(HQ) was obtained from J. T. Baker Chemical Co. and was recrystallized from a 50% water–ethyl ether solution before use.

Spectroquality N,N-dimethylformamide containing approximately 0.03% water was obtained from Eastman Organic Chemicals. The solvent was distilled from anhydrous $CuSO_4$ before use.

Tetra-*n*-propylammonium perchlorate was employed as supporting electrolyte throughout. The salt was prepared and purified as previously described.[8]

Acknowledgment. The financial support of the Robert A. Welch Foundation (Grant No. AO-337) and Midwestern University is gratefully acknowledged.

Unusual Influence of Nitrogen on Rates of Anion Formation. Hydrogen–Deuterium Exchange of Pyridine and the Diazines[1,2]

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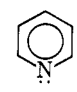
Abstract: Rates of hydrogen–deuterium exchange of pyridine (I), pyrimidine (II), pyridazine (III), and pyrazine (IV) in CH_3OD–CH_3ONa at 164.6° were obtained by an nmr method. Relative rates for I at positions 2,6:3,5:4 are 1.0:9.3:12, for II at 2:4,6:5 are 1.0:3.2:48, and for III at 3,6:4,5 are 1.0:14. Log partial rate factors for nitrogen are *ortho*, 1.31; *meta*, 2.43; *para*, 2.46. Activation at a center *ortho* to nitrogen is less than at a *meta* or *para* position. Exhange is believed to take place by simple deprotonation reactions. The unusual acidity pattern may be the result of two reinforcing factors. They are (1) pair–pair electron repulsion between the carbanion and nitrogen and (2) decreased s character in the *ortho* CH bond associated with an increased *endo* ring angle.

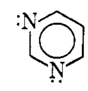
The electron-attracting inductive effects of fluoro and oxygen-containing substituents are expected to facilitate the formation of carbanions at adjacent centers. However, a number of examples now have been found indicating that these first-row atoms either may retard anion formation or may increase the rate of anion formation to a smaller degree than would be predicted.[4,5] These deviations from expectation are larger for fluorine. The effects of fluorine and of oxygen on carbanion formation are said to be determined by the state of hybridization of the carbanion. When the anion is pyramidal net stabilization results; when the anion is part of a planar system there may be destabilization.[4,5]

Nitrogen, another first-row atom, also is expected to facilitate the formation of carbanions by means of an inductive effect. Contrary to a prediction based upon inductive activation alone, we have found that nitrogen does not facilitate the formation of carbanions at adjacent positions to the degree that it facilitates anion formation at more removed centers.

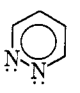
Rates of hydrogen–deuterium exchange of pyridine (I), pyrimidine (II), pyridazine (III), and pyrazine (IV) in CH_3OD–CH_3ONa were determined. In the case of these substrates, H–D exchange takes place more rapidly at those positions which are more removed from the activating nitrogen atom(s).



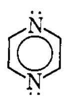
I



II



III



IV

Results

Deuterodeprotonation of I–IV in CH_3OD–CH_3ONa was followed using nmr.[6] Determination of rate constants is complicated by the reverse reaction, D–H exchange, since the solvent pool of deuterium is not "infinitely" large relative to the hydrogen pool of substrate. Exchange reactions of I–III are further complicated because there are several positions in each substrate which introduce hydrogen into the medium at different rates. Some of the isotope lost from a less reactive position comes back into a more reactive site of substrate. The effective equilibrium hydrogen content of a position in I–III may vary with time and may be a function of the reactivity of the other positions. For the positions of IV, position 5 of II, and 4,5 of III it was possible to obtain a constant equilibrium value. But for all positions of I and 2 and 4,6 of II it was practical to obtain a single, composite equilibrium value.

In order to evaluate the effect of back-D–H exchange on the magnitude of the rate constants obtained using the standard first-order rate expression for reversible isotope exchange,[7,8] the data were treated in another way. By pretreating the data using a graphical integration, it is possible to correct for back-D–H exchange and to obtain a linear first-order rate plot which does not employ the equilibrium hydrogen concentration of

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(1) Taken in part from the Ph.D. dissertation of C. L. Smith, University of Florida, 1968.

(2) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 31–April 5, 1968, Abstract P-128.

(3) National Science Foundation Predoctoral Fellow, 1967–1968.

(4) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Am. Chem. Soc.*, **89**, 5911 (1967), and references cited therein.

