Nitrosation of Anisole and Related Compounds. Direct Synthesis of 4-Nitrosoanisole*

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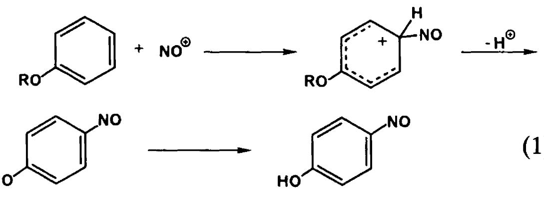
Radner, F., Wall, A. and Loncar, M., 1990. Nitrosation of Anisole and Related Compounds. Direct Synthesis of 4-Nitrosoanisole. – Acta Chem. Scand. 44: 152–157.

The direct introduction of a nitroso group into alkoxy-substituted benzenes without accompanying dealkylation of the alkoxy group is described. 4-Nitrosoanisole is obtained in 56 % isolated yield upon treatment of anisole with $NaNO_2$ in CH_2Cl_2/CF_3COOH. Both 2- and 3-methylanisole were also successfully nitrosated by this method. With anisole, GLC yields of up to 75 % were observed together with ca. 20 % of a mixture of 2- and 4-nitroanisole, formed via nitrous acid catalyzed (NAC) nitration. The kinetic isotope effects observed (3.1 ± 0.2 for nitrosation and 1.0 ± 0.1 for NAC nitration) show that the two reactions occur simultaneously and that nitrosation is not involved in the formation of the nitroanisoles. The possible involvement of electron transfer mechanisms in these reactions is discussed.

Direct introduction of a nitroso group by electrophilic aromatic substitution is normally restricted to aromatic compounds carrying a strongly electron-donating group, i.e. ArOH or $ArNR_2$.[1–3,†] Aromatic ethers, ArOR, are also susceptible to attack by NO^+, but the final product is generally the correspnding phenol, formed by dealkylation of the nitroso compound, which is generally unstable under the acidic reaction conditions employed [eqn. (1)].[2,3,5–7]


(1)

The direct preparation of RO–Ar–NO is also complicated by the often facile oxidation of ArNO into $ArNO_2$ by N_2O_4 or HNO_3.[2,3,§] This oxidation step was earlier considered as a key step in the mechanism for nitrous acid catalyzed (NAC) nitration[2,11] [eqn. (2)], a reaction that is nowadays suspected to be mediated by radical pairs [eqn. (3)].[9–14] Apart from a report on the action of nitrosylsulfuric acid on 2- and 3-methylanisole giving the 4-nitroso compounds,[15a] and on the apparently transient[15b] formation of 1,3-diethoxy-4-nitrosobenzene and 3-ethoxy-4-nitrosophenol in the nitrosation of 1,3-diethoxybenzene,[16] no successful direct nitrosation of ArOR has, to our knowledge, been presented.

$$ArH + NO^+ \xrightarrow{-H^+} ArNO \xrightarrow{ox} ArNO_2 \qquad (2)$$

$$ArH + NO^+ \longrightarrow [ArH^{+\cdot}NO] \to \to ArNO_2 \qquad (3)$$

We recently reported on the formation of biaryls in the NO^+-catalyzed reaction between some substituted naphthalenes and O_2 in CF_3COOH/CH_2Cl_2 [eqn. (4)].[17] Thus, when 1-methoxynaphthalene was exposed to N_2O_4‡/O_2, 4,4′-dimethoxy-1,1′-binaphthyl was formed in good yield. We now report that when anisole, a less readily oxidizable compound, is subjected to similar reaction conditions, no biaryl coupling occurs. Instead, 4-nitrosoanisole, together with 2- and 4-nitroanisole, is formed and the yield of the nitroso compound can be raised to a preparatively useful level by using $NaNO_2$ instead of N_2O_4.

$$2\,ArH + \tfrac{1}{2}\,O_2 \xrightarrow[CF_3COOH]{NO^+} Ar\text{-}Ar + H_2O \qquad (4)$$

Results

When anisole was treated with N_2O_4 in CH_2Cl_2/CF_3COOH without the exclusion of moisture, air, etc., roughly equimolar amounts of 4-nitrosoanisole and 2- and 4-nitroanisole were formed, i.e. the ratio of the rates of formation of the products, k_{NO}/k_{NO_2}, was ca. 1. The initial goal of the present investigation was to obtain a system capable of

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[*] Aromatic Nitration via Electron Transfer. VIII. For Part VII, see Ref. 17.

