

NMR Determination of Reactivity Ratios in the Competitive O-Nitration Reactions of Benzyl and Thienyl Alcohols

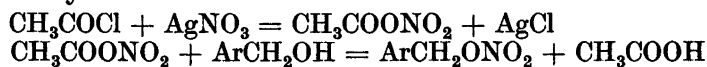
BÖRJE ÖSTMAN

Research Institute of National Defence, Dept. 1, Sundbyberg 4, Sweden

By the competitive method it is shown that 3-thienyl alcohol undergoes O-nitration about two times faster than 2-thienyl alcohol. The competitive reactions have been followed with NMR spectroscopy.

Side chain reactivity in the thiophene series has been studied for the saponification of ethylthienoates,¹ for the base catalyzed racemization of thienylglycolic acids² and for the S_N2 halogen exchange of the thienyl chlorides,³ for example. The relative rates (2-isomer/3-isomer) were 0.95:1, 20:1 and 3.5:1, respectively, for these reactions. The 3-thienyl/phenyl ratios were 0.93, 1.64, and 0.84, respectively. Both the inductive and the resonance effects of the thienyl substituent may contribute in these cases. Thus, the result of the last case has been interpreted as due to a greater resonance effect (+*M*) of the 2-position compared to the 3-position, assuming that the -*I* effect of the 2-position is stronger than that of the 3-position. In the two other cases the reactions are aided by electron withdrawal from the reaction center. The net electronic effects in the first case seem to be nearly the same for the two positions, whereas in the second case the -*I*-*M* effect of the 2-position is stronger than that of the 3-position. It should be of interest to investigate a case where resonance is reduced to a minimum in order to confirm the assumption that the 2-position is inductively stronger electron attracting than the 3-position. O-Nitration of the thienyl alcohols is believed to be such a case, since the reaction center is separated from the π-system by a methylene group making resonance contributions almost negligible.

In order to minimize the possibility of nitration in the thiophene ring, the nitrations were carried out with acetyl nitrate in acetonitrile at 0°, since it has been shown previously that dinitration does not occur when thiophene is nitrated (0°) with benzoyl nitrate in acetonitrile.⁴ The reactions involved are illustrated by the formulas



Ar = 2-thienyl, 3-thienyl, phenyl.

Table 1. Resonance positions of the methylene protons at 0°.

	-CH ₂ OH	Acetonitrile ^a		Carbon tetrachloride ^b	
		-CH ₂ OOCCH ₃	-CH ₂ ONO ₂	-CH ₂ OOCCH ₃	-CH ₂ ONO ₂
2-Thienyl	166.3 ± 0.4	195.9 ± 0.6	222.4 ± 0.5	4.83	4.45
3-Thienyl	157.6 ± 0.4	186.5 ± 0.6	212.4 ± 0.4	4.98	4.62
Phenyl	158 ± 0.6	186.9 ± 0.9	211.3 ± 0.5	4.97 ^c	4.63

^a In cps from solvent peak.

^b In τ-units (TMS reference).

^c In CDCl₃ the chemical shift of the methylene protons of benzylacetate is τ = 4.92 ppm (Varian Spectral Catalog, Vol. II, No. 530).

RESULTS

The formation of the arylmethyl nitrates from their corresponding alcohols has been studied in the present work by observation of the methylene signals (*cf.* Table 1). Thus it is possible to obtain the reactivity ratios for the pairs 2-thienyl/3-thienyl and 2-thienyl/phenyl from the intensity ratios of the methylene signals by utilizing the usual relationship (assuming the same nitrating mechanism in the three cases)

$$\frac{k_2}{k_x} = \frac{\log [1 - (N_2/C_2)]}{\log [1 - (N_x/C_x)]} \quad (k_x = k_3 \text{ or } k_\varphi)$$

where N is the CH₂-intensity of the nitrate ester and C is the sum of the nitrate ester and the alcohol CH₂-intensities. If side reactions are neglected, N and C are then proportional to the nitrate ester concentration and to the alcohol concentration at $t = 0$, respectively. The situation is shown in Fig. 1 which is a typical recording of the reaction between the pair 2-thienyl/3-thienyl and acetyl nitrate.