(5) A. Streitwieser, Jr., and F. Mares, *ibid.*, **90**, 2444 (1968).

(6) For the nmr spectra of I–IV, see J. B. Merry and J. H. Goldstein, *ibid.*, **88**, 5560 (1966); J. N. Murrell and V. M. S. Gil, *Trans. Faraday Soc.*, **61**, 402 (1965); and A. H. Gawer and B. P. Dailey, *J. Chem. Phys.*, 42, 2658 (1965).

(7) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, pp 192–193.

(8) J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, 34, 1405 (1969).

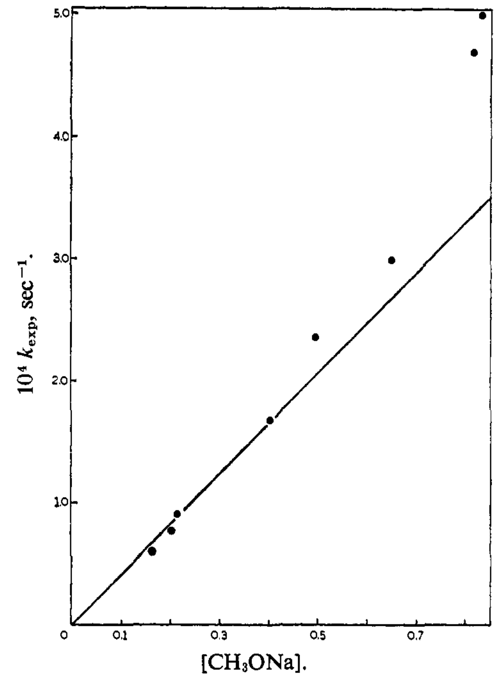

Figure 1. Dependence of the first-order rate constants, k_{exp}, for H-D exchange of the 4,6 positions of pyrimidine (II) on CH_3ONa concentration. Note the positive "salt effect."

substrate.[9] Treatment of the data for exchange of I at 190° in this way gave rate constants which were about 20–30% smaller than those obtained using the standard rate expression. Because of this satisfactory agreement the standard, less laborious method of calculation was employed throughout.

Figure 1 illustrates how the pseudo-first-order rate constants, k_{exp}, for exchange at the 4,6 positions of II vary with the concentration of $NaOCH_3$. A positive "salt effect" is observed; second-order constants, $k_2 = k_{exp}/[CH_3ONa]$, increase in value at larger base concentrations. Such an effect has been reported in other hydrogen-exchange reactions.[10] At lower base concentrations, the order in CH_3ONa was 1.1 for all positions in the diazines. Figures 2 and 3 show the dependence of k_{exp} on [CH_3ONa] for the diazines. Second-order constants for I–IV are given in Table I. The constants for 2,6 of I and 2 of II are likely to have the greatest uncertainty, since exchange was followed for only 1–2 half-lives.

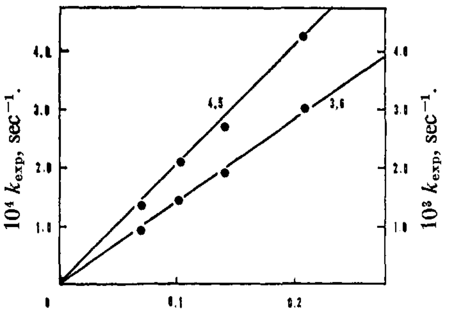

Figure 2. Dependence of the first-order rate constants, k_{exp}, for H-D exchange of pyridazine (III) on CH_3ONa concentration. The left ordinate applies to the 3,6 positions and the right to the 4,5 positions.

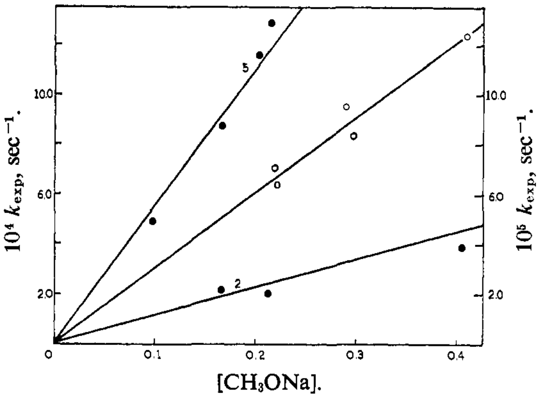

Figure 3. Dependence of the first-order rate constants, k_{exp}, for H-D exchange of pyrimidine (II) (●) and pyrazine (IV) (○) on CH_3ONa concentration. Left ordinate applies to the 5 position of II and the right to IV and to the 2 position of II.

