Nucleophilic Substitution at the Pyrrole Ring. Comparison with Furan, Thiophene, and Benzene Rings in Piperidinodenitration[1]

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The reactivity of the pyrrole ring in nucleophilic aromatic substitution has been evaluated for the first time by rate measurements for the piperidinodenitration of 1-methyl-2,5-dinitropyrrole (1) at varying temperatures. Relative rates (k_{rel}) have been established at 25 ° C and show that 1 is markedly less reactive than 2,5-dinitrofuran and 2,5-dinitrothiophene, the k_{rel} values being 1, 2.4×10^6, and 4.4×10^3, respectively. A less significant difference is found with the rate of 1,4-dinitrobenzene ($k_{rel} = 9.6$). The factors affecting the observed reactivities and activation parameters are discussed.

Nucleophilic aromatic substitution at the pyrrole ring has been little studied. Thus, monographs dealing with the pyrrole chemistry either ignore the subject or sometimes present[2-5] a few instances of this reaction as rather exceptional reactions.[5] One of the reasons for this state of affairs is no doubt the fact that pyrrole derivatives with substituents suitable for nucleophilic displacement, such as halogenonitropyrroles, are not easily available. For example, halogenopyrroles undergo a rapid, spontaneous decomposition[6] and cannot be nitrated. Furthermore, in view of the fact that halogenopyrroles may suffer from the loss of the halogen atom as a positive entity under acidic conditions, some doubt has been cast[7] upon the nature of one of the few known substitutions with nucleophilic reagents at the pyrrole ring, i.e., the conversion of 2,3,4,5-tetrachloro- and 2,3,4,5-tetrabromopyrrole to 2,3,4,5-tetraiodopyrrole with potassium iodide.[8] Moreover, the reactivity of pyrrole derivatives bearing a hydrogen atom bound to nitrogen toward nucleophilic reagents is expected to be depressed by the proton-abstracting action of the electron donor and the resulting formation of an unreactive conjugate base of the starting substrate.

Prior to our report[9] on the easy replacement of a nitro group in 1-methyl-2,5-dinitropyrrole (1) by several nucleophilic reagents, the only well-characterized case of nucleophilic aromatic substitution on the pyrrole ring was the formation of 5-acyl-2,3-dihydropyrrole[2,1-*b*]oxazoles from 2-acyl-1-(2-hydroxyethyl)-5-nitropyrroles, in the presence of bases.[10] Both 1 and the substrates of the latter reaction are characterized by the presence of good leaving groups, electron-withdrawing substituents, and a blocking group at position 1. These structural features are obviously among the factors responsible for the reactivity of these compounds toward the nucleophilic reagents.

In this paper we report on a kinetic investigation of the piperidinodenitration of 1 in acetonitrile and of the related 2,5-dinitrofuran (2) and 2,5-dinitrothiophene (3). These data provide the first evaluation of the reactivity of the pyrrole ring in nucleophilic substitution and of its comparison with the other main five-membered heteroaromatic rings. We have also found of interest to include in this study 1,4-dinitrobenzene (4) as a link to benzenoid reactivity.

Experimental Section

Melting points are uncorrected. Elemental microanalyses were performed at the Microanalysis Laboratory of the University of Trieste. Uv and visible spectra data were obtained on either a Beckman DB-GT instrument, matched by a Kontron W+W 1100 recorder, or a Hitachi Perkin-Elmer 46 BCD instrument. NMR spectra were recorded on a JEOL C-60HL instrument by using $(CH_3)_4Si$ as internal reference. Mass spectra were recorded on an AEI MS 12 spectrometer.

1-Methyl-2,5-dinitropyrrole (1). 1-Methyl-2-nitropyrrole was nitrated in acetic anhydride according to a described procedure.[11] From the mixture containing the 2,4- and 2,5-dinitro isomers, 1 was isolated by chromatography on Al_2O_3, with benzene as eluent, and recrystallized from hexane (mp 98–99 °C, lit.[11] 99 °C).

2,5-Dinitrofuran (2) was prepared from 5-nitrofuran-2-carboxylic acid[12] and recrystallized from hexane (mp 100–100.5 °C, lit.[12] 101 °C).

2,5-Dinitrothiophene (3). A mixture of 2- and 3-nitrothiophene, as obtained from nitration of thiophene, was further nitrated according to a known procedure.[13] The crude nitration product was subjected to chromatography on HCl-washed silica gel, with a mixture of petroleum ether (bp 30–50 °C) and benzene (4:1–3:1) as eluent. The first fractions yielded a 20% crop (based upon the crude) of 3, which was recrystallized from hexane (mp 79.5–80 °C, lit.[14] 80–82 °C). The absence of 2,4-dinitrothiophene was checked by NMR.

