Transmission of Substituent Effects. Correlation of Methyl to Hydrogen Rate Ratios in Diverse Heterocyclic Systems with CNDO/2 Parameters[1a]

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A modification of the Dewar–Grisdale equation, parameterized with Brown's electrophilic substituent constants, σ^+, and CNDO/2 regional charge distributions, is successful in correlating reactivity ratios for the solvolysis of a wide variety of heteroarylethanol derivatives and nuclear substituted analogues. The equation $\log k_{Me}/k_H = 1.41\rho\Delta q_{ij}$, predicted by this development, is closely obeyed by the observed reactivity ratios for 34 pairs of compounds.

Recent reports from this laboratory have explored the possibilities for correlating the reactivity of a variety of heterocyclic systems with simple benzene derivatives. We have successfully applied a modification of the Dewar–Grisdale equation[2] to benzofuran,[3,4] furan,[5] thiophene,[6] and benzothiophene[7] systems. We examined substituent effects on the rates of solvolysis of heteroarylmethyl derivatives; generally excellent correlations resulted.

It is the purpose of the present report to extend these observations and, in particular, to explore a further consequence of the earlier derivations: namely, that the methyl group, as a substituent, will exert its influence almost entirely through its ability to stabilize an electron-deficient species (carbonium ion).

The modified Dewar–Grisdale equation developed by Noyce and Nichols is given in eq 1.[3,6]

$$(\sigma_{ij}^+) = \frac{F_x^+}{r_{ij}} + M_x^+\Delta q_{ij} \quad (1)$$

Here, $(\sigma_{ij}^+)_x$ is the substituent constant for any substituent X; r_{ij} is the distance (in benzene bond lengths) between the reaction center located at ring position j and the substituent at position i; Δq_{ij} is the regional charge developed at the point of substitution as determined from CNDO/2 calculations (see below). F_x^+ and M_x^+, the field and resonance capabilities of substituent X, are determined by substituting into eq 1 the σ_p^+ and σ_m^+ values from the benzene series[8] and their associated r_{ij} and Δq_{ij} values generated by CNDO/2 calculations and solving the resulting pair of simultaneous equations. In this manner *unique* values of F_x^+ and M_x^+ for each substituent are obtained. This procedure removes the necessity for considering any set of special σ values for substituents on heterocyclic rings. The possibilities for extension to other aromatic systems are obvious.

Regional charges are determined by molecular orbital calculations for the transformation $ArCH_3 \rightarrow ArCH_2^+$. The methyl and methylene groups located at position j represent a model for the starting state and the transition state along the reaction coordinate of the limiting solvolysis reaction. The regional charges are determined from the differences between the gross atomic populations at position i in $ArCH_3$ and $ArCH_2^+$. Since Ar can be any aromatic or heteroaromatic nucleus, regional charges at many positions for a large number of aromatic systems may be determined.

The effective response to the introduction of a substituent at any position may then be predicted. For the methyl group as a substituent, F^+ is determined to be -0.028 and M^+ is determined to be -1.41. Insertion of these values into eq 1 yields eq 2.

$$(\sigma_{ij}^+)_{CH_3} = \frac{-0.028}{r_{ij}} - 1.41\Delta q_{ij} \quad (2)$$

Inasmuch as the field component (F^+) for the methyl group is quite small,[9] and r_{ij} is always greater than 1.0, the resonance component (M^+) dominates and eq 2 can be approximated by eq 3.

$$(\sigma_{ij}^+)_{CH_3} = -1.41\Delta q_{ij} \quad (3)$$

Thus the modified Hammett equation, eq 4, can be written for the correlation of the methyl substituent effect in a variety of systems.

$$\log \frac{k(CH_3)}{k(H)} = \rho(\sigma_{ij}^+)_{CH_3} \quad (4)$$

or

$$\log \frac{k(CH_3)}{k(H)} \cong -1.41\rho\Delta q_{ij} \quad (5)$$

Inspection of eq 5 reveals that the solvolytic rate enhancement observed upon methyl substitution in the aromatic nucleus should be directly predictable from the regional charge developed at the point of substitution. Data with which to test this hypothesis are available from a wide range of aromatic systems (see Table I), including data from previous studies from this laboratory. The plots shown in Figures 1 and 2 show the quality of the linear correlation of methyl rate enhancement and regional charge predicted by eq 5.

We have combined data from several sources to generate the results presented in Table I. It is well known that ρ is temperature sensitive; for solvolysis reactions it decreases in magnitude with increasing temperature. Hence, the data are presented in two groups, at 25° or at 75°.

On the other hand, the value of ρ for the solvolysis of 1-phenylethanol derivatives shows very little sensitivity to the leaving group, be it *p*-nitrobenzoate ion, chloride, or tosylate. The value of ρ is also relatively insensitive to modest changes in solvent for these systems. Thus we have combined data for *p*-nitrobenzoate solvolysis for the most reactive aromatic substrates, with data for chlorides, and even for tosylates, involving the least reactive aromatic substrates.

A number of the individual cases reported in Table I merit additional comment. The solvolysis of the 5-methyl analogue of 1-(3-thienyl)ethyl *p*-nitrobenzoate (entry 20) shows a relatively large rate acceleration for introduction of a methyl group at a nonconjugating position (compare benzene, entries 3, 8, and 21). This magnitude of acceleration is predicted by the value of Δq. Such an effect is also observed with the furan system (entries 18 and 19). Most striking is the result for imidazole (entry 16). Again the magnitude of the acceleration is in line with the value of Δq.

