was crystallized from $CHCl_3$-pentane. **10**: mp 105.5-106.0 °C; NMR ($CDCl_3$) δ 0.9 (t, 6 H), 1.3 (m, 4 H), 2.0 (m, 4 H), 3.3 (s, 3 H), 7.35 (m, 5 H), 7.9 (s, 1 H); IR (KBr) 1150 and 1350 (-SO_2-) and 1695 cm^{-1} (C=O). Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.48; N, 7.40; N, 4.47; S, 10.23. Found: C, 57.12; H, 7.35; N, 4.54; S, 10.52.

pK_a Measurements. The pK_a's of the sulfonamides have been determined by potentiometric titration in 1:1 (v/v) EtOH-H_2O at an ionic strength of 1.0 M (NaCl). Employing the procedure given by de Ligny et al.,[27] we substracted a quantity δ from the meter readings to afford corrected pK_a values in order to account for the differences in the pH scale in water and the mixed aqueous solution. The general method for the determination of the pK_a was as follows. Carboxylic acid (ca. 40 mg) was dissolved in ca. 50 mL of 1:1 EtOH-H_2O at an ionic strength of 1.0 M (NaCl) at 50.0 °C. In order to exclude CO_2 absorption of the solvent all measurements were carried out under a N_2 atmosphere. The pH of the solution was measured by a KCl electrode and reproduced on a recorder. The pH meter and the recorder were calibrated by means of two buffer solutions of pH 4.0 and 7.0. Thereupon, a constant flow of a 0.1 N NaOH solution was added until pH >10, while the change of the pH with time was followed by the recorder. The pK_a of the carboxylic acid could be calculated directly from the sigmoid curve obtained. All measurements were carried out in duplicate or in triplicate. The reproducibility was within 0.03 pK_a unit.

Kinetic Measurements. The rates of hydrolysis were determined by following the decrease in absorption at a suitable wavelength in the UV spectrum (method A) or by following the decrease and the increase of the *N*-phenyl (or *N*-methyl) peak of the sulfonamide and the amine, respectively, in the NMR spectrum (method B). The accuracy of method A is higher than that of method B. Because of the low solubility of **7**, the rate of hydrolysis could only be measured in 1:1 (v/v) EtOH-H_2O. Usually the k_{obsd} values obtained by method B are a factor of 1.5-2 smaller than those determined by method A. Most likely, the relatively high concentration of the substrate (ca. 0.4 M) brings about a change in the properties of the reaction medium which leads to this difference.

Method A. The rates of hydrolysis were determined by monitoring the change in absorbance at 234 nm. The procedure was given previously.[3] Initial concentrations were ca. 4×10^{-5}-10^{-4} M. The k_{obsd} values were reproducible to within 2%.

Method B. The rate of hydrolysis was determined by monitoring the disappearance and the appearance of the *N*-phenyl (*N*-methyl)peak of the sulfonamide and of *N*-methylaniline, respectively, in the NMR spectrum as a function of time. The NMR tube was filled with 40 mg of the sulfonamide and 0.4 mL of the 1:1 (v/v) EtOH-H_2O solution (containing 0.5 N HCl) and sealed. The sulfonamide was dissolved by stirring and heating, whereupon the tube was placed immediately in a thermostated Haake F3 oil bath (±0.05 °C). At least three NMR spectra were taken per half-life. The period necessary for recording one NMR spectrum was about 1.5 min, which could be neglected in view of the long half-lives of the reactions. The concentration of unreacted sulfonamide could be calculated from the intensities of the two *N*-phenyl peaks (which are singlets in 1:1 (v/v) EtOH-H_2O). The k_{obsd} value could be obtained from the slope of the plot of ln [sulfonamide] vs. time. Measurements were taken up to at least 85% conversion of the sulfonamide into the sulfonic acid and *N*-methylaniline. The k_{obsd} values were reproducible to within 3-4%.

Solvents. The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit. The ethanol was of the highest grade available (Merck).

Thermodynamic Activation Parameters. For all sulfonamides the temperature dependence of the rate constant for hydrolysis (k_{obsd}) was determined at at least four temperatures over a temperature range of at least 14° within the range 50-70 °C (method A). Since the reproducibility of the k_{obsd} values was within 2%, the estimated errors are 0.02 kcal mol^{-1} in $\Delta G^{\ddagger}$, 0.3 kcal mol^{-1} in $\Delta H^{\ddagger}$, and 1 eu in $\Delta S^{\ddagger}$. For method B, the reproducibility of the k_{obsd} values was in all cases 4%.

X-ray Structural Determinations. Full details for the sulfonamides **1**, **3**, **8**, and **9** will be published elsewhere.[28]

Registry No. 1, 7117-20-6; **1** ethyl ester, 87712-30-9; **2**, 87712-31-0; **3**, 87712-32-1; **4**, 87712-33-2; **5**, 87712-34-3; **6**, 87712-35-4; **7**, 87712-36-5; **8**, 72519-81-4; **9**, 75599-75-6; **10**, 87712-37-6; **15**, 87712-38-7.

Supplementary Material Available: Tables with bond lengths, bond angles, and dihedral angles for the sulfonamides **1**, **3**, **8**, and **9** (4 pages). Ordering information is given on any current masthead page.

(27) Gelsema, W. J.; De Ligny, C. L.; Remijnse, A. G.; Blijleven, H. A. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 647.

(28) Stam, C. H.; Schenk, H., to be published.

Correlation of Nonadditive Kinetic Effects with Molecular Geometries. Structure and Reactivity of Alkyl- and Cycloalkenylpyridines[1]

Jeffrey I. Seeman,*[2a] Jimmy W. Viers,*[2b] John C. Schug,*[2b] and Michael D. Stovall[2b]

Contribution from the Philip Morris Research Center, Richmond, Virginia 23261, and the Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061. *Received April 8, 1983*

Abstract: The hypothesis that ground-state geometries can be used to quantify chemical reactivity is examined by evaluating a variety of geometrical parameters and steric congestion models for the methylation of a wide series of alkylpyridines. The ground-state minimum energy conformations of these pyridines were determined by using MINDO/3 semiempirical all-valence electron calculations. Nonadditive kinetics were observed for a series of 2,3-dialkylpyridines compared with the analogous 2,5-dialkylpyridines; correlations are found between the nonadditive portion of the rates of alkylation of these pyridines and both the N-C_2-C_{2_α} angle and d_{NH}, the distance between the pyridine nitrogen and the closest C_{2_α}-hydrogen atom. Long-range buttressing effects on reactivity were quantified by geometry modeling of the reactivity of 3,5-dialkylimidazo[1,2-*a*]pyridines. Steric substituent constants, $S°$, were derived on the basis of the Brønsted relationship for the pyridines bearing at least one C_{2_α} substituent. A geometric accessibility factor for the nitrogen in pyridines was developed and correlated with $S°$. This accessibility factor represents the free solid angle about a point 1.75 Å from the pyridine nitrogen along the C_4-N axis and in the pyridine ring plane. Another model based on overlapping van der Waals radii of substituents was evaluated; this latter model had previously been developed by Sternhell to predict the energy barriers for an intramolecular process, namely biphenyl ring-ring rotation. It was shown that the model works equally well for the intermolecular alkylation reaction. The relationships between nonadditive kinetics, buttressing effects, and the various steric substituent parameters and models are discussed in detail.

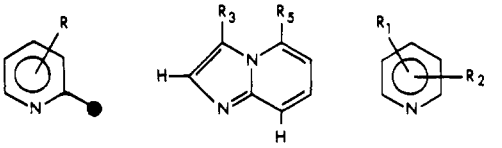
The correlation of molecular structure with chemical reactivity is a fundamental objective in organic chemistry. For the last forty years, the Hammett equation has played a well-deserved central role in determining structure-reactivity relationships for a wide

0002-7863/84/1506-0143$01.50/0

variety of chemical reactions and substituents.[3] Extension of the original Hammett concept by application of numerous modified substituent constants has allowed the dissection of total molecular reaction into its inductive, resonance, and steric components.[3a] The wide range of treatments reported in this area is exemplified by the use in recent years of at least eleven different steric substitution parameters.[4]

Linear free energy (LFER) treatments do not attempt to deal with structural (bond angles and lengths) parameters per se. Few studies have been reported which relate molecular geometry and reaction kinetics. The pioneering work of Westheimer on hindered rotation[5] and de la Mare and Ingold on the S_N2 reactions of alkyl halides[6] has been advanced by more rigorous force-field calculations of Allinger,[7] DeTar,[8] and McKenna.[9] Wipke and Gund reproduced the experimental stereoselectivity of hydride attack on ketones by calculating the accessibility of reagents to the carbonyl carbon as limited by hindering atoms in the substrate molecule.[10] Dunitz has advanced his elegant structural correlation principle which derives reaction path information based on crystallographic analyses of related molecules.[11] Berg and Gallo have recently applied Allinger's MMI force field to calculate transition state structures for the quaternization of 2-alkylpyridines and thiazoles, though they used idealized ring geometries which were maintained independent of ring substituent.[12]

To examine the hypothesis that ground-state molecular geometry can be used to *quantify* chemical reactivity, we have studied the structures and Menschutkin reactivity of three systems, generalized by **1**–**3**.[1b,13,14] In section I of this paper, we will



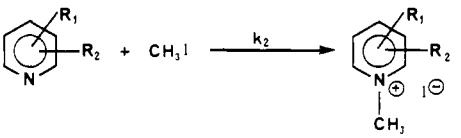
1 **2** **3**

consider the effects of varying degrees of kinetic nonadditivity by quantifying the buttressing effects of pyridines having one α-substituent, generalized by structure **1**. In section II this study is broadened by examining rate data for the methylation of several imidazo[1,2-*a*]pyridines (**2**) which exhibit buttressing effects remote from the reaction site. We will correlate the experimental rates of methylation of **1** and **2** with the heterocycle's nitrogen accessibility to an external reagent.