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[†] Direct *C*-nitrosation of azulene and certain *N*-heterocyclic compounds has been reported.[2–4]

[§] This step has repeatedly been demonstrated not to be a high-yield process, since, in addition to $ArNO_2$, products of intermediate diazonium salts and of further nitration, etc., have been observed.[8–10]

[‡] In this paper N_2O_4 refers to what is actually an equilibrium mixture of NO_2 and N_2O_4.

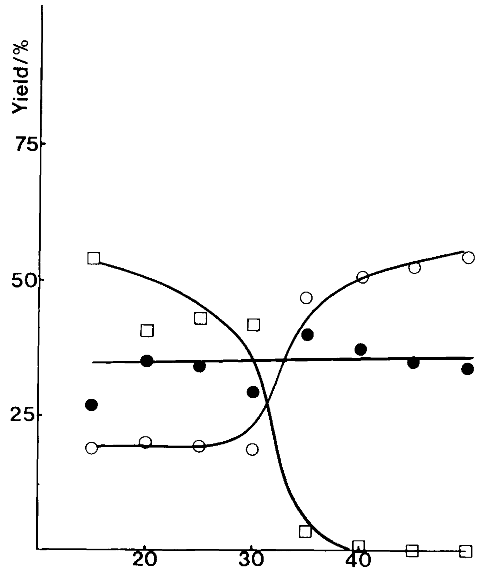

Fig. 1. Plot of formation of 4-nitrosoanisole (●) and 2- and 4-nitroanisole (○) vs. [CF_3COOH] in CH_2Cl_2 in the reaction of anisole (□) and N_2O_4 at 0 °C under Ar for 20 min. [Anisole] = [N_2O_4] = 0.050 M.

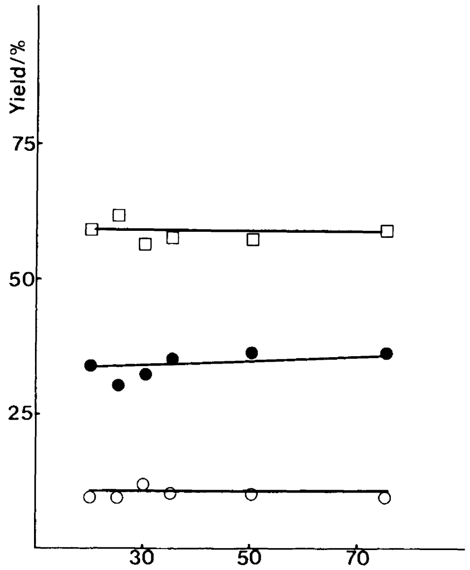

Fig. 2. Plot of formation of 4-nitrosoanisole (●) and 2- and 4-nitroanisole (○) vs. [CF_3COOH] in CH_2Cl_2 in the reaction of anisole (□) and $NaNO_2$ at 0 °C under Ar for 20 min. [Anisole] = [NO_2^-] = 0.050 M.

producing a high value of k_{NO}/k_{NO_2} as well as high conversion of anisole into products.

Initially we examined the reaction between N_2O_4 and anisole (molar ratio 1:1) at 0 °C under Ar in CH_2Cl_2 containing 15–50 vol % of CF_3COOH. The results are summarized in Fig. 1. Obviously, neither k_{NO}/k_{NO_2} nor the conversion of anisole can be raised to an acceptable level in this system, and on increasing the acid strength of the system, nitration becomes predominant. Increasing the amount N_2O_4 also favours nitration; using a threefold excess in 25 % CF_3COOH, a very high conversion but a value of k_{NO}/k_{NO_2} as low as 0.11 was observed.

