Response of Nitro-Activated Benzene and Five-Membered Heteroaromatic Systems to the Nucleophilic Reagent. Kinetics of p-Tolylthio Denitration in Methanol

Paolo Mencarelli and Franco Stegel*

Centro C.N.R. di Studio sui Meccanismi di Reazione, c/o Istituto di Chimica Organica dell'Università di Roma, 00185 Roma, Italy

Received March 31, 1977

The rates of p-tolylthio denitration of 1-methyl-2,5-dinitropyrrole, 2,5-dinitrofuran, 2,5-dinitrothiophene, and 1,4-dinitrobenzene have been measured in methanol at 25 °C. The reactivity order observed differs from that observed in the piperidino denitration of the same substrates for the inversion of the reactivity between the pyrrole and benzene derivatives. A possible cause is suggested for this inversion.

The relative reactivities of 1-methyl-2,5-dinitropyrrole (**1**), 2,5-dinitrofuran (**2**), and 2,5-dinitrothiophene (**3**) in the reaction of piperidino denitration have recently been determined[1] and compared with the reactivity of 1,4-dinitrobenzene (**4**). The results were characterized by the reactivity sequence **2** > **3** > **4** > **1**, where the reactivity of the pyrrole derivative was only slightly lower than that of the benzenoid substrate.

Besides the presence of activating substituents and the nature of the leaving group, the nature of the nucleophilic reagent is known to affect the relative rates of nucleophilic aromatic substitutions of different substrates.[2]

We wish to report here on the relative reactivities of substrates **1–4** in the substitution with the p-toluenethiolate ion, a charged nucleophilic reagent much more reactive than piperidine. As a consequence of the change of nucleophile, we find an interesting alteration of the reactivity sequence previously observed.

Experimental Section

Melting points are uncorrected. Microanalytical, UV–visible, NMR, and MS characterizations of the products were made as described in ref 1.

Materials. Substrates **1–4** were available from previous work.[1] Methanol was purified from magnesium; sodium methoxide was prepared and titrated as previously described.[3] p-Toluenethiol (Fluka purum) was sublimated under reduced pressure; its purity was checked by TLC.

The **kinetics** of 2,5-dinitrothiophene were followed spectrophotometrically at the wavelength corresponding to the absorption maximum of the reaction product. Since the absorption maxima of the reaction products of the other substrates fall in the region where the p-toluenethiolate ion shows a somewhat intense absorption, the kinetics of these compounds were followed at a longer wavelength (390 nm), where this inconvenience is less important. The substitutions of the pyrrole and benzene compounds were followed in the thermostated compartment of a Beckman DB-GT spectrophotometer; owing to the higher reactivity of the furan and thiophene derivatives, a Durrum D-110 stopped-flow spectrophotometer was used for the reactions of these substrates. The range of concentrations of the substrates was $0.5–1 \times 10^{-4}$ M. The thiolate solutions were obtained by mixing a slight excess of thiol with a methanol solution containing a known amount of methoxide ion and by taking up to volume. The concentrations of the thiolate ion were in the range $1–10 \times 10^{-3}$ M and were corrected, when required, for the thermal expansion of the solvent.

1-Methyl-2-nitro-5-(p-tolylthio)pyrrole. Sodium methoxide in methanol was slowly added, at room temperature, to a methanol solution (10 mL) containing equivalent amounts of 1-methyl-2,5-dinitropyrrole and p-toluenethiol (3.2×10^{-4} M). After 2 h the solvent was removed, and the residue was washed with water and purified by chromatography on silica gel with petroleum ether and benzene 1:1: mp (ligroin) 84.5–85.5 °C; λ_{max} (CH_3OH) 354 nm; M^+ at *m/e* 248; δ (in CCl_4) 2.30 (s, 3 H), 3.90 (s, 3 H), 6.38 (d, 1 H, J = 4.0 Hz), 6.95 (br s, 4 H), 7.06 (d, 1 H, J = 4.0 Hz); yield, 75%.

Anal. Calcd: C, 58.05; H, 4.87; N, 11.28; S, 12.91. Found: C, 58.18; H, 4.95; N, 11.12; S, 13.01.

