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Calculations of Steric Hindrance in Ester Hydrolysis Based on Estimation of van der Waals Strain Energies of Alkanes

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Abstract: Steric hindrance is traditionally defined by the Taft E_s values, which are derived empirically from rates of acid-catalyzed hydrolysis of esters: $E_s = -\log (k/k_0)$, where k is the rate constant for any ester RCOOEt and k_0 is for ethyl acetate. We have explored the utility of hydrocarbon models for calculating E_s for R alkyl and cycloalkyl. The postulate is that E_s is proportional to $\Delta\Delta H = [\Delta H_f°\ (\text{neoalkane}) - \Delta H_f°\ (\text{isoalkane})]$, where neoalkane is $RC(CH_3)_3$. The neoalkane is intended to reflect the degree of steric strain in the tetrahedral intermediate and the isoalkane that is in the ester. Empirical procedures for estimating $\Delta H_f°$ prove relatively useless for these calculations. However, $\Delta H_f°$ estimated from molecular mechanics does provide good values: for example, $E_s = 4.419 + 0.552\Delta\Delta H$ has a standard deviation of 0.4 for a total range of 4, and the correlation coefficient is 0.95 for 24 esters.

The present study continues our calculations of steric hindrance and steric acceleration.[1] The Taft E_s values, based on relative rates of acid-catalyzed ester hydrolysis, have long served as an important empirical measure of steric hindrance;[2] $E_s = -\log (k/k_0)$ where k is the rate constant for any ester RCOOEt and k_0 is for CH_3COOEt. E_s values are relatively independent of reaction conditions and have a standard deviation of the order of 0.1 over a range of 4. The group R may be alkyl or cycloalkyl and may have benzene rings, halogens, or other substituents. However, R may not be aryl or hydrogen; Taft gives a separate E series for benzoic acids.

Several reported attempts to relate E_s values to empirical van der Waals radii have given no generally useful results.[1,3] In this paper we develop a procedure for calculating E_s values for R alkyl or cycloalkyl based on hydrocarbon models, the isoalkane $RCH(CH_3)_2$ being taken as the structural analogue of RCOOEt, and the neoalkane $RC(CH_3)_3$ as the analogue of $RC(OH)_2OEt$, the tetrahedral intermediate. A previous attempt based on RCH_2CH_2Et-$RCMe_2CH_2Et$ pairs gave relatively poor results,[4] but might be improved by the techniques we have used.

The postulate is that the difference in "strain" energies between neoalkane–isoalkane pairs, computed for the gas phase at 298 K, may parallel activation energy differences between starting esters and their tetrahedral intermediates. This requires that solvation and entropy factors remain constant or proportional to "strain" energies for all esters treated. There is no a priori way to calculate that this condition will hold. It is also clear that isoalkanes are not the best possible structural analogues for esters; acids RCOOH, for example, are closer. We will report later on the use of such "improved" models.

For present purposes we will use enthalpies of formation, ($\Delta H_f°$) as the thermodynamic property related to E_s. The justification is that we are interested in strain energy differences, and much of the strain energy is reflected in the enthalpy of formation.

Hydrocarbon models have an especially important advantage; there are more extensive data and better estimation procedures for the thermodynamic properties of hydrocarbons than of any other class of compounds.[5] Direct experimental values, however, are available for only a few trivial pairs, and it is therefore necessary to resort to estimation. Many dozens of empirical recipes have been used for estimating enthalpies of formation of hydrocarbons[6] and the powerful methods of molecular mechanics have also been explored by several groups.[12-18] It was our hope that by focusing initial efforts on a critical use of hydrocarbon models we could maintain a reasonable check against temptation to resort to procedures only weakly grounded on experimental data.

Any success of relating $\Delta\Delta H$ to E_s depends primarily on how well the strain component can be evaluated. Examination of typical empirical procedures for estimating enthalpies of formation shows that their success is oblivious to serious deficiencies in treating strain. The strain component is only a small fraction of the total enthalpy of formation and can be absorbed by other terms. These deficiencies would become apparent if experimental data were available for a sufficient range of strained molecules, but such all-important data are scarce indeed.

