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SELECTIVE FUNCTIONALISATION PART 10[1]. THE NITRATION OF PHENOLS BY PYRIDINE DERIVATIVES CARRYING A TRANSFERABLE NITRO GROUP

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Abstract: Pyridinium salts bearing carboxylate side chains and pyridones are shown to react with nitronium tetrafluoroborate or nitrogen dioxide to yield activated intermediates capable of selectively nitrating phenol ortho to the hydroxyl group with virtually complete selectivity and in quantitative yield in aprotic solvents. Although the nitration of phenol itself is exceptionally selective, the nitration of some substituted phenols lead to mixtures of mononitrated products and in especially reactive cases such as 4-methoxyphenol and naphthols, to dinitrated products also. The reactions can be most conveniently carried out on a polymeric support. Spectroscopic evidence is presented to show that intermolecular association between pyridinium salts and the phenols takes place under conditions similar to the reaction conditions and that hydrogen bonding between the phenolic hydroxyl group and acceptor groups on the pyridine ring can also occur. It is suggested that the combination of these two effects leads to the observed selectivity. Attempts to extend the scope of the reaction to other electrophiles and substrates are outlined.

A major stimulus to the discovery of new selective organic reactions over the last 15 years has been the imitation of the selectivity of enzymic catalysis through so-called biomimetic chemistry.[2] Our studies in this field[1,3-6] together with those of others[7-12] have shown that the presence of surfactant micelles can influence the course of organic reactions, in particular electrophilic substitution. During these studies, we observed that there was a strong association between pyridinium head groups of some surfactants and phenol molecules[1,13] and that in order to obtain a highly selective reaction, it was necessary to have the substitution reagent localised within the surfactant.[1,3] With the well-known difficulties in obtaining clean, selective mononitration of phenols in mind, we initiated an investigation into the possibility of selective biomimetic nitration.

RESULTS AND DISCUSSION

The nitration of phenol with substituted pyridinium salts

Initially, in a direct extension of the studies with surfactant derivatives, N-dodecylpyridinium 3-carboxylate 1 was suspended in dry acetonitrile and treated with a solution of nitronium tetrafluoroborate in acetonitrile until a clear solution was obtained. The product showed a carbonyl absorption in the i.r. spectrum at 1720-1230 cm^{-1} in place of 1635 cm^{-1} in the starting material consistent with the formation of the acyl nitrate 2. A solution of the acyl nitrate in acetonitrile rapidly nitrated phenol quantitatively and analysis of the products by g.l.c. showed that 2-nitrophenol (95%) and 4-nitrophenol (5%) had been formed. The selectivity, speed, and cleanness of this reaction were all remarkable. Under comparable conditions, both phenol and anisole underwent complex reactions with nitronium tetrafluoroborate leading to

polynitration and purple pigments. The closest analogy for a selective reaction involving an acyl nitrate comes from the work of Rees who showed that biphenyl 2-carboxylic acid underwent nitration in the 2'-position on treatment with dinitrogen pentoxide;[14] the selectivity here is clearly due to an intramolecular reaction.

	R^1	R^2	R^3	X
1	$nC_{12}H_{25}$	H	CO_2^-	-
2	$nC_{12}H_{25}$	H	CO_2NO_2	BF_4
3	$nC_{12}H_{25}$	H	CO_2H	Cl
4	$nC_{12}H_{25}$	CO_2H	H	Cl
9	C_2H_5	H	$CONHCH_3$	Br^-
10	CH_2Ph	H	SO_2NHMe	Br^-

$Me_3\overset{+}{N}CH_2CO_2^-$

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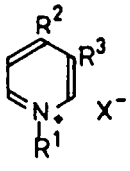

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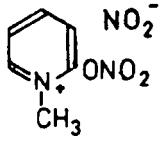

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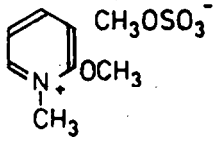

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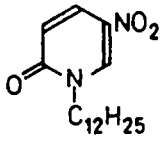

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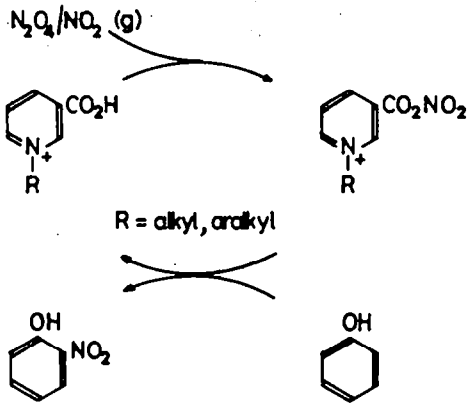
Having discovered a new reaction of high selectivity, we investigated the structural requirements for selective nitration of phenol. Acyl nitrate derivatives of acetic acid, 4-nitrobenzoic acid, salicylic acid and trifluoroacetic acid were all prepared in acetonitrile solution with nitronium tetrafluoroborate and their presence confirmed by i.r. spectroscopy. However under the same conditions as the selective nitration of phenol with 2, no significant nitration occurred. These observations suggested that in dilute solutions in non-hydroxylic solvents, it was necessary for a close interaction between the phenol and the nitrating agent akin to an intramolecular interaction to take place before substitution would occur. Nitration of anisole by 2 was unselective and potassium phenoxide was nitrated slowly and unselectively. Since both phenoxide and anisole will form donor-acceptor complexes with pyridinium salts, an important role for the hydroxyl group was indicated.

