Methylimidazole-Catalyzed Ester Hydrolysis: Nonlinear Kinetics[1]

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The rate constants for acyl transfer from some *p*-nitrophenyl esters (of trimethylacetate, -butyrate, and -acetate) and from phenyl acetate to imidazole and to the various monomethylimidazole derivatives were examined over a wide range of amine concentration (0.03–3 M). These are all effective nucleophilic catalysts for ester hydrolysis. At low amine concentrations (with limiting ester) the rate constants for imidazole-catalyzed and 1-methylimidazole-catalyzed hydrolysis are nearly identical (2-methylimidazole is ≈3 times smaller and 4-methylimidazole is ≈3 times larger with the *p*-nitrophenyl esters). At high concentrations, however, the reactivities of the methylimidazoles differ markedly from that of imidazole. The observed pseudo-first-order rate constants appear to be an essentially linear function of imidazole concentration (up to ~0.5 M imidazole) but show a nonlinear dependence on methylimidazole concentration. With increasing methylimidazole concentration the reaction varies from first order to zero order in catalyst concentration. Ester hydrolysis is thus *inhibited* at high methylimidazole concentrations relative to the reaction with imidazole. Various explanations for this phenomena are explored, and results are interpreted in terms of a possible noncovalent complexation between the methylimidazoles and the ester.

Imidazole is a well-known nucleophilic catalyst in organic chemistry and enzymology. For compounds with good leaving groups, such as *p*-nitrophenyl esters, nucleophilic catalysis by imidazole is well documented.[2-6] To further explore the nature of displacement reactions by imidazole at the carbonyl carbon of *p*-nitrophenyl esters, particularly with respect to the role of proton transfer, advantage can be taken of an imidazole derivative with an immobile substituent (e.g., a methyl group) replacing a hydrogen, viz., *N*-methylimidazole. We have recently shown[7] with a series of *p*-nitrophenyl esters that the ρ^* values for acyl transfer to low concentrations of imidazole and to *N*-methylimidazole are identical ($\rho^* = 1.6$). The identical ρ^* values indicate that proton transfer from the zwitterionic tetrahedral intermediate occurs *after* the rate-limiting step.[7] Due to the high reactivity of imidazole derivatives they are typically used in relatively low concentrations (<0.1 M) in kinetic studies with reactive esters. In this study, when high concentrations of *N*-methylimidazole are used with esters of lower reactivity [e.g., *p*-nitrophenyl pivalate (trimethylacetate) or phenyl acetate] we found significant deviations from linearity when the observed first-order rate constants are plotted as a function of nucleophile concentration. When this observation was followed up with other methylimidazoles (where the methyl group is located on a position other than a nitrogen) similar nonlinear behavior was observed. This suggested the likelihood of complex formation. This study was undertaken to further explore this possibility.

Materials and Methods

Materials. The *p*-nitrophenyl esters of trimethylacetic acid (*p*-NP pivalate) and phenyl acetate were obtained from Aldrich Chemical Co. The *p*-nitrophenyl esters of *n*-butyric acid (*p*-NP butyrate) and of acetic acid were obtained from Sigma Chemical Co. These esters were found to be >98% pure as judged by monitoring the change in absorbance (at 400 or 288 nm) following alkaline hydrolysis (0.1 M NaOH) and used without further purification. CHES (2-(cyclohexylamino)ethanesulfonic acid) and CAPS (3-(cyclohexylamino)propanesulfonic acid) buffers as well as 1-methylimidazole and imidazole (grade III) were also obtained from Sigma Chemical Co. 2- and 4-methylimidazole were obtained from Aldrich. Reaction solutions in H_2O were prepared in glass-distilled deionized water and titrated to the desired pH with either NaOH or HCl. The ionic strength was maintained at 1.0 M with NaCl. For reactions in D_2O (obtained from Sigma Chemical Co.) the solutions were adjusted to the desired pD value with either NaOD or DCl. The pD values were estimated from the formula pD = pH (meter reading) + 0.41.[8] pH measurements were made with a combination glass electrode on a Metrohm (Brinkman) combititrator.

