Pathways of Nitrosobenzene Reduction by Thiols in Alcoholic Media

Stefano Montanari, Cristina Paradisi,* and Gianfranco Scorrano

Centro Studio Meccanismi di Reazioni Organiche del CNR, Dipartimento di Chimica Organica, Via Marzolo 1, 35131 Padova, Italy

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The biologically important reaction of nitrosobenzenes with thiols has been investigated in 2-propanol solution at room temperature, experimental conditions which allow for the detection and characterization of key intermediates. Final stable products of such complex reactions include azoxybenzenes and anilines, formed in relative proportions and at a rate which depend on the reagents initial molar ratio. A detailed description of the reaction of 4-chloronitrosobenzene with benzenethiol in 2-propanol was achieved by means of ^{1}H NMR in situ analysis. The reaction is initiated by rapid and quantitative coupling of the two reagents into a covalent adduct, an *N*-hydroxysulfenamide (N(OH)S), which decays to *N*-(4-chlorophenyl)hydroxylamine. This second intermediate is then converted via competing paths to 4,4′-dichloroazoxybenzene and to *N*-(4-chlorophenyl)benzenesulfenamide (4-ClC_6H_4NHSPh), which in turn decays to 4-chloroaniline. Interestingly, sulfinamides (ArNHS(O)R), major products of the reaction in aqueous media, do not form in 2-propanol.

Introduction

Nitrosoarenes are key intermediates in oxidation/reduction pathways of aza-substitued aromatic compounds. In alcoholic solutions, nitrosoarenes form as intermediates in the alkoxide[1]- or thiolate[2]-induced reduction of nitroarenes to the corresponding azoxyarenes and anilines. In the course of our work with S-anions[2] our interest was captured by the reactions of nitrosobenzenes with neutral thiols. While toxicologists have long been interested in such processes for their important role in biological systems, relatively little information is found in the organic chemistry literature about these reactions.[3,4] Nitrosobenzenes, which form in biological systems either by metabolic N-oxidation of arylamines (nitrosoarenes and *N*-hydroxyarylamines, which are in metabolic equilibrium, are often indicated as N-oxygenated arylamines[5a]) or by reduction of aromatic nitro compounds, react readily with SH groups in proteins in vivo.[6,5a] Indeed biomonitoring of hemoglobin-bound nitrosoarenes (binding to cystein residue) can be used to control exposure to and toxication of potentially hazardous arylamines and nitroarenes in persons at risk.[7] This reactivity is involved in "damaging" processes leading to methemoglobinemia, carcinogenesis, or mutagenesis. Research in this field has focused mostly on the reactions of N-oxygenated arylamines in red cells,[5] particularly on the reaction of nitrosobenzenes with glutathione. The results of mechanistic investigations, which employed mostly reduced glutathione[8−12] but also 2,3-dihydroxy propanethiol[13] as model sulfhydryl reagents (RSH), indicated that in buffered aqueous media the reaction of nitrosobenzenes (ArNO) leads to the corresponding *N*-arylhydroxylamines (ArNHOH), *N*-arylsulfinamides (ArNHS(O)R), *N*-arylsulfenamides (ArNHSR), and anilines ($ArNH_2$) in amounts which depend on the reactants structure and concentration and on the reaction conditions. Notably, sulfenamides, ArNHSR, were not observed in some of these studies because of fast hydrolysis to $ArNH_2$.[13] A common feature of the different mechanistic proposals emerged from these studies is that the first product of the reaction between a nitrosobenzene and a thiol is a covalent adduct,[6] the stability of which was found to increase with decreasing solvent polarity and temperature.[13] The structure of a semimercaptal, the *N*-arylhydroxysulfenamide ArN(OH)SR, was proposed for this species, which was never isolated and was examined in solution by means of UV, FAB-MS, and ^{13}C NMR analyses.[13,11] Increasing pH was found to increase the rate of formation of the adduct,[10] suggesting involvement of RS^- formed from RSH in a predissociation equilibrium step.[10,4] It was proposed that this adduct decays along three competing routes: (1) rearrangement to the corresponding sulfinamide (ArNHS(O)R), (2) reaction with

* Corresponding author. e-mail: paradisi@mail.chor.unipd.it; phone: ++39 0498275661; fax: ++39 0498275239.