1,4-Dinitrobenzene (4). A commercial sample (Merck) was sublimated under reduced pressure (mp 173–174 °C, lit.[15] 174 °C).

1-Methyl-2-nitro-5-piperidinopyrrole. Piperidine (0.22 ml, 2.3×10^{-3} mol) was added to a solution of 0.1 g of 1 (5.85×10^{-4} mol) in 5 ml of dimethyl sulfoxide. The mixture was kept for three days at room temperature, poured into an excess of water, and repeatedly extracted with small portions (5 ml) of hexane. The combined hexane extract was washed with water. Upon evaporation from the dried solution, an orange-colored residue was obtained (90 mg), that was sublimed under reduced pressure and recrystallized from hexane: mp 80.5–81.5 °C; λ_{max} (CH_3CN) 399 nm (ϵ_{399} 1.634×10^4 l. mol^{-1} cm^{-1}); τ (in CCl_4) 3.12 (d, 1 H, $J = 4$ Hz), 4.51 (d, 1 H, $J = 4$ Hz), 6.32 (s, 3 H), 7.0–7.25 (m, 4 H), 8.37 (m, 6 H); M^+ at *m/e* 209.

Anal. Calcd: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.3; H, 7.1; N, 20.1.

2-Nitro-5-piperidinofuran was obtained from 2 according to the method reported by Severin:[16] mp 94–94.5 °C (lit.[16] 99 °C); λ_{max} (CH_3CN) 436 nm (ϵ_{436} 2.98×10^4 l. mol^{-1} cm^{-1}). The same procedure was followed for the preparation of **2-nitro-5-piperidinothiophene** from 3: mp 122–124 °C (lit.[17] 126 °C); λ_{max} (CH_3CN) 450 nm (ϵ_{450} 3.11 $\times 10^4$ l. mol^{-1} cm^{-1}).

1-Nitro-4-piperidinobenzene was obtained by adding 0.47 g of piperidine (5.4×10^{-3} mol) to a solution of 0.11 g of 4 (6.5×10^{-4} mol) in 25 ml of acetonitrile, and by refluxing for 60 h. Evaporation of the solvent left an oily residue, which was extracted with ether. After evaporation of the ether solution, the residue was crystallized from hexane: mp 102 °C (lit.[18] 105.5 °C); λ_{max} (CH_3CN) 397 nm (ϵ_{397} 2.02 $\times 10^4$ l. mol^{-1} cm^{-1}).

Piperidine was kept over Na until evolution of hydrogen ceased, and was refluxed for 4 h over Na and distilled from K.

Acetonitrile was refluxed upon P_4O_{10} and distilled therefrom.

The kinetics were followed spectrophotometrically at wavelengths corresponding to the absorption maxima of the reaction products, under pseudo-first-order conditions (excess of nucleophile). The substitutions on 2 and 3 were followed in the thermostated compartment of a Beckman DB-GT or a Hitachi Perkin-Elmer 46 BCD spectrophotometer; owing to the high reactivity of the furan derivative, we used a two-compartment cell (optical length 0.875 cm) where the solutions of the reagents were thermostated separately before mixing. The kinetics of 1 and 4 were run in ampules. The range of concentration of the substrates was nearly 10^{-5} M (2 and 3) or 10^{-4} (1 and 4). The concentration of piperidine was chosen according to the reactivity of the substrates. In any case, no evidence was found for the presence of terms other than first order in piperidine in the kinetic expression.

Table I. Kinetic Data for the Piperidinodenitration of Compounds 1–4 in Acetonitrile at Different Temperatures

Compd	k,[a] l. mol^{-1} sec^{-1} (temp, °C)			
1	3.42×10^{-6} (59.5)	5.80×10^{-6} (67.4)	8.96×10^{-6} (74.7)	14.7×10^{-6} (81.7)
2	0.455 (19.9)	0.624 (26.5)	0.834 (34.0)	1.068 (40.0)
3	1.06×10^{-3} (25.0)	1.84×10^{-3} (34.9)	2.94×10^{-3} (44.3)	
4	1.42×10^{-5} (54.4)	2.07×10^{-5} (61.1)	3.13×10^{-5} (68.4)	4.43×10^{-5} (75.9)

[a] Corrected for statistical factors.

