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Electrophilic Heteroaromatic Substitutions. 8.[1] Studies on the Mechanism of the α-Side-Chain Aminomethylation and Hydrogen/Deuterium Isotope Exchange Reactions of α-Methylpyrroles

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A kinetic investigation of the acid-mediated α-side-chain (dimethylamino)alkylation and hydrogen/deuterium isotope exchange reactions of ethyl 1,3,4,5-tetramethylpyrrole-2-carboxylate (**1**) and ethyl 4-bromo-1,3,5-trimethylpyrrole-2-carboxylate (**2**) in aqueous acetonitrile has been carried out. The effect of a number of variables, such as nature and concentration of the catalyzing acid, amount of water in the reaction medium, and concentration and type of the electrophile, on the reaction rate indicates that both processes are subject to general acid catalysis and that their limiting step is electrophilic attack on an α-methylenepyrroline. The influence on the rate of the Mannich reaction of the nuclear substituent adjacent to the side chain undergoing attack is also discussed. The conditional dissociation constants of acetic and formic acid in 95% aqueous acetonitrile have been measured.

Among the three electrophilic α-side-chain substitution processes known to date in pyrrole chemistry (i.e., halogenation,[2] hydrogen/deuterium isotope exchange,[1] and (dialkylamino)methylation[3]) only the halogenations by molecular chlorine or bromine have been the object of mechanistic investigations.[2] In previous papers of this series[1,3] a qualitative description of the other two nonconventional reactions has been given. These reactions occur only in a moderately acidic aqueous medium, the processes are reversible, and, in the case of the Mannich reaction, a consecutive N-substitution eventually takes place with formation of double bases if the pyrrole is N-unsubstituted and the reaction is carried out in the daylight.

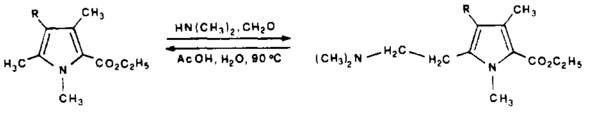
We now report on investigations undertaken in order to throw some light on the mechanistic features of the α-side-chain aminoalkylation and H/D isotope exchange processes, which appear to differ in many details from those of the side-chain halogenation.

Results and Discussion

N-Methylpyrroles **1** and **2** were used in order to avoid any conventional reaction and complications due to a possible incursion of the consecutive, light-induced N-aminomethylation. The secondary amine chosen was dimethylamine, and the solvent was acetonitrile containing a small percent of water (due to solubility problems, the concentration of water could not exceed ca. 5%). The kinetic runs were performed at 90 °C in the dark, keeping the molar ratio formaldehyde/amine always as unity. It should be noted that reproducible results could be obtained only if the Mannich reagent was prepared at least 12 h before the measurements were started, i.e., only after the time required for the attainment of equilibrium 1 had elapsed. Both **1** and **2** have previously been shown[3] to

$$CH_2O + H_2N^+(CH_3)_2 \rightleftarrows {}^+CH_2N(CH_3)_2 + H_2O \quad (1)$$

afford the corresponding 5-(dimethylamino)ethyl derivatives **3** and **4**, respectively, as the sole products when heated in the dark with dimethylamine and formaldehyde in aqueous acetic acid (eq 2).



(2)

1, R = CH$_3$
2, R = Br

3, R = CH$_3$
4, R = Br

Table I. Observed Third-Order Kinetic Coefficients for the Reaction of Pyrroles 1 and 2 with Dimethylamine and Formaldehyde in 15.98 M Acetic Acid in Aqueous Acetonitrile at 90 °C[a]

pyrrole 1[b]		pyrrole 2[c]	
t, h	$10 \times k_3$, s^{-1} M^{-2}	t, h	$10 \times k_3$, s^{-1} M^{-2}
0.5	6.40	1.0	9.30
3	6.39	2.0	9.45
5.5	6.40	3.0	9.34
7.0	6.38	5.0	9.29
10.0	6.41	6.0	9.30
12.0	6.40	8.0	9.30
16.0	6.39	12.0	9.28
18.0	6.40	15.0	9.28
24.0	6.38	20.0	9.25
40.0	6.40	24.0	9.32