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thiol to give ArNHOH—the ratio of *N*-arylhydroxylamine to sulfinamide was found to increase with increasing glutathione initial concentration,[6] and (3) reaction with thiol to give the sulfenamide ArNHSR. As remarked recently,[4] little is known about the mechanisms involved. The ArN(OH)SR → ArNHS(O)R "rearrangement" (route 1) requires, according to one proposal,[4] one molecule of ionized thiol and occurs either in a single- or in a two-step sequence.[4] An alternative proposal involves rate-limiting heterolytic N—O cleavage, either uncatalyzed or catalyzed by acids, to a nitrenium ion intermediate ArN^+-SR, followed by reaction with water.[8] The mechanism by which sulfenamides are formed has also remained controversial.[9,6]

Evidence for the presence of radicals in these systems has been collected by ESR analysis.[14−17] In aqueous media nitrosobenzene reacts with thiols to give the phenylhydronitroxyl radical, PhN(O•)H, according to eq 1.[14,17] This species was observed in buffered (pH 7.4) aqueous equimolar solutions of nitrosobenzene and glutathione. No ESR signal was, however, detected in the presence of larger concentrations of glutathione.[14] It was indeed shown that glutathione rapidly reduces the phenylhydronitroxyl radical to PhNHOH, eq 2.[15] Unstable thiyl radicals (RS•) were also detected in these systems by spin-trapping techniques.[15,17]

$$\mathrm{PhNO + RSH \rightleftharpoons PhN(O\cdot)H + RS\cdot} \quad (1)$$

$$\mathrm{PhN(O\cdot)H + RSH \rightleftharpoons PhN(OH)H + RS\cdot} \quad (2)$$

The phenylhydronitroxyl radical was also observed in a 2-propanol solution of nitrosobenzene and thiophenol.[16] In benzene solution, on the other hand, the thionitroxyl radical (PhN(O•)SPh) was observed, instead of the PhN(O•)H radical, its formation being attributed to the sequence of eq 3.[16]

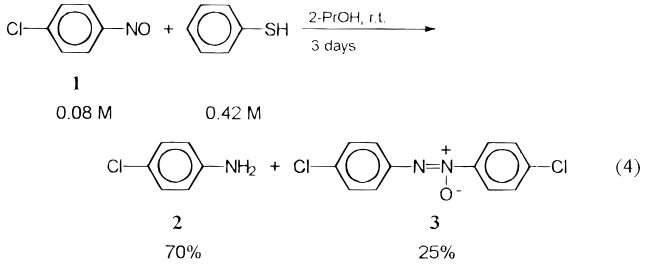
$$\mathrm{PhNO + PhSH \longrightarrow Ph{-}N(OH){-}SPh \xrightarrow{oxdn} Ph{-}N(O\cdot){-}SPh} \quad (3)$$

Different conclusions were reached concerning the involvement of such radicals in the processes described above. Mason and Eyer noted that "clearly there are also many other reactions of nitrosobenzene with thiols by non free-radical processes to yield semimercaptals and other metabolites".[15] In contrast, only radical mechanisms (involving mostly the thionitroxyl radical) were proposed to account for all the different products formed in the benzene reaction of benzenethiol with nitrosobenzenes.[16]

We report in this paper the results of a mechanistic investigation of the reaction of nitrosobenzenes with thiols in 2-propanol, based mainly on in situ ^{1}H NMR analysis. The advantages of this analytical approach with respect to those previously employed (HPLC, UV) are obvious if one considers that some of the crucial reaction intermediates are not stable (vide infra) under the conditions used for chromatographic analysis (HPLC, GC).[4] The choice of 2-propanol as solvent proved especially advantageous, relative to both aqueous and apolar (benzene)[16] media, since clean solutions containing *only* the initial intermediate were readily obtained, thus simplifying the study of its reactivity.

Results

The 2-propanol reaction of nitrosobenzenes with benzenethiol at room temperature gives as final stable products, besides diphenyl disulfide, the corresponding aniline and azoxybenzene derivatives, in relative proportions and at a rate which depend on the reagents' initial molar ratio. An example of a typical product distribution is given in eq 4 (isolated yields are reported). As the concentration of thiol was reduced, the yield of the azoxy product increased while that of 4-chloroaniline decreased. The long reaction time indicated in eq 4 is due to slow reactions of various intermediate species, the reactivity of 4-chloronitrosobenzene toward benzenethiol being in fact remarkably high (vide infra).