Methods. Spectrophotometric measurements were carried out in a Hewlett-Packard diode array spectrophotometer (HP 8452) with a circulating water bath to maintain the temperature at 27 °C. The stock ester solutions (≈5 mM) were prepared in acetonitrile (distilled after refluxing over P_2O_5). The reactions were initiated by the addition of 5 μL of the ester solution to 1 mL of a thermally equilibrated solution of imidazole (Im) or to one of the methyl derivatives (MI). At lower pH values (7.3–8.3) the pH was maintained by the buffering capacity of the amine (Im or MI). At higher pH values, 0.01 M CHES[9] or CAPS was used. The ester hydrolysis catalyzed by these buffers was found to be negligable ($k_2 < 0.01\ M^{-1}\ min^{-1}$). The reaction rates were measured by observing the absorbance (400 nm) due to *p*-nitrophenoxide formation. The reactions were carried out under pseudo-first-order conditions (Im or MI in excess) and found to follow first-order kinetics for at least 3 half-lives. The more rapid reactions with high concentrations of 1-methylimidazole with *p*-nitrophenyl acetate were followed in a Dionex Model D-110 stopped-flow spectrophotometer, interfaced with a Biomation 810 transient recorder and a strip-chart recorder. The reactions of MI with phenyl acetate were followed in a pH-stat (Metrohm) because the high background absorbance of MI precluded direct spectrophotometric measurements of phenoxide (at 288 nm). The reactions were carried out in a thermostated reaction vessel (10 mL of solution containing MI, 1 M NaCl, and 0.1 mM phenyl acetate). The reactions were initiated by addition of the ester and followed by the addition of 1 mM NaOH to maintain a constant pH (=10). At low concentrations of 1-methylimidazole (≤0.2 M) the rate constants obtained by this method were found to be identical with those determined spectrophotometrically in solutions buffered at pH = 10 (containing 0.01 M CAPS).

Rate constants were evaluated by nonlinear regression[10] to a single exponential and determined at least in triplicate for each reaction. The internal standard deviations of the rate constants (within each run) were consistently less than ±0.7%. Plots of

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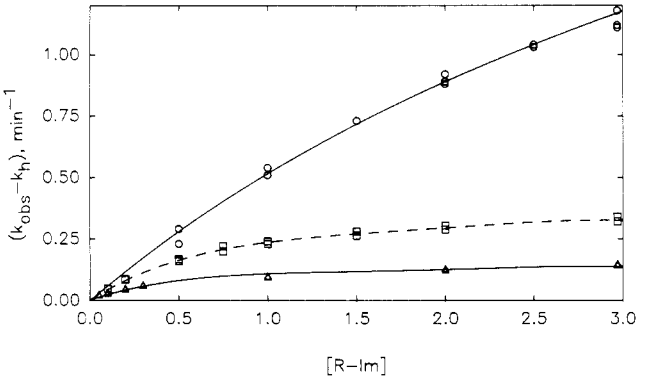

Figure 1. Dependence of the corrected pseudo-first-order rate constant for the hydrolysis of *p*-nitrophenyl pivalate (pH = 9.3) on the concentration of imidazole (○) or of 1-methylimidazole (□) and for the hydrolysis of phenyl acetate (pH = 10) on the concentration of 1-methylimidazole (△) (27 °C, μ = 1.0 M). For *p*-nitrophenyl pivalate the spontaneous hydrolysis (in the absence of catalyst) was negligible ($k_h \approx 0.002$ min^{-1}), for phenyl acetate $k_h = 0.011$ min^{-1}. The curves are the theoretical fits based on eq 1. The kinetic parameters (95% confidence interval) are k_{max} = 3.3 (3.0–3.6) min^{-1}, K = 5.4 (4.9–5.9) M for *p*-nitrophenyl pivalate and imidazole; k_{max} = 0.41 (0.36–0.45) min^{-1}, K = 0.75 (0.66–0.87) M for *p*-nitrophenyl pivalate and 1-methylimidazole; k_{max} = 0.16 (0.14–0.17) min^{-1}, K = 0.48 (0.42–0.54) M for phenyl acetate and 1-methylimidazole.

the observed rate constants, k_{obs} [or, at high pH, $(k_{obs} - k_h)$, where k_h is the rate constant for ester hydrolysis in the absence of amine] versus [imidazole] were found to be nearly linear up to concentrations of ~0.5 M. The rate constant, however, was found to level off with increasing concentration of methylimidazole, [MI]. The data were fit to the empirical equation

$$k_{obs} - k_h = \frac{k_{max}[MI]_0}{K + [MI]_0} \quad (1)$$

The kinetic parameters k_{max} and K were estimated by the median method of Cornish-Bowden and Eisenthal,[11] and the nonparametric 95% confidence intervals for the parameters were calculated by the method of Cornish-Bowden et al.[12] The limiting second-order rate constants calculated for low MI concentrations, obtained from the parameters in eq 1 ($k_2 = k_{max}/K$), were in excellent agreement with values measured directly under pseudo-zero-order (initial velocity) conditions at low nucleophile concentrations.

