dissolved in 27 mL of glacial acetic acid. The solution was deoxygenated for 20 min and irradiated for 1 h. The solvent was removed by distillation in vacuo, and the residue was examined by ^{1}H NMR spectroscopy. In addition to some starting material, the only product observed was **16**. No **14** was apparent.

Triplet-Sensitized Irradiation of 12. Compound **12** (27.1 mg, 0.081 mmol) was dissolved in 100 mL of spectrograde acetone and 4 mL of distilled water. The solution was deoxygenated for 20 min and irradiated for 2 h. The solvent was removed by distillation in vacuo and the residue examined by ^{1}H NMR spectroscopy. The residue was a mixture of starting material **12** and **15-OH** in a ratio of 3:5.

Triplet Quenching of the Acetone-Sensitized Irradiation of 12. A solution of 25.8 mg (0.077 mmol) of **12** and 800 mg (12 mmol) of *cis*-piperylene in 100 mL of spectrograde acetone and 5 mL of water was deoxygenated for 20 min and irradiated at 300 nm for 2 h. The solvent was removed by distillation in vacuo and the residue examined by ^{1}H NMR spectroscopy. The proton NMR revealed only starting material.

Relative Photoreactivities for the Triplet Reactions of 10, 11, and 12. Solutions of **10**, **11**, and **12**, each containing 25–26 mg of substrate in 100 mL of acetone and 4 mL of water, were deoxygenated for 15 min, placed in a merry-go-round apparatus, and irradiated at 300 nm for 30 min. The solvent was removed by distillation in vacuo and the residue was examined by ^{1}H NMR spectroscopy. Fifty-five percent of **10** and 19% of **12** were converted to **15-OH**, while 71% of **11** was converted to **14-OH**.

Acknowledgment. We are indebted to the Office of Basic Energy Sciences, U.S. Department of Energy (Contract DE-ACO2-79ER10366), for support of this work. S.J.C. is also indebted to the John Simon Guggenheim Memorial Foundation and to the University of Colorado Council on Research and Creative Work for fellowship support. D.H.'s stay in Boulder was sponsored by the Fulbright Commission. Thanks are also due to LeRoy Jones for aid in the synthesis of 7-*syn*-**2** (X = CN).

Registry No. *trans*-**1** (X = H), 6476-15-9; 7-*syn*-**2** (X = $COCH_3$), 89909-65-9; 7-*syn*-**2** (X = CN), 89955-36-2; 7-*syn*-**2** (X = NO_2), 89909-66-0; 7-*anti*-**3** (X = $COCH_3$), 89955-35-1; 7-*anti*-**3** (X = NO_2), 89955-37-3; 7-*anti*-**3** (X = CN), 89955-38-4; **4**, 89909-67-1; **5**, 89909-68-2; **6** (X = Ac, Y = OAc), 89909-72-8; **6** (X = Ac, Y = OH), 89909-73-9; **6** (X = CN, Y = OAc), 89909-75-1; **6** (X = CN, Y = OH), 89909-76-2; **6** (X = NO_2, Y = OAc), 89909-78-4; **6** (X = NO_2, Y = OH), 89909-79-5; **7**-Ac, 89909-74-0; **7**-CN, 89909-77-3; **7** (X = NO_2), 89909-80-8; **8** (X = Ac, Y = OAc), 89909-69-3; **8** (X = Ac, Y = OH), 89909-70-6; **9**-Ac, 89909-71-7; **10**, 75920-61-5; **11**, 87637-75-0; **12**, 87637-76-1; **14-OH**, 87637-68-1; **15-OH**, 87637-68-1; **15-OAc**, 87637-67-0; 2-acetoanthracene, 10210-32-9; *trans*-1,2-dichloroethene, 156-60-5; 2-anthronitrile, 1921-72-8; *cis*-piperylene, 1574-41-0; *o*-xylene, 95-47-6.

