Meisenheimer-Type Compounds from Heteroaromatic Substrates. The Reaction of Methoxide Ion with 3,5-Dinitro-2-methoxypyridine in Methanol and Dimethyl Sulfoxide–Methanol Mixtures[1]

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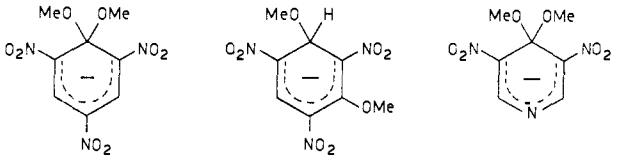
Abstract: The interaction between 3,5-dinitro-2-methoxypyridine and sodium methoxide in methanol and dimethyl sulfoxide–methanol mixtures is investigated by visible and nmr spectral measurements. A Meisenheimer-type adduct, the 2-aza-1,3-dimethoxy-4,6-dinitrocyclohexadienate ion (VI), is rapidly formed and is fairly stable in DMSO solution, the equilibrium constant in methanol being 1.9 M^{-1} at 20°. The data are consistent with a compound resulting from the attack of the methoxide ion on a CH ring position. Structure VI is conclusively established by the aid of a deuterated starting substrate. Methanol promotes the demethylation of the substrate, probably by an SN2 process, to yield the sodium salt of 3,5-dinitro-2-hydroxypyridine.

Alkoxide ions have been shown to attack the aromatic ring of picryl ethers in two different ways, at the alkoxyl-bearing carbon atom (I) and at a CH position (II).[2-5] The first mode was detected in the reaction of 3,5-dinitro-4-methoxypyridine[6] that leads to III. The reaction of the isomeric 3,5-dinitro-2-methoxy compound yields a different picture; in this paper we wish to report on the behavior of this compound.[7]

This project required the synthesis of 2-deuterio-3,5-dinitro-6-methoxypyridine which was effected by the application of an oxidative method of decomposition of



I II III

hydrazino derivatives for use in the replacement of the hydrazino group by hydrogen.[8-10]

Results and Discussion

With 3,5-dinitro-2-methoxypyridine (HetOMe) the study of adduct formation by methoxide ion in methanol solution is complicated by the irreversible formation of the sodium salt of the 2-hydroxypyridine derivative (HetONa). The latter separates out soon after mixing the reactants in highly concentrated solution (0.4–0.5 M). The adduct and "phenolate" ion formations are assumed to be competitive, rather than consecutive, reactions according to eq 1 and 2

$$\mathrm{HetOCH_3} + \mathrm{CH_3O^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{adduct} \qquad (1)$$

$$\mathrm{HetOCH_3} + \mathrm{RO^-} \xrightarrow{k_2} \mathrm{HetO^-} + \mathrm{ROCH_3} \qquad (2)$$

where RO^- can be either CH_3O^- or OH^-. The latter reaction will be discussed in the last section and will be referred to in the following as the dealkylation reaction. For the accumulation and detection of the adduct to be possible it is necessary that k_2 be sufficiently lower than k_1. That this is the case was shown by a preliminary structural examination of the nmr spectra in methanol and mixed solvents. As a consequence, in dilute solution equilibrium 1 was expected to be more amenable for quantitative investigation and a spectrophotometric study in the visible was indeed possible at the low concentrations required by this method.

Adduct Formation. The Equilibrium Constant. Addition of sodium methoxide to about 10^{-5} M 3,5-dinitro-2-methoxypyridine in methanol solution leads to the rapid formation of a yellow species, which shows an absorption band at 455 mμ. The reaction is too fast for kinetic measurements by standard methods; the absorbance of the solution was found to decrease slowly presumably because of the subsequent dealkylation reaction. Since the equilibrium is not sufficiently shifted toward the formation of the colored species, the extinction coefficient at 455 mμ (ϵ_{max} $3.66 \times 10^4 \pm 0.42 \times 10^4$) and the equilibrium constant (K, 1.91 ± 0.15 M^{-1} at 20°) were conveniently determined by the method of Benesi and Hildebrand.[11,12]

The probable errors were calculated from the probable errors in the slope and intercept of the plot of the Benesi and Hildebrand equation and in the methoxide ion concentration.