From Table 1 is seen that the replacement of the phenyl substituent with 2-thienyl causes a downfield shift of 5 and 10 cps for the alcohol and the nitrate, respectively, whereas the replacement with 3-thienyl causes hardly any shift at all. This is undoubtedly due to the greater electron attracting properties of the 2-position of thiophene as compared to the 3-position or to a benzene position. This has been observed before by Hoffmann and Gronowitz⁵ in the case of the isomeric methylthiophenes where a downfield shift of 8 cps was obtained for the methyl resonance of the 2-isomer as compared to that of the 3-isomer.

The CH₂-signals of the alcohols are somewhat concentration dependent. Thus the signals are shifted upfield with increasing dilution with 1.13, 0.55, and 1.82 cps l mole⁻¹ for 2-thienyl-, 3-thienyl-, and benzyl alcohol, respectively. Hence, the CH₂-shifts at infinite dilution were obtained from extrapolation to be 164, 156, and 156 cps at 0°C in acetonitrile with the solvent peak as reference.

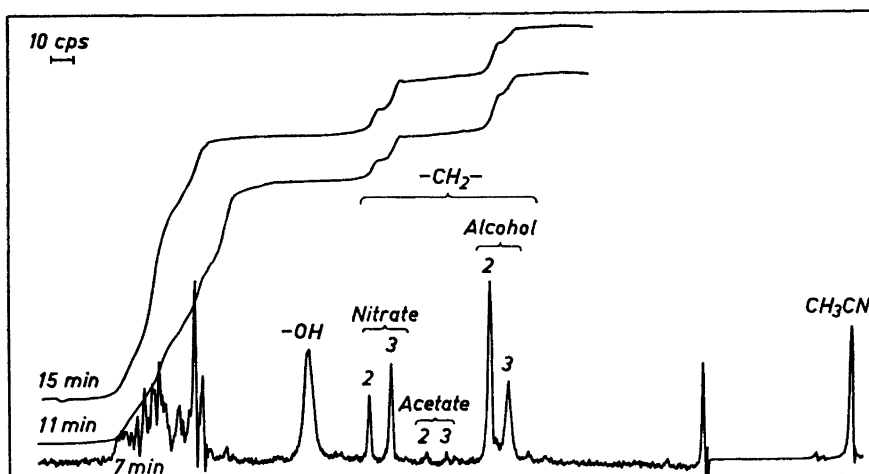


Fig. 1. 60 Mc NMR spectrum of a reaction mixture consisting of 2-thienyl alcohol, 3-thienyl alcohol, and acetylnitrate. Initial mole ratio acetylnitrate/alcohol = 0.75:1. Spectrum amplitude decreased with a factor of ten in the acetonitrile region.

In the present work large differences in the hydrogen bond forming ability of the alcohols could possibly influence their relative reactivity towards the nitrating agent. According to NMR and IR measurements of the concentration dependence of the OH absorption the difference in this respect may be ignored, however.

In the competitive as well as the single experiments extra signals around 190 cps (from CH₃CN) were always obtained. For the benzyl case this signal was identified with the methylene protons of benzyl acetate. By analogy the corresponding signals in the thienyl cases were assigned to the methylene protons of the thienyl acetates. The resonance positions are given in Table 1. Control experiments with the alcohols and acetyl chloride when carried out under nitrating conditions showed fast growing signals at 196.5, 187.5, and 188 cps (from CH₃CN) for 2-thienyl-, 3-thienyl-, and phenyl-, respectively. Thus the acetate formation in the nitration experiments are most likely due to acetylation of the alcohols by acetyl chloride present as a contaminant in the acetyl nitrate reagent (due to the incompleteness of the acetyl chloride — silver nitrate reaction). Similar control experiments when carried out with acetic anhydride did not show any spectral changes of the alcohols. The acetate content in the reaction products was found to be within 10 ± 6 mole % (all experiments).

The resonance position of the OH-signal will be determined by the concentrations of alcohol and acetic acid and consequently this signal showed a continuous low field shift as the reaction proceeded. In Fig. 2 this situation is graphically represented as a plot of the alcohol fraction which has been nitrated (α_N) versus the resonance position of the OH-signal. The linear correlation is fair considering that the diagram represents the results of all experiments performed. The OH shift is largely dominated by changes in the acetic

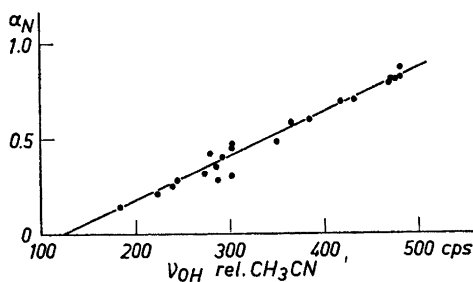


Fig. 2. Plot of the extent of nitration (α_N) versus ν_{OH} (measured from CH_3CN) at 0° .

