New Insights into the Reactivity of Nitrogen Dioxide with Substituted Phenols: A Solvent Effect

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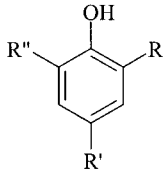
Various alkyl-substituted phenols react readily with nitrogen dioxide ($^{\cdot}NO_2$) in different solvents at room temperature. In all cases nitration is the major reaction and leads to the formation of mono- and dinitrophenols and 4-nitrocyclohexa-2,5-dienones from 2,4,6-tri-substituted phenols. Oxidation, dimerisation and, in one case, nitrosation are also observed. The reaction pathway followed changes according to the solvent and to the nature and the number of substituents on the phenolic ring.

Introduction

Nitrogen dioxide is presently receiving considerable attention because of the biochemical reactions in which this species and other nitric oxide derived oxidants are involved. The deleterious effects caused by the exposure of cells, animals and humans to this species, a common pollutant, have been studied extensively.[1] The pathophysiological consequences of low levels of endogenous nitrogen dioxide are also being considered[2] because it is particularly soluble in apolar environments, such as cell membranes and hydrophobic protein domains, where it can initiate lipid peroxidation, nitrate lipids and proteins and oxidize amino acids. Particularly interesting is the formation of nitrated proteins in several inflammatory diseases after the recombination of protein-tyrosyl radicals, which are presently used as markers of nitric oxide-derived species, with nitrogen dioxide.[3] The reactivity of nitrogen dioxide is also interesting from a mechanistic viewpoint as $^{\cdot}NO_2$ is a highly reactive paramagnetic molecule. In fact, there are a variety of potential pathways by which it can react and cause oxidation: H-atom abstraction,[4] addition to unsaturated bonds,[5] electron-transfer reactions[6] and recombination with other radicals.[7] The possibility for these different reactions to take place depends not only on the nature of the substrate, i.e. aromatic and unsaturated compounds, phenols or thiols, but, most likely, also on the reaction conditions, such as the concentration of the reagents or the particular solvent used. Evidence for such a complex behaviour can be found in the literature in the reaction between phenols and nitrogen dioxide. Although nitration is the main process observed and the reaction is commonly described to proceed by phenolic hydrogen atom abstraction by $^{\cdot}NO_2$,[4b,8] other compounds besides nitrophenols, derived from distinct oxidation processes, are often obtained.[8,9] Nitrogen dioxide is a potent one-electron oxidant ($E°$ = 0.99 V in water)[10] and electron transfer is a common pathway in $^{\cdot}NO_2$ reactivity. Factors such as the bond-dissociation enthalpies (BDE) or the redox potentials of the species involved in the reactions, together with the specific solvent in which the reaction is carried out, have to be considered in order to describe the mechanism followed. With the aim of determining the role exerted by the solvent on nitrogen dioxide reactivity, the reaction between different substituted phenols (Figure 1) and gaseous nitrogen dioxide in different solvents was studied and the results are discussed in this paper.



	R	R'	R''
1a	*t*Bu	H	*t*Bu
1b	*t*Bu	*t*Bu	H
1c	H	*t*Bu	H
1d	*t*Bu	*t*Bu	*t*Bu
1e	*t*Bu	Me	*t*Bu

Figure 1. Chemical structures of phenols **1a**–**e**.

Results and Discussion

The reactions between phenols **1a**–**e** (Figure 1) and gaseous nitrogen dioxide were carried out at room temperature by dissolving the phenol in the chosen solvent (benzene, methanol or dimethyl sulfoxide) and adding the appropriate amount of nitrogen dioxide dissolved in the same solvent in order to obtain a 1:2 ratio of phenol and $^{\cdot}NO_2$. Removal of the solvent under reduced pressure gave crude reaction mixtures which were examined by ^{1}H NMR spectroscopy to identify the products formed and determine their percen-

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tage composition in the mixtures, as reported in Table 1. The ^{1}H NMR spectral parameters were compared with the data present in the literature on these compounds or with ^{1}H NMR spectra of authentic samples. The structures of the products **2**–**15** obtained in the reactions are shown in Figure 2.

Phenols **1a**–**e** all react with $^{\cdot}NO_2$ in the three solvents where differences were observed. In fact, while phenols were almost instantaneously converted into the corresponding products when the reactions were carried out in benzene, the reactions were slower in methanol and in DMSO. In particular, reactions of phenols **1b** and **1c** were quite slow both in methanol and in DMSO while **1d** was partially recovered even after many hours in methanol. It seems that the presence of *tert*-butyl groups in both the *ortho* positions of phenols **1a**, **1d** and **1e** enhances their reactivity in meth-

Table 1. Products obtained in the studied reactions carried out at room temperature in the three different solvents used, together with the percentage composition (in brackets) of the crude mixtures.

