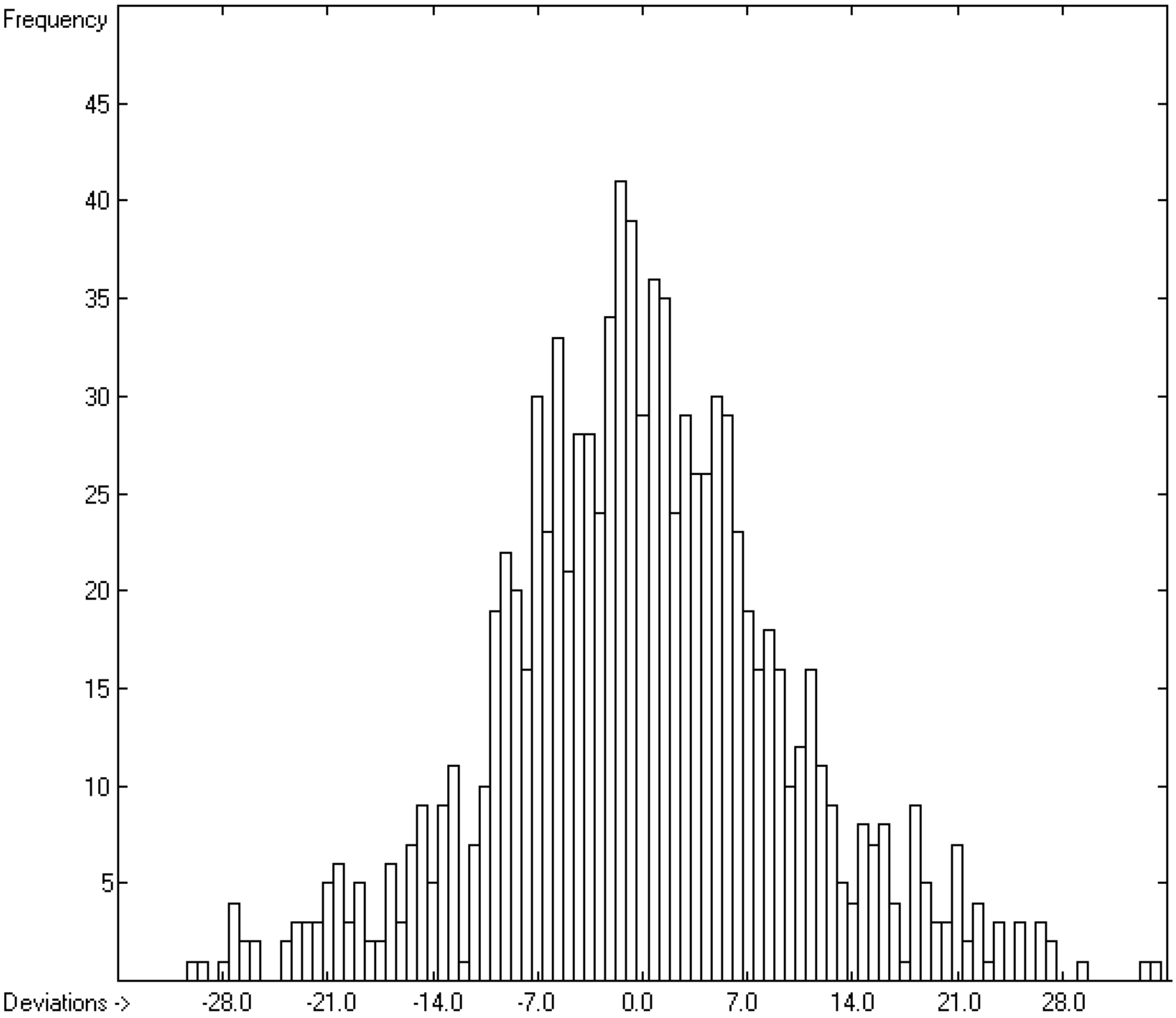

Figure 6. Histogram of the Enthalpy-of-Fusion Data (S=9.78 kJ/mol; Exp. values range: 0.30<–>164, kJ/mol)

The supplementary material offers the related list of molecules together with the experimental data under the file names "Experimental and Calculated Heat-of-Fusion Data Table.xls" and "Compounds List for Heat-of-Fusion Calculations.sdf". The list of the outliers is available under the name of "Compounds List of Heat-of-Fusion Outliers.xls".

3.4. Enthalpy of Solvation

Literature referencing experimental enthalpy-of-solvation data is relatively scarce. The most yielding source was found in Ch. Mintz et al.'s [69] paper on the application of the Abraham model mentioned earlier on gaseous solutes dissolved in water and 1-octanol. Further studies were made on N-methylimidazole [70], urea and its derivatives [71-73], thiourea and its derivatives [74], carboxamides and their N-substituted derivatives [75-78], and uracil and its alkyl-, amino-, nitro- and halosubstituted derivatives [79-82]. Of the accordingly limited number of 465 compounds having experimental enthalpy-of-solvation values in their datalist, 436 have been entered into the calculation of the atom-group parameters, resulting in 61 valid groups allowing the evaluation of the cross-validated prediction of the solvation enthalpy of 373 compounds with a cv-goodness of fit of 0.9546

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and a corresponding standard deviation Q^2 of 4.34 kJ/mol as is shown in aggregated manner in Table 3.

Table 3. Atom Groups and their Contributions (in kJ/mol) for Heat-of-Solvation Calculations

Nr	Atom Type	Neighbours	Contribution	Occurrences	Molecules
1	Const		-13.33	436	436
2	C sp3	H3C	-4.44	483	265
3	C sp3	H3N	-31.51	47	28
4	C sp3	H3N(+)	-31.22	1	1
5	C sp3	H3O	-15.38	34	29
6	C sp3	H3S	-12.79	7	4
7	C sp3	H2C2	-3.86	506	186
8	C sp3	H2CN	-31.29	55	37
9	C sp3	H2CN(+)	-22.60	2	2
10	C sp3	H2CO	-15.26	178	90
11	C sp3	H2CS	-12.03	9	6
12	C sp3	H2CF	-6.02	1	1
13	C sp3	H2CCl	-8.52	15	11
14	C sp3	H2CBr	-11.73	1	1
15	C sp3	H2CJ	-13.80	2	2
16	C sp3	H2O2	-14.86	1	1
17	C sp3	HC3	-2.51	45	35
18	C sp3	HC2N	-29.99	6	5
19	C sp3	HC2N(+)	-20.74	1	1
20	C sp3	HC2O	-14.95	32	29
21	C sp3	HC2F	-5.77	1	1
22	C sp3	HC2Cl	-8.53	1	1
23	C sp3	HC2J	-14.39	1	1
24	C sp3	HCF2	-5.07	3	3
25	C sp3	HCCl2	-11.02	5	4
26	C sp3	C4	0.43	10	10
27	C sp3	C3N	-24.37	3	3
28	C sp3	C3O	-16.23	6	6
29	C sp3	C3Cl	-1.29	1	1
30	C sp3	C3Br	1.24	1	1
31	C sp3	C3J	-7.51	1	1
32	C sp3	C2F2	-5.12	2	2
33	C sp3	COF2	0.74	1	1
34	C sp3	CF3	-2.85	11	9
35	C sp3	CF2Cl	-3.44	3	2
36	C sp3	CFCl2	-12.04	1	1
37	C sp3	CCl3	-12.64	2	2
38	C sp2	H2=C	-2.93	15	13
39	C sp2	HC=C	-2.16	26	20
40	C sp2	HC=O	-16.45	9	9
41	C sp2	H=CN	-13.78	17	13
42	C sp2	H=CO	-10.21	1	1
43	C sp2	H=CS	-6.13	2	1

44	C sp2	H=CCl	-7.34	5	3
45	C sp2	HN=N	-10.70	2	2
46	C sp2	HN=O	-33.05	4	4
47	C sp2	HO=O	-14.45	7	7
48	C sp2	C2=C	1.28	11	11
49	C sp2	C=CN	-15.51	2	2
50	C sp2	C=CN(+)	-39.48	1	1
51	C sp2	C2=O	-17.65	20	20
52	C sp2	C=CF	-6.97	2	2
53	C sp2	C=CCl	-31.39	1	1
54	C sp2	C=CBr	-28.79	1	1
55	C sp2	C=CJ	-31.42	1	1
56	C sp2	=CN2	-32.45	3	3
57	C sp2	CN=O	-39.35	30	30
58	C sp2	=CNCl	-30.33	1	1
59	C sp2	CO=O	-17.24	63	52
60	C sp2	=CF2	0.44	3	2
61	C sp2	=CCl2	-11.89	2	2
62	C sp2	N2=O	-35.29	25	25
63	C sp2	N2=S	-41.79	6	6
64	C aromatic	H:C2	-2.84	437	100
65	C aromatic	H:C:N	-14.82	29	18
66	C aromatic	:C3	-3.23	13	6
67	C aromatic	C:C2	-1.72	90	63
68	C aromatic	C:C:N	-15.13	7	6
69	C aromatic	:C2N	-10.35	13	13
70	C aromatic	:C2N(+)	-21.83	6	6
71	C aromatic	:C2:N	-15.19	1	1
72	C aromatic	:C2O	-9.63	21	17
73	C aromatic	:C2F	-1.79	1	1
74	C aromatic	:C2Cl	-3.91	37	19
75	C aromatic	:C2Br	-5.99	1	1
76	C aromatic	:CN:N	-16.20	1	1
77	C sp	H#C	-1.37	1	1
78	C sp	C#C	0.00	1	1
79	C sp	C#N	-17.66	15	12
80	N sp3	H2C	-2.40	25	20
81	N sp3	H2C(pi)	-16.13	32	30
82	N sp3	HC2	24.30	6	6
83	N sp3	HC2(pi)	11.97	26	22
84	N sp3	HC2(2pi)	3.09	21	12
85	N sp3	C3	57.51	5	5
86	N sp3	C3(pi)	52.51	10	9
87	N sp3	C3(2pi)	36.53	13	8
88	N sp2	C=C	-19.81	2	2
89	N aromatic	:C2	5.38	19	19
90	N(+) sp2	CO=O(-)	8.85	11	11
91	O	HC	-17.23	61	50
92	O	HC(pi)	-18.29	32	26

