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THE KINETICS OF DEUTERATION OF PYRAZOLE^{1a}

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Abstract: The kinetics of deuteration of the 4 position and the 3(5) position in pyrazole was studied in sealed tubes at 200° and higher temperatures. The mechanism proposed for 4 position deuteration involved general acid-catalyzed formation of sigma intermediates from the molecular and conjugate base forms of pyrazole. The rate of deuteration of the 3(5) position exhibited neither buffer catalysis nor pD dependence. This behavior is consistent with formation of an ylid intermediate from attack of the conjugate acid of pyrazole by OD⁻ ions.

Pyrazole exhibits both weakly basic and very weakly acidic properties in aqueous solution ($pK_b = 11.53$ and $pK_a \sim 14$).²

2. A. Albert, "Physical Methods in Heterocyclic Chemistry," Academic Press, New York, 1963, Vol. I, A.R. Katritzky, Ed.

Therefore, the molecule (I), the conjugate acid (II), and the conjugate base (III) may be subject to electrophilic attack in aqueous media. Thus, the conjugate acid undergoes nitration in

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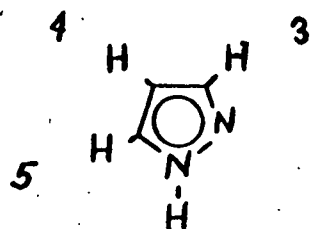
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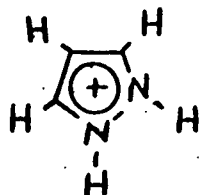
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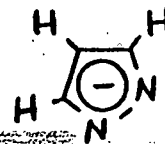
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I



II



III

the 4 position in strongly acidic media,³ whereas iodination in

3. M.W. Austin, J.R. Blackborow, J.H. Ridd, and B.V. Smith, *J. Chem. Soc.*, 1051 (1965).

media ranging from pH = 6.0 to 8.0 appears to involve the conjugate base in the 4 position.^{4,5} Prior to the research reported

4. J.D. Vaughan, D.G. Lambert, and V.L. Vaughan, *J. Amer. Chem. Soc.*, 86, 2857 (1964).

5. J.D. Vaughan, G.L. Jewett, and V.L. Vaughan, *Ibid.*, 89, 6218 (1967).

in this paper, there has been no report of kinetic studies of the deuteration of unsubstituted pyrazole. However, Olofson, Thompson, and Michelman⁶ observed that the 3(5) position but not

6. R.A. Olofson, W.R. Thompson, and J.S. Michelman, *Ibid.*, 86, 1865 (1964).

the 4 position in 1,2-dimethylpyrazolium cation undergoes hydrogen exchange at 31°. Accordingly, it is of interest to study the kinetics of deuteration of pyrazole in heavy aqueous solution to ascertain the relative reactivities of the 4 and equivalent 3 and 5 positions, to determine the rate laws for deuteration of these positions, to propose mechanisms compatible with these rate laws, and to interpret the reactivities of ring positions theo-

retically and mechanistically.

Experimental Section

Materials. Aldrich Chemical Company pyrazole was recrystallized three times from cyclohexane; m.p. 68.5°. D₂O (99.5%), DCl (38% in D₂O), ND₄OD (26% in D₂O), and pyridine-d₅ obtained from Merck, Sharpe, and Dohme of Canada, Ltd., were used without further purification. Reagent grade NaCl was also used without further purification.

Kinetic Runs. The details of the kinetic procedure are given in the preceding paper of this series.⁷ The ionic strength

7. J.D. Vaughan, Z. Mughrabi, and E.C. Wu, J. Org. Chem., Submitted for Publication.

was adjusted to 1.00 M by NaCl in all runs. Runs were made with ammonia-d₃, ammonium-d₄ buffer, pyridine-d₅, pyridinium-d₆ buffer, and with no added buffer. Deuterations were carried out in heavy water solutions in sealed heavy wall borosilicate glass ampoules at temperatures ranging from 200° to 250°. Temperatures were reproducible to within ± 1° and rate constants to within ± 10%. Uncertainties in concentrations of reagents arising from thermal changes in volume are discussed in the preceding paper.⁷

pD values were measured at room temperature with the Beckman Zeromatic pH meter, corrected by the formula of Glaskoe and Long (pD = pH (meter reading) + 0.4).⁸