Similar results were also obtained for the reaction of nitrosobenzene, a somewhat less reactive substrate. It was reported earlier that reactivity increases with increasing electronegativity of para and meta substituents.[18,4] Sulfenamides ArNHSPh (Ar = Ph, 4-ClC_6H_4) were detected by GC-MS and HPLC analysis. Both techniques, however, proved unsuitable for monitoring the reaction course because of the complexity of the mixtures and of the lability of some of the species involved. Thus, both *N*-aryl-hydroxylamines and *N*-aryl-sulfinamides decomposed during GC analysis, and HPLC conditions of adequate resolution and reproducibility could not be found in the present study. We, therefore, turned to NMR in situ analysis. Since 4-chloronitrosobenzene (**1**) has a very characteristic ^{1}H NMR spectrum (AA′XX′) and chemical modifications of its nitroso function produce significant changes in the signal due to the ring protons, this compound served as an ideal model to monitor reactions with both aliphatic thiols and benzenethiol (to avoid interference by the protons of the PhS group, perdeuterated benzenethiol was prepared and used in these experiments). Our research focused on the reaction with benzenethiol for its convenient rate and for the possibility to access most potential intermediates as stable compounds to be used as references for the attribution of NMR signals. The following compounds, available commercially or through reported synthetic procedures, constituted our reference basis set: 4-chloroaniline (**2**), 4,4′-dichloroazoxybenzene (**3**), *N*-(4-chlorophenyl)hydroxylamine (**4**), *N*-(4-chlorophenyl)benzenesulfenamide (**5**), *N*-(4-chlorophenyl)benzenesulfinamide (**6**), *N*-(4-chlorophenyl)-*N*-(phenylthio)benzenesulfena-

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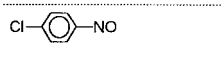
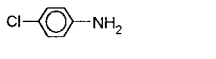
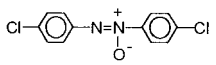
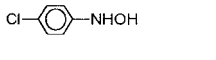
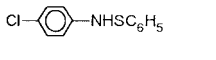
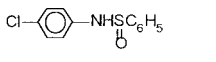
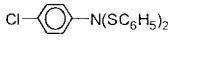
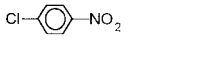
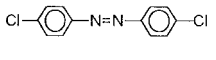
Table 1. ^{1}H NMR (400 MHz) Data for 4-ClC$_6$H$_4$NXY Compounds in 2-Propanol-d_8

Compound		δ, ppm[a]	*J*, Hz[b]
	(**1**)	7.68, 7.88	8.9
	(**2**)	6.64, 6.95	8.8
	(**3**)	7.45, 8.23 7.55, 8.31	9.0 9.1
	(**4**)	6.92, 7.07	8.9
	(**5**)	7.04 (singlet)	
	(**6**)	7.38, 7.42	9.0
	(**7**)	7.32, 7.48	7.0
	(**8**)	7.64, 8.23	9.0
	(**9**)	7.51, 7.91	8.7

[a] Center of gravity of the two "doublets" of the AA′XX′ system, relative to TMS. [b] Separation between adjacent peaks of the two "doublets" of the AA′XX′ system.

mide (**7**), 4-chloronitrobenzene (**8**), and 4,4′-dichloroazobenzene (**9**). Relevant NMR spectral data obtained in 2-propanol-d_8 are reported in Table 1. It should be noted that for some of these compounds the appearance of the spectrum is highly dependent on the solvent. In the case of **5**, for example, the slightly broad "singlet" observed in 2-propanol-d_8 (7.04 ppm) resolves into a characteristic AA′XX′ signal in $CDCl_3$ (two "doublets" centered at 6.97 and 7.17 ppm). It was therefore essential to compare spectra recorded in the same solvent. Chemical shifts and coupling constants values reported in Table 1, as well as in the text, are approximations derived directly from the spectra as explained in the table footnotes.

All evidence collected in this study indicates that the reaction between a nitrosobenzene and benzenethiol is best described as a two-phase process: (1) formation of a first intermediate (fast) and (2) decay of this common intermediate (slow) through a complex sequence of reactions to give eventually anilines and azoxybenzenes as major stable products. For convenience the two phases are discussed separately.