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93	O	HO	-22.54	2	1
94	O	C2	8.60	68	39
95	O	C2(pi)	10.97	56	49
96	O	C2(2pi)	9.97	2	2
97	S2	HC	1.98	4	4
98	S2	C2	6.62	3	3
99	S2	C2(2pi)	0.00	1	1
100	S2	CS	2.30	4	2
101	S4	C2=O	-33.00	1	1
102	H	H Acceptor	10.02	2	2
103	Alkane	No of C atoms	0.96	142	23
104	Unsaturated HC	No of C atoms	0.25	307	37
A	Based on	Valid groups	61		436
B	Goodness of fit	R^2	0.9731		388
C	Deviation	Average	2.68		388
D	Deviation	Standard	3.53		388
E	K-fold cv	K	10		373
F	Goodness of fit	Q^2	0.9546		373
G	Deviation	Average (cv)	3.22		373
H	Deviation	Standard (cv)	4.34		373

Due to the limited number of compounds, the histogram in Figure 7 reveals a slightliy distorted Gaussian bell form. Nevertheless, the analysis of the error distribution reveals that 78.8% of the compounds deviated by less than one cv-standard deviation, whereas for only 5% the deviation was larger than twice this value. The small number of only 61 valid atom groups limited the range of compounds in the database eligible for a heat-of-solvation prediction to 40%.

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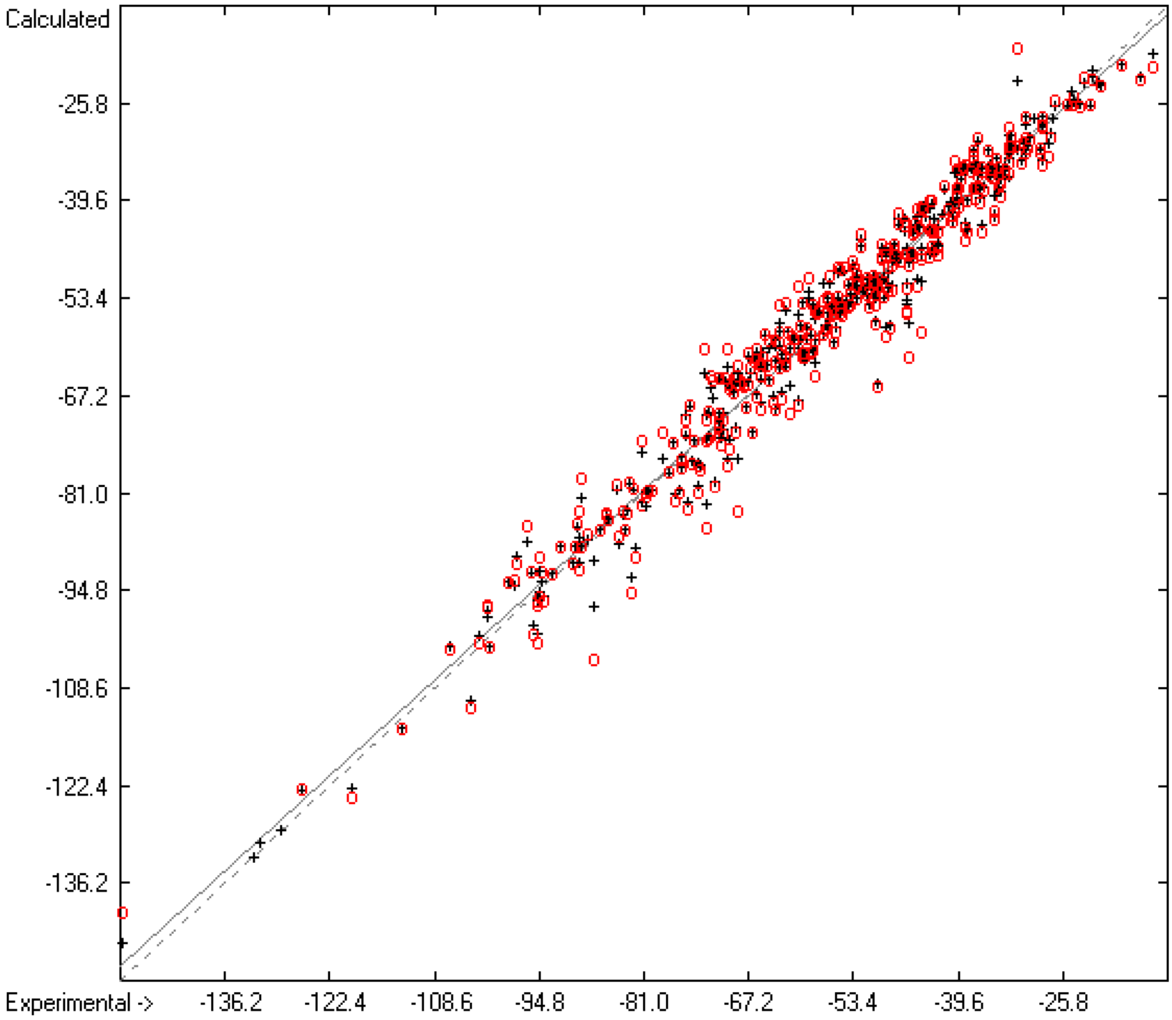

Figure 7. Correlation Diagram of the Enthalpy-of-Solvation Data (N=388; R^2=0.9731; Q^2=0.9546; regression line: intercept =-1.4422, slope=0.9759)