8. P.K. Glaskoe and F.A. Long, J. Phys. Chem., 64, 188 (1960).

Results and Discussion

Rate constants for the deuteration of the 4 position and the equivalent 3 and 5 positions are recorded in Tables I and II, re-

TABLE I

Pseudo-First Order Rate Constants for the Deuteration of the
4 Position in Pyrazole

ND ₃ , ND ₄ ⁺ Buffer				
Base Concentration ^a	Buffer Ratio ^{b,c}	pD ^c	t(°C)	k ₄ ^{obsd.} x 10 ⁴ sec ⁻¹
1.92	3.75	10.56	200	7.68
0.96				4.43
0.48				2.45
0.24				1.78
0.12				1.35
1.09	8.50	10.92	200	4.68
0.70	1.37 ₅	10.13	200	3.53
Pyridine-d ₅ , Pyridinium-d ₆ Buffer				
0.70	1.34	6.15	200	21.9
0.35				17.8
0.17				15.8
0.09				14.6
0.67	2.08	6.34	200	16.2
0.34				13.1
0.17				12.3
0.08 ₅				11.8
0.78	6.03	6.80	200	8.16
0.39				6.15
0.20				5.47
0.10				5.00
0.068	12.7	7.13	200	5.23
0.034				3.98
0.017				3.10
0.0085				2.78
No Added Buffer				
0.0	--	7.50	200	0.82
			215	1.61
			230	3.12
			238	4.13
			245	6.48
			245	6.53

- a. Mol./l.
b. [Base]/[Acid]
c. Room temperature value

TABLE II

Pseudo-First Order Rate Constants for the Deuteration of the
3(5) Position in Pyrazole

ND ₃ , ND ₄ ⁺ Buffer				
Base Concentration ^a	Buffer Ratio ^{b,c}	pD ^c	t(°C)	k ₃₍₅₎ ^{obsd.} x 10 ⁵ sec ⁻¹
1.92	3.75	10.56	230	3.95
1.92				3.27
0.96				4.03

1.85	3.44	10.53	230	4.17
0.79				1.1

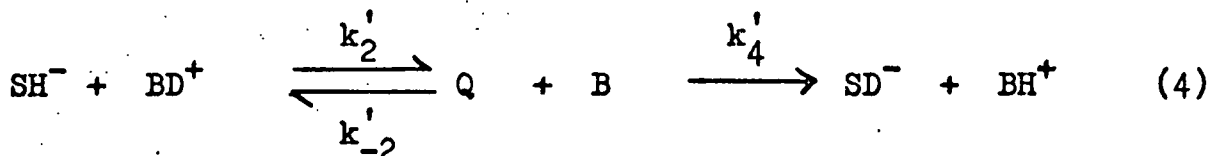
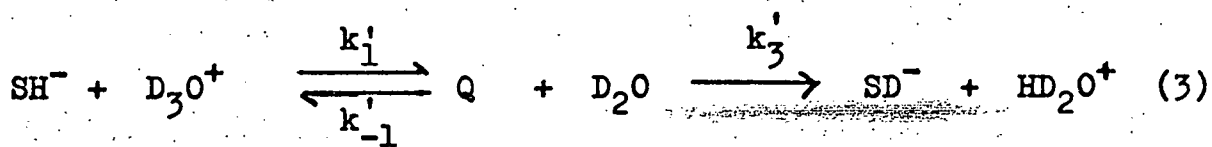
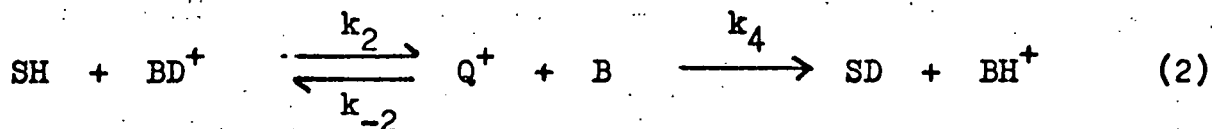
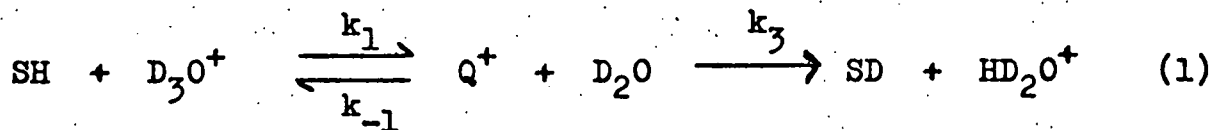
Pyridine-d ₅ , Pyridinium-d ₆ Buffer				
1.90	3.69	6.60	230	2.28
0.95				2.08
0.47				2.27
0.24				2.28

