removal of solvent at reduced pressure the product was crystallized in aqueous acetic acid, 66 mg (72%), decomposed above 290°, λ_{max}^{MeOH} 365, 265, and 249 mμ. The acetate VIIIb, prepared by heating VIIIa with acetic anhydride and potassium acetate, had mp 210–213° and λ_{max}^{MeOH} 356, 268, and 238 mμ.

Anal. Calcd for $C_{18}H_{14}O_6$: C, 65.0; H, 4.49. Found: C, 64.9; H, 4.40.

Lithium Aluminum Hydride Reduction of IV. The reduction of IV, performed similar to that of II, gave IX in pink needles in 58% yield, mp 143–145°.

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.4; H, 5.66. Found: C, 67.3; H, 5.81.

Basic Potassium Permanganate Oxidation of IV. The mixture of 100 mg of (0.27 mmole) of IV, 474 mg (3 mmoles) of potassium permanganate, and 20 ml of 1 *N* potassium hydroxide was heated on a steam bath for 1 hr. Ethanol was added to reduce the excess permanganate and the reaction mixture was acidified with 1 *N* HCl and extracted (four times) with ether. The combined ether solution was extracted with a saturated solution of sodium bicarbonate. Acidification of the bicarbonate solution and reextraction with ether gave 14 mg of *m*-hemipinic acid (X), mp 183–190°.[9] Sublimination at reduced pressure dehydrated the acid to its anhydride, mp 176–178°.[9]

Potassium Permanganate Oxidation of IV in Acetone. The solution of 0.5 g (1.4 mmoles) of IV, 0.1 ml of acetic acid, and 0.8 g (5 mmoles) of potassium permanganate in 500 ml of acetone, freshly distilled over potassium permanganate, was stirred at room temperature for 1 hr, and the solvent was removed under reduced pressure. The residue was extracted with 100 ml of hot chloroform and upon removal of solvent 165 mg of product mixture was obtained. This crude mixture was triturated with 10 ml of methanol to rid it of *m*-meconine, and the residue was crystallized in chloroform–methanol mixture, from which 70 mg (15%) of lactone XII was obtained, mp 322–324°, λ_{max}^{MeOH} 362, 348, 270, and 262 mμ, ν (KBr) 1730 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}O_8$: C, 62.5; H, 4.20; OCH_3, 32.6. Found: C, 62.6; H, 4.25; OCH_3, 32.2.

The methanol extract of the oxidation product mixture was evaporated to dryness and chromatographed through a silica gel column (25 g eluted with ethyl acetate) giving 36 mg of *m*-meconine (XI), mp 155–157°.[9]

Irradiation of I in Oxygenated Methanol. The irradiation experiment was conducted as described in deoxygenated methanolic solution except that a slow stream of oxygen was passed through the stirred solution during irradiation.

Irradiation of I with Anthracene. The reaction was carried out under identical conditions as described in the irradiation of I in deoxygenated methanol except that an equimolar (6.7 mmoles) amount of anthracene was added to the solution.

Irradiation of I in Deoxygenated Benzene. In this experiment benzene was used as solvent instead of methanol; otherwise the reaction was performed under identical conditions.

In another experiment the benzene used in the reaction was heated and cooled under a stream of nitrogen, followed by the addition of triethylaluminum to remove last traces of oxygen, and was then vacuum transferred to the reaction flask containing I. The reaction was carried out in a sealed flask.

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Kinetics of Iodination of 1-Alkylpyrazoles. Relative Electrophilic Reactivities of 1-Substituted and 1-Unsubstituted Pyrazoles[1]

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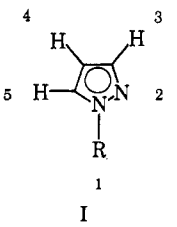
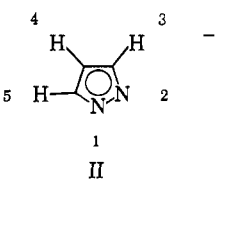
Contribution from the Departments of Chemistry of Colorado State University, Fort Collins, Colorado, and Virginia Polytechnic Institute, Blacksburg, Virginia.
Received July 5, 1967

Abstract: The kinetics of iodination of 1-methylpyrazole, 1-ethylpyrazole, and 1-isopropylpyrazole was studied. The rate laws were found to be the same as that of aniline and the reactivities of these alkyl-substituted pyrazoles followed the inductive order. The rate of iodination of the pyrazole molecule was estimated from that of 1-methylpyrazole and compared with the rate of iodination of the anion of pyrazole. The varying sensitivities of aromatic substrates to particular bases in base-catalyzed reactions was noted and suggestions regarding the transition states of these reactions were made.

