Amine 14c. See footnote *f* of Table I.

Amine 9c: ^{1}H NMR ($CDCl_3$) δ 6.90–7.45 (m, 3 H, Ar H), 3.33 (br s, 2 H, bridgeheads), 3.13 (m, 1 H, NCH), 1.10–2.17 (m, 6 H, includes C_9 methylene at 1.90, NH_2 singlet at 1.60, and C_3 methylene); IR (film) 3500, 3400, 3045, 3000, 2890, 1605, 1465, 1430, 1345, 1320, 1300, 1220, 1160, 1120, 1070, 1050, 965, 915, 800, 740, 710 cm^{-1}. **9c·HCl**: mp 262–263 °C, mass spectrum, *m/e* (relative intensity) 228 (3), 227 (15, $M^{+}\cdot$), 210 (5), 185 (12), 184 (100), 164 (8), 115 (63). Anal. Calcd for $C_{12}H_{12}F_3N\cdot HCl$: C, 54.66; H, 4.97; N, 5.31. Found: C, 54.31; H, 5.20; N, 5.18.

Acknowledgment. We thank Ruth Pazhenchevsky for technical assistance in the preparation of 22. Helpful discussions with Professor Richard Givens of the University of Kansas are gratefully acknowledged.

Registry No. **6a**, 85977-26-0; **6b**, 86022-65-3; **6c**, 83118-49-4; **6c**·HCl, 86022-69-7; **7a**, 50781-99-2; **7b**, 86022-66-4; **7c**, 83118-50-7; **7c**·HCl, 86022-71-1; **8a**, 50782-00-8; **8b**, 86022-67-5; **8c**, 83118-51-8; **8c**·HCl, 86022-73-3; **9a**, 85977-27-1; **9b**, 86022-68-6; **9c**, 83118-52-9; **9c**·HCl, 86022-74-4; **10a**, 13153-47-4; **10b**, 85977-34-0; **10c**, 62624-26-4; **11a**, 86022-61-9; **11b**, 85977-30-6; **11c**, 83118-47-2; **11c**·HCl, 86023-21-4; **12a**, 86022-62-0; **12b**, 85977-31-7; **12c**, 83118-48-3; **12c**·HCl, 86022-70-0; **13a**, 86022-63-1; **13b**, 85977-32-8; **13c**, 86022-72-2; **13c**·HCl, 86087-02-7; **14a**, 86022-64-2; **14b**, 85977-33-9; **14c**, 86022-76-6; **15a**, 13153-75-8; **15b**, 86022-75-5; **15c**, 58742-04-4; **16**, 85977-24-8; **17**, 121-01-7; **18**, 400-66-8; **19**, 85977-20-4; **20**, 85977-21-5; **21**, 85977-22-6; **21** (amine), 58458-13-2; **22**, 85977-23-7; **23**, 85977-25-9; **24**, 85977-28-2; **25**, 69103-41-9; **26**, 69103-42-0; **27**, 85977-29-3; cyclopentadiene, 542-92-7; phthalimide, 85-41-6.

3-Substituted 1-Methoxypyridinium Ions: Substituent Effects on Rates of Hydrogen–Deuterium Exchange

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Pyridinium ylides are formed by deprotonation of the 2- and 6-positions of 3-substituted 1-methoxypyridinium ions in D_2O buffer solutions at 75.0 °C in reactions catalyzed by deuterioxide ion. Dual substituent parameter equations employing inductive and resonance effects correlate rate constants very well. Both 1- and 3-substituents have an additive influence on the reactivity of the 2-position even when reactivity approaches a diffusion-controlled limit.

Various N-substituted pyridinium ions and pyridine *N*-oxides form ylides by a simple deprotonation process.[1] The reaction is catalyzed by the deuterioxide ion and not by buffer bases. Pathways are illustrated in Scheme I.