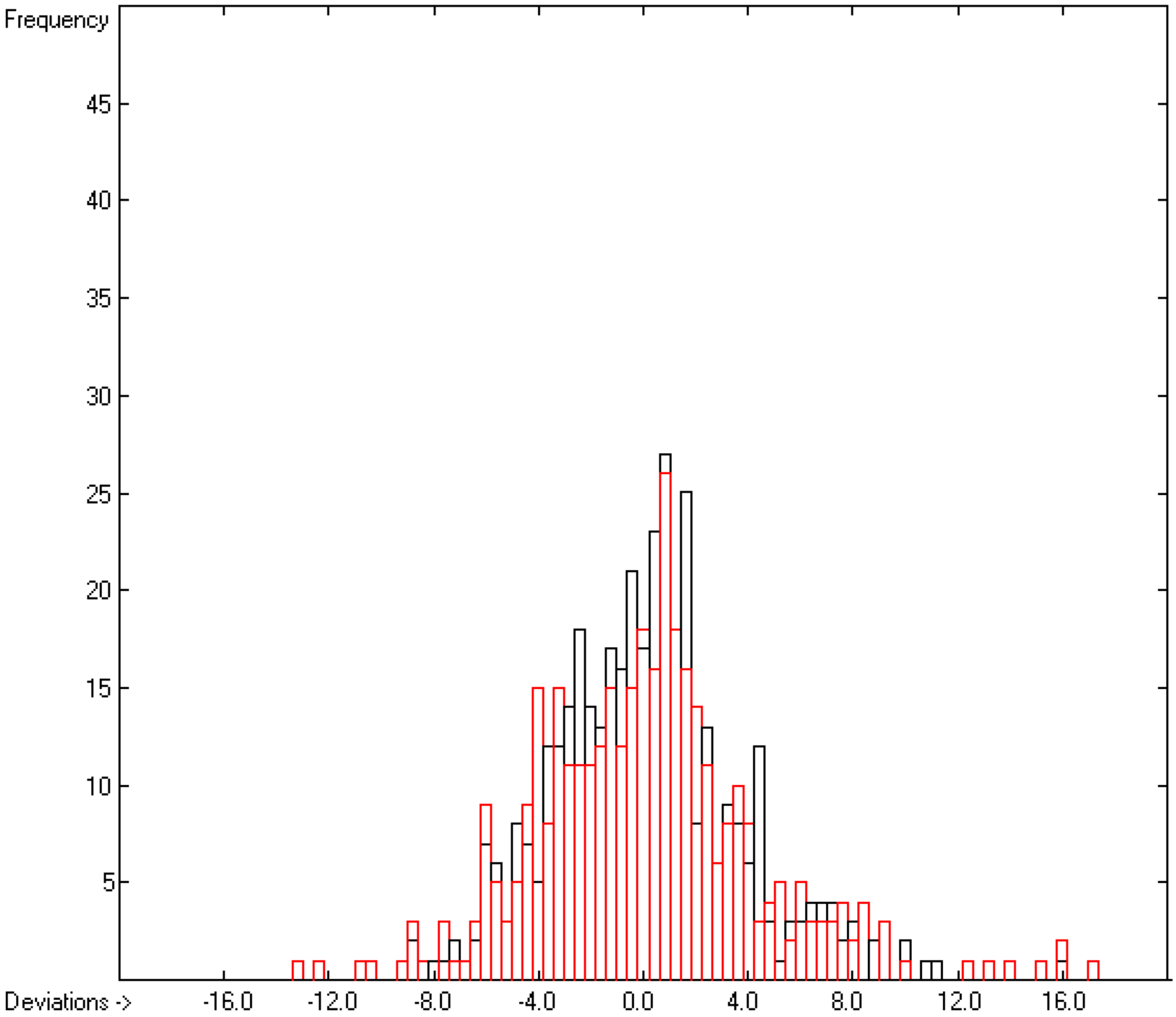

Figure 8. Histogram of the Enthalpy-of-Solvation Data (S=4.34 kJ/mol; Exp. values range: -149.51<–>-13.7 kJ/mol)

The result list, encompassing the molecule names, experimental and calculated heats of solvation, are available in the supplementary material under the name "Experimental and Calculated Heat-of-Solvation Data Table.doc"; the molecules list, encompassing their name and 3D coordinates are collected under the name "Compounds List for Heat-of-Solvation Calculations.sdf" and the list of outliers in "Compounds List of Heat-of-Fusion Outliers.xls".

3.5. Entropy of Fusion

The entropy of fusion under this subtitle is defined as the entropy change associated with the phase change from the crystalline to the isotropic liquid state of a molecule without passing any intermediate anisotropic, semiliquid phases. In most cases this transition indeed occurs in one stage, but several molecules, on addition of heat, undergo a change from one crystalline phase to a second or even third energetically less stable phase prior to melting. In the following, the entropy-of-fusion values cited in the tables are the sum of all the entropies associated with these solid-solid phase changes including the final solid-liquid phase change. The main source for these values was found in the comprehensive collection of Chickos,

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Acree and Liebman [21] and in its update [60]. More recent entropy-of-fusion data were found for long-chain fluorinated alcohols [33], halogenated fluorenes [35], di- and tri(cyanatophenyl)alkanes and -silanes [62], 2-cyano-4′-methylbiphenyl [83], diphenyl cyclohexyl-phosphoramidate [84] and 3,4-dinitrofurazanfuroxan [85]. The complete set of compounds with experimental entropy-of-fusion values amounted to a total of 2809 used for the evaluation of the atom-group parameters, yielding 188 valid atom groups. Various tentative calculations including or excluding certain special groups revealed a distinct improvement of the goodness of fit of the optimization process, if the group "Endocyclic bonds" was involved, which counts all single endocyclic bonds in a molecule. However, for small molecules containing small rings this group parameter tended to overcompensate the decrease of freedom of mobility and, therefore, the three special groups "Angle60", "Angle90" and "Angle102" were added as counter-correctives. The cross-validation calculation with 2637 samples resulted in a very satisfying goodness of fit Q^2 of 0.8727 and a standard deviation of 17.93 J/mol/K. In Table 4 the results of these calculations are summarized. 55 compounds had to be removed from the calculations as their experimental values deviated from prediction by more than three times the cv-standard deviation. The large number of valid atom groups, on the other hand, enabled the calculation of the entropy of fusion for 81.8% of the database's compounds,

Table 4. Atom Groups and their Contributions (in J/mol/K) for Entropy-of-Fusion Calculations

Nr	Atom Type	Neighbours	Contribution	Occurrences	Molecules
1	Const		31.12	2809	2809
2	B	C3	12.34	2	2
3	B	CO2	51.11	5	5
4	C sp3	H3B	-4.93	3	1
5	C sp3	H2BC	4.93	3	1
6	C sp3	H3C	1.90	2944	1402
7	C sp3	H3N	15.63	279	149
8	C sp3	H3N(+)	7.07	2	2
9	C sp3	H3O	14.42	366	232
10	C sp3	H3P	21.07	3	3
11	C sp3	H3S	12.93	35	31
12	C sp3	H3Si	8.19	283	46
13	C sp3	H2C2	8.46	8600	1239
14	C sp3	H2CN	14.85	505	257
15	C sp3	H2CN(+)	19.09	29	21
16	C sp3	H2CO	14.52	952	473
17	C sp3	H2CP	17.50	3	2
18	C sp3	H2CS	16.77	166	83
19	C sp3	H2CF	12.36	1	1
20	C sp3	H2CCl	10.67	30	24
21	C sp3	H2CBr	11.79	24	17
22	C sp3	H2CJ	3.10	2	2
23	C sp3	H2CSi	8.50	62	20

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24	C sp3	H2N2	5.03	20	11
25	C sp3	H2NO	8.98	8	7
26	C sp3	H2NS	43.70	4	4
27	C sp3	H2O2	22.34	23	14
28	C sp3	H2S2	29.21	7	5
29	C sp3	H2SCl	22.89	1	1
30	C sp3	H2Si2	12.02	6	3
31	C sp3	HC3	0.64	817	388
32	C sp3	HC2N	18.09	117	103
33	C sp3	HC2N(+)	-9.91	16	16
34	C sp3	HC2O	10.63	357	226
35	C sp3	HC2S	9.80	18	13
36	C sp3	HC2F	8.23	2	2
37	C sp3	HC2Cl	10.38	22	10
38	C sp3	HC2Br	8.94	5	4
39	C sp3	HC2Si	-14.02	1	1
40	C sp3	HCN2	1.21	2	1
41	C sp3	HCNO	23.14	7	6
42	C sp3	HCNS	23.70	1	1
43	C sp3	HCO2	19.18	30	26
44	C sp3	HCOCl	19.13	2	1
45	C sp3	HCF2	4.20	4	4
46	C sp3	HCFCl	-10.16	1	1
47	C sp3	HCCl2	9.01	10	9
48	C sp3	HCClBr	-3.80	1	1
49	C sp3	C4	-0.23	435	256
50	C sp3	C3N	14.87	22	20
51	C sp3	C3N(+)	12.86	6	5
52	C sp3	C3O	4.63	81	74
53	C sp3	C3S	16.54	6	6
54	C sp3	C3F	18.64	14	12
55	C sp3	C3Cl	9.23	14	9
56	C sp3	C3Br	3.44	2	2
57	C sp3	C3J	31.10	1	1
58	C sp3	C2N2	52.69	3	2
59	C sp3	C2N2(+)	4.24	7	6
60	C sp3	C2NO	34.66	1	1
61	C sp3	C2NF	47.27	1	1
62	C sp3	C2NCl(+)	13.35	1	1
63	C sp3	C2O2	13.44	47	29
64	C sp3	C2S2	10.13	1	1
65	C sp3	C2F2	-0.09	262	37
66	C sp3	C2Cl2	10.32	9	7
67	C sp3	CN3(+)	7.29	6	5
68	C sp3	CNF2	6.86	7	3
69	C sp3	COF2	-3.57	4	3
70	C sp3	CS3	30.56	4	1
71	C sp3	CSF2	41.61	2	1
72	C sp3	CSCl2	46.90	2	2

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73	C sp3	CF3	3.38	91	76
74	C sp3	CF2Cl	-1.55	6	5
75	C sp3	CF2Br	8.94	4	3
76	C sp3	CFCl2	-6.89	3	2
77	C sp3	CCl3	0.92	17	16
78	C sp3	NF3	11.04	1	1
79	C sp3	O2F2	20.23	1	1
80	C sp3	OF3	2.25	2	2
81	C sp3	SF3	24.96	4	4
82	C sp3	SCl3	46.90	1	1
83	C sp3	SiCl3	14.20	1	1
84	C sp2	H2=C	5.49	84	76
85	C sp2	HC=C	2.46	607	323
86	C sp2	HC=N	-0.81	48	40
87	C sp2	H=CN	3.18	44	37
88	C sp2	HC=O	8.29	18	18
89	C sp2	H=CO	5.29	19	17
90	C sp2	H=CS	-1.85	43	33
91	C sp2	H=CCl	10.11	3	3
92	C sp2	H=CSi	2.92	3	3
93	C sp2	HN=N	9.78	30	22
94	C sp2	HN=O	-10.25	3	3
95	C sp2	H=NO	21.94	1	1
96	C sp2	H=NS	1.04	4	4
97	C sp2	HO=O	14.63	2	2
98	C sp2	C2=C	0.30	212	166
99	C sp2	C2=N	7.33	35	33
100	C sp2	C2=N(+)	2.31	1	1
101	C sp2	C=CN	-2.70	51	45
102	C sp2	C=CN(+)	0.00	2	1
103	C sp2	C2=O	1.57	386	298
104	C sp2	C=CO	5.58	70	52
105	C sp2	C=CS	0.18	38	25
106	C sp2	C=CCl	3.68	20	13
107	C sp2	C=CBr	45.90	1	1
108	C sp2	=CN2	12.85	17	17
109	C sp2	=CN2(+)	6.14	1	1
110	C sp2	CN=N	1.47	25	19
111	C sp2	=CNO	-1.47	6	4
112	C sp2	CN=O	0.63	366	234
113	C sp2	C=NO	9.33	5	5
114	C sp2	C=NS	7.20	7	7
115	C sp2	CN=S	-2.87	10	8
116	C sp2	=CNCl	11.25	1	1
117	C sp2	CO=O	5.68	718	546
118	C sp2	CO=O(-)	-16.84	19	19
119	C sp2	C=OF	9.78	3	2
120	C sp2	C=OCl	14.97	2	1
121	C sp2	C=OS	16.72	1	1