When N_2O_4 was replaced by $NaNO_2$ the sensitivity of the outcome of the reaction to the acid strength of the system almost disappeared. Fig. 2 shows the reaction between equimolar amounts of anisole and $NaNO_2$ at 0 °C under Ar in 20–75 % of CF_3COOH in CH_2Cl_2. Here an acceptable preference for nitrosation was obtained (k_{NO}/k_{NO_2} = ca. 3.5), but the conversion was consistently slightly lower than 50 % which indicates the existence of a stoichiometric dependence on more than 1 equiv. of $NaNO_2$ per equiv. of anisole. Therefore, the influence of the ratio of $NaNO_2$ to anisole was examined in 25 % CF_3COOH in CH_2Cl_2. As evident from Fig. 3 we now had at hand a system fulfilling our initial goal, since at a molar ratio of $NaNO_2$ to anisole of 2.2, a value of k_{NO}/k_{NO_2} of 3.5 was obtained at high conversion. On a 10 mmol scale 4-nitrosoanisole could be prepared in 56 % isolated yield.

Minor modifications of this procedure, such as the addition of $(CF_3CO)_2O$ and lowering of the temperature to −10 °C had a slightly beneficial effect on k_{NO}/k_{NO_2}, whereas the presence of $CF_3COO^-Na^+$ and a decrease in the amount of CF_3COOH to 10 % resulted in lower conversions.

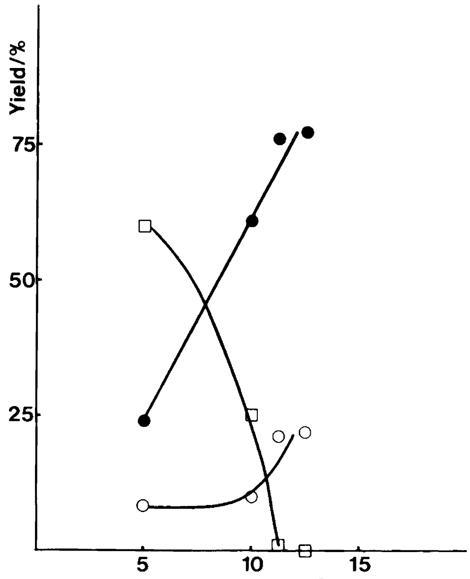

Fig. 3. Plot of formation of 4-nitrosoanisole (●) and 2- and 4-nitroanisole (○) vs. [NO_2^-] in the reaction of anisole (□) and $NaNO_2$ in 25 vol % of CF_3COOH in CH_2Cl_2 at 0 °C under Ar for 20 min. [Anisole] = 0.050 M.

The ratio of 2-nitroanisole to 4-nitroanisole in the reactions of Figs. 1–3 was invariably 0.7 ± 0.1, indicating that these compounds are not formed either by NO_2^+-nitration or via nitrosation followed by oxidation. We therefore determined the 2/4 ratio under a variety of conditions and the results are summarized in Table 1, together with a few values of the 2/4 ratio for nitration of anisole and phenol

Table 1. Nitration of anisole and phenol under different conditions.[a]

Conditions for nitration	2/4-Ratio	Ref.	Mechanism operating
$NaNO_3$, NaN_3, H_2SO_4 (20 %) in CH_3COOH[b]	2.5	This work	EAN[q]
HNO_3, NaN_3 in $(CH_3CO)_2O$[c]	2.5	This work	EAN
NO_2BF_4, NaN_3, CH_3COOH (50 %) in $C_4H_8SO_2$[d]	2.6	This work	EAN
HNO_3, urea in $C_4H_8SO_2$[e]	2.2	11, 23	EAN
$NaNO_2$, CF_3COOH (25 %) in CH_2Cl_2, 0 °C[f]	0.6	This work	NAC[r]
$NaNO_3$, H_2SO_4 (20 %) in CH_3COOH[g]	0.6	This work	NAC
N_2O_4 in CH_2Cl_2[h]	0.8	This work	NAC
N_2O_4 in CH_3NO_2[i]	0.6	24	NAC
$NaNO_3$, $NaNO_2$, H_2SO_4 (62 %) in H_2O[j]	0.06	6	NOX[s]
HNO_3, $NaNO_2$, H_2SO_4 (66 %) in H_2O[k]	0.06	11, 23	NOX
HNO_3, $NaNO_2$, H_2SO_4 (45 %) in H_2O[l]	0.6	This work	NAC
HNO_3, $NaNO_2$, H_2SO_4 (55 %) in H_2O[l]	0.2	This work	NAC + NOX
HNO_3, $NaNO_2$, H_2SO_4 (65 %) in H_2O[l]	0.09[m]	This work	NOX
HNO_3, sulfamic acid, H_2SO_4 (56 %) in H_2O[n]	2.4	25	EAN
$NaNO_3$, H_2SO_4 (56 %) in H_2O[o]	0.8	10	NAC
$NaNO_3$, $NaNO_2$, H_2SO_4 (56 %) in H_2O[p]	0.03	10	NOX