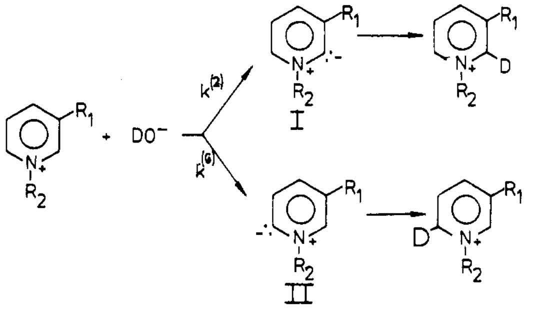
We report the results of hydrogen–deuterium exchange kinetic studies involving 3-substituted 1-methoxypyridinium ions ($R_2 = CH_3O$) in aqueous buffers. Reactive centers are situated ortho and para to the ring substituents (R_1). Ylides I and II are formed when the carbon acids are deprotonated by deuterioxide ion at the 2- and 6-positions. Our study involving ortho and para substituents in the *N*-methoxypyridinium ions is the most extensive to date. The results of this study along with those presented by Zoltewicz et al.[2,3] allow us to generalize about the effects of substituents on the rates of ylide formation. Some of our substrates are among the most acidic simple carbon acids known.

Experimental Section

Chemicals and Stock Solutions. All common laboratory chemicals were reagent grade. Deuterium oxide was 99.8%.

Deuterated stock solutions of acetic, formic, and boric acids, sodium dihydrogen phosphate, sodium carbonate, sodium acetate, and sodium chloride were prepared by dissolving an appropriate weight of anhydrous reagent in a volumetric flask. Dilute DCl was prepared by diluting commercial concentrated DCl with D_2O. Stock sodium deuterioxide solution was prepared by dissolving freshly cut sodium in D_2O. Pyridinium perchlorates were prepared as previously.[4]

Scheme I



Kinetic Procedure. The pyridinium salt was weighed into a volumetric flask (2 mL). Stock solutions of buffer and NaCl were added by syringe. After dilution to the mark with D_2O, the substrate concentration was 0.5 M, and the ionic strength was 1.0 M. Samples in an NMR tube were placed in a constant-temperature bath at 75.0 ± 0.5 °C. Periodically, the tube was removed and quenched in ice, and the NMR spectrum of the solution was recorded. Rate constants for exchange at H-2,6 were obtained in the usual way from plots of log (H-2 and/or H-6/H-5) vs. time.[5] H-5 served as the NMR reference standard.

Following a kinetic run, pD measurements were made at 75.0 ± 0.5 °C on the reaction mixture from the NMR tube as well as on a portion of the original unheated mixture according to the method of Bates[6] by using a Radiometer PHM 61 pH meter and

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(1) Elvidge, J. A.; Jones, J. R.; O'Brien, C.; Evans, E. A.; Sheppard, H. C. *Adv. Heterocycl. Chem.* **1974**, *16*, 1.

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Table I. Rate of H-D Exchange at the 2- and 6-Positions of 3-Chloro-*N*-methoxypyridinium Ion in D_2O at 75.0 ± 0.5 °C and 1.0 M Ionic Strength

2-position[a]		6-position[b]	
$10^4 k_\psi$, s^{-1}	pD	$10^4 k_\psi$, s^{-1}	pD
1.39	2.78	0.44	4.80
1.67	2.95	0.81	4.82
2.17	3.03	0.62	4.85
2.91	3.08	0.89	4.97
3.51	3.25	1.12	4.98
4.24	3.30	1.19	5.00
6.11	3.45	0.83	5.00
		1.22	5.02
		1.19	5.05
		1.48	5.20
		1.94	5.29
		1.68	5.30
		1.98	5.34
		2.31	5.40
		3.27	5.48
		3.13	5.50
		6.02	5.78
		6.06	5.80

[a] Buffer was formate. [b] Buffer was acetate.

a miniature combination electrode, Type GK 2401 B. The pD values of the two solutions agreed within 0.05, indicating that no significant change occurred.