0.70	1.34	6.15	230	2.08
0.35				2.58
0.17				2.88
0.088				2.88
0.044				2.85
0.022				2.58

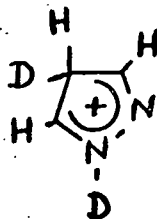
No Added Buffer				
0.00	--	7.50	220	1.65
			230	3.05
			240	8.55
			250	14.5

- a. Mol./l.
b. [Base]/[Acid]
c. Room temperature value

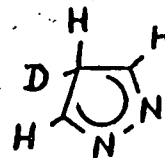
spectively. These rate constants are pseudo-first order in pyrazole, since D₂O was in great excess. The rate data for the 4 position conforms to general acid catalyzed deuteration, according to the following mechanism:



Here SH refers to pyrazole (I), SD to pyrazole-4d, SH⁻ and SD⁻ to the conjugate bases of SH and SD, respectively, BD⁺ and BH⁺ to general acids, and Q⁺ and Q to Wheland intermediates IV and V, respectively:



IV



V

This mechanism is similar to that proposed by Kresge and Chiang⁹

9. A.J. Kresge and Y. Chiang, J. Amer. Chem. Soc., 89, 4411 (1969).

for acid-catalyzed hydrogen exchange in 1,3,5-trimethoxybenzene, complicated by the presence of added buffer and by the appearance of two rather than one substrate. The kinetic analysis that follows is an extension of that reported by Kresge and Chiang. We assume that

$$k_1 < k_{-1} \sim k_3$$

$$k_2 < k_{-2} \sim k_4$$

$$k'_1 < k'_{-1} \sim k'_3$$

$$k'_2 < k'_{-2} \sim k'_4$$

where the pairs on the right of the inequality (eg k_{-1} , k_3 , etc.) differ only because of the primary isotope effect. Therefore

$$\begin{aligned} \text{Rate (4 position)} &= k_1 [\text{SH}] [\text{D}_3\text{O}^+] - k_{-1} [\text{Q}^+] [\text{D}_2\text{O}] \\ &+ k_2 [\text{SH}] [\text{BD}^+] - k_{-2} [\text{Q}^+] [\text{B}] + k'_1 [\text{SH}^-] [\text{D}_3\text{O}^+] \\ &- k'_{-1} [\text{Q}] [\text{D}_2\text{O}] + k_2 [\text{SH}^-] [\text{BD}^+] - k_{-2} [\text{Q}] [\text{B}]. \end{aligned}$$

Using the steady state approximation to eliminate $[\text{Q}^+]$ and $[\text{Q}]$, together with the relations

$$K_a = \frac{[\text{SH}^-] [\text{D}_3\text{O}^+]}{[\text{SH}]}$$

$$K_b = \frac{[\text{BD}^+] K_w}{[\text{B}] [\text{D}_3\text{O}^+]}$$

to eliminate $[\text{SH}^-]$ and $[\text{BD}^+]$, we derive the pseudo-first order rate constant for 4 position deuteration to be

$$k_4^{\text{obsd.}} = \left\{ k_1 X [D_3O^+] + k_1' K_a X' \right\} + \left\{ (k_2 K_b X / K_w) [D_3O^+] + (k_2' K_a K_b X' / K_w) \right\} [B] \quad (5)$$

where

$$X = \frac{k_3 [D_2O] + k_4 [B]}{(k_{-1} + k_3) [D_2O] + (k_{-2} + k_4) [B]}$$

$$X' = \frac{k_3' [D_2O] + k_4' [B]}{(k_{-1}' + k_3') [D_2O] + (k_{-2}' + k_4') [B]}$$

and $K_w = [D_3O^+][OD^-]$. If no buffer is present and if the reacting medium is strongly acidic, then $[SH] \gg [SH^-]$, $[BD^+] = [B] = 0$, and equation (5) reduces to the Kresge and Chiang rate equation:⁹

$$k_4^{\text{obsd.}} = \left(\frac{k_1}{1 + k_{-1}/k_3} \right) [D_3O^+] \quad (6)$$