[a] Reactions performed at 25 °C unless otherwise noted. Anisole: first 13 entries; phenol: last three entries. [b] [ArH] = 0.10 M, $[NO_3^-]$ = 0.080 M, $[N_3^-]$ = 0.050 M. [c] [ArH] = 0.20 M, $[HNO_3]$ = 0.10 M, $[N_3^-]$ = 0.020 M. [d] [ArH] = 0.33 M, $[NO_2BF_4]$ = 0.25 M, $[N_3^-]$ = 0.005 M. [e] [ArH] < 0.1 M, $[HNO_3]$ = 6.5 M, [urea] = 0.040 M. [f] [ArH] = 0.050 M, $[NO_2^-]$ = 0.11 M (i.e. conditions for nitrosation; see the Experimental and Fig. 3). [g] [ArH] = 0.10 M, $[NO_3^-]$ = 0.080 M. [h] [ArH] = $[N_2O_4]$ = 0.10 M. [i] [ArH] = 0.46 M, $[N_2O_4]$ = 0.50 M. [j] [ArH] = 0.0038 M, $[NO_3^-]$ = 0.42 M, $[NO_2^-]$ = 0.043 M. [k] [ArH] < 0.1 M, $[HNO_3]$ = 0.030 M, $[NO_2^-]$ = 0.040 M. [l] [ArH] = 0.030 M, $[HNO_3]$ = 0.030 M, $[NO_2^-]$ = 0.040 M. [m] 4-Nitrophenol (10 % of the amount of nitroanisoles formed) was also formed. [n] [ArH] = 0.00010 M, $[HNO_3]$ = 0.00020 M, [sulfamic acid] = 0.020 M. [o] [ArH] = $[NO_3^-]$ = 0.0061 M. [p] As in *o* with $[NO_2^-]$ = 0.061 M. [q] Electrophilic aromatic nitration. [r] Nitrous acid catalyzed nitration. [s] Nitrosation followed by oxidation.

(last three entries) taken from the literature. The literature values[18] have deliberately been selected to emphasize three distinctive groups of 2/4 ratios (i.e. those resulting from NO_2^+-, NAC- and (NO^+ + oxidant) nitration, respectively), but often less clear-cut values than these are obtained,[6] e.g. as in entry 12 of Table 1. That the formation of the nitro compounds occurs independently of the formation of 4-nitrosoanisole was further established by a set of experiments on the kinetic isotope effects of the reaction. When equimolar amounts of anisole and $C_6D_5OCH_3$ were allowed to compete for $NaNO_2$ under the reaction conditions presented above, an isotope effect of 3.1 ± 0.1 was observed for the formation of 4-nitrosoanisole, in accordance with earlier observations.[5,6] However, the nitroanisoles were formed (in the same batch) without any isotope effect, i.e. k_H/k_D was invariably 1.0 ± 0.1 for the formation of 2-nitroanisole as well as of 4-nitroanisole. Also note that 0.1–3 % of a by-product, 1,4-benzoquinone, was invariably formed in all of the experiments presented so far. We conclude that the nitrosation of anisole is preferentially carried out with 2.2 equiv. of $NaNO_2$ in 25 % of CF_3COOH in CH_2Cl_2 at 0 °C, under Ar, for 20 min, a system that will be referred to as 'standard conditions' below. However, before turning to the nitrosation of some other substrates, a few comments on the reaction of $NO^+BF_4^-$ with anisole may be appropriate.