acid concentration, since control experiments showed that a threefold increase of acetic acid concentration moved the OH-signal 210 cps towards low field, whereas a decrease of alcohol concentration with the same factor caused a high field shift of 14 cps. Thus the correlation is interpreted as a linear increase in acid concentration as the reaction proceeds. Extrapolation of the curve to zero conversion gives $\nu_{OH} = 120$ cps. This value is to be compared with the OH shift for the alcohols (in the starting concentration range) which is between 85 and 107 cps. The agreement in this respect improves if the conversion to acetate is included. Then, a similar plot gives a straight line that extrapolates to $\nu_{OH} = 105$ cps, a value which is within the expected limits.

In Table 2 the reactivity ratios k_2/k_3 and k_2/k_φ are given as averages of three consecutive readings at different mole ratios acetyl nitrate/alcohol. The mole ratios are uncorrected for the presence of acetyl chloride. The alcohol concentration is the sum of both alcohols (in the competitive experiments). Some of the reactivity ratios are, however, the result of fewer readings because the OH-signal obscured the methylene signals and in some of the cases, where excess of acetyl nitrate was used, the CH_2 -intensity of the remaining alcohols was too low to permit measurement.

The reactivity ratios have been computed as if all alcohol consumed has been converted to nitrate, *i.e.* the competing reaction with acetyl chloride is neglected. Non-competitive experiments were also performed chiefly to establish the correct position of the various methylene signals. The results of these experiments with respect to the α_N - ν_{OH} relationship are included in the diagram of Fig. 2.

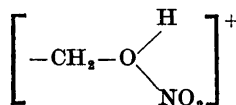
Table 2. Reactivity ratios k_2/k_3 , k_2/k_φ in the competitive nitration reactions of 2-thenyl alcohol/3-thenyl alcohol and 2-thenyl alcohol/benzyl alcohol, respectively, at different mole ratios acetylnitrate/alcohol. (Deviations from the mean values).

	2:1	1.5:1	1:1	0.75:1	0.5:1
k_2/k_3	0.50 ± 0.02	0.54 ± 0.10	0.48 ± 0.04	0.50 ± 0	0.50
k_2/k_φ	0.43 ± 0	0.41	0.55 ± 0.01	0.47 ± 0.03	0.50 ± 0.05

Since the measurements of Table 2 are performed before all of the starting material has been consumed, fair competition between the alcohols for the reagent is ensured and the product ratios should therefore give reasonably good information on the relative reactivity. Thus from Table 2 the average 2-thienyl/3-thienyl and 2-thienyl/phenyl ratios are found to be 0.50 ± 0.06 and 0.49 ± 0.06 , respectively. From these ratios the 3-thienyl/phenyl ratio is found to be 0.98. This ratio could not be measured directly since (see Table 1) the methylene signals for 3-thienyl and benzyl have almost identical positions in the spectrum.

DISCUSSION

The O-nitration has been shown by Ingold *et al.*⁶ to follow the same mechanism as the one accepted for aromatic nitration, *i.e.* it involves the attack of the nitronium ion and passes (presumably) through an intermediate of the type



Thus the non-bonded oxygen electrons play the same role as the π -electrons in aromatic substitution in forming the intermediate. Difference in reactivity between structurally similar substrates will then largely be due to the ability of the oxygen atom to put these electrons at disposal for attachment of the electrophile, in this case the nitronium ion.

As in aromatic substitution, electron withdrawal from the reaction center will retard the reaction. This electron withdrawal, however, is in the present case largely transmitted through the sigma bonds; resonance contributions in the usual sense may be neglected.* Thus, the results are most naturally interpreted in terms of inductive effects only, those being in the order (*cf.* Table 2 and Results) $-I_2 > -I_3 \approx -I_p$. From Table 1 is seen that the amount of deshielding of the methylene hydrogens correlates with this sequence. The fact that the pK_a of the 2-thenoic acid is greater than that of 3-thenoic acid is commonly interpreted as being due to a larger $-I$ effect for the 2-position compared to the 3-position, but conjugation between the carboxyl group and the thiophene ring is certainly not negligible in that case.