In the general case (equation (5)), X and X' each are functions of B, so that $k_4^{\text{obsd.}}$ contains terms in the second degree. However, Figures 1 and 2 exhibit first order dependence upon [B] for the ammonia- d_3 and pyridine- d_5 buffers, respectively. This behavior is consistent with equation (5) provided X and X' are constant, irrespective of [B]; the conditions for constancy of X and X' are that

$$\frac{k_3}{k_{-1} + k_3} = \frac{k_4}{k_{-2} + k_4} \quad (7)$$

$$\frac{k_3'}{k_{-1}' + k_3'} = \frac{k_4'}{k_{-2}' + k_4'} \quad (8)$$

Because paths (1) and (2) are quite similar in nature, as are paths (3) and (4) respectively; we conclude that the conditions expressed by (7) and (8) are realized, and that X and X' are indeed constant. In the ammonia buffer case, pD is large and $[D_3O^+]$ vanishingly small; therefore, equation (5) predicts that $k_4^{obsd.}$ will be independent of pD , as observed in Figure 1. In the pyridine buffer case, where the solutions range from neutral to weakly acidic, $[D_3O^+]$ is 10^3 to 10^4 times larger than in ammonia buffer, so that one might expect the $[D_3O^+]$ terms in (5) to become significant. Therefore, in pyridine buffer, equation (5) predicts a family of linear plots of $k_4^{obsd.}$ versus $[Pyridine]$ for given pD values, as seen in Figure 2. According to equation (5), the intercepts (k^0) and slopes (k^S) observed in Figures 1 and 2 should depend linearly upon $[D_3O^+]$; this behavior is exhibited in Figure 3. In earlier work, electrophilic attack of a free molecule and its conjugate base was proposed by Katritzky and co-workers¹⁰ to account for the deu-

10. G.P. Bean, P.J. Brignell, C.D. Johnson, A.R. Katritzky, B.J. Ridgewell, H.O. Tarham, and A.M. White, J. Chem. Soc. (B), 1222 (1967).

teration of phenol (2,4,6 positions).

The results of Figures 1 and 3 may be used to estimate the relative electrophilic reactivities of the pyrazole molecule and its conjugate base. In Figure 1, the intercept $k^0 = 0.8 \times 10^{-4} \text{ sec}^{-1} = k_1'K_aX'$; in Figure 3, $k^0 = 5 \times 10^{-4} \text{ sec}^{-1}$ at $[D_3O^+] = 2 \times 10^{-7}$. Therefore, since $k^0 = k_1X[D_3O^+] + k_1'K_aX'$ and if we let $K_a = 10^{-14}$ for pyrazole,² we find that $k_1X \sim 2 \times 10^3 \text{ sec}^{-1} \text{ M}^{-1}$ and that $k_1'X' \sim 8 \times 10^9 \text{ sec}^{-1} \text{ M}^{-1}$. Accordingly, we estimate that the conjugate base is about 4×10^6 more reactive than the mole-

cule with respect to the D_3O^+ electrophile; the rates of deuteration of the anion and molecule are calculated to be about equal at $pD = 7.4$ (room temperature value)¹¹. By comparative iodina-

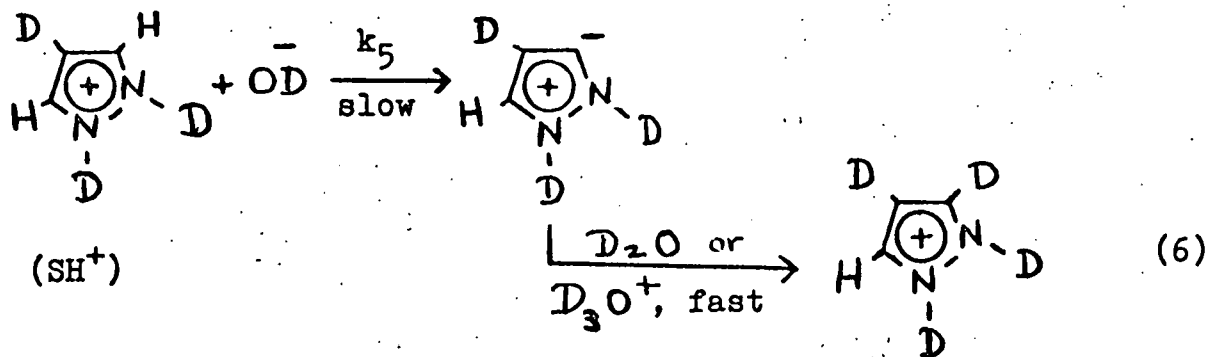
11. Compare phenol, where the phenoxide anion is estimated to be 2×10^7 more reactive than the phenol molecule, and the rates of deuteration of the two substrates to be equal at $pD = 3.4$ (reference 10).