Table I. Rate Constants for the Deuteration of Pyridine and the Diazines in CH_3OD-CH_3ONa[a]

Compound[b]	*T*, °C[c]	Position	k_2, M^{-1} sec^{-1}
Pyridine[d]	164.6[e]	2,6[f]	3.2×10^{-6}
		3,5[g]	3.0×10^{-5}
		4[h]	3.8×10^{-5}
	190.6[i]	2,6	3.1×10^{-5}
		3,5	2.6×10^{-4}
		4	3.7×10^{-4}
	203.5[j]	2,6	8.9×10^{-5}
		3,5	7.5×10^{-4}
		4	1.2×10^{-3}
Pyrimidine[k]	164.6	2	1.2×10^{-4}
		4,6	3.9×10^{-4}
		5	5.6×10^{-3}
Pyridazine[k]	164.6	3,6	1.4×10^{-3}
		4,5	2.1×10^{-2}
Pyrazine[k]	164.6	2,3,5,6	3.1×10^{-4}

[a] Concentrations corrected for thermal expansion. [b] 0.4–0.8 *M*. [c] ±0.5°. [d] [$NaOCH_3$], 0.6–0.8 *M*. [e] Average of three runs. [f] E_a = 34 kcal/mole. [g] E_a = 33 kcal/mole. [h] E_a = 36 kcal/mole. [i] One run. [j] Average of two runs. [k] Number of runs indicated in each figure.

The ratio of the second-order constants for the 2,6, 3,5, and 4 positions of I at 164.6° is 1.0:9.3:12 and 1.0:8.4:14 at 203.5°, respectively. Positional reactivity does not show a marked temperature dependence. It is to be noted that this reactivity pattern is also found in other solvents. This same positional ratio for exchange in D_2O-NaOD at 200° is 1:2.3:3.0[11] and 1:72:~700 at −25° in NH_3-$NaNH_2$.[12] Relative rates of exchange of the 2, 4,6, and 5 positions of II are 1.0:3.2:48, respectively. Similarly, the 3,6 and 4,5 positions of III are 1.0:14, respectively. These results show that for I and III the least reactive center is that adjacent to nitrogen, and for II it is the position between two nitrogen atoms.

The results of a kinetic study similar to our own appeared recently. Rates of hydrogen exchange of pyridine-2, -3, or -4-*d* and pyrimidine-5-*d* or -2,4,6-d_3 in CH_3OH and also of pyrazine in CH_3OD were obtained using 0.6 *M* CH_3OK.[13] We agree about the positional

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(9) A. Streitwieser, Jr., and F. Mares, *J. Am. Chem. Soc.*, **90**, 644 (1968).

(10) W. D. Kollmeyer and D. J. Cram, *ibid.*, **90**, 1784 (1968).

(11) J. A. Zoltewicz and C. L. Smith, *ibid.*, **89**, 3358 (1967).

(12) I. F. Tupitsyn and N. K. Seminova, *Tr. Gos. Inst. Prikl. Khim.*, **49**, 120 (1962); *Chem. Abstr.*, 60, 6721c (1964).

(13) I. F. Tupitsyn, N. N. Zatzepina, A. W. Kirowa, and J. M. Kapustin, *Reaktsionnaya Sposobnost Organ. Soedin., Tartusk. Gos. Univ.*, **5**, 601 (1968).

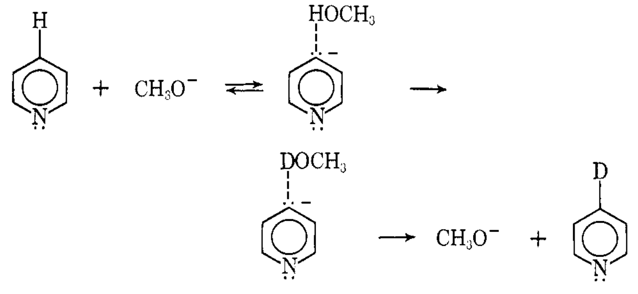
reactivity order for I. Differentiation between the 4,6 and 2 positions of II was not reported. In addition, rate constants are smaller than ours by factors ranging up to about 5. For example, our rate constant for IV is 4.7 times larger than the reported constant (extrapolated). In this study isotope analyses were carried out using mass spectrometry. Since data regarding the composition of reaction mixtures and the method of calculating rate constants are not available to us, we are unable to account for differences.

