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Reactivity of nitrite with 2-chlorophenol, *t*-butyl phenol and resorcinol in mild acidic conditions

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Summary — The influence of ionic strength, pH, oxygen, organic solvents and nitrite concentration on the kinetics and the regioselectivity of 2-chlorophenol nitration by nitrous acid to form 4-nitro and 6-nitro derivatives was studied. There was quantitative *para* substitution at pH 3.5 in the absence of oxygen using 3 equiv of nitrite. In acetate-buffered solution, 4-*t*-butylphenol gave 90% 2-nitro-4-*t*-butylphenol, and resorcinol gave 85% 2,4-dinitrosoresorcinol. Nitration proceeded via nitrosation followed by oxidation of the nitroso intermediate into the corresponding nitro derivative. Oxidation could be due to reduction of nitrous acid to nitric oxide. The possibility that the reaction proceeds via radical formation, with which NO_2 and NO interfere, is discussed.

nitrous acid / nitrosation / phenol / 2-chlorophenol / resorcinol / 4-*t*-butylphenol / 2,4-dinitrosoresorcinol / 2-nitro-4-*t*-butylphenol / 2-chloro-4-nitrophenol

Résumé — Réactivité du nitrite avec le 2-chlorophénol, le *t*-butylphénol et le résorcinol en solution modérément acide. *Le 2-chlorophénol et l'acide nitreux donnent les 4-nitro et 6-nitrophénol isomères, suivant une cinétique et une régiosélectivité qui dépendent de la force ionique, du pH, de la présence d'oxygène ou de solvants organiques et de la concentration initiale du nitrite. Lorsque la réaction est réalisée à pH 3,5 avec 3 équiv de nitrite, la substitution en position* para *est quantitative en absence d'oxygène. Les 4-t-butylphénol et résorcinol en solution acétate tamponnées avec du nitrite donnent respectivement 90 % de 2-nitro-4-t-butylphénol et 85 % du 2,4-dinitrosorésorcinol. Les nitrations semblent provenir d'une nitrosation suivie de l'oxydation du dérivé nitrosé intermédiaire. L'oxydation serait complémentaire à la réduction de l'acide nitreux en monoxyde d'azote NO. Un mécanisme radicalaire à partir de NO_2 et NO permet de rendre compte des nitrosations et nitrations observées.*

acide nitreux / nitration / nitrosation / 2-chlorophénol / résorcinol / *t*-butylphénol / 2,4-dinitrosorésorcinol / 2-nitro-4-*t*-butylphénol / 2-chloro-4-nitrophénol

Introduction

Nitration of substituted phenols by nitrate solutions is generally studied in strong acid conditions [1]. The catalytic role of nitrous acid generated in situ from nitric acid dismutation has been discussed [2]. Extra nitrite often appears to be necessary to induce the nitration of phenols via the formation of nitrosophenol intermediates [3]. Reactivity is increased when the reaction is carried out in a two-phase system [3, 4]. The mechanism of these reactions remains under discussion.

Nitroso and/or nitro derivatives can however be isolated when the nitration of substituted phenols is carried out with nitrous acid in the absence of nitrate. It has been suggested that *C*-nitration reactions occur via a completely different mechanism from that of *C*-nitrosation. Beake and Moodie [5] pointed out the influence of dissolved oxygen and low pH on the kinetics, and proposed a mechanism of nitration by nitrous acid which accommodates the concomitant oxidation reaction leading to quinone formation from 4-(phenoxy or methoxy)phenol. These authors defended a radical-based mechanism using NO_2 as nitrating agent. In view of the discrepancies found in literature concerning the mechanisms and reactive species involved in such reactions, this paper examines the reactivity of phenol models such as 2-chlorophenol, 4-*t*-butylphenol and resorcinol with nitrous acid in order to have a better understanding of the reactivity of nitrite in mild acidic solutions. We propose here that for the studied phenols, nitrosation and/or nitration occur through a radical-based mechanism. The corresponding nitro or nitroso derivatives were formed in good yields.