122	C sp2	=CS2	-7.29	12	2
123	C sp2	=CSCl	2.93	3	2
124	C sp2	=CSBr	-4.03	1	1
125	C sp2	=CF2	11.60	3	2
126	C sp2	=CFCl	1.87	1	1
127	C sp2	=CCl2	5.32	9	8
128	C sp2	=CBr2	46.05	1	1
129	C sp2	N2=N	11.87	9	9
130	C sp2	N2=O	-3.48	90	84
131	C sp2	N=NO	3.41	1	1
132	C sp2	N2=S	0.55	32	31
133	C sp2	N=NS	-3.08	23	23
134	C sp2	NO=O	0.38	62	60
135	C sp2	N=OS	20.86	2	2
136	C sp2	NO=S	-2.08	8	8
137	C sp2	NS=S	25.24	3	3
138	C sp2	=NS2	-12.86	2	2
139	C sp2	O2=O	-9.60	10	10
140	C sp2	=OS2	6.53	1	1
141	C aromatic	B:C2	-47.51	5	5
142	C aromatic	H:C2	2.57	8600	1498
143	C aromatic	H:C:N	1.17	108	68
144	C aromatic	H:N2	-1.12	5	3
145	C aromatic	:C3	-1.60	481	153
146	C aromatic	C:C2	-2.58	2198	1062
147	C aromatic	C:C:N	5.44	46	38
148	C aromatic	:C2N	-0.38	524	389
149	C aromatic	:C2:N	-5.26	33	20
150	C aromatic	:C2N(+)	4.26	203	144
151	C aromatic	:C2O	2.82	853	532
152	C aromatic	:C2P	-2.68	12	5
153	C aromatic	:C2S	0.30	98	73
154	C aromatic	:C2Si	3.80	45	21
155	C aromatic	:C2F	4.24	150	69
156	C aromatic	:C2Cl	5.68	860	318
157	C aromatic	:C2Br	4.73	92	57
158	C aromatic	:C2J	6.30	26	19
159	C aromatic	:CN:N	5.87	28	27
160	C aromatic	:CN:N(+)	0.05	2	1
161	C aromatic	:C:NO	3.76	9	7
162	C aromatic	:C:NS	2.70	2	1
163	C aromatic	:C:NCl	9.38	8	8
164	C aromatic	N:N2	-9.59	85	40
165	C aromatic	:N2O	-5.16	4	2
166	C aromatic	:N2S	-2.43	5	5
167	C aromatic	:N2Cl	19.07	8	7
168	C sp	H#C	2.83	26	23
169	C sp	C#C	-0.52	183	83
170	C sp	=C2	7.54	4	4

171	C sp	C#N	2.66	120	94
172	C sp	#CSi	3.40	3	2
173	C sp	N#N	-16.19	1	1
174	C sp	=N2	23.07	1	1
175	C sp	#NO	6.78	10	4
176	C sp	=N=O	14.08	6	3
177	N sp3	H2C	9.39	34	21
178	N sp3	H2C(pi)	7.89	190	160
179	N sp3	H2N	0.92	5	5
180	N sp3	H2P	-16.37	1	1
181	N sp3	H2S	10.07	7	7
182	N sp3	HC2	-1.65	20	20
183	N sp3	HC2(pi)	-9.81	190	133
184	N sp3	HC2(2pi)	4.73	204	169
185	N sp3	HCN	-5.80	4	3
186	N sp3	HCN(pi)	-2.85	8	6
187	N sp3	HCN(+)(pi)	16.06	4	2
188	N sp3	HCN(2pi)	0.95	12	11
189	N sp3	HCO(pi)	30.19	1	1
190	N sp3	HCP	-6.83	2	2
191	N sp3	HCS	17.10	2	2
192	N sp3	HCS(pi)	9.38	22	22
193	N sp3	HSi2	1.67	7	2
194	N sp3	C3	-32.04	41	37
195	N sp3	C3(pi)	-17.08	137	97
196	N sp3	C3(2pi)	-12.64	136	108
197	N sp3	C3(3pi)	4.26	22	20
198	N sp3	C2N	-18.10	3	3
199	N sp3	C2N(pi)	-6.67	7	5
200	N sp3	C2N(+)(pi)	20.95	32	17
201	N sp3	C2N(2pi)	-3.87	15	14
202	N sp3	C2N(3pi)	1.17	6	6
203	N sp3	C2N(+)(2pi)	-0.16	12	12
204	N sp3	C2O	-41.10	5	5
205	N sp3	C2O(pi)	9.25	39	15
206	N sp3	C2O(2pi)	29.03	1	1
207	N sp3	C2P	7.24	1	1
208	N sp3	C2S	-25.22	3	3
209	N sp3	C2S(pi)	-22.07	1	1
210	N sp3	C2S(2pi)	-6.25	3	3
211	N sp3	CF2	-2.10	6	2
212	N(+) sp3	H2C2	4.33	19	19
213	N(+) sp3	C3O(-)	-33.09	1	1
214	N sp2	H=C	16.94	3	3
215	N sp2	C=C	-7.28	122	101
216	N sp2	C=N	-11.24	64	32
217	N sp2	C=N(+)	10.95	10	7
218	N sp2	=CN	-0.51	38	31
219	N sp2	=CO	0.98	32	31

220	N sp2	=CS	-4.17	3	2
221	N sp2	N=N	-0.32	10	6
222	N sp2	N=O	18.24	4	2
223	N aromatic	:C2	5.43	222	128
224	N aromatic	:C:N	-4.60	6	3
225	N(+) sp2	C=NO(-)	-19.90	4	4
226	N(+) sp2	CO=O(-)	1.45	248	163
227	N(+) sp2	=CO2(-)	-3.88	1	1
228	N(+) sp2	NO=O(-)	-1.33	48	31
229	N(+) sp2	O2=O(-)	1.85	7	5
230	N(+) sp	C#C(-)	10.24	1	1
231	N(+) sp	=N2(-)	2.76	6	3
232	O	HC	-2.00	452	254
233	O	HC(pi)	3.39	478	400
234	O	HN	0.63	36	12
235	O	HN(pi)	-1.02	19	19
236	O	HP	-8.39	2	1
237	O	HS	60.03	5	2
238	O	BC	0.00	5	5
239	O	BN	0.00	5	5
240	O	C2	-4.67	357	135
241	O	C2(pi)	-5.72	740	513
242	O	C2(2pi)	-3.04	267	217
243	O	CN	-20.33	4	4
244	O	CN(pi)	0.00	1	1
245	O	CN(2pi)	1.82	12	11
246	O	CN(+)(pi)	0.47	7	5
247	O	CO	1.80	8	4
248	O	CP	-6.11	47	25
249	O	CP(pi)	6.35	20	17
250	O	CS(pi)	1.11	3	3
251	O	CSi	-12.94	5	2
252	O	N2(2pi)			
253	O	N2(+)(2pi)	0.00	1	1
254	O	Si2	2.53	84	24
255	P3	C3	-6.01	3	2
256	P4	C3=O	-6.07	1	1
257	P4	C=OF2	-1.93	1	1
258	P4	C=OFCl	-4.92	1	1
259	P4	C=OCl2	6.84	1	1
260	P4	N2O=O	6.11	1	1
261	P4	NO2=O	-7.48	1	1
262	P4	NOS=S	6.11	1	1
263	P4	O3=O	-5.29	2	2
264	P4	O3=S	-3.13	13	12
265	P4	CO2=O	0.00	1	1
266	P4	CO2=S	7.66	2	2
267	P4	O2S=S	-5.52	7	7
268	S2	HC	-0.29	19	19

