Morpholino Demethoxylation on Pyrylium and Pyridinium Rings: Rate Parameters and Base Catalysis

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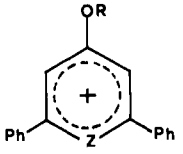
Abstract: The kinetics of morpholino demethoxylation of 4-methoxy-1-methyl-2,6-diphenylpyridinium (**1**) and 4-methoxy-2,6-diphenylpyrylium (**2**) ions were studied in methanol, in the presence of morpholine/morpholinium buffers, at 25 °C. Both reactions display general base catalysis and can be assumed to proceed through tetrahedral intermediates. By steady-state treatment the rate constant for the adduct formation and the several rate ratios in the base catalysis scheme were evaluated. Attack of the nucleophile to pyrylium occurs 3×10^6 times as fast as that to pyridinium. The detailed mechanism of base catalysis seems to differ in the two reactions. The reaction of cation **1** appears to involve a rate-limiting proton transfer, as generally observed in nucleophilic aromatic substitutions of activated benzene derivatives with amines in protic solvents. In contrast, the more reactive cation **2** seems to prefer the less common specific base–general acid mechanism.

Six-membered heteroaromatic cations, such as pyrylium and pyridinium cations, display varying tendencies to react with nucleophilic reagents, yielding pyran and dihydropyridine derivatives, respectively. The most reactive sites of these rings are the α and γ positions. If a leaving group is released from the reaction center and a nucleophilic substitution ensues, intermediate adducts may be hard to detect.[1] However, in the substitutions of pyridinium cations the intermediacy of dihydropyridines has been established in kinetic studies.[2]

As an extension of our recent studies[3,4] concerning the formation of adducts between heteroaromatic cations and nucleophilic reagents, we have examined the behavior of six-membered heteroaromatic cations in the substitution process.

In this paper we report results concerning the kinetics and mechanism of morpholino demethoxylation of 4-methoxy-1-methyl-2,6-diphenylpyridinium (**1**) and 4-methoxy-2,6-diphenylpyrylium (**2**) ions at 25 °C, in methanol. In nucleophilic aromatic substitution alkoxy groups are not very good leaving groups. However, dealkoxylation may be of synthetic value with activated substrates,[5] such as pyrylium ions.[6]



1, **3** Z = NMe
2 Z = O
1, **2** R = Me
3 R = H

The phenyl groups at the α positions of **1** and **2** are expected to have some hindering effect and to decrease the tendency to nucleophilic addition at these positions as well as the formation of dienic open-chain compounds formed from the resulting σ adducts. Such an effect seems to be more important with secondary amines than with the less crowded primary amines.[6b]

Experimental Section

Materials. 4-Methoxy-1-methyl-2,6-diphenylpyridinium perchlorate was obtained from 1-methyl-2,6-diphenyl-4-pyridone[7] and an excess of dimethyl sulfate. The reaction mixture, made up from 1 g of the former and 6 mL of the latter, was kept 24 h in a sealed tube at 100 °C. The addition of 20 mL of ethyl ether to the cold reaction mixture caused the separation of an oil, which was dissolved in the least amount of methanol and treated with 2.5 mL of 60% $HClO_4$. After cooling at 0 °C, a white solid was collected. A preliminary purification of this solid involved solution in MeCN and recrystallization upon addition of ethyl ether.

The ^1H NMR spectrum in MeCN was in accordance with the presence of the expected product and of another pyridinium perchlorate, which was tentatively identified from its ^1H NMR spectrum as the perchlorate of 4-hydroxy-1-methyl-2,6-diphenylpyridinium (**3**), the conjugate acid of the starting pyridone.

The separation of these perchlorates was accordingly made by adding the calculated amount of a methanol solution of potassium methoxide to the MeCN solution of this mixture in order to convert **3** back to the pyridone. After removing $KClO_4$ by filtration, ethyl ether was added and the perchlorate of cation **1** was precipitated as a white solid, mp 167–169 °C: ^1H NMR, $\delta(CD_3CN)$: 3.52 (s, 3 H, $N-CH_3$), 4.07 (s, 3 H, OCH_3), 7.25 (s, 2 H, pyridinium ring), 7.55 (apparent s, 10 H, C_6H_5). Besides the signals of **1**, the ^1H NMR spectrum of the reaction mixture before purification showed two singlets at δ 7.15 and 3.5, in correspondence of the ring protons and the 1-methyl protons, respectively, of cation **3**, and a more intense signal in the phenyl region. From the relative intensities of the signals, the [**1**]/[**3**] ratio was estimated to be nearly 3.