Phenol	Products obtained in: Benzene	Methanol	Dimethyl sulfoxide
1a	**2** (80) **4**(20) 0.5 h	**2** (63) **6**(37) 1 h	**1a** (17) **2** (3) **5** (80) 2 h
1b	**7** (95) **8** (5) 0.5 h	**1b** (59) **7** (25) **9** (14) 2 h	**1b** (85) **7** (25) 2 h
1c	**10** (93) **11** (7) 0.5 h	**1c** (57) **10** (43) 2 h	**1c** (67) **10** (33) 2 h
1d	**12** (81) **13** (9) **4** (2) **8** (8) 0.5 h	**1d** (53) **12** (27) **13** (8) **4** (12) 2 h	**12** (36) **13** (52) **4** (4) **8** (8) 2 h
1e	**14** (89) **15** (11) 0.5 h	**14** (81) **15** (19) 2 h	**14** (70) **15** (30) 1 h

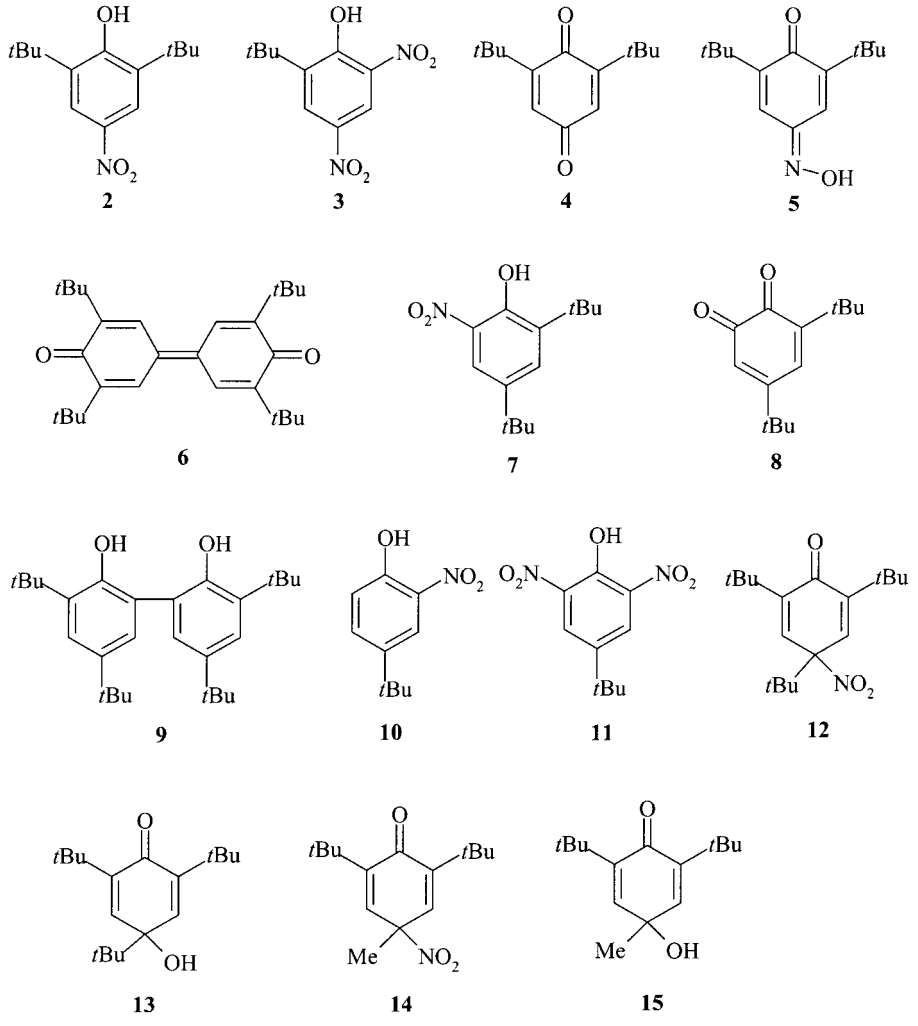


Figure 2. Chemical structures of all the products obtained.

anol and DMSO with respect to **1b** and **1c**. This could be due to steric hindrance, which reduces solvation effects, together with lower BDE values (Table 2) and lower oxidation potentials (see below).

Table 2. Bond dissociation enthalpies for the O–H bond in phenols **1a**–**e**.

Phenol	BDE_{O-H} [kJ mol^{-1}][a]
1a	346.7
1b	357.5
1c	356.9
1d	339.0
1e	339.0

[a] All BDE values are taken from ref.[23]

A possible reaction pathway, as will be discussed below, is phenolic hydrogen abstraction by nitrogen dioxide with formation of a phenoxyl radical. Since H-bond formation between phenols and the solvent plays an important role in every H-transfer process, three different solvents were used in this study, the choice being ordered by their different hydrogen-bond-accepting abilities (as given by the Abraham parameter β_H^2).[11] However, the solvents used also differ in their polarity, which may determine the particular pathway followed. Another important aspect to be considered when the results of the reactions are discussed is that nitrogen dioxide, being a radical, can also react with other radical species, including itself. In fact, it is often described to exist in equilibrium with its dimer, whose most stable structure[12] is generally thought to contain a nitrogen–nitrogen bond. However, as shown in Figure 3, other structures for the dimer are possible (the unsymmetrical nitro-nitrito structure or its ion-pair equivalent $NO^+NO_3^-$) and they may all have an influence on the reaction pathways or on the products formed, although it is not always easy to distinguish between the reactions involving the monomer and those involving the dimers in equilibrium with it.