Results

Nitration of 2-chlorophenol and 4-t-butylphenol

The reactivity of phenols with nitrous acid in weakly acid aqueous solutions (pH 2–6) was studied using two model substrates, 2-chlorophenol **1** and 4-*t*-butylphenol **4**.

* Correspondence and reprints

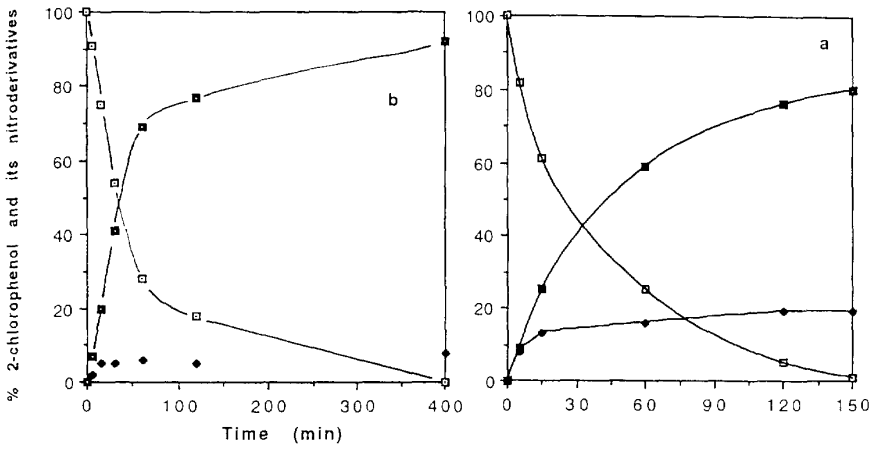
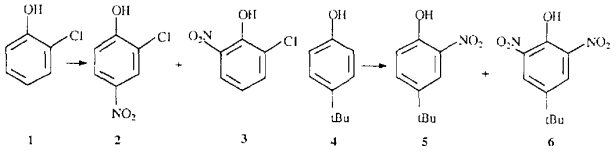


Fig 1. Kinetics of nitration of 40 mmol.dm^{-3} 2-chlorophenol using 3 equiv of nitrite in a two-phase medium (**a**) and in 0.2 mol.dm^{-3} acetate buffer (**b**).



Treating **4** with sodium nitrite gave almost exclusively 2-nitro-4-*t*-butylphenol **5**, while **1** with at least 3 equiv nitrite in non-degassed acetate buffer at pH 2–6 gave a mixture of 2-chloro-4-nitrophenol **2** and 2-chloro-6-nitrophenol **3** in quantitative yield. In the case of phenols **1** in acetate buffer (pH 3.4) or **4** in a two-phase system (cyclohexane/acetic acid), kinetic studies showed that the concentration of the products, *p*-nitro or *o*-nitro derivatives **2** and **5**, fell linearly with time for 1 h (fig 1, results not shown for **4**), whereas kinetic studies of the formation of *p*-nitro and *o*-nitro isomers **2** and **3** indicated slower reactions that lost linearity with time in a two-phase system (fig 1). Only a small quantity of **6** was formed in a 12 h incubation.

A more precise study was carried out on compound **1**. In this case, the kinetics and the selectivity were measured by the ratio $r = ([\mathbf{2}] - [\mathbf{3}])/([\mathbf{2}] + [\mathbf{3}])$ and appeared to depend on pH, oxygen and ionic strength.

- *Influence of the organic phase on the nitration of* **1** *in a two-phase medium*

Addition of an organic solvent to the acetate buffer allowed the dissolution of phenol but decreased the yield and the regioselectivity of the reaction (table I).

