DMSO was added to a solution of 4.5 mmol of dimethyloxosulfonium methylide in DMSO.[14] After 45 min at 20–25° the reaction solution was diluted with H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated leaving 310 mg of pure **2a** (nmr analysis). No 1-phenylcyclopropylcarboxaldehyde was detected.

Acknowledgment. We thank Professor Joseph L. Kurz for several helpful suggestions and Professor Alfred Hassner for a stimulating discussion. Financial support originating from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and from a grant (NSG 581-26-008-006) to Washington University from the National Aeronautics and Space Administration, is also gratefully acknowledged.

A Search for the α Effect among Heteroaromatic Nitrogen Nucleophiles[1a]

John A. Zoltewicz* and L. W. Deady[1b]

Contribution from the Department of Chemistry, University of Florida, Gainesville, Florida 32601. *Received May 10, 1971*

Abstract: Relative rates of methylation of heteroaromatic compounds by methyl iodide in DMSO at 23° were obtained using an nmr method. Nucleophiles examined include pyridines, diazines, and their benzologs. Cinnoline, pyridazine, and phthalazine are about three times more reactive than predicted by a Brønsted relationship established by the pyridines. Cinnoline gives a 9:1 mixture of N-2:N-1 methylated products. Rates of acetylation of pyridazine, phthalazine, and three pyridines by *p*-nitrophenyl acetate at 25° in water were obtained. Pyridazine and phthalazine acetylated 20 and 30 times faster, respectively, than predicted by a Brønsted plot established by the pyridine nucleophiles. Rate accelerations for the α-diaza nucleophiles are discussed in terms of pair–pair electron repulsion and the α effect.

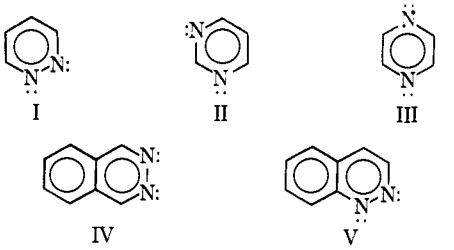
The term α effect was first applied in 1962 to nucleophiles which had an enhanced reactivity toward *p*-nitrophenyl acetate (PNPA).[2] The abnormal reactivity was evidenced by positive deviations from a Brønsted plot established by other nucleophiles.[3] These "supernucleophiles,"[4] *e.g.*, $RONH_2$, H_2NNH_2, ClO^-, and ROO^-, have an unshared electron pair α to the nucleophilic center.

In the ensuing years additional examples of the α effect were found.[5] Many explanations for the enhanced reactivity have been advanced and rejected.[5,6] Current opinion favors the view that no one factor can account for the enhanced reactivity of the entire class of α-effect nucleophiles.[7]

Electron pair–electron pair repulsions were suggested to be a dominant cause of the α effect for certain nucleophiles.[4,8] More recently, it has been suggested that conformational factors may be important in influencing the magnitude of pair–pair repulsion. Thus, ClO^- and ROO^- were said to show the effects of pair–pair repulsion but $HONH_2$ and H_2NNH_2 were said to have conformations which minimize this interaction.[9]

Spectroscopy[10,11] and molecular orbital calculations[12] indicate that the electron pairs on the annular nitrogen atoms in heteroaromatic diazines I–III interact repulsively. Such interactions are not limited to pyridazine (I) where the electron pairs are on adjacent atoms but are also found in pyrimidine (II) and pyrazine (III) where the heteroatoms are more widely separated.

We have employed the diazines and benzologs of I, phthalazine (IV), and cinnoline (V) as nucleophiles in a



I II III IV V

(1) (a) Presented in part at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 13–17, 1971, Abstract ORGN-150. (b) On leave from LaTrobe University, Melbourne, Australia.

(2) J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

(3) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 1778 (1960).

(4) G. Klopman, K. Tsuda, J. B. Louis, and R. E. Davis, *Tetrahedron*, **26**, 4549 (1970).

(5) For examples and discussions, see (a) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 107–111; (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, pp 78–80, 287–288.

(6) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967); M. J. Gregory and T. C. Bruice, *ibid.*, **89**, 2327 (1967).