Table I. Methyl Rate Enhancements and Regional Charges for 1-Aryl-1-ethyl Systems[a]

Entry	Compd	Leaving group[a]	i[b]	j[c]	$k(CH_3)/k(H)$	Δq_{ij}	Ref
			25°C				
1	Furan	OPNB	5	2	212	0.2763	10
2	Thiophene	OPNB	5	2	81	0.2051	6
3	Benzene	Cl	3	1	2.20	0.0368	e
4	Benzene	Cl	4	1	58.0	0.2115	e
5	Thiazole	OPNB	2	5	45.5	0.2030	11
6	Thiazole	OPNB	5	2	89.5	0.2268	11
7	Toluene	Cl	5	2	45.5	0.2028	e
8	Toluene	Cl	4	2	2.00	0.0337	e
9	Benzothiazole	OTs	4	2	4.47	0.1036	e
10	Benzothiazole	OTs	5	2	2.80	0.0371	e
11	Benzothiazole	OTs	6	2	10.09	0.1238	e
12	Benzimidazole	Cl	5	2	8.15	0.0600	e
13	Benzimidazole	Cl	5, 6	2	82.8	0.1880[d]	e
14	Pyrazole	Cl	3	5	3.74	0.0479	e
15	Imidazole	OPNB	5	2	59.7	0.2396	12
16	Imidazole	OPNB	4	2	20.3	0.1111	12
17	Imidazole	OPNB	4, 5	2	1013	0.3507[d]	12
			75°C				
18	Furan	OPNB	5	3	8.85	0.1076	5
19	2-Methylfuran	OPNB	5	3	7.53	0.1166	e
20	Thiophene	OPNB	5	3	3.92	0.0735	e
21	Benzene	Cl	3	1	2.02	0.0368	e
22	Benzene	OPNB	4	1	58.00	0.2115	e
23	Benzo[b]thiophene	OPNB	5	2	2.57	0.0398	7
24	Benzo[b]thiophene	OPNB	6	2	9.00	0.1246	7
25	Benzo[b]thiophene	OPNB	7	2	1.59	0.0323	7
26	Benzo[b]furan	OPNB	5	2	2.78	0.0473	4
27	Benzo[b]furan	OPNB	6	2	11.70	0.1377	4

[a] Solvent, 80% ethanol; Cl = chloride, OPNB = p-nitrobenzoate, OTs = tosylate. [b] i = position of methyl substitution. [c] j = position of 1-ethyl side chain. [d] Assuming additivity. [e] Present study. [f] $k(C_2H_5)/k$ (H).

The slope of the line in Figure 1, for secondary systems at 25°C, is 7.9 (correlation coefficient r = 0.973). This compares favorably with the slope of 8.6 predicted by eq 5 (−1.41 × −6.1). At 75°C the observed slope (Figure 2) of 8.0 (r = 0.992) compares equally favorably with a predicted value of 7.8. The results seem eminently satisfactory, considering the very wide diversity of compound types brought together for this correlation.

There are also appreciable data available on tertiary systems, and this information is collected in Table II. The naphthalene case (33) is instructive; treating the data of Baliah and Nadar[14] in this fashion is particularly satisfy-

Table II. Methyl Rate Enhancements and Regional Charges for 2-Aryl-2-propyl Systems at 25°C

Entry	Compd	Leaving group[a]	i[b]	j[c]	$k(CH_3)/k(H)$	Δq_{ij}	Ref
28	Pyridine[d]	Cl	2	4	1.85	0.0286	13
29	Pyridine[d]	Cl	2	5	19.00	0.2212	13
30	Pyridine[d]	Cl	3	5	1.96	0.0441	13
31	Benzene[e]	Cl	3	1	2.00	0.0368	8
32	Benzene[e]	Cl	4	1	26.00	0.2115	8
33	Naphthalene[f]	Cl	6	2	6.10	0.1232	14
34	Furan[d]	OPNB	5	3	6.00	0.1076	5

[a] Cl = chloride; OPNB = p-nitrobenzoate. [b] i = position of methyl substitution. [c] j = position of 2-propyl side chain. [d] Solvent, 80% ethanol. [e] Solvent, 90% acetone. [f] Solvent, 95% acetone, 30°C.

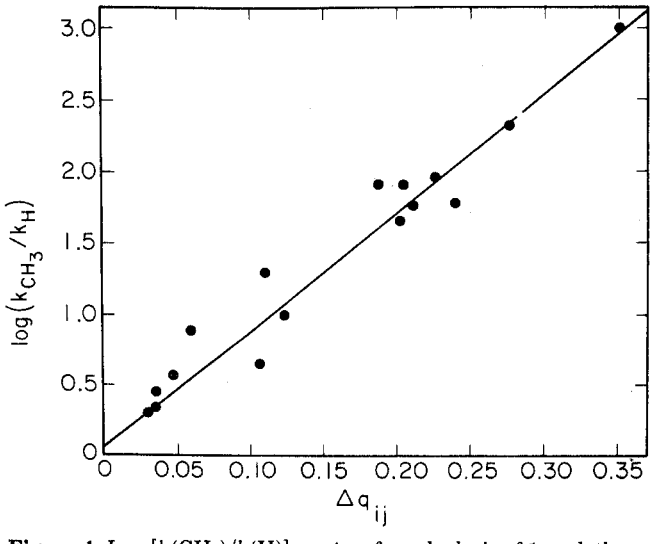

Figure 1. Log $[k(CH_3)/k(H)]$ vs. Δq_{ij} for solvolysis of 1-arylethanol derivatives in 80% ethanol at 25° (r = 0.973).