4-Methoxy-2,6-diphenylpyrylium perchlorate was available from our previous work.[4]

1-Methyl-4-morpholino-2,6-diphenylpyridinium cation was isolated as the perchlorate salt and characterized through its ^1H NMR spectrum in acetone-d_6: δ 3.57 ($N-CH_3$, 3 H), 3.89 (NCH_2 and OCH_2, broad s, 8 H), 7.15 (s, pyridinium ring, 2 H), 7.7 (C_6H_5, 10 H).

4-Morpholino-2,6-diphenylpyrylium cation was characterized in situ in Me_2SO-d_6 through its ^1H NMR spectrum: δ 3.7–4.4 (NCH_2 and OCH_2, 8 H), 7.97 (s, pyrylium ring, 2 H), 8.3–8.7, 7.7–7.9 (C_6H_5, 10 H).

Methanol and methanol solutions of $HClO_4$ were prepared as previously described.[3] Morpholine was freshly distilled from sodium and potassium.

Kinetic Measurements. The kinetics were followed spectrophotometrically, in methanol, at 25 °C, under pseudo-first-order conditions, in the presence of an excess of morpholine. Most measurements were made in buffers prepared by partial neutralization of morpholine (pK_a = 8.69 at 25 °C in CH_3OH)[8] with a MeOH solution of $HClO_4$. The MeO^- ion concentration of each buffer was calculated from the methanol autoprotolysis constant (pK_s = 16.92 at 25 °C).[9] The reactions of **1** were

(1) Krivun, S. V.; Alfërova, O. F.; Sayapina, S. V. *Russ. Chem. Rev.* **1974**, *43*, 835.
(2) O'Leary, M. H.; Stach, R. W. *J. Org. Chem.* **1972**, *37*, 1491.
(3) Doddi, G.; Fornarini, S.; Illuminati, G.; Stegel, F. *J. Org. Chem.* **1979**, *44*, 4496.
(4) Bersani, S.; Doddi, G.; Fornarini, S.; Stegel, F. *J. Org. Chem.* **1978**, *43*, 4112.
(5) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
(6) (a) Anker, R. M.; Cook, A. H. *J. Chem. Soc.* **1946**, 117. (b) Van Allan, J. A.; Reynolds, G. A.; Petropoulos, C. C. *J. Heterocycl. Chem.* **1972**, *9*, 783. (c) Sib, S. *Tetrahedron*, **1975**, *31*, 2229. (d) Sammes, M. P.; Yip, K. L. *J. Chem. Soc., Perkin Trans 1* **1978**, 1373.
(7) Light, R. J.; Hauser, C. R. *J. Org. Chem.* **1960**, *25*, 538.
(8) (a) Calculated from the pK_a value reported in ref 8b and the pK_S value of ref 9. (b) Izmailov, N. A.; Mayhazova, H. *Zh. Phys. Chem.* **1960**, *34*, 814.

0002-7863/81/1503-6148$01.25/0

Table I. Kinetic Data for the Morpholino Demethoxylation of Pyridinium Cation **1**, in MeOH, at 25 °C

(a) At Low MeO^- Ion Concentration

[mor], M	[mor]/[morH$^+$]	[MeO^-], M × 10^7	k_{obsd}, s^{-1} × 10^5	k_{obsd}/[mor], s^{-1} M^{-1} × 10^4
0.12	30.9	1.82	1.26	1.10
0.16	22.6	1.33	2.16	1.32
0.24	16.3	0.96	3.52	1.49
0.31	28.4	1.68	7.26	2.34
0.39	42.4	2.50	10.6	2.75
0.47	52.1	3.07	16.5	3.50
0.55	29.3	1.72	21.8	3.99
0.63	25.4	1.50	27.4	4.36
0.66	22.6	1.33	30.7	4.67
0.82	22.7	1.34	47.8	5.82
0.91	30.6	1.81	56.0	6.13
1.15	30.8	1.81	80.1	6.96