As an example, the Franklin protocol[7] predicts a total of just three distinct $\Delta\Delta H$ values for the 24 neoalkane–isoalkane pairs to which it is applicable, and in consequence provides no correlation at all with E_s values. As another example, of all the methods we have used, the Allen protocol[8] provides the best calculated enthalpies of formation for the compounds in Table

Table I. Calculated and Observed Enthalpies of Formation of Alkanes (Gas Phase, 298 K)

			Schleyer 1973 force field			Allinger 1971 force field		
Alkane	$-\Delta H_f{}^a$ obsd	$-\Delta H_f{}^b$ calcd (Allen)	Steric energy^c	Stat mech corr^d	$-\Delta H_f{}^e$ calcd	Steric energy	Stat mech corr^d	$-\Delta H_f{}^g$ calcd
Ethane	20.24	20.14	1.04	0.	19.92	2.37	0.	20.04
Propane	24.82	25.12	1.72	0.	25.01	3.08	0.	25.11
Butane	30.15	30.10	2.35	0.27	29.87	3.71	0.27	30.00
Pentane	35.00	35.08	2.94	0.39	34.94	4.33	0.41	35.02
Hexane	39.96	40.06	3.52	0.63	39.88	4.95	0.64	39.95
Heptane	44.89	45.05	4.10	0.86	44.83	5.56	0.87	44.90
Octane	49.82	50.03	4.67	1.10	49.79	6.17	1.10	49.84
Isobutane	32.15	32.03	2.08	0.	32.92	2.10	0.	32.50
Neopentane	39.67	40.07	2.16	0.	41.10	0.38	0.	40.24
Isopentane	36.92	36.47	3.80	0.09	36.88	3.47	0.09	36.82
2,2-DiMeC4	44.35	43.96	5.03	0.	44.00	1.91	0.	43.73
2-MeC5	41.66	41.45	4.38	0.27	41.89	4.11	0.26	41.79
2,2-DiMeC5	49.29	48.94	5.59	0.12	49.09	2.55	0.17	48.70
2-MeC6	46.60	46.43	4.93	0.52	46.86	4.69	0.50	46.75
2,2-DiMeC6	53.71	53.93	6.12	0.38	54.07	3.10	0.42	53.68
2-MeC7	51.50	51.42	5.50	0.76	51.82	5.30	0.73	51.69
2,5-DiMeC6	53.21	52.80	6.50	0.26	53.82	4.69	0.23	53.24
2,3-DiMeC4	42.49	42.84	6.28	0.27	42.49	3.85	0.27	42.65
2,2,3-TriMeC4	48.96	49.00	8.68	0.	48.62	3.00	0.	49.04
2,4-DiMeC5	48.30	47.82	5.66	0.11	49.04	3.66	0.13	48.77
2,2,4-TriMeC5	53.57	53.57	8.91	0.03	54.13	4.20	0.05	53.57
2,3-DiMeC5	47.62	47.28	8.89	0.50	45.42	5.91	0.43	46.21
2,2,3-TriMeC5	52.61	53.44	10.92	0.20	51.95	4.81	0.23	52.77
2,2,3,3-TetraMeC4	53.99	54.38	12.41	0.	53.15	3.08	0.	54.20
2-Me-3-EtC5	50.48	50.38	10.84	0.43	49.31	7.38	0.49	50.47
SD of calcd values		0.34			0.67			0.40
Correlation coeff		0.999			0.998			0.999

[a] Heats of formation of gaseous alkane at 298 K in kcal mol^{-1} taken from API Research Project 44, 1947. [b] Reference 8. [c] Using the Schleyer 1973 force field, ref 13. [d] Calculated by the method of ref 19. [e] Using revised increment values $CH_3 = -10.48$, $CH_2 = -5.77$, $CH = -3.56$, $C = -1.34$. ΔH_f = base value + steric energy + statistical mechanical correction. [f] Using the Allinger 1971 force field, ref 20, as corrected. [g] Using revised group increment values $CH_3 = -11.21$, $CH_2 = -5.78$, $CH = -0.97$, $C = 4.98$.