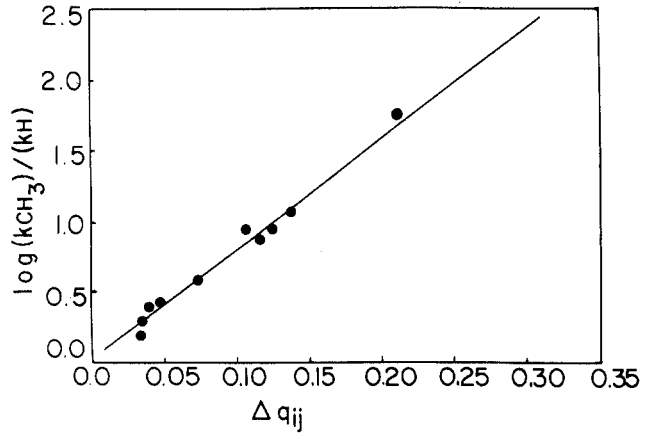

Figure 2. Log $[k(CH_3)/k(H)]$ vs. Δq_{ij} for solvolysis of 1-arylethanol derivatives in 80% ethanol at 75° (r = 0.992).

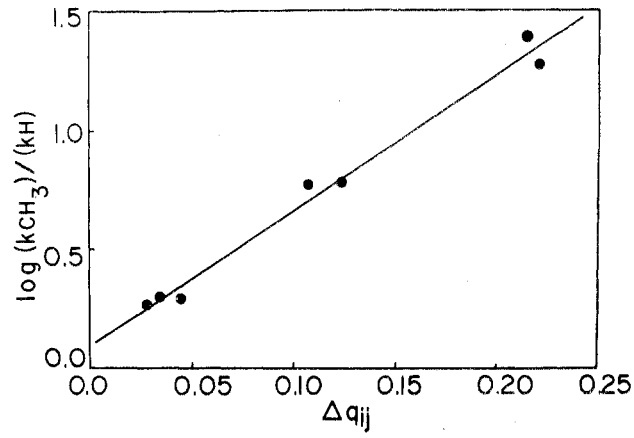

Figure 3. Log $[k(CH_3)/k(H)]$ vs. Δq_{ij} for solvolysis of tertiary systems at 25° (r = 0.990).

ing, as it immediately explains their "unexpected" difficulty with high reactivity for 6-methoxy-2-naphthyl-2-chloropropane. The results for the tertiary systems are presented graphically in Figure 3. The observed slope, 5.8 (r = 0.990) is to be compared with the predicted slope of 6.3 [ρ = −4.5 (from Brown's studies) × −1.41].

Since ρ incorporates influences such as variation of solvent, temperature, and reaction center (primary, secondary, or tertiary) on the magnitude of the response to the influence of the substituent, eq 5 can be reorganized to give eq 6.

$$\frac{1}{\rho}\log\frac{k(CH_3)}{k(H)} = -1.41\Delta q_{ij} \qquad (6)$$

Equation 6 permits all of the data presented above to be correlated by a single function. When the data are treated together in this fashion, the best slope of the line is −1.33, which is in excellent agreement with the theoretical slope of −1.41.

The correlations presented in Figures 1–3 support the assumption introduced in eq 3, that the resonance capability of the methyl group is the predominant component of the methyl substituent effect. Furthermore, the use of regional charges to obtain a quantitative picture of charge delocalization in the solvolysis transition state is supported by these correlations.

The relationship between methyl rate enhancement and regional charge seen in eq 6 is not solely applicable to the limiting solvolysis of substituted heteroarylcarbinyl systems. With suitable transition state models, which are necessary for the calculation of regional charges, methyl rate enhancements observed for other reactions, e.g., electrophilic bromination, should also be successfully predicted by eq 5. In a reverse manner, the methyl group might be used as a sensitive probe for charge delocalization in the transition states of many organic reactions.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected as are boiling points. Proton magnetic resonance spectra were obtained on a Varian T-60 instrument with tetramethylsilane as the internal standard. Chemical shifts are given in parts per million downfield from Me_4Si (δ values), and the following legend is used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; and b, broad. All elemental analyses were performed by the Analytical Services Laboratory, College of Chemistry, University of California, Berkeley.

Kinetic rate constants were evaluated from the raw experimental titers by the LSKIN 1 program.[15]

1-(2-Methylphenyl)ethyl chloride[16] **(1)** was prepared, using thionyl chloride with the alcohol, which was from *o*-methylbenzaldehyde and methylmagnesium bromide. **1-(2,4-Dimethylphenyl)ethyl chloride**[16] **(2)** was prepared from the corresponding alcohol[16] using thionyl chloride. **1-(2-,5-Dimethylphenyl)ethyl chloride (3)** was prepared from 1-(2,5-dimethylphenyl)ethanol,[17] using thionyl chloride in dichloromethane.