Cyano and Nitro Group Effect on the Rate of Methoxy Denitration Reaction in the Pyrrole and Benzene Ring

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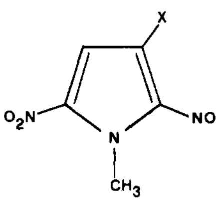
In both the pyrrole and benzene ring the methoxy denitration reaction is accelerated by a nitro or a cyano group flanking the reaction center. However, because of the different geometry of the rings, in the pyrrole ring a nitro group is more effective than a cyano group, at variance with what is observed in the benzene ring.

Nucleophilic aromatic substitution reactions can be carried out on activated pyrrole derivatives provided that a suitable leaving group is present and that the nitrogen atom is bound to a group other than hydrogen, in order to avoid the formation of the scarcely reactive conjugate base of the substrate.[1] In these substitution reactions the reactivity of the pyrrole ring has already been compared with that of the benzene ring by measuring the rates of the denitration reactions of 1-methyl-2,5-dinitropyrrole and 1,4-dinitrobenzene.[2]

Further information has now been obtained about the factors affecting the reactivity of the pyrrole ring by comparing the effects of electron-withdrawing substituents in the nucleophilic substitution in pyrrole and benzene rings. The rate of the methoxy denitration reaction in MeOH has been measured for the structurally related 3-X-1-methyl-2,5-dinitropyrroles (**1a–c**) and 2-X-1,4-dinitrobenzenes (**2a–c**) (X = H, CN, NO_2). Compounds of series **1** and **2** share a comparable pattern of activating groups and a nitro group as a leaving group.



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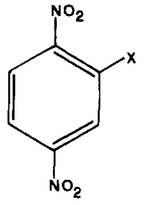

2

	X
a	H
b	NO_2
c	CN

Experimental Section

Melting points are uncorrected. UV spectra were recorded on a Cary 219 instrument. Electron-impact mass spectra were obtained on an AEI MS12 spectrometer. ^{1}H NMR spectra were

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obtained with a JEOL C60-HL apparatus. Elemental analyses were carried out by the Microanalytical Laboratory of the Institute of Pharmaceutical Chemistry of the Padova University.

Synthesis and Purification of Compounds. 1-Methyl-2,5-dinitropyrrole[3] (**1a**) and 1-methyl-2,3,5-trinitropyrrole[4] (**1b**) were prepared as described in the literature.

1-Methyl-2,5-dinitropyrrole-3-carbonitrile (1c) was obtained upon nitration (1 h, 0 °C) of 3-cyano-1-methylpyrrole-2-carboxylic acid[5] (1.0 g) with a nitrating mixture made up from 0.84 mL of 100% HNO_3 and 6 mL of 96% H_2SO_4. The reaction mixture was poured on crushed ice, and the resulting solid was collected by filtration and combined with the Et_2O extract of the filtrate. The Et_2O solution was dried, and the solvent was removed. Compound **1c** (110 mg, yield 8%) was separated from the isomeric 1-methyl-2,4-dinitropyrrole-3-carbonitrile (**3**) (240 mg, yield 18%) by chromatography on a silica gel column (benzene). The isomers were identified by their ^1H NMR spectra.

1c: mp 114.5–115 °C (acetone–hexane); ^1H NMR (CD_3COCD_3) δ 4.38 (s, 3 H), 7.78 (s, 1 H); mass spectrum, m/z 196 (M^+); UV–visible (MeOH) λ_{max} 316, 263 nm. Anal. Calcd for $C_6H_4N_4O_4$: C, 36.7; H, 2.05; N, 28.6. Found: C, 37.2; H, 1.93; N, 29.6.

3: mp 136.5–137 °C ($CHCl_3$); ^1H NMR (CD_3COCD_3) δ 4.27 (s, 3 H), 8.38 (s, 1 H); mass spectrum, m/z 196 (M^+); UV–visible (MeOH) λ_{max} 318, 246 nm.