When equimolar amounts of $NO^+BF_4^-$ and anisole were allowed to react under otherwise standard conditions, a very dark solution was formed but no conversion of anisole could be detected. Running the reaction in 100 % CH_2Cl_2 or in CH_2Cl_2 with added 2,6-di-*t*-butylpyridine or in CH_3NO_2 did not cause any conversion. However, when 2.5 equiv. of $NO^+BF_4^-$ were treated with anisole at 0 °C under Ar in $CH_3NO_2/CH_3O(CH_2)_2OCH_3$ for 20 min, 6 % 4-nitrosoanisole was formed. Unfortunately, prolonged reaction times caused degradation of the product since, interestingly, *no traces* of either 2-nitroanisole, 4-nitroanisole or 1,4-benzoquinone were formed according to GLC.

When 3-methylanisole was exposed to the standard conditions, 3-methyl-4-nitrosoanisole was formed in 60 % yield, together with 29 % of a mixture of the four 3-methyl-*x*-nitroanisoles and 10 % 2-methyl-1,4-benzoquinone. From 2-methylanisole 40 % of the 4-nitroso compound, together with 49 % of a 69:31 mixture of 2-methyl-4-nitro- and 2-methyl-6-nitroanisole and 7 % 2-methyl-1,4-benzoquinone were formed.

Finally we note that 2,6-dimethylanisole could not be converted into the 4-nitroso compound, either by the standard procedure or by variations such as decreasing the amount of CF_3COOH. The standard procedure led to the formation of 60 % 2,6-dimethyl-4-nitroanisole and 9 % 2,6-dimethyl-1,4-benzoquinone.

Discussion

The substantial kinetic deuterium isotope effect observed for the formation of 4-nitrosophenol from anisole in aq. $HClO_4$ ($k_H/k_D = 2.7 \pm 0.3$)[5] or aq. H_2SO_4 ($k_H/k_D = 4.0 \pm 0.4$)[6] suggests that the formation of products occurs via the slow loss of a proton from the Wheland intermediate, followed by rapid dealkylation to give 4-nitrosophenol [eqn. (1)].[1–7] The isotope effect observed in the present system suggests that the formation of the nitrosating agent, the electrophilic attack and the proton loss occur in a similar manner in aqueous mineral acids and in non-aqueous CF_3COOH. Since only minor amounts of nitroso- or nitrophenols were detected, we conclude that the dealkylation step, which probably occurs via nucleophilic attack by H_2O on 4-nitrosoanisole,[6] is obviously almost completely inhibited in this system. 4-Nitrosoanisole is sufficiently stable in CF_3COOH/CH_2Cl_2 to be successfully isolated, and is not converted into 4-nitroanisole under the reaction conditions or during work-up as is evident from the lack of an isotope effect for the formation of 2- as well as 4-nitroanisole.

Although the 'classical' electrophilic mechanism for aromatic nitrosation appears to be operating in this system, a few comments on the possibility of an electron transfer (ET) mechanism will be made. As pointed out by Williams,[2] the ET mechanism for aromatic nitration,[13,19] may have its counterpart for aromatic nitrosation in the scheme summarized by eqns. (5) and (6).

$$ArH + NO^+ \longrightarrow ArH^{+\cdot} + NO \qquad (5)$$

$$ArH^{+\cdot} + NO \longrightarrow Ar(H)NO^+ \xrightarrow{-H^+} ArNO \qquad (6)$$

As discussed below, it may be questioned whether NO^+ is powerful enough as an ET oxidant towards anisole to bring about the conversion of eqn. (5).[20] Further counterevidence is provided by reactions with more readily oxidizable aromatic compounds, such as 1-methoxynaphthalene and perylene with $NO^+BF_4^-$. Here the products (the binapthyl and the radical cation salt, respectively)[13,17] clearly arise through an initial ET step, and no observations of the formation of nitroso compounds have ever been made, raising the question of to what extent aromatic radical cations actually can couple with NO.