(b) At High MeO^- Ion Concentration

[mor], M	[MeO^-], M × 10^3	k_{obsd}, s^{-1} × 10^3	k_{obsd}/[mor], s^{-1} M^{-1} × 10^4
0.55	1.72	0.21	3.99
0.55	0.29	0.347	6.35
0.55	0.52	0.640	11.7
0.55	0.74	0.730	13.4
0.55	1.11	0.815	14.9
0.58	1.48	0.906	15.7
0.58	1.79	1.082	18.8
0.58	2.55	1.250	21.7
0.57	2.22	1.163	20.5
0.57	1.85	1.070	19.0
0.57	1.64	1.060	18.7
0.57	1.35	0.930	16.4
0.57	0.96	0.820	14.5
0.57	0.48	0.609	10.8
0.57	1.93	1.160	20.5
0.57	1.54	0.939	16.6

conveniently followed in the thermostated compartment of a Beckman DB-GT spectrophotometer, whereas the reactions of the more reactive pyrylium cation **2** were carried out in a Durrum 110 stopped-flow apparatus. For the stopped-flow measurements the buffer was obtained at time zero upon mixing morpholine solutions with solutions of the substrate containing a known amount of $HClO_4$. The measurements of Table IIa were carried out in the presence of higher MeO^- concentrations, as obtained upon dilution of a concentrated sodium methoxide solution.

In MeOH, cation **1** shows two absorption maxima, at 243 (log ε 4.29) and 284 nm (log ε 4.01). The morpholine derivative shows two maxima, at 253 (log ε 4.20) and 304 nm (log ε 4.32). The kinetics of morpholino demethoxylation of **1** were followed at 304 nm. Cation **2** is characterized by two maxima, at 274 (log ε 4.39) and 355 nm (log ε 4.41). The substitution product shows two maxima, at 260 (log ε 4.20) and 320 nm (log ε 4.57). The kinetic measurements were carried out at 300 nm.

Results

Both cations **1** and **2** undergo the expected substitution, although at different rates. Owing to the absence of absorbance in the 440–460-nm range it was possible to exclude the formation of any open-chain product that can be formed after attachment of the amine to the α-position of the cations. At room temperature, pyridinium ion **1** undergoes substitution much more slowly than pyrylium cation **2**, whose reaction must be followed by the stopped-flow technique. The kinetic data are collected in Tables I and II.

The reactions of both **1** and **2** with morpholine were found to be base catalyzed. Unlike pyridinium cation **1**, which does not show any appreciable tendency to undergo addition of the MeO^- ion present in the medium, pyrylium cation **2** undergoes the latter reaction as a fast reversible side reaction of the substitution process.

For all these reasons an evaluation of the relative reactivities of **1** and **2** toward morpholine cannot be obtained directly.

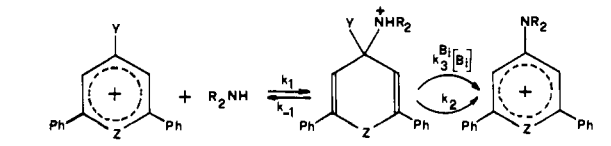
(9) Koskikallio, J. *Suom. Kemistil. B* **1957**, *30*, 111.

Table II. Kinetic Data for the Morpholino Demethoxylation of Pyrylium Cation **2**, in MeOH, at 25.0 °C[a]

[CH_3O^-], M × 10^6	k^{mor}, s^{-1}	k^{mor}/[mor], s^{-1} M^{-1} × 10^3
1.8	56.6	3.2_1
2.2	68.8	3.9
2.7	66.7	3.8
3.9_4	82.5	4.7
4.8	80.9	4.6
5.4_8	95.9	5.4_5

[a] At constant morpholine concentration ([mor] = 1.76 × 10^{-3} M).

Scheme I



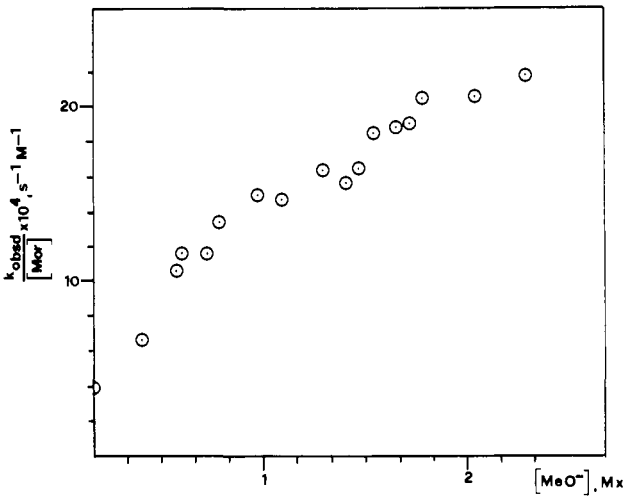


Figure 1. Plot of k_a ($=k_{obsd}/[Mor]$) vs. [MeO^-], at constant morpholine concentration, for the morpholino demethoxylation of **1**.