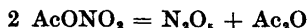
The difference in inductive effects for 2- and 3-thienyl is not without interest, considering that sulfur is assigned the same value as carbon on Pauling's electronegativity scale. From the present results it seems, however, as if sulfur (in thiophene) is slightly more electronegative than the ring sp^2 -carbons. Electron attraction will then be felt most strongly at the 2-

* Preliminary investigation of the 100 Mc spectra of the aromatic protons of the thienyl alcohols through adjustment of the calculated ABC spectra show, however, that coupling with the side chain protons split the bands assigned to the 3-proton in 2-thienyl alcohol and the 2-proton of 3-thienyl alcohol into triplets. The coupling constants, 0.7 and 0.9 cps, respectively, are to be compared with $J_{3-\text{CH}_3} = J_{2-\text{CH}_3} = 1.1$ cps reported for the two isomeric methyl thiophenes.⁵ In those cases the coupling was believed to be transmitted through a hyperconjugative mechanism. In the present cases this may well be the explanation also.

position. It is conceivable that difference in the degree of hybridization of the carbons in question could contribute by making the 2-carbon inherently more electronegative than the 3-carbon. From the bond angles in thiophene it seems, however, that such differences in hybridization should be slight.

The near equivalence between the 3-thienyl carbon and a benzene carbon is again demonstrated and the relative reactivity (k_3/k_p) obtained in O-nitration is nearly the same as that obtained in ester hydrolysis¹ and in halogen exchange.³

The discussion above has been carried out under the assumption that the attacking entity is the nitronium ion. Norman and Radda⁷ conclude from an investigation of aromatic nitration with different acyl nitrates in acetonitrile, that the most likely mode of the nitrating action of these reagents consists in slow heterolysis of dinitrogen pentoxide to the nitronium ion. The formation of pentoxide is due to



However, in certain cases the pentoxide itself serves as the nitrating agent, notably in the *ortho* position of methyl phenethyl ether, where the reaction is thought to proceed through a cyclic six membered transition state involving the ethereal oxygen. Bonner⁸ concludes from a kinetic investigation of the O-nitration of 2,4-dinitrobenzyl alcohol with nitric acid in acetic anhydride-acetic acid solvent, that dinitrogen pentoxide is responsible for the nitration, the pentoxide being formed from acetyl nitrate as above. It is conceivable therefore that the intermediate referred to above is really the transition state of a concerted displacement reaction on oxygen. Yet, there can be no doubt that there is a positive charge which develops, although with pentoxide as the attacking entity this charge will probably be smaller than if there is a nitronium ion attacking.

Although it has been shown, by using ¹⁸O labelling techniques,⁹ that the conversion of alcohols to their nitrate esters proceed through O-nitration, the conditions here are different and the replacement of OH⁻ by NO₃⁻, *i.e.* a nucleophilic attack, can not be dismissed entirely as a possible reaction. This mode of attack could then arise from the dissociation of acetyl nitrate into acetyl ion and nitrate ion. The formation of acetate esters (*cf.* Results) could possibly be explained under such circumstances, but then the acetate ester concentration would show a continuous increase as the reaction proceeds. This, however, is not the case. Burton and Praill¹⁰ also failed to isolate any acylated products from the reaction of anisole with acyl nitrates. Nucleophilic attack by nitrate ion is therefore considered unlikely but the straightforward proof should of course be to carry out the reactions with ¹⁸O-labelled alcohol.

EXPERIMENTAL

The NMR measurements were made with a Varian A 60A Analytical NMR Spectrometer equipped with the Varian V 6057 variable temperature system. The IR determinations were performed with a Perkin Elmer Model 225 Grating Infrared Spectrometer equipped with an RIIC VLT-2 variable temperature cell.

Acetyl chloride (Hopkin and Williams, "Analar", Merck, *p.a.*), silver nitrate (Merck, *p.a.*, Kebo, puriss.), benzyl alcohol (Merck, *p.a.*) and acetonitrile (Eastman Kodak,

Spectroscopic) were used without further purification. The 2- and 3-thenyl alcohols were prepared from the corresponding thenoic acids with lithium aluminium hydride according to well known methods,¹¹ (2-thenyl alcohol b.p. 90°/11 mm Hg, 3-thenyl alcohol b.p. 102°/10 mm Hg). The yields were about 80 % and the isomeric purity was checked with GLC. The 2-thenoic acid was obtained from Fluka, and 3-thenoic acid was synthesized according to Gronowitz.¹² Acetyl nitrate was prepared at about 0°C according to Burton and Praill¹⁰ from acetyl chloride (0.09 moles) and silver nitrate (0.09 moles) dissolved in 32 and 18 ml acetonitrile, respectively. When the reaction was finished the liquid layer was transferred with a hypodermic syringe to a glass stoppered vessel. The reagent was always freshly prepared before use in the nitration experiments.