In order to extend the scope of our work, we have developed (section III) a geometric steric factor which quantifies methylation rates for pyridines **3** having more complex substitution patterns than for **1**, e.g., 2-ethyl- and 2-isopropylpyridines, where the substituent pattern is unsymmetrical, and 2,6-diisopropylpyridine, where there are two α-substituents. It is shown that kinetic steric factors can be related to geometrically calculated accessibility factors[10] for the nitrogen atoms in the equilibrium substrate molecules. We note that almost all studies aimed at evaluating steric effects do so with regard to intramolecular processes, e.g., conformational changes. In section IV, we demonstrate that steric substituent parameters derived for intramolecular interactions correlate with analogous parameters derived herein for intermolecular reactions. In particular, it is shown in section IV that the kinetic steric factors can be related to the overlap of atomic van der Waals spheres in model transition states constructed from undistorted reactants. Such a model was recently used by Sternhell and co-workers[15] to study steric barriers to internal rotation in substituted biphenyls.

Discussion

I. Buttressing Effects in 2,*x*-Disubstituted Pyridines. The classical work of Brown and Cahn demonstrated the sensitivity of methylation rates of alkylpyridines (eq 1) to their substitution pattern.[16] Subsequent work by Clark and Rothwell indicated



(1)

that the reaction rate of 2,3-lutidine with allyl bromide was significantly less than expected based on the reactivities of 2-picoline and 3-picoline relative to pyridine.[17] Brown and his students observed buttressing effects in the reactions of a series of 2-methyl-3-alkylpyridines compared to the analogous 2-methyl-5-alkylpyridines.[18] We reasoned that kinetic nonadditivity would be coupled with structural parameter nonadditivity. For com-

(1) (a) For the previous paper in this series, see: Seeman, J. I.; Schug, J. C.; Viers, J. W. *J. Org. Chem.* **1983**, *48*, 2399. (b) For a preliminary account of this work, see: Seeman, J. I.; Galzerano, R.; Curtis, K.; Schug, J. C.; Viers, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 5982–5984.

(2) (a) Philip Morris. (b) Virginia Polytechnic Institute and State University.

(3) (a) "Correlation Analysis in Chemistry"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978. (b) "Advances in Linear Free Energy"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: London, 1972. (c) Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1978**, *16*, 87–157. (d) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 569–575. (e) Johnson, C. D. "The Hammett Equation"; Cambridge University Press: New York, 1973. (f) Hansch, C.; Leo, A. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley: New York, 1979.

(4) (a) E_S: Taft, R. W., Jr. In "Steric Effects in Organic Chemistry"; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 13. (b) E_S^c: Hancock, C. K.; Meyers, E. A.; Yager, B. J. *J. Am. Chem. Soc.* **1961**, *83*, 4211–4213. (c) E_S^o: Palm, V. A. "Fundamentals of the Quantitative Theory of Organic Reactions"; Khimiya: Leningrad, 1967. (d) E_S': MacPhee, J. A.; Panaye, A.; Dubois, J. E. *Tetrahedron Lett.* **1978**, 3293–3296. (e) E_S^e: Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, Chapter 4. (f) v: Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552–1556. (g) σ_S: Farthing, A. C.; Nam, B. In "Steric Effects in Conjugated Systems"; Gray, G. W., Ed.; Academic Press: Interscience, 1958. (h) *SF*: Hussey, W. W.; Diefendorfer, A. J. *J. Am. Chem. Soc.* **1967**, *89*, 5359–5362. (i) ρ_f: Beckhaus, H.-D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 593–594. (j) S^o: Berg, U.; Gallo, R.; Klatte, G.; Metzger, J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1350–1355. (k) θ: Sjostrom, M.; Wold, S. *Ibid.* **1979**, 1274–1278.

(5) Westheimer, F. H. In "Steric Effects in Organic Chemistry"; Newman, M. S., Ed.; Chapman & Hall: New York, 1956; Chapter 12.

(6) de la Mare, P. B. D.; Bowden, L.; Hughes, E. D.; Ingold, C. K.; Mackie, J. D. H. *J. Chem. Soc.* **1955**, 3200–3236.

(7) Allinger, N. L. In "Advances in Physical Organic Chemistry"; Gold, V., Bethell, D., Eds.; Academic Press: London, 1976; Chapter 1.

(8) (a) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505–4512. (b) DeTar, D. F.; McMullen, D. F.; Luthra, N. P. *Ibid.* **1978**, *100*, 2484–2493. (c) DeTar, D. F.; Tenpas, C. J. *Ibid.* **1976**, *98*, 7903–7908.

(9) (a) Chalk, C. D.; Hutley, B. G.; McKenna, J.; Sims, L. B.; Williams, I. H. *J. Am. Chem. Soc.* **1981**, *103*, 260–268. (b) McKenna, J.; Sims, L. B.; Williams, I. H. *Ibid.* **1981**, *103*, 268–272. (c) Chalk, C. D.; McKenna, J.; Williams, I. H. *Ibid.* **1981**, *103*, 272–281. (d) Chalk, C. D.; McKenna, J.; Sims, L. B.; Williams, I. H. *Ibid.* **1981**, *103*, 281–284.

(10) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *98*, 8107–8118.

(11) Dunitz, J. D. "X-Ray Analysis and the Structure of Organic Molecules"; Cornell University Press: Ithaca, NY, 1979; Part II.

(12) (a) Gallo, R. In "Progress in Physical Organic Chemistry"; Taft, R. W., Ed.; Wiley: New York, in press. (b) Berg, U.; Gallo, R., unpublished. We thank Prof. Gallo for supplying us with these preprints and unpublished results. (c) See also: Gallo, R.; Chanon, M.; Lund, H.; Metzger, J. *Tetrahedron Lett.* **1972**, 3857–3860. (d) Following completion of this manuscript, we became aware of an interesting study by Roussel and co-workers[12e] that discusses, in part, the relationship of geometric nonadditivities of polysubstituted pyridines and their alkylation kinetic nonadditivities. (e) Roussel, C.; Balaban, A. T.; Berg, U.; Chanon, M.; Gallo, R.; Klatte, G.; Memiaghe, J. A.; Metzger, J.; Oniciu, D.; Pierrot-Sanders, J. *Tetrahedron*, in press. We thank Professor Roussel for sending a preprint of this manuscript.

(13) For a recent discussion of a transition-state model for the Menschutkin reaction of substituted pyridines, see ref 1a and: (a) Viers, J. W.; Schug, J. C.; Seeman, J. I. *J. Am. Chem. Soc.* **1982**, *104*, 850–851. (b) Schug, J. C.; Viers, J. W.; Seeman, J. I. *J. Org. Chem.*, in press.

(14) For an evaluation of pyridine and *N*-methylpyridinium cation geometries and energetics, see ref 1a.

(15) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618–5626.

(16) Brown, H. C.; Cahn, A. *J. Am. Chem. Soc.* **1955**, *77*, 1715–1723.

(17) Clarke, K.; Rothwell, K. *J. Chem. Soc.* **1960**, 1885–1895.

(18) (a) See the Ph.D. Dissertations of J. Donahue (1957), M. S. Howie (1959), D. H. McDaniel (1954), H. Podall (1955), J. S. Olcott (1957), and S. Bank (1960), all from the H. C. Brown group, Purdue University. (b) Brown, H. C. "Boranes in Organic Chemistry"; Cornell University Press: Ithaca, NY, 1972; Chapters V–VIII. (c) Brown, H. C. *J. Chem. Ed.* **1959**, *36*, 424–431. (d) Brown, H. C. *J. Chem. Soc.* **1956**, 1248–1268. (e) Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1966**, *88*, 986–992.