The possibility exists that NO may be unable to couple with the more stable (i.e. formed from the more readily oxidizable aromatic compounds) radical cations. This may be the result of reasons similar to those reponsible for the reluctance of NO_2 to couple with $[\text{perylene}]_2^{+\cdot}PF_6^-$, as opposed to the facile coupling reaction between different naphthalene radical cation salts and NO_2.[13,21] The latter reactions are very highly selective, e.g. $[\text{naphthalene}]_2^{+\cdot}PF_6^-$ yields, with NO_2, nitronaphthalenes with a 1-/2- ratio of > 45, as compared with 1-/2- = 10 for electrophilic aromatic nitration. The almost, or totally, complete preference for 4-substitution in the nitrosation of anisole may hence be a consequence of the high regioselectivity of the coupling reaction [eqn. (6)]. However, at present we do not favour this pathway, mainly because of the unfeasibility of the ET step.

Turning to the implications of these findings on the mechanism of NAC nitration, we note that the present system offers some advantages over the aq. H_2SO_4-based system recently described by Dix and Moodie,[6] since neither dealkylation nor nitroso-to-nitro conversion occurs. Hence, the products of NAC nitration (2- and 4-nitroanisole), remain separated from those of nitrosation (4-nitrosoanisole), whereas in the aqueous systems 2- and 4-nitrophenol are formed from NAC nitration, while 4-nitrosophenol and, again, 4-nitrophenol are the products from nitrosation.

The isomer distribution for the formation of the nitroanisoles was invariably 2/4 = 0.7 ± 0.1 (Table 1, entry 5) as compared with 2/4 > 2 for NO_2^+-nitration (Table 1, entries 1–4) and 2/4 < 0.1 for nitrosation followed by oxidation (Table 1, entries 9, 10, 13). Values of 2/4 = 0.6–0.8 were found for nitration with N_2O_4 (Table 1, entries 7, 8) and with (initially) N^V under conditions where NO_2^+-nitration can be ruled out (Table 1, entry 6), and since exactly the same observations have been made in the case of phenol[10] (Table 1, entries 14–16) wer conclude that 2- and 4-nitroanisole are formed via NAC nitration and that NAC nitration occurs *simultaneously* with nitrosation. Note that NAC nitration does not exhibit an isotope effect and that at high $[CF_3COOH]$ in the N_2O_4-based system nitration dominates.

The electron transfer mechanism for NAC nitration, originally proposed by Ridd,[12] is schematically represented

$$ArH + NO^+ \rightarrow ArH^{+\cdot} + NO \qquad (7)$$

$$(NO^\cdot + NO_2^+ \rightarrow NO_2^\cdot + NO^+) \qquad (8)$$

$$ArH^{+\cdot} + NO_2 \rightarrow Ar(H)NO_2 \qquad (9)$$

by eqns. (7)–(9). The validity of this mechanism has been under discussion for some time,[13,22] mainly concerning the ability of NO^+ to act as an ET oxidant towards some of the less readily oxidizable aromatic compounds that are susceptible to NAC nitration. We have argued that the detection of radical cations or radical pairs from substrates such as naphthalene and mesitylene must be a consequence of processes other than direct outer-sphere ET, mainly because the rate of the ET step has been estimated to be much lower than that actually observed for the overall reaction.[13,20]

In this work we have observed that anisole is not converted into 4,4′-dimethoxybiphenyl (or higher oligomers/polymers) under conditions where 1-methoxynaphthalene readily undergoes radical-cation-mediated oxidative biaryl coupling. Instead, anisole is simultaneously subjected to electrophilic attack by NO^+ and to NAC nitration. As a consequence, assuming that our reasoning above is correct, the initial approach of NO^+ onto anisole does not lead to

ET but rather to electrophilic nitrosation. The possibility exists that ET does occur and that $[\text{anisole}]^{+\cdot}$ and NO do not couple, thus avoiding nitrosation. However, it is then necessary to picture the escape of NO from the radical pair, its conversion into NO_2 and re-entry (or at least the substitution of NO for NO_2 within the solvent cage) without any leak of $[\text{anisole}]^{+\cdot}$ into the bulk of the solution in order to avoid biaryl and polymer formation. We believe that the material balances presented here and in general for NAC nitration are too high to be accommodated within such a scheme.