The relative reactivity of the 3,5 and 4 positions of pyridine-d_5 toward $NaNH_2$ was determined in boiling NH_3 of such a volume that the proton pool was large enough to prevent back-deuteration effectively. Comparison of the one-point, pseudo-first-order rate constants indicates that the 4 position underwent exchange 3.3 times faster than the 3,5 positions. There was no detectable exchange at 2,6. Combining our and earlier[12] data gives a 1.0:72:240 ratio for the rates of H-D exchange of the 2,6:3,5:4 positions of pyridine in NH_3.[14]

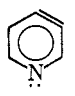
Discussion

Pyridine and the diazines probably undergo base-catalyzed H-D exchange by a common mechanism, since I-III show the same type of reactivity pattern. A position adjacent to one nitrogen or between two nitrogens is less reactive than more removed centers. This mechanism probably involves deprotonation by base to give a H-bonded anion which then abstracts a deuteron from solvent, Scheme I.

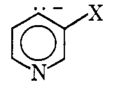
Scheme I



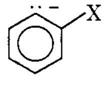
Several facts from a variety of sources support this contention. (1) Pyridine N-oxide and N-methylpyridinium ion undergo hydrogen exchange by such a mechanism.[15] (2) 3-Halopyridines in NH_3 form 3,4-pyridyne (V). 3-Halo-4-pyridyl anions (VI) are likely to be generated during the dehydrohalogenation reaction.[16,17] (3) The partial rate factor for an *o*-chloro atom obtained from the rates of H-D exchange of chloropyridines in methanol[17] is similar in magnitude to that derived from the rates of H-D exchange of chloropyridine N-oxides in methanol[8] (800 at 75° *vs.* 1900 at 50°). This suggests a common mechanism of H-D exchange. (4) Rates of base-catalyzed H-D exchange at the 4 position of 3-substituted pyridines vary in a way consistent with inductive activation by the substituents.[13,16,17] Similarly, inductive effects control the reactivity of the *ortho* position of substituted benzenes during H-D exchange.[18] Phenyl anions (VII) are likely intermediates. (5) Lithium derivatives of pyridine[19] and the diazines[20] are known. These undergo reactions characteristic of carbanion nucleophiles. (6) Loss of a proton from pyridine to give pyridyl anion is similar to



V



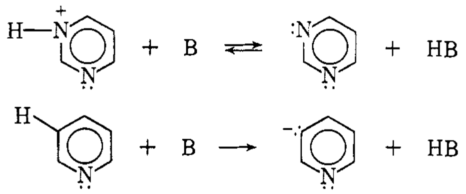
VI



VII

the loss of a proton from protonated diazine to give diazine. Consider the deprotonation of the conjugate acid of II and the loss of proton from the 3 position of I, Scheme II. In both the proton is lost

Scheme II



from a position *meta* to an annular nitrogen. Similar spacial relationships exist for deprotonation at positions *ortho* and *para* to nitrogen in pyridine and in the conjugate acids of the other two diazines. Qualitatively, the equilibrium acidity pattern for the protonated diazines is similar to the kinetic acidity pattern for H-D exchange of I. The *ortho*:*meta*:*para* equilibrium acidity ratio is 1.0:10:50[21-23] while the kinetic acidity ratio is 1.0:9.3:12. This suggests that deprotonation of pyridine and the conjugate acids of the diazines occurs by similar mechanisms and that both processes are influenced by similar factors. All these diverse observations when taken together provide support for a mechanism of H-D exchange of I-IV which involves carbanion formation by simple proton transfer.

The diazines undergo H-D exchange more rapidly than pyridine, indicating the activating effect of an annular nitrogen atom. Assuming that the effects of nitrogen on exchange rates are additive, partial rate factors for nitrogen may be calculated. Nitrogen may be situated *ortho*, *meta*, or *para* to the reactive site. Using logarithmic symbolism exchange at each position of substrate may be expressed as a linear combination of the various nitrogen rate factors and the rate constant, k_0, for hydrogen exchange of benzene, the reference compound.[24] A set of simultaneous, linear equations

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(14) The 3,5:4 ratio had been determined indirectly by combining rate data for exchange in NH_3 and in ND_3.[12]

(15) J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *J. Am. Chem. Soc.*, **90**, 5939 (1968).