A further question of practical significance was the use of the expensive reagent nitronium tetrafluoroborate. We found that it was possible to substitute NO_2-N_2O_4 gas for nitronium tetrafluoroborate and to prepare activated pyridinium carboxylates not only from 1, but also from the carboxylic acids 3 and 4. Both of these activated compounds nitrated phenol selectively (Table 1). Thus the expensive nitronium salt was not required and the pyridinium salt could be reused in further reactions (Scheme 1). These results are also relevant to the structural requirements for selectivity since they show that the position of the carboxyl group in the pyridine ring is not important. Further, the aliphatic quaternary ammonium salt 5 was shown to

Table 1 Nitration of Phenol

Carrier molecule	Solvent	2-nitro %	4-nitro %	yield %
1 (2)	a	95	4	> 99
3	a	95	5	> 99
4	a	95	5	> 99
2-pyridone (6)	a	> 99	< 1	> 98
7a	a	< 5	< 5	< 5
	b	15	10	25
8a	a	61	15	76
	b	92	3	97

Reactions carried out in 0.04-0.1M solution in a acetonitrile or b 1,2-dichloroethane. Yields of products were determined by glc or by work up and weighing products.



Scheme 1 Nitration of phenol with recycling of the transfer agent

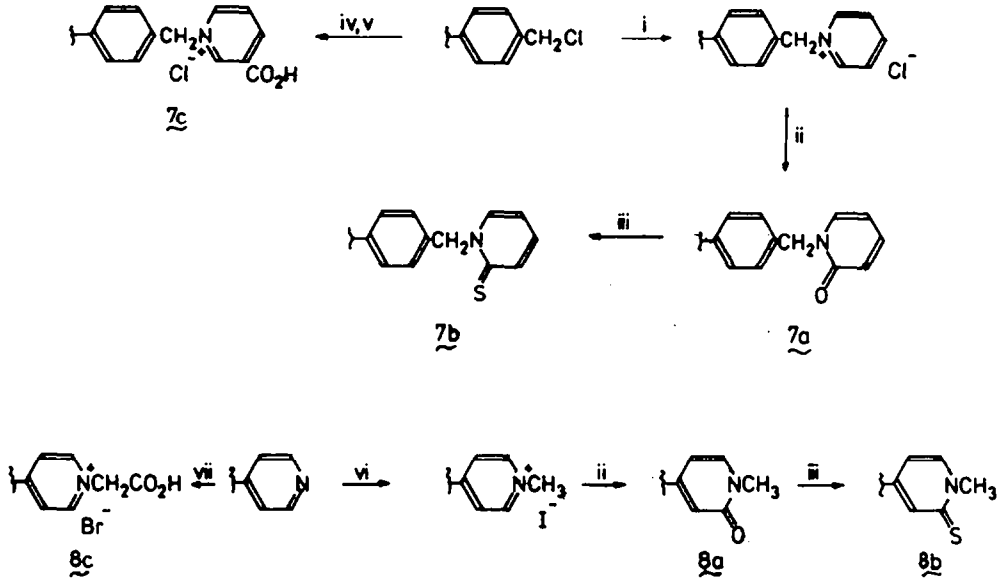
promote nitration of phenol but with diminished yield and selectivity in comparison with the pyridinium salts. The working hypothesis that selectivity requires a planar, electron accepting carrier molecule such as a pyridinium salt together with a hydrogen bond that orients the substrate with respect to the reagent was devised. If this hypothesis is correct, then other pyridinium salts should be capable of acting as transfer agents.

To test the hypothesis, N-methyl 2-pyridone was treated with NO_2-N_2O_4 gas in acetonitrile solution to yield the pyridinium salt 6 as indicated by the loss of the carbonyl absorption at 1665 cm^{-1} in the i.r. spectrum. Nitration of phenol with 6 was quantitative and highly selective (>98% ortho). This result shows that not only is the scope of pyridinium salt used as a transfer agent expanded, but also that long N-alkyl chains are not required.

Polymer supported reagents

The key test of a biomimetic reaction is that it should combine selectivity with practicality. The structural flexibility discovered for the transfer agent in the above reactions encouraged us to investigate the synthesis and properties of polymeric supported reagents which would, of course, obviate the need for extraction procedures. Derivatives of chloromethylated polystyrene

and of a styrene/4-vinyl pyridine copolymer were prepared as shown in Scheme 2. Quaternisation of the chloromethylated polystyrene with pyridine and treatment with alkaline potassium ferricyanide led to the pyridone, **7a**; sulphurisation of the pyridone afforded the thiopyridone, **7b**. Alternatively, quaternisation with nicotinamide followed by acidic hydrolysis led to the 3-carboxypyridine bearing polymer **7c**. The pyridone, **8a**, and thiopyridone, **8b**, derivatives of the 4-vinylpyridine copolymer were prepared in the same way as the polystyrene derivatives. A further polymer, **8c**, was prepared by alkylation of the 4-vinyl pyridine copolymer with bromoacetic acid. Difficulties were experienced in bringing all the conversions of polymers to completion and in removal of excess reagents. However all the polymer samples used for reactions showed i.r. spectra consistent with their modification.



Scheme 2 Synthesis of polymer-supported pyridinium derivatives. Reagents: i pyridine, ii $K_3Fe(CN)_6$ KOH, iii P_4S_{10}, iv nicotinamide, v aq HCl, vi MeI, vii $BrCH_2CO_2H$.

The polymers were used in nitration in a similar manner to the soluble transfer agents being activated with NO_2/N_2O_4. Before introducing a substrate, the polymers were thoroughly washed. The results of nitrating phenol are shown in Table 2. In most cases, the yields of nitrated products were disappointing showing generally low conversions with poor selectivity in acetonitrile solution, especially using the polystyrene derivatives. Since the polymers are predominantly hydrophobic, a less polar solvent, 1,2-dichloroethane, was also investigated. In this solvent, in which reagents presumably have greater accessibility to reactive sites, the pyridone derivative of the 4-vinylpyridine copolymer **8a** was conspicuously successful. Evaporation of the reaction mixture gave a crystalline product that was predominantly 2-nitrophenol, the i.r. spectrum of which was superimposable with that of an authentic sample. This polymer also showed its value in the nitration of naphthols (see below) by avoiding difficult separation procedures. The simplicity of the reactants and the ease of separation of products and polymeric transfer agents makes large scale applications of processes of this type feasible.[15]