1,2,4-Trinitrobenzene (2b). A mixture of 1,4-dinitrobenzene (Merck, 0.5 g, 2.98 mmol), 6 mL of fuming H_2SO_4 (d 1.94), and 4 mL of 100% HNO_3 was heated at 110–120 °C for 20 h. The reaction mixture was poured on crushed ice, the solid was collected by filtration, dissolved in Et_2O, and dried, and the ether was removed; the residue showed the presence of unreacted 1,4-dinitrobenzene and another compound (TLC). These compounds were separated by column chromatography on silica gel (benzene–petroleum ether (30–50 °C), 1:1). After the elution of 25 mg of 1,4-dinitrobenzene, **2c** was collected: yield 21%; mp 58.5–59 °C (lit.[6] mp 57–59 °C).

2,5-Dinitrobenzonitrile (2c). 2,5-Dinitrobenzoic acid[7] was converted into the corresponding amide by a conventional method. The amide was converted into 2,5-dinitrobenzonitrile by the method employed for the preparation of 3,5-dinitrobenzonitrile:[8] yield 38%; mp 192.5–193.5 °C (EtOH); NMR (CH_3COCH_3) δ 8.32 (m, 2 H), 9.02 (m, 1 H); mass spectrum, m/z 193 (M^+); UV–visible λ_{max} (MeOH) 257 nm. Anal. Calcd for $C_7H_3N_3O_4$: C, 43.53; H, 1.56; N, 21.76. Found: C, 43.63; H, 1.48; N, 21.85.

Substitution Products. To a solution of the substrate in methanol (2–3 × 10^{-2} M) the equivalent amount of 2.6 M sodium methoxide was added dropwise at room temperature. At the end of the addition a TLC analysis generally indicated the disappearance of the substrate and the formation of one product only. After evaporation of the solvent, the product was purified from any salts and traces of tars by chromatography on a short silica gel column (benzene) and recrystallized.

2-Methoxy-1-methyl-5-nitropyrrole was described elsewhere.[1]

2-Methoxy-1-methyl-3,5-dinitropyrrole was obtained according to the general procedure upon reaction of 1-methyl-2,3,5-trinitropyrrole (210 mg in 30 mL of MeOH) and recrystallized from hexane: yield 75%; mp 86–86.5 °C; NMR (CD_3COCD_3) δ 3.9 (s, 3 H), 4.25 (s, 3 H), 7.55 (s, 1 H); mass spectrum, m/z 201 (M^+); UV–visible (MeOH) λ_{max} 342, 239, 295 (sh) nm. Anal. Calcd for $C_6H_7N_3O_5$: C, 35.8; H, 3.51; N, 20.9. Found: C, 36.3; H, 3.52; N, 21.3.

1-Methyl-2-methoxy-5-nitropyrrole-3-carbonitrile was obtained from 1-methyl-2,5-dinitropyrrole-3-carbonitrile (**1c**) (85 mg in 18 mL of MeOH) and recrystallized from CCl_4: yield 95%; mp 121–122 °C; NMR ($CDCl_3$) δ 3.81 (s, 3 H), 4.38 (s, 3 H), 7.35 (s, 1 H); mass spectrum, m/z 181 (M^+); UV–visible (MeOH) λ_{max} 350, 226, 206 nm. Anal. Calcd for $C_7H_7N_3O_3$: C, 46.4; H, 3.90; N, 23.2. Found: C, 46.0; H, 3.85; N, 23.4.

Table I. Rate Constants and Activation Parameters for the Methoxy Denitration Reactions of 1a–c and 2a–c

compd	k_2(25 °C), $M^{-1}\ s^{-1}$	$\Delta H^{\ddagger}$,[a] kcal mol^{-1}	$-\Delta S^{\ddagger}$,[a] cal $deg^{-1}\ mol^{-1}$
1a[b]	1.36 × 10^{-3}	20.4 (0.2)	3.4 (0.7)
1b[c]	20.7	11.2 (0.3)	15.1 (1.0)
1c[d]	6.3	13.6 (0.3)	9.5 (0.9)
2a[e]	1.7 × 10^{-4}	21.8 (0.1)	2.5 (0.4)
2b[f]	16.3	10.5 (0.1)	17.4 (0.4)
2c[g]	24.2	12.2 (0.1)	11.2 (0.3)