(7) For discussions of the factors influencing nucleophilicity, see J. F. Bunnett, *Annu. Rev. Phys. Chem.*, 14, 271 (1963); R. F. Hudson, *Chimia*, **16**, 173 (1962); R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); and A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

(8) K. M. Ibne-Rasa and J. O. Edwards, *J. Amer. Chem. Soc.*, 84, 763 (1962); C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Bell, London, 1969, pp 452–453; J. D. Aubort and R. F. Hudson, *J. Chem. Soc. D*, 1378 (1970).

(9) J. D. Aubort and R. F. Hudson, *ibid.*, 937 (1970).

(10) R. Gleiter, E. Heilbroner, and V. Hornung, *Angew. Chem., Int. Ed. Engl.*, **9**, 901 (1970).

(11) S. F. Mason, *J. Chem. Soc.*, 1240 (1959); M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.*, **51**, 263 (1969); A. Y. Yencha and M. A. El-Sayed, *ibid.*, **48**, 3469 (1968).

(12) W. Adam, A. Grimison, and R. Hoffmann, *J. Amer. Chem. Soc.*, **91**, 2590 (1969); R. Hoffmann, *Accounts Chem. Res.*, 4, 1 (1971); T. Yonezawa, H. Yamabe, and H. Kato, *Bull. Chem. Soc. Jap.*, **42**, 76 (1969); R. Hoffmann, A. Imamura, and W. J. Hehre, *J. Amer. Chem. Soc.*, **90**, 1499 (1968).

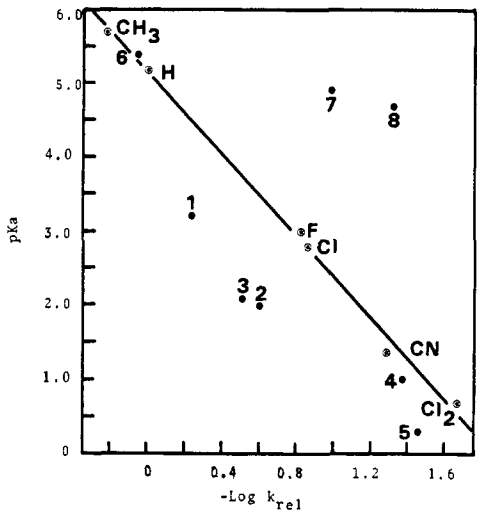


Figure 1. Brønsted plot of the relative rate constants, k_{rel}, for methylation of heteroaromatic nitrogen nucleophiles by methyl iodide in DMSO at 23° *vs.* pK_a. Pyridine (H) is the standard. The line is drawn through points for pyridine nucleophiles. Other compounds include: 1, phthalazine; 2, pyridazine; 3, cinnoline; 4, pyrimidine, 5, pyrazine; 6, isoquinoline; 7, quinoline; and 8, 1,10-phenanthroline.

search for the α effect. These nucleophiles are rigid and hence are free of conformational factors which can change the degree of pair–pair interactions. Methyl iodide and PNPA were selected as electrophiles. The saturated carbon electrophile is said to show a low sensitivity to the α effect[4,13,14] but the sensitivity of the carbonyl carbon is large.[3,4,15] Our approach is a standard one. Brønsted log k–pK_a plots were constructed using substituted pyridine nucleophiles. Results for the potential α-effect nucleophiles then were compared with those expected from the Brønsted reference lines for each electrophile. This study provides the first quantitative comparison of the nucleophilicity of these heteroaromatic molecules.

Results

Methylation. Relative rates of methylation were obtained by competition experiments at 23° involving pairs of heterocycles and methyl iodide in dimethyl sulfoxide (DMSO). These studies were carried out using nmr to determine product ratios. Product ratios were converted to rate constant ratios using a standard method.[16,17] Pyridazine and 1,10-phenanthroline generally served as standards in the competition reactions. Compounds examined include substituted pyridines, the three diazines, and benzologs of pyridine and the diazines. Results are summarized in Table I. Experimental rate constant ratios then were converted to relative rate constants, k_{rel}, using pyridine as a standard and are given in parentheses in Table I.

A Brønsted plot of log k_{rel} *vs.* pK_a,[18] Figure 1, gives a good correlation for the substituted pyridines. The least-squares line (r = 0.99) is given by eq 1. The

$$\log k_{rel} = 0.36pK_a - 1.85 \quad (1)$$

slope, β = 0.36, is similar to those reported for other alkylation experiments which compare pK_a values obtained using aqueous solutions and rate data for reactions carried out in nonaqueous solvents.[19,20] Statistical corrections have been applied to all the rate and equilibrium constants given in this and other Brønsted plots. For substrates having two equivalent nitrogen atoms a correction factor of $^1/_2$ was employed.