[a] $[H_2O] = 2.77$ M; $[1]_0 = [2]_0 =$ ca. 0.080 M. Reactions were followed up to ca. 90% completion. [b] $[CH_2O] = [HN(CH_3)_2]_0 =$ ca. 0.080 M; kinetic law, eq 3. [c] $[CH_2O] = [HN(CH_3)_2]_0 =$ ca. 0.16 M; kinetic law, eq 4.

Since side-chain aminomethylation and side-chain hydrogen/deuterium isotope exchange do not occur in neutral or basic media,[3] the reactions turn out to be subject to acid catalysis. Therefore, a study of the effect of the protonating ability of the reaction medium was carried out first, by changing both the acid (acetic, chloroacetic, or formic) and its concentration. The concentration of the water and the pyrrole/Mannich reagent molar ratio were kept constant. By analogy with other Mannich-type reactions,[4] the kinetic data were treated according to a third-order law,[5] eq 3, for $[\text{pyrrole}]_0 = [CH_2O]_0 = [HN(CH_3)_2]_0 = A_0$, and

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[1] Part VII: Curulli, A.; Sleiter, G. *Isotopenpraxis* **1983**, *19*, 207.

[2] Angelini, G.; Illuminati, G.; Monaci, A.; Sleiter, G.; Speranza, M. *J. Am. Chem. Soc.* **1980**, *102*, 1377. Angelini, G.; Giancaspro, C.; Illuminati, G.; Sleiter, G. *J. Org. Chem.* **1980**, *45*, 1786 and references cited therein.

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Table II. Observed Third-Order Kinetic Coefficients for the Reaction of Pyrroles 1 and 2 with Dimethylamine and Formaldehyde in Aqueous Acetonitrile at 90 °C under Diverse Conditions[a]

			$10 \times k_3$,[b] $s^{-1}\ M^{-2}$	
entry	acid	acid, M	pyrrole 1	pyrrole 2
1	acetic	15.98	6.40	3.20
2		15.98		0.008[c]
3		15.98		9.30[d]
4		12.87	5.00	2.50
5		8.55	3.20	1.51
6		5.28	1.40	0.652
7		1.91	0.30	0.146
8	chloroacetic	8.56		2.92
9	formic	0.211		0.880
10		0.020[e]		0.080
11		0.010[e]		0.051

[a] Unless otherwise indicated $[\text{pyrrole}]_0 = [CH_2O]_0 = [HN(CH_3)_2]_0 = 0.08$ M, $[H_2O] = 2.77$ M; kinetic law, eq 3. [b] Mean values from duplicate experiments. [c] $[H_2O] = 0.28$ M. [d] $[\text{Pyrrole}]_0 =$ ca. 0.08 M; $[CH_2O]_0 = [HN(CH_3)_2]_0 =$ ca. 0.16 M; kinetic law, eq 4. [e] In the presence of a formic acid/sodium formate buffer, at pH* 3.8 (see ref 8).

$x = [CH_2O]$ at time t or eq 4, for $[\text{pyrrole}]_0 = B_0 \neq [CH_2O]_0 = [HN(CH_3)_2]_0 = A_0 - A = 2(B_0 - B)$.

$$2kt = (2A_0x - x^2)/A_0^2(A_0 - x)^2 \qquad (3)$$

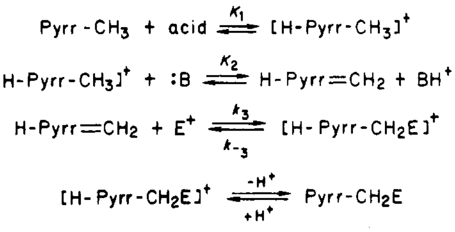
$$kt = \frac{2}{2B_0 - A_0}\left(\frac{1}{A} - \frac{1}{A_0}\right) + \frac{2}{(2B_0 - A_0)^2} \ln \frac{B_0 A}{A_0 B} \qquad (4)$$

The fit of the experimental data with these laws was always satisfactory, as shown by the examples reported in Table I.