The data reported in Table 1 indicate that nitro compounds were, in almost all cases, the main products obtained from the different phenols in the solvents tested. Mononitrophenols **2**, **7** and **10** were obtained from **1a**, **1b** and **1c**, respectively. The reaction of trialkyl-substituted phenols **1d** and **1e** with nitrogen dioxide mainly gave the nitrocyclohexadienones **12** and **14**. Besides nitration, other processes took place in these reactions: quinones **4** and **8** were obtained from **1a**, **1b** and **1d**; phenols **1a** and **1b** gave diphenoquinone **6** and *o*,*o*′-biphenol **9**, respectively, when the reactions were carried out in methanol. Finally, the main product obtained in the reaction of **1a** with nitrogen dioxide in DMSO was benzoquinone monooxime **5**. All these products may be justified by considering the classical description of the reaction of a phenol with $^{\bullet}NO_2$:[13] abstraction of the hydrogen atom from the hydroxyl group by $^{\bullet}NO_2$ to give an equilibrium mixture of nitrous acid and the corresponding phenoxyl radical, which may then couple with a second $^{\bullet}NO_2$ molecule. The possible mechanisms for the reaction of phenol **1a** are reported in Scheme 1.

The radical **16a**′, derived from an H-abstraction reaction by $^{\bullet}NO_2$ and stabilised by a resonance effect, couples with another $^{\bullet}NO_2$ molecule to give 4-nitrocyclohexa-2,5-dienone (**17**), which readily rearranges, after a keto-enol tautomerism,[14] to nitrophenol **2** (path a). Phenols **1b** and **1c** react in the same way, whereas the presence of three substituents on the aromatic ring of phenols **1d** and **1e** does not allow keto-enol tautomerism; in these cases, nitrocyclohexadienones (**12** and **14**) were the sole nitro compounds obtained.

Formation of quinone **4** (or **8**) may be justified by two different reaction pathways: i) nitro-nitrito interconversion[15,16] of the initially formed 6-nitro ketone **17**, or ii) coupling of $^{\bullet}NO_2$ (through its oxygen atom) with phenoxyl radical **16** with C–ONO bond formation (path b). This latter possibility may be due to the fact that the unpaired electron of nitrogen dioxide can be delocalized throughout the molecule, as the mesomeric structures in Figure 4 demonstrate, thus the phenoxyl radical may couple both with the nitrogen and the oxygen atom of $^{\bullet}NO_2$. Quinone **4** was obtained not only from **1a** but also from **1d**. In this latter case, the C–C bond between the *tert*-butyl group and the phenolic ring has to be broken and *t*Bu-NO has to be formed together with **4**.

In order to verify the formation of *t*Bu-NO, the reaction between phenol **1d** and nitrogen dioxide was carried out in the EPR spectrometer: 2-methyl-2-nitrosopropane (*t*Bu-NO) is unstable and may react further to give di-*tert*-butyl nitroxide $(tBu)_2NO^{\bullet}$. The signal of this radical was, in fact, observed after the disappearance of the phenoxyl radical signal.

Formation of quinones from trisubstituted phenols requires a de-*tert*-butylation process, which is favoured in **1d** because of the relatively weak bond between the *tert*-butyl group and the aromatic ring, but not in **1e**.

The same reaction pathways − nitro-nitrito interconversion or coupling of the phenoxyl radical with nitrogen dioxide through the oxygen atom − may also be active in the formation of the 4-hydroxycyclohexadienones **13** and **15** from **1d** and **1e**, respectively. Nitrito ketones are easily hydrolysed[17] to hydroxycyclohexadienones: water is present in the reaction mixture since it is produced by the dismutation of nitrous acid.[18]

Another point that could be raised from the analysis of the data in Table 1 and shown in Scheme 1 is the fact that the reaction between nitrogen dioxide and phenol **1a** or **1b**