tions of pyrazole and 1-methylpyrazole, the reactivity (relative to I_2 or IOH_2^+) of the conjugate base of pyrazole was estimated to be between 10^9 and 10^{13} greater than that of the molecule.⁵

Numerous other examples of Wheland-intermediate mechanisms have been proposed for hydrogen exchange in aromatic substrates, chiefly in six member ring systems.¹²

12. For example, see G.P. Bean, C.D. Johnson, A.R. Katritzky, B.J. Ridgwell, and A.M. White, J. Chem. Soc. (B), 1219 (1967).

The deuteration of the 3(5) position of pyrazole at 230° is sensibly independent of both buffer and pD from $pD = 6.15$ to $pD = 10.56$ (Table II). This behavior conforms to deuterioxide-catalyzed ylid formation:



Here Rate (3(5) position) = $k_5 [\text{SH}^+][\text{OD}^-]$; noting that $K'_a = \frac{[\text{SH}][\text{D}_3\text{O}^+]}{[\text{SH}^+]}$, we derive

$$k_{3(5)}^{\text{obsd.}} = \frac{k_5 K_w}{K'_a} \quad (7)$$

which agrees with experiment. Similar independence of the rate of deuteration upon $[\text{OD}^-]$ attributable to the ylid-intermediate mechanism has been reported.^{7,13,14} An alternative path for 3(5)

13. J.A. Zoltewicz and J.D. Meyer, Tetrahedron Letters, 421 (1968).

14. T.M. Harris and J.C. Randall, Chem. Ind. (London), 1728 (1965).

deuteration independent of pD could involve attack of the conjugate base (III) by D_3O^+ to form a Wheland intermediate. However, the independence of the rate upon ND_4^+ and pyridinium- d_5 casts doubt upon this alternative. Further, the numerous examples of other heteroatomic aromatic substrates^{6,15-20} that appear to

15. H.S. Staub, Tetrahedron Letters, 845 (1964).

16. P. Beak and J. Bonham, J. Amer. Chem. Soc., 87, 3365 (1965).

17. P. Haake and W.B. Miller, Ibid., 85, 4044 (1963).

18. R. Breslow, Ann. N. Y. Acad. Sci., 98, 445 (1962).

19. R.A. Olofson, J.M. Landesberg, K.N. Houk, and J.S. Michelman, J. Amer. Chem. Soc., 88, 4265 (1966).

20. P. Haake, L.S. Bauscher, and W.B. Miller, Ibid., 91, 1113 (1969).

undergo hydrogen exchange in α positions through ylid-intermediates support this mechanism for the 3(5) position in pyrazole. Of particular interest, 1,2-dimethylpyrazolium cation undergoes deu-

teration in the 3(5) position at 31° in alkaline solution.⁶ Here, the much smaller rate of deuteration of the 3(5) position in pyrazole in terms of the ylid path is a consequence of the very weak base strength of pyrazole.²

The experimental activation energy for the 4 position is 21.8 ± 1.6 Kcal and that for the 3(5) position is 38.8 ± 6.4 Kcal. Corresponding pseudo-unimolecular collision factors are $7.6 \times 10^5 \text{ sec}^{-1}$ and $2.1 \times 10^{12} \text{ sec}^{-1}$ respectively. The activation energy for the 3(5) position is unexpectedly large;²¹ the smaller exchange re-

21. For example, the activation energy for exchange in the 4(5) position in imidazole is about 22 Kcal.⁷

activity for the 3(5) position compared to the 4 position is due to the great difference in activation energies of these positions, partially offset by the larger pre-exponential factor of the 3(5) position.