I. Yet the Allen protocol proves to be relatively worthless for the problem at hand.

There are three inherent limitations to any empirical protocol for estimating the strain energy component of enthalpies of formation: (1) as molecules become more complex, the list of possible types of nonbonded strain interaction becomes progressively longer and only a limited number can be implemented; (2) for large molecules it becomes increasingly difficult to decide which conformations to evaluate; (3) the logistics problem reaches a stage where it is unreasonably time-consuming to achieve a rigorous count of the interactions, and anything short of complete accuracy is useless.

In applying molecular mechanics to the estimation of enthalpies of formation we used the Allinger 1971[12] and the Schleyer 1973[13] force fields. It is possible that other force fields would give comparable or better results. Although both Allinger's and Schleyer's groups have reported extensive sets of calculations covering an impressive range of ring strain, data have been reported for very few of the hydrocarbons needed in the present study.

A molecular mechanics calculation gives a steric energy summed over bond stretch and angle deformations, torsion energy terms, and nonbonded van der Waals interactions. The calculated enthalpy of formation,

$$\Delta H_f{}^\circ = \text{SE} + \text{base value} + \text{SM} \qquad (1)$$

is given as the sum of the steric energy (SE), of a base value which depends on group increment terms for the CH_3, CH_2, CH, and C groups, and of a statistical mechanical correction (SM) due to the fact that the SE is evaluated for the single conformation of minimum energy, while the molecule at 298 K has other conformations populated. It is important to realize that, while the steric energy includes the strain energy component, it also includes a large and varying amount of base value components as well.

In the present work we have used statistical mechanical corrections based on a general empirical procedure.[19] $\Delta H_f{}^\circ$ values based on the group increment terms recommended by Schleyer[13] showed unacceptable bias when applied to the experimental data in Table I, and we therefore reoptimized these terms for use in the present work. The data in Table I compare our best calculations of enthalpies of formation to experimental values at 298 K, gas phase. Table I includes most of the strained molecules for which data are available, and, for completeness, the inevitable set ethane–neopentane.

Table II extends the calculations to the rest of the isoalkane–neoalkane pairs required for modelling the available ester hydrolysis data. Equations 2–4 summarize the calculations of $\log k_{\text{rel}}$ ($=\log (k/k_0) = -E_s$) using $\Delta H_f{}^\circ$(neoalkane) − $\Delta H_f{}^\circ$(isoalkane) ($=\Delta\Delta H_f{}^\circ$) values from the Schleyer 1973 force field, the Allinger 1971 force field, and the Allen protocol. The limitations of the empirical Allen procedure are evident. Figure 1 illustrates the degree of fit based on eq 2. Details are provided in Table III.

$$\log k_{\text{rel}} = -4.419 - 0.552\Delta\Delta H \qquad (2)$$

SD 0.4, correlation coef −0.95, 24 esters, range 4.0

$$\log k_{\text{rel}} = -4.772 - 0.617\Delta\Delta H \qquad (3)$$

SD 0.4, correlation coef −0.93, 23 esters, range 3.8

$$\log k_{\text{rel}} = -7.659 - 0.991\Delta\Delta H \qquad (4)$$

SD 0.72, correlation coef −0.76, 22 esters, range 3,8

Table II. Calculated Enthalpies of Formation of Alkanes (Gas Phase, 298 K)[a]