Since we consider the intermediacy of radical cations and radical pairs in NAC nitration to be proven beyond all doubt,[12,22] we conclude that the Ridd scheme [eqns. (7)–(9)] must be modified with regard to the nature of the initially attacking species. We have previously suggested that the initial step of NAC nitration involves electrophilic attack by protonated or nitrosated N_2O_4, followed by homolytic cleavage of the resulting Wheland intermediates to give radical cation/radical pairs [eqns. (10)–(12)].[14] Although the present investigation does not present any further evidence in favour of such a scheme, we feel that the discussion concerning the nature of the initial and radical-forming step of NAC nitration necessarily must be continued.

$$\mathrm{ArH} + \mathrm{ONO}\overset{+}{\mathrm{N}}\mathrm{ONO_2} \rightarrow \mathrm{Ar(H)N(ONO)ONO_2} \qquad (10)$$

$$\mathrm{Ar(H)N(ONO)ONO_2} \rightarrow \mathrm{Ar(H)N(O{\cdot}NO{\cdot})ONO_2} \qquad (11)$$

$$\mathrm{Ar(H)N(O{\cdot}NO{\cdot})ONO_2} \rightarrow \mathrm{Ar(H)NO_2} + \mathrm{NO} + \mathrm{NO_2} \qquad (12)$$

Finally, we would like to suggest the possibility of another mechanism, analogous to the inner-sphere mechanism of aromatic nitration, which was invoked in order to explain the formation of radical cations under conditions where outer-sphere ET from ArH to NO_2^+ could not be operative.[13,21b]

Assuming that NO^+ initially, and with high regiospecificity, attacks the 4-position of anisole, the resulting Wheland intermediate can, in principle, undergo deprotonation, denitrosation and/or homolytic cleavage of the C–N bond [eqns. (13)–(15)].

$$\begin{array}{llr} & \mathrm{ArNO} + \mathrm{H^+} & (13) \\ \mathrm{ArH} + \mathrm{NO^+} \rightarrow \mathrm{Ar^+(H)NO} \rightarrow & \mathrm{ArH} + \mathrm{NO^+} & (14) \\ & \mathrm{ArH^{+\cdot}} + \mathrm{NO} & (15) \end{array}$$

If eqn. (15) offers a way into the mechanism of NAC nitration, we may here have an explanation as to why nitrosation and NAC nitration occurs simultaneously and also as to how certain alterations of the reaction conditions can affect the product composition. It is possible that, when NO_2 is the starting materal, reaction via eqn. (15) could to be more important than in the $NaNO_2$ case while with $NO^+BF_4^-$ only reaction via eqn. (13) occurs.

The attractive feature of eqn. (15) is that no direct ET from a less readily oxidizible aromatic compound to NO^+ is required. The unfavourable energetics of the overall ET process can be compensated by the energy gained in the breaking of the C–N bond in the transition state, using a similar reasoning to that applied earlier to aromatic nitration.[13] However, explanations must still be provided to account for why a very reactive radical cation firstly refuses to couple with NO, secondly avoids reaction with all species other than NO_2 (a species that somehow has to be provided in vicinity of the radical cation) and finally couples with NO_2 to give isomer distributions different from those obtained in the reactions between presynthesized $ArH^{+\cdot}$ and NO_2.[21]

Experimental

Material and methods. Dichloromethane (Merck) and nitromethane (Fluka, > 99 %) were dried and stored over 3 Å molecular sieves. Diethyl ether was distilled from Na. Other solvents were of *p.a.* grade and were used as supplied. Aromatic compounds (purity > 99 %, GLC) were commercial samples, as were all inorganic compounds, also used as supplied. Solutions of N_2O_4 were made up as previously described.[21a] 4-Nitrosoanisole was prepared by oxidation of 4-methoxyaniline with 3-chloroperbenzoic acid.[3,26] Anisole-d_5 was prepared from phenol-d_5 (> 99 % D) and CH_3I in a phase-transfer catalyzed reaction.