The observed rate of iodination of pyrazole (I, R = H) has been shown[2a] to be inversely proportional to the hydrogen ion concentration in aqueous media at constant ionic strength. This dependence is understood if the anion II undergoes electrophilic attack rather than the molecule itself.[2] Since pyrazole is a very weak acid ($K_a \sim 10^{-14}$), it follows that the anion of pyrazole must have far greater electrophilic reactivity than the undissociated molecule. It is of considerable theoretical interest to ascertain how much more reactive the anion is than the corresponding molecule. An indirect approach



I



II

to this problem would be to determine the relative rates of iodination of 1-alkylpyrazoles. Since 1-alkylpyrazoles do not have acidic properties, only the molecule is subject to attack by the electrophile. Accordingly, one purpose of this investigation was to conduct a detailed rate study of the aqueous iodination of 1-alkylpyrazoles,

(1) Supported in part by a Colorado State University Faculty Grant.
(2) (a) J. D. Vaughan, D. G. Lambert, and V. L. Vaughan, *J. Am. Chem. Soc.*, 86, 2857 (1964); (b) J. H. Ridd, *J. Chem. Soc.*, 1238 (1955).

in order that their electrophilic reactivities be compared to that of pyrazole under specified conditions. A second purpose was to infer similarities or differences in the mechanisms of electrophilic substitution reactions of the molecular and anion forms of pyrazoles by comparing their rate laws. Of additional interest is the order of reactivities of 1-alkylpyrazoles, *i.e.*, whether Baker–Nathan[3] or inductive.[3]

Experimental Section

Materials. 1-Methylpyrazole, 1-ethylpyrazole, and 1-isopropylpyrazole were prepared by the method of Dedicher.[4] Each was purified by distillation: 1-methylpyrazole, bp 123° (632 mm), $n^{25}D$ 1.4718; 1-ethylpyrazole, bp 132° (632 mm), $n^{25}D$ 1.4659; 1-isopropylpyrazole, bp 137° (632 mm).

Anal. Calcd for 1-ethylpyrazole ($C_5H_8N_2$): C, 62.47; H, 8.39; N, 29.14. Found: C, 62.65; H, 8.58; N, 29.36.

Anal. Calcd for 1-isopropylpyrazole ($C_6H_{10}N_2$): C, 65.42; H, 9.15; N, 25.43. Found: C, 65.66; H, 9.37; N, 25.49.

Reagent grades of KI, Na_2HPO_4, KH_2PO_4, and $NaNO_3$ were dried at 120° and used without further purification. Reagent grade sublimed iodine was resublimed prior to use.

Kinetic runs were made in aqueous solution adjusted to constant ionic strength of 1.00 *M* with excess 2.50 *M* $NaNO_3$. Some runs were buffered with HPO_4^{2-}–$H_2PO_4^-$ and others were not buffered. In all runs, the ratio of substrate and $[I_3^-]$ was greater than 20 and the ratio of $[I^-]$ and $[I_3^-]$ was also greater than 20. Kinetic runs were made at 30 and 40°. All solutions were prepared at room temperature. Thermal expansions were assumed uniform for all runs at a given temperature, since the ionic strength was the same for each solution. The effect of small variations in solution volume was shown in preliminary experiments to be negligible in comparison to the effect of the temperature changes. The pseudo-first-order rate constants were determined titrimetrically, after the procedure described by Berliner.[5] The product of the iodination of 1-methylpyrazole is known to be 4-iodo-1-methylpyrazole.[6,7] Since pyrazole and nearly all substituted pyrazoles undergo electrophilic substitution in the 4 position in acidic, alkaline, and neutral solution,[6,7] we have assumed that 1-ethyl- and 1-isopropylpyrazoles become iodinated in the 4 position.

