it reflects a noncovalent complex formation between the ester and methylimidazole. There is no a priori reason why such a complex would necessarily show a significant alteration in the NMR spectrum or be resistant to reaction with hydroxylamine. One such scheme involving formation of a noncovalent intermediate, consistent with the kinetics, is illustrated in I, where E is the ester and MI is the methylimidazole. Under pseudo-first-order conditions ([MI] ≫ [E]) the observed rate constant is given by

$$\mathrm{E{\cdot}MI} \overset{K}{\rightleftharpoons} \mathrm{E} + \mathrm{MI} \xrightarrow{k_2} \mathrm{P} \qquad \text{(I)}$$

$$k_{\mathrm{obs}} = \frac{k_2K[\mathrm{MI}]}{K + [\mathrm{MI}]} \qquad (2)$$

Equation 2 is identical with the empirical eq 1 where the limiting first-order rate constant $k_{\max} = k_2K$ and $K$ is the dissociation constant of the complex. In (I) the ester–methylimidazole complex is assumed to be nonproductive. A mechanism in which the ester–methylimidazole complex is on the reaction path (between reactants and products) is kinetically indistinguishable from that represented in (I). While this cannot be ruled out, it does seem less likely because the reaction with 1-methylimidazole is slower than the reaction with imidazole in a concentration region where a complex is formed with the former but not with the latter nucleophile.

While there are many examples of noncovalent complexation between esters and nucleophiles that result in rate enhancements[21] as well as examples of inhibition of hydrolysis caused by binding to an added molecule,[22,23] the *inhibition* of hydrolysis caused by increasing concentrations of added *nucleophile* is unusual. The origin of the relatively weak interaction between the methylimidazole and the ester is not known. van der Waals–London dispersion forces and hydrophobic interactions are the two most likely (and general) possibilities. The observation that the dissociation constant between *p*-NP pivalate and 1-MI increases 2.5-fold as the organic solvent composition of the solution is increased (Table I) is consistent with the apolar nature of the interaction. Although it is possible that the interaction between the ester and the nucleophile could be due to a $\pi$–$\pi$ interaction between the *p*-nitrophenyl moiety and the imidazole ring, this does not explain (a) the requirement of a methyl group on the imidazole for significant complex formation, (b) the absence of a detectable charge-transfer complex formed between 1-methylimidazole and *p*-nitroanisole or methyl *p*-nitrobenzoate under conditions that lead to complex formation between 1-MI and the ester, or (c) the stronger complexation of 1-methylimidazole with phenyl acetate than with *p*-nitrophenyl acetate. Another possibility is that complexation is a result of a hydrophobic interaction between the methyl group on the imidazole and the ester. In either case the kinetics of hydrolysis of *p*-nitrophenyl pivalate in the presence of appropriately substituted imidazoles may provide a convenient system for studying the effect of structural changes on the magnitude of relatively weak interactions.

**Acknowledgment**. We thank Nick Psomas for carrying out some of the kinetics with 2-methylimidazole and Yaw-Kuen Li for carrying out most of the NMR determinations.

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[21] For a summary of several examples see: (a) Reference 5, Chapter 8. (b) Bender, M. L.; Bergeron, R. J.; Komiyama, M. *The Bioorganic Chemistry of Enzymatic Catalysis*; Wiley: New York, 1984; Chapter 12.

[22] Higuchi, T.; Lachman, L. *J. Am. Pharm. Assoc.* **1955**, *44*, 521–526.

[23] Duynstee, E. F. J.; Grunwald, E. *Tetrahedron* **1965**, *21*, 2401–2412.

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# Estimating Vaporization Enthalpies of Organic Compounds with Single and Multiple Substitution

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A simple method of estimating vaporization enthalpies of hydrocarbon derivatives containing one or more functional groups is described. The relationship previously reported for monosubstituted derivatives has been modified to included additional structural information and is now applicable to both mono- and polyfunctional compounds. The new relationship is given by: $\Delta H_{\mathrm{v}} = 1.12\tilde{n}_{\mathrm{c}} + 0.31n_{\mathrm{Q}} + 0.71 + \sum F_{\mathrm{i}}b_{\mathrm{i}} + C$. The terms $n_{\mathrm{Q}}$ and $\tilde{n}_{\mathrm{c}}$ refer to the number of quaternary and nonquaternary carbon atoms, respectively. $F_{\mathrm{i}}$ is a structural factor characteristic of the hybridization and substitution pattern of the carbon bearing the functional group, and $b_{\mathrm{i}}$ is a constant characteristic of the polarity of the functional group. The product $F_{\mathrm{i}}b_{\mathrm{i}}$ is summed over each functional group i in the molecule. $C$ is a term that corrects for the effects of intramolecular hydrogen bonding, remote carbon branching in acyclic molecules, the ortho effect observed in five- and six-membered rings, and for interactions observed in cyclic derivatives where the functional group is part of a ring. A total of 147 critically reviewed vaporization enthalpies is used in the correlation to derive $F$ values for eight hybridization and substitution patterns. Tentative values are provided for five more patterns on the basis of an additional 12 enthalpies. Experimental enthalpies for monosubstituted and multisubstituted compounds are reproduced to 3.4 and 5.0%, respectively.