Formation of the Intermediate. Figure 1 shows some representative ^{1}H NMR results relative to the formation of the intermediate. The spectrum of 4-chloronitrosobenzene (**1**), shown in trace a changes, after addition of 1 equiv of PhSH-d_5, into b in which the original signal has been replaced by a new one (AA′XX′, two "doublets" at 7.08 and 7.23 ppm; J = 8.9 Hz). In an analogous experiment in which only 0.5 equiv of PhSH-d_5 was used, trace c was obtained, comprising the signals of **1** and of the product in approximately a 1 to 1 ratio. These and other similar experiments show that, upon addition of benzenethiol, the nitroso compound is rapidly converted into a new species, named **i**, the stoichiometry requiring 1 equiv of each reagent. A few experiments were also carried out with aliphatic thiols (MeSH, 2-PrSH, and t-BuSH). In each of the reactions with MeSH and 2-PrSH, one initial species formed that was characterized by ^{1}H NMR signal patterns closely resembling

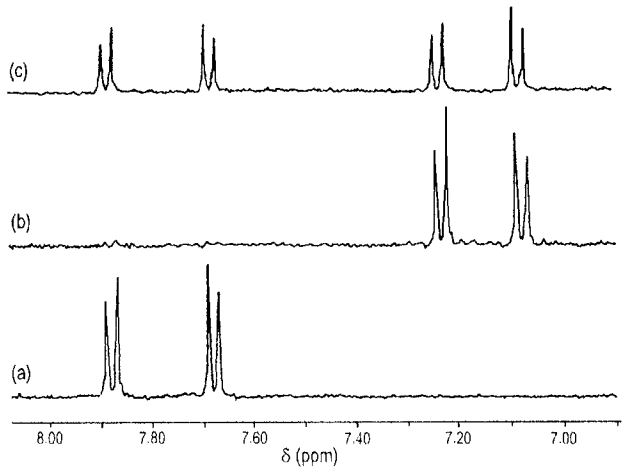


Figure 1. Partial ^{1}H NMR (400 MHz) spectra in oxygen-free 2-PrOH-d_8 at room temperature of (a) **1** (7 mM); (b) solution (a) analyzed 2 min after addition of 1 equiv of benzenethiol-d_5 (20 μL of a 0.39 M 2-PrOH-d_8 solution); (c) solution of **1** (7 mM) analyzed 2 min after addition of 0.5 equiv of benzenethiol-d_5.

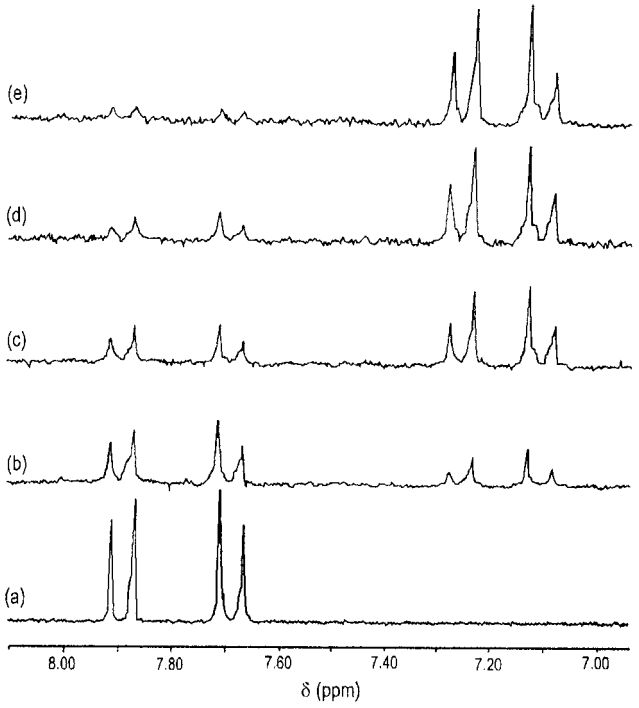


Figure 2. Partial ^{1}H NMR (400 MHz) spectra in oxygen-free 2-PrOH-d_8 at room temperature of (a) **1** (7 mM) and of the same solution recorded, after addition of 5 equiv of 2-propanethiol, at the indicated times: (b) 50 s; (c) 5 min; (d) 10 min; (e) 25 min.

that of **i**, the product of the benzenethiol reaction. However, these aliphatic thiols react more slowly than benzenethiol, the complete conversion of **1** in the presence of excess thiol requiring ca. 15 min with MeSH and ca. 30 min with 2-PrSH (Figure 2). With t-BuSH the signals of **1** remained unchanged for 24 h. A very low reactivity was reported for this thiol also in aqueous media.[6] The reaction with aliphatic thiols was not further investigated.