(16) J. A. Zoltewicz and C. L. Smith, *ibid.*, **88**, 4766 (1966).

(17) J. A. Zoltewicz and C. L. Smith, *Tetrahedron*, in press.

(18) G. E. Hall, R. Piccolini, and J. D. Roberts, *J. Am. Chem. Soc.*, 77, 4540 (1955); A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, 1, 156 (1963); C. D. Ritchie and W. F. Sager, *Progr. Phys., Org. Chem.*, 2, 323 (1964).

(19) H. Gilman and S. M. Spatz, *J. Org. Chem.*, 16, 1485 (1951); J. P. Wibaut, A. P. de Jonge, H. G. P. van der Voort, and P. Ph. H. L. Otto, *Rec. Trav. Chim.*, 70, 1054 (1951).

(20) S. Gronowitz and J. Röe, *Acta Chem. Scand.*, 19, 1741 (1965); A. Hirschberg, A. Peterkofsky, and P. E. Spoerri, *J. Heterocyclic Chem.*, 2, 209 (1965).

(21) A. Albert, R. J. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

(22) Although there is some disagreement on the individual K_a values the relative order of acidity of the protonated diazines has been established firmly.[23]

(23) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth Inc., Washington, D. C., 1965, pp 203, 206, 210.

(24) Compounds I-IV are considered to be derivatives of benzene, nitrogen being a "substituent."

for exchange at 165° is given. Logarithmic values for

$$\log k_{(\mathrm{I}\text{-}2,6)} = \log k_0 + o_f^{\mathrm{N}} = -5.50$$

$$\log k_{(\mathrm{I}\text{-}3,5)} = \log k_0 + m_f^{\mathrm{N}} = -4.52$$

$$\log k_{(\mathrm{I}\text{-}4)} = \log k_0 + p_f^{\mathrm{N}} = -4.42$$

$$\log k_{(\mathrm{II}\text{-}2)} = \log k_0 + 2o_f^{\mathrm{N}} = -3.94$$

$$\log k_{(\mathrm{II}\text{-}4,6)} = \log k_0 + o_f^{\mathrm{N}} + p_f^{\mathrm{N}} = -3.41$$

$$\log k_{(\mathrm{II}\text{-}5)} = \log k_0 + 2m_f^{\mathrm{N}} = -2.26$$

$$\log k_{(\mathrm{III}\text{-}3,6)} = \log k_0 + o_f^{\mathrm{N}} + m_f^{\mathrm{N}} - -2.85$$

$$\log k_{(\mathrm{III}\text{-}4,5)} = \log k_0 + m_f^{\mathrm{N}} + p_f^{\mathrm{N}} = -1.69$$

$$\log k_{(\mathrm{IV}\text{-}2,3,5,6)} = \log k_0 + o_f^{\mathrm{N}} + m_f^{\mathrm{N}} = -3.52$$

the rate factors with their average deviations are o_f^{N}, 1.31 ± 0.30; m_f^{N}, 2.43 ± 0.31; and p_f^{N}, 2.46 ± 0.25. Log k_0 is −6.88 ± 0.22. The modest uncertainty in these values shows there is an internal consistency in the rate constants, supports the assumption that all positions react by a common mechanism, and suggests that additivity is reasonably approximated. The annular nitrogen atom is a moderately good activating "substituent," even at this elevated temperature.[25] An *ortho* nitrogen activates about 12 times less than a *meta* or *para* nitrogen.

The pattern of activation by the annular nitrogen, *para* ~ *meta* ≫ *ortho*, is unique.[26] This contrast with the positional reactivity order found for H–D exchange of pyridine N-oxide,[15] N-methylpyridinium ion,[15] and monosubstituted benzenes containing an activating group.[18] In all these exchange follows the order *ortho* ≫ *meta* > *para*.

It is likely that hydrogen exchange of I–IV in CH_3OD is complicated by the effects of internal return.[27] The rate of reprotonation of H-bonded carbanion by CH_3OH is likely to be competitive with the rate of replacement of CH_3OH by CH_3OD to give the precursor to exchanged product, Scheme I. But the observed, unusual reactivity pattern in methanol is not an artifact of internal return, since the same positional reactivity pattern is found for exchange of I in ammonia. Internal return is not likely to be important for hydrogen exchange of I in ammonia.[28] Supporting this are the reports that benzene, which is less acidic than pyridine, shows a kinetic isotope effect[29] $k_{\mathrm{D}}/k_{\mathrm{T}} = 2.3$–2.5 for exchange in ammonia.[30] An isotope effect of this magnitude is not in keeping with the possibility of significant internal return.