Vaporization enthalpies are an important physical property of pure liquids, and a reliable measure of this quantity is a necessary requirement for any study that references the gas phase as a standard state.[1] Although

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**Table I**

| class of compds | functional group | functional class | $b^a$ | class of compds | functional group | functional class | $b^a$ |
|---|---|---|---|---|---|---|---|
| hydrocarbons | | | (138) | | | | |
| acids | [$CO_2H$] | I | 9.27 (10) | iodides | [I] | I | 4.30 (17) |
| alcohols | [OH] | I | 7.02 (31) | ketones | [CO] | II | 2.50 (38) |
| aldehydes | [CHO] | I | 3.08 (7) | nitriles | [CN] | I | 3.98 (31) |
| amides [monosub] | [CONH] | II | 10.16 (8) | nitro compds | [$NO_2$] | I | 5.44 (9) |
| | | | | pyridines | | III | 2.91 (12) |
| amines [pri] | [$NH_2$] | I | 3.54 (16) | sulfides | [S] | II | 3.20 (41) |
| amines [sec] | [NH] | II | 2.12 (13) | disulfides | [SS] | II | [5.32] (5) |
| bromides | [Br] | I | 3.43 (16) | sulfoxides | [SO] | II | [10.13] (4) |
| chlorides | [Cl] | I | 2.59 (22) | sulfones | [$SO_2$] | II | [12.67] (5) |
| esters | [$CO_2$] | II | 2.50 (64) | thioesters | [COS] | II | [4.03] (5) |
| ethers | [O] | II | 1.19 (56) | thiols | [SH] | I | 3.32 (20) |

[a] Numbers in parentheses represent the number of data points used to evaluate *b*; values of *b* enclosed in brackets are tentative assignments.

vaporization enthalpies have been reported for a large variety of hydrocarbon derivatives, most still remain to be measured. In addition, the accuracy and reliability of numerous values reported in the literature are questionable. Compendia usually do not convey enough information to allow the reader to assess the data critically. Concerns such as these have prompted us to examine the possibility of developing general methods of estimating vaporization enthalpies both for purposes of providing some rational value in cases when experimental data are lacking and to screen the reliability of the data when such data are available. Numerous estimation methods have been reported previously.[2] Most relationships developed to date are useful but very limited in their scope. The most general techniques available in addition to our own[3,4] are the group additivity methods of DuCros[6] and Guthrie.[5]

We have been interested in developing equations that rely heavily on structure and combine flexibility and accuracy while maintaining the number of parameters at a minimum. Our goal has been to reproduce experimental enthalpies within 5%, the accuracy of many of the experimental numbers in the literature.

We have reported previously a simple relationship that was used to estimate the enthalpies of vaporization of 138 hydrocarbons of diverse structure.[3] Recently, we expanded this relationship to estimate successfully the enthalpies of vaporization of 433 monosubstituted liquid hydrocarbon derivatives, typically within 5% of the experimental value.[4] We now report on some additional modifications of this relationship that allow us to improve significantly the correlation observed in monosubstituted compounds and to expand the range of compounds that can be correlated successfully to include hydrocarbon derivatives with multiple substitution.

The equations reported previously for hydrocarbon and monosubstituted hydrocarbon derivatives are given by eq 1 and 2, respectively.

$$\Delta H_v = 1.12\tilde{n}_c + 0.31n_Q + 0.71 \quad (1)$$

$$\Delta H_v = 1.12\tilde{n}_c + 0.31n_Q + 0.71 + b \quad (2)$$

The terms $n_Q$ and $\tilde{n}_c$ refer to the number of quaternary $sp^3$ and nonquaternary carbon atoms, respectively, and *b* is a value that is characteristic of the functional group for monosubstituted hydrocarbons. Values of *b* previously reported are summarized in Table I. Values of *b* that are considered tentative because of the limited amount of data available are enclosed in brackets. The number of data points used to generate each value is enclosed in parentheses in Table I following the value of *b* (columns 5 and 10). Modification of eq 2 as shown below allows this relationship to reproduce successfully the vaporization of an additional 175 multisubstituted hydrocarbon derivatives for which we have been able to find reliable data.[7]

$$\Delta H_v = 1.12\tilde{n}_c + 0.31n_Q + 0.71 + \sum_i F_i b_i + C \quad (3)$$

Equation 3 modifies eq 2 by introducing two additional parameters, $F_i$ and *C*. $F_i$ are structural factors characteristic of the substitution pattern of the carbon atom bearing the substituent and $b_i$ values are a function of the polarity of the substituent as described previously.[4] The product, $F_ib_i$, measures the contribution of each functional group i to the overall vaporization enthalpy in the structural environment in which it resides. For multisubstituted compounds, a $F_ib_i$ term for each functional group in the molecule is included in the sum. In monosubstituted compounds, $F_i$ equals unity, thereby generating eq 2 exclusive of the *C* term. The *C* term contains corrections for

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(1) See, for example: Benson, S. W. *Thermochemical Kinetics: Methods for the Estimation of Thermochemical Data and Rate Parameters*, 2nd ed.; Wiley: New York, 1976. Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic Press: New York, 1978.

(2) Watson, K. M. *Ind. Eng. Chem.* **1943**, *35*, 398; **1931**, *23*, 360. Cottrell, T. L. *The Strength of Chemical Bonds*, 2nd ed.; Butterworths: London, 1958; Section 7.4. Wadso, I. *Acta Chem. Scand.* **1966**, *20*, 544. Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic: New York, 1970. Reid, R. C.; Prausnitz, J. M.; Poling, B. E. *Properties of Gases and Liquids*, 4th ed.; McGraw-Hill: New York, 1986, and references cited. Morawetz, E. *J. Chem. Thermodyn.* **1972**, *4*, 139, 145, 455, and 461. Stridh, G.; Sunner, S. *J. Chem. Thermodyn.* **1975**, *7*, 161. Mannson, M.; Sellers, P.; Stridh, G.; Sunner, S. *J. Chem. Thermodyn.* **1977**, *9*, 91. Stridh, G.; Sunner, S.; Svensson, Ch. *J. Chem. Thermodyn.* **1977**, *9*, 1005. Gardner, P. J.; Hussain, K. S. *J. Chem. Thermodyn.* **1972**, *4*, 819. Green, J. H. S. *Q. Rev. Chem. Soc. (London)* **1961**, *15*, 125. Thomson, G. W. In *Physical Methods of Organic Chemistry*, 2nd ed.; Weissberger, A., Ed.; Interscience: New York, 1949, Part 1, pp 235–244.