- *Influence of ionic concentration on the nitration of* **1**

When the concentrations of sodium acetate or nitrite were varied, the regioselectivity stayed unchanged (0.75 ± 0.07) whereas the kinetic parameters were affected. Indeed, at pH 3.5, the nitration rate doubled when initial nitrite concentration varied from 3 equiv (1.5×10^{-6} mol.dm^{-3}.min^{-1}) to 10 equiv (3.0×10^{-6} mol.dm^{-3}.min^{-1}), in 0.2 mol.dm^{-3} acetate buffer. It also doubled when acetate buffer molarity varied from 0.2 (3.0×10^{-6} mol.dm^{-3}.min^{-1}) to 1 mol.dm^{-3} (6.0×10^{-6} mol.dm^{-3}.min^{-1}) with 10 equiv nitrite used (table II).

Table I. Influence of the nature of the organic phase on the nitration yield obtained in 1 h and on the regioselectivity.

Organic phase	*Yield (regioselectivity) after 3 h reaction*
Cyclohexane	83 ± 7% (0.02 ± 0.005)
Pentane,heptane,hexane	60 ± 5% (0.15 ± 0.03)
Diethyl ether	41 ± 4% (0.01 ± 0.005)
Dichloromethane,ethyl acetate, toluene,chloroform	30 ± 3% (0.03 ± 0.01)

- *Influence of pH on the nitration of* **2** *and* **4** *in aqueous solution*

The kinetics and regioselectivity of the nitration of chlorophenol were evaluated in 0.2 mol.dm^{-3} acetate buffer at pH 2.6–6.0. The regioselectivity was unchanged (results not shown), but the rate of formation of the nitro derivative varied and was optimal at pH 3.5 (fig 2).

- *Influence of nitrite concentration and oxygen on nitration of chlorophenol in aqueous solutions*

The yields were quantitative when the reaction was carried out with 3 equiv or more of nitrite, either in the presence of oxygen or under argon. However, the rate was significantly slower in the absence of oxygen (0.5×10^{-6} mol.dm^{-3}.min^{-1}) than in its presence (1.3×10^{-6} mol.dm^{-3}.min^{-1}). The rate was considerably reduced when phenol was treated with an equimolar concentration of nitrite (0.9×10^{-6} mol.dm^{-3}.min^{-1}), but a 73% conversion was obtained, in spite of the loss of NO gas from stirred aerated solutions (table III). The yield was only 42% under argon, even after an incubation of 72 h.

Table II. Effects of initial concentrations of nitrite or acetate on nitration rate, yield and regioselectivity.

Nitrite (equiv)	*Acetate buffer molarity ($mol.dm^{-3}$)*	*Nitration rate (10^{-6} $mol.dm^{-3}$ min^{-1})*	*Yield (regioselectivity) after 1 h reaction*
1	0.2	0.9 ± 0.1	25% (0.73 ± 0.05)
2	0.2	1.1 ± 0.1	33% (0.85 ± 0.05)
3	0.2	1.3 ± 0.3	40% (0.8 ± 0.05)
5	0.2	1.5 ± 0.3	42% (0.9 ± 0.05)
10	0.2	2.7 ± 0.5	70% (0.7 ± 0.05)
10	0.02	2 ± 0.1	56% (0.46 ± 0.05)
10	0.2	3.2 ± 0.3	95% (0.70 ± 0.05)
10	1	6 ± 0.5	100% (0.72 ± 0.05)
10	2	6.6 ± 0.5	100% (0.78 ± 0.05)

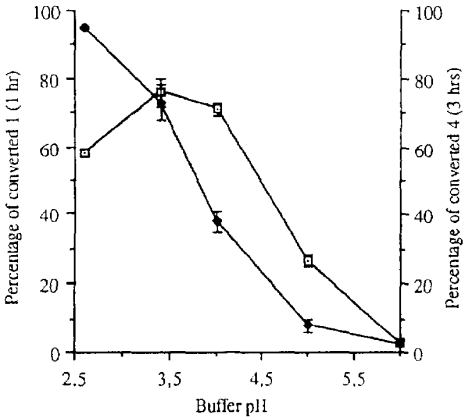


Fig 2. Effects of pH on the nitration rate of 40 $mmol.dm^{-3}$ 2-chlorophenol and 4-*t*-butylphenol by 200 $mmol.dm^{-3}$ nitrite in 0.2 $mol.dm^{-3}$ acetate buffer. □: **1**; ♦: **4**.