Table 2 Nitration of Phenol in the Presence of Polymers

Polymer	Solvent	% phenol	2-nitro	4-nitro
7a	CH_3CN		< 5%	
	$C_2H_4Cl_2$	75	15	10
7b	CH_3CN	100	0	
7c	CH_3CN	58	27	15
8a	CH_3CN	24	61	15
	$C_2H_4Cl_2$	5	92	3
8b	CH_3CN	83	13	4
	$C_2H_4Cl_2$	30	63	8
8c	CH_3CN	100	0	

The scope of the nitration reaction

The first aspect of the scope of the reaction to be investigated was the effect of substituents in the phenol on the extent of nitration. Accordingly, 4-substituted phenols were examined as substrates. Whereas 4-methyl and 4-chlorophenols cleanly underwent mononitration with 2 in the 2-position as expected, 4-methoxyphenol afforded 2,6-dinitrophenol as the sole product. 3-Methylphenol led to a mixture of products: 5-methyl-2-nitrophenol (46%), 3-methyl-4-nitrophenol (19%), 2,6-dinitro-3-methylphenol (31%), and 2,4-dinitro-5-methylphenol (3%) as shown by h.p.l.c. In no case was a tarry product obtained. Clearly the nitrating agent 2 is capable of nitrating a variety of phenols cleanly although electron donating substituents can promote dinitration and alkyl substituents can disrupt the intimate arrangement of substrate and reagent required to give high selectivity. The next test of the selectivity was using 1- and 2-naphthols. In these cases, the nitration occurred readily to give a mixture of products which proved very difficult to separate chromatographically from the pyridinium salt carrier molecule. The utility of the polymer supported reagents was well demonstrated with naphthols as substrates because it was possible to isolate the nitration products totally uncontaminated by reagent. The reactions were, however, unselective presumably reflecting the higher reactivity of naphthols compared with phenol. The products identified from 1-naphthol were 2-nitro-1-naphthol (20%), 2,4-dinitro-1-naphthol (67%), and 2,2'-dinitro-4,4'-bi-1-naphthol (13%). 2-Naphthol reacted more selectively as would be expected from its intrinsic reactivity affording 1-nitro-2-naphthol (68%) and 2,6-dinitro-2-naphthol (32%). It is probable that a more detailed investigation of reaction conditions would make a selective nitration of naphthols possible.

Although in some of these reactions mixtures of products were obtained, all were free from intractable products and the cleanness of this type of nitration procedure is one of its major advantages. We therefore investigated the possibility of using it to nitrate reactive heterocyclic compounds. The results were, however, disappointing. Even at low temperature (-78°C), pyrrole and indole, afforded tarry products when treated with nitrating agents derived from pyridine carboxylic acids or 2-pyridones.

The structural studies carried out to identify suitable carrier molecules for the nitration of phenol suggested that the hydrogen bonding ability of the phenol was important in determining the outcome of the nitration reaction. It was therefore of interest to see whether aniline could be

cleanly nitrated; however, as with the heterocyclic compounds, nitration led to tarry products. A role for a weakly acidic hydrogen atom was supported by the observation that whereas acetanilide was totally unreactive to the activated pyridone reagents, both free and polymer supported, methylsuphonylaniline underwent nitration to give a mixture of approximately equal proportions of 2- and 4-nitro products in comparison with a 2:1 preference for 4-nitration in the absence of the carrier molecule.

The final series of extensions of the reactions investigated was designed to discover whether any further substitution reactions could be brought about with the pyridinium salts acting as carrier molecules. To investigate this, the bromination of phenol was studied using 1-ethyl-3-methylcarbamoylpyridinium bromide **9** and the corresponding 1-benzyl sulphonamide **10**. These compounds were found to react with bromine as shown by elemental analysis but there was no evidence for the loss of N-H vibrations in the i.r. spectrum of the brominated product; in fact the i.r. spectra were superimposable with the starting pyridinium salts. This result suggests that pyridinium perbromides were formed and indeed their reactivity was typical of a soft brominating agent in that phenol was exclusively brominated in the 4-position. Neither pyridinium amide reacted readily with chlorine. An alternative carrier molecule, 1-ethyl-2-thiopyridone was investigated because of its anticipated high reactivity towards electrophilic reagents to form activated pyridinium salts. Such reactions did in fact occur with acetyl choride, cyanogen bromide, chlorine, and bromine but at room temperature, none of these derivatives reacted with phenol, anisole, or naphthalene. Reactions under more vigorous conditions were not attempted because the association of pyridinium salts and phenols is relatively weak (see below) and an increase in temperature would be expected to destroy any likelihood of achieving selectivity. 1-Dodecyl-5-nitro-2-pyridone was found to mediate nitration of phenol under typical conditions and, because of its deactivated pyridine ring, was chosen as a carrier molecule for attempted sulphonation reactions. Treatment of this compound with sulphur trioxide in 1,2-dichloroethane led to a product that had lost the i.r. absorption at 1680 cm^{-1} but had gained one at 1225 cm^{-1} suggesting that the activated pyridone had indeed formed. The product was used in an attempted sulphonation of naphthalene in acetonitrile but without success. It is possible that a more extensive study of some of these reactions would lead to preparatively useful processes but before undertaking such an investigation it was important to establish some of the mechanistic factors responsible for selective nitration of phenol.

Phenol-pyridinium salt interactions

With the reactions of phenol and naphthol in mind, we firstly investigated the relative strengths of interaction of these substrates with simple unsubstituted pyridinium salts by n.m.r. As we had found in our earlier work with amphiphilic molecules,[13] there were substantial changes in the chemical shifts of both phenolic molecule and pyridinium salt when the two were brought together into solution. The results of a concentration dependence study are shown in Tables 3 and 4. Analysis of these data allows an estimate of the association constant for each pair to be obtained. Assuming 1:1 complexation, the association constant can be obtained from the equation

$$\frac{\Delta\delta_{max}}{\Delta\delta_{obs}} = 1 + K_a[ArOH]$$

As can be seen from the tables, most of the associations are quite weak, the exception being the interaction of pyridinium with naphthol. This, together with the intrinsically greater reactivity of naphthols than phenol, may account for the observed polynitration of naphthols. The chemical shift changes, $\Delta\delta$, used in this estimation were the largest observed in the experiment. An upfield shift of H^2 and H^3 of the pyridinium ring is consistent with the combined effects of shielding and reduced electron density. It is probable that the favoured structure in the molecular complex that leads to these results is one in which the phenol and pyridinium dipoles are antiparallel.