1-(2-Methyl-3-furyl)ethyl *p*-Nitrobenzoate (4). 2-Methyl-3-acetylfuran[18] was reduced with sodium borohydride in anhydrous methanol, and the 1-(2-methyl-3-furyl)ethanol was obtained in 91% yield: bp 38–40° (0.3 mm); NMR ($CDCl_3$) δ 1.33 [d, 3, J = 6 Hz, $-CH(CH_3)_2$], 1.87 (s, 3, 2-CH_3), 3.63 (broad singlet, 1, –OH), 4.67 [q, 1, J = 6 Hz, $-CH(OH)CH_3$], 6.23 (d, 1, J = 2 Hz, 4-H), 7.13 (d, 1, J = 2 Hz, 5-H).

The alcohol was converted directly to the *p*-nitrobenzoate, using *p*-nitrobenzoyl chloride in pyridine. 1-(2-Methyl-3-furyl)ethyl *p*-nitrobenzoate was purified by crystallization from mixed hexanes: mp 84–85°; yield 61%; NMR (CCl_4) δ 1.62 [d, 3, J = 6 Hz, $-CH(OPNB)CH_3$], 2.35 (s, 3, 2-CH_3), 6.05 [q, 1, J = 6 Hz, $-CH(OPNB)CH_3$], 6.32 (d, 1, J = 2 Hz, 4-H), 7.15 (d, 1, J = 2 Hz, 5-H), 8.12 (s, 4, ArH).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.73; N, 5.09. Found: C, 61.11; H, 4.93; N, 4.98.

1-(2,5-Dimethyl-3-furyl)ethyl *p*-Nitrobenzoate (5). Reduction of 2,5-dimethyl-3-acetylfuran[19] with sodium borohydride in methanol afforded 1-(2,5-dimethyl-3-furyl)ethanol, NMR (CCl_4) δ 1.22 (d, 3, J = 6 Hz, $>CHCH_3$), 2.13 (s, 6, 2-CH_3 and 5-CH_3), 3.52 (broad, 1, OH), 4.45 (q, 1, J = 6 Hz $>CHCH_3$), 5.70 (s, 1, 4-H), which was converted directly to the *p*-nitrobenzoate using *p*-nitrobenzoyl chloride and pyridine. The crude ester **5** was purified by recrystallization from mixed hexanes: mp 79–80°; NMR (CCl_4) δ 1.58 [d, 3, J = 6 Hz, $-CH(OPNB)CH_3$], 2.20 and 2.28 (two singlets, 6, 2-CH_3 and 5-CH_3), 5.88 (s, 1, 4-H), 5.93 [q, 1, J = 6 Hz, $-CH(OPNB)CH_3$], 8.08 (s, 4, C_6H_4).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.52; H, 5.20; N, 4.72.

1-(3-Thienyl)ethyl *p*-Nitrobenzoate (6) was prepared as previously reported.[20]

1-(5-Methyl-3-thienyl)ethanol. 4-Bromo-2-methylthiophene, prepared by the method of Gol'dfarb, Vol'kenshtein, and Lopatin[21] (22 g), was dissolved in 100 ml of dry ether and added dropwise to a solution of *n*-butyllithium ether (90 ml of 15%) under nitrogen at −78°. The reaction mixture was stirred for 1 h. Acetaldehyde (17.0 ml, 13.2 g, 0.30 mol) in 50 ml of ether was added. The mixture was stirred for another 1 h and then removed from the dry ice bath and quenched with 100 ml of water. The ether layer was separated and the aqueous phase was washed with 3 × 50 ml of ether. The combined ether layers were dried (Na_2CO_3) and filtered, and the ether was removed on the rotary evaporator. The residue was distilled to yield 1-(5-methyl-3-thienyl)ethanol: 6.0 g (34%); bp 65–66° (0.03 mm); NMR (CCl_4) δ 1.32 [d, 3, J = 6 Hz, $-CH(OH)CH_3$], 2.38 (s, 3, 5-CH_3), 6.52 (broad doublet, 1, 4-H, coupled to 5-CH_3 with J < 1 Hz), 6.63 (d, 1, J < 1 Hz, 2-H).

Anal. Calcd for $H_7H_{10}OS$: C, 59.11; H, 7.09; S, 22.55. Found: C, 58.96; H, 7.09; S, 22.36.

1-(5-Methyl-3-thienyl)ethyl *p*-Nitrobenzoate (7). The alcohol was treated with freshly recrystallized *p*-nitrobenzoyl chloride in dichloroethane solution to which triethylamine had been added. The crude product was crystallized from mixed hexanes to yield ester **7**: mp 45.5–47°; NMR (CCl_4) δ 1.65 [d, 3, J = 6 Hz, $CH(OPNB)CH_3$], 2.45 (bs, 5-CH_3), 6.03 [q, 1, J = 6 Hz, $CH(OPNB)CH_3$], 6.62–6.75 (m, 1, 4-H, coupled to 5-CH_3 and 2-H), 6.92 (d, 1, J < 1 Hz, 2-H), 8.07 (s, 4, C_6H_4).

Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found: C, 57.67; H, 4.39; N, 4.90; S, 10.92.

1-(2-Benzothiazolyl)ethanol was prepared from benzothiazole by metalation with butyllithium and addition of acetaldehyde to the lithio derivative. Work-up and distillation gave a viscous liquid, bp 112–116° (0.4 mm), which slowly solidified at room temperature (12.2 g, 68%). The solid was recrystallized from hexane–ether to give white needles: mp 62–63.5° (lit.[22] 68°); NMR (CCl_4) δ 1.62 (d, 3, $-CHCH_3$, J = 7 Hz), 4.33 (s, 1, –OH), 5.13 (s, 1, $-CHCH_3$, J = 6.5 Hz), 7.15–7.44 (m, 2, 5-H and 6-H), and 7.64–7.90 (m, 2, 4-H and 7-H).