(3) Chickos, J. S.; Hyman, A. S.; Ladon, L. H.; Liebman, J. F. *J. Org. Chem.* **1981**, *46*, 4294.

(4) Chickos, J. S.; Hesse, D. G.; Liebman, J. F.; Panshin, S. *J. Org. Chem.* **1988**, *53*, 3424.

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(6) DuCros, M.; Greison, J. F.; Sannier, H. *Thermochim. Acta* **1980**, *36*, 39. DuCros, M.; Greison, J. F.; Sannier, H.; Velasco, I. *Thermochim. Acta* **1981**, *44*, 134.

(7) All experimental data used in this work have been obtained from the following references and have been critically reviewed. Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data of Organic Compounds*, 2nd ed.; Methuen: New York, 1986. Pedley, J. B.; Rylance, J. *N.P.L. Computer Analysed Thermochemical Data: Organic and Organometallic Compounds*; University of Sussex, 1977. Majer, V.; Svoboda, V. *Vaporization of Organic Compounds*; IUPAC Chemical Data Series No. 32; Blackwell Scientific Publications: Boston, MA, 1985.

(8) Dreisbach, R. B. *Physical Properties of Chemical Compounds I-III*; Advances in Chemical Series 15, 22, 29; American Chemical Society: Washington, DC, 1955, 1959, 1961. The equations used to calculate the latent heats of vaporization are defined on pages 4–8.

**Table II. Contributions of Multiple Substituents to Vaporization Enthalpies**

| substituent substitution pattern[a] | substitution[b] factor *F* | total[c] number of entries | average absolute deviation, % |
|---|---|---|---|
| Single Substitution (Nongeminal) | | | |
| primary $sp^3$ carbon atom | 1.62 | 15 (0) | 3.3 |
| secondary $sp^3$ carbon atom | 1.08 | 42 (42) | 4.7 |
| tertiary $sp^3$ carbon atom | 0.60 | 23 (9) | 5.2 |
| quaternary $sp^3$ carbon atom | [0.65] | 2 | [1.0] |
| tertiary $sp^2$ carbon atom | [0.8] | 3 | [2.2] |
| quaternary $sp^2$ carbon atom | 0.85 | 10 (4) | 5.0 |
| quaternary sp carbon atom | | no data | |
| Disubstitution (Geminal) | | | |
| secondary $sp^3$ carbon atom | 0.94 | 19 (4) | 5.0 |
| tertiary $sp^3$ carbon atom | 0.78 | 21 (6) | 5.3 |
| quaternary $sp^3$ carbon atom | [0.7] | 3 | [14.3] |
| quaternary $sp^2$ carbon atom | [0.8] | 2 | [1.3] |
| 1,1,1-Trisubstitution | | | |
| tertiary $sp^3$ carbon atom | 0.81 | 7 (2) | 5.8 |
| quaternary $sp^3$ carbon atom | [0.7] | 2 | [2.9] |
| 1,1,1,1-Tetrasubstitution | | | |
| quaternary $sp^3$ carbon atom | 0.59 | 9 (2) | 8.1 |

[a] Primary, secondary, tertiary, and quaternary positions are defined by the number of hydrogens attached to the carbon bearing the substituent, 3, 2, 1, 0, respectively. [b] Values in brackets are tentative assignments. [c] Numbers in parentheses refer to the number of type A data points as discussed in the text.

**Table III. Components of the *C* Correction Term**

| nature of the correction [*C*] | correction, kcal/mol | entries |
|---|---|---|
| (1) intramolecular hydrogen bonding | | |
| alcohols (5–9-membered rings) | −1.81 | 12 |
| enols (from β-diketones) | −4.30 | 5 |
| (2) ring correction for cyclic class II functional groups | +0.7 | 30 |
| cyclic ethers | | 8 |
| cyclic ketones | | 9 |
| cyclic sulfides | | 11 |
| cyclic secondary amines | | 2 |
| (3) branching correction | | |
| (A) acyclic compounds | | |
| alkyl branching on $sp^3$ hybridized carbon[a] | −0.5 | |
| α branching [applicable to monosubstituted compounds only] | | 65 |
| β, γ, ··· branching [applicable to both mono- and polysubstituted compounds] | | 30 |
| (B) Cyclic Compounds | | |
| ortho alkyl branching [applicable to mono- and polysubstituted compounds] on $sp^2$ and $sp^3$ hybridized carbon in 5- and 6-membered rings. | −0.5 | 9 |

[a] The total correction depends on the number of alkyl branches excluding quaternary centers (one branching correction/quaternary center) and on the number of functional groups in the molecule.

carbon branching occuring at an $sp^3$ carbon atom, for intramolecular hydrogen bonding, and for correcting the interaction found in cyclic derivatives when the functional group is part of a ring. The *C* term has been added to improve the correlation between calculated and experimental $\Delta H_v$ values for both mono- and multisubstituted hydrocarbons and is discussed below in detail.

The following analysis is based on the assumption that vaporization enthalpies are group properties and can be estimated from simple additivity of the contributions of each functional group once the environment of the functional group is taken into account. Before discussing the origins of the $F_i$ and *C* terms and the manner in which they are applied, we first define the meaning of our terms. Primary, secondary, tertiary, and quaternary carbon atoms in this article are defined by the number of hydrogens that are attached to carbon, 3, 2, 1, and 0, respectively. This definition differs from the normal convention. The terms α, β, γ, ... are defined in the conventional sense, referring to groups attached 1, 2, 3, ... carbons removed from the functional group. The atoms that are included in each functional group are defined in Table I. Additional details on how each *F* value and correction term *C* were derived are given below.