To investigate the possibility of the control of selectivity being due to a hydrogen bond, we prepared the model activated pyridinium salt, 1-ethyl-2-methoxypyridinium methosulphate **11**. The

Table 3 Changes in chemical shift of pyridinium protons observed for the interaction of N-methylpyridinium ions [40 mM] with phenol, naphthol and indole in CD_3CN_3 solution at 29°C

Compound	Conc mM		H^2 Δδ Hz	H^3 Δδ Hz	K_a M^{-1}
Phenol	53.5		-14.6	-7.3	
	10.7		-19.0	-8.8	
	1.07		-19.7	-9.5	
		max	-20.1	-9.5	9.7
Naphthol	44.6		0	0	
	22.3		-5.1	-2.9	
	8.92		-8.8	-5.1	
	0.892		-10.2	-6.6	
		max	-13.2	-6.6	1300
Indole	31.2		-26.3	-17.5	
	15.6		-27.8	-18.3	
	6.2		-29.2	-18.1	
	0.62		-30.7	-19.4	
		max	-32.2	-19.4	5.7

Table 4 Changes in chemical shift of quinolinium protons observed for the interaction of N-methylquinolinium ions [40 mM] with phenol, naphthol and indole in CD_3CN_3 solution at 19°C

Compound	Conc mM		Δδ H^2 Hz	Δδ H^3 Hz	K_a M^{-1}
Phenol	53.5		-28.5	-1.5	
	26.8		-32.2	-2.2	
	10.7		-35.1	-2.9	
	1.07		-36.6	-2.9	
		max	-38.0	-3.7	8.3
Naphthol	44.6		-6.6	-2.2	
	22.3		-9.5	-5.1	
	8.9		-17.5	-5.9	
	0.892		-20.5	-7.3	
		max	-22.7	-10.2	277
Indole	31.2		-72.4	-28.5	
	15.6		-74.6	-29.2	
	6.2		-76.8	-30.0	
	0.62		-76.4	-30.7	
		max	-77.0	-30.7	2.3

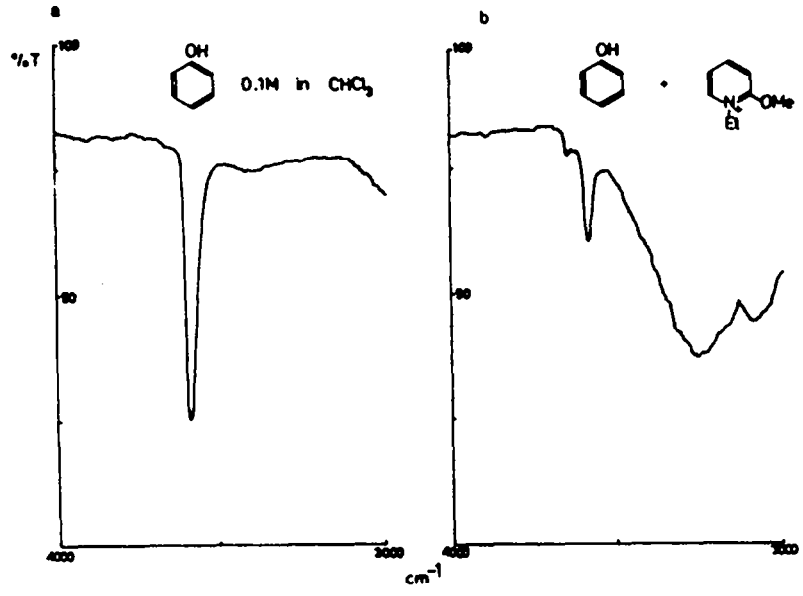


Figure 1 Solution phase i.r. spectra of phenol and its 2-methoxypyridinium complex in $CHCl_3$.

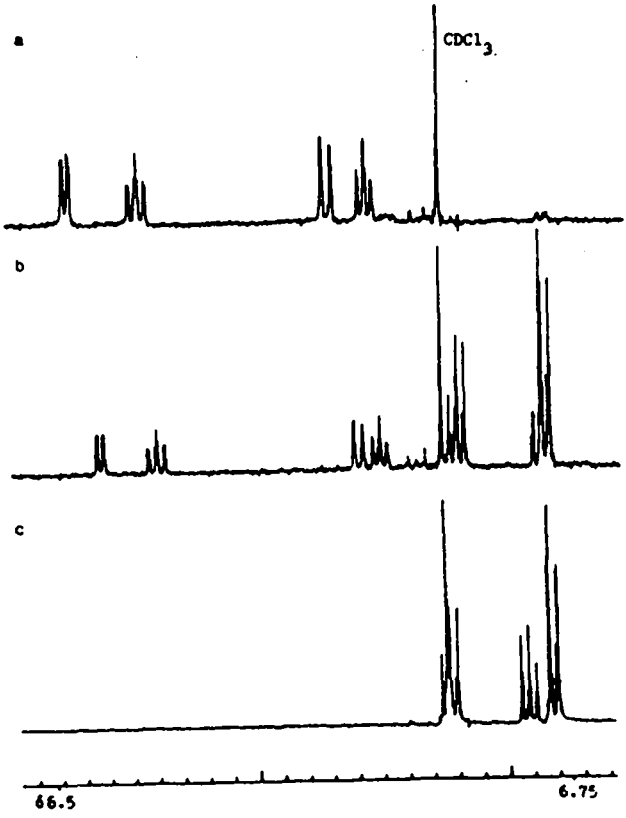


Figure 2 250 MHz ^1H n.m.r. spectra of (a) 1-ethyl-2-methoxypyridinium methosulphate, (b) mixture of phenol and 1-ethyl-2-methoxypyridinium methosulphate, and (c) phenol, each 20mM solutions in $CDCl_3$.

i.r. spectra of dilute solutions of phenol in chloroform in the presence and absence of the pyridinium salt **11** were determined (Figure 1). The spectrum of phenol alone showed a sharp free O-H stretching vibration at 3950 cm^{-1} (Figure 1a), but in the presence of **11**, the intensity of this band was greatly diminished with the concomitant appearance of a broad band between 3400 and 3200 cm^{-1} characteristic of an intermolecular hydrogen bond.