Anal. Calcd for C_9H_9NOS: C, 60.34; H, 5.03; N, 7.82; S, 17.88. Found: C, 60.25; H, 4.98; N, 7.64; S, 18.02.

1-(2-Benzothiazolyl)ethyl Tosylate (8). A solution of 1-(2-benzothiazolyl)ethanol (5.00 g) and triethylamine (2.82 g) was prepared in 10 ml of 1,2-dichloroethane. Recrystallized *p*-toluenesulfonyl chloride (5.32 g) dissolved in 15 ml of 1,2-dichloroethane was added in portions to the alcohol–amine solution. The resulting solution was stirred for 1 h at room temperature. The mixture was refrigerated for 24 h, after which time it was warmed to room temperature and filtered. The triethylammonium chloride precipitate

was washed with fresh solvent, and the combined organic portions were concentrated under vacuum. The orange oil thus obtained was taken up in several portions of boiling hexane (ca. 800 ml total), and the combined hexane extracts were set aside to crystallize. Filtration afforded 8 as a fine white solid (4.7 g, 51%): mp 59–60°; NMR (CCl_4) δ 1.77 (d, 3, $-CHCH_3$, J = 6 Hz), 2.35 (s, 3, $ArCH_3$), 5.77 (q, 1, $-CHCH_3$, J = 6.5 Hz), 7.06–7.35 (m, 4, 5-H and 6-H and m-ArH), and 7.61–7.89 (m, 4, 4-H and 7-H and o-ArH).

Anal. Calcd for $C_{16}H_{15}NO_3S_2$: C, 57.66; H, 4.50; N, 4.20; S, 19.22. Found: C, 57.59; H, 4.51; N, 4.31; S, 19.32.

6-Methylbenzothiazole 6-Methylbenzothiazole-2-carboxylic acid, mp 108–110° (7.3 g),[23] was decarboxylated by steam distillation. The steam distillates were extracted with chloroform and dried ($MgSO_4$). Removal of solvent gave a yellow oil (5.2 g), which was distilled to give a colorless liquid (4.6 g, 81%): bp 81–82° (1.4 mm) [lit.[24] 118–120° (1.3 mm)]; NMR (CCl_4) δ 2.36 (s, 3, 6-CH_3), 7.15 (dd, 1, 5-H), 7.47–7.54 (m, 1, 7-H), 7.93 (d, 1, 4-H, J = 8 Hz), and 8.77 (s, 1, 2-H).

Anal. Calcd for C_8H_7NS: C, 64.43; H, 4.70; N, 9.40; S, 21.48. Found: C, 64.21; H, 4.67; N, 9.49; S, 21.34.

1-(6-Methyl-2-benzothiazolyl)ethanol was prepared by metalation of 6-methylbenzothiazole with butyllithium at −78° and subsequent addition of acetaldehyde. The isolated product was crystallized from hexane to afford white crystals (50%): mp 108.5–110.5°; NMR ($CDCl_3$) δ 1.68 (d, 3, $-CHCH_3$, J = 6 Hz), 2.47 (s, 3, 6-CH_3), 5.18 (q, 1, $-CHCH_3$, J = 6.5 Hz), 7.15–7.31 (m, 1, 5-H), and 7.65–7.89 (m, 2, 4-H and 7-H).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.18; H, 5.70; N, 7.25; S, 16.58. Found: C, 62.05; H, 5.88; N, 7.03; S, 16.62.

1-(6-Methyl-2-benzothiazolyl)ethyl tosylate (9) was prepared from the alcohol as above. The crude material isolated was found by NMR to be a mixture of alcohol (30%) and tosylate 9 (70%). Further purification was extremely tedious. Hence, this mixture was used in kinetic runs without further purification: NMR (CCl_4) δ 1.75 (d, 3, $-CHCH_3$, J = 6 Hz), 2.45 (s, 3, $ArCH_3$), 5.78 (q, 1, $-CHCH_3$, J = 6 Hz), 7.11–7.24 (m, 3, m-ArH and 5-H), and 7.54–7.80 (m, 4, o-ArH and 4-H and 7-H).

1-(5-Methyl-2-benzothiazolyl)ethanol. Metalation of 5.6 g of 5-methylbenzothiazole[25] with butyllithium at −78° was followed by addition of acetaldehyde (3.31 g). The dry ice bath was then removed and stirring was continued for 15 min. The yellow mixture was poured into saturated ammonium chloride (200 ml), and the resulting solution was extracted with ether. After drying ($MgSO_4$) and removing solvent, a golden oil was obtained, which was distilled to give a light yellow solid (6.0 g), bp 124–127° (0.05 mm). Recrystallization from hexane gave white needles (4.0 g, 55%): mp 83–85°; NMR ($CDCl_3$ and CCl_4 mixture) δ 1.60 (d, 3, $-CHCH_3$, J = 6 Hz), 2.38 (s, 3, 5-CH_3), 4.83 (b, 1, −OH), 5.10 (q, 1, $-CHCH_3$, J = 6 Hz), 6.98 (bd, 1, 6-H), 7.50 (bs, 1, 4-H), and 7.51 (d, 1, 7-H, J = 8 Hz).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.18; H, 5.70; N, 7.25; S, 16.58. Found: C, 61.99; H, 5.55; N, 7.12; S, 16.45.