Results

The Rate Law. Since 1-isopropylpyrazole (1-*i*-PrPy) is the most reactive of the substrates studied, we used it to determine the rate law and then used the least reactive substrate, 1-methylpyrazole (1-MePy), to test the rate law. In Table I, the rate of iodination is seen to be first order in substrate. Similarly, the expected inverse second-order dependence of the observed rate upon the iodide concentration is shown in Table II. A plot of log k_1^{obsd} against log $[I^-]$ for the iodination of 1-isopropylpyrazole gave a slope of -2.0 ± 0.2.

Table I. Dependence of the Rate of Iodination upon Substrate Concentration (30°)

[Substrate] × 10^2	$k_1^{obsd} \times 10^6$, sec^{-1}	$\{k_1^{obsd}/[substrate]\} \times 10^4$, l. $mole^{-1}$ sec^{-1}
	1-*i*-PrPy[a]	
1.175	6.63	5.65
2.35	14.4	6.12 } 5.82 ± 0.20
3.525	20.0	5.68
	1-MePy[b]	
4.254	20.75	10.0 } 10.3 ± 0.3
6.38	69.3	10.65

[a] $[I^-] = 5.00 \times 10^{-3}$ *M*; $[HPO_4^{2-}] = 0.00$ *M*; $[H_2PO_4^-] = 0.00$ *M*. [b] $[I^-] = 4.00 \times 10^{-3}$ *M*; $[HPO_4^{2-}] = 0.049$ *M*; $[H_2PO_4^-] = 0.046$ *M*.

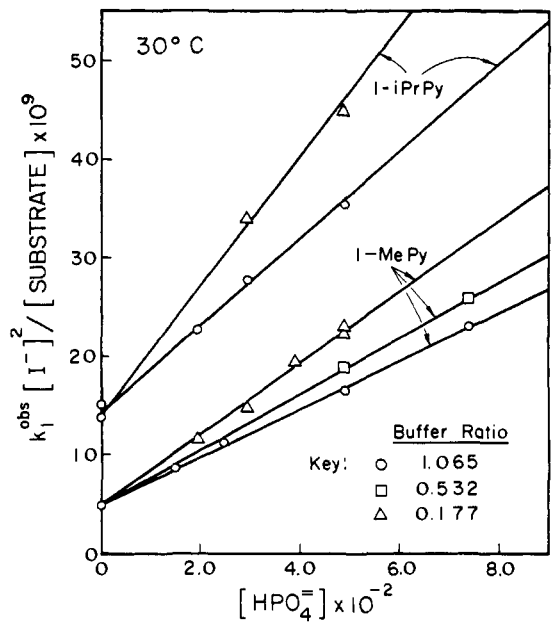


Figure 1. Buffer dependence, 30°.

Figures 1 and 2 exhibit the buffer dependence of the rates of iodination of 1-*i*-PrPy and 1-MePy. The vertical axes represent the observed pseudo-first-order rate constant for the iodination corrected for the dependences upon the substrate and iodide concentrations. The corrected rate constant is seen to depend linearly upon $[HPO_4^{2-}]$ for a given buffer ratio $[HPO_4^{2-}]/[H_2PO_4^-]$. Similarly, the dependence upon $[H_2PO_4^-]$ is observed to be linear if the corrected rate constant is plotted against $[H_2PO_4^-]$, again for constant buffer ratio. In the limit of vanishing buffer, the extrapolated corrected rate constants fall onto the observed corrected rate constants for zero buffer concentration, which clearly indicates the absence of a dependence upon $[H^+]$. The experimental rate law for the iodination is just that found by Berliner[8] for the iodination of aniline

$$-\frac{d[I_3^-]}{dt} = k_1^{obsd}[I_3^-]$$

where

$$k_1^{obsd} = \{k_0 + k_A[HPO_4^{2-}] + k_B[H_2PO_4^-]\}\frac{[S]}{[I^-]^2}$$

Table II. Dependence of the Rate of Iodination upon Iodide Concentration (30°)

$[I^-] \times 10^3$	$k_1^{obsd} \times 10^4$, sec^{-1}	$k_1^{obsd}[I^-]^2 \times 10^6$, $mole^2$ $l.^{-2}$ sec^{-1}
	1-*i*-PrPy[a]	
5.0	13.3	3.32
7.5	7.02	3.95 } 3.49 ± 0.20
10.0	3.45	2.45
12.5	2.33	3.64
	1-MePy[b]	
2.0	1.30	5.20 } 5.52 ± 0.31
3.0	0.65	5.85

[a] [1-*i*-PrPy] = 2.35×10^{-2} *M*; $[HPO_4^{2-}] = 0.00$ *M*; $[H_2PO_4^-] = 0.00$ *M*. [b] [1-MePy] = 4.25×10^{-2} *M*; $[HPO_4^{2-}] = 0.049$ *M*; $[H_2PO_4^-] = 0.046$ *M*.