The position of the visible absorption band and the high ϵ value are both consistent with the general structure of an adduct of the Meisenheimer type. However,

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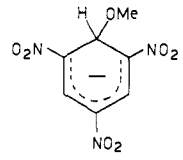
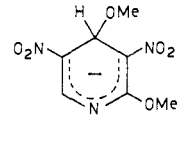
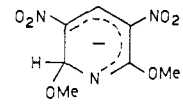
the value of the formation constant K is much lower than that expected for an attack at the methoxyl-bearing carbon. For such adducts as I and III the K values at 20° were found[6] in the order of 10^4 and 10^3 M^{-1}, respectively. In contrast, although the K value for adduct II is not known, that for adduct IV was found to be as low as 15 M^{-1} at 28°.[12] As to reaction kinetics, adducts II and IV are formed more rapidly than any of the types I and III. These data suggest the existence of a close correspondence in dynamic behavior relative to the nature of the attacked position between trinitrobenzene substrates[12] and dinitropyridine substrates as shown in the present and in the preceding papers.[6] In particular, for the product of the interaction of 3,5-dinitro-2-methoxypyridine with methoxide ion, either structures V or VI, rather than VII, are the most likely ones. This is fully confirmed by the nmr results recorded in DMSO solution (see following section).



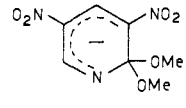
IV



V



VI



VII

Adduct Formation. Nmr Structure Determination. An accurate structure determination of the adduct by the nmr method is not practicable in methanol solution because, owing to the much higher concentration required by this method, the subsequent dealkylation reaction becomes predominant soon after mixing the reactants. For example, at 1-min reaction time, the nmr spectrum already records a mixture of the complex with the "phenolate" salt. However, we found that in DMSO and in DMSO-rich mixed solvents the dealkylation reaction slows down quite markedly, and an adduct is formed rapidly and quantitatively. For the proof of structure, the nmr spectra are best recorded in DMSO-d_6 as solvent, which enables the identification of the methoxyl as well as the nuclear protons. The spectrum of the starting 2-methoxypyridine derivative consists of an AB system centered at τ 0.76 ($\Delta\nu$ = 14 cps, J = 3 cps) and of a singlet at τ 5.76, whose intensities are in a 2:3 ratio; these peaks were assigned to the nuclear protons and to the three equivalent methoxyl protons, respectively. When 1 equiv of solid sodium methoxide is added the spectrum changes sharply and consists of a pair of doublets at τ 1.41 and 4.01 ($J \simeq 1$ cps), and of two singlets at τ 6.23 and 6.74. The intensity ratios of the four peaks were found to be 1:1:3:3, respectively. Thus, the methoxyl protons are not all equivalent, but form two sets of three equivalent protons each. Relative to the 2-methoxypyridine derivative, the nuclear protons were both shifted upfield, but the shift was only slight for one of them ($\Delta\tau \simeq 0.6$) and quite large for the other ($\Delta\tau \simeq 3.2$). The latter shift was interpreted as the consequence of the attack of the reagent on a CH position and of the sp^2 to sp^3 change in the hybridization state of the carbon atom at this position. These results are similar to those reported for the adduct obtained from 1,3,5-trinitrobenzene,[2] and unequivocally rule out a structure of type VII and support either structure V or VI instead; they fully confirm the indications from the dynamic behavior as obtained by studying the visible spectrum in dilute methanol solution.

The nmr pattern also indicates that only one of the two possible isomers, rather than a mixture, is formed. In order to assign the structure of the correct isomer to the adduct, the 6-deuterio derivative of 3,5-dinitro-2-methoxypyridine was synthesized and examined. As expected, the nmr spectrum of this compound in DMSO-d_6 solution shows two singlets, at τ 0.93 and 5.81, in the intensity ratio 1:3. The former peak corresponds to the aromatic hydrogen at the position 4 of the substrate. If the methoxide ion attacks this position to give adduct V, a large shift close to $\Delta\tau \simeq 3.2$ should result; however, if position 6 is attacked instead, the expected shift is small and close to 0.6. Since the latter alternative was neatly experienced ($\Delta\tau$ = 0.64) the correct structure of the adduct is given by formula VI. It is of interest to note that this conclusion is perfectly analogous to the one arrived at in the case of 2-cyano-4,6-dinitroanisole by an independent criterion;[13] the point of attachment of the methoxide ion for the formation of a transient intermediate was found to be at a CH position flanked by a cyano and a nitro group rather than one flanked by two nitro groups.