Alkane	$-\Delta H_f$ calcd (Allen)	Schleyer 1973 force field			Allinger 1971 force field		
		Steric energy	Stat mech corr	$-\Delta H_f$ calcd	Steric energy	Stat mech corr	$-\Delta H_f$ calcd
i-PrCyc4		25.93	0.27	19.19	26.76	0.27	14.67
t-BuCyc4		30.01	0.00	23.64	27.44	0.00	19.52
2,2-DiMeC7	58.91	6.68	0.62	59.04	3.69	0.65	58.64
2,2,5-TriMeC6	59.52	7.53	0.17	61.14	2.73	0.21	60.66
2-MeC10	66.36	7.22	1.48	66.69	7.11	1.42	66.53
2,2-DiMeC10	73.86	8.39	1.34	73.92	5.51	1.35	73.46
2,2,5,5-TetraMeC6	67.01	8.73	0.03	68.34	1.23	0.05	67.58
i-PrCyc5		22.31	0.27	28.58	11.97	0.27	35.24
t-BuCyc5		29.81	0.00	29.61	15.42	0.00	37.32
i-PrCyc6	47.62	10.35	0.27	46.31	6.86	0.27	46.13
t-BuCyc6	53.78	12.65	0.00	52.54	5.98	0.00	52.54
i-BuCyc6	52.21	9.48	0.11	53.11	6.29	0.13	52.62
Neo-pentylCyc6	58.35	12.06	0.03	58.87	6.15	0.05	58.10
i-PrCyc7		19.74	0.27	42.69	15.25	0.27	43.52
t-BuCyc7		21.79	0.00	49.17	14.27	0.00	50.03
2,2,4,4-TetraMeC5	59.32	11.68	0.00	59.65	4.47	0.00	58.61
2,2,4,5-TetraMeC6	64.38	14.48	0.48	62.15	7.17	0.44	62.39
2,2,3,5,5-PentaMeC6	70.54	16.67	0.15	68.55	6.23	0.18	68.85
2,2-DiMe-3-EtC5	56.13	13.90	0.30	54.64	7.91	0.32	55.37
2-Me-3-*n*-PrC6	60.35	11.74	0.43	59.95	8.40	0.49	61.01
2,2-DiMe-3-*n*-PrC6	66.10	14.72	0.30	65.36	8.87	0.32	65.97
2,5-DiMe-3-*i*-BuC6	72.17	14.75	0.43	73.48	8.31	0.49	73.90
2,2,5-TriMe-3-*i*-BuC6	78.84	19.37	0.30	77.25	9.60	0.32	78.04
2,3,3,5,5-PentaMeC6	68.25	19.23	0.09	66.05	8.87	0.24	66.15
2,2,3,3,5,5-HexaMeC6	73.63	23.32	0.00	70.31	9.41	0.00	71.11
2,2,5-TriMe-4-neopentylC6	88.21	18.52	0.00	86.66	7.13	0.00	86.09
2,2,5,5-TetraMe-3-neopentylC6		28.07	0.00	85.37	15.82	0.00	82.66
2,2,3,4-TetraMeC5	58.07	17.63	0.21	57.15	9.41	0.23	54.58
2,2,3,4,4-PentaMeC5	62.49	21.58	0.00	58.02	10.25	0.00	59.23
2,2,3,3,4-PentaMeC5	61.57	24.01	0.08	55.51	11.96	0.08	57.44
2,2,3,3,4,4-HexaMeC5	66.78	31.47	0.00	56.39	15.55	0.00	59.19
2-Me-3,3-DiEtC5	56.58	19.99	0.34	54.28	12.45	0.41	56.52
2,2-DiMe-3,3-DiEtC5	60.82	27.50	0.23	55.14	17.05	0.29	57.30
2,2,4,5-TetraMe-4-*t*-BuC6		35.25	0.00	72.42	19.12	0.00	73.58
2,2,3,5,5-PentaMe-3-*t*-BuC6		42.14	0.00	73.79	29.76	0.00	68.20
Tri-*t*-Bu-methane		48.21	0.00	53.69	31.67	0.00	55.25

[a] Footnotes in Table I.

We note for the record that it is equally possible to relate log k_{rel} to ΔSE directly; the group increment differences between neoalkane and isoalkane are constant for all pairs, and ΔSM differences are constant within about 0.2 kcal/mol.

There are several limitations to these calculations which need to be considered, but first we may acknowledge our surprise that the estimation of log k_{rel} is so good, for it must depend on a remarkable degree of cancellation. It will be interesting to discover whether similar calculations will be equally useful for treating hindrance in the alcohol group.

The first limitation we consider concerns the imperfect structural relationship between isoalkane and esters. Deviation of this sort becomes excessive in ethyl cyclobutanecarboxylate and ethyl cyclopentanecarboxylate and is relatively evident from inspection of models. We have omitted these compounds from eq 2-4. One limitation of the hydrocarbon models will be the ability to recognize such examples a priori.