A Hammett plot for methylation of the substituted pyridines has ρ = −2.30 (r = 0.99). Others have reported ρ = −2.94 for the ethylation of substituted pyridines in nitrobenzene at 60°.[20]

The good agreement of our results with β as well as ρ values from other studies serves to establish the validity of our kinetic method and shows that valid correlations may be made between rate constants obtained using DMSO as a solvent and pK_a values derived from aqueous solution studies.

Some uncertainty has existed concerning the position of quaternization of cinnoline.[21] Ultraviolet absorption data are said to indicate that N-2 is the more reactive center.[22] We have found that methylation of cinnoline gives two products in about a 9:1 ratio, the minor product having its *N*-methyl signal at lower field. Our conclusion that N-2 is more reactive than N-1 follows from a consideration of chemical shifts and reactivity of model compounds. Because the *N*-methyl peak of *N*-methylquinolinium ion occurs at lower field than that of *N*-methylisoquinolinium ion, the smaller peak in the spectrum of methylated cinnoline was assigned to the N-1 isomer. Moreover, comparison of pyridine and quinoline rate data shows that fusion of a benzene ring onto the 2,3 positions of pyridine leads to an eightfold rate retardation while 3,4 fusion, as in iso-

Table I. Results of Competition Experiments to Give Rate Constant Ratios for the Methylation of Nitrogen Heterocycles with Methyl Iodide in DMSO at 23° [a]

Heterocycle	Competition standard: Pyridazine	Competition standard: 1,10-Phenanthroline
Pyridine	4.0 (1.0)	
3-Methylpyridine	6.6 (1.6)	
3-Fluoropyridine	0.60 (0.15)	
3-Chloropyridine	0.56 (0.14)	2.90 (0.14)
3-Cyanopyridine		1.11 (0.053)
3,5-Dichloropyridine		0.46 (0.022)
Pyrazine		0.74 (0.036)
Quinoline		2.2 (0.11)
Isoquinoline	4.60 (1.2)	
Cinnoline	1.24[b] (0.31)	
Pyridazine	(0.25)	
Pyrimidine[c]	1.25[d] (0.044)	
Phthalazine	0.50[e] (0.58)	
1,10-Phenanthroline	(0.047)	

[a] Relative rate constants compare heterocycle to competition standard. Results are statistically corrected when two equivalent nitrogen atoms are present. Rate constant ratios in parentheses refer to pyridine as a standard. [b] Corrected to reflect reaction at N-2 only. [c] 2.1 relative to 3,5-dichloropyridine. [d] Relative to pyrazine. [e] Relative to isoquinoline.

(13) R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, **90**, 319 (1968); S. Oae, Y. Kadoma, and Y. Yano, *Bull. Chem. Soc. Jap.*, 42, 1110 (1969).
(14) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967).
(15) T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).
(16) C. K. Ingold and F. R. Shaw, *J. Chem. Soc.*, 2918 (1927).
(17) L. W. Deady and J. A. Zoltewicz, *J. Amer. Chem. Soc.*, **93**, 5475 (1971).
(18) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964).
(19) K. Clarke and K. Rothwell, *ibid.*, 1885 (1960).
(20) A. Fischer, W. J. Galloway, and J. Vaughan, *ibid.*, 3596 (1964).
(21) M. H. Palmer and B. Semple, *Chem. Ind. (London)*, 1766 (1965).
(22) D. E. Ames, G. V. Boyd, A. W. Ellis, and A. C. Lovesey, *ibid.*, 458 (1966); D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.*, 283 (1964).