Since the meter was standardized with protio buffers, it was necessary to add a correction to the meter readings to convert these to pD values. By use of the method of Zoltewicz and Cross,[3] a pD value was obtained by adding a correction of 0.35 to the meter reading; pK_w was taken to be 13.53.[3]

Control Experiments. A series of control runs in protio buffers was performed for the following 3-substituted 1-methoxypyridinium perchlorates: R_1 = CN, Cl, OMe, and COMe. No decomposition was detected by NMR after a period corresponding to 5–10 half-lives for hydrogen exchange.

Results and Discussion

Rates of deuterioxide ion-catalyzed hydrogen–deuterium exchange at the 2- and 6-positions of a series of 3-substituted 1-methoxypyridinium ions in buffered D_2O solutions of 1.0 M ionic strength at 75.0 ± 0.5 °C were obtained by using NMR to follow the reaction. In order to check for possible catalysis by buffer base or water, we selected the 3-chloro compound for extensive examination. This substrate is one of the most reactive in our series, undergoing rapid deprotonation in formate and acetate buffers. Consequently, it is an especially sensitive substrate to reveal the presence of catalysis by bases other than lyate ion. One claim has been made for catalysis by several bases in ylide-forming reactions in dilute aqueous acid.[7] A plot of $k\psi$ for the 6-position against $[OD^-]$ for 18 kinetic runs on the 3-chloro derivative (Table I) gave a straight line with a slope of 3.29×10^4 M^{-1} s^{-1} and an intercept of 1.11×10^{-6} s^{-1}. A *t* test confirmed that the line goes through the origin ($t_{cal} = 1.5$; $t_{99.9} = 3.96$). In the case of the 2-position of the 3-chloro derivative (Table I) the slope is 7.26×10^6 M^{-1} s^{-1} and the intercept is -2.16×10^{-6} s^{-1}. Clearly neither buffer nor D_2O catalysis was detected for either position. It has become clear from a variety of investigations that hydrogen isotope exchange reactions of the type considered here do not show significant buffer base (general base) catalysis and our results confirm this conclusion.[1,2]

When the base concentration remains constant and deuterium oxide is present in large excess, rates are pseudo first order. The rates of deprotonation are then described by eq 1 where $k\psi$ is the observed pseudo-first-order rate constant.

$$k\psi[PyrOCH_3^+] = k_2[PyrOCH_3^+][OD^-] \qquad (1)$$

The second-order rate constant k_2 may then be calculated from $k\psi$ and the apparent concentration of deuterioxide ion as determined from pD measurements at 75.0 ± 0.5 °C. The apparent concentration of deuterioxide ion was calculated from the expression $pOD = pK_W{}^D - pD$ where $K_W{}^D$ is the dissociation constant for D_2O ($pK_W{}^D$ = 13.526 at 75.0 °C[2,3]).

Table II lists rate constants, the range of pD values, and the identity of the buffers employed in the study. Where comparison is possible with published data, as in the case of *N*-methoxypyridinium ion,[2] the agreement is satisfactory.

Linear and multilinear regressions were performed by using six different scales of substituent parameters δ_I, δ_p, $\delta_R{}^-$, $\delta_R{}^0$, $\delta_{R(BA)}$, and $\delta_R{}^+$. The linear regression coefficient *r* in the single substituent parameter (MSP) treatment or the multiple regression coefficient *R* in the dual substituent parameter (DSP) treatment was used as a tendency estimator. With this estimator, the hypothesis of the existence of a nonaccidental correlation[8] has been tested at the 99% confidence level by comparison with tables of Student's *t* test values or Snedecor *F* values.[9]

The MSP treatment shows that the effects of the ortho substituents are primarily inductive in nature (eq 2). In

$$\log k_2 = (3.13 \pm 0.23) + (8.53 \pm 0.62)\delta_I;\ r = 0.997 \qquad (2)$$

this and other correlation equations uncertainty limits are given by one standard deviation. The standard deviation of the estimate is 0.20, and a comparison of the calculated intercept (1.35×10^3 L mol^{-1} s^{-1}), which gives the reactivity of the parent ion, with the measured reactivity (2.13×10^3 L mol^{-1} s^{-1}) shows that the calculated value is 37% smaller than the observed one. Clearly, the effects of ortho substituents are large and primarily inductive in nature.