Three classes of functional groups are defined in Table I. Class I functional groups can be described as univalent substituents, while class II functional groups can be considered as either bi- or trivalent bridging substituents. Class III functional groups refer to specific classes of compounds. This class for pyridines was necessitated by the lack of sufficient experimental data on other related tertiary amines.

As noted above, the $F_i$ term in eq 3 for all monosubstituted hydrocarbon derivatives [class I, II, III] equals unity. Thus with the exception of the *C* term, this simplifies eq 3 to eq 2. Structural factors [$F_i$] for multisubstituted hydrocarbon derivatives containing only class I functional groups can be obtained directly from Table II. The $F_i$ value is dependent only on the substitution pattern and hybridization of the carbon atom to which the class I functional group is attached. Class II functional groups are attached to multiple carbon atoms where the substitution pattern and/or hybridization at each carbon atom may differ. Structural factors for these functional groups are obtained by arithmetically averaging the $F_i$ value characteristic of the substitution pattern of each carbon atom to which the substituent is attached. The contribution of each class II functional group to the overall enthalpy is given by the product $F_{av}b_i$ where $F_{av}$ refers to the arithmetic average of each $F_i$ value. Class III functional groups refer to specific classes of molecules and should be treated similar to monosubstituted hydrocarbon derivatives. Molecules that contain combinations of Class I, II, and III functional groups should be treated by the appropriate combinations of $F_ib_i$ characteristic of each substitution. Some examples illustrating the application of eq 3 to mono- and polysubstituted hydrocarbon derivatives are given in Table IV and are discussed below.

Several additional correction terms have been added to improve the correlation for both mono- and polyfunctional compounds. These include a ring correction for class II functional groups when the functional group is part of a ring, a carbon branching correction for acyclic molecules, an ortho (or α) branching correction for five- and six-membered rings (both aromatic and aliphatic), and corrections for intramolecular hydrogen bonding. The ring and carbon branching corrections are effects observed previously in monosubstituted ethers and branched hydrocarbon derivatives.[4] A more detailed analysis reveals that whenever a class II functional group is part of a ring, the observed vaporization enthalpy generally is larger than the value calculated. A comparison of experimental and calculated vaporization enthalpies of various monosubstituted hydrocarbon derivatives that included cyclic ethers (8 entries), cyclic ketones (9 entries), cyclic secondary amines (2 entries), and cyclic sulfides (11 entries) resulted in differences of +0.86, 0.7, 0.6, and 0.58 kcal/mol, respectively. The similarity in magnitude of these values and our interest in keeping the number of parameters to a minimum prompted us to use the weighted average of 0.7 kcal/mol for this correction. Table III lists this correction as a ring correction for all cyclic class II functional groups and is recommended for all estimations of these classes of molecules. This correction is applicable to both mono- and multisubstituted compounds and where applicable has been applied once, regardless of the number of class II functional groups in the ring, the size of the ring, or the number of rings in the molecule. This action has been prompted for the most part by the limited amount of experimental data available. This correction, when applied to the 30 cyclic compounds discussed above, reduced the observed average deviation (between experimental and calculated (eq 2)) from 6.7 to 3.6%.

Monosubstituted molecules with alkyl branches at $sp^3$-hybridized carbon atoms typically exhibit slightly smaller vaporization enthalpies than calculated by eq 2. It was found previously that with the exception of quaternary $sp^3$ carbon centers, this effect generally is small and not very sensitive to the location of the branch relative to the position of the functional group. In an effort to quantify the magnitude of this effect, the vaporization enthalpies of all available acyclic monosubstituted hydrocarbon derivatives containing alkyl branching were grouped, and the differences between experimental values and those calculated with the aid of eq 2 were compared. An analysis of 75 monobranched compounds containing both class I and class II functional groups branched at the $\alpha$-, $\beta$-, and $\gamma$-positions gave differences (between experimental and calculated values) that averaged to −0.48 kcal/mol. A similar effect was observed for ortho alkyl branching on five- and six-membered aliphatic and aromatic rings (5 entries, −0.61 kcal/mol). An additional 22 acyclic compounds containing two alkyl branches located at various distances from the functional group, two ortho substituents, or two substituents $\alpha$ to the heteroatom in a five- or six-membered heterocyclic ring resulted in an effect of −0.44 kcal/mol/branch. As in the case of the ring corrections, the similarity of the magnitude of the effects we have observed has prompted us to average the branching effects of all 102 entries to obtain a universal branching correction of −0.5 kcal/mol/branch (after rounding) as listed in Table III. Additional details on the effects of branching on the position of attachment are available in the supplementary tables. This branching term when added to the result calculated by eq 2 reduces the average deviation observed for the 102 branched compounds from 5.3 to 3.0%. This correction term is recommended for all branching corrections at $sp^3$ carbon ($\alpha$, $\beta$, ...) in acyclic monosubstituted molecules and for correction of the effects of ortho- and $\alpha$-alkyl branching in five- and six-membered rings. We have applied this correction to branching occurring in both mono- and polyfunctional compounds. The only exceptions have been in cases where branching directly results in the formation of a cyclic, bicyclic, or polycyclic fused ring system. For example, the $\alpha$-branching correction applicable to 2-hexanol (i.e. 1-methyl-1-pentanol) would not be applied to cyclohexanol or to 2-hydroxybicyclo[2.2.2]octane. Branching in cyclic and polycyclic systems appears to be compensated by the rigidity of the ring system. In addition, double branching occurring at the same carbon to generate a quaternary center has been treated as a single branch correction. Branching in this case has already been partially compensated by the quaternary carbon factor in eq 2. These corrections are summarized in Table III, and some applications of these corrections are illustrated in Table IV.