Table II. Kinetic Data for Reaction between Nitrogen Heterocycles and *p*-Nitrophenyl Acetate in Water at 25.0° [a]

Substrate	$[B]_t$, M [b]	pH	pK_a	k_ψ, sec^{-1}	k_2, M^{-1} sec^{-1}
Pyridine	0.63	5.42	5.37	6.3×10^{-4}	1.9×10^{-3}
	1.06	5.36	5.31	9.0×10^{-4}	1.6×10^{-3}
	1.91	5.60	5.15	17.3×10^{-4}	1.2×10^{-3}
3-Methylpyridine	0.42	5.19	5.74	5.0×10^{-4}	5.55×10^{-3}
	0.64	5.12	5.67	6.5×10^{-4}	4.65×10^{-3}
3-Chloropyridine	0.59	2.70	3.00	2.85×10^{-6} [c]	1.5×10^{-5}
	0.73	2.62	2.96	3.50×10^{-6} [c]	1.5×10^{-5}
Phthalazine[d]	0.30	3.33	3.33	1.5×10^{-4}	1.0×10^{-3}
	0.50	3.22	3.22	1.8×10^{-4}	7.2×10^{-4}
Pyridazine[d]	0.21	2.53	2.49	1.0×10^{-5}	8.9×10^{-5}
	0.41	2.47	2.45	2.0×10^{-5}	9.65×10^{-5}
	0.78	2.44	2.41	3.4×10^{-5}	8.4×10^{-5}
	1.02	2.87	2.38	5.7×10^{-5}	7.45×10^{-5}
	1.04	2.41	2.38	4.85×10^{-5}	9.0×10^{-5}
	1.63	2.82	2.33	6.0×10^{-5}	4.9×10^{-5}
	2.04	2.80	2.31	6.4×10^{-5}	4.15×10^{-5}

[a] 0.5 ionic strength. [b] Total concentration of substrate. [c] Corrected for ester hydrolysis using k_{H_2O} taken from ref 27. [d] pK_a and k_2 values are not statistically corrected for two equivalent nitrogen centers. However, corrections are made when Brønsted plots are constructed from these data.

quinoline, results in a 15% rate acceleration. That is, isoquinoline methylates faster by a factor of 11 than quinoline. (This value is similar to the value of 8.2 reported for methylation of these two isomers in acetonitrile.[23]) Comparison of rate data for cinnoline (major isomer) and pyridazine shows that the former is 24% more reactive. The rate acceleration resulting from benzo fusion is similar to that in the isoquinoline–pyridine case and indicates N-2 is the major site of methylation.

Quinazoline was studied to provide a check on the cinnoline analysis. Methylation results in the formation of two products in about an 8:1 ratio, the minor product being at lower field. Again quinoline and isoquinoline serve as model compounds and suggest that about an 11:1 isomer ratio is expected for the products of methylation of quinazoline. The similarity between the observed and predicted isomer ratio as well as the chemical shifts suggests that quinazoline methylates largely at N-3. Although other assignments have been reported, our conclusion agrees with the recent report that methylation of quinazoline in ethanol gives a 5:1 isomer ratio, N-3 being favored.[24]

When the results for all the heterocycles are added to the Brønsted plot, two types of deviations are noted, Figure 1. Quinoline and 1,10-phenanthroline alkylate more slowly than predicted by their pK_a values. Quinoline is 8 times and 1,10-phenanthroline is 12 times less reactive. These deviations probably reflect steric hindrance to alkylation. Note that isoquinoline fits the pyridine correlation line. However, all three diazines and the benzologs phthalazine and cinnoline (N-2) are more reactive than indicated by their pK_a values. The positive deviations are about a factor of 3 for phthalazine, cinnoline, and pyridazine and only 38% for pyrimidine. Since a range of pK_a values[25] (0.5–1.1) has been reported for pyrazine, the deviation in the Brønsted plot is uncertain in magnitude. Unfortunately it is difficult to obtain an accurate pK_a value when the value is low.[26] However, positive rate deviations are obtained for pyrazine over this entire pK_a range; the maximum is a factor of two.

Acetylation. Rates of reaction of three pyridines, pyridazine, and phthalazine with PNPA in water at 0.5 ionic strength and 25.0 ± 0.1° were obtained. These studies employed the heterocycle both as reactant and buffer. Results are given in Table II.

Second-order rate constants, k_ψ/[B], where [B] is the concentration of unprotonated buffer (heterocycle), generally decrease as the total concentration of heterocycle increases, Table II. For pyridazine, k_2 varied by about a factor of two. This variation is similar in magnitude to that found in the K_a value for pyridazine.