It is evident that two types of exchange mechanism are operative in aromatic heterocyclic systems. The first type involves base catalyzed proton removal from the exchange site of the substrate. The second type involves acid catalyzed Wheland intermediate formation. In general, in neutral, weakly acidic, or weakly alkaline solutions, positions next to nitrogen, oxygen, or sulfur heteroatoms undergo exchange by the first type,^{6,7,15-20} whereas positions with carbon neighbors may react through the first²² or the second type.^{10,12,23} The relative reactivities of the conju-

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

23. The beta position in 4-aminopyridines exhibits mechanism type 1 in alkaline solution and type 2 in acid solution. See reference 13.

gate acid, conjugate base, and molecule forms of the substrates differ, depending upon which type mechanism is operative. Thus, for the proton abstraction mechanism, the conjugate acid is most reactive, the molecule next,^{7,19} and the conjugate base apparently unreactive. Here protonation of the heteroatom leads to rate enhancement in two ways: first, by increased inductive stabilization of transition states leading to ylid or anion intermediates^{6,7,20} and second, by the increased entropy of activation attending reactions between ions of opposite charge. For the Wheland intermediate mechanism, the conjugate base is most reactive, the molecule next, and the conjugate acid least. In the latter case, deprotonation of the heteroatom appears to stabilize transition states leading to the Wheland intermediate, and also to cause the entropy of activation to increase for positively charged electrophiles.