The cumulative effect of these two correction terms when applied to eq 2 reduces the average deviation observed between calculated and experimental enthalpies of the 433 compounds reported previously[4] from 5.3 to 3.4% without significantly affecting the $b_i$ values.[9] The new correlation observed between experimental and calculated enthalpies is illustrated in Figure 1. The equation of the line by a least-suares fit of the data is given by eq 4. This can be compared to eq 5, which was previously reported for the same compounds without the $C$ correction terms.

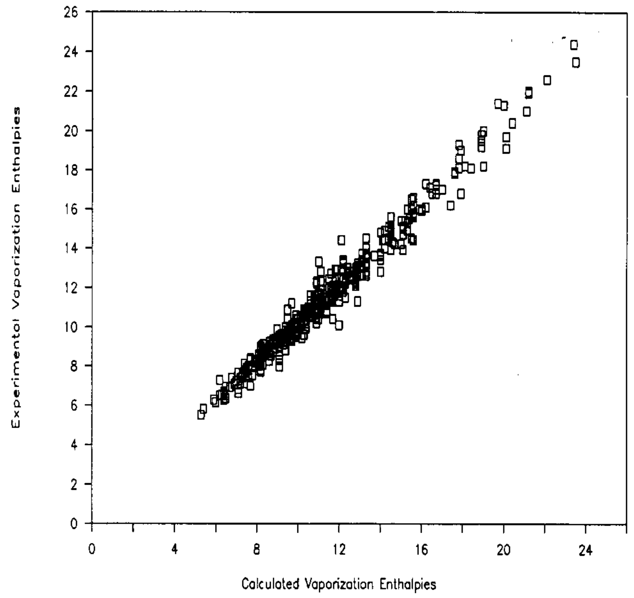

**Figure 1.** A comparison of experimental and calculated vaporization enthalpies of 433 monosubstituted hydrocarbon derivatives.

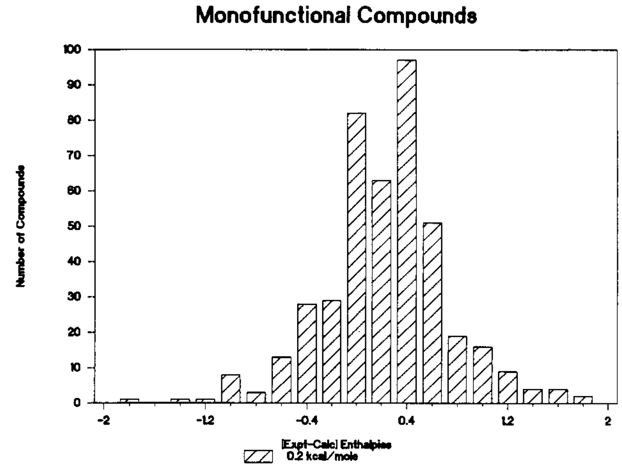

**Figure 2.** The distribution of errors obtained for 433 monosubstituted hydrocarbon derivatives at 0.2 kcal/mol intervals.

$$\Delta H_v(\text{expt}) = 0.998\Delta H_v(\text{calcd}) + 0.167 \qquad r = 0.9876 \tag{4}$$

$$\Delta H_v(\text{expt}) = 0.996\Delta H_v(\text{calcd}) + 0.037 \qquad r = 0.9809 \tag{5}$$

The histogram in Figure 2 provides some idea of the distribution of errors. The distribution of errors obtained

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[9] The reader may question the effects of introducing these correction terms on the values of $b$ since the $b$ terms were originally generated from the difference in enthalpy observed between the parent hydrocarbon and the hydrocarbon derivative. An evaluation of the cumulative effects of the ring and branching corrections on the magnitude of the $b_i$ terms shows that this term increased for most functional groups. The $b$ value for pyridines and disulfides showed the greatest absolute change, increasing 0.42 and 0.40 kcal/mol, respectively. The magnitude of these changes are mainly a reflection of the few data points available for the generation of the $b$ value. The $b$ values for all the remaining function groups changed an average of 0.14 kcal/mol. These changes are well within the "noise level" typical of the experimental data, and since we would like to prevent a profusion of "best values" for $b$, we have used the original values previously reported[4] in evaluating the structural factors reported here.