Table II. Activation Parameters and Relative Rates for the Piperidinodenitration of Compounds 1–4 in Acetonitrile at 25 °C

Compd	$\Delta H^{\ddagger}$, kcal mol^{-1}	$-\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}	k,[a] l. mol^{-1} s^{-1}	k_{rel} (25 °C)
1	14.5 (± 1)	40 (± 2)	$2.4 (\pm 0.7) \times 10^{-7}$	1
2	7.0 (± 0.3)	36 (± 1)	0.57 (± 0.01)	2.4×10^{6}
3	9.3 (± 0.3)	41 (± 1.5)	$1.06 (\pm 0.01) \times 10^{-3}$	4.4×10^{3}
4	11.5 (± 0.6)	46 (± 2)	$2.3 (\pm 0.3) \times 10^{-6}$	9.6

[a] Corrected for the statistical factor.

The second-order rate constants, as derived from experimental pseudo-first-order rate constants, were corrected for the thermal expansion of the solvent and for the statistical factor (two alike leaving groups).

Results and Discussion

Compounds 1–4 undergo the piperidinodenitration reaction in acetonitrile solution. Under kinetic conditions, only the expected nitropiperidino products were observed (TLC and infinity absorbance values) for the reactions of **2**, **3**, and **4**; minor amounts of a side product, which became detectable when the reaction had progressed by no less than 20%, were revealed by TLC for the reaction of **1**. For preparative purposes, 1-methyl-2-nitro-5-piperidinopyrrole was conveniently obtained from **1** in dimethyl sulfoxide, which is a faster solvent than acetonitrile in nucleophilic aromatic substitution,[19] with no interference of side products.

Good pseudo-first-order linear plots were obtained for the reactions of **2** and **3**. However, deviations from linearity were observed for compounds **1** and **4** beyond 15% reaction. In the latter cases the first-order rate constants were evaluated from initial rate determinations. It is worth noting that in the piperidinodebromination of 2-bromo-5-nitrofuran (**5**) in methanol solution,[20] which leads to the same product as the reaction of **2**, a pseudo-first-order kinetics law is obeyed only in the initial stages of the reaction (up to nearly 10%), because the reaction product decomposes at a rate comparable with that of its formation. This complication is not observed in the reaction of **2** because in the latter case the rate is 400 times as high as for compound **5**. Solvent[19] as well as leaving group effects are held responsible for this difference in rate.

Rate data have been obtained for the piperidinodenitration reactions at varying temperatures (Table I). Activation parameters and relative rates at 25 °C are reported in Table II.

The observed order of reactivity is

$$2 > 3 > 4 > 1 \qquad (1)$$

For the first three compounds it is in agreement with that found for the piperidinodebromination reaction.[17,20] As expected, the reactivity of the pyrrole ring is markedly lower than that of the other, similarly activated, heteroaromatic substrates; surprisingly, it is just one order of magnitude lower than that of the benzene derivative.

Owing to the geometry of the five-membered ring, the steric effect of the *N*-methyl group is not expected to play a significant role;[21] in particular, repulsive interactions between adjacent groups appear to be smaller than in the benzenoid ring. Presumably the moderate electron-releasing effect of that group can be transmitted through nitrogen to depress the reactivity of the ring to some extent. In any case, the overall rate-depressing influence of the *N*-methyl group should be small and the observed rate constant for the reaction of **1**, though a lower limit for the expected reactivity of un-ionized 2,5-dinitropyrrole, should be a fair measure of the latter.

The differences in reactivity between the heteroaromatic substrates are mainly caused by changes in enthalpy of activation, the entropy of activation varying within rather narrow limits. Although the benzene ring system (**4**) is not strictly comparable with the heteroaromatic substrates (**1–3**), its place in the reactivity order of compounds 1–4 is still controlled by the enthalpy of activation. The entropy of activation of **4** is somewhat lower than that for the other compounds but is more than offset by the enthalpy of activation. As a result, **4** is only moderately more reactive than the pyrrole substrate. The entropy data indicate that the reactions of the heteroaromatic substrates require essentially similar reorganization of the solvent in going from substrate to transition state.

The observed relative reactivity of the five-membered ring systems, as shown by sequence 1, is worth some comments in terms of stabilization of the transition state (rate enhancement) and of the ground state (rate depression) by electronic effects. In connection with the former point the heteroatom is expected to contribute to accommodate the negative charge in the ring system by its electronegativity and, in the case of thiophene, by the use of sulfur d orbitals. The pyrrole system (**1**) is less favored by this rate-enhancing effect than the other two systems (**2** and **3**).