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269	S2	HC(pi)	-11.91	2	2
270	S2	C2	-10.10	74	47
271	S2	C2(pi)	1.44	44	37
272	S2	C2(2pi)	8.54	74	60
273	S2	CN	0.00	3	3
274	S2	CN(pi)	5.57	1	1
275	S2	CS	1.49	8	4
276	S2	CS(pi)	0.18	6	4
277	S2	CP	0.00	8	8
278	S2	N2(2pi)	-3.71	1	1
279	S4	C2=O	-10.46	6	4
280	S4	C2=O2	-10.18	22	22
281	S4	CN=O2	1.23	31	31
282	S4	CO=O2	0.00	8	5
283	S4	C=OS	4.07	2	2
284	S4	N2=O2	4.49	2	2
285	Si	H3C	0.00	1	1
286	Si	HC2O	-77.65	3	3
287	Si	HCO2	18.28	1	1
288	Si	C4	-12.05	23	18
289	Si	C3O	-15.58	14	9
290	Si	C3Cl	-8.02	2	2
291	Si	C3Si	-6.42	6	3
292	Si	C2N2	0.00	7	2
293	Si	C2O2	1.03	75	18
294	Si	C2Cl2	-1.79	2	2
295	Si	C2Si2	-10.09	34	5
296	Si	CCl3	4.64	8	7
297	Si	O4	13.30	1	1
298	H	H Acceptor	6.31	153	128
299	Angle60		0.54	120	33
300	Angle90		2.37	138	29
301	Angle102		0.12	1131	342
302	Endocyclic bonds	No of single bds	-4.42	5302	680
A	Based on	Valid groups	188		2809
B	Goodness of fit	R^2	0.8875		2701
C	Deviation	Average	12.33		2701
D	Deviation	Standard	16.72		2701
E	K-fold cv	K	10		2637
F	Goodness of fit	Q^2	0.8727		2637
G	Deviation	Average (cv)	13.23		2637
H	Deviation	Standard (cv)	17.93		2637

The correlation diagram in Figure 9 exhibits a large concentration of the entropy values in the range between 0 and ca. 140 J/mol/K; values of 200 J/mol/K or more are exclusively reserved for molecules carrying long, mostly un-branched methylene or poly-ether chains. The histogram (Figure 10) reveals a slight overweight of the positive deviations, indicating a minor trend to predict too low values.

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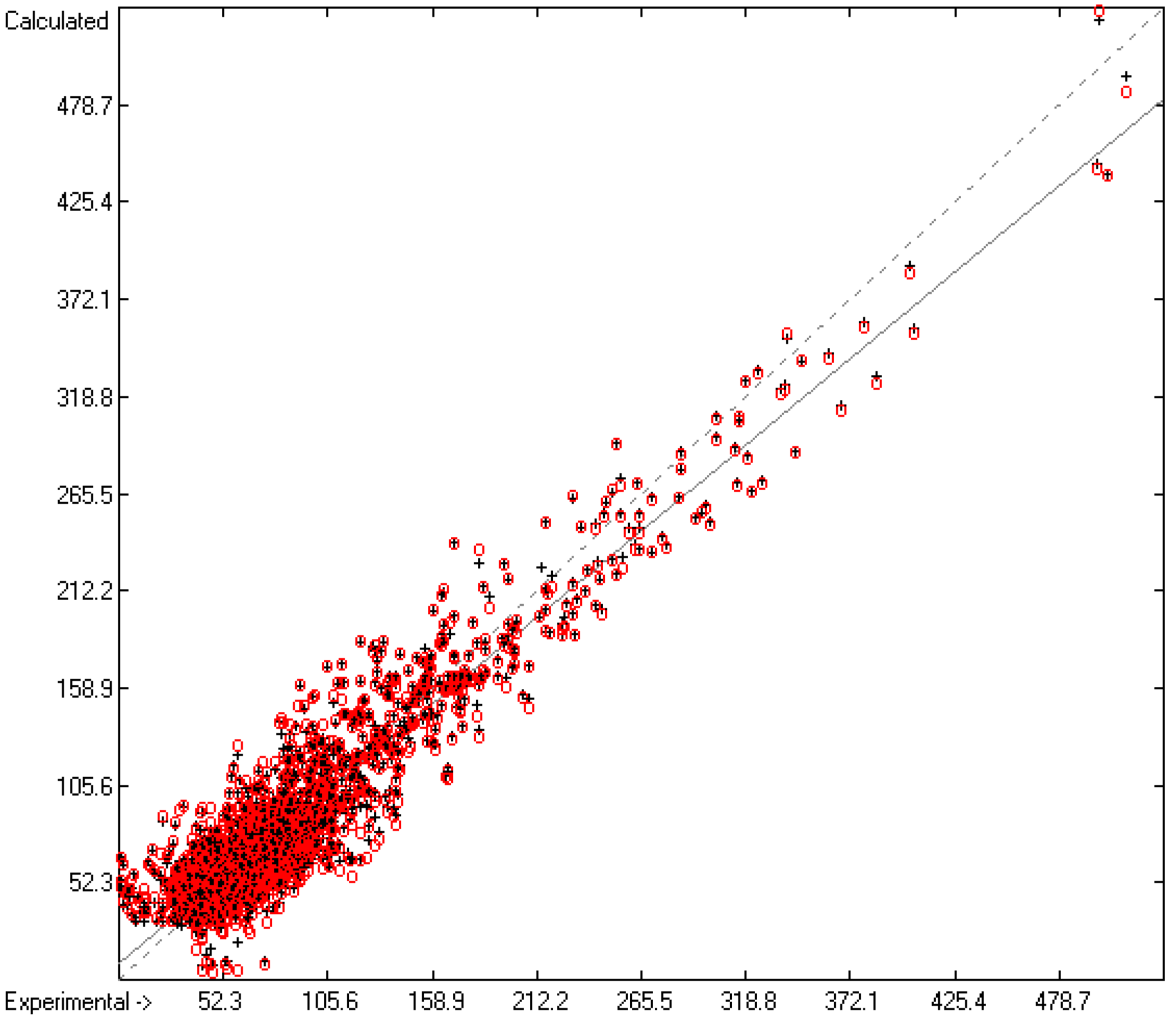

Figure 9. Correlation Diagram of the Entropy-of-Fusion Data (N=2701; R^2=0.8874; Q^2=0.8727; regression line: intercept =8.6540; slope=0.8883)

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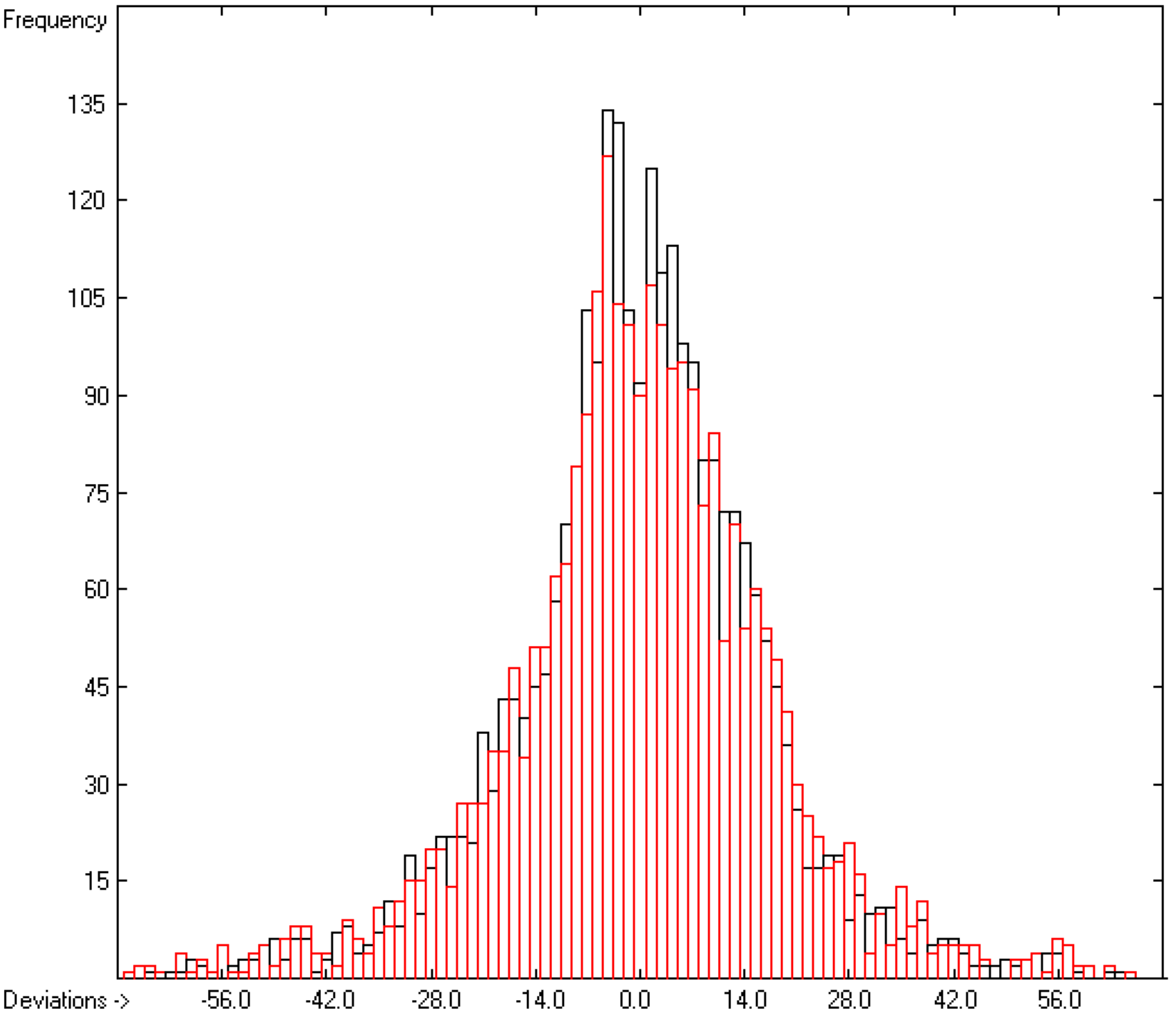

Figure 10. Histogram of the Entropy-of-Fusion Data (S=17.93 J/mol/K; Exp. values range: 0.65<–>513.5 J/mol/K)

The supplementary material provides the list of compounds for these calculations, together with experimental and calculated data under the name of “Experimental and Calculated Entropy-of-Fusion Data Table.doc”. The related compounds’ 3D-structures are available in “Compounds List for Entropy-of-Fusion Calculations.sdf”, the list of outliers in the Excel sheet called “Compounds List of Entropy-of-Fusion Outliers.xls”.