**Table IV. Applications of Eq 3 in Estimating Vaporization Enthalpies of a Variety of Organic Compounds**

| contribution of the [hydrocarbon portion] + {functional group} + (correction term) | | | | | | |
|---|---|---|---|---|---|---|
| $[1.12\tilde{n}_c + 0.31n_A + 0.71]$ | + | $\{\sum F_i b_i\}$ | + | (C) | $\Delta H_v$ [calc] | $\Delta H_v$ [exp] |
| $C_3H_3Cl_3O_2$, Methyl Trichloroethanoate | | | | | | |
| [1.12(2) + 0.31 + 0.71] | + | {0.59(3)(2.59) + (1.62 + 0.59)(0.5)(2.5)} | | | 10.6 | 11.4 |
| $C_3H_6BrCl$, 1-Bromo-3-chloropropane | | | | | | |
| [1.12(3) + 0.71] | + | {1.08(3.43 + 2.59)} | | | 10.6 | 10.5 |
| $C_5H_{10}O$, 3,3-Dimethyloxetane | | | | | | |
| [1.12(4) + 0.31(1) + 0.71] | + | {1.19} | + | (0.7) | 7.4 | 8.1 |
| $C_5H_{12}O_2$, 2-Isopropoxyethanol | | | | | | |
| [1.12(5) + 0.71] | + | {1.08(7.02) + (1.08 + 0.60)(0.5)(1.19)} | – | (1.81) | 13.1 | 12.0 |
| $C_5H_{12}S$, 3-Methyl-2-butanethiol | | | | | | |
| [1.12(5) + 0.71] | + | {3.32} | – | 2(0.5) | 8.6 | 9.0 |
| $C_6H_{12}O_2$, 4,5-Dimethyl-1,3-dioxane | | | | | | |
| [1.12(6) + 0.71] | + | {((1.08 + 0.94) + (0.94 + 0.60))(0.5)(1.19)} | + | (0.7) | 10.2 | 10.2 |
| $C_6H_{12}O_3$, 2-Ethoxyethyl Ethanoate | | | | | | |
| [1.12(6) + 0.71] | + | {1.08(1.19) + (1.08 + 1.62)(0.5)(2.5)} | | | 12.1 | 12.6 |
| $C_7H_{13}ClO_2$, 2-Methylpropyl 3-Chloropropionate | | | | | | |
| [1.12(7) + 0.71] | + | {(1.08)(2.59 + 2.5)} | – | 2(0.5) | 13.0 | 13.0 |
| $C_8H_{15}ClO_2$, 3-Methylbutyl 2-Chloropropionate | | | | | | |
| [1.12(8) + 0.71] | + | {(1.08 + 0.78)(2.5)/2 + (0.78)(2.59)} | – | 2(0.5) | 13.0 | 12.5 |
| $C_9H_{10}O_2$, 2,3-Benzo-1,4-dioxacycloheptane | | | | | | |
| [1.12(9) + 0.71] | + | {(1.08 + 0.85)(1.19)} | + | (0.7) | 13.8 | 13.3 |
| $C_9H_{20}O$, *tert*-Butyl Isopentyl Ether | | | | | | |
| [1.12(8) + 0.31(1) + 0.71] | + | {1.19} | – | 2(0.5) | 10.2 | 10.5 |
| $C_{10}H_{18}O_2$, 2,2,6-Trimethyl-3,5-heptanedione[a] | | | | | | |
| [1.12(9) + 0.31 + 0.71] | + | {(0.85)(7.02) + (2(0.80) + 0.60 + 0.65)(2.5)/4} | – | ((4.3) – 2(0.5)) | 13.5 | 13.8 |

[a] Calculated for the enol form as an equal mixture of two tautomers.

between experimental and calculated values is presented at a 0.2 kcal/mol interval. As evident in this graph, the distribution does not appear to be significantly skewed from zero as would be expected if the $b_i$ values were affected. The absolute average deviation of this correlation is 0.39 kcal/mol.

The major impetus for introducing the corrections just described has been our interest in reproducing the experimental vaporization enthalpies of multifunctional compounds within 5%. The branching and ring corrections derived for monosubstituted compounds, therefore, are also relevant to eq 3 with one major exception. The $\alpha$-branching correction applicable to monosubstituted compounds is replaced by the substituent factor, $F$, in multisubstituted compounds. For example, the $\alpha$-alkyl branching correction in 2-chloro- and 3-chloropentane is replaced by the substitution factor, $F$, of 0.64 for each chlorine in the dichlorinated derivative, 2,3-dichloropentane. Similarly, the single branching correction in 3-chloro-3-methylpentane (see above) is replaced by $F_i$ values of 0.61 and [0.65] in 2,3-dichloro-3-methylpentane. As noted previously, the effects of carbon branching have been attributed in part to an attenuation of the effectiveness of the functional group in solvation. The question arises whether the effect of a single alkyl branch on the two chlorines in 2,3-dichloro-4-methylpentane would be cumulative. Examination of the limited experimental data available on branched multisubstituted compounds seems to suggest that such is the case. The effects of the carbon branch in 2,3-dichloro-4-methylpentane would therefore result in a branching correction of 1.0 kcal/mol. The number of examples of polysubstituted compounds with multiple branches are very few, but their vaporization enthalpies seem to support a correction of −0.5 kcal/mol/branch/functional group. We have applied this branching correction to polysubstituted compounds with alkyl branches as remote as $\delta$ and $\epsilon$ from the functional group with a general improvement in correlation. Additional examples illustrating the applications of these corrections are given in Table IV.

The 13 structural factors listed in Table II for multifunctional compounds were derived from experimental data according to the following procedure. First, the 160 multifunctional compounds were separated according to the hybridization and substitution pattern of the carbon atoms containing the functional groups. This resulted in two sets of the 13 categories listed in column 1 of Table II. One set included entries that contained all functional groups in identical structural environments (type A entries, e.g. 1-bromo-3-chloropropane). The other set contained entries with functional groups in mixed structural environments (type B entries, e.g. 1-bromo-2-chloropropane). Since the number of entries available for each hybridization and substitution pattern differed, the following protocol was used to establish the most reliable values for each pattern. The structural factor was first established for the substitution pattern with the most type A entries. This resulted in establishing the $F$ value for secondary sp$^3$ carbons. Once this factor was established, it was then used whenever necessary in type B entries to establish $F$ values for other structural environments. This resulted in a hierarchy of values in which the $F$ value for secondary sp$^3$ carbons was first used to establish the $F$ value for tertiary sp$^3$ carbons. The combination of these two parameters, in turn, was used when necessary to establish the $F$ values for each of the remaining structural parameters listed in Table II (a table summarizing the genealogy of the $F$ values is available in the supplementary material). Column 3 of Table II lists the total number of data points available to derive each structural factor and includes, in parentheses, the number of type A data points that were available for each structural factor. Each value of $F$ listed in Table II