Table I. Methylation Rate Constants, Nonadditive Rate Factors, and Steric Factors of 4-38

compd	k_{rel}	k_{calcd}[a]	S[a]	$S°$[b]	f[k]	Ω_T	Σr^*
pyridine (4)	1				1	1	0.488
2-picoline (5)	0.43[c]			−0.734	0.20	0.925	1.01
3-picoline (6)	1.7[c]				1	0.998	0.516
4-picoline (7)	2.1[c]				1	1.00	0.464
2,3-lutidine (8)	0.43[c]	0.74	0.59	−0.917	0.11	0.917	1.10
2,4-lutidine (9)	0.92[c]	0.90	1.0	−0.636	0.20	0.926	0.990
2,5-lutidine (10)	0.82[c]	0.73	1.1	−0.593	0.22	0.923	1.04
2,6-lutidine (11)	0.040[c]	0.18	0.22	−2.01	0.0083	0.846	1.53
3,4-lutidine (12)	3.4[c]	3.6	0.95		0.95	1.0	0.493
3,5-lutidine (13)	2.6[c]	2.9	0.90		0.90	1.0	0.542
2,4,6-trimethylpyridine (14)	0.11[d,e]	0.17	0.65	−1.83	0.011	0.846	1.53
2,3,5,6-tetramethylpyridine (15)	0.013[f]	0.034	0.38	−2.86	0.00093	0.822	1.71
pentamethylpyridine (16)	0.015[f]	0.071	0.21	−3.05	0.00051	0.824	1.72
2-ethylpyridine (17)	0.22[g]			−1.01	0.10	0.881	
3-ethylpyridine (18)	2.2[d]				1	0.998	0.518
2-isopropylpyridine (19)	0.075[g,h]			−1.44	0.034	0.877[l]	1.43
						0.796[m]	
3-isoporpylpyridine (20)	2.4[d]				1	0.998	0.516
2-*tert*-butylpyridine (21)	0.00022[g,h]			−3.96	0.00010	0.665	2.83
3-*tert*-butylpyridine (22)	2.8[d]				1	0.990	0.622
2-methyl-3-ethylpyridine (23)	0.48[d]	0.95	0.51	−0.878	0.099	0.915	1.12
2-methyl-5-ethylpyridine (24)	1.1[d]	0.95	1.2	−0.475	0.23	0.915	1.12
2-methyl-3-isopropylpyridine (25)	0.51[d]	1.0	0.49	−0.864	0.097	0.915	1.13
2-methyl-5-isopropylpyridine (26)	1.2[d]	1.0	1.2	−0.452	0.23	0.915	1.05
2-methyl-3-*tert*-butylpyridine (27)	0.33[d]	1.2	0.27	−1.11	0.054	0.897	1.22
2-methyl-5-*tert*-butylpyridine (28)	1.3[d]	1.2	1.1	−0.449	0.21	0.914	1.04
2-ethyl-3-methylpyridine (29)	0.24[d]	0.37	0.64	−1.12	0.064	0.862	
2-ethyl-5-methylpyridine (30)	0.54[d]	0.37	1.5	−0.765	0.14	0.880	
2-ethyl-6-methylpyridine (31)	0.0035[i]	0.095	0.037	−3.06	0.00072	0.785	
2-isopropyl-3-methylpyridine (32)	0.0031[d]	0.13	0.024	−3.00	0.00083	0.858[l]	1.52
						0.766[m]	
2-isopropyl-5-methylpyridine (33)	0.17[d]	0.13	1.3	−1.25	0.045	0.877[l]	1.43
						0.795[m]	
2,6-diethylpyridine (34)	0.0037[j]	0.048	0.076	−3.01	0.00076	0.750	
2,6-diisopropylpyridine (35)	0.00015[j]	0.0056	0.027	−4.30	0.000031	0.746[l]	2.39
						0.587[m]	
2,3-cyclopentenopyridine (36)	1.9[c,n]	0.73	2.6	−0.0815	0.39	0.947	
2,3-cyclohexenopyridine (37)	1.1[c]	0.73	1.5	−0.537	0.23	0.918	
2,3-cycloheptenopyridine (38)	0.30[c]	0.73	0.41	−1.05	0.062	0.897	

[a] Calculated by using relative rate constants for the monosubstituted pyridines and applying LFER. See eq 2. Nonadditive rate factor $S = k_{rel}/k_{calcd}$. Perfect additivity is obtained when $S = 1$. [b] Derived using eq 8. [c] Reference 1b, acetonitrile, 25 °C. [d] Reference 18, nitrobenzene, 25 °C. [e] Reference 17, nitromethane, 60 °C. [f] References 20 and 21, acetone, 25 °C. [g] Reference 16, nitrobenzene, 25 °C. [h] Reference 4j, acetonitrile, 30 °C. [i] Reference 23, dimethylsulfoxide, 23 °C. [j] Reference 23, acetone, 25 °C. [k] Derived by factoring out the electronic component of alkyl substituents based on the relative rate constants of the monoalkyl pyridines under the appropriate reaction conditions. See the text for additional discussion of this point. [l] $\tau(HC_{2\alpha}C_2N) = 0°$. See text for additional discussion of this point. See ref 38. [m] $\tau(HC_{2\alpha}C_2N) = 180°$. See ref 38. [n] The rate of methylation of **36** relative to that for pyridine has been reported by Epsztajn (ref 21a,b) to be 1.26 (DMF, 20 °C) significantly lower than observed herein. We have carefully repeated our methylation experiment (acetonitrile, 25 °C) and have satisfactorily replicated our value for **36**. This inconsistency is unusual, given our previous observation (ref 1a and 13) that relative alkylation rates for pyridines under various conditions are highly correlated.

pounds generalized by **1**, this would mean that the $N–C_2–C_{2_\alpha}$ bond angle would be dependent on the number and type of other substituents and their position on the pyridine ring nucleus.

In order to examine geometry and specific bonding effects and to minimize electronic factors, we chose to examine first a series of 2,3- and 2,5-dialkylpyridines. The rates of alkylation of 3- and 4-alkylpyridines are essentially independent of the nature of the alkyl substituent.[18] Thus, a comparison of 2,3-dialkylpyridines with the related 2,5-dialkylpyridines should focus primarily on the relative steric consequences of these two different substitution patterns. Kinetic data[1b,18-30] for the methylation of the substrates discussed in this paper are listed in Table I. We have defined the parameter S to quantify kinetic nonadditivity observed for these reactions (eq 2, where $k_{calcd} = \prod_i (k_{rel})_i$ and $(k_{rel})_i$ are the

$$S \equiv k_{rel}/k_{calcd} \tag{2}$$

relative rate constants for monosubstituted 2-, 3-, and 4-alkylpyridines).

The deviation of S from unity is a measure of kinetic nonadditivity, and these values are tabulated in Table II. The definition

(19) For reviews of the Menschutkin reaction, see: (a) Zoltewicz, J. A.; Deady, L. W. *Adv. Heterocycl. Chem.* **1978**, *22*, 71–212. (b) Tomasik, P.; Johnson, C. D. *Ibid.* **1976**, *20*, 1–64. See also ref 16–18 and 20–29.

(20) (a) Balaban, A. T.; Bota, A.; Oniciu, D. C.; Klatte, G.; Roussel, C.; Metzger, J. *J. Chem. Res., Synop.* **1982**, 44–45. (b) Balaban, A. T.; Bota, A.; Oniciu, D. C.; Klatte, G.; Roussel, C.; Metzger, J. *J. Chem. Res., Miniprint* **1982**, 559–583.

(21) (a) Epsztajn, J.; Bieniek, A.; Brzezinski, J. Z. *Pol. J. Chem.* **1980**, *54*, 341–347. (b) Epsztajn, J.; Marcinkowski, R. M. K. *Ibid.* **1979**, *53*, 601–609. (c) J. Epsztajn, University of Lodz, personal communication, Nov 10, 1982. We thank Professor Epsztajn for sharing with us unpublished information.

(22) Deady, L. W.; Finlayson, W. L.; Korytsky, O. L. *Aust. J. Chem.* **1979**, *32*, 1735–1742.

(23) le Noble, W. J.; Ogo, Y. *Tetrahedron* **1970**, *26*, 4119–4124.

(24) Deady, L. W.; Zoltewicz, J. A. *J. Org. Chem.* **1972**, *37*, 603–607.

(25) Seydel, J. K.; Schaper, K.-J.; Wempe, E.; Cordes, H. P. *J. Med. Chem.* **1976**, *19*, 483–492.

(26) Schaper, K.-J. *Arch. Pharm. (Weinheim, Ger.)* **1978**, *311*, 641–649, 650–663.

(27) Berg, U.; Gallo, R.; Metzger, J.; Chanon, M. *J. Am. Chem. Soc.* **1976**, *98*, 1260–1263.

(28) Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591–3599.

(29) Johnson, C. D.; Roberts, I.; Taylor, P. G. *J. Chem. Soc., Perkin Trans. 2*, **1981**, 409–413.

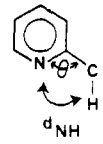
(30) Rate constants of the methylation of pyridines 4–**38** are taken from our previous publication (ref 13) and from references cited in our tables.