The pK_a value of the heterocyclic nucleophile was calculated using eq 2, the measured pH and the buffer

$$pK_a = pH + \log [BH^+]/[B] \quad (2)$$

ratio given by the stoichiometry of the buffer preparation. Solutions used in the kinetic studies were employed for this purpose. The K_a of the heterocycle was found to increase as the total amount of heterocycle increased. However, the variation is small. For example, a tenfold change in the total concentration of pyridazine, the most extensively studied substrate, results in an increase in K_a by a factor of 1.5.

The similarity in the changes of k_2 and K_a with varying pyridazine concentration suggests a common cause. As the pyridazine concentration increases pyridazine becomes less nucleophilic and less basic. This result is likely to be due to association of the heterocyclic molecules at higher concentrations. Similar explanations have been advanced to account for the dependence of the second-order rate constant on the concentration of pyridine nucleophiles in other reactions.[27,28] The variations in k_2 encountered here are not likely to be associated with a change in the rate-determining step in the reaction of the nucleophile with PNPA.[29]

Because of the association of the nucleophile, k_2 values obtained at >1 M concentration were discarded. Values then were averaged. Our average k_2 value of 1.75×10^{-3} for pyridine is similar to values of 1.67,[3]

(23) R. A. Y. Jones and N. Wagstaff, *J. Chem. Soc. D*, 56 (1969).
(24) J. W. Hunting and W. G. Meathrel, *Can. J. Chem.*, 48, 3449 (1970).
(25) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.
(26) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.
(27) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 90, 2622 (1968).
(28) A. J. Kirby and W. P. Jencks, *ibid.*, 87, 3209 (1965).
(29) S. L. Johnson, *Advan. Phys. Org. Chem.*, 5, 237 (1967).

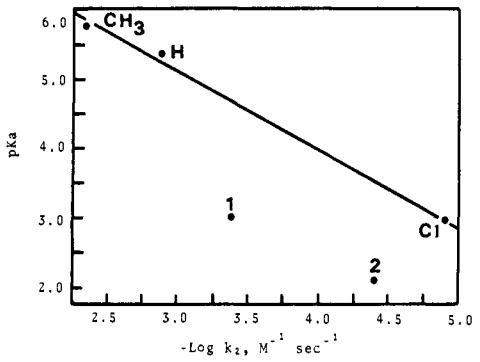


Figure 2. Brønsted plot of pK_a *vs.* the second-order rate constants for acetylation of heteroaromatic nitrogen nucelophilies by PNPA in water at 25°. The line is drawn through points for pyridine nucleophilies. Values for phthalazine and pyridazine are given by points 1 and 2, respectively.

1.78,[30] and 2.83 × 10^{-3} [27] M^{-1} sec^{-1} reported earlier. But our value for 3-methylpyridine, 4.10 × 10^{-3}, is larger than a reported value of 2.62 × 10^{-3} M^{-1} sec^{-1} (26.2°).[31]

A Brønsted plot was constructed using results for pyridine and 3-methyl- and 3-chloropyridine. Our average K_a values were employed. The Brønsted correlation line is given by eq 3; the slope of this plot,

$$\log k_2 = 0.89pK_a - 7.55 \quad (3)$$

Figure 2, is 0.89 and is to be compared with values of 0.8[27,32] and 1.08[30] found for other pyridine nucleophiles reacting with PNPA.

Rate constants for pyridazine and phthalazine deviate positively from the Brønsted line established by pyridine nucleophiles, Figure 2. These two substrates react with PNPA about 20 and 30 times faster, respectively, than predicted.

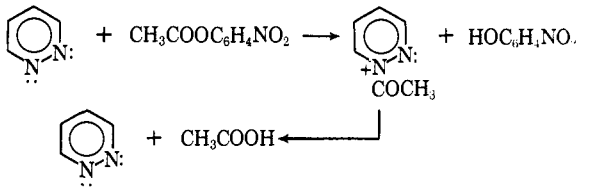
No attempt was made to study pyrimidine and pyrazine nucleophiles. In the absence of a substantial rate acceleration it is expected that both would react with PNPA at inconveniently slow rates and that the water-catalyzed hydrolysis of PNPA would constitute the major reaction.[27]

Discussion

Consider first a mechanism for the reaction of heteroaromatic nitrogen nucleophiles with PNPA.[29] It has been shown that pyridine nucleophiles react with PNPA by a nucleophilic catalysis mechanism.[27,29] It seems very likely that diazine nucleophiles react by the same pathway. This mechanism involves addition of the nucleophile to the ester to give an *N*-acetyl intermediate which in subsequent fast steps hydrolyzes to give acetic acid and regenerated heterocycle.[33] Scheme I illustrates the mechanism for pyridazine.