(3) E. Berliner, *Tetrahedron*, **5**, 202 (1959).
(4) T. Dedicher, *Chem. Ber.*, **38**, 1381 (1906).
(5) E. Berliner, *J. Am. Chem. Soc.*, **73**, 4307 (1951).
(6) R. Huttel, O. Schaefer, and P. Jochum, *Ann.*, **593**, 200 (1955).
(7) J. Ridd, *Phys. Methods Heterocyclic Chem.*, **1**, 134 (1963).
(8) E. Berliner, *J. Am. Chem. Soc.*, **72**, 4003 (1950).

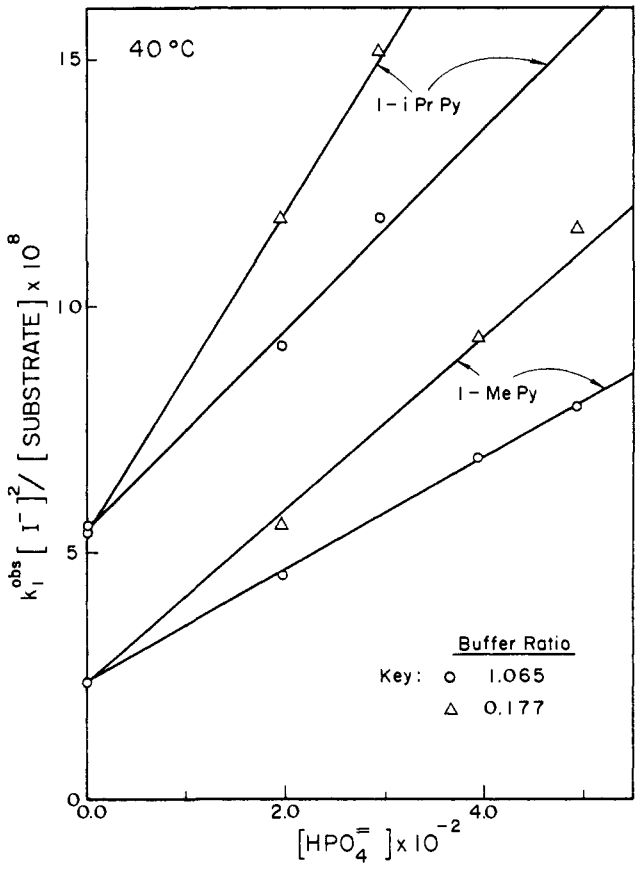


Figure 2. Buffer dependence, 40°.

Here k_0 is the rate constant for the "uncatalyzed" iodination of substrate S, k_A is the rate constant for the HPO_4^{2-}-catalyzed reaction, and k_B is the rate constant for the $H_2PO_4^-$-catalyzed reaction.

Values of k_0, k_A, and k_B are given in Table III for 1-MePy and 1-*i*-PrPy and of k_0 for 1-EtPy. The k_0 values were determined in the absence of buffer. The k_A and k_B values were determined by solution of appropriate simultaneous equations, as described by Berliner.[8] Since the uncertainties in k_0 values were smaller than in k_A or k_B values, we elected to use k_0 values for reactivity comparisons between 1-alkylpyrazoles and pyrazole.

Table III. Rate Constants for the Iodination of 1-Alkylpyrazoles

Substrate	Temp, °C	k_0[a] × 10⁹, mole l.⁻¹ sec⁻¹	k_A[b] × 10⁷, sec⁻¹	k_B[b] × 10⁸, sec⁻¹
1-MePy	30	4.9	2.18	2.35
	40	23.9₅	10.2	12.6
1-EtPy	30	7.8	...	...
	40	30.2	...	...
1-*i*-PrPy	30	14.4	4.13	4.03
	40	54.7	18.2	25.5

[a] ±1% (average deviation from the mean). [b] ±6% (estimated graphically).

Experimental Activation Energies. The experimental activation energies calculated for the uncatalyzed rate constants at 30 and 40° are given in Table IV. The experimental activation energy for the uncatalyzed iodination of pyrazole is given for purposes of comparison.