3.6. Total Phase-Change Entropy of Liquid Crystals

Liquid crystals are a class of molecules characterized by the special feature to often exhibit several distinct semiliquid states between their crystalline and isotropic liquid phases, i. e. anisotropic phases which are stable over an extended temperature range. Depending on their intermediate structure these phases are either called meso, cholesteric, smectic or nematic. This strange self-associative behaviour has typically been found with compounds the molecular structure of which contains rigid moieties and highly flexible pendant alkyl or polyether chains of various length, but also with molecules where certain parts exhibit strong intermolecular hydrogen bonds besides moieties of intermolecular inertness. Due to the variability of their entire melting processes resulting from their structural characteristics, the

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only common entropy term to possibly be generally applicable is the total phase-change entropy, defined as "the sum of all the entropy changes associated with phase transitions occurring from T=0K to the clearing temperature, $T=T_{iso}$." [22]. This definition only differs from the one given for the entropy of fusion in the previous chapter, in that here not only the potential solid-solid entropy-phase changes but also the entropy changes of the semiliquid intermediate phases are considered. Based on this definition, only the total phase-change entropy data of liquid crystals have been entered into the evaluation of the related atom-group parameters. The only source for these data was the large collection of more than 3000 compounds in the compendium work of W. E. Acree Jr. And J. S. Chickos [22]. The parameters calculation finally rested on 2686 compounds, yielding a direct goodness of fit R^2 of 0.6094 and a cross-validated goodness Q^2 of 0.5804 with a standard deviation of 32.79, as condensed at the bottom of Table 5. (In order to compare these data directly with those of the entropy-of-fusion calculation, the special groups "Angle60" and "Angle90" are kept in the parameters list although obviously no compound met any of these two criteria, i. e.. bond angle <=90 or <60.) These data compare favourably with those of Acree and Chickos [22], who reported a correlation coefficient of only 0.35 for 627 liquid crystals. The present results, however, required the removal of 56 compounds from the evaluation of the parameters, as their deviation from prediction was much larger than three times the cv-standard deviation.

Table 5. Atom Groups and their Contributions (in J/mol/K) for Total Phase-Change Entropy Calculations

Nr	Atom Type	Neighbours	Contribution	Occurrences	Molecules
1	Const		60.14	2686	2686
2	C sp3	H3C	5.33	5873	2490
3	C sp3	H3N	16.05	12	6
4	C sp3	H3O	2.66	195	172
5	C sp3	H3Si	3.08	110	5
6	C sp3	H2C2	4.04	30650	2478
7	C sp3	H2CN	-1.70	286	114
8	C sp3	H2CO	-0.01	3584	1901
9	C sp3	H2CS	-8.01	68	42
10	C sp3	H2CCl	-27.41	2	2
11	C sp3	H2CBr	-10.24	3	3
12	C sp3	H2CJ	30.88	1	1
13	C sp3	H2CSi	-2.48	6	3
14	C sp3	HC3	-9.84	1088	414
15	C sp3	HC2N	-17.47	4	4
16	C sp3	HC2O	-19.96	428	324
17	C sp3	HC2S	-42.59	18	18
18	C sp3	HC2Cl	-12.96	53	53
19	C sp3	HC2Br	6.97	4	4
20	C sp3	HCO2	7.19	34	28
21	C sp3	HCF2	-21.83	11	11
22	C sp3	C4	-0.53	212	120
23	C sp3	C3O	12.06	10	10

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24	C sp3	C3F	-25.29	2	2
25	C sp3	C2F2	4.67	272	57
26	C sp3	CSF2	-1.17	5	5
27	C sp3	CF3	-8.30	67	54
28	C sp3	OF3	24.11	2	2
29	C sp3	SF3	-196.06	1	1
30	C sp2	H2=C	14.81	58	56
31	C sp2	HC=C	-2.97	946	440
32	C sp2	HC=N	-2.07	922	704
33	C sp2	HC=N(+)	32.39	9	9
34	C sp2	HC=O	15.32	6	6
35	C sp2	H=CN	-16.69	43	41
36	C sp2	H=CO	-2.30	28	28
37	C sp2	H=CS	-4.67	2	2
38	C sp2	H=NS	74.91	1	1
39	C sp2	C2=C	-13.21	186	160
40	C sp2	C2=N	9.17	17	17
41	C sp2	C2=O	2.80	266	202
42	C sp2	C=CN	2.69	28	21
43	C sp2	C=CO	-53.38	21	21
44	C sp2	C=CS	-5.66	340	150
45	C sp2	C=CF	31.70	10	5
46	C sp2	CN=N	-13.68	15	15
47	C sp2	CN=O	-1.75	326	171
48	C sp2	C=NO	-39.68	45	30
49	C sp2	CN=S	-6.95	8	6
50	C sp2	C=NS	38.49	105	77
51	C sp2	=CNS	-47.14	22	11
52	C sp2	CO=O	8.07	3115	1580
53	C sp2	=COS	128.10	5	5
54	C sp2	C=OS	5.46	91	81
55	C sp2	=CSCl	15.27	9	9
56	C sp2	=CSJ	10.36	2	2
57	C sp2	N=NS	-11.16	72	72
58	C sp2	NO=O	38.80	6	6
59	C sp2	=NOS	96.96	24	12
60	C sp2	O2=O	26.06	3	3
61	C aromatic	H:C2	3.37	28602	2538
62	C aromatic	H:C:N	-0.02	151	82
63	C aromatic	H:C:N(+)	-9.49	12	6
64	C aromatic	:C3	-8.40	322	107
65	C aromatic	C:C2	-9.58	7933	2410
66	C aromatic	C:C:N	-38.40	89	61
67	C aromatic	:C2N	-13.66	1866	1124
68	C aromatic	:C2N(+)	-5.68	135	119
69	C aromatic	:C2:N	16.73	34	33
70	C aromatic	:C2O	-4.24	5711	2230
71	C aromatic	:C2S	-29.84	116	105
72	C aromatic	:C2Si	10.60	4	2

73	C aromatic	:C2F	4.38	525	266
74	C aromatic	:C2Cl	-3.87	197	151
75	C aromatic	:C2Br	2.55	24	23
76	C aromatic	:C2J	-35.42	9	9
77	C aromatic	C:N2	-43.07	27	21
78	C aromatic	:C:NCl	-51.42	2	2
79	C aromatic	N:N2	-17.88	6	3
80	C aromatic	:N2O	-31.16	4	4
81	C sp	H#C	15.40	1	1
82	C sp	C#C	-1.90	929	304
83	C sp	=C2	-15.98	9	9
84	C sp	C#N	4.72	229	212
85	C sp	#CO	29.96	2	1
86	C sp	=N=O	0.85	3	2
87	C sp	=N=S	15.48	42	42
88	C sp	#NS	7.49	26	26
89	N sp3	H2C	-12.08	5	5
90	N sp3	H2C(pi)	-66.66	6	6
91	N sp3	HC2(pi)	18.61	17	9
92	N sp3	HC2(2pi)	-4.58	233	143
93	N sp3	HCN(pi)	-6.87	6	3
94	N sp3	HCN(2pi)	42.99	12	12
95	N sp3	HCS(pi)	157.30	1	1
96	N sp3	C3	-75.12	10	10
97	N sp3	C3(pi)	-20.84	64	33
98	N sp3	C3(2pi)	8.12	34	25
99	N sp3	C3(3pi)	29.75	24	14
100	N sp2	C=C	14.07	1014	778
101	N sp2	C=N	9.88	722	295
102	N sp2	C=N(+)	8.87	32	32
103	N sp2	=CN	-40.91	206	94
104	N sp2	=CO	33.53	26	26
105	N aromatic	:C2	18.59	169	125
106	N aromatic	:C:N	17.07	12	3
107	N(+) sp2	CO=O(-)	0.77	94	78
108	N(+) sp2	C=CO(-)	-3.27	9	9
109	N(+) sp2	C=NO(-)	0.00	32	32
110	N(+) aromatic	:C2O(-)	23.39	6	6
111	O	HC	20.86	186	70
112	O	HC(pi)	16.46	202	156
113	O	C2	1.72	100	57
114	O	C2(pi)	-0.12	3901	2018
115	O	C2(2pi)	-2.52	2419	1340
116	O	CN(2pi)	-4.06	26	26
117	S2	HC(pi)	-10.11	2	2
118	S2	C2	12.90	18	18
119	S2	C2(pi)	14.58	55	42
120	S2	C2(2pi)	15.10	379	314
121	S4	CN=O2	-36.49	1	1