Morpholino Demethoxylation of Pyridinium Cation 1. The kinetic data of Table Ia were obtained at a low MeO^- concentration (1–20 × 10^{-7} M). The plot of $k_a = k_{obsd}/[mor]$ against [mor] gives a straight line. The kinetic effect of the amine shows that this reaction is subjected to general base catalysis. According to the mechanism of nucleophilic aromatic substitution of activated benzene systems with amines,[10] this reaction may be described by Scheme I. Application of the steady-state approximation to the overall reaction scheme gives the expression

$$k_a = \frac{k_1k_2 + k_1\sum_i k_3^{B_i}[B_i]}{k_{-1} + k_2 + \sum_i k_3^{B_i}[B_i]} \quad (1)$$

The linear dependence of k_a on the amine concentration indicates that the relationship $k_{-1} \gg (k_2 + \sum_i k_3^{B_i}[B_i])$ holds, so that eq 1 becomes

$$k_a = \frac{k_1k_2}{k_{-1}} + \frac{k_1}{k_{-1}}\sum_i k_3^{B_i}[B_i] \quad (2)$$

Under these conditions the k_1 term cannot be obtained directly from the kinetic data.

When the methoxide ion concentration is raised and the morpholine concentration is kept practically constant (Table Ib), a downward curvature is observed for the plot of k_a against [MeO^-] (Figure 1). This curvature shows that the (k_2 +

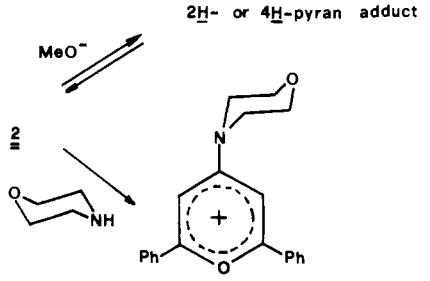
(10) Bernasconi, C. F. *MTP Int. Rev. Sci.: Org. Chem., Ser. One* **1973**, *3*, 33.

Table III. Summary of Kinetic Results for the Morpholino Demethoxylation of 1 and 2, in MeOH, at 25 °C

	1	2
k_1, M^{-1} s^{-1}	2.85×10^{-3}	8.6×10^{3}
k_3^{mor}/k_{-1}, M^{-1}	0.28	7
k_3^{MeO}/k_{-1}, M^{-1}	1.1×10^{2}	3.1×10^{5}
k_2/k_{-1}	3.8×10^{-3}	1.0×10^{-2}
k_3^{mor}/k_2, M^{-1}	75	6.9×10^{2}
k_3^{MeO}/k_2, M^{-1}	2.9×10^{4}	3.1×10^{7}
k_3^{MeO}/k_3^{mor}	3.7×10^{2}	4.5×10^{4}

$\sum_i k_3^{B_i}[B_i])$ term now cannot be neglected with respect to k_{-1}. Under these conditions the catalytic effect of MeO^- is found to be stronger than that of morpholine, $k_3^{MeO}[MeO^-] \gg (k_2 + k_3^{mor}[mor])$. Using standard procedures[11] we have calculated k_1 and the several ratios as reported in Table III.