Table IV. Experimental Activation Energies

Substrate	E_a, kcal/mole
1-MePy	30.0
1-EtPy	26.4
1-*i*-PrPy	25.2
Pyrazole[a]	18.5

[a] See ref 2a.

Discussion

Effect of Alkyl Groups. The results of Table III reveal that the effect of N-alkyl groups upon the reactivity of pyrazole follows the inductive rather than the Baker–Nathan (hyperconjugative) order. The inductive order of alkyl groups has also been observed for *meta*-position iodinations of *p*-alkylanilines[9] and *p*-alkylphenols.[10] In contrast, the *para*-position bromination of alkylbenzenes in acetic acid, and many other *para*-position reactions involving the benzene nucleus, exhibit the Baker–Nathan order.[3,11] Like the benzene analogs, the change in reactivity attending replacement of a methyl group by an ethyl or isopropyl group is quite small (*i*-Pr:Me ~ 2:1). These observations suggest that N-alkyl groups affect the electrophilic reactivity through the π-inductive, the σ-inductive, and the field effects[12] to a greater extent than through a hyperconjugative interaction[10] and that the 4 position in 1-alkylpyrazole is analogous to *meta* positions in alkyl-substituted six-member aromatic systems.

Comparative Reactivities of the Anion and Molecule of Pyrazole. To estimate the electrophilic reactivity of the pyrazole molecule from that of 1-methylpyrazole, we require a means to gauge the effect of ring methyl groups upon electrophilic substitution in five-member aromatic heterocycles. The relative rates of iodination of pyrazole and 3(5)-methylpyrazole and of imidazole and 2-methylimidazole are pertinent to this question, where the *anions* of these substrates undergo iodination.[2a] 3(5)-Methylpyrazole undergoes aqueous iodination about 150 times more rapidly than pyrazole[13] and 2-methylimidazole about 20 times more rapidly than imidazole.[13] The bromination of toluene in acetic acid occurs about 2500 times more rapidly than that of benzene[11] and the benzoylation about 590 times more rapidly.[11] In view of these relative rates, it seems reasonable to take the uncatalyzed rate constant (k_0) of iodination of 1-methylpyrazole as an upper limit of the uncatalyzed rate of iodination of the pyrazole molecule and $k_0/2500$ as a lower limit. Thus, we have k_0(pyrazole molecule) $\sim 2 \times 10^{-12}$ to 5×10^{-9} (30°).

If we wish to compare the rates of iodination of the pyrazole molecule and its anion, we must recognize that the rate of iodination of the latter depends upon the hydrogen ion concentration (constant ionic strength).[2a] We can compare the two rates if we specify $[H^+]$. The acid dissociation constant K_a[14] for pyrazole is $\sim 10^{-14}$. If we let [1-MePy] = [Py] = 1.0 *M* and let $[H^+] = 10^{-7}$ *M*, then $[Py^-] \sim 10^{-7}$. The rate constant for the un-

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(10) E. Berliner, F. Berliner, and I. Nelidov, *ibid.*, 76, 507 (1954).
(11) M. J. S. Dewar, "Hyperconjugation," The Ronald Press Co., New York, N. Y., 1962, p 110.
(12) M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, 84, 3539 (1962).
(13) J. D. Vaughan and V. L. Vaughan, unpublished data.
(14) A. Albert, "Heterocyclic Chemistry," Essential Books, Fairlawn, N. J., 1959, p 143.

catalyzed iodination of pyrazole[2a] is given as $k_0 = 1.5 \times 10^{-13}$ l.^{2} mole^{-2} sec^{-1}, corrected for first-order dependence upon the *stoichiometric* concentration of pyrazole, [Py], and for [H$^+$] and [I$^-$]^2. The ratio of the relative second-order rates of iodination of Py$^-$ and Py would therefore be

$$\frac{k_2^{Py^-}}{k_2^{Py}} = \frac{1.5 \times 10^{-13}/K_a}{(2 \times 10^{-12} \text{ to } 5 \times 10^{-9})} = 3 \times 10^9 \text{ to } 7 \times 10^{12} \quad (1)$$

where K_a is the acid dissociation constant of pyrazole. This result is meaningful if both Py$^-$ and Py undergo iodination by a common iodinating agent.