Further data are presented in Table II. These clearly show that the reaction rate depends not only on the concentration and the nature (strength) of the acid present but also that there is a strong influence of the concentration of water (an ca. 10-fold reduction in the concentration of water causes an ca. 400-fold decrease in the rate of the side-chain aminomethylation of pyrrole **2**). This is further substantiated by the fact that under anhydrous conditions (15.98 M acetic acid in acetonitrile), with use of the more reactive pyrrole **1** and the preformed Mannich reagent, *N,N*-dimethylmethyleneammonium chloride,[6] no reaction took place: after ca. 200 h at 90 °C not even a trace of aminomethylation product could be detected in the reaction mixture. Therefore, the presence of water appears to be necessary for side-chain aminomethylation to occur. (The same proved true for the α-side-chain hydrogen isotope exchange: no deuterated pyrroles could be detected even after prolonged heating of **1** or **2** in 15.98 M CD_3CO_2D in anhydrous acetonitrile). This could be confirmed by the fact that if 2.77 M of freshly fused sodium acetate was added to the above-mentioned anhydrous mixture, the side-chain substitution product **3** formed, although at a considerably slower rate (80% reaction after 150 h at 90 °C) than in the presence of water. The reduced efficiency of AcO^- as a base as compared with that of water may probably be attributed either to the very low concentration of free acetate ions in acetic acid or to a specific rate-enhancing effect, in addition to that of a base, of water in the rate-limiting step of the reaction.

The reaction rate is also dependent on the concentration of the Mannich reagent, which therefore participates in the slow step of the reaction. The mechanism is thus analogous to that commonly accepted for the halogenation of ketones,[7] the rate of which is however independent of the concentration of the electrophile. This conclusion is also supported by measurements of the kinetics of α-side-chain hydrogen/deuterium isotopic exchange for pyrrole **2** under conditions identical with those of entry 9 of Table II with use of DCO_2D and D_2O in CD_3CN. Under such conditions, where the concentration of the electrophile may be roughly estimated (from the dissociation constant of formic acid in the reaction medium, see Experimental Section) as ca. 10^{-2} M (i.e., one order of magnitude less than that of the Mannich reagent), the isotope exchange occurred at a rate 2 orders of magnitude larger.

Scheme I[a]



$$\text{Pyrr-CH}_3 + \text{acid} \overset{K_1}{\rightleftharpoons} [\text{H-Pyrr-CH}_3]^+$$

$$[\text{H-Pyrr-CH}_3]^+ + :\text{B} \overset{K_2}{\rightleftharpoons} \text{H-Pyrr}{=}\text{CH}_2 + \text{BH}^+$$

$$\text{H-Pyrr}{=}\text{CH}_2 + \text{E}^+ \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [\text{H-Pyrr-CH}_2\text{E}]^+$$

$$[\text{H-Pyrr-CH}_2\text{E}]^+ \underset{+\text{H}^+}{\overset{-\text{H}^+}{\rightleftharpoons}} \text{Pyrr-CH}_2\text{E}$$

[a] Pyrr-CH_3 means an α-methylpyrrole (e.g., **1** or **2**), [H-Pyrr-CH_3]$^+$ its protonated form, :B a base, H-Pyrr=CH_2 an α-methylenepyrroline, E^+ an electrophile ($^+CH_2$-$N(CH_3)_2$, D^+).

Evidence has also been sought for general acid catalysis and for the protonation of the pyrroles examined in the acid reaction medium chosen.

As to the former, using a formic acid/sodium formate buffer in aqueous acetonitrile[8] at constant pH* 3.8 and varying the concentration of the formic acid from 0.01 to 0.02 M, an increase of the observed third-order rate coefficient from 5.1×10^{-3} to 8.8×10^{-3} $s^{-1}\ M^{-3}$ was observed (Table II) for pyrrole **2**.

