not hold, which will be more the case for naphthalene-d_8 than for naphthalene, because $(k_2/k_{-1})_H > (k_2/k_{-1})_D$. This would seem to argue in favor of the former interpretation.

There is no ambiguity about the inverse isotope effect in the first step. According to Streitwieser and coworkers,[14] secondary inverse isotope effects can be caused by the rehybridization of the carbon–hydrogen bonding orbitals from sp^2 to sp^3, which are, however, often compensated by hyperconjugation in the transition state which leads to the intermediate. An additional factor ought to be of importance in the present instance. Because of anharmonicity effects, C–D bonds behave as if they were more electron releasing than C–H bonds.[15] The inductive effect of seven C–D bonds not involved in the reaction must combine with the rehybridization effect to more than compensate for the rate-decreasing effect of hyperconjugation and thus lead to the inverse isotope effect observed here.

Experimental Section

Materials and kinetic procedures were as described before.[3] A sample of naphthalene was recrystallized five times from ethanol and had mp 80.1–80.5° (corrected). The sample of naphthalene-d_8, obtained from Merck Sharpe and Dohm of Canada Limited, was recrystallized three times and had mp 79.6–80.2°. Its nmr spectrum showed no indication of incomplete deuteration. The rate constants listed in Table I are averages of at least two runs. More runs were conducted if average runs differed by more than 2%.

Registry No.—Perdeuterionaphthalene, 1146-65-2; naphthalene, 91-20-3.

Acknowledgment.—This work was supported by National Science Foundation Grant GP-4986, which is gratefully acknowledged.

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Hydrogen–Deuterium Exchanges in Pyrimidine *N*-Oxides

SHARON A. KRUEGER AND WILLIAM W. PAUDLER*

Department of Chemistry, Ohio University, Clippinger Laboratories, Athens, Ohio 45701

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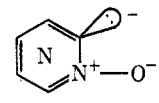
Acid- and base-catalyzed H → D exchange processes in pyridine *N*-oxides,[1] pyrazine *N*-oxides,[2] and pyridazine *N*-oxides[3] have been the subject of several recent papers.

The general conclusions that can be drawn from these studies are as follows.

(1) The hydrogens on the carbon atom α to the *N*-oxide group are much more readily exchanged under base catalysis than are any of the other ring protons.

(2) The exchange process occurs *via* "anionic ylides" such as depicted by structure **1**.



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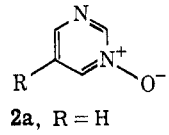
(3) The replacement of a ring =CH function in a pyridine *N*-oxide by a =N atom has a dramatic rate-enhancing effect on these exchange reactions.

This pattern is significantly different from that observed in the nonoxidized parents of these compounds where the hydrogens α to the ring nitrogen atom exchange *less* readily than do the other ring protons.[4–6] (The relative $H_2:H_4:H_5$ exchange rates in pyrimidine, for example, are 1:3.25:46.7). A comparison of the α-proton exchange rate in pyridine with those in pyrimidine and in pyrazine show that the latter two compounds undergo this exchange 100 times as readily. An even more dramatic increase is noted when the α-proton exchange rate in pyridine is compared with that observed in pyridazine, where the latter exchanges 1000 times as readily as the former.

Zoltewicz and coworkers[6] have suggested that the rate difference between the exchange of α protons and those further removed from the ring nitrogen atom is due to a decreased s character of the carbon–hydrogen bond adjacent to the sp^2 nitrogen atom and the repulsive interaction between the electron pairs on nitrogen and the (developing) carbanion.

In an effort to delineate the effect that sp^2 nitrogen atoms have upon the H → D exchange rates of "azapyridine *N*-oxides" we have now examined the behavior of several 5-substituted pyrimidine 1-oxides when they are subjected to base-catalyzed H → D exchange (Table I). In these *N*-oxides (**2a–e**) we expect H-2 as well as H-6 to exchange.



2a, R = H
b, R = CH_3
c, R = Br
d, R = OCH_3
e, R = $N(CH_3)_2$

The second-order rate constants, determined as described in the previous paper of this series,[2] for H-2 and H-6 of pyrimidine *N*-oxide (**2a**) are 1.8×10^{-3} and 4.7×10^{-2} l. mol^{-1} min^{-1}, respectively. Thus, H-6 exchanges 26 times as rapidly as does H-2, while both of these protons exchange much less readily than do H-2 and H-6 in pyrazine 1-oxide (0.16 l. mol^{-1} min^{-1}). Thus, the nonoxidized nitrogen atom, when situated ortho or para to the exchanging proton, is much less effective in faciliting H → D exchange than when it is located meta to the exchanging position.