From the nmr spectral behavior that is observed in the nuclear proton region by adding increasing proportions of methanol to the DMSO solution, there are good indications that the same adduct is formed in both solvents. In absolute DMSO, the spectrum for the adduct keeps unchanged for some days before the subsequent dealkylation reaction progresses to any detectable extent. On going to mixed solvents with DMSO–methanol ratios equal to 5:1, 3:2, 2:3, and 1:4 the peaks at τ 1.4 and 4.0 are still observed, although the fine structure due to spin–spin interaction tends to disappear on increasing the amount of protic solvent. When the reaction is performed with less than 1 equiv of sodium methoxide the spectrum of the unreacted 3,5-dinitro-2-methoxypyridine also becomes less resolved. This solvent effect is probably due to an acceleration in the dynamics of the processes at equilibrium.

As the alcohol concentration increases, the dealkylation reaction shows up earlier and earlier, as indicated by the appearance of an AB system centered at τ 1.08 ($\Delta\nu$ = 13 cps, $J \sim 3$ cps). This pattern was identical with that shown in the spectrum of an authentic specimen of the dealkylation product, *i.e.*, the sodium salt of 3,5-dinitro-2-hydroxypyridine in DMSO solution.

The Dealkylation Reaction. The formation of the sodium salt of 2-hydroxy-3,5-dinitropyridine from the 2-methoxy derivative (eq 2) deserves a comment. A reaction of this kind has been observed by several authors,[14–16] and has been interpreted as consisting of either an SN2 reaction by RO^- ($RO^- = CH_3O^-, OH^-$)

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on the methoxyl carbon (3) or an aromatic substitution by OH^- (4). The hydroxide ion would form when contaminating water is present in the reaction medium.

$$ArOCH_3 + RO^- \xrightarrow{S_N2} ArO^- + ROCH_3 \quad (3)$$

$$ArOCH_3 + OH^- \longrightarrow ArO^- + CH_3OH \quad (4)$$

In our case, we are strongly in favor of the first alternative with $RO^- = CH_3O^-$. There are several reasons for this choice. First of all, the dealkylation reaction was especially fast in the less hygroscopic solvent, *i.e.*, methanol, where the water content was as low as 0.013% (7×10^{-3} *M*) as determined by the Karl–Fisher method. Second, according to the relatively high value of the equilibrium constant[17] for the reaction $CH_3OH + OH^- \rightleftharpoons CH_3O^- + H_2O$, the equilibrium concentration of OH^- under the present conditions becomes exceedingly small. In the third place, the methoxide ion is a more powerful nucleophile than the hydroxide ion.[18,19] Finally, the present results do not provide any evidence for a massive attack of the nucleophile on the methoxyl-bearing carbon at position 2. So both reactions (3) with $RO^- = OH^-$ and (4) are very unlikely. It should be noted that an S_N2 reaction on alkyl aryl ethers is not surprising provided that the aryl group is activated by electron-withdrawing substituents.[20]

Implications on the Mechanism of Nucleophilic Heteroaromatic Substitution. The present results show that with an aza-activated substrate the primary attack of the nucleophile can occur at a CH position, *i.e.*, at a position other than the one bearing a potential leaving group such as methoxyl. This behavior does neither differ from the case of 3,5-dinitropyridine,[21] where no methoxyl is present, nor from the case of 2,4,6-trinitro-[5] and cyanodinitroanisoles.[13]

Nevertheless, unlike the latter cases, there is no evidence of rearrangement to a 1,1-dimethoxy adduct such as VII since in the DMSO solution adduct VI keeps unchanged for days. Thus, the behavior of the 2-methoxypyridine derivative under investigation in this solvent bears no simple relationship to the problem of nucleophilic heteroaromatic substitution. A similar conclusion cannot be drawn in methanol solution, at concentrations suitable for the nmr measurements, because of the fast interfering demethylation reaction.

Experimental Section

The nmr, uv, and visible spectral measurements were carried out as described in the preceding paper.[6]

Methanol, sodium methoxide, and DMSO-d_6 were also described there. DMSO (Erba, reagent grade) was used as such, or kept over molecular sieves.

2-Chloro-3,5-dinitropyridine was prepared as described by Signor, *et al.*,[22] and 2,6-dimethoxy-3,5-dinitropyridine by the nitration of 2,6-dimethoxypyridine as described by Johnson, *et al.*[23]

3,5-Dinitro-2-methoxypyridine. A solution of 2.0 g of 2-chloro-3,5-dinitropyridine (1.05×10^{-2} mole) in the least amount of acetone was added to a mixture of sodium bicarbonate (13.2 g, 0.157 mole), water (170 ml), and methanol (170 ml) at room temperature. The mixture was kept under stirring for 1.5 hr, and then neutralized with 6 *N* HCl. On removing the organic solvents at low pressure with gentle heating, the product separated out of the aqueous solution. It was crystallized from methanol–water to constant mp 93.0–93.5° (lit.[24] mp 92°). The yield was 42%. Its nmr spectrum was in accord with the structure of the expected compound (see, also, the Discussion Section).