Rate-depressing effects may derive from the conjugative interaction of the ring heteroatom with the leaving group (NO_2) in the ground state and the aromaticity of the ring system. The low reactivity of the pyrrole system, **1**, in nucleophilic substitution may thus be mainly interpreted in terms of the stability of the ground state, since a significant conjugative interaction between the electron-releasing ring nitrogen and the nitro group, as occurring in the starting substrate, must be lost in the transition state. Such an interaction is expected to be stronger than that of the ring oxygen of sulfur, in view of the stronger tendency of nitrogen to share its electrons,[22] and may well be responsible for the position of **1** in the rate sequence 1.

The low aromatic character of the furan system may be a major factor for the higher reactivity of **2** relative to that of **3** in nucleophilic substitution as well as for the higher tendency of furan derivatives, with respect to similarly activated thiophene derivatives, to form Meisenheimer-type adducts.[23] The importance of this effect also stems out of the fact that it does not depend on the charge type of substitution. Accordingly, in the electrophilic substitution of admittedly not strictly comparable substrates, the furan ring is also more reactive than the thiophene ring, in spite of the very large inversion of the pyrrole reactivity (i.e., pyrrole > furan > thiophene) relative to nucleophilic substitution.

As to the position of 1,4-dinitrobenzene (4) in the observed sequence, although the rate-depressing effect deriving from the conjugative effect is absent here, the low reactivity may derive from a substantially large resonance energy of the benzenoid ring of this compound.

The influence of the leaving group and other structural effects will be the object of further investigations.

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Registry No.—**1,** 56350-95-9; **2,** 826-03-9; **3,** 59434-05-8; **4,** 100-25-4; 5-nitrofuran-2-carboxylic acid, 645-12-5; 1-methyl-2-nitro-5-piperidinopyrrole, 56350-96-0; piperidine, 110-89-4; 2-nitro-5-piperidinofuran, 4818-49-9; 2-nitro-5-piperidinothiophene, 19991-84-5; 1-nitro-4-piperidinobenzene, 6574-15-8.

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Pyrrole Chemistry. The Cyanovinyl Aldehyde Protecting Groups†

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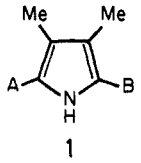
Protection of pyrrolic aldehyde groups with either methyl or ethyl cyanoacetate or malononitrile gives the corresponding cyanovinyl derivatives which are stable toward a variety of acids, oxidants, and reductants. Removal of the protecting groups with aqueous base regenerates the parent aldehyde.

The aldehyde function is one of great importance in the chemistry of pyrroles.[2] Alone, its electron-withdrawing properties can confer considerable stability on an otherwise sensitive system. 2-Formylpyrroles condense readily with 2-unsubstituted pyrroles in the presence of acid to form the very stable and synthetically useful 2,2′-dipyrromethene salts.[3] This reaction forms the basis for several well-known routes to porphyrins,[4] including the regiospecific synthesis of Johnson et al.[5] It is often convenient, given the nature of the readily available pyrrollic starting materials (usually 5-methylpyrrole-2-carboxylate esters), to introduce the formyl group several steps before it is required in the dipyrromethene synthesis. Although 2-formylpyrroles are resistant to autoxidation or Cannizzaro disproportionation, they are very susceptible to decomposition under acidic conditions and in the presence of many of the reagents commonly used in pyrrole syntheses (bromine, sulfuryl chloride, lead tetraacetate).

We report here further applications of the cyanovinyl protecting groups which were first employed by Fisher[6] in, for example, the synthesis of 2,5-diformyl-3,4-dimethylpyrrole (**1a**), and later by Woodward[7] in the synthesis of chlorophyll. Similar use of these protecting groups has been made by Davies,[8] and by Badger[9] in an unsuccessful assault on porphyrin a.

Cyanovinyl derivatives are prepared from the Knoevenagel reaction of 2-formylpyrroles with malononitrile or esters of



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	A	B
a	OHC	CHO
b	H	CH=C(CN)CO_2Me
c	H	CHO
d	Me	CH=C(CN)CO_2Me
e	ClH$_2$C	CH=C(CN)CO_2Me
f	BrH$_2$C	CH=C(CN)CO_2Me
g	MeCO$_2$CH$_2$	CH=C(CN)CO_2Me
h	MeOH$_2$C	CH=C(CN)CO_2Me
i	Me	CO_2Et
j	Me	CHO
k	H	CH=C(CN)$_2$
l	Me	H
m	Me	CH=$\overset{+}{N}$Me$_2$Cl$^-$
n	Me	CH=C(CN)$_2$
o	ClH$_2$C	CH=C(CN)$_2$

† Dedicated to Professor H. H. Inhoffen on the anniversary of his 70th birthday.