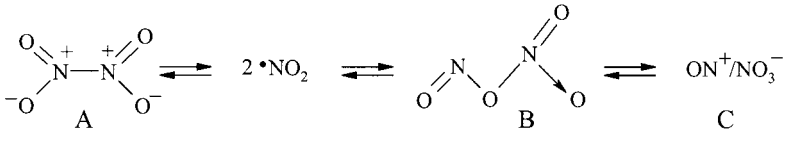
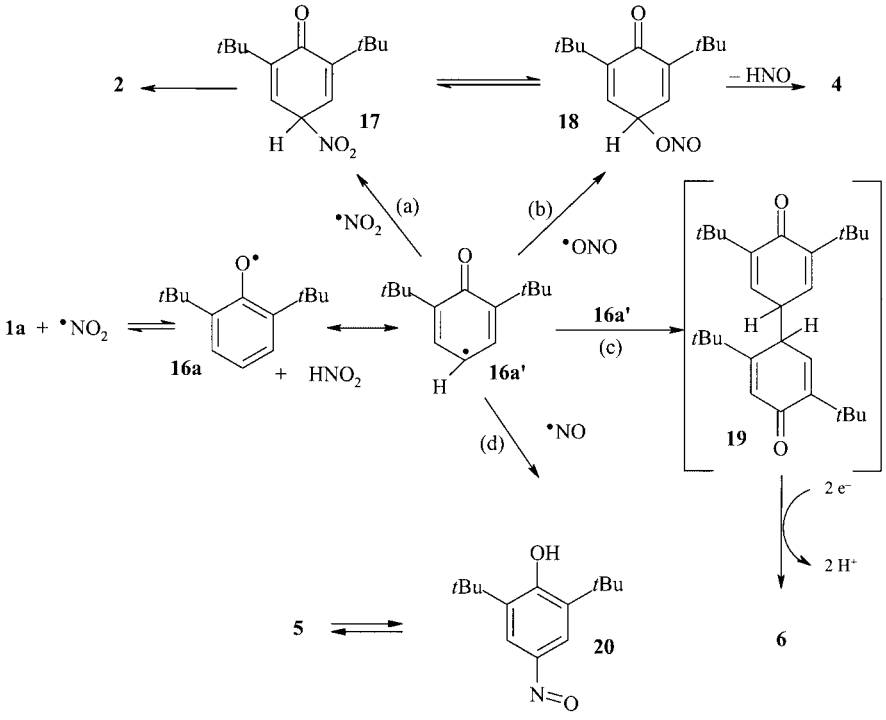


Figure 3. Possible chemical structures of N_2O_4 (the dimeric form of nitrogen dioxide).



Scheme 1.

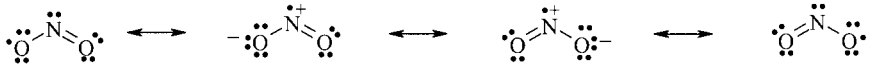


Figure 4. Mesomeric structures of nitrogen dioxide.

in methanol resulted in phenoxyl radical dimerisation together with nitration. As shown in Scheme 1 (path c), phenoxyl radical **16a′**, derived from **1a**, dimerises to give an unstable intermediate (**19**), which is easily oxidized to diphenoquinone **6**. *o*,*o′*-Biphenol **9** is formed by the coupling of two phenoxyl radicals derived from **1b**. According to the kinetic constants reported in the literature for nitration[19] and dimerisation[20] of tyrosine (another phenolic compound) in aqueous solution, nitration is the favoured path for tyrosyl radical in the presence of nitrogen dioxide, and this reaction is diffusion controlled. In our case nitration is still the favoured mechanism but dimerisation is not a negligible process, since nitrophenols **2** and **7** (from **1a** and **1b,** respectively) and the dimeric compounds **6** and **8** are obtained in almost a 2:1 ratio. This may be due to a solvation effect of nitrogen dioxide by methanol, which slows down phenoxyl radical/$^{\cdot}NO_2$ coupling and favours phenoxyl radical dimerisation. In fact, although the effect of polar solvents in radical reactions is not expected to be dominant, it is not negligible, especially in reactions of relatively polar radicals such as nitrogen dioxide (Figure 2).

Phenoxyl radical **16** is also involved in the formation of benzoquinone monooxime **5** (the tautomeric form of the corresponding nitroso phenol), which is obtained, as the main product, in the reaction between 2,6-di-*tert*-butylphenol (**1a**) and nitrogen dioxide in DMSO.

The same reactions were repeated using a further excess of nitrogen dioxide: the most relevant result obtained is represented by the fact that dinitrophenols **3** and **11** were formed not only from phenol **1c**, which has both the *ortho* positions available, but also from the dialkyl-substituted phenols **1a** and **1b** after a nitro-de-*tert*-butylation[21] of the mononitrophenol initially formed. Interestingly, the formation of dinitrophenols occurred only when benzene was used as the solvent for the reaction and not in the other two cases. This fact deserves some comments, as does the mechanism of formation of the phenoxyl radical, which is the key intermediate in the reaction studied. Nitrogen dioxide is a fairly good H-atom abstractor, with a BDE value for the H–O bond in nitrous acid of about 327 kJ mol^{-1}.[22] However, if this value is compared to the BDE values of the phenolic hydrogen atom in compounds **1a**–**e** (Table 2), it appears less certain that direct hydrogen abstraction by $^{\cdot}NO_2$ occurs.