2-Nitro-5-(p-tolylthio)furan. 2 (0.20 g, 0.13×10^{-3} mol), dissolved in 10 mL of MeOH, was slowly added to a methanol solution containing 1.4×10^{-3} mol of both toluenethiol and sodium methoxide. A TLC analysis at the end of the addition showed the formation of one product only and the absence of **2**. After removal of the solvent under reduced pressure, the organic material was immediately dissolved in benzene and purified from traces of unreacted thiol by chromatography on silica gel with benzene. The product was recrystallized from hexane: mp 39.5–40.5 °C; λ_{max} (CH_3OH) 358 nm; M^+ at *m/e* 235; δ (in CD_3COCD_3) 2.35 (s, 3 H), 6.92 (d, 1 H, J = 3.6 Hz), 7.1–7.5 (m, 4 H), 7.58 (d, 1 H, J = 3.6 Hz); yield, 67%.

Anal. Calcd: C, 56.16; H, 3.86; N, 5.96. Found: C, 55.7; H, 3.6; N, 5.8.

This product decomposes within a few days on standing, and more rapidly in the presence of bases, to give black tars. It should be stored in the cold, away from light.

2-Nitro-5-(p-tolylthio)thiophene. A procedure substantially similar to the one just described was used. The product had a melting point 39–40 °C, significantly different from that previously reported (57 °C).[4] However, the presence in the NMR spectrum of two doublets with the coupling constant typical of 2,5-disubstituted thiophenes[5] leaves no doubt about the structure of the product: M^+ at *m/e* 251; λ_{max} (MeOH) 385 nm; δ (in CCl_4) 2.39 (s, 3 H), 6.87 (d, 1 H, J = 4.2 Hz), 7.0–7.5 (m, 4 H), 7.68 (d, 1 H, J = 4.2 Hz); yield, 41%.

1-Nitro-4-(p-tolylthio)benzene. The substitution on **4** was performed under conditions similar to the substitution of **1**; because of the lower reactivity of **4**, the reaction was run with a small excess of thiolate nearly 20 h: mp 78–78.5 °C (lit.[6] 80–81 °C); λ_{max} (MeOH) 341 nm; yield, 62%.

Results and Discussion

Compounds **1–4** undergo the p-tolylthio denitration reaction in methanol by the action of the conjugate base of p-toluenethiol. As expected, in going from the neutral piperidine to an anionic nucleophilic reagent, a strong rate enhancement is observed. However, it must be remarked that the rate increase in the thiolate reaction may be partially offset by the use of methanol, a solvent that is generally slower[7] than acetonitrile in nucleophilic aromatic substitution and is also expected to decrease the reactivity of anionic nucleophiles through the formation of strong hydrogen bonds. A direct comparison of the reactivity of all substrates in both piperidino and arylthio denitration was not feasible in the same solvent, owing to the large reactivity range in the series **1–4**; thus, the pyrrole and benzene derivatives (**1** and **4**) are very poorly reactive toward piperidine in methanol, whereas 2,5-dinitrofuran reacts very fast with anionic nucleophiles in acetonitrile.

The formation of the expected thioethers occurs in a straightforward way under both preparative and kinetic conditions, and no side-products were detected by TLC analysis.

The kinetics were run in the presence of an excess of the nucleophilic reagent and were characterized by good pseudo-first-order plots up to 90% in all cases. This is contrasted by the fact that the kinetics of piperidino denitration

Table I. Kinetic Data for the p-Tolylthio Denitration of Compounds 1–4 in Methanol at 25 °C

Compd	Registry no.	k,[a] L mol^{-1} s^{-1}	k_{rel}
1	56350-95-9	2.60	1
2	826-03-9	4.4×10^3	1.7×10^3
3	59434-05-8	4.2×10^2	1.6×10^2
4	100-25-4	2.24×10^{-2}	8.8×10^{-3}

[a] Corrected for statistical factors.