Several attempts to obtain a solid adduct between this ether and sodium methoxide, either by precipitation with nonpolar solvents or by evaporating quickly the solvent, did not lead to any well-defined compound, but only to brown-red tar.

Sodium Salt of 3,5-Dinitro-2-hydroxypyridine. This compound was obtained by heating a suspension of the hydroxy derivative in methanol with an equivalent of sodium methoxide, and removing the solvent on evaporation. It melted at 293°. Also, it was obtained in the reaction of 0.5 *M* 3,5-dinitro-2-methoxypyridine with 0.5 *M* methoxide in methanol. In this case it separated out of the solution and, after filtration, it was washed with methanol and dried, mp 295–296°. The products obtained by the two routes proved to be identical by comparing their ir spectra in Nujol and the nmr spectra in DMSO (see, also, the Discussion Section).

3,5-Dinitro-2-hydrazino-6-methoxypyridine. To an ice-cooled solution of 3.0 g of 2,6-dimethoxy-3,5-dinitropyridine (13 mmoles) in 1000 ml of methanol, 0.63 g of hydrazine hydrate 99% (13 mmoles) in 100 ml of methanol was added under stirring in 30 min. The reaction mixture was kept at the same temperature for 2 hr and, then, for another 30 min, at −20°. The red solid thus obtained was collected by filtration. The yield was 1.2 g (40%), mp 180–182°. The nmr spectrum of this compound in DMSO-d_6 showed two singlets, at τ 1.13 and at τ 5.87, of relative intensities 1:3, respectively. Very broad signals were obtained from the protons bound to nitrogen atoms.

Anal. Calcd for $C_6H_7N_5O_5$: C, 31.45; H, 3.08; N, 30.56. Found: C, 31.34; H, 3.25; N, 30.81.

2-Methoxy-3,5-dinitropyridine-6-*d*. A mixture of 1.0 g (4.4 moles) of 3,5-dinitro-2-hydrazino-6-methoxypyridine and 3.5 g of silver acetate in 35 ml of commercial (Fluka) deuterium oxide (99.7%) was stirred in a flask provided with a reflux condenser and protected from moisture with a "Drierite" tube. The mixture was gently warmed and vigorously shaken for 20 min. After cooling it was neutralized with dilute ammonia and extracted with ether. From the ether extract 0.9 g of a brown-red solid, mp 80–85°, was obtained. Most of this solid was dissolved by treatment with 15 ml of a 1:1 mixture (by volume) of benzene and petroleum ether, bp 30–50°, and purified by elution with the same solvent through a short column of alumina. From the first 50 ml of eluate 0.32 g of a light-yellow solid, mp 89.5–91°, was obtained. A mixture melting point with an authentic sample of 2-methoxy-3,5-dinitropyridine was 90.5–91.5°, yield 36%. The nmr spectra of this product and of the adduct formed on addition of methoxide ion are reported and discussed in the Results section.

Spectrophotometric Study of the Interaction between 3,5-Dinitro-2-methoxypyridine and Sodium Methoxide. A yellow species, having a maximum absorbance at 455 mμ, is formed immediately after mixing 3,5-dinitro-2-methoxypyridine with sodium methoxide in methanol solution. Equilibrium constant determinations were obtained from spectrophotometric measurements at this wavelength. The absorbance was found to decrease with time, but this complication was minimized at methoxide ion concentrations as low as 0.5 *M*, and the value of absorbance could be kept sufficiently constant for the duration of the measurement (about 30 sec).

The *K* and ε values were calculated from the equation $OD^{-1} = (K\epsilon[MeO^-][substrate])^{-1} + (\epsilon[substrate])^{-1}$, on the basis of the Benesi–Hildebrand treatment.[11,12] The relevant data are reported in Table I.

Table I. Absorbance of the System 3,5-Dinitro-2-methoxypyridine[a]–Sodium Methoxide, in Methanol, at 20°

$[MeO^-]$, *M*	$[MeO^-]^{-1}$, M^{-1}	OD	OD^{-1}
0.119	8.44	0.177	5.65
0.238	4.22	0.301	3.32
0.297	3.38	0.350	2.86
0.415	2.41	0.419	2.39

[a] [3,5-Dinitro-2-methoxypyridine] = 2.62×10^{-5} *M*.

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