As to the latter, evidence for the presence of protonated **1** in the reaction medium at the highest concentration of acetic acid used has been gained both by UV spectrophotometry (λ_{max} of **1** = 286 nm, λ_{max} of protonated **1** = 296 nm) and by ^1H NMR spectroscopy, by using 15.98 M CD_3CO_2D in CD_3CN–D_2O, which strongly indicates the ester carbonyl group as the preferred protonation site.

The mechanism depicted in Scheme I can therefore be proposed for the α-side-chain aminomethylation and the hydrogen/deuterium isotope exchange reactions.

As a final remark, the modest influence of the nature of the substituent in position 4 may be noted: on passing from the 4-methylpyrrole **1** to the 4-bromopyrrole **2**, only an ca. 50% reduction of the reaction rate is observed. This might well be due to nearly opposite (and compensating) effects of the methyl and bromo groups on the basicity of the starting pyrroles and the acidity of the intermediate protonated pyrroles (first two equilibria of Scheme I): as a consequence, the concentration of the assumed α-methylenepyrroline intermediate (which undergoes the rate-limiting electrophilic attack) is affected only slightly.

Experimental Section

Materials. Ethyl 1,3,4,5-tetramethylpyrrole-2-carboxylate (**1**) and ethyl 4-bromo-1,3,5-trimethylpyrrole-2-carboxylate (**2**) were prepared as described previously.[3] For use in kinetic experiments, they were recrystallized to constant melting point and stored in sealed amber-glass ampules under argon in a refrigerator.

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(6) Kinast, G.; Tietze, L.-F. *Angew. Chem.* **1976**, *88*, 261.

(7) Gould, E. S. "Mechanismus und Struktur in der Organischen Chemie", 2nd ed.; Verlag Chemie: Weinheim, 1964; p 441.

(8) Perrin, D. D.; Dempsey, B. "Buffers for pH and Metal Ion Control"; Chapman and Hall: London, 1974; pp 77 and 132.

Dimethylamine and formaldehyde were used as commercial aqueous solutions. The titer of the 33% amine solution was determined volumetrically and found to be 6.6347 M, that of the 40% formaldehyde solution was determined gravimetrically[9] and found to be 38.5% (w/w).

N,*N*-Dimethylmethyleneammonium chloride ("preformed Mannich reagent") for use in anhydrous conditions was prepared from bis(dimethylamino)methane (Aldrich) and acetyl chloride in dry diethyl ether according to Kinast and Tietze.[6]

Commercial anhydrous sodium acetate was fused twice, ground in a mortar, and stored in a desiccator over P_2O_5.

Sodium formate was recrystallized twice from aqueous ethanol and dried.

Glacial acetic acid was refluxed over CrO_3, distilled, and fractioned over P_2O_5.

Acetonitrile was distilled under an argon atmosphere, first from P_2O_5 and then from anhydrous potassium carbonate.

The solutions of water in acetonitrile were prepared by weight, as were those of the acids considered in aqueous acetonitrile.

Chloroacetic acid was distilled under reduced pressure: it melted at 63–63.5 °C.

99% formic acid (C. Erba, RPE) was used as received.

Acetonitrile-d_3 (99.95% deuteriated), acetic acid-d_4 (99.9% deuteriated), formic acid-d_2 (94% in D_2O as determined by Karl-Fischer titration, 99.5% deuteriated), and heavy water (99.9%) were C. Erba products.