Morpholino Demethoxylation of Pyrylium Cation 2. Kinetic data for this reaction are reported in Table II. The very low amount of methoxide ion formed upon interaction of the solvent with the base is sufficient to effect some ring addition. The latter reaction can be minimized by the presence of morpholinium ion. The general reaction pattern for **2** is shown. At a methoxide ion



concentration higher than 10^{-6} M, k_{obsd} for the overall reaction is satisfactorily given by

$$k_{obsd} = k^{mor} + k_2^{MeO}[MeO^-] + k_4^{MeO}[MeO^-] \qquad (3)$$

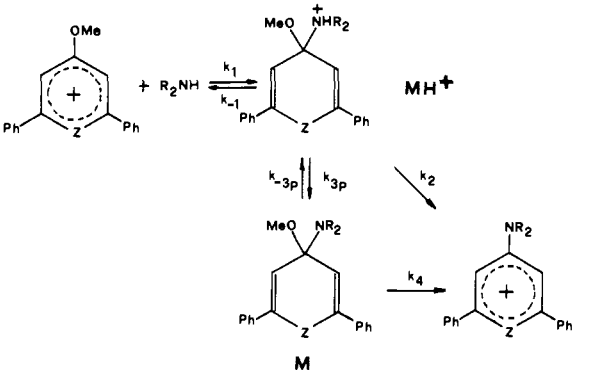
where k^{mor} is the pseudo-first-order rate constant for substitution with morpholine; k_2^{MeO} and k_4^{MeO} are the second-order rate constants for the addition of MeO^- to positions 2 and 4, respectively. The k^{mor} term is obtained by appropriate subtraction of the $k_2^{MeO}[MeO^-]$ and $k_4^{MeO}[MeO^-]$ terms from k_{obsd} ($k_2^{MeO} = 5.05 \times 10^5$ M^{-1} s^{-1}, $k_4^{MeO} = 3.15 \times 10^6$ M^{-1} s^{-1}).[3] The k^{mor} term is thereafter treated as described above for the k_{obsd} term in the reaction of cation **1**. Relevant kinetic parameters are summarized in Table III.

Discussion

Stepwise Nature of the Substitution Reaction. Indirect support to a stepwise substitution of heteroaromatic cations has been provided by isolation and/or detection of the related adducts (2*H*- and 4*H*-pyrans, and 1,2- and 1,4-dihydropyridines) upon reaction of pyrylium and pyridinium cations, respectively, with nucleophilic reagents. These adducts are the neutral counterparts of the anionic Meisenheimer adducts as formed from polynitro benzene derivatives and nucleophilic reagents. 4*H*-Pyrans similar to the possible intermediates for the substitution of cation **2** were detected as kinetically controlled products in the reaction of 2,6-diphenylpyrylium cation with MeO^-, but easily converted into the more stable 2*H*-pyrans or their open-chain valence tautomers, especially in the presence of protic solvents.[4]

The occurrence of base-catalysis in the reactions of cations **1** and **2** with morpholine gives further support to the stepwise nature of the substitution process of heteroaromatic cations, involving the formation of σ adducts as intermediates (Scheme I). Such evidence often has been reported in the aromatic substitution of activated benzene derivatives, particularly in the replacement of

Scheme II



poor leaving groups with secondary amines,[10] but so far has not been reported for the replacement reactions with heteroaromatic cations.

Relative Reactivity of Pyrylium and Pyridinium Cations. The reactivity ratio between **2** and **1**, as measured by the $(k_1)_2/(k_1)_1$ ratio, is 3×10^6. So far this is the first evaluation of the relative reactivity of pyrylium and pyridinium cations toward nucleophiles. It is in agreement with the large reactivity difference qualitatively recognized also in other previously examined nucleophilic substitutions.[12,13] It must be noted that pyrylium cations also show a greater tendency to undergo nucleophilic attachment of MeO^- ion in methanol than pyridinium cations; thus, whereas the equilibrium for the formation of 2*H*- or 4*H*-pyrans is completely shifted toward the pyrans, the corresponding equilibrium between methoxide ion and 1,2,4,6-tetraphenylpyridinium cations is shifted toward the reactants.[14]

As evidenced by ^{13}C NMR data and theoretical calculations, the electron density at the α and γ positions of the pyrylium ring appears to be lower than at the corresponding positions of the pyridinium cation.[15] In other words, resonance structures such as **4** and **5** seem to give a more important contribution to the delocalization of the charge in the pyrylium cations.