Zoltewicz and coworkers[6] have shown that in the diazines themselves the activating effects of the sp^2 nitrogen atoms are in the order para ≈ meta ≫ ortho. This positional reactivity differs from that found in

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TABLE I

SECOND-ORDER RATE CONSTANTS FOR H-D EXCHANGE IN NaOD/D_2O[a,b] OF SOME 5-X-PYRIMIDINE 1-OXIDES

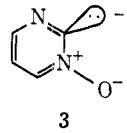
X	Compd no. (cf. Figure 1)	k_{H-6},[c] l. mol^{-1} min^{-1}	k_{H-2},[c] l. mol^{-1} min^{-1}
Br	1	$5.4 \pm 0.5 \times 10^{2}$	*d*
CH_3O	2	4.7 ± 0.5	$3.1 \pm 0.3 \times 10^{-3}$
$(CH_3)_2N$	3	$1.7 \pm 0.2 \times 10^{-1}$	*e*
CH_3	4	$9.8 \pm 0.9 \times 10^{-2}$	$1.7 \pm 0.2 \times 10^{-2}$
H	5	$4.7 \pm 0.5 \times 10^{-2}$	$1.8 \pm 0.2 \times 10^{-3}$

[a] The various concentrations of NaOD used were 0.3–0.002 *N*. The pyrimidine *N*-oxide concentrations employed varied from 0.5 to 0.2 *M*. [b] The rate constants were obtained at 31 ± 0.5°, the HA-100 probe temperature, as determined with methanol and ethylene glycol in the usual manner. In order to ascertain the temperature stability, several runs were made using a capillary insert in the nmr tube which contained methanol, and the signal separation between the methyl and hydroxyl protons were checked at 5-min intervals. In several cases adjustments were made to assure identical ionic strengths of the solutions. No significant changes in the rate constants were noted. [c] The indicated errors represent standard deviations. [d] No exchange was observed within 23 days at 0.1 *N* NaOD. [e] No exchange was observed within 14 days in 0.1 *N* NaOD.

pyridine 1-oxide, *N*-methylpyridinium ion, and monosubstituted benzenes which contain an activating group, since the sequence in these compounds is ortho ≫ meta > para, the order expected if the inductive effect is the controlling factor.

When one considers the exchange rates of H-2 (1.2×10^{-4}), H-4 (3.9×10^{-4}), and H-5 (6.5×10^{-3}) in pyrimidine, we note that H-4 exchanges 3.25 times as rapidly as does H-2. Thus, the presence of a 1-oxide function either decreases the H-2 or increases the H-4 exchange rates relative to each other.

In view of the fact that the presence of the negative charge on the oxide function would be expected to decrease the ease of formation of the "anionic ylide" **3** much more so than the lone pair repulsion hinders the formation of the corresponding pyrimidine anion **4** it is not surprising that the H-4/H-2 exchange ratio



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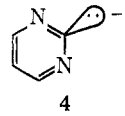

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is greater in pyrimidine 1-oxide than it is in pyrimidine. Some, but not all, of this difference may also be due to the fact that the pyrimidine exchange reactions were done at a temperature 135° higher than the exchange reactions in the pyrimidine *N*-oxides.

A comparison of these various rate constants nevertheless suggests that the activating influence of an sp^2 nitrogen in "azapyridine 1-oxides" is meta > para > ortho. Thus, the presence of the *N*-oxide function significantly alters the relative activating effect of an additional sp^2 nitrogen atoms in comparison to its nonoxidized isomer.

An examination of the exchange rates of H_2 and H_6 of various 5-substituted pyrimidine 1-oxides reveals that, akin to the behavior of 3-substituted pyrazine 1-oxides,[2] there exists a linear free energy relationship between log k_{H-6} and σ_I substituent constants. Thus, the inductive effect of a 5 substituent situated ortho