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122	Si	C3Si	0.00	10	5
123	Si	C2Si2	-3.55	45	5
124	H	H Acceptor	-17.84	151	107
125	Angle60		0.00	0	0
126	Angle90		0.00	0	0
127	Angle102		7.37	513	138
128	Endocyclic bonds	No of single bds	-1.14	3024	309
A	Based on	Valid groups	108		2686
B	Goodness of fit	R^2	0.6094		2663
C	Deviation	Average	23.83		2663
D	Deviation	Standard	31.62		2663
E	K-fold cv	K	10		2643
F	Goodness of fit	Q^2	0.5804		2643
G	Deviation	Average (cv)	24.65		2643
H	Deviation	Standard (cv)	32.79		2643

Nevertheless, it was to be expected that the additional entropy terms relating to the semiliquid phases would blur the picture in comparison with the previous chapter, since not only each homologous series of liquid crystals but even individual molecules proceed via different melting pathways. This feature is even observable in the list of outliers where several entire homologous series had to be removed. As a consequence of this inhomogeneity, the scatter of the total phase-change entropy of the liquid crystals in Figure 11 is extraordinarily high, but, as the histogram in Figure 12 shows, is evenly distributed about the regression line. This, and the close similarities of R^2 and Q^2 as well as of the direct and the cross-validated standard deviations, collected at the bottom of Table 5, may lead to the assumption that the associated atom-group parameters are reliable enough for phase-change entropy predictions within the class of liquid crystals. Two homologous examples may prove whether this assumption is justified.

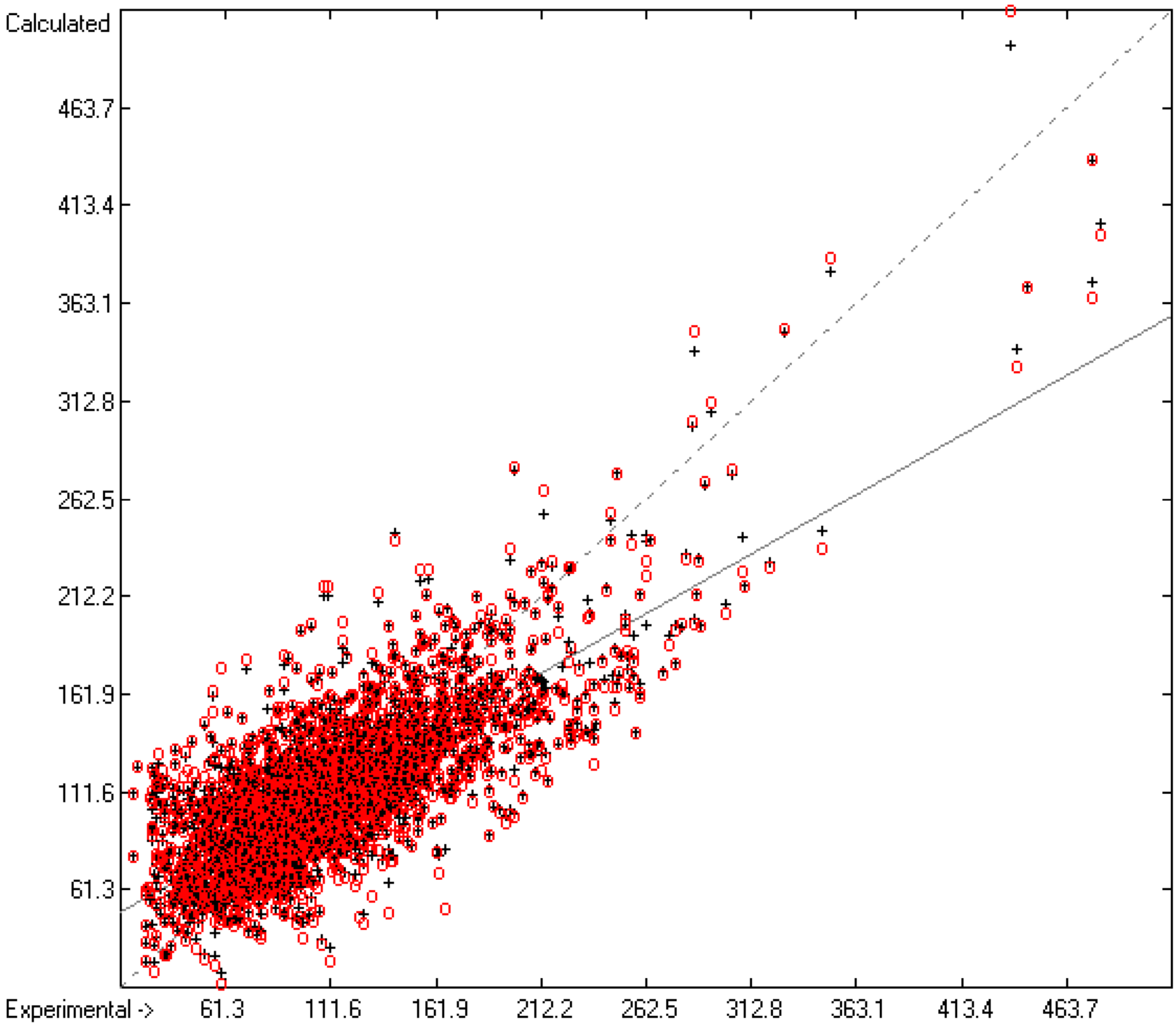

Figure 11. Correlation Diagram of the Total Phase-change Entropy Data (N=2663; R^2=0.6091; Q^2=0.5804; regression line: intercept =43.5325, slope=0.6083)

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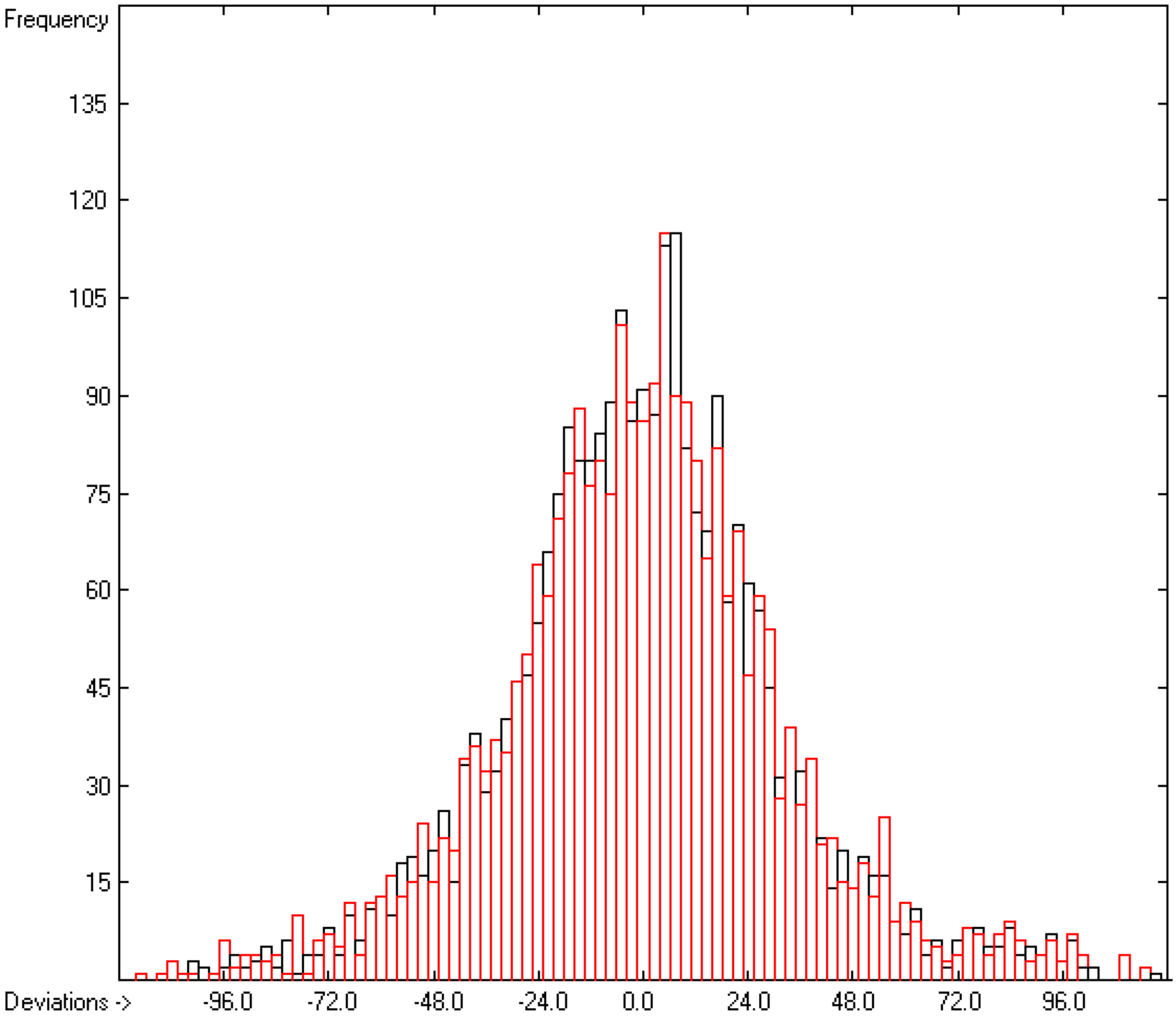