The parallel experiment by n.m.r. showed the characteristic upfield shifts of the pyridinium protons and the differential upfield shifts of the 3, 4, and 5-protons of the phenol and the downfield shifts of the 2 and 6-protons (Figure 2). Together the data suggest that a complex of the type illustrated in Figure 3 may be a major contributor to the species found in non-polar solvents. The results are consistent with the postulate of hydrogen bonding and a donor-acceptor interaction being the cause of the selectivity in the nitration of phenol. Although in this model experiment, the partners in the hydrogen bond are clear, the nitration reactions themselves, the situation is ambiguous because of the possibility that oxygen atoms of either the carrier molecule or the nitro group itself could act as a hydrogen bond acceptor (Figure 3). To investigate these possibilities, further nitration reactions were carried out with structurally modified carrier molecules.

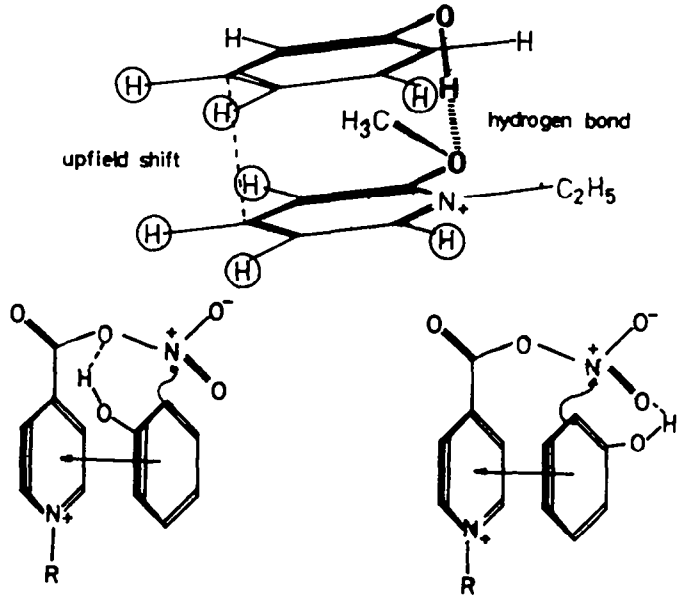


Figure 3 Orientations in pyridinium-phenol complexes suggested by spectroscopic data.

Modified nitration reagents

The most efficient nitrating reagents and the ones with the least hydrogen bonding possibilities were those formed from the 2-pyridones. The first experiment to probe the question of the nature of the hydrogen bonding in the nitration reactions was carried out with the nitropyridone **12**. Whereas nitration with unsubstituted pyridone derivatives gave exclusive 2-nitration, the product of reaction using **12** as transfer agent was 55% 2-nitration and 45% 4-nitration. This reaction can be interpreted in terms of alternative orientations of hydrogen bonds; hydrogen bonding to the pyridone oxygen atom leads to 2-nitration whereas hydrogen bonding to the nitro group promotes 4-nitration. Specific hydrogen bonding patterns related to these have been proposed to account for the selectivity of chlorination and nitration of phenols by cyclohexadienone derivatives[16,17] and an eloquent test of the model depicted in Figure 4 would be to remove the hydrogen bonding site at the reagent end, except for the inevitable nitro group site, by replacing the pyridone oxygen atom by sulphur. We made extensive efforts to prepare N-alkyl-5-nitro-2-thiopyridones without success. Direct sulphurisation of **12** led to intractable

tars and N-ethyl-2-thiopyridone was resistant to nitration under very vigorous conditions. An alternative approach whereby 2-chloro-5-nitropyridine was alkylated before introduction of the sulphur by nucleophilic substitution also failed even with sealed tube reactions for several days at 200°C. Alternative carrier molecules in which the hydrogen bonding group was placed in the N-alkyl chain were therefore devised and prepared following the routes shown in Scheme 3.

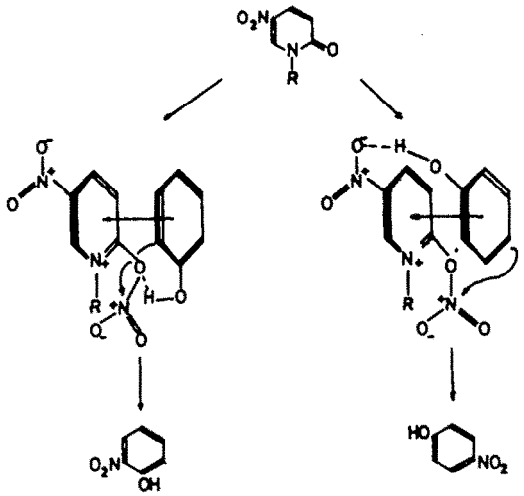
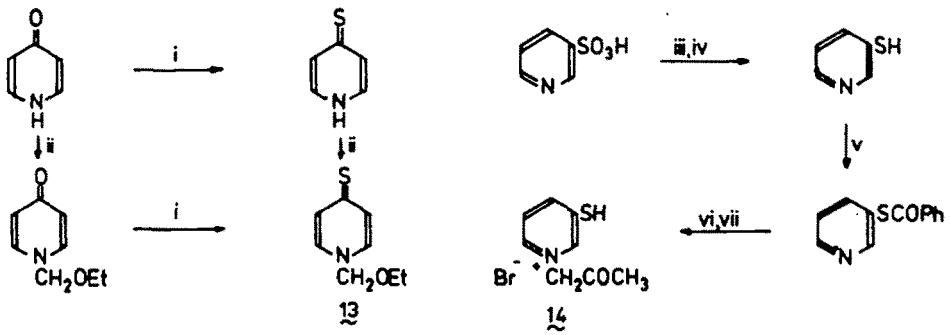