1-(5-Methyl-2-benzothiazolyl)ethyl tosylate (10) was prepared in the usual fashion. The crude product was crystallized from hexane to give fine white needles (75%): mp 116–117°; NMR (CCl_4) δ 1.78 (d, 3, $-CHCH_3$, J = 6 Hz), 2.36 (s, 3, $ArCH_3$), 2.47 (s, 3, 5-CH_3), 5.78 (q, 1, $-CHCH_3$, J = 6 Hz), 7.00–7.24 (m, 3, 6-H and m-ArH), and 7.51–7.81 (m, 4, 4-H and 7-H and o-ArH).

Anal. Calcd for $C_{17}H_{17}NO_3S_2$: C, 58.79; H, 4.90; N, 4.03; S, 18.44. Found: C, 58.72; H, 4.82; N, 4.17; S, 18.32.

1-(4-Methyl-2-benzothiazolyl)ethanol. Decarboxylation of 4-methylbenzothiazole-2-carboxylic acid[23] gave 4-methylbenzothiazole.[25] Metalation with butyllithium and subsequent addition of acetaldehyde gave 1-(4-methyl-3-benzothiazolyl)ethanol in 73% yield: mp 65–68° (white crystals from hexane); NMR (CCl_4) δ 1.60 (d, 3, $-CHCH_3$, J = 6 Hz), 2.62 (s, 3, 4-CH_3), 4.12 (b, 1, −OH), 5.09 (q, 1, $-CHCH_3$, J = 6 Hz), 6.97–7.21 (m, 2, 5-H and 6-H), and 7.34–7.54 (m, 1, 7-H).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.18; H, 5.70; N, 7.25; S, 16.58. Found: C, 62.37; H, 5.68; N, 7.14; S, 16.74.

1-(4-Methyl-2-benzothiazolyl)ethyl tosylate (11) was prepared in the usual fashion. Crystallization of crude 11 from hexane was induced by chilling in dry ice and scratching, which produced a fine white solid: mp 74–75°; NMR (CCl_4) δ 1.77 (d, 3, $-CHCH_3$, J = 7 Hz), 2.34 (s, 3, $ArCH_3$), 2.60 (s, 3, 4-CH_3), 5.80 (q, 1, $-CHCH_3$, J = 6 Hz), 7.06–7.22 (m, 4, 5-H and 6-H and m-ArH), and 7.44–7.75 (m, 3, 7-H and o-ArH).

Anal. Calcd for $C_{17}H_{17}NO_3S_2$: C, 58.79; H, 4.90; N, 4.03; S, 18.44. Found: C, 58.77; H, 5.05; N, 4.22; S, 18.62.

1-(1-Methyl-2-benzimidazolyl)ethyl Chloride (12). This preparation followed the procedure of Skolnick, Miller, and Day.[26]

1-(1,5-Dimethyl-2-benzimidazolyl)ethanol. This procedure followed the sequence used by Beaven et al.[27] The N-methyl-2-amino-4-methylaniline was treated with lactic acid by the Phillips method[28] to give the title compound, mp 94–95°, NMR ($CDCl_3$) δ 1.65 (d, 3, $-CHCH_3$), 2.45 (s, 3, 5-CH_3), 3.70 (s, 3, NCH_3), 3.95 (bs, 1, OH), 5.10 (q, 1, $CHCH_3$), 7.20 (m, 3, ArH), which was converted directly to the chloride.

1-(1,5-Dimethyl-2-benzimidazolyl)ethyl Chloride (13). To a stirred solution of 1-(1,5-dimethyl-2-benzimidazolyl)ethanol (4.0 g) in 50 ml of methylene chloride was added 4.4 g of phosphorus pentachloride. The exothermic reaction gently refluxed during the 1-h stirring period. The solution was then concentrated to a light yellow oil which was digested in 100 ml of methylene chloride and stirred with a slurry of aqueous sodium bicarbonate (5–10 ml) to neutralize the remaining acid. After effervescence ceased, the solution was diluted with methylene chloride (25 ml) and dried over $MgSO_4$. Rotary evaporation yielded 1.98 g (45%) of 13 as very light beige crystals: mp 107–109°; NMR ($CDCl_3$) δ 2.15 [d, 3, $CH(Cl)CH_3$], 2.55 (s, 3, 5-CH_3), 3.80 (s, 3, NCH_3), 5.40 [q, 1, $CH(Cl)CH_3$], 7.50 (m, 3, H-4, -6, -7).

Anal. Calcd for $C_{11}H_{13}ClN_2$: C, 63.31; H, 6.24; N, 13.43; Cl, 17.02. Found: C, 63.11; H, 6.17; N, 13.26; Cl, 17.24.

1-(1,5,6-Trimethyl-2-benzimidazolyl)ethyl Chloride (14). Treatment of 4,5-dimethyl-1,2-diaminobenzene with lactic acid and HCl[29] gave 1-(5,6-dimethyl-2-benzimidazolyl)ethanol in 68% yield, mp 219–221° (lit.[30] 221–222°). Following the procedures of Skolnick, Miller, and Day,[26] dimethyl sulfate and base gave 1-(1,5,6-trimethyl-2-benzimidazolyl)ethanol, mp 138–140° (93% yield), which was converted to 14 by the procedure of Skolnick, Miller, and Day,[26] mp 127–130°. The crude chloride was used directly for kinetic measurements.