The second limitation concerns the fact that the force fields we used fail for certain highly hindered alkanes such as dineopentyl-*tert*-butylmethane. In these structures the cubic correction term in the angle energy expression allows one C-C-C bond to open to unreasonable values (135°, for example) where the steric energy of angle strain may actually reverse sign. We have also omitted these examples; they are readily identified by careful examination of bond angles.

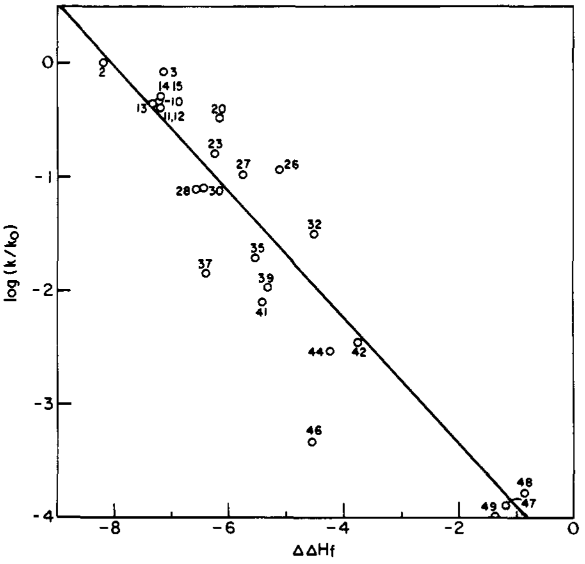

Figure 1. Logarithms of relative rates of acid-catalyzed hydrolysis of esters as reported by Taft (ref 2) vs. differences in enthalpies of formation of corresponding neoalkanes and isoalkanes. The numbers correspond to the order in which the compounds are listed in Table VI of ref 2.

Table III. Calculation of Relative Rates of acid-Catalyzed Ester Hydrolysis[a]

R	Log k_{rel}[b] obsd	ΔH_f (NA) − ΔH_f (IA)[c]	Log k_{rel}[d] calcd
CH_3	0.00	−8.18	−0.10
CH_3CH_2	−0.07	−7.12	−0.49
n-C_3H_7	−0.36	−7.20	−0.44
n-C_4H_9	−0.39	−7.21	−0.44
n-C_5H_{11}	−0.40	−7.22	−0.43
i-C_5H_{11}	−0.35	−7.32	−0.38
n-C_8H_{17}	−0.33	−7.23	−0.43
t-$BuCH_2CH_2$	−0.34	−7.20	−0.44
i-Pr	−0.47	−6.13	−1.04
c-C_6H_{11}	−0.79	−6.23	−0.98
i-Bu	−0.93	−5.09	−1.61
c-$C_6H_{11}CH_2$	−0.98	−5.76	−1.24
sec-Bu	−1.13	−6.53	−0.81
c-C_7H_{13}	−1.10	−6.48	−0.84
t-Bu	−1.54	−4.53	−1.92
t-$BuCH_2$	−1.74	−5.52	−1.37
t-$BuCH_2CH(CH_3)$	−1.85	−6.40	−1.53
$(C_2H_5)_2CH$	−1.98	−5.33	−1.48
(*n*-$C_3H_7)_2CH$	−2.11	−5.41	−1.43
(*i*-$C_4H_9)_2CH$	−2.47	−3.77	−2.34
t-$BuCH_2C(CH_3)_2$	−2.57	−4.26	−2.07
t-$BuCH(CH_3)$	−3.33	−0.87	−3.93
t-$BuC(CH_3)_2$	−3.90	−0.88	−3.94
$(C_2H_5)_3C$	−3.80	−0.86	−3.94
t-$BuCH_2C(CH_3)$(*t*-Bu)	−4.00	−1.37	−3.66

[a] Hydrolysis in acetone–water at 25 °C., R. A. Taft, ref 2. [b] Relative to ethyl acetate. [c] Using heats of formation for neoalkane and for isoalkane calculated by molecular mechanics (Schleyer force field), gas phase, 298 K. (Table I and II). Values using the Allinger force are comparable. [d] From eq 2.