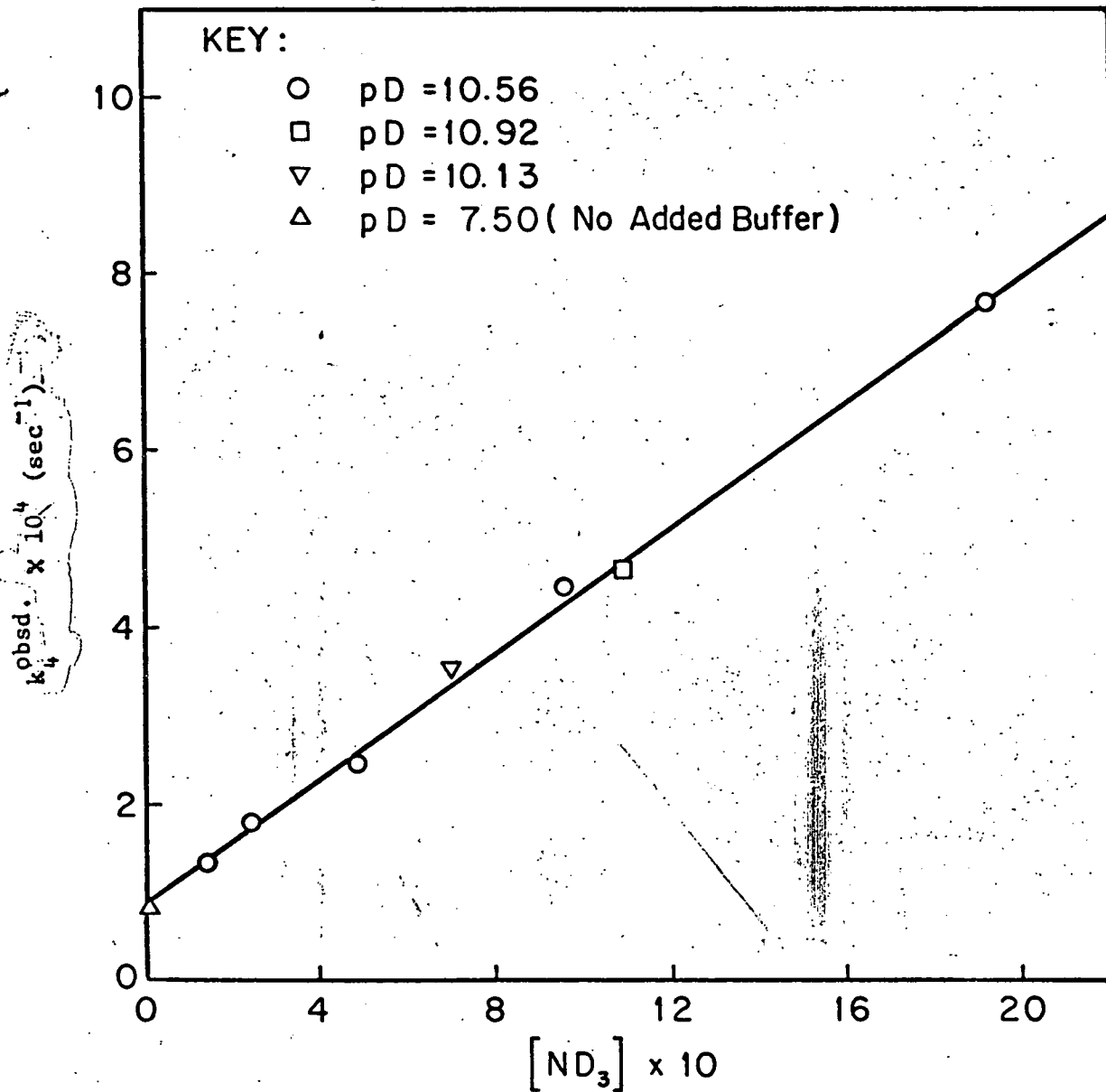


Figure 1. Rate of Deuteration of the 4 Position of Pyrazole at 200°
in Ammonia Buffer

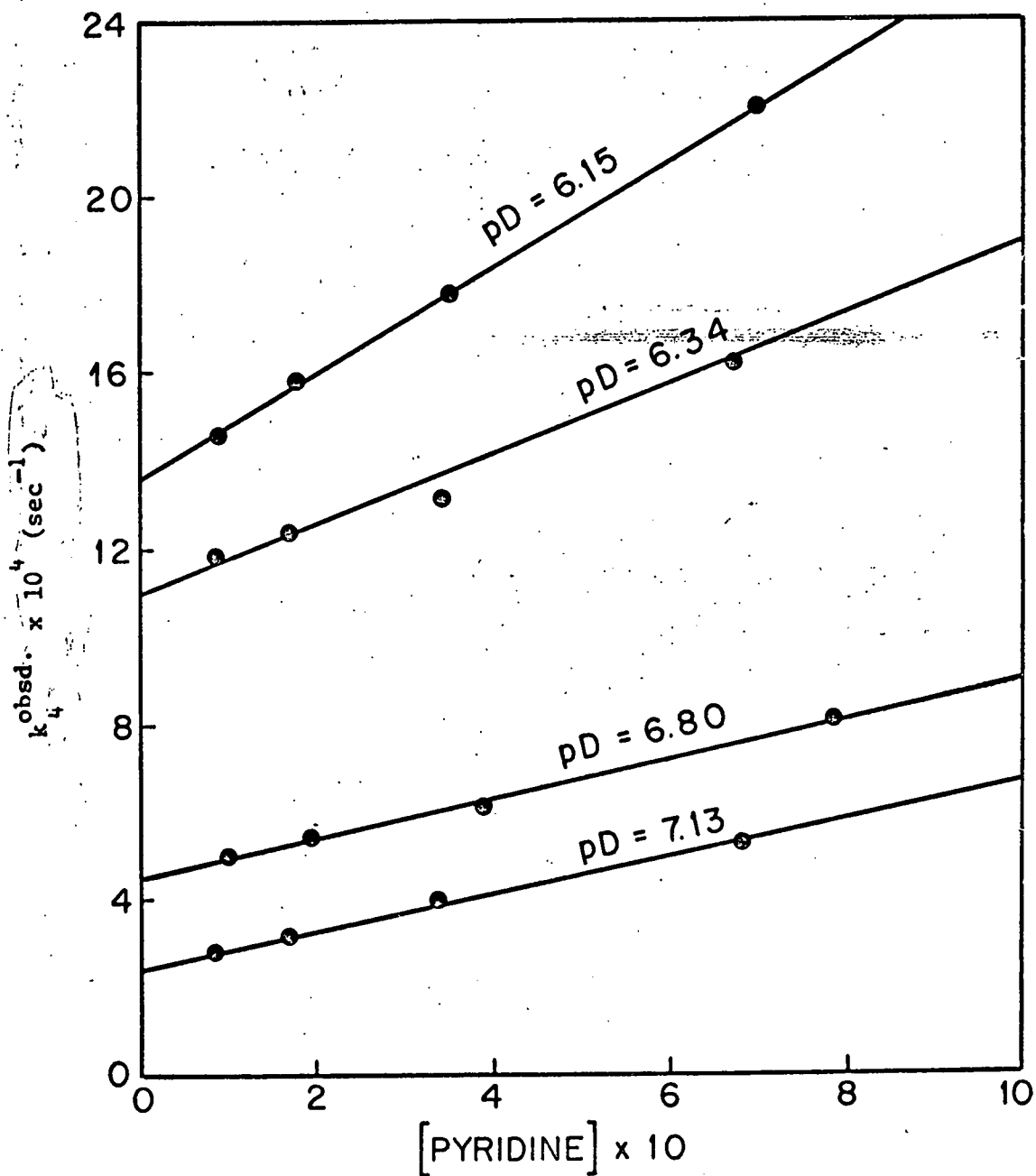


Figure 2. Rate of Deuteration of the 4 Position of Pyrazole at 200° in Pyridine Buffer