The assumption that both substrates undergo iodination by the same iodinating agent is not necessarily valid. The rate laws for the iodination of pyrazole and 1-alkylpyrazoles are compatible with iodination by either molecular I_2 or the hydrated iodinium ion IOH_2^+.[2a,8] The ratio of the molar concentrations of these possible iodinating agents in aqueous solution[15] is given by

$$\frac{[I_2]}{[IOH_2^+]} \sim [I^-] \times 10^{11}$$

It is just as reasonable to assume that anion substrates undergo attack by molecular iodine and molecular substrates by IOH_2^+ than to assume the substrates are attacked by *either* I_2 or IOH_2^+. In justification, we note that the probability of encounter between anion substrates and IOH_2^+ will be very small, whereas the probability of encounter between molecular substrates and IOH_2^+ will be comparatively large, since the substrate concentration here is the stoichiometric concentration. If the latter assumption were made, we must conclude that the ratio of reactivities would be even greater than the limits expressed by eq 1.

Theoretical Considerations. The great difference in the reactivities of the anion and molecular forms of pyrazole, and in the reactivities of aromatic heterocycles in general, provides an interesting and difficult theoretical problem. The complexity of the problem is illustrated by the following considerations. In phosphate-buffered iodinations of 1-alkylpyrazoles, both HPO_4^{2-} and $H_2PO_4^-$ were catalytically active (Table III). The ratio k_A/k_B is about 10 for 1-methylpyrazole and also for 1-isopropylpyrazole. In the iodination of aniline,[8] this ratio is about 100 and in the iodination of pyrazole[2] HPO_4^{2-} was catalytically active but $H_2PO_4^-$ was not detectably active. Clearly, the degree of participation of a base in the transition state of the proton-removal step is quite sensitive to the identities of the substrate and the base. Quantum theoretical interpretation of the relative magnitudes of rate constants should therefore utilize models of the transition states that include the base explicitly. This argument applies also to the "uncatalyzed" rate as well, since water presumably is the catalyst in this case. Brønsted correlations between catalytic rates and base strengths would be germain to this problem, since the sensitivity of the rate to the base strength can be interpreted as a measure of the degree of proton removal in the transition state.[16] We are presently making base catalytic studies of heterocyclic iodinations, which we plan to report later, together with theoretical interpretation of the results.

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Kinetics of Nucleophilic Substitution on 6-Chloropurine Ribonucleoside in Aqueous Solution[1]

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Contribution from Frick Chemical Laboratory, Princeton University, Princeton, New Jersey 08540. *Received July 18, 1967*

Abstract: Nitrogen, sulfur, and oxygen compounds displace chloride from 6-chloropurine ribonucleoside in water at room temperature at rates which are proportional to the first power of the free base of the attacking nucleophile in all cases. When analogs of various amino acid side chains are compared in their rate of reaction with this compound, which is a substrate for the enzyme adenosine deaminase, thiols are found to be the dominant nucleophiles at pH 7 by four orders of magnitude; imidazole is relatively unreactive. Successive addition of methyl groups to ammonia strongly enhances its nucleophilicity for 6-chloropurine ribonucleoside, 1-fluoro-2,4-dinitrobenzene, and *p*-nitrophenyl acetate. However, attack by trimethylamine seems to be sterically hindered except in the purine substrate, yielding a quaternary amine which is readily hydrolyzed by alkali.

The action of a number of hydrolytic enzymes involves nucleophilic displacement yielding an enzyme derivative which is easily hydrolyzed. Recent evidence suggests that purine aminohydrolases may form purinyl–enzyme intermediates in a reaction analogous to nucleophilic aromatic substitution.[2-4] Nu-

(1) Supported by Research Grant GM-12725 from the National Institutes of Health, U. S. Public Health Service, and by a National Science Foundation fellowship held by B. T. Walsh. Inquiries should be addressed to R. Wolfenden.

(2) R. Wolfenden, *J. Am. Chem. Soc.*, **88**, 3157 (1966).

(3) H. Bar and G. I. Drummond, *Biochem. Biophys. Res. Commun.*, **24**, 584 (1966).

(4) A recent report [L. G. Howell and I. Fridovich, *Federation Proc.*, **26**, 448 (1967)] that yeast adenine aminohydrolase catalyzes an apparent exchange of hypoxanthine into 6-chloropurine tends to contradict formation of a purinyl–enzyme intermediate in the case of this enzyme.