Furthermore, phenols may form H-bonds with the solvent, as indicated by their a^2_H values[24] of around 0.55 for **1a**–**c**[24] and 0.18–0.25 for **1e**,[25] and the solvent effects observed in previous kinetic studies of reactions between various radicals and phenols[26] confirm that the large kinetic solvent effect observed for H-abstractions from phenols is mainly, if not solely, a consequence of hydrogen bonding to the solvent when the latter is a hydrogen-bond acceptor.

Even steric protection of the OH group in 2,6-di-*tert*-butylphenols does not prevent the formation of a hydrogen bond with suitable acceptors,[27] although **1e** is often described[28] as a molecule that does not form hydrogen bonds even with strong hydrogen-bond acceptors. Phenols **1a–e** have high BDE values when compared to the H-O BDE in nitrous acid and also a fairly good tendency to form hydrogen bonds with the solvent, as indicated by their α_H^2 values. Among the three solvents used in the present work, methanol and DMSO are good hydrogen-bond acceptors (β_H^2 = 0.41 and 0.78, respectively)[11] and, most likely, they can form H-bonds with phenols, thus avoiding H-abstraction by $^{\cdot}NO_2$. On the other hand, the β_H^2 value for benzene is only 0.14,[11] which means that hydrogen bonding between benzene and compounds **1a–e** is not relevant and that, in effect, nitrogen dioxide may abstract the phenolic hydrogen atom. The formation of dinitrophenols **3** and **11** was observed in benzene and not in the other two solvents. This may be due to the fact that hydrogen abstraction by $^{\cdot}NO_2$ to form phenoxyl radicals is even more difficult, especially in hydrogen-bond-acceptor solvents such as methanol or DMSO, since nitrophenols have both higher BDEs and α_H^2 values than the corresponding phenols (BDE_{O-H} = 358 kJ mol^{-1} for compound **2**[23] and α_H^2 = 0.82 for 4-nitrophenol and 0.59 for phenol).[24]

If phenoxyl radicals are not derived from direct hydrogen abstraction by $^{\cdot}NO_2$, other routes leading to their formation have to be considered. As stated above, nitrogen dioxide is a good one-electron oxidant and it could be able to oxidize phenols to the corresponding radical cations[9] [Equation (1)], which deprotonate to form phenoxyl radicals.

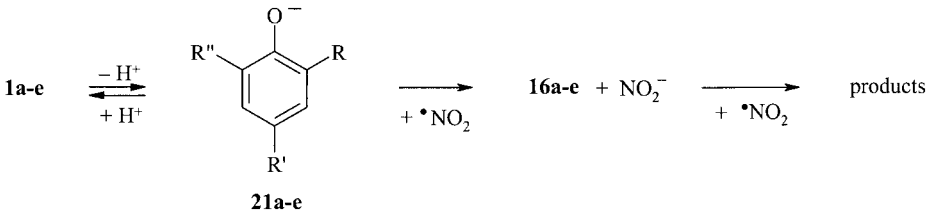
$$ArOH + NO_2 \rightarrow ArOH^+ + NO_2^- \quad (1)$$

An electron-transfer process is unlikely to occur since the oxidation potentials of phenols are very high in organic solvents. For example, **1a** and **1c** have oxidation potentials measured in acetonitrile against an Ag/AgI electrode referenced to ferrocenium couple ($E_{1/2}$ = 0.875 V) of 2.12 and 2.00 V,[29] respectively; for **1d**, under the same conditions, E_{ox} = 1.85 V.[29] However, phenols are acidic compounds (pK_a = 11.7, 10.3, 12.19, and 12.23 for **1a**, **1c**, **1d**, and **1e**, respectively).[30] In polar solvents such as methanol or DMSO, these phenols may be partly dissociated and may exist in equilibrium with the corresponding phenoxide anions, which have much smaller oxidation potentials (E_{ox} = 0.256, 0.44, and 0.23 V for **1a**, **1c**, and **1d**, respectively, measured in DMSO relative to Ag/AgI taken with the ferrocenium couple as an internal standard).[29] Thus, nitrogen dioxide may easily oxidize the phenoxide anion to the corresponding radical, which can then react with other $^{\cdot}NO_2$ molecules to form the observed products (Scheme 2).