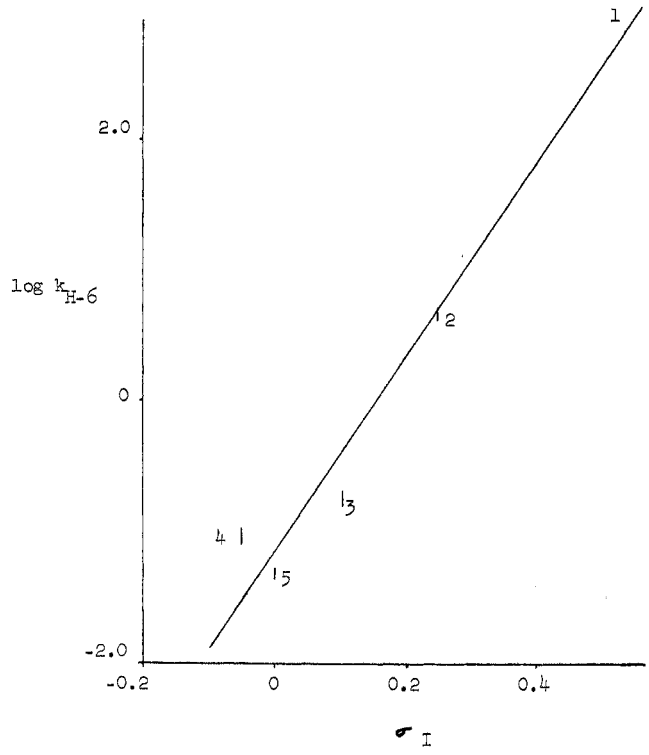
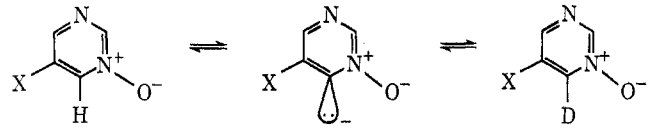


Figure 1.—Hammett correlation for base-catalyzed H-6 → D-6 exchange of some 5-X-pyrimidine 1-oxides.

to the exchanging proton is the controlling factor in this exchange process.



A comparison of the slope of the Hammett correlation (Figure 1) for the pyrazine 1-oxides (5.71) as compared with that of the pyrimidine 1-oxides (6.67) reveals that the pyrimidine 1-oxide exchange reactions are more strongly influenced by an electron-withdrawing substituent than are the pyrazine 1-oxides.

The effect of the substituent on the rate of exchange for the para hydrogen (H-2 in 5-X-pyrimidine 1-oxides) is, as in the pyrazine 1-oxides, considerably muted. The exchange rates for H-2 cannot be correlated with any substituent constant. It is hoped that the factors influencing these exchange rates may become more clear with the results of further studies on other heterocyclic ring systems.

When the exchange reactions of some of the pyrimidine *N*-oxides were studied in strongly basic media (0.3 *N* NaOD) the pmr spectra (Table II) revealed the existence of a "new" compound in addition to the pyrimidine *N*-oxide. The amount of this material increases with increasing base concentration. In pyrimidine *N*-oxide one finds, in addition to the "*N*-oxide" peaks, a one-hydrogen singlet at δ 8.08, one-hydrogen doublets at δ 8.07 and δ 8.76, and a one-hydrogen triplet at δ 5.70. A correlation of the rate of disappearance of these signals, for what must be a covalently hydrated species, with the rate of disappearance of the protons in the known positions of the "free" *N*-oxide makes it possible to assign the peaks at δ 8.08, 8.07, 6.76, and 5.70 to H-2, H-6, H-4, and H-5, respectively.

TABLE II
PMR CHEMICAL SHIFTS (δ) OF SOME PYRIMIDINE 1-OXIDES[a]

Compd	H_2	H_4	H_5	H_6	Substituent
Pyrimidine 1-oxide	9.14	8.62	7.75	8.66	
5-Methylpyrimidine 1-oxide	8.97	8.51		8.59	2.44
5-Bromopyrimidine 1-oxide	9.08	8.70		8.96	
5-Methoxypyrimidine 1-oxide	8.78	8.38		8.44	4.73
5-Dimethylaminopyrimidine 1-oxide	8.38	8.00		8.11	3.03
4-Methylpyrimidine 1-oxide	9.03		7.64	8.55	2.63
6-Methylpyrimidine 1-oxide	9.12	8.47	7.74		2.61

[a] Dilute 0.2 *M* solutions in D_2O.

Neutralization of these strongly basic solutions regenerates the pyrimidine *N*-oxides quantitatively. That these covalent hydration processes are indeed independent of the exchange reactions was shown by converting the pyrimidine *N*-oxide to its totally covalently hydrated species (as shown by pmr) by dissolving it in 2.5 *N* NaOD. After 3 hr, the pyrimidine *N*-oxide was recovered unchanged (no H → D exchange) upon acidification.