Table V. Comparison of Experimental and Calculated Vaporization Enthalpies

| compound | $\Delta H_v$ | | | | |
|---|---|---|---|---|---|
| | [expt] | [eq 3] | [DuCros[a]] group additivity | [Guthrie] group additivity | [Guthrie] bond additivity |
| amines | | | | | |
| 1,2-ethanediamine | 10.8 | 10.6 | 10.8 | 9.5 | 9.2 |
| 1,3-propanediamine | 12.0 | 11.7 | 12.0 | 10.7 | 10.3 |
| alcohols | | | | | |
| 1,2-ethanediol | 16.2 | 16.3 | 16.1 | 14.9 | 12.3 |
| 1,2-propanediol | 15.4 | 14.1 | 15.2 | 15.4 | 13.4 |
| 1,3-propanediol | 17.4 | 17.4 | 17.3 | 16.1 | 13.4 |
| 1,3-butanediol | 16.4 | 15.2 | 16.4 | 16.4 | 14.6 |
| 1,4-butanediol | 18.3 | 18.5 | 18.5 | 17.3 | 19.5 |
| 2,3-butanediol | 14.1 | 11.8 | 14.3 | 15.9 | |
| halides | | | | | |
| 1,2-dibromoethane | 10.0 | 10.4 | [9.2] | 10.4 | 10.0 |
| 1,2-dibromopropane | 10.0 | 9.9 | [9.9] | 11.0 | 11.2 |
| 1,3-dibromopropane | 11.3 | 11.5 | [10.4] | 11.7 | 11.2 |
| 2,3-dibromobutane | 9.0 | 9.3 | [10.6] | 11.5 | 12.4 |
| 1,2-dibromo-2-methylpropane | 10.4 | 10.3 | [10.3] | N/A | 12.4 |
| 1,2-dibromoheptane | 13.0 | 14.3 | 14.7 | 15.8 | 15.9 |
| 1,5-dichloropentane | 12.1 | 11.9 | [12.7] | 12.0 | 10.9 |
| 1,2-dichlorobenzene | 11.4 | 11.8 | N/A | 11.2 | 11.3 |
| ethers | | | | | |
| 1,3-dioxane | 8.5 | 8.3 | 7.5 | 7.0 | 7.7 |
| 1,4-dioxane | 9.0 | 8.5 | 9.3 | 7.4 | 7.7 |
| 1,2-diethoxyethane | 10.3 | 10.0 | 10.4 | 10.1 | 10.6 |
| thiols | | | | | |
| 1,2-ethanedithiol | 10.7 | 9.9 | 9.8 | 10.3 | 9.8 |
| 1,4-butanedithiol | 13.2 | 12.1 | 12.1 | 12.7 | 12.1 |
| 1,5-pentanedithiol | 14.2 | 13.2 | 13.3 | 14.0 | 13.3 |
| mixed | | | | | |
| 2-chlorobenzaldehyde | 13.3 | 13.4 | N/A | 14.2 | 13.6 |
| isobutyl 4-chlorobutanoate | 12.9 | 14.2 | N/A | 15.2 | 15.6 |
| 2-propoxyethyl acetate | 13.3 | 13.4 | N/A | 13.5 | 13.7 |
| butyl dichloroacetate | 12.5 | 14.0 | N/A | N/A | 15.5 |
| glycerol tributyrate | 25.6 | 24.4 | 25.5 | 25.8 | 28.4 |
| 3-chloro-1,2-propanediol | 16.0 | 13.9 | 16.7 | 15.8 | 15.7 |
| 2-propoxyethanol | 13.5 | 14.5 | 13.6 | 13.7 | 13.7 |
| 2-isopropoxyethanol | 12.1 | 13.1 | 12.2 | 11.8 | 12.5 |

[a] Values for these compounds are included in the tables of DuCros et al. (see ref 6, 10), but group constants for all the functional groups used in this table could not be found; N/A: not available.

was derived by comparing the experimental data to the value calculated from eq 3 using each $F_i$ as the only variable and minimizing the difference between experimental and calculated enthalpies by the method of least squares. In some cases, enough data is not available to establish reliable values. Tentative values based on a few entries are included in brackets in Table II. The correction terms for carbon branching, ortho substitution, and for ring corrections for class II functional groups also were included when appropriate in the least-squares calculations.

As might be expected, compounds capable of forming intramolecular hydrogen bonds were found to exhibit vaporization enthalpies lower than those predicted by eq 3. The magnitude of this effect would be expected to depend on several factors including the size of the resulting ring and steric effects. Two types of intramolecular hydrogen bonding could be differentiated from the data. Analysis of the vaporization enthalpies of 13 alcohols and hydroxy ethers capable of forming intramolecular hydrogen bonds containing from 5 to 9 atoms in the ring gave similar differences between experimental and calculated vaporization enthalpies. These differences were averaged and resulted in a correction of −1.81 kcal/mol. This correction when added to eq 3 was able to reproduce the vaporization enthalpies of these diols and hydroxy ethers to within 5.7%. A second type of intramolecular hydrogen bond correction could be identified for the enol form of β-diketones. On the basis of the vaporization enthalpies of five β-diketones, a value of −4.3 kcal/mol was determined. This correction permitted eq 3 to reproduce the vaporization enthalpies of these compounds to within 2.4%. Corrections for intramolecular hydrogen bonding in other compounds such as amines and thiols was not necessary.