[a] Standard deviation in brackets. [b] k_2, $M^{-1}\ s^{-1}$ (°C): 7.83 × 10^{-4} (20.4), 1.77 × 10^{-3} (27.2), 3.72 × 10^{-3} (33.9), 7.74 × 10^{-3} (40.3). [c] k_2, $M^{-1}\ s^{-1}$ (°C): 14.34 (19.25), 20.3 (25.05), 32.2 (32.15), 64.4 (42.8). [d] k_2, $M^{-1}\ s^{-1}$ (°C): 3.47 (17.95), 6.98 (26.0), 10.15 (31.2), 16.1 (37.40). [e] k_2, $M^{-1}\ s^{-1}$ (°C):[h] 1.7 × 10^{-4} (25.0), 1.03 × 10^{-3} (40.0), 3.20 × 10^{-3} (50.0). [f] k_2, $M^{-1}\ s^{-1}$ (°C): 9.38 (16.5), 15.9 (24.45), 24.45 (31.6), 38.25 (39.4). [g] k_2, $M^{-1}\ s^{-1}$ (°C): 13.8 (17.5), 26.35 (26.05), 41.7 (32.85), 59.2 (37.85). [h] Data from Tommila, E.; Murto, J. *Acta Chem. Scand.* **1962**, *16*, 53 and checked by the authors.

2-Methoxy-5-nitrobenzonitrile was obtained from 2,5-dinitrobenzonitrile (**2c**) (300 mg in 35 mL of MeOH) and recrystallized from EtOH: yield 95%; mp 129–130 °C; NMR (dioxane) δ 7.12 (br d, J = 9 Hz, 1 H), 8.40 (a pair of doublets, J = 9 and 2.8 Hz, 1 H), 8.60 (d, J = 2.8 Hz, 1 H) (lit.[9] (dioxane) δ 7.23 (a pair of doublets, J = 9 and 0.5 Hz), 8.44 (a pair of doublets, J = 9.3 and 2.8 Hz), 8.61 (a pair of doublets, J = 2.8 and 0.5 Hz)); mass spectrum, m/z 178 (M^+); UV–visible (MeOH) λ_{max} 307, 222, 235 (sh), 243 (sh) nm.

Kinetic Measurements. The kinetics were followed spectrophotometrically in the thermostated compartment of a Cary 219 instrument, under pseudo-first-order conditions, in the presence of an excess of sodium methoxide. Kinetic experiments were carried out at the absorbance maximum of each reaction product. The substrate concentration was in the range 1.5–6 × 10^{-5} M. Rate constants were corrected for the thermal dilatation of methanol. All the reactions were found to be second order, first order in both substrate and nucleophile. The rate constants increased linearly with methoxide ion concentration, even at high MeO^- ion concentration. Kinetic experiments under these conditions were carried out by the stopped-flow technique on a Durrum-110 instrument.

Results and Discussion

On treatment with sodium methoxide in methanol all the substrates gave the expected 3-X-2-methoxy-1-methyl-5-nitropyrrole or 2-X-4-nitroanisoles in very good yield (TLC and UV–visible spectrophotometric analysis at infinite time). No evidence was obtained for MeO^- ion attachment to the cyano group to yield methoxyimidates. This kind of attachment is likely to be disfavored by the presence of any bulky group adjacent to the CN group,[10] as it involves the increase of coordination at the CN group carbon atom. However, it cannot be excluded that the attachment reaction occurs in some limited measure but escapes detection because, being reversible, it would be followed by the irreversible denitration reaction. Attachment of the nucleophile to the cyano group of the substitution products of **1c** and **2c** is unlikely because in the presence of only one electron-withdrawing group the attachment of the nucleophile to the CN group is less favored.

Rate constants and activation parameters are collected in Table I.

If the dinitro derivatives **1a** and **2a** are taken as reference compounds, the introduction of a further electron-

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withdrawing group in the position adjacent to the reaction center leads to a rate increase. This fact is in agreement with a mechanism requiring the formation of an anionic intermediate as the rate-limiting step.