1-(1-Methyl-5-pyrazolyl)ethanol. A solution of 6.6 g of 1-methylpyrazole in 450 ml of anhydrous ether was stirred under nitrogen in an ice bath as 0.1 mol (59 ml of a 1.69 M solution of n-butyllithium in hexane) in 50 ml of ether was added dropwise. Stirring was continued for 2 h, as formation of a bright yellow precipitate was observed. Acetaldehyde (11.9 g) was added cautiously. The ice bath was removed and the reaction mixture was stirred for an additional 15 min. Water (150 ml) was added, the layers were separated, and the aqueous layer was washed with chloroform (4 × 75 ml). The organic layers were collected and dried ($MgSO_4$), and the solvents were evaporated. The residue was distilled under vacuum to yield 3.5 g (3) of 1-(1-methyl-5-pyrazolyl)ethanol: bp 93–94° (0.5 mm); NMR (CCl_4) δ 1.48 (d, J = 6 Hz, 3, CH_3CHOH–), 3.68 (s, 3, NCH_3), 4.4 (bs, 1, −OH), 4.73 (q, J = 6 Hz, 1, CH_3CHOH–), 5.98 (d, J = 2 Hz, 1, 4-H), 7.03 (d, J = 2 Hz, 1, 3-H).

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.20; H, 7.99; N, 22.20. Found: C, 57.27; H, 7.72; N, 22.34.

1-(1-Methyl-5-pyrazolyl)ethyl Chloride (15). To a solution of 0.6 g of thionyl chloride in 10 ml of 1,2-dichloroethane was carefully added 0.63 g of 1-(1-methyl-5-pyrazolyl)ethanol in ca. 1 ml of the solvent. The mixture was stirred and heated under reflux for 30 min. It was cooled and 0.5 g (0.005 mol) of triethylamine was added dropwise. The solution was cooled and the precipitated triethylamine hydrochloride was removed by filtration and then rinsed with a small amount of cold solvent. Evaporation of the solvent gave 0.70 g (98%) of crude 1-(1-methyl-5-pyrazolyl)ethyl chloride (15) which was used directly for kinetic studies: NMR ($CDCl_3$) (no alcohol present) δ 7.47 (d, J = 2 Hz, 1, 3-H), 6.22 (d, J = 2 Hz, 1, 4-H), 5.12 (q, J = 6.5 Hz, 1, CH_3CHCl–), 3.85 (s, 3, NCH_3), 1.87 (d, J = 6.5 Hz, 3, CH_3CHCl–).

1-(1,3-Dimethyl-5-pyrazolyl)ethanol. The procedure of Burness[31] for the preparation of 1,3-dimethylpyrazole led to a mixture of the 1,3- and 1,5-dimethyl isomers composed of roughly two-thirds of the 1,3 product by NMR. A solution of 14 g of this mixture (ca. 9.3 g or 0.097 mol of the 1,3-dimethylpyrazole) in 450 ml of anhydrous ether was stirred in an ice bath as 0.11 mol (65 ml of a 1.69 M solution) of butyllithium in 50 ml of anhydrous ether was added dropwise. Cooling and stirring were continued for 2 h after addition was complete. Three 5-ml portions of acetaldehyde were syringed into the flask, and stirring was continued for 15 min. Saturated ammonium chloride solution (150 ml) was added and the layers were separated. The aqueous layer was extracted with methylene chloride (4 × 75 ml). The organic layers were combined and dried, and the solvents were removed. Distillation afforded first a mixture of 1,5-dimethylpyrazole and unreacted 1,3-dimethylpyrazole boiling at 37–43° (1 mm). The higher boiling fraction [>90° (1 mm)] was redistilled to yield 3.55 g (26%, based on the amount of 1,3-dimethylpyrazole originally present) of 1-(1,3-dimethyl-5-pyrazolyl)ethanol: bp 125–127° (1 mm); NMR ($CDCl_3$) δ 1.45 (d, J = 6.5 Hz, 3, CH_3CHOH–), 2.08 (s, 3, C_3CH_3), 3.62 (s, 3, NCH_3), 4.70