Results

The pseudo-first-order rate constants for the reaction of imidazole with *p*-NP pivalate or with *p*-NP butyrate were found to give a reasonable fit to a linear function of amine concentration up to ~0.5 M at all pH values examined (7.1–9.9). (An attempted fit of the imidazole data to eq 1 for the reaction of *p*-NP pivalate with imidazole at pH < 8 indicates a value of $K > 5$ M.) The pH dependence of the second-order rate constant indicates that only the unprotonated imidazole is reactive and the kinetically determined pK_a value [7.2 (±0.1)] is identical with the potentiometrically value of pK_a = 7.18 (±0.05). The solvent kinetic isotope for the reaction of imidazole with *p*-NP pivalate was examined (pH = 9.3, pD = 9.7) at nine different concentrations of imidazole (0.1–2.0 M) and found to be 1.14 (±0.06). This is consistent with the well-known role of imidazole as a nucleophilic, rather than general base, catalyst for *p*-nitrophenyl ester hydrolysis.[2-6]

Unlike the situation with imidazole, the rate constant for the reaction with 1-methylimidazole at concentrations greater than 0.25 M markedly deviates from linearity (Figure 1). 1-Methylimidazole does not appear to associate under these conditions as judged from the linear dependence (r = 0.995) of the UV spectrum up to 2 M 1-MI [e.g., ϵ_{275}(shoulder) = 0.47 M^{-1} cm^{-1}, ϵ_{250} = 0.93 M^{-1} cm^{-1}). The spectrum of a 2 M solution of 1-methylimidazole (1 M NaCl, 0.01 M CHES, pH = 10) in a 0.1-cm-path-length cell is identical with that of a 0.2 M solution in a 1-cm cell. Furthermore, no ^{1}H NMR evidence could be obtained for association of 1-methylimidazole in D_2O [1 M NaCl, 0.01 M CHES, pD = 9.82 (±0.03), T = 26 °C]. The chemical shifts (ppm relative to DSS, ±S.E.) of the methyl protons (3.69 ± 0.005), the protons on C-4 and C-5 (7.01 ± 0.004 and 7.10 ± 0.004), and the proton on C-2 (7.61 ± 0.004) remained essentially constant as the MI concentration was increased (in 11 steps) from 0.08 to 3.0 M. The chemical shifts for these signals decreased by less than 0.03 ppm. This can be compared with stacking associating systems such as purines and pyrimidines where (up to concentrations of 0.2 M) the chemical shifts were found to decrease by 0.1–0.3 ppm in D_2O.[13]

The data for the reaction of 1-MI with either *p*-NP pivalate or *p*-NP butyrate give an excellent fit to eq 1. When the reaction between 1-MI and *p*-NP pivalate was examined at pH = 7.3, 7.6, 8.3, 9.3, and 9.9, the value of K was found to decrease from 0.89 (±0.13) to 0.75 (±0.11) M. While the data are not sufficiently precise or extensive enough for a comparison of the kinetic pK_a values of the parameters (K or k_{max}) with the potentiometric pK_a of 1-MI [=7.38 (±0.05)], it does appear as if K is the parameter with the predominant pH dependence. As indicated in Table I, a rectangular hyperbolic dependence of the pseudo-first-order rate constant (eq 1) on [2-MI] and [4-MI] is also observed. The "saturation" effect of 1-MI with phenyl acetate (K = 0.48 M, k_{max} = 0.16 min^{-1}, Figure 1) is even more pronounced than the effect with *p*-NP acetate.

The solvent isotope effect for the reaction of 1-MI with *p*-NP pivalate at pH = 9.3 (pD = 9.7) was examined as a function of the amine concentration ([1-MI] = 0.2–2.0 M). Values of $k_{obs}(H_2O)/k_{obs}(D_2O)$ were found to be 1.05 (±0.03) at each 1-methylimidazole concentration.