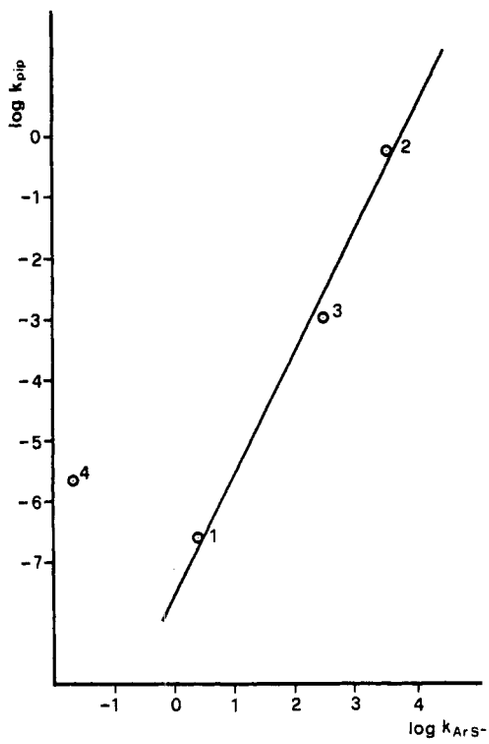

Figure 1. Free-energy correlation between piperidino denitration in CH_3CN (log k_{pip}) and p-tolylthio denitration in CH_3OH (log k_{ArS^-}), at 25 °C, of substrates 1–4.

of the less reactive substrates 1 and 4 did not show such a well-behaved pattern, probably because of the occurrence of side reactions.[1]

Rate data for the p-tolylthio denitration reaction at 25 °C are reported in Table I. They show that in this reaction the reactivity order for the heterocyclic substrates (2 > 3 > 1) is the same as that observed in the piperidino denitration reaction.

In contrast, an interesting inversion of reactivity is obtained for the reactions of the pyrrole and benzene derivatives; thus, while the benzenoid substrate 4 is decidedly more reactive than the pyrrole derivative 1, the less reactive of the heteroaromatic substrates, in the reaction with piperidine (k_1/k_4 = 0.1), the reverse is true for the reaction with the thiolate ion. For this reaction, the reactivity ratio k_1/k_4 is 1.1×10^2, so that the benzenoid substrate is far less reactive in the series 1–4.

It becomes thus evident that, since the reactivity ratio k_1/k_4 is strongly dependent on the nature of the nucleophile, it is not possible to indicate in a general way whether pyrrole derivatives are more or less reactive than similarly substituted benzene derivatives.

It is also worth noting that the reaction of the three heteroaromatic substrates with the more reactive reagent, i.e., the thiolate ion, is less selective than that with piperidine, as shown in the free-energy plot of Figure 1. The straight line described by the three heteroaromatic substrates 1–3 has a slope of nearly 2. This correlation indicates that the factors involved in determining the relative reactivities of these substrates are probably the same in both reactions, even if the higher reactivity of the thiolate and, consequently, the lower perturbation expected for the ring in the formation of the transition state may be held responsible for the lower selectivity in the reaction with this reagent.

Table II. Comparison of Activation Parameters for the p-Tolylthio[a] and Piperidino Denitration[b] of Compounds 1 and 4 at 25 °C

	p-Toluenethiolate		Piperidine	
Compd	$\Delta H^{\ddagger}$, kcal mol^{-1}	$-\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$-\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
1	13.7 (±0.5)	10.7 (±1.0)	14.5 (±1)	40 (±2)
4	16.8 (±0.9)	9.7 (±2.9)	11.5 (±0.6)	46 (±2)

[a] Present work. Pertinent kinetic data at different temperatures are reported as follows (k corrected, L mol^{-1} s^{-1}): 1, 1.43 (18.0 °C), 2.60 (25.0 °C), 4.86 (32.7 °C), 7.86 (39.6 °C); 4, 1.14×10^{-2} (18.0 °C), 2.24×10^{-2} (25.0 °C), 4.77×10^{-2} (32.5 °C), 9.56×10^{-2} (40.4 °C). [b] Reference 1.

As expected from the noted inversion of the k_1/k_4 ratio, the benzenoid substrate 4 is located definitely out of the straight line (Figure 1).

It may be not surprising to find a lack of correlation between the data of 1–3 and those of 4, as the absence of the heteroatom and the larger dimensions of the benzene ring are expected to affect the delocalization of the negative charge developing in the benzene compound.