Table IV illustrates the applications of eq 2 and 3 in estimating the vaporization enthalpies of a variety of complex molecules. In most instances, identification of the appropriate $F$ value is straightforward. A few examples serve to emphasize the conventions used. Methyl trichloroethanoate is an example of a molecule containing a quaternary carbon atom with two different types of substituents, chlorine (class I) and a carbomethoxy group (class II). In addition to the contribution of each carbon and the intercept (0.71), the total contribution of the chloro groups to the vaporization enthalpy is determined by the number and substitution factor of each. The $F$ value, 0.59 in this case, is obtained directly from Table II. The carbomethoxy group is a bidentate group. The substitution factor is determined by averaging the $F$ values appropriate to the substitution pattern at each position of attachment, 1.62 and 0.59. The vaporization enthalpy of 4,5-dimethyl-1,3-dioxane can be evaluated in a similar manner. Both oxygens are attached to the same geminally substituted sp$^3$ carbon. One is also attached to a secondary sp$^3$ carbon while the other is attached to a tertiary sp$^3$ carbon. In this instance, a ring correction is applied. No branching correction is necessary since the methyl group at position 4 has been corrected by the substitution factor and the methyl group group at position 5 is meta to the functional

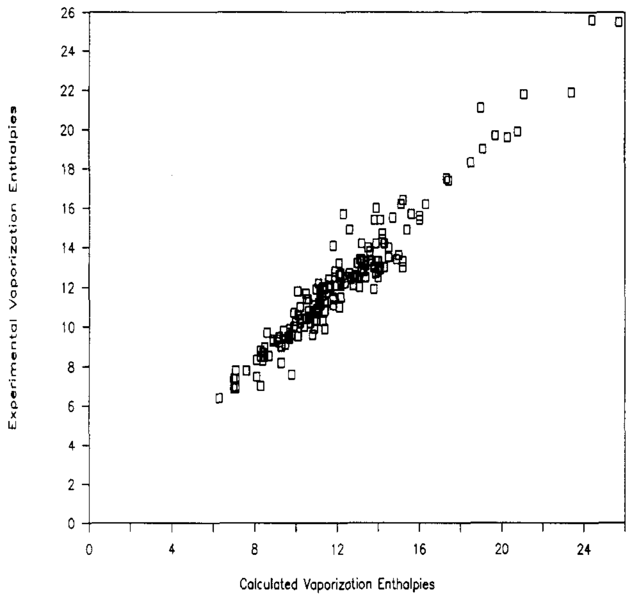

**Figure 3.** A comparison of experimental and calculated vaporization enthalpies of 176 multisubstituted hydrocarbon derivatives.

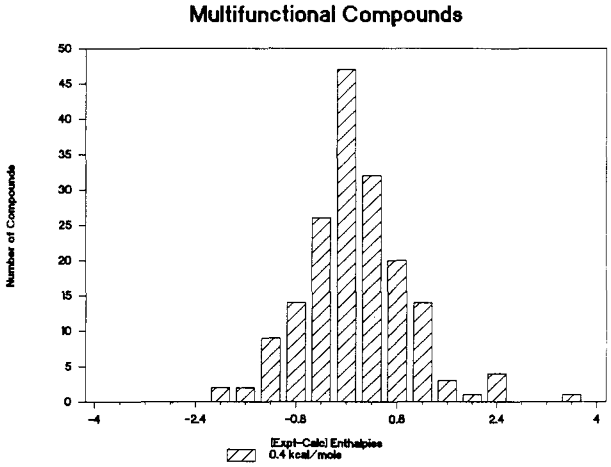

**Figure 4.** The distribution of errors obtained for 175 multisubstituted hydrocarbon derivatives at 0.4 kcal/mol intervals.

group. Vaporization enthalpies for all 175 compounds were determined in this manner. An indication of the correlation achieved with eq 3 in this study is shown in Figure 3. Experimental and calculated vaporization enthalpies are compared. A least-squares analysis of the data give the following parameters for the best fit:

$$\Delta H_v(\text{expt}) = 0.971\Delta H_v(\text{calcd}) + 0.390 \qquad r = 0.966 \tag{6}$$

The average deviation of the 175 compounds used in the correlation was 5.0%, with 19 compounds exhibiting deviations between 10 and 20% and one with a deviation above 20%. This distribution of errors at a 0.4 kcal/mol interval is illustrated in the histogram in Figure 4. In absolute terms, this translates to an average deviation of 0.60 kcal/mol.

In our previous work on monosubstituted hydrocarbon derivatives, we compared the results obtained from eq 2 to those estimated by the group additivity scheme of Guthrie[5] and previous semiempirical calculations of Dreisbach.[8] Data for only a few di- and polysubstituted compounds are available from the Dreisbach Tables. Instead, we have included for comparison predictions by the group and bond additivity methods of Guthrie[5] and a few by the group additivity method of DuCros.[6] Ducros' method, although similar in nature to the Guthrie method, contains some parameters which themselves are dependent on structure and is considerably more complex to use and more limited in the diversity of structure that can be handled at present.[10] These comparisons are given in Table V. The estimates obtained using eq 3 reveal a good compromise between the structural diversity that can be handled by the bond additivity approach and the accuracy that is possible with the multiple parameter approach of group additivity. The major limitations to all estimation methods at present is the limited amount of experimental data available. This seems to pose the most serious problem to estimates by group additivity.

The relationship of $b$ to the polarity of the functional group has been noted previously.[4] The results of this empirical study suggests that the effective polarity of a functional group in multifunctional compounds is sensitive to the position of substitution (Table III). Methyl substitution seems to accentuate the polarity of functional groups, while increasing carbon substitution at the functional group appears to attenuate the effective polarity. This effect was also observed in the simplest monosubstituted hydrocarbon derivatives previously studied.

In summary, it has been possible to reproduce the vaporization enthalpies of 608 compounds of diverse structure by using a total of 41 parameters. The average deviation of each estimation is 3.9% or ±0.45 kcal/mol.

**Supplementary Material Available:** Tables containing the names and vaporization energies of the 30 ring compounds and 102 branched monosubstituted hydrocarbon derivatives used to generate the $C$ terms and the 175 compounds used to generate the $F_i$ values and intramolecular hydrogen bonding corrections reported in Tables II and III (the table also includes a comparison between literature and estimated values) (31 pages). Ordering information is given on any current masthead page.

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(10) An additional complication in using the Ducros method arises from the fact that we are not able to exactly reproduce the calculated values for those compounds that contain functional groups dependent on their function $\gamma$, as defined in their tables.[6]