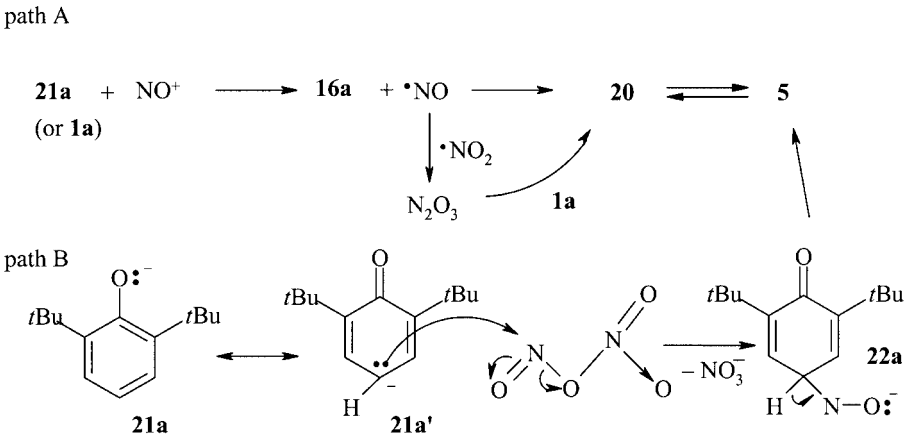
It has been shown recently that phenols react with electron-deficient radicals $^{\cdot}Y$ by electron transfer, rather than hydrogen-atom transfer, in alcoholic solvents.[31] In these cases, the rate constants for ArOH/$^{\cdot}Y$ were much greater than those expected on the basis of the hydrogen bond donor ability of ArOH and of the hydrogen bond acceptor ability of the solvent. These anomalies are due to ionization (even partial) of the phenol and to a very fast electron transfer from the phenoxide anion to the radical. Addition of small amounts of acid suppressed ionization and the rate constants (for hydrogen-atom transfer only) were dramatically reduced.[31a,31c] We used this simple test to verify that, also in our case, the reacting species in solvents which support ionization, such as methanol or DMSO, is effectively represented by phenoxide anion. When 50 mM acetic acid was added to the reaction mixture (20 mM **1a** + 20 mM nitrogen dioxide in methanol) the reaction was slower than in the absence of acid: after 90 minutes 70% of the initial amount of **1a** was still present in the acidified methanol, whereas in pure methanol only 50% of **1a** was present. Addition of a higher amount of acetic acid suppressed the reaction almost completely: 90% of the phenol was present after the same time when 100 mM acetic acid was added. It may thus be concluded that, in polar solvents, phenoxyl radicals are formed by the oxidation of phenoxide anions, while in a solvent which does not support ionization, such as benzene, they are formed by direct hydrogen abstraction by nitrogen dioxide.

The same experiment (addition of acetic acid to the solvent) was repeated in DMSO: a small enhancement of the reaction rate was observed. In fact, after one hour 40% and 60% of **1a** was still present in acidified and pure DMSO, respectively. Nevertheless, we are still convinced that the phenoxide anion is the active species also in this case and that electron transfer is the actual reaction pathway. The fact that addition of the acid to the solvent does not slow down the reaction may be explained by the high basicity of DMSO.

As shown in Table 1, the main product obtained in the reaction between phenol **1a** and nitrogen dioxide was the isonitroso derivative **5**, when DMSO was used as the solvent. Nitrosation, as well as nitration, is a common reaction for nitrogen dioxide.[32] However, nitrosation is most likely due not to $^{\cdot}NO_2$ but to its dimeric form, dinitrogen tetraoxide N_2O_4 (Figure 1). Different reaction paths are possible



Scheme 2.



Scheme 3.

for nitrosation, depending on the particular N_2O_4 form involved, as shown in Scheme 3 for the formation of compound **5**. Nitrosonium ion, NO^+, formed by disproportionation[33] of nitrito dimer **B** (Figure 3), is a good single-electron oxidant, as indicated by its reduction potential ($E°$ = 1.19 V vs. SCE).[34] In path A, an electron transfer between phenoxide anion **21a** (or from the corresponding phenol **1a**) and nitrosonium ion NO^+ gives the phenoxyl radical **16a** and nitrogen monoxide. Coupling of these two radicals leads to nitrosophenol.[35] Alternatively, $^{\cdot}NO$ may react with nitrogen dioxide to form N_2O_3, a well-known nitrosating agent. However, the nitro-nitrito dimer **B** (Figure 1) may also be responsible for the observed nitrosation: the phenoxide anion, in its resonant form, may nucleophilically attack the electrophilic nitrogen atom in the dimer with formation of nitrosocyclohexadienone, which rearranges to benzoquinone monooxime **5**. An isonitroso derivative was obtained only in this reaction (**1a** + $^{\cdot}NO_2$ in DMSO): no traces of compound **5** were observed in the reaction carried out in methanol. The different behaviour of **1a** in the two solvents could be due to the greater nucleophilicity of the phenoxide anion in a polar aprotic solvent (DMSO) than in a protic solvent such as methanol,[36] although it cannot be excluded that the gaseous nitrogen dioxide used in these reactions could be contaminated by other nitrogen oxides ($^{\cdot}NO$, N_2O_3) that are capable of acting as nitrosating agents. Phenols **1b** or **1c** were repeatedly reacted with nitrogen dioxide in dimethyl sulfoxide but nitrophenols were the sole products obtained, with no evidence for nitrosophenol formation. A possible explanation for this particular behaviour of phenol **1a** could be the presence of steric and resonance effects, which most likely favour the nucleophilicity of the anion **21a/21a′** with respect to the phenoxide ions from **1b** or **1c**.