4 **5**

Mechanism of Substitution. Following the approach recently suggested by Bernasconi,[16] we have analyzed our kinetic data according to Scheme II, where $k_{3p} = k_{3p}^{MeO}[MeO^-] + k_{3p}^{mor}[mor]$, $k_{-3p} = k_{-3p}^{morH}[morH^+] + k_{-3p}^{MeOH}$, $k_4 = k_4^{MeOH} + k_4^{morH}[morH^+]$. In this scheme k_1, k_{-1}, and k_2 are defined as in Scheme I; k_{3p}^{mor} and k_{3p}^{MeO} refer to the deprotonation of MH^+ to M by morpholine and methoxide ion, respectively; k_{-3p}^{morH} and k_{-3p}^{MeOH} refer to the protonation of M to MH^+ by morpholinium ion and methanol, respectively; k_4^{MeOH} refers to uncatalyzed or solvent-assisted leaving group departure, and k_4^{morH} corresponds to the same process, as catalyzed by morpholinium ion. Application of the steady-state approximation to Scheme II gives

$$k_a = \frac{k_1 k_2 (k_{-3p} + k_4) + k_1 k_{3p} k_4}{(k_{-1} + k_2)(k_{-3p} + k_4) + k_{3p} k_4} \qquad (4)$$

Two limit situations have been envisaged for the approximation of this equation.

(11) (a) Bunnett, J. F.; Garst, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 3875. (b) Bunnett, J. F.; Bernasconi, C. F. *Ibid.* **1965**, *87*, 5209. (c) Bernasconi, C. F. *J. Org. Chem.* **1967**, *32*, 2947.

(12) King, L. C.; Ozog, F. J. *J. Org. Chem.* **1955**, *20*, 448.

(13) Yoneda, S.; Sugimoto, T.; Tanaka, O.; Moriya, Y.; Yoshida, Z. *Tetrahedron* **1975**, *31*, 2669

(14) Aveta, R.; Doddi, G.; Insam, N.; Stegel, F. *J. Org. Chem.* **1980**, *45*, 5160.

(15) Balaban, A. T.; Wray, V. *Org. Magn. Reson.* **1977**, *9*, 16.

(16) Bernasconi, C. F.; de Rossi, R. H.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99*, 4090.

(a) $k_{-3p} \gg k_4$ ($k_{-1} \gg k_{3p}k_4/k_{-3p}$). These conditions are peculiar of the SB–GA mechanism (specific base–general acid catalysis), which holds in nucleophilic aromatic substitutions of activated derivatives in aprotic solvents, as shown by Orvik and Bunnett in the reaction of naphthalene derivatives.[17] The rate-limiting step is the transformation of M into the products (k_4).

Under the validity range of this mechanism, any $k_3^{B_i}$ term coincides with the product of $K_{MH}^{B_i}$ (the equilibrium constant between the MH intermediate and any base B_i) and $k_4^{BH_i}$ ($k_3^{mor} = K_{3p}^{mor}k_4^{morH}$; $k_3^{MeO} = K_{3p}^{MeO}k_4^{MeOH}$). Since $K_{3p}^{mor}/K_{3p}^{MeOH} = K_S^{MeOH}/K_a^{mor}$, it is possible to write eq 5, which indicates the relative effectiveness of different acids as catalysts:

$$\frac{k_4^{MeOH}}{k_4^{morH}} = \frac{k_3^{MeO}K_S^{MeOH}}{k_3^{mor}K_a^{mor}} \qquad (5)$$

where K_a^{mor} is the dissociation constant of the conjugate acid of morpholine, and K_S^{MeOH} the autoprotolysis constant of methanol.

(b) $k_4 \gg k_{-3p}$ ($k_{-1} \gg k_{3p}$). Under these conditions the proton-transfer step corresponds to the rate-limiting process, and the k_{3p} terms coincide with the k_3 terms of eq 1.

In order to distinguish between mechanisms corresponding to the conditions defined in (a) or (b), our kinetic data were examined in order to test their consistency with either of the different hypotheses.

Thus, if the SB–GA mechanism were operating, the introduction in eq 5 of the experimental values of K_S^{MeOH}, K_a^{mor}, and the k_3^{mor}/k_3^{MeO} ratios would allow one to calculate the hypothetical k_4^{morH}/k_4^{MeOH} ratios for the reactions of pyridinium cation **1** and of pyrylium cation **2** as 4.6×10^5 and 3.8×10^3, respectively.

Under these assumptions, morpholinium cation would be much more effective than the solvent in promoting the final reaction step.