Column chromatography was performed on short columns on Florisil 60–100 mesh or on silica gel 60 (Merck). GLC analyses were performed on 2 m×3 mm NPGS on Chromosorb W on an HP 5380 gas chromatograph or by capillary GLC as previously described.[27] ^1H NMR and mass spectra were recorded as previously described.[27]

Products were identified by comparison of GLC retention times with authentic samples and by their mass and NMR spectra. GLC yields were determined via internal or external standard methods using 4-nitrotoluene as the reference compound. Isomer distributions were determined by capillary GLC and 3-nitroanisole was found never to be formed in > 0.5 % of the amount of 2- and 4-nitroanisole.

Nitrosation of anisole: general procedure. Anisole (0.0030 mol) was dissolved in CH_2Cl_2/CF_3COOH (Figs. 1–3) in an Erlenmeyer flask which was then flushed with Ar, stoppered and cooled to 0 °C (solution A). $NaNO_2$ or N_2O_4 (for amounts, see Figs. 1–3) was dissolved in CF_3COOH or CH_2Cl_2, respectively, and adjusted to the appropriate concentration of CF_3COOH in CH_2Cl_2. After being flushed with Ar, the solution was cooled to 0 °C (solution B).

While being flushed with Ar, solution A was poured onto solution B with continuous magnetic stirring and cooling on an ice–salt bath. After 20 min the reaction was quenched by the addition of water and CH_2Cl_2 (prolonged reaction times had no beneficial effect on any of the reactions). The resulting mixture was washed with 3×200 ml of water, dried, evaporated and passed through a short column (eluent 20% CH_2Cl_2 in pentane) and analyzed by GLC (passage through > 10 cm of silica gel causes considerable degradation of 4-nitrosoanisole).

Nitrosation under 'standard conditions.' Using the technique presented above (solution A = 0.0030 mol of $ArOCH_3$ in 15 ml of CH_2Cl_2 and 5 ml of CF_3COOH; solution B = 0.0066 mol of $NaNO_2$ in 10 ml of CF_3COOH and 30 ml of CH_2Cl_2) 2-methylanisole, 3-methylanisole and 2,6-dimethylanisole were subjected to nitrosation as summarized in the results section. Yields were determined by GLC.

Preparative nitrosation of anisole. Anisole (0.010 mol) in 50 ml of CH_2Cl_2 and 16 ml of CF_3COOH (solution A) and $NaNO_2$ (0.022 mol) in 33 ml of CF_3COOH and 100 ml of CH_2Cl_2 (solution B) were treated and mixed as described above. After 20 min, water was added, and after being washed, dried and evaporated, passage of the crude reaction product through a short column (eluent 10% CH_2Cl_2 in pentane) yielded a green solution, from which blue crystals (> 90% pure) were obtained on evaporation. Recrystallization of these from heptane yielded essentially pure 4-nitrosoanisole (0.0057 mol, 57%).

Competitive nitration/nitrosation of anisole and anisole-d_5. Anisole (0.00030 mol) and anisole-d_5 (0.00030 mol) were treated with $NaNO_2$ (0.00012 mol) under conditions analogous to those presented above. The kinetic isotope effects presented in the results section were determined by GLC/MS as previously described.[27] When anisole and anisole-d_5 were allowed to compete for 10 mol% of N_2O_4 for 100 h, a value of k_H/k_D of 1.0 was obtained for the formation of 2- and of 4-nitroanisole.

Nitration of anisole under different conditions. The reactions were performed as previously described for the methylnaphthalenes,[21c] or by variations of these methods as summarized in Table 1. The reactions were generally allowed to reach a conversion (based on N) of > 50% and then worked-up and analyzed by GLC.

Acknowledgements. We thank Professor Lennart Eberson for stimulating discussions and the Swedish Natural Science Research Council for financial support.

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Received July 6, 1989.