Table III. Effects of oxygen and initial concentration of nitrite on nitration yield and regioselectivity.

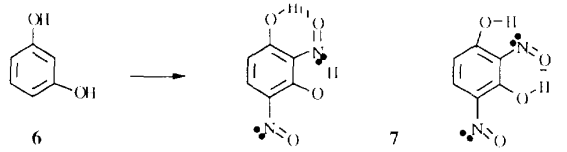
Nitrite equivalents	*Yield of the 2-chlorophenol conversion (regioselectivity) after 72 h reaction*	
	In aerated buffer	*Under argon*
1	73% (0.74 ± 0.05)	42% (0.98 ± 0.05)
3	99% (0.78 ± 0.05) (67% after 1 h)	94% (0.98 ± 0.05) (16% after 1 h)

• *Transient formation of a 4-nitrosophenol*

During the nitration of **1**, a peak ($M^{+\cdot}$ = 157) corresponding to the 2-chloro-4-nitrosophenol adjoining the peak ($M^{+\cdot}$ = 173) due to 2-chloro-4-nitrophenol **2** was detected by GC-MS. Because the nitration of **1** was quantitative (97%) without traces of nitroso compounds detected after extraction and purification, we suggest that *p*-nitration occurs in two steps, a nitrosation followed by an oxidation. In contrast, *o*-nitroso intermediates were not detected during the *o*-nitration of **1** and **4**.

Nitrosation of resorcinol

Treating resorcinol **6** with sodium nitrite in acetate buffer or in a two-phase cyclohexane/acetate buffer medium produced a brown precipitate. The insoluble material identified as 2,4-dinitroso-1,3-dihydroxybenzene **7** was previously obtained by Gay-Lussac [6]. The ^1H NMR spectra of **7** recorded in d_6-DMSO, d_6-acetone and d_3-acetonitrile differed from that in d_5-pyridine. They showed two groups of coupled *ortho* protons with coupling constants of 10 Hz, attributed to an equilibrium between two forms which differed by the position of the hydrogen bonds between the nitroso and hydroxyl groups. The ^1H NMR spectrum obtained in d_5-pyridine also showed a doublet at 6.75 ppm and a large peak at 8.35 ppm, attributed to one system of *ortho* protons.



6 **7**

The ^{13}C NMR spectrum obtained in d_6-DMSO contained six peaks corresponding to quaternary carbons and four peaks to tertiary carbons in agreement with the structure **7**.

Formation of NO gas during the nitration of phenols

A gas evolved during the nitration of 2-chlorophenol **1** and 4-*t*-butylphenol **4**. This gas reacted with dithionite-reduced oxyhemoglobin, which was converted into methemoglobin and was detected by its absorption at 406 nm. The same gas gave nitrite when trapped in undegassed water. These reactions indicate that NO gas was produced in the air space of the vessel during nitration. This did not occur during the nitrosation of resorcinol.

Conclusions

The present study shows that phenols can be efficiently nitrosated or nitrated by treatment with nitrite under mild acidic conditions. The rate of nitration of 2-chlorophenol **1** appears to be optimal at pH around 3.4 but it is only significant at pH 6 (fig 1). Replacement of nitrite by nitrate, even in the presence of a catalytic amount of nitrite, resulted in no substitution

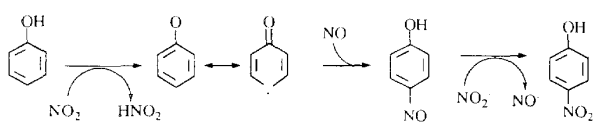
of the aromatic proton. Whereas 2-chlorobenzene and 2-chloroanisole are unreactive (results not shown), phenols are rapidly nitrosated or nitrated. This indicates that the hydroxyl group plays a role in the mechanism.