In order to probe for contributions by resonance effects, we evaluated the DSP treatments. The best correlation results when $\delta_R{}^0$ constants are employed to measure resonance (eq 3) at the 2 position. The standard deviation

$$\log k_2 = (3.26 \pm 0.20) + (8.29 \pm 0.54)\delta_I + (0.69 \pm 0.62)\delta_R{}^0 \qquad (3)$$
$$R = 0.999$$

of the estimate is 0.12, and the calculated reactivity of the parent ion is 15% smaller than the measured. Correlations with the other three resonance substituent constants are not decidedly inferior. In all cases the multiple correlation coefficients are >0.99. Thus substituents influence the reactivity of the ortho position by both inductive and resonance effects, the inductive effect as measured by ρ values being 12 times larger than the resonance effect.

The reactivity of the para position cannot be expressed adequately in terms of a δ_I inductive parameter, but a useful correlation does exist with δ_p. These substituent constants are composed of a blend of inductive and resonance effects. The calculated rate constant (eq 4) for the parent ion is 12% larger than the experimental value. The standard deviation of the estimate is 0.51.

$$\log k_2 = (3.38 \pm 0.21) + (3.54 \pm 0.50)\delta_p;\ r = 0.945 \qquad (4)$$

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Table II. Second-Order Rate Constants of H–D Exchange at the 2- and 6-Positions of 3-Substituted *N*-Methoxypyridinium Ions in D_2O at 75.0 ± 0.5 °C and 1.0 M Ionic Strength

	2-position			6-position		
substituent	range of pD (buffer[a])	no. of measurements	k_2, 1 mol^{-1} s^{-1}	range of pD (buffer[a])	no. of measurements	k_2, 1 mol^{-1} s^{-1}
NO_2	1.00 (D)	3	$(7.36 \pm 0.48) \times 10^8$	3.00–3.75 (F)	6	$(2.62 \pm 0.61) \times 10^6$
CN	1.38–2.85 (D, F)	3	$(9.91 \pm 0.94) \times 10^7$	3.75–4.63 (A)	9	$(7.99 \pm 1.20) \times 10^5$
Cl	2.78–3.45 (F)	7	$(7.22 \pm 0.64) \times 10^6$	4.80–5.80 (A)	18	$(3.34 \pm 0.48) \times 10^4$
OCH_3	5.10–6.25 (A, P)	2	$(1.49 \pm 0.60) \times 10^5$	6.85–7.00 (P)	2	$(7.26 \pm 0.66) \times 10^2$
$COCH_3$	4.05–4.63 (A, F)	4	$(3.15 \pm 0.52) \times 10^5$	5.23–5.30 (A, P)	2	$(7.02 \pm 0.15) \times 10^4$
COO^-	6.90–8.05 (C)	2	$(4.20 \pm 0.02) \times 10^2$	6.90–8.05 (C)	2	$(6.72 \pm 0.20) \times 10^2$
CH_3	6.68–6.85 (P)	2	$(7.89 \pm 0.13) \times 10^2$			
H	6.60–6.68 (P)	2	$(2.13 \pm 0.14) \times 10^3$			

[a] Buffers: A, acetate; C, bicarbonate; F, formate; D, DCl; P, phosphate.