Conclusions

The reaction of nitrogen dioxide with phenols has been known for many years to yield nitrophenols. In fact, all the reactions reported in the present study give nitrophenols as the main products. But, as pointed out in this work, different reaction routes leading to nitrophenols are possible depending on the experimental conditions and, in particular, on the solvent used (the main factor considered in the present work): H-atom abstraction in solvents such as benzene, which have a low hydrogen-bond-accepting ability, and electron transfer in hydrogen-bond-accepting and polar solvents such as methanol and dimethyl sulfoxide. Other products besides nitrophenols are obtained in the reactions described in this paper; their formation depends on the reaction solvent. Furthermore, the particular form in which nitrogen dioxide reacts may be a consequence of the reaction environment, with the monomer being favoured in apolar solvents and the dimer in polar solvents, although it is not easy to distinguish between the two reactions. The nature of the substituents on the aromatic ring is another factor that has a role in the outcome of the reactions: nitrodealkylation or quinone formation (in the case of 2,4,6-trialkylphenols) occurs only when the alkyl group is a *tert*-butyl.

From the results reported here, it is evident how complex the reactivity of nitrogen dioxide is and that many factors (BDE, oxidation potentials, nature of the substrate or solvent) have to be considered simultaneously when the behaviour of this biologically important molecule is described.

Experimental Section

General Remarks: ^1H NMR spectra were recorded at room temperature in $CDCl_3$ solution on a Varian Gemini 200 spectrometer (TMS was taken as reference peak). EPR spectra were run on a Varian E4 instrument. Melting points are uncorrected and were measured with an Electrothermal apparatus. IR spectra were recorded in the solid state on a Nicolet Fourier Transform Infrared 20-SX Spectrophotometer equipped with a Spectra Tech.

Gaseous nitrogen dioxide (98.5% purity) was purchased from Fluka. It was used without purification in the volumetric preparation of the solutions: a 20 mL volumetric flask was filled with the indicated volume of the chosen solvent and was weighed. Nitrogen dioxide was bubbled through for a few seconds and the flask was weighed again: the difference between the two weights gave the amount, and hence the number of mols, of $^{\cdot}NO_2$ dissolved in

20 mL. $^{\cdot}NO_2$ solutions generally contained from 5×10^{-4} to 2×10^{-3} mols in 20 mL.

Benzene, methanol, and dimethyl sulfoxide were purchased from Carlo–Erba or Aldrich RP-ACS and were distilled prior to use. Phenols **1a**–**e** were all Aldrich products and were used as received.

Reaction of Phenols 1a–e with Nitrogen Dioxide. General Procedure: Phenol (0.1 mmol) was dissolved in 5 mL of the chosen solvent and treated, at room temperature, with 0.2 mmol of $^{\cdot}NO_2$ dissolved in the same solvent. TLC, with toluene as the eluent, was used to check the course of the reactions. Removal of the solvent under reduced pressure gave crude reaction mixtures, which were dissolved in $CDCl_3$ and examined by ^1H NMR spectroscopy to determine their composition (Table 1). When DMSO was used as the solvent, the reaction mixtures were repeatedly washed with water, extracted with ethyl acetate, and the organic layer was evaporated. The products formed were identified by comparing their ^1H NMR spectral parameters with the data present in the literature for the same compounds. In some cases authentic samples were prepared following methods reported in the literature.

All the reactions were repeated using a further excess of nitrogen dioxide by bubbling the gas directly through solutions of the phenols. These results are not reported since no great differences were found.

Reaction of Phenols 1a–e with Nitrogen Dioxide in Benzene: All the reactions were very fast. As soon as nitrogen dioxide was added, the colourless solutions of phenols turned yellowish and TLC indicated that the starting phenols had been partially consumed. After 30 min the reactions were complete and the solvent was evaporated. ^1H NMR spectroscopy allowed the identification of the products formed: 2,6-di-*tert*-butyl-4-nitrophenol (**2**)[21] and 2,6-di-*tert*-butyl-1,4-benzoquinone (**4**)[37] from **1a**, 2,4-di-*tert*-butyl-6-nitrophenol (**7**)[21] and 3,5-di-*tert*-butyl-1,2-benzoquinone (**8**)[38] from **1b**, 4-*tert*-butyl-2-nitrophenol (**10**)[39] and 4-*tert*-butyl-2,6-dinitrophenol (**11**)[40] from **1c**, 2,4,6-tri-*tert*-butyl-4-nitrocyclohexadienone (**12**),[41] 2,4,6-tri-*tert*-butyl-4-hydroxycyclohexadienone (**13**),[42] **4**, and **8** from **1c**, and 2,6-di-*tert*-butyl-4-methyl-4-nitrocyclohexadienone (**14**)[43] and 2,6-di-*tert*-butyl-4-hydroxy-4-methylcyclohexadienone (**15**)[44] from **1e**.

For comparison, nitrophenol **2** was prepared following the procedure described in ref.[45]: m.p. 154–156 °C (petroleum ether). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.48 (s, 18 H, 2 × *t*Bu), 5.94 (s, 1 H, OH), 8.12 (s, 2 H, arom) ppm. IR (KBr): $\tilde{\nu}$ = 3548 cm^{-1} (OH), 1507 (NO_2). MS (EI^+): *m*/*z* = 251 (18) [M^+], 236 (100), 208 (42).