The reactions carried out at high MI concentrations contain substantial amounts of organic solvent (24% v/v in the case of 3 M 1-methylimidazole). To examine the possibility that a nonspecific solvent effect is responsible for the nonlinear dependence of the rate constants on the methylimidazole concentrations, the effect of these high concentrations on the reaction with another nucleophile was examined. The observed rate constant for the reaction of 0.05 M hydroxylamine with *p*-nitrophenyl pivalate (pH = 10, 1 M NaCl) was found to be 0.346 (±0.007) min^{-1}. Under the same conditions the rate constant for the re-

Table I. Reaction of *p*-Nitrophenyl Esters (RCO_2NP) with Methylimidazoles[a]

R	imidazole	k_{max}, min^{-1}	K, M	k_2, M^{-1} min^{-1}
CH_3	1-methyl-	37.8 (±1.8)	0.98 (±.09)	29 (±1)
nPr	1-methyl-	24 (±5)	1.2 (±0.2)	20 (±5)
tBu	1-methyl-	0.10 (±0.02)	1.9 (±0.4)[b]	0.05 (±0.01)[b]
tBu	1-methyl-	0.41 (±0.05)	0.75 (±0.09)	0.55 (±0.15)
tBu	2-methyl-	0.13 (±0.01)	0.7 (±0.1)	0.19 (±0.03)
tBu	4-methyl-	2.06 (±0.05)	1.21 (±0.0 6)	1.71 (±0.09)
tBu	H-	3.3 (±0.2)	5.4 (±0.4)	0.53 (±0.02)[c]

[a] 27 °C, 0.5% v/v CH_3CN, μ = 1.0 M, 0.01 M CHES, pH = 9.3. [b] In buffer (pH = 9.3) containing 30% v/v CH_3CN. [c] Second-order rate constant obtained at low (<0.5 M) imidazole concentration.

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action of this ester with 2.7 M 1-methylimidazole was found to be 0.278 (±0.003) min^{-1}. In the presence of *both* 0.05 M hydroxylamine and 2.7 M 1-methylimidazole the rate constant for *p*-nitrophenoxide release is 0.628 (±0.008) min^{-1}. This indicates that high concentrations of 1-MI have no effect on the rate constant for the hydroxyaminolysis reaction.

No spectral evidence could be obtained for the existence of a covalent intermediate in the reaction of *p*-NP pivalate with any of the methylimidazoles. UV detection is particularly difficult due to the substantial absorbance of the high concentrations of methylimidazole required for the buildup of the intermediate and the low solubility of *p*-NP pivalate in aqueous (0.5% CH_3CN) solution. As a potential model for the complexation of the ester with methylimidazole, the effect of 2 M 1- or 4-methylimidazole on the electronic spectrum of *p*-nitroanisole (≈0.1 mM) was examined. No charge-transfer bands in the transparent region ($\lambda > 320$ nm, 1-cm path length) were detected.

A similar experiment was carried out with methyl *p*-nitrobenzoate (0.5 mM) and 1.9 M 1-methylimidazole in a 0.1-cm light path. The spectrum (240–500 nm) was the sum of the spectra of 1-MI and the methyl ester obtained separately. No charge-transfer complex or accumulation of an intermediate with significantly perturbed absorption could be detected by following the reaction of 1.97 M 1-methylimidazole with *p*-nitrophenyl pivalate (0.6 mM, 5% v/v acetonitrile, pH = 9.3, 0.1-cm light path) for 15 half-lives. The reaction proceeds with a sharp isosbestic point (ϵ_{323} = 859 M^{-1} cm^{-1}). An attempt was also made to detect an intermediate by proton NMR. The solubility of *p*-NP pivalate was increased (≈4 mM) in the presence of 30% v/v CD_3CN (pH* = 9.3; see Table I). Even at this concentration, no new signals in the presence of 2 M 1-methylimidazole could be detected.

Discussion

Imidazole is well-known as a nucleophilic catalyst for hydrolysis of *p*-nitrophenyl esters[2-6] as are 2-alkylimidazoles.[14] The similarity of second-order rate constants for the reaction of imidazole and the methylimidazoles with *p*-nitrophenyl pivalate and the similarity of the ρ^* (=1.6) values for the reactions of imidazole and 1-methylimidazole with a series of acyl-substituted *p*-nitrophenyl esters suggest a similar transition-state structure for these reactions.[7] The imidazole-catalyzed hydrolysis of phenyl acetate has also been indicated to follow a nucleophilic mechanism and was demonstrated to be first order in imidazole up to, at least, a concentration of 1 M.[15] The unusual feature in the kinetics of the reaction of the various methylimidazoles with these esters is that there is a leveling off of the pseudo-first-order rate constants with increasing methylimidazole concentration.