We suggest that the decreased reactivity of positions adjacent to nitrogen relative to more removed centers in base-catalyzed hydrogen exchange reactions may be the result of two reinforcing factors—decreased s character in the bond between H and the C adjacent to nitrogen of reactant and repulsive interaction between the electron pairs on nitrogen and the (developing) carbanion.

Rates of carbanion formation are influenced by the amount of s character in the bond being broken.[31] A measure, but a fallible one,[32] of the state of hybridization of an atom may be obtained from bond angles.[33] Pyridine[34] and the diazines[35] do not have the regular geometry of benzene.[36] For example, the difference in the *endo* ring angles at C-5 and C-2 of II is about 12°.[35b] An indication of the influence of such angle changes and associated hybridization changes on the H–D exchange reactivity of I–IV may be obtained from a consideration of pyridine, since the effects of two nitrogen atoms on the magnitude of the angle changes are additive.[37] In pyridine the *endo* angle at C-2 is 4° larger, and the *endo* angles at C-3 and C-4 are 1° 24′ and 1° 54′ smaller, respectively, than the 120° angle found in benzene.[34] This angle change at C-2 indicates there may be a 5% reduction in the s character of the HC-2 bond, relative to benzene. Such a reduction is expected to result in decreased acidity of the HC-2 center. The s character of the HC-3 and HC-4 bonds should increase slightly and this may be associated with an acidity increase. It is to be noted that a change from sp to sp^2 hybridization results in a 17% reduction in s character for a CH bond and that the equilibrium acidity of acetylene is about 10^{11} times greater than that of ethylene.[38]

Limited correlations of the ground-state hybridization of carbon with ^{13}C chemical shifts and with ^{13}C–H coupling constants have been found.[39] Good correlations of total carbon electron densities ($\sigma + \pi$) with ^{13}C and proton chemical shifts exist for a variety of heterocyclic compounds including I–IV.[40] However, we find no correlation between the rates of H–D exchange for all positions of I–IV and ^{13}C chemical shifts[41] or proton shifts[6] or ^{13}C–H coupling constants.[42]

Electron pairs on adjacent atoms may interact repulsively.[43] We suggest that there is electrostatic repulsion between the coplanar nitrogen electron pair and the electron pair of the adjacent anion formed by deprotonation. This unfavorable interaction, present in the transition state for deprotonation and in the intermediate anion, results in destabilization of the anion and brings about a decreased carbon acidity.

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(25) For comparison with other rate factors for base-catalyzed H–D exchange, see ref 8, 13, 17, and 18.

(26) The *para* > *meta* reactivity pattern found for exchange of I in methanol, water,[11] and ammonia[12] is a curious one. Since the reactivity difference is small, it is difficult to provide an unambiguous rationalization for it.

(27) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 3688 (1961); A. Streitwieser, Jr., and H. F. Koch, *ibid.*, **86**, 404 (1964); M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

(28) Since the effects of nitrogen on the exchange rates of I–IV are approximately additive, the effects of internal return on the rate constants must be approximately constant throughout.

(29) A. I. Shatenshtein, A. G. Kamrad, I. O. Shapiro, Y. I. Ranneva, and E. N. Zvyagintseva, *Dokl. Akad. Nauk SSSR*, **168**, 364 (1966).

(30) I. F. Tupitsyn and N. K. Seminova, *Tr. Gos. Inst. Prikl. Khim.*, **49**, 133 (1962); *Chem. Abstr.*, **60**, 1164g (1964).

(31) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 48–52.

(32) D. R. Lide, Jr., *Tetrahedron*, **17**, 125 (1962); L. S. Bartell, *ibid.*, **17**, 177 (1962).

(33) C. A. Coulson, "Valence," 2nd ed, Oxford University Press, London, 1963, Chapter 8.

(34) B. Bak, L. Hansen, and J. Rastrup-Andersen, *J. Chem. Phys.*, **22**, 2013 (1954).

(35) (a) P. J. Wheatley, *Acta Cryst.*, **10**, 182 (1957); (b) *ibid.*, **13**, 80 (1960).