Studies that are directed towards establishing the structures of these products and the equilibria involved in these processes are in progress.

Experimental Section

Nmr spectra were obtained with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E instrument equipped with a solid sample injector. The ionizing voltage employed was 80 eV. Elemental analyses were determined by Mrs. K. Decker and Mrs. V. Gindelsperger of this department.

Preparation of the *N*-Oxides.—The pyrimidine *N*-oxide[7] and the methylpyrimidine *N*-oxides[8] were prepared by known procedures.

5-Bromopyrimidine 1-Oxide.—This compound was prepared according to the oxidation procedure described by Kobayashi, Kumadaki, and Sato.[9] The compound was obtained in 19% yield, mp 166–167°. *Anal.* Calcd for $C_4H_3N_2BrO$: C, 27.44; H, 1.73; N, 16.01. Found: C, 27.43; H, 2.03; N, 15.79.

5-Methoxypyrimidine 1-Oxide.—This compound was prepared from 5-methoxypyrimidine in 61% yield by the procedure described in ref 9, mp 161.5–162.5°. *Anal.* Calcd for $C_5H_6N_2O_2$: C, 47.61; H, 4.80; N, 22.22. Found: C, 47.70; H, 4.83; N, 22.21.

5-Dimethylaminopyrimidine 1-Oxide.—This compound was prepared by heating a solution of 5-bromopyrimidine 1-oxide (0.1 g, 0.57 mmol) in 40% aqueous dimethylamine (3 ml) in a sealed tube on a steam bath for 4 hr. The cooled solution was made basic and continuously extracted with chloroform. The chloroform extract was dried, and the solvent was removed *in vacuo*. The crude product was purified by sublimation followed by recrystallization from carbon tetrachloride to afford 0.46 g (20%) of 5-dimethylaminopyrimidine 1-oxide, mp 153–154°. *Anal.* Calcd for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.70; H, 6.55; N, 30.23.

Determination of Rate Constants.—The appropriate *N*-oxide was weighed into an nmr tube and 0.4 ml of D_2O was added. The solution was then allowed to come to 31°, and the HA-100 instrument was adjusted. An initial spectrum was then obtained, and 0.1 ml of the appropriate concentration of aqueous NaOD at 31° was then added with shaking.

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Registry No.—**1**, 36529-69-8; **2**, 36529-70-1; **3**, 36529-71-2; **4**, 17758-50-8; **5**, 17043-94-6; 4-methylpyrimidine 1-oxide, 17758-54-2; 6-methylpyrimidine 1-oxide, 33342-83-5.

Selective Dehydration of Secondary Alcohols with Methyltriphenoxyphosphonium Iodide in Hexamethylphosphoramide

ROBERT O. HUTCHINS,* M. GAIL HUTCHINS, AND CYNTHIA A. MILEWSKI[1]

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

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The perennial problem of effecting mild dehydrations of alcohols without rearrangement and the recent interest in elimination reactions induced by nucleophiles in polar aprotic solvents[2] prompt this report of the use of methyltriphenoxyphosphonium iodide (MTPI) in hexamethylphosphoramide (HMPA) as a mild reagent system for the selective dehydration of secondary alcohols.

An attempt to convert *trans*-4-*tert*-butylcyclohexanol into the corresponding cis iodide with MTPI[3] in HMPA resulted instead in an excellent yield (88%) of 4-*tert*-butylcyclohexene in only 15 min at room temperature. In view of the ease and effectiveness of the procedure and its potential utility as a mild dehydration method, the generality of the reaction was investigated.

A variety of alcohol types was subjected to MTPI and the results presented in Table I. In each case the alcohol was treated with a twofold excess of MTPI in HMPA (5 ml per mmol of alcohol) at the temperature listed. The reactions were conveniently monitored by glpc using internal standards and, upon completion, worked up by dilution with water or aqueous potassium hydroxide and extraction with cyclohexane. The results indicate that secondary alcohols are effectively dehydrated with no indication of rearrangements detected. Furthermore, in most cases a high predominance of the more stable Saytzeff alkene is formed (entries 5, 7, 8, 12, 13), often with substantial stereoselectivity for the *E* geometric isomer (entries 12, 14, 15). Primary alcohols are converted into the corresponding iodide in excellent yield (entry 16), but subsequent dehydrohalogenation is evidently slow under

(1) Undergraduate National Science Foundation Fellow, 1971.

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