Table III. Rate Constants for Solvolyses in 80% Ethanol

Compd solvolyzed	Temp, °C	k, s^{-1}
1	24.83	$1.28 \pm 0.02 \times 10^{-4}$
	24.83	$1.27 \pm 0.02 \times 10^{-4}$
2	24.93	$5.88 \pm 0.03 \times 10^{-3}$
3	24.93	$2.56 \pm 0.01 \times 10^{-4}$
4	75.10	$1.65 \pm 0.02 \times 10^{-3}$
	75.10	$1.69 \pm 0.02 \times 10^{-3}$
5	75.03	$1.21 \pm 0.02 \times 10^{-2}$
	75.03	$1.19 \pm 0.02 \times 10^{-2}$
6[a]	75.50	$1.10 \pm 0.01 \times 10^{-5}$
	75.50	$1.08 \pm 0.01 \times 10^{-5}$
7[a]	75.45	$4.34 \pm 0.2 \times 10^{-5}$
	75.45	$4.20 \pm 0.2 \times 10^{-5}$
8	25.00[b]	2.55×10^{-5}
	45.01	$2.38 \pm 0.01 \times 10^{-4}$
	45.02	$2.32 \pm 0.01 \times 10^{-4}$
	59.97	$1.05 \pm 0.01 \times 10^{-3}$
	75.00	$4.15 \pm 0.02 \times 10^{-3}$
9	25.30	$2.59 \pm 0.02 \times 10^{-4}$
	25.31	$2.56 \pm 0.02 \times 10^{-4}$
10	24.98	$7.19 \pm 0.03 \times 10^{-5}$
	24.99	$7.07 \pm 0.01 \times 10^{-5}$
11	25.06	$1.14 \pm 0.01 \times 10^{-4}$
	25.08	$1.13 \pm 0.01 \times 10^{-4}$
12	25.00[b]	7.45×10^{-6}
	45.0	$8.84 \pm 0.10 \times 10^{-5}$
	60.0	$3.62 \pm 0.10 \times 10^{-4}$
	75.0	$1.83 \pm 0.06 \times 10^{-3}$
13	25.00[b]	6.07×10^{-5}
	45.0	$5.57 \pm 0.06 \times 10^{-4}$
	60.0	$2.81 \pm 0.03 \times 10^{-3}$
14	25.00	$6.17 \pm 0.01 \times 10^{-4}$
15	25.04	$3.38 \pm 0.03 \times 10^{-4}$
	25.08	$3.45 \pm 0.01 \times 10^{-4}$
16	25.08	$1.269 \pm 0.002 \times 10^{-3}$
	25.08	$1.282 \pm 0.009 \times 10^{-3}$

[a] Rates measured using sealed ampules. [b] Extrapolated from data at other temperature.

(q, J = 6.5 Hz, 1, CH_3CHOH–), 5.13 (bs, 1, OH), 5.78 (s, 1, 4-H). The alcohol was characterized as the p-nitrobenzoate derivative: mp 106–107° (from hexane); NMR ($CDCl_3$) δ 1.73 (d, J = 7 Hz, 3, $CH_3CHOPNB$–), 2.23 (s, 3, C_3CH_3), 3.83 (s, 3, NCH_3), 6.12 (superimposed on q, 1, 4-H), 6.29 (q with superimposed s, J = 7 Hz, 1, $CH_3CHOPNB$–).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 57.96; H, 5.09; N, 14.64.

1-(1,3-Dimethyl-5-pyrazolyl)ethyl Chloride (16). The 1-(1,3-dimethyl-5-pyrazolyl)ethanol was converted to the chloride as above, using dichloroethane as solvent. The solvent was evaporated to yield the chloride quantitatively. The compound was utilized directly for kinetic studies: NMR (CCl_4) δ 1.82 (d, J = 7 Hz, 3, CH_3CHCl–), 2.14 (s, 3, C_3CH_3), 3.73 (s, 3, NCH_3), 4.98 (q, J = 7 Hz, 1, CH_3CHCl–), 5.87 (s, 1, 4-H).

Kinetic Methods. Kinetic methods have been described previously.[4,13,32] All rate methods were carried out at constant pH using a Radiometer automatic titrator (Model TTT 1c). The newly determined rate constants are assembled in Table III.

Registry No.—**1,** 55968-39-3; **2,** 51270-91-8; **3,** 57527-74-9; **4,** 57527-75-0; **5,** 57527-76-1; **6,** 23516-72-5; **7,** 57527-77-2; **8,** 57527-78-3; **9,** 57527-79-4; **10,** 57527-80-7; **11,** 57527-81-8; **12,** 58282-03-4; **13,** 57527-82-9; **14,** 57527-83-0; **15,** 57527-84-1; **16,** 57527-85-2; 2-methyl-3-acetylfuran, 16806-88-5; 1-(2-methyl-3-furyl)ethanol, 57527-86-3; p-nitrobenzoyl chloride, 122-04-3; 2,5-dimethyl-3-acetylfuran, 10599-70-9; 1-(2,5-dimethyl-3-furyl)ethanol, 38422-61-6; 1-(5-methyl-3-thienyl)ethanol, 57527-87-4; 4-bromo-2-methylthiophene, 29421-92-9; 1-(2-benzothiazolyl)ethanol, 17147-80-7; benzothiazole, 95-16-9; p-toluenesulfonyl chloride, 98-59-9; 6-methylbenzothiazole, 2942-15-6; 6-methylbenzothiazole-2-carboxylic acid, 3507-18-4; 1-(6-methyl-2-benzothiazolyl)ethanol, 54469-51-1; 1-(5-methyl-2-benzothiazolyl)ethanol, 57527-88-5; 5-methylbenzothiazole, 2942-16-7; 1-(4-methyl-2-benzothiazolyl)ethanol, 57527-89-6; 4-methylbenzothiazole-2-carboxylic acid, 3507-47-9; 1-(1,5-dimethyl-2-benzimidazolyl)ethanol, 57527-90-9; N-methyl-2-amino-4-methylaniline, 39513-19-4; lactic acid, 50-21-5; phosphorus pentachloride, 10026-13-8; 4,5-dimethyl-1,2-diaminobenzene, 3171-45-7; 1-(1,5,6-trimethyl-2-benzimidazolyl)ethanol, 57527-91-0; 1-(1-methyl-5-pyrazolyl)ethanol, 57527-92-1; 1-methylpyrazole, 930-36-9; 1-(1,3-dimethyl-5-pyrazolyl)ethanol, 57527-93-2; 1,3-dimethylpyrazole, 694-48-4; 1,5-dimethylpyrazole, 694-31-5; 1-(1,3-dimethyl-5-pyrazolyl)ethanol p-nitrobenzoate, 57527-94-3.

References and Notes

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