Figure 4 *Possible competing complexation modes in the nitration of phenol by nitro-substituted transfer agent 12.*

1-Ethoxymethylpyridin-4(1H)thione, **13**, was obtained by alkylation of the 4-thiopyridone[18] anion prepared using sodium hydride in dimethylformamide. In contrast to normal alkylation of thiopyridones, this reaction gave only the N-alkylated product. Under the same reaction conditions, 4-pyridone gave a mixture of O- and N-alkylated products which were separated by chromatography. Sulphurisation of the N-alkylated product gave an alternative route to the thiopyridone, **13**. A second new transfer agent, **14**, in which sulphur is present at the 3-position was prepared from 3-benzoylthiopyridine[19,20] and alkylation with chloroacetone.



Scheme 3 Reagents: i Lawrenson's reagent, ii $ClCH_2OEt$, iii $PCl_5/POCl_3$, iv $SnCl_2$, v PhCOCl, vi $BrCH_2COCH_3$, vii aq HCl.

Both compounds were readily activated by NO_2/N_2O_4 in the conventional manner and mediated quantitative nitration of phenol with virtually complete selectivity for 2-nitrophenol. It was also possible to demonstrate the occurrence of hydrogen bonds between phenol and the methyl thiothers of **13** and **14** by i.r. spectroscopy as described above. However the exclusive

2-nitration observed in these reactions implies that hydrogen bonding to the reagent site as indicated in Figure 3 is important in the product-determining complex. Hence it may not be possible to obtain a high yielding para nitrating transfer agent based upon this strategy. None of these arguments impinge upon the question of the mechanism of nitro group transfer and substitution of phenol which remains to be investigated; they refer to selectivity alone.

EXPERIMENTAL

^{1}H n.m.r. spectra were obtained either on a Perkin Elmer R32 spectrometer operating at 90 MHz (a), or a Bruker WM250 spectrometer operating at 250 MHz (b) in the solvents stated. Nitration of phenol was determined by g.l.c. using 5% Apiezon L on Chromosorb G at 190°C and by n.m.r. and i.r. spectroscopy. The products of nitration of other substrates were determined after separation by chromatography on silica gel and characterisation by m.p. in comparison with literature data, elemental analysis, or mass spectrum and n.m.r. The following compounds were so characterised: 5-methyl-2-nitrophenol,[21] 3-methyl4-nitrophenol,[22], 2,6-dinitro-3-methylphenol and 2,4-dinitro--5-methylphenol,[23] 4-methyl-2-nitrophenol,[24] 4-chloro-2-nitrophenol,[25] 2,6-dinitro-4-methoxyphenol,[26] 2-nitro-1-naphthol,[27] 2,4-dinitro-2-naphthol,[28] 2,2'-dinitro-4,4'-bi-1-naphthol,[29] 2-nitro-2-naphthol,[30] 1,6-dinitro-2-naphthol.[31]

3-Carboxy-1-dodecylpyridinium chloride (1)

Nicotinamide (12.21 g), dodecylbromide (24.9 g), and nitromethane (80 ml) were mixed together and refluxed gently overnight. The reaction mixture was then allowed to cool and the product filtered by suction. Washing twice with a small quantity of acetone and drying by desiccation over P_2O_5 afforded the crude amide (26.5 g, 71%) which was used as such for further preparation.

The amide (24 g) was heated under reflux with concentrated hydrochloric acid (350 ml) for 2 h. The solution obtained was allowed to cool overnight. A little of the hydrochloric acid was removed on rotary evaporator causing a thick cream coloured precipitate to separate. The precipitate was filtered by suction and crystallised from acetone. Recrystallisation from n-propanol/acetone afforded the acid (16.8 g, 79%), m.p. 180°C (Found: C 65.9, H 9.28, N, 4.27. $C_{18}H_{30}ClNO_2$ requires C, 65.93; H, 9.22; N, 4.27); ν_{max} (KCl) 3040 (C-H arom.), 2900-2840 (C-H aliph.), 2700-2300 (OH, dimer), 1675 (C=O), 1630 (quaternary N), 1590 (C=C, arom.), 1460 (C-H, aliph.); δ_H (90 MHz; DMSO-d_6) 9.56 (1H, s, C(2)H), 9.37 (1H, d, C(6)H, 8.95 (1H, d, C(4)H), 8.28 (1H, dd, C(5)H), 4.72 (2H, t, N-C$\underline{H}_2$, 2.08-1.72 (2H, m, N-CH$_2$-C$\underline{H}_2$), 1.28 (18H, br. s, $(CH_2)_n$), 0.9 (3H, t, $(CH_2)_n$-C$\underline{H}_3$.

4-Carboxy-1-dodecylpyridinium chloride (3)

This compound was prepared by using the respective starting material (isonicontinamide) under the conditions described for compound (1).

Recrystallisation from water afforded the acid (23.8 g, 72%), m.p. 185°C (Found: C 65.91, H 9.60, N 4.09. $C_{18}H_{30}ClNO_2$ requires 65.93; H, 9.22; N, 4.27)+ ν_{max} (KCl) 3050 (C-H arom.), 2910-2840 (C-H, aliph.), 2700-2300 (OH, dimer), 1700 (C=O) 1635 (quaternary N), 1570 (C=C, arom.), 1460 (C-H, aliph.); δ_H (90 MHz; DMSO-d_6) 9.40 (2H, d, C(2,6)H), 8.45 (2H, d, C(3,5)H), 4.78 (2H, t, N-C$\underline{H}_2$), 1.77 (2H, m, N-CH$_2$C$\underline{H}_2$), 1.27 (18H, br. s, $(CH_2)_n$), 0.9 (3H, t, $(CH_2)_n$-C$\underline{H}_3$).