Table II. Steric Accessibility Factor and Geometric Parameters[a] of 2-Substituted Pyridines

compd	S[b]	S^{oc}	d_{NH},[a,d] A	θ,[a,e] deg	pK_a
2-picoline (**5**)	1	−0.734	2.596	117.01	5.97[f]
2,3-lutidine (**8**)	0.59	−0.917	2.537	114.23	6.56[f]
2,4-lutidine (**9**)	1.0	−0.636	2.595	117.07	6.72[f]
2,5-lutidine (**10**)	1.1	−0.593	2.601	117.36	6.42[f]
2-methyl-3-ethylpyridine (**23**)	0.51	−0.878	2.523	113.59	6.59[g]
2-methyl-5-ethylpyridine (**24**)	1.2	−0.475	2.603	117.45	6.45[g]
2-methyl-3-isopropylpyridine (**25**)	0.49	−0.864	2.515	113.15	6.63[g]
2-methyl-5-isopropylpyridine (**26**)	1.2	−0.452	2.604	117.50	6.50[g]
2-methyl-3-*tert*-butylpyridine (**27**)	0.27	−1.11	2.452	110.30	6.81[g]
2-methyl-5-*tert*-butylpyridine (**28**)	1.1	−0.449	2.605	117.64	6.60[g]
2,3-cyclopentenopyridine (**36**)	2.6	−0.0815	2.924	127.12	5.95[h]
2,3-cyclohexenopyridine (**37**)	1.5	−0.537	2.688	117.44	6.65[h]
2,3-cycloheptenopyridine (**38**)	0.41	−1.05	2.473	114.12	6.48[i]

[a] Geometries obtained via complete MINDO/3 energy minimization calculations. [b] $S = k_{rel}/k_{calcd}$. k_{calcd} was derived using LFER. See eq 2. The deviation of S from unity is a measure of kinetic nonadditivity. [c] Derived using eq 8. [d] Distance from pyridine nitrogen to closest hydrogen on $C_2\alpha$. [e] N-C_2-$C_2\alpha$ angle. [f] Reference 17. [g] Reference 18b. [h] Thummel, R. P.; Kohli, D. K. *J. Org. Chem.* **1977**, *42*, 2742–2747. [i] References 21a and 21b.

of S leads to a value of $S = 1$ for 2-picoline, consistent with DeTar's recent criterion for a sterically unstrained standard.[31] A value of $S < 1$ implies that the effect of the two or more substituents on the substrate molecule results in a slower, nonadditive reaction rate than would have been predicted based on the effects of the individual substituents themselves; a value of $S > 1$ implies the converse. As structural measures of the accessibility of the nitrogen atom to attack, we have focused attention on two structural features for **1**, namely d_{NH}, the distance between the



nitrogen atom and the closest C_{2_α}-hydrogen, and θ, the $NC_2C_{2_\alpha}$ bond angle.

As can be seen from inspection of Tables I and II, there is a considerable degree of kinetic nonadditivity in the series of 2,3-dialkylpyridines. The range in rate constants is somewhat greater than a factor of six, the fastest being 2,3-cyclopentenopyridine (**36**) and the slowest being 2,3-cycloheptenopyridine (**38**) and 2-methyl-3-*tert*-butylpyridine (**27**). The significance of this factor of six in relative rates can be appreciated by comparing it with (a) a factor of two for pyridine relative to 2-picoline and (b) a factor of less than 6 for 2-picoline relative to 2-isopropylpyridine. In these comparisons, we are changing the 2-substituent from a hydrogen to a methyl in the former and from a methyl to an isopropyl in the latter. Yet, the net effect on reactivity is less than that observed in the series of 2,3-dialkylpyridines where the 2-alkyl group remains essentially the same.

To relate kinetic nonadditivity (S) to structural features, we have performed complete geometry optimizations using the GEOMO/RV program[32a] which utilizes the MINDO/3 semiempirical all-valence electron self-consistent field procedure along with the Rinaldi optimization routine.[32b] All geometric parameters were optimized and no symmetry restrictions were imposed. The final geometries were insensitive to the starting structures except for cases involving rotation of alkyl groups; these cases will be discussed subsequently. We have previously justified the use of MINDO/3 for these types of pyridines and for similarly substituted benzene analogues, in part on the basis of the favorable comparison of the calculated geometries with the experimentally available structural data, including X-ray and microwave analyses and electron diffraction studies.[1b,13,14] We chose a semiempirical quantum mechanical approach over molecular mechanics because,

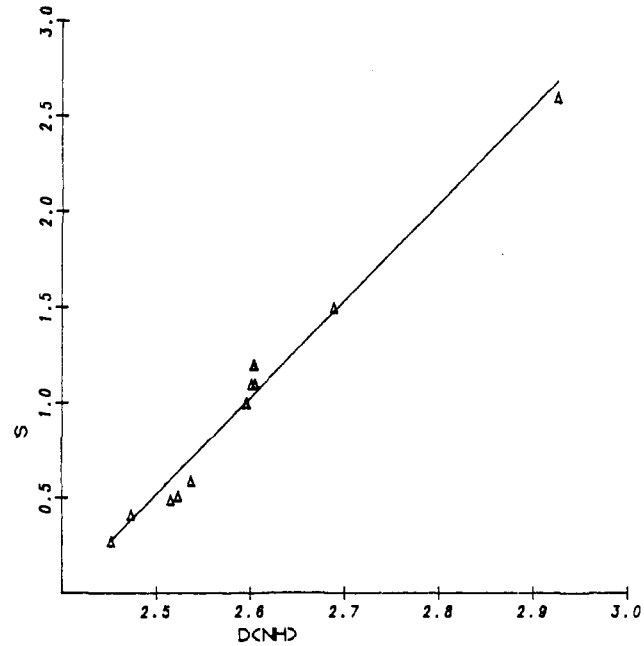


Figure 1. Relationship between the nonadditivity parameter S and d_{NH} for 2-substituted pyridines listed in Table II (cf. eq 3).

unfortunately, a suitable force field for nitrogen containing heterocycles is not available.[34] Ab initio procedures were not used because complete geometry optimizations for a series of these rather large molecules would have been impractical.

For the 2,*x*-substituted pyridines **1**, we determined d_{NH} and θ; these values are listed in Table II. A wide range for both d_{NH} and θ is observed in this system, spanning 0.47 Å and 16.8°, respectively. A pairwise comparison of a 2,3-disubstituted pyridine with the analogous 2,5-disubstituted pyridine illustrates the degree of kinetic and structural parameter nonadditivity. For example, 2-methyl-3-*tert*-butylpyridine methylates ca. four times slower than the comparably substituted 2-methyl-5-*tert*-butylpyridine. This rate difference is due to nonadditive structural effects, namely a buttressing phenomenon, and is reflected by a 7.3° decrease in θ and a 0.15 Å decrease in d_{NH} in 2-methyl-3-*tert*-butylpyridine relative to 2-methyl-5-*tert*-butylpyridine. At the other extreme, tying the methyl groups together with a methylene unit in 2,3-cyclopentenopyridine (**36**) *increases* both θ (by 12.89°) and d_{NH} (by 0.387 Å) relative to 2,3-lutidine (**8**); **36** methylates almost five times faster than **8**.

Evidence that the structural parameters d_{NH} and θ are related to the kinetic nonadditivity is seen in the excellent correlations

(31) DeTar, D. F.; Tenpas, D. J. *J. Org. Chem.* **1976**, *41*, 2009–2013.
(32) (a) Schmidling, D. *QCPE* **1978**, *11*, 350. (b) Rinaldi, D. *Comput. Chem.* **1976**, *1*, 109–114.
(33) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285–1293, 1294–1301, 1302–1305.
(34) (a) Ōsawa, E.; Musso, H. *Top. Stereochem.* **1982**, *13*, 117–193. (b) Profeta, S., Jr. Ph.D. Dissertation, University of Georgia, Athens, GA, 1978.

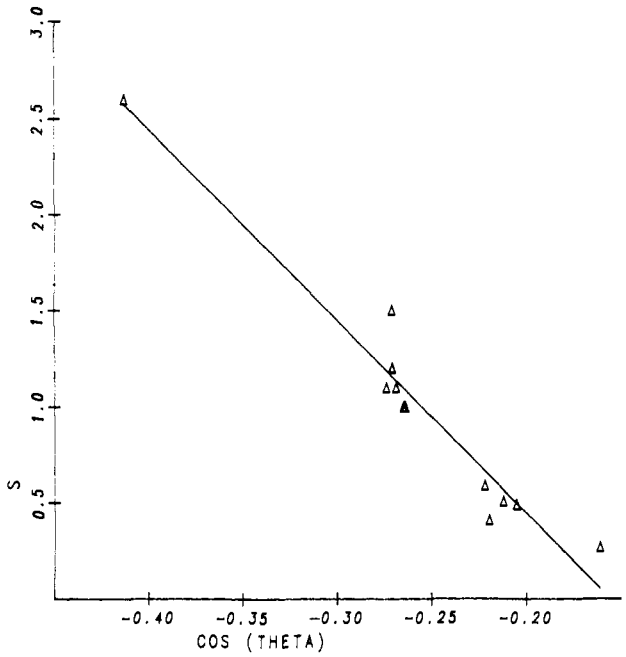


Figure 2. Relationship between S and θ for 2-substituted pyridines (cf. eq 4).