Figure 12. Histogram of the Total Phase-change Entropy Data (S=32.79 J/mol/K; Exp. values range: 17.6<–>480.76 J/mol/K)

In Figure 13, the experimental total phase-change entropy data of the liquid-crystal homologues of 7-alkyl-2-(4-cyanophenyl)-fluorene (with alkyl=ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and nonyl) are correlated with predicted values, revealing an excellent correlation coefficient R^2 of 0.9176. The slope of the regression line, however, is at 0.8830 considerably lower than 1.0. Figure 14 shows the analogous correlation of the homologues of 3-(4-alkyloxyphenylamino)-1-(2-(5-cyanothienyl))-2-propen-1-one (with alkyl=pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl and tetradecyl). Here, the correlation coefficient has been calculated to 0.0023 and the slope of the regression line is even slightly negative at -0.0364! These examples prove that the class of liquid crystals is too heterogeneous for the present atom-group additivity model to be applicable. Consequently, if even within the class of liquid crystals reliable predictions are impossible, attempts to do so outside this class would not make sense at all.

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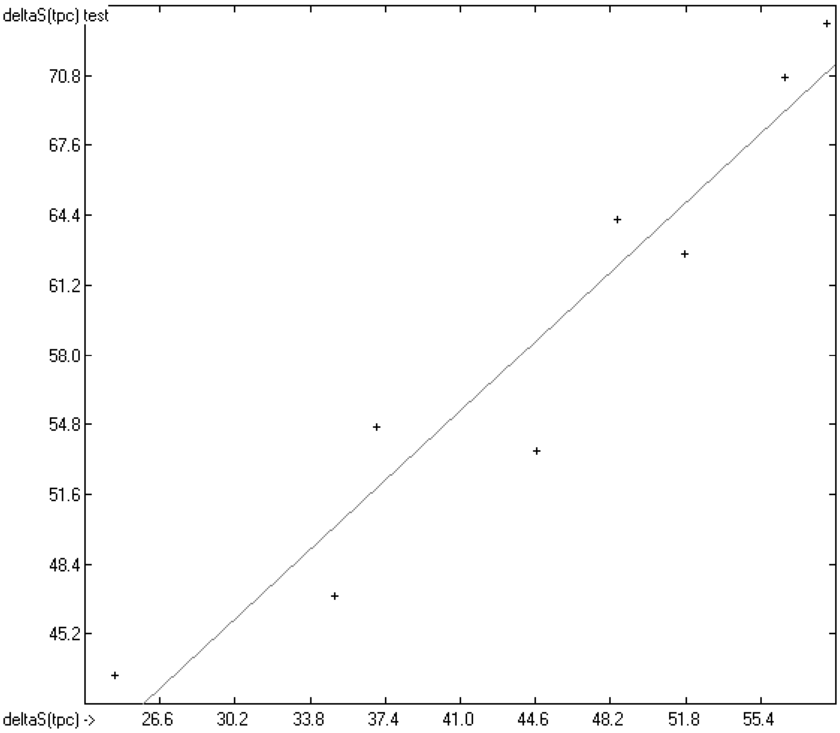

Figure 13. Correlation Diagram of the Total Phase-change Entropy Data of the homologues of 7-alkyl-2-(4-cyanophenyl)-fluorenes. (N=8; R^2=0.9176; σ=2.90 J/mol/K)

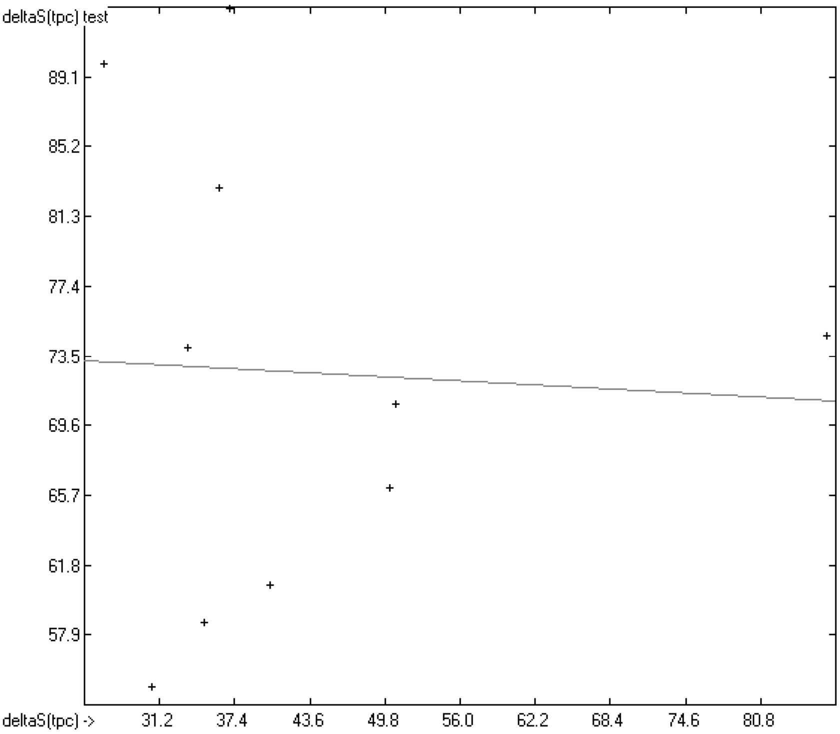

Figure 14. Correlation Diagram of the Total Phase-change Entropy Data of the homologues of 3-(4-alkyloxyphenylamino)-1-(2-(5-cyanothienyl))-2-propen-1-one. (N=10; R^2=0.0023; σ=12.29 J/mol/K)

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The list of the experimental and calculated data for the total phas-change entropy calculations is provided in the supplementary material under “Experimental and Calculated Tpc-Entropy Data Table.doc”, the related compounds under the name “Compounds List for Tpc-Entropy Calculations.sdf”, and the outliers list under the name “Compounds List of Tpc-Entropy Outliers.xls”.

4. Conclusions

The application of a computer algorithm described in detail in an earlier paper [1], based on the atom-group additivity principle to calculate reliable values of the heat of combustion (and - indirectly - formation), $\log P_{o/w}$, logS, refractivity, polarizability and toxicity, has successfully been extended to the prediction of the heats of vaporization, sublimation and solvation, and the entropy of fusion of ordinary molecules as well as the total phase-change entropy of liquid crystals. The principle to only accept experimental vaporization and sublimation data measured at or reduced to standard conditions also enabled the indirect calculation of the standard heat of fusion by applying Equation 2. It has been shown, however, that this indirect approach leads to rather rough estimates, yet still comparable to the often large differences of experimental values originating from different authors. The limits of the present method have been reached in the attempt to predict the total phase-change entropy of liquid crystals. In contrast to ordinary molecules which allow the entropy of fusion to be determined in a mutually comparable manner due to a mostly straightforward, uniform melting process, liquid crystals have proven to be an inconsistent class of compounds in that their melting processes pass through several individual semiliquid phases, preventing a standardized approach for the prediction of their phase-change entropy.

On the whole, the present computer algorithm, integrated in a project called ChemBrain IXL, has proven its versatility in that any extension to calculate the presented and future descriptors only requires a few more lines of controlling code to include the corresponding tables and descriptor names. At present, the project covers thermodynamic (heats of combustion, formation, solvation, vaporization, sublimation and fusion as well as entropy of fusion), solubility-related ($\log P_{o/w}$ and logS), optics-related (refractivity), charge-related (polarizability) and environment-related (toxicity) descriptors. On the other hand, it also shows its limitations where the descriptor is either not addressable by the atom groups (e. g. with logBB) or does not describe a uniform characteristic (e. g. the total phase-change entropy). Yet, there is no limit to this ongoing project to extend the number of calculable descriptors beyond the present twelve, provided that there is a number of experimental data available that are large enough and reliable. ChemBrain IXL is available from Neuronix Software (www.neuronix.ch, Rudolf Naef, Lupsingen, Switzerland).

Supplementary Materials

Supplementary materials can be accessed at: ...

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Conflicts of Interest

The authors declare no conflict of interest.

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