The nucleophilicities of the α-diaza compounds considered here are estimated from their pK_a values. But the relationships between pK_a values and structures are not entirely clear.[34] Hydrogen-bonding studies suggest that the pK_a values for pyridazine and phthalazine are abnormally large.[35] If "corrected" pK_a values are employed, then the rate enhancements become even greater than those given here. Moreover, conflicting points of view have been advanced concerning the influence of pair–pair electron interactions on pK_a values and on rate constants.[4-6]

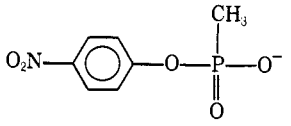
Scheme I



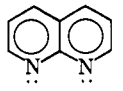
The magnitudes of the rate accelerations found for the diaza heterocyclic nucleophiles should be compared with those found for authentic α-effect nucleophiles. For example, rate factors reflecting accelerations in reactions with PNPA are.[3,27,36]: $(CH_3)_2NOH$, 150; $HONH_2$, 205; H_2NNH_2, 14; CH_3OO^-, 2; HOO^-, 7; and OCl^-, 460.

Note that the apparent magnitudes of rate accelerations often are highly dependent on the class of reference nucleophiles.[30,32] We have employed the reactivities of pyridine bases as reference standards throughout.

Interestingly, pyridazine and hydrazine show no rate enhancements in their reactions (SN2(P)) with *p*-nitrophenyl methylphosphonate anion (VI). But other α-effect nucleophiles do show moderate rate accelerations toward VI.[37]



VI



VII

The rate enhancements found for the α-diaza nucleophiles pyridazine, phthalazine, and cinnoline are in the lower end of the range of accelerations reported for authentic α-effect nucleophiles. Toward methyl iodide these three nucleophiles show only about a threefold acceleration. But toward PNPA, pyridazine and phthalazine react about 20 and 30 times faster than predicted. However, the α-diaza compounds, by having unshared electron pairs on adjacent atoms and by deviating positively from Brønsted plots, meet the criteria for the class, α-effect nucleophiles. Therefore, they should be added to this classification as new members.

Other geometrical arrangements of heteroatoms in heterocyclic molecules should be considered as possibilities which can give rise to unusual nucleophilicity reactivity. One may be found in 1,8-naphthyridine (VII) where the nitrogen atoms with their unshared electron pairs are in a peri relationship. This nucleophile shows approximately a fourfold rate acceleration in its reaction with methyl iodide.[5,38]

(30) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).
(31) M. L. Bender and B. W. Turnquest, *J. Amer. Chem. Soc.*, **79**, 1656 (1957).
(32) T. C. Bruice and R. Lapinski, *ibid.*, **80**, 2265 (1958).
(33) A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5432, 5442 (1970).
(34) A. Albert in "Physical Methods in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, Chapter 1; J. Clark and D. D. Perrin, *Quart. Rev., Chem. Soc.*, **18**, 295 (1964).
(35) L. Joris and P. v. R. Schleyer, *Tetrahedron*, **24**, 5991 (1968).
(36) Values calculated using eq 3.
(37) H. J. Brass, J. O. Edwards, and M. J. Biallas, *J. Amer. Chem. Soc.*, **92**, 4675 (1970); E. J. Behrman, M. J. Biallas, H. J. Brass, J. O. Edwards, and M. Isaks, *J. Org. Chem.*, **35**, 3069 (1970).
(38) We have calculated this value using known rate data for pyridine[39] and an assumed Brønsted relationship with $\beta = 0.36$. pK_a values are taken from ref 25.
(39) C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells, *J. Chem. Soc.*, 6797 (1965).