The quantitative significance of these differences in reactivity can be further worked out by comparing the activation parameters for both reactions of the pyrrole and benzene terms (Table II). Unfortunately, the relatively high reactivity of the furan and thiophene derivatives in the thiolate reaction made it impossible to obtain activation data as reliable as those for 1 and 4.

In going from the piperidino to the arylthio denitration the most important changes which seem responsible for the general increase of rate concern the activation entropy, which becomes much less negative. The direction of these changes is consistent with a greater requirement of reorganization of the solvent for the formation of a dipolar transition state from uncharged reagents.

The data in Table II show, on the other hand, that the activation enthalpy is a very important factor in determining the inversion of reactivity between the pyrrole and the benzene derivative. Thus, the reaction of the benzenoid substrate with piperidine is characterized by a $\Delta H^{\ddagger}$ lower than that of the pyrrole substrate, and the reverse is observed for the reaction with the thiolate ion.

In dealing with the reactions of substrates 1–4 with piperidine, it was suggested[1] that some rate-depressing effect could arise in the heteroaromatic substrates from the conjugation of the leaving group with the heteroatom in the ground state. However, in the thiolate reaction this effect must be more than counterbalanced by some other factors, since 1,4-dinitrobenzene is the less reactive in the series, even if the conjugation of the nitro group in this substrate should be particularly weak, owing to the absence of heteroatoms.

In seeking an explanation of this fact, we can observe that a similar situation may be found in the nucleophilic substitution of 4-nitrohalogenobenzenes[8] (and of other similarly activated halogenobenzenes),[9] where the fluorine atom, which is expected to be strongly conjugated with the nitro group, is displaced more rapidly than iodine. It must be noted that this effect is much more intense with CH_3O^- than with CH_3S^-.[10]

This difference in behavior has been accounted for by the higher affinity of the polarizable nucleophilic reagent CH_3S^- for the reaction center bound to the more polarizable iodine atom.[11] The less reactive iodo derivative shows in both reactions a higher activation enthalpy than the fluoro derivative; however, the difference $\Delta\Delta H^{\ddagger} = (\Delta H^{\ddagger}_I - \Delta H^{\ddagger}_F)$ becomes smaller[10] in going from the reaction with CH_3O^- ($\Delta\Delta H^{\ddagger} = 3.9$ kcal/mol) to the reaction with the more polarizable CH_3S^- ($\Delta\Delta H^{\ddagger} = 1.8$ kcal/mol).

Another striking example of the role of the polarizability of the ring-leaving group bond is given by the comparison of reactivity of methoxide and benzenethiolate ions with 2-halobenzothiazoles.[12] In the reaction of otherwise unsubstituted 2-halobenzothiazoles, where the polarizability factor is relatively unimportant, methoxide ion is more reactive than PhS^-; the reverse is true in the reaction of 2-halo-6-nitrobenzothiazoles, where the polarizability of the Hal–C bond becomes stronger, owing to the conjugation with the nitro group.

Therefore, we suggest that the observed inversion of reactivity between the pyrrole and the benzene derivatives may be associated with the polarizability of the leaving groups on the different substrates. In the pyrrole derivative, as well as in the other five-membered heteroaromatic substrates, the bond between the reaction center and the nitro groups should be more polarizable than in 1,4-dinitrobenzene because of the possibility of an extended conjugation between the heteroatom and both nitro groups. The reaction of the benzene compound with the polarizable thiolate ion could not benefit from this possibility, thus becoming slower than the reaction of pyrrole compound 1. However, at the moment, a detailed evaluation among the heteroaromatic substrates of the role of this factor, as compared to other important factors[1] (electronegativity of the heteroatom, aromaticity of the ring), is not yet feasible.

Acknowledgments. We wish to thank Professor G. Illuminati for helpful discussions and Dr. G. Doddi for the stopped-flow measurements.

Registry No.—Methanol, 67-56-1; *p*-toluenethiol, 106-45-6; 1-methyl-2-nitro-5-(*p*-tolylthio)pyrrole, 63059-30-3; 2-nitro-5-(*p*-tolylthio)furan, 63059-31-4; 2-nitro-5-(*p*-tolylthio)thiophene, 19991-81-2; 1-nitro-4-(*p*-tolylthio)benzene, 22865-48-1.