Preparation of benzyl and thenyl nitrates. Benzyl alcohol (0.06 moles) dissolved in 6 ml acetonitrile and cooled to -5°C was added in one dose to an acetyl nitrate solution (0.09 moles in 46 ml acetonitrile) at -5°C. The reaction mixture was allowed to stand at this temperature for 20 min. The extent of reaction was followed by taking samples for NMR analysis. Thus when there was no alcohol left according to NMR the reaction mixture was poured out in ice water. The mixture was filtered and the filter rinsed with about 25 ml of carbon tetrachloride. The organic layer was shaken with 10 ml of water and finally dried over calcium chloride. The solution was distilled giving benzyl nitrate (0.039 moles), b.p. 91°/10 mm Hg.

Attempts to isolate the thenyl nitrates in the same manner as described for benzyl nitrate failed, since upon distillation of the carbon tetrachloride solutions the nitrates rapidly decomposed. Therefore the work up procedure for these compounds was modified so that temperatures above 0° was avoided. Thus the CCl₄-extracts were kept at -15°C while the solvent was distilled away at low pressure (~0.5 mm Hg). The residue was dissolved in CCl₄ and subjected to NMR and IR-analysis (sample cells at 0°C). From the NMR spectra the residue was found to contain, besides the nitrates, also some unreacted alcohol and acetic acid. Only traces of acetonitrile were left. The extent of the nitration was followed with NMR, thus at a mole ratio acetyl nitrate/thenyl alcohol about 1.5:1, 70 % conversion to nitrate was obtained. The preparations were otherwise carried out in the same manner as described for benzyl nitrate.

The NMR-shifts in CCl₄ solution of the nitrates are given in Table 1. The infrared spectra show strong absorption bands at 1635-1640 cm⁻¹ and 1275-1280 cm⁻¹ for the three derivatives. According to Bellamy,¹³ the 1600-1650 cm⁻¹ and the 1250-1300 cm⁻¹ bands are due to the antisymmetric and symmetric stretching vibrations, respectively, of NO₂ in organic nitrates.

Reactivity experiments. Mixtures (1:1) were prepared - 2-thenyl/3-thenyl and 2-thenyl/benzyl - from ca. 2 M stock solutions of the alcohols in acetonitrile to be used in the competitive experiments.

The mixtures and the acetyl nitrate solution were kept at about -20°C. The NMR sample tubes (dried, stoppered and kept at -20°C) were filled by means of hypodermic syringes with the appropriate volumes of acetyl nitrate (apparent concentration before mixing 1.9 moles/l) and of the alcohol mixtures to give the required mole ratios acetyl nitrate/alcohol. (The total volume for the NMR study was from 0.45 ml to 0.70 ml). The sample tube was turned rapidly to achieve good mixing of the reagents and then rapidly transferred to the NMR probe which was at 0°C. Time of mixing was $t = 0$. The sample tube was then allowed to be in the probe for 1 min before any recording was made. The recordings were made with 250 sec sweep time and at 500 cps sweep width. The spectrum was then integrated with a sweep time of 25 sec. The time when integration started was noted. The procedure was then repeated immediately, scanning once more the entire spectrum usually followed by two integrations (see Fig. 1).* The alcohol concentrations (total) at $t = 0$ were between 0.66 mole/l and 1.32 mole/l. The acetyl nitrate concentrations at $t = 0$ ranged from 0.7 to 1.3 mole/l. Non-competitive experiments were made with the same stock solutions in the same manner as described above. The alcohol concentrations at $t = 0$ were in the range 0.73-0.80 mole/l, the mole ratio acetyl nitrate/alcohol was kept at 1.5. The reactions were followed for about 15 min, when the conversion to nitrate ester was more than 50 % complete.

* The intensity ratios aromatic hydrogens/methylene hydrogens were found to be 4 % higher than the theoretical values. Thus aromatic nitration does not occur.

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