As to the k_4^{morH}/k_4^{MeOH} ratio for the pyrylium system, it seems to be consistent with our findings concerning the relative ability of weak acids and the solvent in promoting the conversion of 2-methoxy-2,4,6-triphenyl-2*H*-pyran to the 2,4,6-triphenylpyrylium cation in methanol.[18] On the other hand, even if similar data concerning the pyridinium system were not available, dihydropyridine adducts, as compared to pyran adducts, have a stronger tendency to restore the aromaticity by loss of the MeO^- ion.[3,19] Therefore, it is reasonable to assume that the role of acids in promoting the departure of methoxy group from the dihydropyridine moiety should be less important than from the pyran system, in contrast with what could be obtained on the assumption of an SB–GA mechanism.

We can turn now to verify whether, according to the alternative mechanism indicated under conditions b, the proton abstraction may be the rate-limiting step.

Some indications about the likelihood of this mechanism can be given by k_3^{MeO}/k_3^{mor} (Table III), which is a measure of the relative ability of MeO^- ion and morpholine to abstract a proton from the positively charged adduct MH^+. Under the hypothesis that the proton abstraction is the rate-limiting step, this ratio coincides with the $k_{3p}^{MeO}/k_{3p}^{mor}$ ratio, k_{3p}^{MeO} and k_{3p}^{mor} being defined in Scheme II.

In a protic solvent a thermodynamically favored proton transfer from an NH^+ acid to an oxygen or nitrogen base should be a diffusion-controlled process.[20] Therefore, the value of the ratio should not be different from 1. Whenever a different ratio is observed, it has to be ascribed to a hindering effect for the slower proton transfer. Thus, a ratio different from 1 was observed in the hydrogen abstraction from Meisenheimer-type adducts formed from 1,3,5-trinitrobenzene and amines[21] and was ascribed to a steric retardation in the hydrogen abstraction from amines with respect to the same process promoted by the conjugate base of the solvent. A similar explanation was offered for the base catalysis in aromatic substitution of nitro-activated benzene derivatives with amines in protic solvents.[16] The corresponding k_3^{MeO}/k_3^{amine} ratios, as observed in the nitrobenzene series, were 10^2 at most. The k_3^{MeO}/k_3^{mor} ratio observed in the reaction of the pyridinium substrate **1**, $\sim 4 \times 10^2$, falls within this range, whereas a higher value, ca. 5×10^4, is observed in the reaction of the pyrylium cation. The increase of the k_3^{MeO}/k_3^{mor} ratio in going to the pyrylium cation can hardly be explained in terms of an increase of steric hindrance during the approach of the base to the NH^+ acid center, because of the similarity of the steric situation at the reaction centers of **1** and **2**. The approach of the base to the pyridine adduct is actually expected to be retarded, since 4*H*-pyrans are reported to be planar,[22] whereas 1,4-dihydropyridines may assume a boat conformation.[23]

The above discussion leads us to conclude that cations **1** and **2** are likely to follow different mechanisms of substitution. The present evidence suggests a rate-limiting proton transfer for the reaction of the pyridinium ion, in analogy with what is observed with nitro-activated benzene derivatives. In contrast, the data are consistent with an SB–GA mechanism for the pyrylium ion, whereas a rate-limiting proton transfer can be fairly safely excluded.

We may also ask whether the difference in the substitution mechanism is supported by the different structure and reactivity of the rings involved in the reaction. The proposed difference in mechanism requires that the k_{-3p}/k_4 ratio is significantly affected in going from the pyridinium cation (rate-limiting proton transfer, $1 \gg k_{-3p}/k_4$) to the pyrylium ring (SB–GA, $k_{-3p}/k_4 \gg 1$). The k_{-3p} term, which refers to the rate of proton transfer to the neutral intermediate, is not likely to be strongly affected by the different heteroatom. However, the k_4 term, corresponding to an aromatization step, is likely to be larger in the reaction of the dihydropyridine than in the reaction of the pyran, in correspondence to the formation of the more aromatic pyridinium ion.

A final remark may be made about the nature of the uncatalyzed conversion of the MH^+ intermediate into the products (k_2), concerning the departure of the methoxy group from the positively charged intermediate. This process is not likely to involve the preliminary breaking of the C–OMe bond and the formation of a dication, according to the model suggested for substitutions starting from activated neutral substrates,[16] but, rather, at some stage, a proton transfer to the departing alkoxy group, either directly from the NH^+ group or through the intermediacy of the solvent.

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