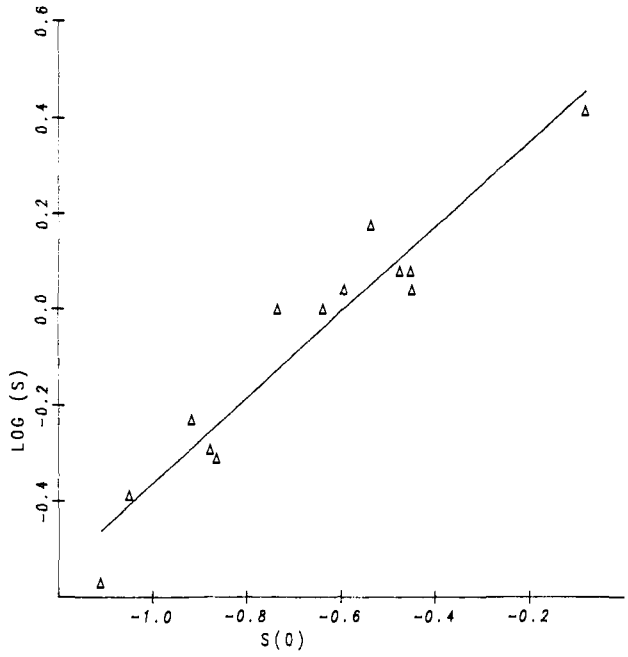


Figure 3. Relationship between the Brønsted equation derived $S°$ and log S for 2-substituted pyridines (cf. eq 9).

found between these two properties and S, as indicated by eq 3 and 4 and Figures 1 and 2. The parameters d_{NH} and θ are highly

$$S = 5.16d_{NH} - 12.4 \quad (3)$$

[$r = 0.983$, $n = 13$, $p \approx 0.00001$, std dev of residuals = 0.118]

$$S = -10.0 \cos \theta - 1.56 \quad (4)$$

[$r = 0.971$, $n = 13$, $p \approx 0.00001$, std dev of residuals = 0.152]

correlated with one another (eq 5) and are not independent.

$$\cos \theta = -0.482d_{NH} + 0.995 \quad (5)$$

[$r = 0.964$, $n = 13$, $p \approx 0.00001$, std dev of residuals = 0.0165]

We now examine the postulate that the nonadditivity factor S is directly correlated to steric effects. Gallo and co-workers recently utilized the Brønsted relationship (eq 6) for the methylation of 3- and 4-alkyl substituted pyridines and solved for the constants α and c; they then derived steric substituent parameters $S°$ for pyridines with one α-substituent using eq 7, in

$$\log (k_{obsd}/k_H) = \alpha\ pK_a + c \quad (6)$$

$$S° = \log (k_{obsd}/k_H) - (\alpha\ pK_a + c) \quad (7)$$

which $S°$ quantifies the portion of the reactivity not accounted for on the basis of electronic effects.[4j]

We emphasize at this point the distinction between S (eq 2) which indicates the degree of nonadditivity observed in the alkylation rate constants of polysubstituted pyridines and $S°$ (eq 7) which is a steric effect parameter derived using the well-known Brønsted relationship. The similarity in nomenclature (S and $S°$) is coincidental and is maintained here to be consistent with the original literature derivations.[1b,4j]

Using the reactivity data from Table I for those compounds unsubstituted at C_2 (and C_6), we derived eq 8 following the Gallo procedure[4j] and applied this equation toward the derivation of $S°$ for the 2-substituted pyridines listed in Table II. In that $S°$ failed to correlate ($r = 0.15$) with the pK_a of the corresponding ortho-substituted pyridines, Gallo et al. concluded that $S°$ was a measure of steric effects and not of electronic effects.[4j] We find that $S°$ is significantly correlated with log S, the latter by definition being the kinetic nonadditivity factor for the pyridines having a single α-substituent (eq 9 and Figure 3). We conclude that kinetic nonadditivity is a direct measure of relative steric effects, and in particular, structural parameter nonadditivity, for the methylation of the pyridines listed in Table II.

$$S° = \log (k_{rel}) - 0.311\ pK_a + 1.49 \quad (8)$$

$$k_{rel} \equiv k_{obsd}/k_H$$

$$\log (S) = 0.859S° + 0.515 \quad (9)$$

[$r = 0.950$, $n = 14$, $p = 0.00001$, std dev of residual = 0.084]

We note that since $S°$ was derived using the Brønsted relationship (eq 6 and 7), it bears a logarithmic relationship with S which is simply the ratio of the rate constants (eq 2). Further, since S is highly correlated with both d_{NH} and θ and since log S is highly correlated with $S°$, then $S°$ is correlated with d_{NH} and θ. Clearly, log S and $S°$ are measures of the same effect. The intercept of eq 9 should be equal to the slope multiplied by $S°_{(2\text{-picoline})}$. The derivation of the slope from unity essentially measures the lack of perfect additivity of the pK_a values.

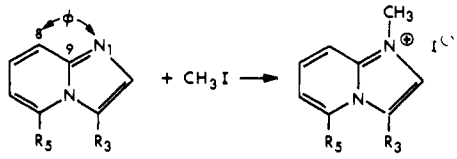
Equation 8 represents a classical application of LFER. The log (k_{rel}) is divided into electronic effects, represented by ($\alpha\ pK_a + c$), and steric effects, represented by $S°$. This conclusion is validated by our finding that $S°$ correlates with a function of d_{NH}, via eq 3 and 9. The validity of eq 3 and 4 further implies that the electronic substituent effects on log (k_{rel}) are strictly additive for multiply substituted molecules in this series, as is evidenced by good substituent effect additivity on the pK_a values of these compounds.[18e] All of the preceeding relationships are therefore completely consistent with one another.

Thus, a very important consequence of the design of this study was the incorporation of substituent patterns in which steric effects would be predominant and *variable* nonadditive electronic effects minimal. This can be noted by comparing the constant 2,3-substitution pattern for **8**, **23**, **25**, **27**, and **36–38**. See Table II. It is for this reason that we were able to focus on geometric and steric factors in eq 3 and 4.

II. Buttressing Effects in Imidazo[1,2-*a*]pyridines. In order to extend the correlation between structural parameters and kinetic nonadditivities, we decided to examine the methylation of a series of 3,5-dialkylimidazo[1,2-*a*]pyridines for which kinetic data have recently become available.[35] In Table III, the experimental

(35) Maury, G.; Pigiere, C. *Tetrahedron*, **1981**, *37*, 83–90, 91–95.

Table III. Rate Constants[a] and Kinetic Nonadditivities for the Methylation of Imidazo[1,2-a]pyridines and Relevant MINDO/3-Derived Structural Data

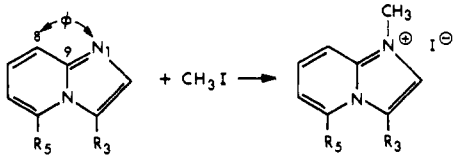


39–43

imidazo[1,2-a]pyridine	k_{rel}[b]	k_{calcd}[c]	S[d]	angle $N_1C_9C_8$ (ϕ), deg
3,5-dimethyl- (39)	2.22	2.36	0.943	130.4
3-ethyl-5-methyl- (40)	2.25	2.49	0.901	130.2
3-isopropyl-5-mehyl- (41)	2.09	2.55	0.820	129.8
3-isopropyl-5-ethyl- (42)	2.02	2.72	0.741	129.1
3,5-diisopropyl- (43)	2.08	2.98	0.694	128.2

[a] From ref 35. [b] Relative to imidazo[1,2-a]pyridine, where $k_2 = 8.43 \times 10^{-4}$ L mol^{-1} s^{-1} at 35.9 °C. [c] Calculated by using the relative rate constants for the monosubstituted alkylimidazo[1,2-a]pyridines and applying LFER. The relative rate constants k_{rel} are as follows: 3-methyl-, 1.83; 5-methyl-, 1.29; 3-ethyl-, 1.93; 3-isopropyl-, 1.98; 5-ethyl-, 1.41; 5-isopropyl-, 1.51. From ref 35. [d] Derived according to eq 2.

methylation rate constants $k_{2\,rel}$, the LFER-derived methylation rate constants k_{calcd}, and the steric accessibility factors S are listed for **39–43**. Also included in Table III are the values of ϕ, the



39, $R_3 = R_5 = Me$
40, $R_3 = Et$; $R_5 = Me$
41, $R_3 = i\text{-Pr}$; $R_5 = Me$
42, $R_3 = i\text{-Pr}$; $R_5 = Et$
43, $R_3 = i\text{-Pr}$; $R_5 = i\text{-Pr}$

angle $N_1C_9C_8$, these being derived by complete geometry optimization using the MINDO/3 algorithm.

As can be seen from Table III, a definite trend in kinetic nonadditivity is observed with S decreasing as the C_3- and/or C_5-substituent increases in size. Noteworthy, the range in reactivity is quite small, varying by a factor of only 12.5%; the range in S is also much less than found for the pyridines discussed above. However, a long-range, indirect buttressing effect[36] is noted: for the 3,5-dimethyl derivative **39**, ϕ is 2.2° greater than that for the more hindered 3,5-diisopropyl analogue **43**. It is valuable to note that ϕ monotonically decreases as the C_3- and/or C_5-substituents increase in size, consistent with the reactivity results. Also presented in Table III are the kinetic and geometry parameters for additional imidazo[1,2-a]pyridines which exhibit additive kinetics and additive structural features.