Reaction of Phenols 1a–e with Nitrogen Dioxide in Methanol: The reactions of phenols **1a** and **1e** were complete in 1 and 2 h, respectively. In the other cases, the starting phenols were still present when the solvent was evaporated after 2 h. Starting from **1a**, a brown solid precipitated from methanol during the reaction, which was identified as 3,5,3′,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (**6**) by comparison with an authentic sample prepared according to the literature.[46] M.p. 255–256 °C (acetone). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.38 (s, 36 H, 4 × *t*Bu), 7.71 (s, 4 H, arom) ppm. IR (KBr): $\tilde{\nu}$ = 1655 cm^{-1} (C=O). MS (EI^+): *m*/*z* = 408 (51) [M^+], 366 (21), 351 (46).

^1H NMR spectroscopy of the crude reaction mixtures after evaporation of the solvent allowed the identification of the products formed: **2** and **6** from **1a**, **7** and 3,5,3′,5′-tetra-*tert*-butylbiphenyl-2,2′-diol (**9**)[47] from **1b**, **10** from **1c**, **12** and **13** from **1d**, and **14** and **15** from **1e**.

Reaction of Phenols 1a–e with Nitrogen Dioxide in Dimethyl Sulfoxide: After 2 h only phenols **1d** and **1e** were completely consumed. ^1H NMR spectroscopy of the crude reaction mixtures obtained after repeated washing with water and extraction with ethyl acetate allowed the identification of the products formed: **2** and 2,6-di-*tert*-butyl-1,4-benzoquinone monooxime (**5**)[48] from **1a**, **7** from **1b**, **10** from **1c**, **12** and **13** from **1d**, and **14** and **15** from **1e**.

An authentic sample of **5** was prepared as follows: 25 mmol of **1a** in 20 mL of acetic acid was stirred at –10 °C, then 25 mmol of sodium nitrite in 20 mL of water was added dropwise and the mixture was stirred at room temperature for 1 h. A precipitate was obtained, which was filtered, washed with water, and dried. It was found to be a mixture of different products, but after washing with petroleum ether only compound **5** remained undissolved. M.p. 210–212 °C (petroleum ether). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.30 (s, 18 H, 2 × *t*Bu), 6.92 (d, *J* = 2.3 Hz, 1 H, arom), 7.52 (d, *J* = 2.3 Hz, 1 H, arom) ppm. IR (KBr): $\tilde{\nu}$ = 3322 cm^{-1} (OH), 1610 (C=O), 1557 (C=N). MS (EI^+): *m*/*z* = 235 (100) [M^+], 220 (46), 180 (97), 162 (65).

Reaction of Phenol 1a with Nitrogen Dioxide in Methanol with and without Acetic Acid: Phenol **1a** (0.1 mmol) was dissolved in 5 mL of methanol to which 29 μL (or 58 μL) of acetic acid had been added, and treated with 0.1 mmol of nitrogen dioxide dissolved in methanol. A similar reaction mixture, but lacking acetic acid, was simultaneously prepared. After 90 min both solutions were evaporated and the residues were analysed by ^1H NMR spectroscopy.

1a + $^{\cdot}NO_2$ + CH_3COOH (50 mM): **1a** (75%), **2** (10%), and **6** (15%).

1a + $^{\cdot}NO_2$ + CH_3COOH (100 mM): **1a** (90%), **2** (6%), and **6** (4%).

1a + $^{\cdot}NO_2$: **1a** (45%), **2** (35%), and **6** (20%).

Reaction of Phenol 1a with Nitrogen Dioxide in Dimethyl Sulfoxide with and without Acetic Acid: Phenol **1a** (0.1 mmol) was dissolved in 5 mL of DMSO to which 50 μL of acetic acid had been added, and was treated with 0.2 mmol of nitrogen dioxide dissolved in DMSO. A similar reaction mixture, but lacking acetic acid, was simultaneously prepared. After 1 h both solutions were washed with water, extracted with ethyl acetate, and the organic layers were evaporated. Analysis of the residue by ^1H NMR spectroscopy gave:

1a + $^{\cdot}NO_2$ + CH_3COOH (50 mM): **1a** (40%), **2** (6%), and **5** (54%).

1a + $^{\cdot}NO_2$: **1a** (60%), **2** (2%), and **5** (38%).

Reaction of 2,4,6-Tri-*tert*-butylphenol (1d) with Nitrogen Dioxide in the EPR Spectrometer: Dilute solutions of **1d** and $^{\cdot}NO_2$ in benzene were mixed in an EPR tube (the solutions used in the reactions described above were diluted about 100 times in order to have a suitable concentration for EPR measurements). After several minutes the typical three-line spectrum of di-*tert*-butyl nitroxide[49] was observed.

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