References and Notes

(1) G. Doddi, G. Illuminati, P. Mencarelli, and F. Stegel, *J. Org. Chem.*, **41**, 2824 (1976).
(2) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, Amsterdam, 1968.
(3) P. Bemporad, G. Illuminati, and F. Stegel, *J. Am. Chem. Soc.*, **91**, 6742 (1969).
(4) C. Dell'Erba and D. Spinelli, *Boll. Sci. Fac. Chim. Ind. Bologna*, **26**, 97 (1968).
(5) R. F. M. White in "Physical Methods in Heterocyclic Chemistry", Vol. 2, A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1963, p 117.
(6) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **69**, 2053 (1947).
(7) G. Illuminati in "Solutions and Solubilities", Part 2, M. R. J. Dack, Ed., Wiley, New York, N.Y., 1976, p 178.
(8) G. P. Briner, J. Miller, M. Liveris, and P. G. Lutz, *J. Chem. Soc.*, 1265 (1954).
(9) A. L. Beckwith, J. Miller, and G. D. Leahy, *J. Chem. Soc.*, 3552 (1952).
(10) J. Miller and K. W. Wong, *J. Chem. Soc.*, 5454 (1965).
(11) J. F. Bunnett and W. D. Merritt, *J. Am. Chem. Soc.*, **79**, 5967 (1957).
(12) P. E. Todesco, P. Vivarelli, and A. Ricci, *Tetrahedron Lett.*, 3703 (1964).

Comparative Use of Benzhydrylamine and Chloromethylated Resins in Solid-Phase Synthesis of Carboxamide Terminal Peptides. Synthesis of Oxytocin Derivatives[1,2]

Victor J. Hruby,* Donald A. Upson, and Nirankar S. Agarwal

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received February 14, 1977

Specifically deuterated derivatives of the peptide hormone oxytocin were synthesized by the solid-phase method of peptide synthesis using either the standard chloromethylated resin or the benzhydrylamine resin as the support for the syntheses, and a comparison of the overall efficiency of the syntheses on the two resins was made. [1-Hemi-DL-[β,β-$^2H_2$]cystine]oxytocin was synthesized using the standard chloromethylated resin, and the two diastereomers were separated and purified by partition chromatography and gel filtration in an overall yield of about 30%. [1-Hemi-DL-[α-$^2H_1$]cystine]oxytocin was prepared using the benzhydrylamine resin to prepare the nonapeptide resin precursor, but otherwise using essentially identical conditions as used for the synthesis on the chloromethylated resin. Again the two diastereomers were separated and purified by partition chromatography and gel filtration. The overall yield of purified diastereomers under the best conditions was about 49%. For the synthesis of the latter compounds, *S*-3,4-dimethylbenzyl protecting groups were used to introduce the cysteine residues. The overall yields of the peptide hormone derivatives prepared on the benzhydrylamine resin were substantially improved if HF reactions were run at lower temperatures (0 °C rather than 25 °C), and if the *S*-3,4-dimethylbenzyl rather than the *S*-benzyl group was used for cysteine protection. Reproducible procedures for preparing benzhydrylamine resins with amino substitution levels of 0.15–0.45 mmol of amino group/g of resin were developed.

Since the introduction of the solid-phase synthesis of peptides by Merrifield,[3] the primary resin support has been chloromethylated polystyrene cross-linked with 1–2% divinylbenzene.[4,5] With this resin, the C-terminal amino acid is attached to the resin to afford a C-terminal resin benzyl ester. Subsequent synthesis of the remaining peptide chain is then accomplished with the resin benzyl ester serving as the C-terminal protecting group. This group is reasonably stable to the usual conditions of solid-phase peptide synthesis, but losses of 1–2% have been observed during each coupling procedure.[6,7] If a carboxamide C-terminal residue is desired, as is the case for many small biologically active peptides, it is generally necessary to first cleave the peptide from the resin as the protected carboxamide terminal derivative and then remove the other protecting groups. The former is usually done by treatment of the peptide resin with ammonia in an-