The correlation between S and angle $N_1C_9C_8$ (ϕ) is excellent, as indicated by the statistical data for eq 10 (c.f. Figure 4). This

$$S = -8.01 \cos \phi - 2.77 \qquad (10)$$

[$r = 0.971$, $n = 5$, $p = 0.0050$, std dev of residual = 0.029]

correlation further substantiates the use of structural features to quantify steric effects in general and nonadditive kinetics in particular, especially for substituent interactions which produce subtle reactivity modifications. In the case of the imidazo[1,2-a]pyridines, the buttressing effects of the 3- and 5-alkyl groups

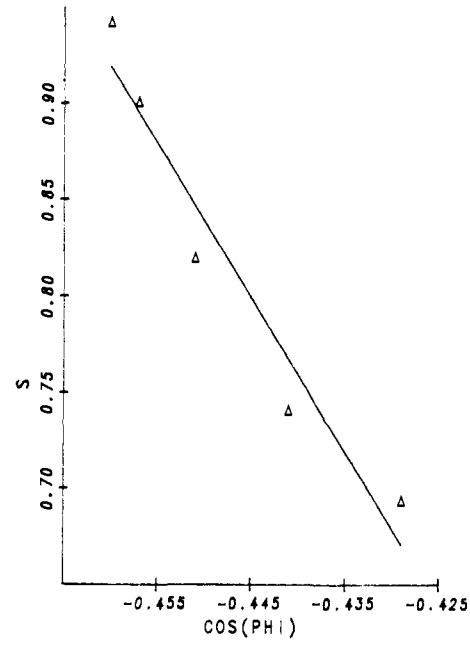


Figure 4. Relationship between the nonadditivity parameter S and ϕ for 3,5-dialkylimidazo[1,2-a]pyridines listed in Table III (cf. eq 10).

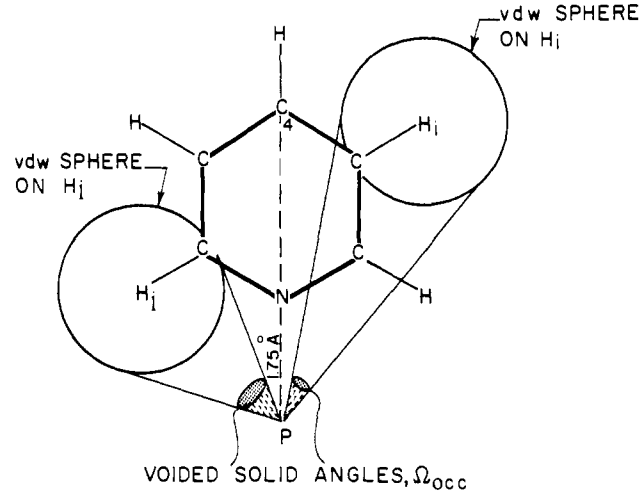


Figure 5. Solid angle about point P which is voided by van der Waals spheres on atoms H_i and H_j used in the derivation of Ω_T.

are rather remote from the reaction site (N_1) but the structural consequences are sufficiently manifested at N_1 for the observation of kinetic nonadditivity.

We note that the experimental reaction rate constant is, in general, not dependent solely on the angle $N_1C_9C_8$ but also on steric and electronic features of the substituents themselves. In addition, dialkylimidazo[1,2-a]pyridines with substituents in nonadjacent positions exhibit additivity in both structural parameter additivity (e.g., angle $N_1C_9C_8$) and kinetic parameters.[35]

III. Pyridine Nitrogen Accessibility Factors. The correlation models discussed in sections I and II demonstrate the quantitative structural influence on chemical reactivity. Clearly, a relationship exists between the heterocycle's nitrogen accessibility[10] to an external reagent and its alkylation rate. We now present a general model for the quantification of pyridine nitrogen accessibility in terms of the equilibrium geometries of the isolated substrate molecules.[37] The model is intended to treat all types of substitution patterns. For this treatment, we first performed complete geometry optimizations using the GEOMO (MINDO/3) algorithm[32,33] for all the pyridines listed in Table I.

(36) For a recent example of a long range buttressing effect on a conformational (bond rotation) process, see: Imashiro, F.; Takegoshi, K.; Terao, T.; Saika, A. *J. Am. Chem. Soc.* **1982**, *104*, 2247–2251.

(37) For an application of the Wipke–Gund model[10] of steric accessibility to nitrogen reactivity, see: Gilmore, C. J.; Bryan, R. F.; Kupchan, S. M. *J. Am. Chem. Soc.* **1976**, *98*, 1947–1952.

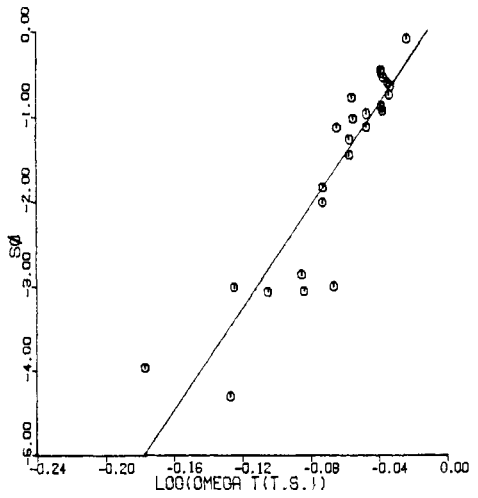


Figure 6. Relationship between the Brønsted equation derived $S°$ and the nitrogen accessibility parameter (cf. eq 11).

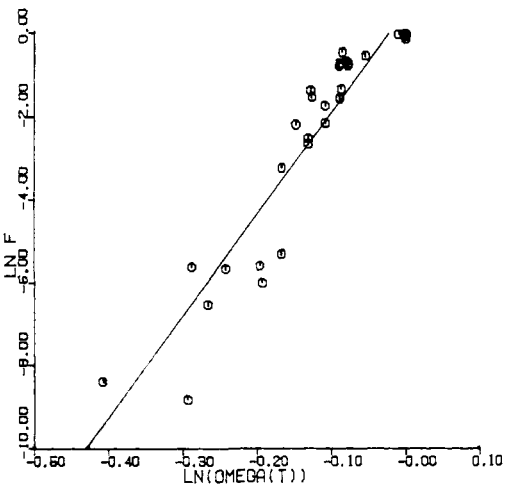


Figure 7. Relationship between the partial rate factor f and the nitrogen accessibility parameter (cf. eq 12).

We assume that the "effective" point of attack (point P) of an alkylating reagent lies along the C_4–N axis, 1.75 Å away from the nitrogen of the completely optimized pyridine free base.[38] See Figure 5. This point was chosen to *model* the position of the methyl carbon of CH_3I in the transition state. The results are rather insensitive to small changes in this distance. We then assumed that there were no restrictions on the direction of approach of the iodomethane to point P, and simply calculated Ω_T as the *free* solid angle about point P. Thus, $\Omega_T = 4\Pi - \Omega_{occ}$, where Ω_{occ} is the total solid angle about point P that is blocked by all atoms in the substrate molecule. To calculate Ω_T, we placed a sphere of appropriate van der Waals radius at the location of each atom. Each sphere defines a cone with point P at the apex and includes a solid angle that can be calculated from the coordinates. However, many of these cones overlap one another. To avoid overcounting solid angles from overlapping cones, we used a Monte Carlo method and obtained Ω_T in terms of the fraction of 20 000 randomly distributed points which fell outside all cones. This purely geometric quantity gives the total solid angle around the point of attack which is not blocked by atoms in the substrate molecule. The calculated steric factors Ω_T relative to pyridine are listed in Table I.

Since this model is based on steric hindrance and was designed to quantify nitrogen accessibility, it is evident that the model will predict that 3- and 4-alkylpyridines will react at essentially the same rate as does pyridine itself. Of course, this is incorrect; 3- and 4-alkylpyridines methylate approximately *twice* as rapidly as does pyridine.[1b,16] Before we can realistically correlate Ω_T with reactivity, we must first factor out electronic contributions of alkyl substituents.

We have factored out electronic contributions to the reaction rate constants in two procedurally different but related fashions.

(1) We can utilize the Gallo formulation[4j] discussed in section I and generalized by eq 6 and 7. With a knowledge of the pK_a's for the pyridines in Table I having at least one α-substituent, we utilized eq 8 and derived $S°$ for these compounds. See Table I for a listing of these parameters. The pK_a's of all the compounds studied cover a range of ca. 1.7 units. With $\alpha = 0.311$, this corresponds to $\Delta(\log k_{rel})_{electronic} = 0.53$. If this value 0.53 is compared with the range of $S°$, i.e., ca. 4 log units, it is clear that the methylation rates of the alkylpyridines used in this study are overwhelmingly determined by steric factors. Note that the total range of log k_{rel} is essentially the same as the range of $S°$. For the twenty-seven compounds bearing at least one α-substituent, we find a significant correlation[38] between $S°$ and Ω_T (eq 11 and Figure 6). This correlation is impressive given that it is derived

$$S° = 30.3(\log \Omega_T) + 0.367 \qquad (11)$$

[$r = 0.911$, $n = 27$, $p = 0.00001$, std dev of residual = 0.496]

for compounds which alkylate over a four order of magnitude rate range.