Concerning the identity of the intermediate **i** formed in the benzenethiol reaction, it appears that the NMR signal due to this species does not match any of those of

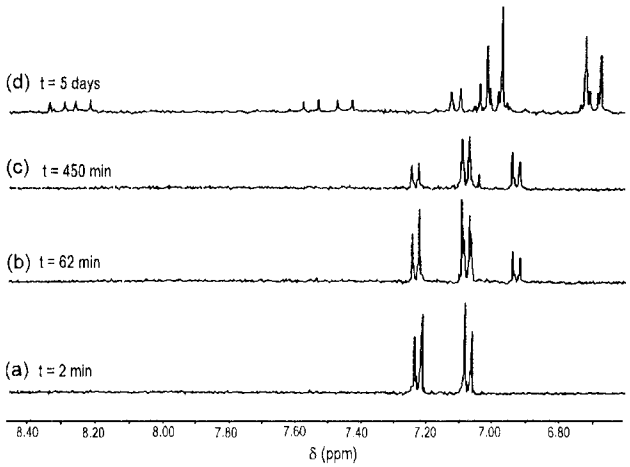


Figure 3. Partial ^{1}H NMR (400 MHz) spectra recorded at the indicated times for the room-temperature reaction of **1** (7 mM) with 5 equiv of benzenethiol-d_5 in oxygen-free 2-PrOH-d_8. Trace d was recorded at 200 MHz.

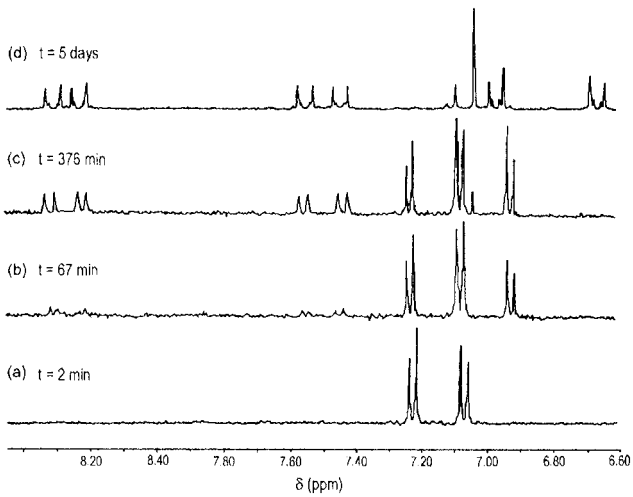


Figure 4. Partial ^{1}H NMR (400 MHz) spectra recorded at the indicated times for the room-temperature reaction of **1** (7 mM) with 1 equiv of benzenethiol-d_5 in oxygen-free 2-PrOH-d_8. Trace d was recorded at 200 MHz.

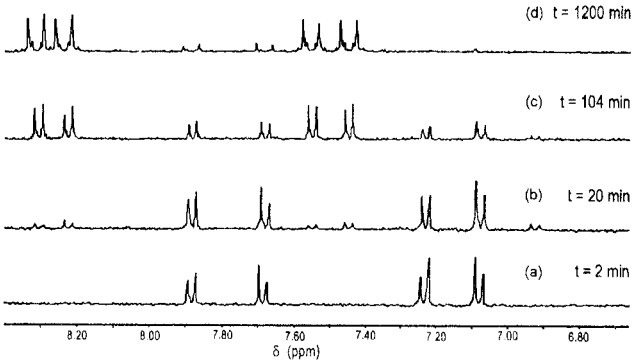


Figure 5. Partial ^{1}H NMR (400 MHz) spectra recorded at the indicated times for the room-temperature reaction of **1** (7 mM) with 0.5 equiv of benzenethiol-d_5 in oxygen-free 2-PrOH-d_8. Trace d was recorded at 200 MHz.

reference compounds **2**−**9** reported in Table 1. Both the stoichiometry of the reaction and the NMR chemical shifts are consistent with the structure of the covalent adduct *N*-hydroxysulfenamide.[13,11] This conclusion is also supported by the results of a mass spectrometric investigation,[19] briefly discussed in the next section.

Attempts to isolate **i** were unsuccessful. It was hoped that fast removal of the solvent under reduced pressure should yield either **1** or **i** depending on whether adduct formation were reversible[6] or not. Instead the isolated residue contained mostly the final reaction products (eq 4). An alternative approach aimed at converting **i** into some stable derivative by functionalizing the hydroxyl group (i.e., to a silyl ether) was unsuccessful since **i** does not appear to form in appreciable concentrations in aprotic solvents ($CDCl_3$, C_6D_6, $(CD_3)_2CO$, $(CD_3)_2SO$). Notably, in benzene solution, the first detectable product was the benzenesulfenamide **5**.