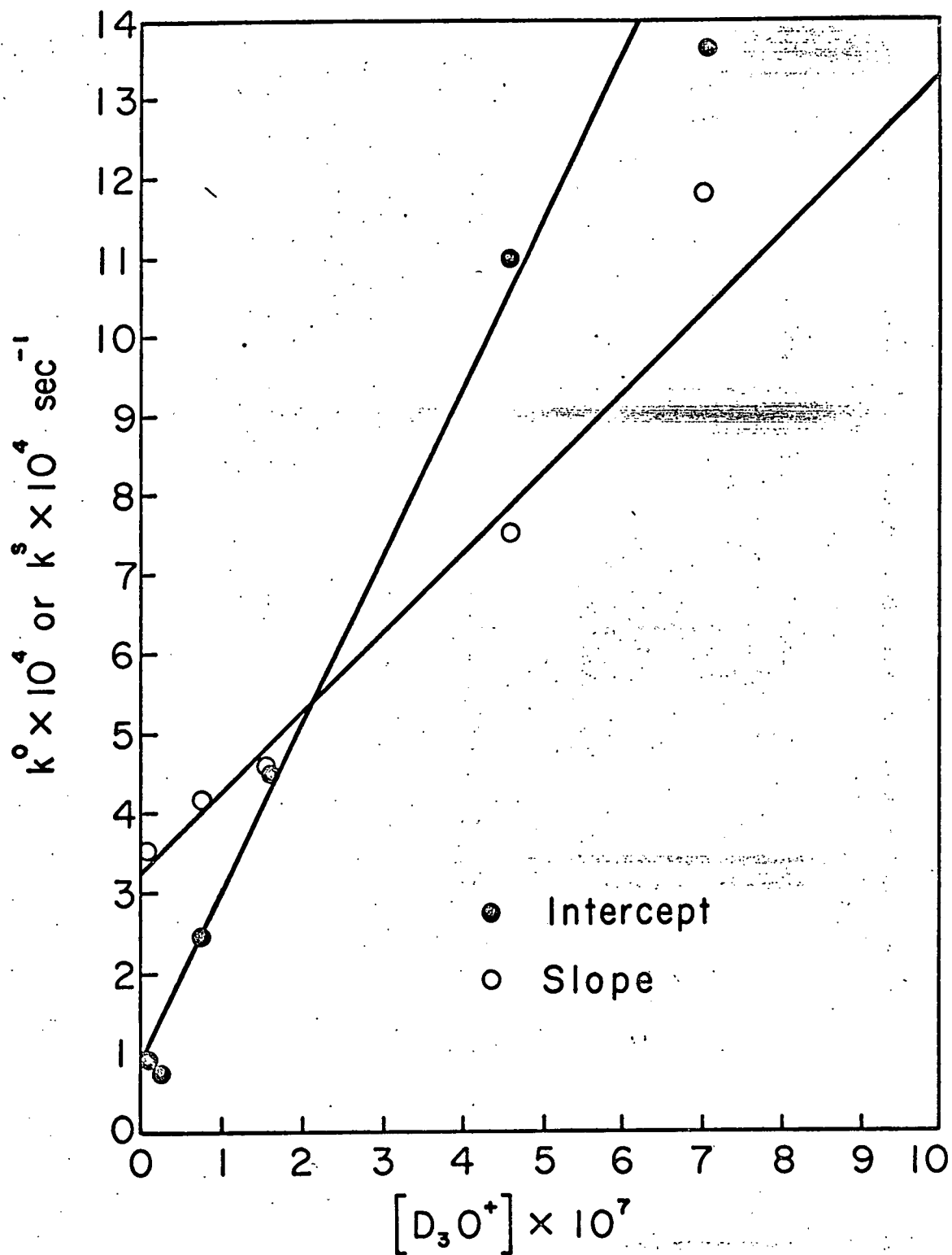


Figure 3. Dependence of Buffer Catalyzed (Slopes) and Uncatalyzed (Intercepts) Deuteration of the 4 Position in Pyrazole at 200°