The third limitation resides in the fact that the force fields have not been systematically optimized, and, more seriously for present purposes, have not been optimized to treat van der Waals strain. These force fields were developed with other ends in mind and were parameterized against an extensive variety of structures for general applicability. It is no wonder that certain limitations turn up as we attempt to extend the calculations to conditions of crowding not previously contemplated. Among the numerous force fields used in molecular mechanics, the expressions chosen to represent the energies of nonbonded interactions show extreme variability, and this aspect deserves much further attention.

The constants appearing in eq 2–4 obviously are going to depend on how the strain energy component is defined de facto by the force field or by the empirical protocol. We recommend the Schleyer force field over the Allinger on the basis of greater simplicity and, therefore, lower cost of calculations. However, as far as results are concerned, these two force fields are on a par.

The success we have had in predicting steric hindrance and steric acceleration[1] and the success of Schleyer's group in treating steric acceleration of solvolysis[21] shows the great promise of molecular mechanics as a tool for the quantitative calculation of relative reaction rates.

Experimental Section

Calculations. The molecular mechanics calculations were carried out with the program MOLMEC, based in general upon the Bartell algorithms.[14] The principal differences are the following: capability and flexibility of treating large molecules, computation of derivatives by numerical difference rather than analytically (for convenience in changing force fields), use of a diagonal matrix in the Taylor's series expansion rather than the full matrix (although both capabilities are present), and provision for explicit rotation of groups as a unit. Among the extensive checks on the algorithms of MOLMEC we recalculated the energy and the geometry of tri-*tert*-butylmethane[22] as follows: we varied all 117 internal parameters, rather than using a symmetry based description,[22] and we divided the torsion barrier calculation into nine pairwise terms for each bond rotation in order to assure that the computed torsional energy terms are independent of the description of the molecule. This treatment differs from that of Bartell and Buergi, since their program identifies the torsion energy with some one specific bond. The energy minimization was carried until the last change per step dropped below one part in a million. Symmetry-related internal consistency of the geometry so obtained was better than 0.0002 Å in C–C distances, 0.0001 Å in C–H distances, 0.001 Å in symmetry-related nonbonded distances, 0.04° in C–C–C angles, 0.02° in H–C–C angles, and 0.05° in torsion angles. Agreement with the Bartell and Buergi figures was excellent, in spite of the above mentioned difference in the treatment of torsion potentials. There is no reason to prefer one approach over the other, but such minor details can have an appreciable effect on the detailed results. For four types of C–C bond, agreement with Bartell and Buergi (BB) was to 0.0005 Å, for nine types of C–H bond to 0.0005 Å, for three types of C–C–C angle to 0.1°, for nine types of C–C–H angle exact agreement for all but two, which differed by 0.05°, for three H(t)–C–C–C torsions to 0.2°, and for three averages of three H–C–C–C methyl torsions to 0.7°. We were also able to reproduce the Engler, Andose, and Schleyer (EAS)[13] average values from the Schleyer and the Allinger force fields to similar precision, although this is a less rigorous comparison since fewer data are being compared.

As a further check, and in order to provide a consistent set of data, we repeated computations of steric energies for some of the hydrocarbons reported by Engler, Andose, and Schleyer.[13] Since steric energies are not reported directly, we back-calculated these from calculated enthalpies of formation in their Table I[13] and from the "general increment" terms from their Table VI.[13] For the following compounds, our results agreed within 0.03 kcal/mol: ethane (A,S), 2-methylpentane (A,S), 2,2-dimethylbutane (A), 2,2,3,4,4-pentamethylpentane (A); where (A) denotes the Allinger force field and (S) the Schleyer force field. There were larger discrepancies with the Allinger force field for the following compounds: (our value is given first, and then the EAS value) *n*-butane 3.71, 4.40; 2-methylbutane 3.47, 3.57; 2,3-dimethylbutane 3.85, 3.80; neopentane −0.38, −0.47; 2,3,3-trimethylbutane 3.00, 3.38; 2,2,3,3-tetramethylbutane 3.08, 4.93.

For the Schleyer force field, steric energies are: 2-methylbutane 3.80, 3.84; 2-methylpentane 4.38, 4.43; 2,3-dimethylbutane 6.28, 6.35; 2,2-dimethylbutane 5.03, 5.10; 2,2,3-trimethylbutane 8.68, 8.80; 2,2,3,3-tetramethylbutane 12.41, 13.37; 2,2,3,4,4-pentamethylpentane 21.58, 22.13.