It is worthy of note that the values for $S°$ in particular and for E_S and other LFER-derived parameters are derived for molecules containing a single substituent.[3,4] The treatment embodied in eq 6 and 7 is clearly amenable to polysubstituted structures in which $S°$ refers to total (steric) ortho effect.

(2) It is also possible to calculate less precise steric factors, f, without any knowledge of the pK_a's. Electronic acceleration factors for 3- and 4-alkylpyridines are set equal to k_{rel} for the monosubstituted compound, and an average factor of 2.2 is used for the electronic acceleration due to any alkyl group at C_2 (and C_6).[39]

Figure 7 illustrates the relationship of Ω_T with the partial rate factor, f. An excellent correlation[38] is obtained, as indicated by the statistical data associated with eq 12.

$$\log f = 0.113 + 28.6 \log \Omega_T \qquad (12)$$

[$r = 0.934$, $n = 35$, $p = 0.00001$, std dev of residual = 0.455]

The correlations illustrated by Figures 6 and 7 and eq 11 and 12 validate the use of Ω_T for estimating the accessibility of the pyridine nitrogen to an external reagent. This is a satisfying conclusion in that the model simply provides the relative fraction of unencumbered paths of approach to point P in Figure 5 from all directions.

IV. Relationships between Steric Parameters for Intermolecular and Intramolecular Processes. The very limited amount of experimental data available supports the conclusion that substituents on an aromatic ring can significantly modify ring geometry.[41] For example, the ipso angle of toluene is 118.6°,[42] and there is evidence that as the alkyl substituent on an aromatic ring becomes increasingly larger, the ipso angle monotonically decreases from 120° for benzene.[43,44] In this and previous studies,[14] we have performed

(38) We subsequently found and discuss in detail in section IV of this paper that Ω_T for pyridines having a C_2 (and/or C_6) isopropyl group was better calculated when $\tau(HC_{2\alpha}C_2N) = 0°$ rather than 180°, the latter being the ground-state minima. For C_2-isopropyl substituents, we have calculated Ω_T for both $\tau(HC_{2\alpha}C_2N) = 180°$ and 0° (see Table I) but use the values for $\tau = 0°$ for the correlations expressed in eq 11, 12, and 16. The only instance in which we report a correlation using $\tau = 180°$ for a C_2-isopropyl group is in eq 15.

(39) The value of 2.2 was derived by consideration of the Gallo results[4j,12] and the relationships derived by McManus[40] based on gas-phase proton affinity correlations with reactivity.

(40) McManus, S. P. *J. Org. Chem.* **1981**, *46*, 635–638.

(41) See ref 1a for discussion of this point and additional references.

(42) Pang, F.; Boggs, J. E.; Pulay, P.; Fogarasi, G. *J. Mol. Struct.* **1980**, *66*, 281–287.

(43) (a) Allen, F. H. *Acta Crystallogr., Sect. B* **1981**, *B37*, 900–906. (b) Domenicano, A.; Vaciago, A. *Ibid.* **1979**, *B35*, 1382–1388. (c) Domenicano, A.; Murray-Rust, P. *Tetrahedron Lett.* **1979**, 2283–2286. (d) Domenicano, A.; Schultz, G.; Kolonits, M.; Hargittai, I. *J. Mol. Struct.* **1979**, *53*, 197–209. (e) Palmer, M. H.; Moyes, W.; Spiers, M.; Ridyard, J. N. A. *Ibid.* **1978**, *49*, 105–123. (f) Rudolph, H. D.; Walzer, K.; Krutzik, I. *J. Mol. Spectrosc.* **1973**, *47*, 34–39. (g) van Bruijnsvoort, A.; Eilermann, L.; van der Meer, H.; Stam, C. H. *Tetrahedron Lett.* **1968**, 2527–2529.

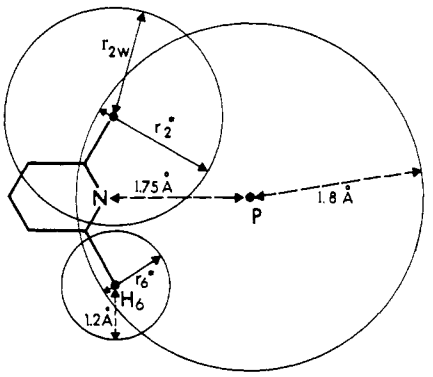


Figure 8. Model used for estimation of radial overlaps $\sum r^*$ of van der Waals spheres. This is patterned after the work of Sternhell (ref 15).

complete geometry optimizations for pyridines, imidazo[1,2-*a*]-pyridines, and related *N*-methylpyridinium cations and have likewise noted significant internal pyridine ring bond angle effects due to substituents bound to the ring. That both external and internal structural modifications result with varying substitution patterns is an important step in the understanding and evaluation of substituent effects in organic reactions.

Most studies designed to quantify the spatial requirements of substituents have been based on the analysis of conformational processes. Forster and Vögtle[45] and Tidwell[46] recently summarized a wide range of studies in which only a handful described the determination of the relative spatial requirements by analysis of chemical reactions while more than one hundred were based on the study of intramolecular effects. Intramolecular and intermolecular steric effects should be susceptible to identical treatments, and we now examine that possibility.[47]

In a recent study of internal rotation in substituted biphenyls, Sternhell et al. introduced the concept of assessing the steric energy penalty in terms of the overlap that would occur between pairs of van der Waals (vdw) spheres if the effective atoms were to move past one another with no geometric distortions allowed.[15] This concept should be applicable to steric effects in bimolecular transition states as well as to intramolecular processes. We therefore calculated these overlaps by considering the model transition states as shown in Figure 8.

At the point P, which is 1.75 Å away from the nitrogen, we placed an effective vdw sphere of 1.8 Å radius to represent the attacking methyl group. The radial overlaps (r^*) of this sphere with those representing atoms in the 2- and 6-positions of pyridine were then calculated. For an unsubstituted 2- or 6-position of pyridine we employed a hydrogen atom with a vdw radius of 1.2 Å. When the position was substituted with a methyl, isopropyl, or *tert*-butyl group, we used Sternhell's effective radii[15] of 1.8, 2.2, or 3.6 Å, respectively, and located the center of the vdw sphere at the position calculated for the α carbon atom. Ethyl groups in the 2- or 6-positions were not treated herein because Sternhell et al. did not determine an effective radius for the ethyl substituent.

The sum of the radial overlap of the effective vdw spheres was calculated by using eq 13, where r_{2w} and r_{6w} are the effective radii

$$\sum r^* = r_2^* + r_6^*$$

$$\sum r^* = (r_{2w} + 1.8 - r_{2\alpha,p}) + (r_{6w} + 1.8 - r_{6\alpha,p}) \quad (13)$$

for the atoms in the 2- and 6-positions, respectively, of the pyridine substrate; $r_{2\alpha,p}$ and $r_{6\alpha,p}$ are the distances from point P to the effective centers of the offending atoms at the 2- and 6-positions,

(44) (a) Stam, C. H. *Acta Crystallogr., Sect. B* **1972**, *B28*, 2715–2720. (b) Destro, R.; Pilati, T.; Simonetta, M. *Ibid.* **1980**, *B36*, 2495–2497. (c) Cutbush, S. D.; Neidle, S.; Foster, A. B.; Leclercq, F. *Ibid.* **1982**, *B38*, 1024–1027.

(45) Forster, H.; Vogtle, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 429–441.

(46) Tidwell, T. T. *Tetrahedron* **1978**, *34*, 1855–1868.

(47) Charton's linear free energy correlations of chiral biphenyl racemization rates is a previous study of this type.[48]

(48) Charton, M. *J. Org. Chem.* **1977**, *42*, 2528–2529.

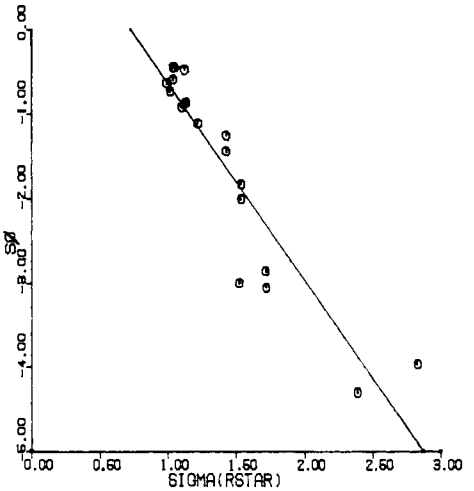


Figure 9. Relationship between $S°$ and the steric overlap parameter $\sum r^*$ (cf. eq 14).