This is reminiscent of the nonlinear dependence of the rate constant for hydrolysis of substituted trifluoroacetanilides on 1-methylimidazole or imidazole concentration.[16] This was originally interpreted as reflecting a change in rate-limiting step from formation to breakdown of a tetrahedral intermediate in a *nucleophilic* mechanism. This, however, was later refuted. Pollack and Dumsha[17] demonstrated that the nonlinear dependence of ($k_{obs} - k_h$) on imidazole concentration *did not* show a rectangular hyperbolic dependence (i.e., a fit to eq 1). They cogently argued against a nucleophilic mechanism and presented persuasive evidence in favor of an exclusive general base-catalyzed formation of an anionic tetrahedral intermediate coupled with general acid-catalyzed breakdown of this intermediate. While there is no strong evidence for a nucleophilic mechanism in the imidazole- or 1-methylimidazole-catalyzed hydrolysis of anilides (such as *p*-nitro-2,2,2-trifluoroacetaniline), this is not the case for the reaction with *p*-nitrophenyl esters. The near-unity solvent isotope effect in the reaction of 1-methylimidazole with *p*-nitrophenyl pivalate also strongly argues against a general base-catalyzed mechanism.

Another possible explanation for the nonlinear dependence of the pseudo-first-order rate constant of methylimidazole concentration in the reaction with the esters is that this represents a change in the rate-limiting step (presumably from formation to breakdown of the tetrahedral intermediate) with increasing nucleophile concentration. One way in which this could happen is that reversion of the tetrahedral intermediate to starting materials becomes faster than breakdown to products at high methylimidazole concentrations. This would require that the reversion step be catalyzed by methylimidazole. In view of the absence of general acid/base catalysis in this reaction, it is difficult to see how this could occur. Another possibility is that the tetrahedral intermediate accumulates. This unlikely situation (e.g., see ref 18) would require an unusually favorable equilibrium constant [$=1/K \approx 1$ M^{-1} for the *p*-NP esters and even *more favorable* value (≈3 M^{-1}) for phenyl acetate] for formation of the tetrahedral intermediate and would require that this equilibrium constant be significantly less favorable with imidazole than with either 1-, 2-, or 4-methylimidazole. If such an intermediate, with a sufficient lifetime, accumulated in the reaction of 1-methylimidazole with *p*-NP pivalate, the NMR spectrum of the imidazole moiety should be similar to that of 1-methylimidazolium rather than that of 1-methylimidazole. No such feature in the NMR could be detected in the course of the reaction under conditions where >50% of the ester should be complexed ([MI] = 2 M, K = 1.9 M). Further evidence against accumulation of a covalent intermediate is the observation that at high 1-methylimidazole concentration there is no inhibition of the hydroxyaminolysis of *p*-nitrophenyl pivalate.

Self-association of the imidazoles at high concentrations is also a possible explanation of the nonlinear kinetics. Such behavior has been observed before. For example, the downward curvature in plots of observed rate constants for reactions of *p*-nitrophenyl phosphate with pyridine derivatives has been accounted for by the dimerization of the heterocyclic base in aqueous solution.[19] Such an explanation for our results, however, is not consistent with several observations: (1) the absorbance of methylimidazole follows the Beer–Lambert law; (2) the downward curvature in plots of k_{obs} versus [MI] shows a much better fit to a rectangular hyperbolic dependence on [MI] than to a square-root dependence on [MI];[20] (3) the "dissociation" constant depends on the nature of the ester (Table I).

The most likely explanation for nonlinear kinetics is that

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(20) For the dimerization model, where it is assumed that only the monomeric species reacts (with rate constant k), the equation is $k_{obs} = k[(1 + [MI]/K)^{1/2} - 1]$. Fitting the data to this equation shows systematic deviations of the residuals and standard errors that are 10 times larger than those obtained by fitting the data to eq 1. This, however, does not rule out an association of methylimidazole more extensive than dimerization.

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] $\gg$ [E]) the observed rate constant is given by

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

$$k_{obs} = \frac{k_2 K[\mathrm{MI}]}{K + [\mathrm{MI}]} \qquad (2)$$

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 π–π 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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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: $\Delta H_v = 1.12\tilde{n}_c + 0.31n_Q + 0.71 + \sum F_i b_i + C$. The terms n_Q and $\tilde{n}_c$ refer to the number of quaternary and nonquaternary carbon atoms, respectively. F_i is a structural factor characteristic of the hybridization and substitution pattern of the carbon bearing the functional group, and b_i is a constant characteristic of the polarity of the functional group. The product $F_i b_i$ 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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