Dihydroxybenzenes are said to be more reactive with nitrate in the presence of a catalytic quantity of nitrite than phenols under the same conditions. Thompson [3] showed that catechol is nitrated at positions 3 (37%) and 4 (58%) and that the reaction led to the formation of a quinone derivative. Resorcinol is not reactive under these conditions, but in the conditions used in our study, resorcinol is rapidly transformed into the corresponding dinitroso derivative in good yield when treated with nitrite at pH 3.5. The production of this nitroso derivative suggests that nitration occurs in two steps. nitrosation followed by oxidation. This is confirmed by the transient formation of the *p*-nitroso derivative of 2-chlorophenol, which was detected by GC-MS. This intermediate is formed throughout the *p*-nitration of 2-chlorophenol, but was entirely oxidized after extraction and purification. Oxidation of this nitroso function to the corresponding nitro group should parallel the reduction of nitrous acid or NO_2 to nitric oxide, which even occurs in the absence of oxygen.

Addition of a low dielectric constant organic solvent to the nitrite/acetate buffer promotes the reaction better than one with a high dielectric constant. This observation is not consistent with the action of an electron-transfer agent, such as NO^+ or NO_2^+, which should be stabilized in media of high dielectric constant. Several authors suggest that a mixture of *p*- and *o*-nitro derivatives are produced in a two-phase procedure using a high dielectric constant solvent, in agreement with an ionic S_NAr reaction [3]. In addition to the S_NAr mechanism, a radical-based mechanism might still account for the selective, quantitative nitration of substituted phenols in dilute nitrous acid solution. The homolytic splitting of nitrous acid in dilute solution has been described [7] as an equilibrium with rates of 13.4 $mol^{-1}.dm^{-3}.s^{-1}$ for radical formation and 1.6×10^8 $mol^{-1}.dm^{-3}.s^{-1}$ for HNO_2 formation at 22 °C [12].

It has been suggested that NO_2 can provide one electron and abstract a hydrogen atom from the phenolic hydroxyl to form a phenoxy radical [8]. Such an entity might react with the NO radical generated by splitting HNO_2 to give 4-nitrosophenol. This intermediate could then react with NO_2 as previously described [9], to give the corresponding nitro derivative. In two cases and in the absence of oxygen, the stoichiometry of the reaction indicates that three molecules of HNO_2 should be consumed per molecule of phenol. In the presence of oxygen, the quantity of HNO_2 consumed should be equimolecular with the phenol consumed, if NO is entirely oxidized to regenerate HNO_2.

$$2\ HNO_2 \Longleftrightarrow NO_2^{\cdot} + NO^{\cdot} + H_2O$$



This sequence of reactions is supported by the observation that when 2-chlorophenol is treated with an equimolar concentration of nitrite, it is 73% converted to the nitro derivative, in spite of an unavoidable partial loss of NO gas during the stirring of the aerated solution, which prevents the total regeneration of the oxidant HNO_2. The yield is much lower (42%) when the reaction is carried out under argon and NO is eliminated.

Formation of 2-nitrophenols **3** and **5** could occur either by a similar mechanism or by a shorter reaction chain coupling the phenoxy and NO_2 radicals. This mechanism was described by Thompson and Zeegers [3] and Eberson [10] and should be promoted by oxygen. The importance of dissolved oxygen has been previously noted during the nitrosation of 2-naphthol and its presence explained the formation of a transient dienone intermediate [5]. The increase of the nitration rate in the presence of O_2 was due either to an influence on the rate-limiting first step, leading to the phenoxy radical (probably by NO_2 reaction), or to an increase in the monoelectronic density in the aromatic ring. It has been suggested that O_2 may oxidize NO into NO_2 or another nitrogen oxide which is more oxidizing and more nitrating than NO [11]. Both compounds should enhance the proposed reactions. Nevertheless, the observed regioselectivity in presence of oxygen was linked to the relative reactivity of *o*- and *p*-positions in agreement with the calculated monoelectronic densities of intermediate radicals [3]. However, the selective *p*-substitution observed without oxygen deserved further investigations.