The rate increase is found to be bound mainly to a decrease of activation enthalpy. In both pyrrole and benzene series the lowest activation enthalpy is displayed by the substrate bearing what should be the most effective activating group (NO_2) at the position flanking the reaction center. However, the effect of the activation enthalpy decrease is partially balanced by that of the activation entropy decrease, which affects the rate in the opposite way. These effects are probably related. The bimolecular nature of the step yielding the σ adduct requires an entropy decrease. At the same time, in going from the starting methoxide ion to the more polarizable anionic σ adduct, some solvent organization is lost because of the dispersion of the charge in the adduct, and entropy correspondingly increases. In the nucleophilic attachment an earlier transition state, such as that for the reaction of the activated **1b**–**c** and **2b**–**c**, as compared to the reaction of the less reactive term in each series (**1a** and **2a**, respectively) is expected to involve a less favorable entropy change (more negative).

Coming now to the relative effect of electron-withdrawing substituents in pyrrole and benzene series on the reaction rate, a different trend is observed, since in the pyrrole series the activation by a nitro group is more effective than by a cyano group, whereas in the benzene series the reverse order is observed.

A similar situation had been already observed when the rates of formation of Meisenheimer adducts from methoxide ion and 3-X-2-methoxy-5-nitrothiophenes were compared with those of formation from 2,4-dinitro-6-X-anisoles (X = CN, NO_2).[11] In the five-membered-ring series a rate increase is found in going from X = CN to X = NO_2 because the CN group is a less effective electron-withdrawing group. In contrast, ring steric factors appear to play a significant role in the reaction of the benzene ring, as the different geometry increases steric interaction between the flanking groups. Increase of F strain or of steric inhibition of resonance decreases the reactivity of the trinitro derivative with respect to that of the dinitrocyano derivative, where the activation from the linear CN group is scarcely affected by the steric crowding increase. The very small relevance of ortho-like interactions in the five-membered rings is also supported by the fact that in nucleophilic substitution of 5-nitro-3-X-2-L-thiophenes, where L is a suitable leaving group, the logarithms of the substitution rate constants are linearly correlated with the σ_p^- values of the 3-X-substituents, provided that steric requirements of the nucleophile are low, as in the case of piperidine.[12]

The logarithms of the rate constants for the methoxy denitration reaction of pyrroles **1a**–**c** are not linearly correlated with the σ_p^- values of the substituents. If the kinetic data of the substrates bearing the smaller substituents (H and CN) are tentatively correlated with the σ_p^- values, the experimental rate constant for the trinitro derivative **1b** turns out to be smaller, by a factor of nearly 10, than the value extrapolated. In other words it appears that even if in the pyrrole ring a nitro group in a position adjacent to the reaction center is more effective than a cyano group in promoting the nucleophilic substitution reaction, its effectiveness is slightly decreased by steric effects, because the reaction center is flanked by two substituents.

The different sensitivity of pyrrole and benzene substrates to the substituent effect is also responsible for the fact that the reactivity ratio $k_{\text{pyrr}}/k_{\text{benz}}$ in nucleophilic substitution of structurally related compounds cannot be defined unequivocally. At 25 °C this ratio is 8.0 for the pair of dinitro derivatives **1a** and **2a**, 1.3 for the trinitro derivatives **1b** and **2b**, and 0.3 for the cyano dinitro derivatives **1c** and **2c**. It can be deduced that the $k_{\text{pyrr}}/k_{\text{benz}}$ ratio is easily modified by structural variations of the substrates or reaction conditions, and that these reactivity changes appear to be relatively important because of the fundamentally similar reactivity of these rings. In contrast, the comparison between thiophene and related benzene substrates is less complicated because the reactivity of a given thiophene derivative is usually much higher than that of a structurally related benzene derivative.

Registry No. **1a**, 56350-95-9; **1b**, 69726-47-2; **1c**, 89998-65-2; **2a**, 100-25-4; **2b**, 610-31-1; **2c**, 2112-24-5; 2-methoxy-1-methyl-3,5-dinitropyrrole, 89998-66-3; 1-methyl-2-methoxy-5-nitropyrrole-3-carbonitrile, 89998-67-4; 2-methoxy-5-nitrobenzonitrile, 10496-75-0.

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