Preparation of pyridone and thiopyridone derivatives of polystyrene

Pyridinium chloride substituted polystyrene

A sample of chloromethylated polystyrene (13 g, crosslinked with 2% divinylbenzene, 25% chloromethylated) was suspended in pyridine (100 ml) and the mixture heated under reflux overnight. The polymer was filtered off and washed with toluene and methanol. Finally the polymer was washed exhaustively with methanol by soxhlet extraction for 5 h. A sample was dried and analysed. (Found: C 81.2, H 7.6, Cl 5.5, N 1.3%. Quantitative conversion requires C 82.7, H 6.9, Cl 7.5, N 2.95%).

2-Pyridone substituted polystyrene (7a)

To a solution of potassium ferricyanide (28 g) and potassium hydroxide (4.76 g) in water was added the product of the above reaction and the mixture heated under reflux overnight. The polymer was then filtered from the resulting green-brown solution and washed successively with acetone and methanol followed by soxhlet extraction with methanol. A sample was dried and

analysed. Yield 14 g. (Found: C 82.4, H 7.5, Cl 1.35, N 1.65%. Quantitative conversion requires C 79.6, H 6.16, N 6.6%).

2-Thiopyridone substituted polystyrene (7b)

The pyridone bearing polymer (7a, 7g) was suspended in xylene (100 ml) and heated under reflux with phosphorus pentasulphide (7 g) overnight. The polymer was filtered off and washed successively with xylene, toluene, and acetone followed by soxhlet extraction with toluene for 6 h. A sample was dried and analysed. (Found: C 84.4, H 5.8, Cl 0.7, N 0.9, S, 6.8%. Quantitative conversion requires C 85.8, H 7.9, N 2.2, S 5.0%).

Preparation of pyridone and thiopyridone derivatives of poly-4-vinylpyridine

Quaternisation of poly-4-vinylpyridone

A sample of poly-4-vinylpyridine copolymer (11.8 g, 18% pendant pyridine and 82% pendant benzene rings) was heated under reflux with iodomethane (100 ml) for 3 d. The product was washed successively with acetone and methanol and finally extracted continuously with methanol in a soxhlet apparatus for 4 h. Yield 21 g. A sample was dried for analysis. (Found C 74.4, H 6.8, N 1.9, I 15.9%. Quantitative conversion requires C 73.7, H 6.5, N 2.0, I 17.8%).

Preparation of poly-4-vinylpyridone copolymer (8a)

The reaction was carried out as described for the polystyrene derivative (7a). After washing with acetone and methanol, elemental analysis showed the presence of excess nitrogen, presumably from potassium ferricyanide. Extraction with water in a soxhlet apparatus overnight afforded the required polymer. (Found C 81.8, H 7.1, N 5.8, I 0.8%. Quantitative conversion requires C 87.5, H 7.5, N 2.3%).

Preparation of poly-4-vinylthiopyridone copolymer (8b)

The reaction was carried out as described for the polystyrene derivative. Analysis of the product showed a substantial loss of carbon suggesting significant degradation of the polymer. (Found C 61.5, H 5.9, N 3.1, S 3.5, I 0.91%. Complete conversion of starting polymer requires C 85.2, H 7.3, N 2.3, S 5.2%).

Preparation of 3-carboxypyridinium derivative of polystyrene (7c)

Chloromethylated polystyrene (25% chloromethylated 2% crosslinked with divinyl benzene, 5 g) was suspended in nitromethane (50 ml) and heated under reflux with nicotinamide (1.64 g) for 3 d. The polymer was filtered off and extracted exhaustively with acetone in a soxhlet apparatus overnight. A small sample was removed and dried for analysis. (Found C 80.5, H 7.4, N 2.9, Cl 5.6%; quantitative substitution requires C 79.8, H 6.7, N 4.8, Cl 6.0%. This data implies 15.2 mol % coupled polymer). The remaining polymer was suspended in hydrochloric acid (20%, 50 ml) and heated gently under reflux overnight. The polymer was then filtered off and washed with 0.1M aqueous sodium hydroxide solution (1 l) and water (1 l). The whole product was dried under reduced pressure at 77°C. (Found C 81.9, H 7.5, N 1.25%; quantitative substitution requires C 84.8, H 6.9, N 2.5%).

Preparation of N-carboxymethyl derivative of poly-4-vinylpyridine/

polystyrene copolymer (8c)

Poly-4-vinylpyridine/polystyrene copolymer (16% poly-4-vinylpyridine, 5 g) was suspended in nitromethane (50 ml) and heated under reflux with bromoacetic acid (1.19 g) overnight. The polymer was then filtered off and washed with acetone exhaustively in a soxhlet apparatus. The product was then washed with 0.1M aqueous sodium hydroxide (1 l) and water (1 l) and dried under reduced pressure at 77°C. (Found % C 77.7, H 6.9, N 2.1%; quantitative substitution requires C 78.8, H 6.7, N 1.6%). The analytical data is consistent with the products being the hydrobromide.

4-Hydroxypyridine was converted to thiopyridone as reported in the literature.[18]

Alkylation of 4-hydroxypyridine

4-Hydroxypyridine (5 g) was added to dimethylformamide (150 ml) and the mixture stirred at room temperature. Sodium hydride (50% excess) was added in portions to the stirring solution. Stirring was continued at 70-80°C for 4 h, after which the reaction mixture was filtered hot. The residue was washed with warm dimethylformamide (15 ml). The combined solution was allowed to

cool to 30-40° before chloromethylethylether (5 g) in dimethylformamide (10 ml) was added. The reaction mixture was stirred for 1 h at room temperature and subsequently at 70-80°C for a further 2 h. The reaction mixture was then allowed to cool, filtered and the filtrate evaporated under reduced pressure. To the residual oil was added chloroform (50 ml) and water (20 ml) and the mixture partitioned. The organic layer was dried ($MgSO_4$ or Na_2SO_4) and evaporated under reduced pressure to give crude alkyl pyridone (6.88 g, 85%).