Experimental section

Phenols were purchased from Sigma. Analysis were carried out by GC, using a Carlo Erba apparatus with a SGE BPI capillary column (25 m/0.5 mm) and a flame ionization detector, or by HPLC using a Waters system, a 5 μm Novapack C18 column (150/3.9 mm) and a UV detector.

The masses of 2-chloro-4-nitrophenol and 2-nitro-4-*t*-butylphenol were measured by GC-MS on a Varian 3400 GC coupled to a INCOS 50 (Finnegan Mat) mass spectrometer equipped with a capillary DB5 (30 m/0.23 mm) column.

2-Chloro-4-nitrophenol **2**

A mixture of 0.2 mL of phenol (40 $mmol.dm^{-3}$) and 140 mg sodium nitrite (400 $mmol.dm^{-3}$) in either 5 mL 0.2 $mol.dm^{-3}$ acetate buffer, or a two-phase medium (4 mL organic solvent/1 mL 2.5 $mol.dm^{-3}$ acetic acid), was stirred vigorously for 3 h at room temperature. When the reaction was carried out in the absence of oxygen, air was eliminated by flushing argon during 30 min through the acidic emulsion of phenol and nitrite solution before mixing them. The constituents of the medium were analysed by GC or GC-MS. The reaction mixture was extracted with ethyl acetate, dried and purified by chromatography on a silica-gel column eluted by a mixture of ethyl acetate/heptane. Yields were 90% of **2** and 7% of **3** in aqueous medium; and 47% of **2** and 43% of **3** in the cyclohexane two-phase system.

*2-Nitro-4-*t*-butylphenol* **5**

Identical treatment of 300 mg of 4-*t*-butylphenol (40 $mmol.dm^{-3}$) with 140 mg of sodium nitrite (400 $mmol.dm^{-3}$) in either 5 mL 0.2 $mol.dm^{-3}$ acetate buffer, or a two-phase medium (5 mL organic solvent/1 mL 2.5 $mol.dm^{-3}$

acetic acid), stirred vigorously for 3 h at room temperature led to **5** according to analysis by GC-MS. The reaction mixture was extracted with ethyl acetate, dried and purified by chromatography on a silica-gel column eluted with a mixture of ethyl acetate/cyclohexane. Yield was 89% of **5**, whatever the conditions used. Formation of **6** was identified by GC-MS after a 12 h incubation.

2,4-Dinitrosoresorcinol **7**

A similar method of treating resorcinol with 10 equiv of sodium nitrite gave **7** which precipitated at once from acetate buffer. The brown solid was filtered, washed with diethyl ether and ethyl acetate, and dried; 85% of pure product was obtained without further purification.

IE MS m/z 168, 108 (M – 2NO) fragment.

^{1}H NMR in d_6-DMSO: 6.47 (d, 1H, J = 10 Hz), 6.59 (d, 1H, J = 10 Hz), 7.89 (d, 1H, J = 10 Hz), 7.94 (d, 1H, J = 10 Hz); in d_5-pyridine: 6.75 (large peak, 1H), 8.35 (d, 1H, J = 10 Hz).

^{13}C NMR in d_6-DMSO: 183, 179.3, 178.2 and 173.8, 147.6 and 147.3, 131.5, 129.8 and 129.2 ppm; in d_5-pyridine: 129.4 and 130.6, 148.0 and 148.6 ppm.

Acknowledgments

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