In a molecular mechanics calculation one must judge how many iterations to use. In all of our examples, we carried out iterations in the energy minimization until the last change in steric energy dropped below one part in 10 000. There is no guarantee that further iterations will not lower the steric energy by several parts per hundred, but in related computations carried for further iterations until the change per iteration dropped below one part in a million, the final energy was not more than one or two parts per thousand lower than the rougher estimate. Most of the difference between the EAS values and ours are of little significance (less than 0.1 kcal/mol) and are probably assignable to different choices of breaking off iterations.

The constants in eq 2–4 and the revised group increment values used in Tables I and II were evaluated under a variety of assumptions using the general least-squares program GENLSS.[23]

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Application of ^{13}C Nuclear Magnetic Resonance Spectroscopy to the Analysis of Charge Distribution Patterns in Unsaturated Carbonyl-Containing Compounds[1]

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Abstract: The proton decoupled carbon-13 nuclear magnetic resonance spectra of a variety of unsaturated carbonyl-containing compounds, as well as the corresponding alkenes, saturated carbonyl derivatives, and alkanes, have been recorded. An empirical treatment is described which relates the obtained data to the relative π charge densities at the various molecular centers. The relative densities are shown to be consistent with expectations.

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy has found wide and increasing application to problems of chemical interest. One area in which ^{13}C NMR spectroscopy has served as a sensitive probe is the analysis of charge distributions in organic ions.[2] The increased advantage of carbon over proton magnetic resonance in such systems stems from its increased sensitivity to substituent effects. This is due to the fact that the carbon nucleus is directly bond to the substituents which donate or withdraw electrons. The proton, on the other hand, monitors the same situation, but from a position once further removed. The approximately 20-fold greater chemical shift range of carbon-13 nuclei as compared to protons also allows for easier identification of the factors responsible for chemical shift differences.

These same features should serve to benefit the investigation of charge distributions in neutral molecules as well. Indeed, a number of generalizations along these lines have been made.[3] Still, the application of ^{13}C NMR spectroscopy to the study of charge variations in neutral, nonaromatic molecules has been much more limited than the role it plays in the corresponding analysis of ions.

Some correlation should exist between ^{13}C NMR chemical shifts and charge densities. It is the paramagnetic screening constant (σ_p) which is thought to control the ^{13}C chemical shift in most cases.[4] The sophisticated expressions developed by Ditchfield and others,[5] as well as the earlier equations of Pople and Karplus,[6] all contain terms which relate σ_p to local atomic charge densities. However, these same expressions also reveal dependencies upon bond orders, orbital energy differences, and other parameters which are not directly related to the sought after atomic densities. Hence, while a relationship between charge densities and ^{13}C NMR shifts is to be expected, it need not be linear.

Some time ago, we elected to carry out a detailed analysis of the ^{13}C NMR spectra of a wide variety of unsaturated carbonyl containing systems. The establishment of a correlation between π charge densities and empirically modified chemical shifts within this series of compounds would be quite significant. Not only would it bode well for extension to other classes of compounds, but it would have a number of immediate applications. It would provide a simple method for obtaining a clear electronic description of a molecule. This technique, unlike theoretical calculations, would not involve assumptions concerning molecular geometry or solvation; observations would be made directly on the molecules in solution. Such a method would also allow us to comment upon the aromatic character of appropriate systems, annulenones, for example. Furthermore, as molecular orbital coefficients and PMO theory serve to relate charge densities to reaction rates,[7] we would hope to eventually apply any such correlation and methodology to the prediction of chemical reactivity.

Our initial efforts with α,β-unsaturated carbonyl compounds were centered on evaluating the relationship between the β-carbon atom ^{13}C NMR shift and the corresponding π-electron density. Our approach is wholly empirical and proceeds as follows. We ascribe the shift difference between the β-carbon atom in the enone and the analogous carbon atom in the corresponding alkene to the total ($\sigma + \pi$) electron deficiency at