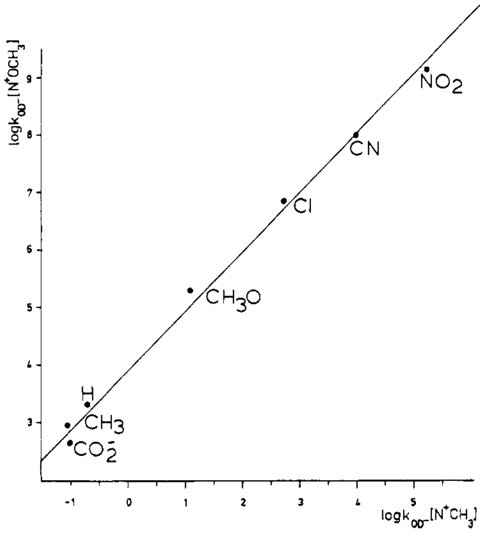

Figure 1. Second-order rate constants for H–D exchange at the 2-position of 3-substituted *N*-methylpyridinium ions[3] plotted against the corresponding rate constants for 3-substituted *N*-methoxypyridinium ions both at 75 °C. The correlation equation is $\log k_2(^+NOCH_3) = 4.17 + 0.92 \log k_2(^+NCH_3)$ with $r = 0.989$.

The DSP treatment gives nearly identical correlations with $\delta_R{}^0$ and $\delta_{R(BA)}$. Correlations using $\delta_R{}^-$ and $\delta_R{}^+$ are inferior as evidenced by lower values for the *F* test. With $\delta_R{}^0$ the calculated constant (eq 5) for the parent ion is 0.5% lower than the measured value, and the standard deviation of estimate is 0.10.

$$\log k_2 = (3.33 \pm 0.18) + (3.93 \pm 0.44)\delta_I + (3.16 \pm 0.51)\delta_R{}^0 \quad (5)$$

$$R = 0.998$$

It is instructive to compare the effects of substituents on the rates of deprotonation of *N*-methoxypyridinium ion carbon acids to give ylides I and II with the effects of substituents on the kinetic acidities of similar *N*-methylpyridinium ions. In Figure 1 are plotted the seven second-order rate constants [$\log k_2{}^{+NOCH_3}$] for 3-substituted *N*-methoxypyridinium ions at the 2-position vs. the corresponding second-order rate constants [$\log k_2{}^{+NCH_3}$] for 3-substituted pyridinium ions determined by Zoltewicz and Cross.[3] A linear relationship of good precision is obtained. The intercept (antilog) is ca. 3% smaller than the experimental ratio of the rate constants of *N*-methoxy- and *N*-methylpyridinium ions. This suggests that the mechanism of hydrogen–deuterium exchange at the 2-position in these series is similar and the effects of both substituents (R_1 and R_2) are additive. The approximately unit (0.921) slope reflects the similar contributions of inductive effects in both series in spite of the 10^4-fold greater reactivity of the *N*-methoxy compounds. Even the point for the nitro compound which has a reactivity approaching the diffusion-controlled limit remarkably falls on the line. A similar comparison between the reactivity of 3-substituted *N*-methoxy- and 3-substituted *N*-methylpyridinium ions at the 6-position is limited to five compounds, mostly with strongly electron-withdrawing groups. The correlation for unknown reasons is poor ($r = 0.7$).

In summary, our studies clearly show that the effects of substituents on pyridinium ylide formation can be large. The reactivity of an ortho position is determined mainly by inductive effects; a small, but real, resonance effect operates as well. The sensitivity of a para position to substituent effects is generally less than that of an ortho position. Both resonance and inductive effects have an important influence on the reactivity of a para position. The effects of both substituents (R_1 and R_2) on the reactivity of a 2-position are additive. General-base catalysis is insignificant.

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Registry No. 1-Methoxy-3-nitropyridinium, 76856-82-1; 3-cyano-1-methoxypyridinium, 54212-25-8; 3-chloro-1-methoxypyridinium, 83961-03-9; 1,3-dimethoxypyridinium, 85850-19-7; 3-acetyl-1-methoxypyridinium, 76856-84-3; 1-methoxy-3-pyridinium carboxylate, 85850-20-0; 1-methoxy-3-methylpyridinium, 60524-08-5; 1-methoxypyridinium, 30718-14-0.