Electrometric pH* and pK_a* Determinations in Aqueous Acetonitrile.[10] A Radiometer G202B glass electrode and a Radiometer K401 modified saturated-calomel electrode[11] were used in connection with a Radiometer 22r pH meter. The saturated aqueous KCl solution of the K401 electrode was replaced by a saturated solution of KCl in 95% aqueous methanol, and the electrode was left immersed in 95% aqueous acetonitrile ($[H_2O] = 2.77$ M) for a week. The glass electrode (new) was held overnight in 0.1 aqueous $HClO_4$ and then left immersed for a week in an ca. pH 7 buffer prepared by mixing equal volumes of 95% aqueous 0.02 M acetonitrile solutions of tribenzylamine and *p*-toluenesulfonic acid.[8]

The electrodes were calibrated by determining the millivolt readings for solutions of perchloric acid and tetraethylammonium hydroxide in 95% aqueous acetonitrile. The concentrations of perchloric acid (equivalent to $[H^+]$, since perchloric acid is known to be completely dissociated in acetonitrile[12]) were 10^{-2}, $10^{-2.5}$, 10^{-3}, $10^{-3.5}$, and 10^{-4} M, while for tetraethylammonium hydroxide (which is also known to be completely dissociated in acetonitrile[11]) $[H^+] = 10^{-8}$, $10^{-8.5}$, 10^{-9}, and 10^{-10} M. On plotting the millivolt readings against $[H^+]$ a straight line was obtained, the slope of which was that required by the Nernst equation within the limits of experimental error. This calibration plot was then used for the determination of the pH* value of the buffer used in the search for general-acid catalysis.

In this connection, also the pK_a* values in 95% aqueous acetonitrile for the acetic and formic acids were determined and found to be 5.10 and 3.40, respectively, at 25.0 °C. No attempt was made to determine the dissociation constant of DCO_2D in the deuterated solvent mixture (6% D_2O in CD_3CN).

Kinetic Measurements. The kinetic experiments were performed at 90.0 ± 0.1 °C in the dark (conventional dark room, red lamp). Appropriate amounts of pyrroles **1** and **2** were weighed in 50-mL volumetric flasks in order to have a final concentration of about 0.08 M. The aqueous acidic acetonitrile solutions were prepared by weight. The exact amount of water to be weighed was determined after allowance has been made for the amount of water introduced with the aqueous solutions used (dimethylamine, formaldehyde, and formic acid) and for that produced in the formation of the Mannich reagent. The concentrations of the acids in acetonitrile solution were checked titrimetrically, with phenolphthalein as the indicator. Once prepared, the kinetic solutions were left standing at room temperature for at least 12 h in the dark in order to allow equilibrium 1 to be established. Equal volumes (2 mL) of the kinetic solution were then filled into amber-glass tubes, which were sealed and immersed at once in the constant-temperature bath. As time zero of the reaction, the time 10 min after the immersion of the tubes was taken. In no case at $t = t_0$, had the reactions progressed to any appreciable extent. The reaction kinetics were followed up to attainment of the equilibrium (>90%) by titrating the unreacted formaldehyde by a mercurimetric method.[13] Blank experiments showed that neither the starting pyrrole nor the reaction product interfered with the determination, which was found to be virtually as precise as the gravimetric one.

The preparation of the solutions needed for the determination of the rate of the α-side-chain hydrogen/deuterium isotopic exchange was carried out in a glovebox under dry nitrogen, using CD_3CN, D_2O, and a concentration of DCO_2D equal to that of the HCO_2H used in the corresponding α-side-chain aminoalkylation. The rate of exchange was measured with the same procedure as above by ^1H NMR spectroscopy (Bruker WP80 instrument): the decrease of the intensity of the singlet at δ 2.17[1] due to the α-methyl hydrogens was determined as a function of time.

The reproducibility of all the values obtained, as ascertained by replicate experiments, was always better than ±2%.

Registry No. **1**, 55770-80-4; **2**, 86614-23-5; H, 1333-74-0; H_2O, 7732-18-5; *N*,*N*-dimethylmethyleneammonium chloride, 30354-18-8; bis(dimethylamino)methane, 51-80-9; dimethylamine, 124-40-3; formaldehyde, 50-00-0; acetic acid, 64-19-7; formic acid, 64-18-6; chloroacetic acid, 79-11-8.

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