The products of this reaction were separated by chromatography on silica or by distillation. The less polar compound (EtOAc), 1.5 g, 8.6%) distilled at 30°C at 0.6 mmHg. The main product was a very polar compound, obtained as a thick oil on chromatography (5% MeOH/EtOAc, 5 g, 62%) and distilled at 215°C at 0.5 mmHg. The former was identified as the O-alkylation product while the latter was the N-alkyl derivative.

4-Ethoxymethoxypyridine δ_H ($CDCl_3$) 2.18, t, 3H($-CH_3$); 3.66 q, 2H, ($O-CH_2-C$); 5.23, s, 2H, ($O-CH_2-O$) 6.89, d, 2H, and 8.40, d, 2H (aromatic protons). The i.r. spectrum showed no C=O absorption.

1-Ethoxymethylpyridin-4(1H)-one δ_H ($CDCl_3$) 1.18, t, 3H ($-CH_3$), 3.48, q, 2H ($O-CH_2-C$) 5.08, s, 2H, ($-N-CH_2-O$); 6.28, d and 7.45 d, 2H each, (aromatic protons). ν_{max} 1635 cm^{-1}. Found C 62.6, H 7.30, N 9.2; $C_8H_{11}NO_2$ requires C 62.73, H 7.24, N 9.14%).

1-Ethoxymethylpyridin-4(4H)-thione (13)

a) 1-Ethoxymethylpyridin-4(1H)-one (3 g) and p-methoxyphenylthionophosphine dimer (4.04 g) in dry toluene (100 ml) were heated at 90-100°C for 5 h. The toluene solution was filtered. The solid mass left in the reaction flask was decomposed with water and then extracted with chloroform. The combined chloroform and toluene solution was evaporated under reduced pressure to give an oil which on chromatography on silica gel gave the thiopyridone (13), among other products. The thiopyridone was eluted with ethyl acetate/petroleum ether (50:50) (1.3 g, 39%). It was purified by distillation (Kugelrohr) at 250°C at 0.3 mmHg. The compound is not very stable in air and tends to deteriorate with storage. (Found: C 56.1, H 6.5, N 8.4, S 18.8. $C_8H_{11}NO_5$ requires C 56.8, H 6.55, N 8.28, S 18.9%).

The 4-thiopyridone (0.8 g) in dimethylformamide was reacted with sodium hydride (25 g of a 50% suspension washed in ether). After stirring at room temperature for 4 h, the reaction mixture was allowed to cool to room temperature and chloromethylethylether (0.7 g) added. The reaction mixture was stirred for 1 h at room temperature and then at 70-80° for 1 h. The cold reaction mixture was poured into water (100 ml) and extracted with chloroform (4 x 15 ml). The combined chloroform extracts were dried, evaporated under reduced pressure to give a thick oil purified by distillation (0.7 g, 57% yield). The product was identical to that obtained by reaction (a). δH 1.2 t, 3H($-CH_3$), 3.64 q, 2H, ($O-CH_2-CH_3$); 5.07 s, 2H ($N-CH_2-O$), 7.28 m, 2H, and 8.36 m, 2H (aromatic protons).

3-Benzoylthiopyridine was prepared from pyridine-3-sulphonic acid as described in the literature.[19,20]

3-Mercapto-1-(2-oxoethyl)pyridine (14)

3-Benzoylthiopyridine (54 g) was dissolved in methanol (30 ml) and redistilled chloroacetone (4.8 g) added. The reaction mixture was heated at reflux temperature (or at 60° in the thermostat) for 48 h, or until no 3-benzoylthiopyridine was present (t.l.c.). Methanol was then evaporated and water (20 ml) and ether (25 ml) were added to the residue. The product was partitioned between ether and water. The aqueous layer was evaporated under reduced pressure to give a solid which was recrystallised (methanol-ethylacetate, charcoal) to give crystals m.p. 120-121°C (3.25 g, 64%). (Found: C 46.7, H 4.75, N 6.6, Cl 7.3, S 15.3. Calculated for $C_8H_{10}NOSCl$ C 47.2, H 4.95, N 6.9, Cl 7.4, S 15.7). δ_H, ($(CD_3)_2SO$) 2.29, s, 3H ($-CH_3$); 4.47 s, 2H ($-CH_2$), 7.9, 1H (S-H); 8.4-9 m, 4H (aromatic protons).

General procedures for nitration

(1) N_2O_4/NO_2 gas generated by strongly heating dry lead nitrate in a 250 ml round bottomed flask and carried by a gentle flow of N_2 gas, was bubbled via a dreschel bottle through a stirred suspension/solution of the carrier molecule (0.001 mol) in dry acetonitrile (10-25 ml) for

0.5-1 h. The solution was stirred further for 1 h without N_2O_4/NO_2, gas bubbling through. Solvent and an excess of N_2O_4/NO_2 gas were then removed under reduced pressure, and the residue redissolved in dry acetonitrile (10 ml) and treated with a solution of substrate (0.001 mol) in dry acetonitrile (10 mol).

(2) N_2O_4/NO_2 gas generated by strongly heating lead nitrate in a 250 ml round bottomed flask and carried by N_2 gas, was bubbled via a dreschel bottle through a stirred suspension of polymer-supported pyridine derivative (0.0011 mol) in acetonitrile or 1,2-dichloroethane (10 ml) for 0.5-1 h. The suspension was further stirred for 1 h without N_2O_4/NO_2 gas bubbling through. The activated polymer was then washed well with the appropriate solvent until the washings were clear. This was then suspended in fresh solvent (10 ml) and stirred overnight with a solution of the substrate (0.0010 mol) in fresh solvent (10 ml).

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