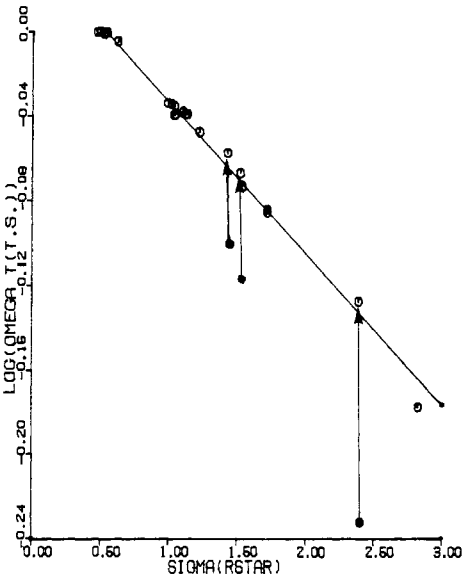


Figure 10. Relationship between the nitrogen accessibility parameter Ω_T and the steric overlap parameter $\sum r^*$. The solid points represent log Ω_T, $\sum r^*$ pairs for the 2-isopropylpyridines **19**, **32**, **33**, and **35** using their respective ground-state geometry [torsional angle $\tau(H_2C_2\alpha C_2N) = 0°$] (cf. eq 15). The correlation line in the figure was calculated using log (Ω_T), $\sum r^*$ pairs for **19**, **32**, **33**, and **35** where $\tau = 180°$ (cf. eq 16). See text for additional discussion.

and 1.8 Å is the vdw radius of the incoming methyl group. This procedure was performed for the 27 pyridines listed in Table I using the GEOMO- (MINDO/3)-derived ground-state geometries.

Figure 9 and eq 14 show the correlation between $\sum r^*$ and the empirical steric factor, $S°$. The relation between our geometric

$$S° = -2.33\sum r^* + 1.67 \quad (14)$$

[$r = 0.927$, $n = 19$, $p = 0.00001$, std dev of residual = 0.477]

accessibility factor, Ω_T, and $\sum r^*$ is shown by eq 15 (see, also, Figure 10).[38]

$$\log \Omega_T = -0.091\sum r^* + 0.052 \quad (15)$$

[$r = 0.942$, $n = 27$, $p = 0.00001$, std dev of residual = 0.019]

These two correlations (eq 14 and 15) indicate the validity of $\sum r^*$ for estimating the reactivity of pyridine methylations. The Sternhell model[15] ($\sum r^*$) was developed to predict the energy barriers for intramolecular processes, namely the barriers for rotation of biphenyls and related compounds. We have thus added support to the derivation of *unified* models for steric hindrance for intra- and intermolecular processes.[47]

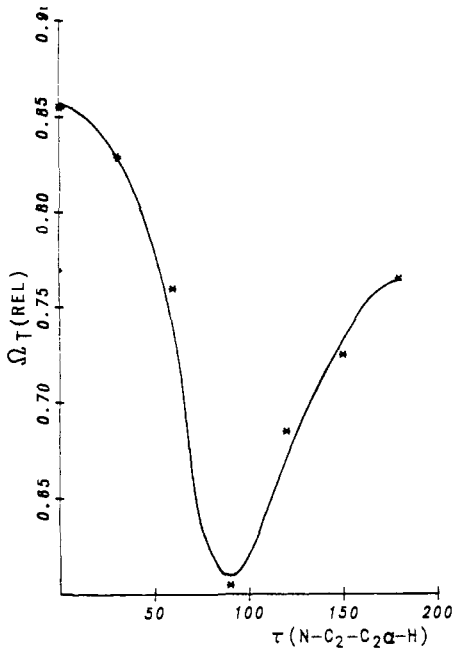


Figure 11. Dependence of the nitrogen accessibility parameter Ω_T on the $C_2\alpha C_2$ torsional angle for 2-isopropyl-3-methylpyridine.

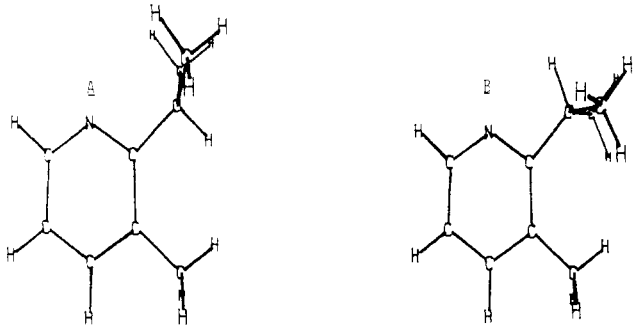


Figure 12. MINDO/3-derived structures for 2-isopropylpyridine having torsional angle $\tau(HC_2\alpha C_2N)$ = 180° (A) and 0° (B).

Four points deviate significantly from the "best" least-squares straight line in Figure 10; these points represent the four pyridines having at least one isopropyl substituent at a C_2 position, namely 2-isopropyl-, 2-isopropyl-3-methyl-, 2-isopropyl-5-methyl-, and 2,6-diisopropylpyridine. These molecules have some unique features regarding steric hindrance models and deserve additional comment.[38]

We have not discussed the effect of rotation of alkyl substituents on the geometric accessibility factor, Ω_T. Figure 11 illustrates how the geometric accessibility factor, Ω_T, varies as a function of dihedral angle, $\tau(NC_2C_{2_\alpha}H)$, i.e., as the isopropyl group rotates about the $C_2C_{2_\alpha}$ bond for 2-isopropyl-3-methylpyridine. The equilibrium ground-state geometry for this molecule was found to have τ = 180°, corresponding to the isopropyl hydrogen lying in the pyridine plane facing the 3-methyl group (Figure 12A). Equation 15 relates Ω_T derived for the minimum-energy ground-state conformations, i.e., for C_2-isopropyl groups, $\tau(NC_2C_{2_\alpha}H)$ = 180°. However, MINDO/3 calculations presented in earlier papers[1a,13] suggested that the most stable methylation transition-state geometry for pyridines having a C_2-isopropyl substituent has τ = 0°, i.e., with the isopropyl hydrogen facing the nitrogen (Figure 12B). Though we are attempting to derive a ground-state model for chemical reactivity, we must keep in mind that transition-state phenomena may not always be accurately mirrored by ground-state features. In Table I, we list Ω_T for **19**, **32**, **33**, and **35** for the two dihedral angles under discussion, $\tau(NC_2C_{2_\alpha}H)$ = 0° and 180°. If we use values of Ω_T for these four 2-isopropylpyridines derived for their minimum-energy transition-state geometries, i.e., $\tau(NC_2C_{2_\alpha}H)$ = 0°, we then obtain a superior correlation between our steric congestion model and that of Sternhell (eq 16 and Figure 10).

$$\log \Omega_T = -0.072\sum r^* + 0.038 \qquad (16)$$

[r = 0.995, n = 27, p = 0.00001, std dev of residual = 0.004]

For the C_2- and C_6-isopropylpyridines, it is interesting to note that the value of Ω_T is smaller when $\tau(NC_2C_{2_\alpha}H)$ = 180° than for τ = 0°, consistent with the intuitive conclusion one reaches by nonmathematical consideration of these conformations. The value calculated for $\sum r^*$ for isopropyl was obtained by placing the effective vdw sphere of the isopropyl group on the α-carbon; since the α-carbon position is not appreciably changed by rotation, the value of $\sum r^*$ does not depend on the value of τ.

The effective size of the isopropyl vdw sphere was obtained from the activation energy for rotation of 2-isopropylbiphenyl[15] in which the isopropyl methyl groups almost certainly point back away from the other phenyl moiety. Hence $\sum r^*$ for this compound is based on a model which has geometry very similar to the TS geometry. One might therefore argue that the proper value to use for Ω_T should be based on this geometry also. The four points which deviate from the initial correlation of the two steric factors with one another can now be reasonably explained.

Summary and Conclusions

In this work, we have confirmed and quantified the important hypothesis that ground-state geometries can correlate and predict chemical reactivity. Nonadditive reactivity has been shown to be directly related to specific geometry parameters. Quantitation of buttressing effects, both close to and remote from the reaction center, in terms of molecular geometry, has proven to be possible.

We report excellent correlations of molecular geometry parameters with chemical reactivity (methylation) for a series of 2-alkylpyridines and imidazo[1,2-*a*]pyridines. We calculated molecular geometry by complete energy minimization (GEOMO–MINDO/3 semiempirical all-valence electron calculations) and determined empirical alkylation rate constants. These two independent sets of experiments were then correlated with each other.

A geometric factor for steric congestion and nitrogen accessibility (Ω_T) was developed which is able to quantify over four orders of magnitude in reactivity for polyalkylated pyridines. This steric congestion model of a bimolecular reaction has been shown to be correlated to a model proposed by others[15] for intramolecular processes, namely conformational rotation barriers of substituted biphenyl analogues. A series of steric substituent parameters $S°$ was derived using Gallo's application[22] of the Brønsted equation and $S°$ was found to be correlated with the steric congestion model (Ω_T), thereby establishing the validity of these models and their interrelationships.

Acknowledgment. The authors thank Dr. James Kao and the Philip Morris Computer Applications Division for their ongoing contributions to our work and to K. McCourt for her technical assistance. We also thank Drs. T. S. Osdene and E. B. Sanders for their encouragement and M. Satterfield for secretarial assistance. Dedicated to Dr. Ulrich Weiss on the occasion of his 75th birthday and in recognition of his aiding the development of young scientists.