(36) The *endo* angles at C-2 of pyridine N-oxides and pyridinium ions appear to be less than 120°. See P. C. Rerat, *Acta Cryst.*, **15**, 427 (1962); P. G. Tsoucaris, *ibid.*, **14**, 914 (1961); P. A. Laurent, *ibid.*, **21**, 710 (1966).

(37) C. A. Coulson and H. Looyenga, *J. Chem. Soc.*, 6592 (1965).

(38) Reference 31, p 49.

(39) D. M. Grant, *Ann. Rev. Phys. Chem.*, **15**, 489 (1964); J. B. Stothers, *Quart. Rev.* (London), **19**, 144 (1965).

(40) W. Adam, A. Grimison, and G. Rodriquez, *Tetrahedron*, **23**, 2513 (1967).

(41) R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.*, **90**, 697 (1968).

(42) K. Tori and T. Nakagawa, *J. Phys. Chem.*, **68**, 3163 (1964).

(43) K. S. Pitzer, *J. Am. Chem. Soc.*, **70**, 2140 (1948); L. Pauling, *Tetrahedron*, **17**, 229 (1962).

The hybridization effect associated with the increased *endo* angle and the coulombic effect oppose the inductively acidifying effect of the annular nitrogen and may be responsible for the observed unusual acidity pattern.[44]

While the chemistry of the π electrons of heteroaromatic molecules has been explored extensively, new chapters are yet to be written concerning the chemistry of their σ-electron framework.[44a]

Experimental Section

Materials. Pyrimidine and pyridazine, purchased from Aldrich Chemical Co., were purified by vacuum distillation. Pyrazine (Aldrich) was sufficiently pure. $NaOCH_3$ in CH_3OD was prepared by adding freshly cut sodium to CH_3OD in a glove bag under dry nitrogen. This solution was standardized (0.785 *M*) by titration with HCl under nitrogen or by titration with NaOH of an aliquot treated with excess HCl. CH_3OD was prepared from D_2O and $NaOCH_3$ following drying of the salt by heating at 150° for 3 hr under vacuum. Drying with Mg and distillation yielded CH_3OD with approximately 3 mole % CH_3OH (nmr analyses).

Control Experiments. In order to determine whether $NaOCH_3$ is destroyed by reaction with a glass nmr tube during a kinetic run, two tubes containing 0.495 *M* CH_3ONa were heated at 165° for 96.3 hr. Titration indicated a 5.9% decrease in base concentration. Destruction of base by etching is unimportant.

In order to determine the stability of the diazines toward CH_3ONa mixtures of diazine, *p*-xylene internal standard and CH_3OH–CH_3ONa were heated at 165° and the ratio of diazine to standard was obtained periodically using nmr. These ratios remained constant to within ±3%. Pyrimidine was heated in 0.306 *M* CH_3ONa for 71.1 hr; pyrazine and pyridazine were stable in 0.341 *M* CH_3ONa over 75.5 hr.

Kinetic Measurements. Reaction mixtures were prepared in the following way: diazine or pyridine and internal standard (*t*-butyl alcohol or *p*-xylene) were weighed into an nmr tube and CH_3ONa and CH_3OD were added by syringe. The molarity of CH_3ONa was calculated assuming the additivity of volumes and the following densities (grams per milliliter):[45] pyrazine 1.03, pyridine 0.98, pyridazine 1.10, pyrimidine 1.10, *p*-xylene 0.857, and *t*-butyl alcohol 0.779. The tube was sealed and placed into a vapor bath (mesitylene, 164.6°; benzonitrile, 190.6°; and benzyl alcohol, 203.5°). Temperatures were determined with a National Bureau of Standards certified thermometer or with an iron–constantan thermocouple with ice–water reference junction. Peaks in the nmr were scanned repeatedly and average areas were determined.

Assuming there is neither a kinetic nor an equilibrium isotope effect, pseudo-first-order rate constants, k_{exp}, are obtained using the equation[7,8]

$$k_{\mathrm{exp}}t = \frac{[\mathrm{D}]2.30}{[\mathrm{D}] + [\mathrm{H}] + y[\mathrm{Het}]}\log\left(\frac{R_0 - R_e}{R - R_e}\right)$$

The ratio of the area of reacting proton to the area of standard is R; D and H refer to the deuterium and hydrogen content of the solvent at t_0. Rate constants were calculated from plots obtained by visually fitting the best straight line through the points. Reactions generally were followed over 2–3 half-lives. Exchange at the 2,6 positions of pyridine and the 2 position of pyrimidine was observed over 1–2 half-lives.