Although we have so far considered the possible influence of pair–pair interactions on the reactivities of nucleophiles or bases, such interactions may also influence the rates of reaction of electrophiles or acids. Pair–pair electron interactions may influence the rates of deprotonation of heteroaromatic carbon acids such as pyridine and the diazines. Here this interaction results as the carbon acids are converted to their conjugate bases and results in rate deceleration. Such an interaction may account, at least in part, for the observation that anion VIII is formed nine times less readily than anion IX.[40]

VIII

IX

There now are a number of examples of systems which have unshared electron pairs and show usual reactivities. Although it seems likely that the unusual reactivity is associated with electron-pair interactions, this conclusion can be accepted only tentatively. The conclusion will become compelling when it is possible to translate molecular orbital splitting energies into rate factors. Moreover, any general theory associating pair–pair interactions and rate accelerations needs to consider not only electron pairs which are α but also pairs which have other geometrical arrangements as well.[40a]

Experimental Section

Materials. All compounds were commercially available and were used as received. Pyridine was dried over KOH pellets. DMSO was dried over molecular sieves.

Relative Rates of Methylation with Methyl Iodide in DMSO. Details of the method appear elsewhere.[17] Solutions were ~0.25 *M* in methyl iodide. Reference (rate) standards were 1,10-phenanthroline for the slower reactions and pyridazine. Each of these standards was compared directly with 3-chloropyridine. Phthalazine was compared with isoquinoline, pyrimidine with pyrazine, and 3,5-dichloropyridine.

(40) J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Amer. Chem. Soc.*, **91**, 5501 (1969).

(40a). NOTE ADDED IN PROOF. For a comparison of the reactivities of the three diazines and phthalazine toward 2,4-dinitrophenyl acetate, see J. A. Zoltewicz and H. L. Jacobson, *Tetrahedron Lett.*, 189 (1972).

Table III. Chemical Shifts of the *N*-Methyl Group of Heteroaromatic Methiodides in DMSO[a]

Methiodide	τ	Methiodide	τ
Pyridine	5.53	Quinoline	5.31
3-Methylpyridine	5.56	Isoquinoline	5.38
3-Fluoropyridine	5.48	Phthalazine	5.30
3-Chloropyridine	5.51	Cinnoline, N-1	4.86
3-Cyanopyridine	5.36	N-2	5.03
3,5-Dichloropyridine	5.46	Quinazoline, N-1	5.38
Pyridazine	5.30	N-3	5.48
Pyrimidine	5.56	1,10-Phenanthroline	4.80
Pyrazine	5.45		

[a] The DMSO satellite peak τ 6.23 served as a reference standard.

Chemical shifts for the *N*-methyl peaks of methylated heterocycles are listed in Table III.

All the methiodides studied here have been reported.[18,21,23,41–45] The nmr spectra of diazine methiodides were compared with those of authentic samples.[46]

Kinetics of Acetylation by *p*-Nitrophenyl Acetate. Pseudo-first-order rate constants, k_ψ, for reactions between nitrogen heterocycles and *p*-nitrophenyl acetate in aqueous solution at 25.0° and 0.5 ionic strength were obtained by monitoring the formation of *p*-nitrophenol at 330 nm. Buffer solutions consisted of the heterocycle, HCl, and KCl. It was assumed that the concentration of protonated heterocycle equals the concentration of added HCl. Buffer solutions were also employed as optical blanks. Reactions were initiated by adding a drop of the ester in ethanol to a cuvette thermostated inside the Zeiss PMQ II spectrophotometer.

Second-order rate constants were obtained by dividing k_ψ by the concentration of unprotonated heterocycle. Hydrolysis of the ester was important only in the case of 3-chloropyridine; known data[27] were employed to make corrections which amounted to ~10% of the total rate. pH measurements were made according to the method of Bates.[47]

Acknowledgment. A conversation with Professor John O. Edwards aroused our interest in the α effect. This work was kindly supported by the National Science Foundation (GP-9488).

(41) R. L. Letsinger and R. Lasco, *J. Org. Chem.*, **21**, 764 (1956); A. E. Blood and C. R. Noller, *ibid.*, **22**, 844 (1957).

(42) N. Whittaker, *J. Chem. Soc.*, 1646 (1953).

(43) C. T. Bahner and L. L. Norton, *J. Amer. Chem. Soc.*, **72**, 2881 (1950).

(44) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965.

(45) B. E. Halcrow and W. O. Kermack, *J. Chem. Soc.*, 155 (1946).

(46) Samples kindly supplied by Dr. L. S. Helmick.

(47) R. Bates, "Determination of pH. Theory and Practice," Wiley, New York, N. Y., 1964.