Equilibrium ratios, R_e, were experimentally determined. When several different positions underwent exchange at similar rates, the same equilibrium value was used for all these positions. For pyridine R_e was determined after about 4 half-lives for exchange at 3,5; this value was used for all positions. For pyridazine separate R_e values were determined for the 3,6 and 4,5 positions. For the 3,6 positions R decreased with time and then increased; the minimum observed value of R was selected to be R_e. Similarly, for pyrimidine R for the 5 position went through a minimum. A composite value representing equilibrium for all positions was employed for R_e of the 2,4,6 positions of pyrimidine.

The value of R_e used in obtaining rate constants determined the selection of y which indicates the approximate number of hydrogen atoms in a heterocycle having undergone exchange when R_e was measured. The value of y was 4 for pyridine, pyrazine, the 2 and 4,6 positions of pyrimidine, and the 3,6 positions of pyridazine; one for the 5 position of pyrimidine; and 2 for the 4,5 positions of pyridazine. The value of the concentration fraction given in the rate equation generally was in the range 0.8–0.9.

Deuterated diazines recovered at the end of a kinetic run were analyzed for deuterium content by low-voltage mass spectrometry. A comparison of the deuterium analysis by nmr and mass spectral analysis was obtained: pyridazine nmr, 80.2% D at 3,6 and 4,5, $d_0 = 0$, $d_1 = 2.2\%$, $d_2 = 14.2\%$, $d_3 = 40.2\%$, and $d_4 = 43.4\%$ (the average per cent D per position indicated by mass spectral analysis is 81.2); pyrimidine nmr, 81.0% D at 2, 83.1% at 4,6, and 80.9% D at 5, $d_0 = 0$, $d_1 = 2.1\%$, $d_2 = 13.7\%$, $d_3 = 39.6\%$, and $d_4 = 44.5\%$ (the average per cent D per position is 82.0 and 81.6% by nmr and mass spectral analysis, respectively).

Pyridine-d_5. A solution of 10 ml of pyridine in about 15 ml of 5 *M* $NaOD$-D_2O was heated at 220° in a stainless steel bomb for 6 hr. Distillation of the ether extract of the reaction mixture afforded 65% of pyridine-d_5, bp 114–115.5°. Analysis by nmr showed H-2, 0.709; H-3, 0.625; and H-4, 0.534. The mass spectrum showed d_0, 0.311; d_1, 0.328; d_2, 0.161; d_3, 0.088; d_4, 0.075; and d_5, 0.037.

Hydrogen–Deuterium Exchange of Pyridine-d_5 in $NaNH_2$–NH_3. To 200 ml of ammonia and a few crystals of ferric nitrate in a flask fitted with an acetone–Dry Ice condenser and magnetic stirrer was added 1 g of sodium in small pieces. When the blue color had dissipated, 2 ml of the above pyridine-d_5 was added. The reaction was quenched after 1 hr by the addition of 4 g of NH_4Cl. After the ammonia evaporated the residue was dissolved in 100 ml of 18% KOH. This was twice extracted with 30 ml of ether. Pyridine, bp 113–116°, was recovered from the dried extracts by distillation. Analysis of this pyridine by nmr showed H-2, 0.725; H-3, 0.733; and H-4, 0.847.

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(44) In thiazole the position between nitrogen and sulfur (C-2) has nearly the same reactivity in H–D exchange as one more removed (C-4): R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *J. Am. Chem. Soc.*, **88**, 4265 (1966).

(44a) Note Added in Proof. Results of extended Hückel theory (EHT) calculations on the carbanions of pyridine and the diazines indicate a dominant effect is destabilization of adjacent carbon electron pairs by nitrogen electron pairs. The calculated positional reactivity pattern for II and III is in agreement with our observed order, and the reactivity trend for the six positions in the three diazines is reproduced in part: W. Adam, A. Grimison, and R. Hoffmann, *J. Am. Chem. Soc.*, **91**, 2590 (1969).

(45) J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Vols. 1 and 2, Elsevier Publishing Co., Inc., New York, N. Y., 1965; "Handbook of Chemistry and Physics," 46th ed, The Chemical Rubber Publishing Co., Inc., Cleveland, Ohio, 1965.