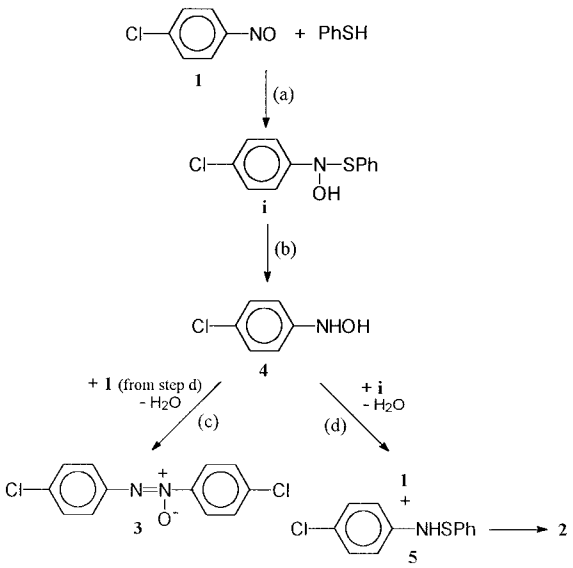
Decay of the Intermediate. In situ NMR analysis of many reaction mixtures of different initial composition allowed us to draw some conclusions concerning the fate of intermediate **i**. The results of three representative experiments in which the concentration of **1** was kept constant (7 mM) while the $[C_6D_5SH]/[\mathbf{1}]$ ratio was fixed at 5, 1, and 0.5, are summarized in Figures 3, 4, and 5, respectively. Out of the many NMR recordings taken over the whole reaction time, four representative traces are shown for each experiment to illustrate the reaction course. The data of Figure 3, which refer to reaction of intermediate **i** run in the presence of excess benzenethiol, are the easiest to analyze. It is seen (trace b) that as **i** decays, a new system of signals develops which in part overlaps that of **i**. This new signal matches exactly that of the ring protons of *N*-(4-chlorophenyl)hydroxylamine (**4**), thus suggesting that **4** is the second reaction intermediate. At longer reaction times a new signal appears (7.04 ppm, singlet), as seen in trace c recorded after 7.5 h, which is attributed to *N*-(4-chlorophenyl)benzenesulfenamide (**5**). As both **i** and **4** slowly decay, **5** builds up (traces not shown) and in turn decays to leave a product mixture composed mainly (trace d) of 4-chloroaniline (**2**) (AA′XX′ "doublets" at 6.64 and 6.95 ppm). Also evident in trace d are the characteristic signals (two AA′XX′ "doublets") of 4,4′-dichloroazoxybenzene (**3**) as well as some minor signals which could not be assigned.

When equimolar amounts of **1** and benzenethiol were used in preparing intermediate **i**, a similar behavior was observed (Figure 4), except for two main differences. First, the azoxy compound **3** appears at earlier stages (it is detectable after 1 h, trace b) and in larger amounts (compare traces d of Figures 3 and 4). Second, the decay of the sulfenamide (**5**) signal appears to be quite slower, so that a significant amount of this intermediate is still present after 5.5 days (again compare traces d of Figures 3 and 4).

When only 0.5 equiv of thiophenol was used (Figure 5), i.e., when the reaction of **i** was initiated in the presence of an equimolar amount of **1** (trace a), production of the azoxy compound **3** was overwhelming. The usual conversion of **i** into the hydroxylamino product **4** is evident in trace b of Figure 5 recorded 20 min after mixing. Note already at this short reaction time the presence of some **3**, which after 1 day (trace d) constitutes the major component of the reaction mixture. A small amount of **1** and a trace amount of an unidentified compound ("singlet" at 7.09 ppm) are also present at this

(19) Montanari, S.; O'Carroll, F.; Paradisi, C.; Scorrano, G.; Traldi, P. *Rapid Commun. Mass Spectrom.* **1995**, *9*, 1081, 1473.

Scheme 1



stage. Interestingly, in contrast to the experiments described previously, the signal of the sulfenamide **5** (7.04 ppm) was not detected at any time in the course of this experiment. A control NMR experiment indicated that **4** and **1** undergo condensation to **3** under the typical reaction conditions used in this study. The spectrum shown as trace d did not undergo further changes over a period of 5 days.

A few experiments were performed to investigate on the origin of the sulfenamide **5**. According to one proposal,[9] the dithioketal **7** (4-$ClC_6H_4N(SPh)_2$) should form as an intermediate species in the conversion of **i** into **5**. We searched for compound **7** ("doublets" at 7.32 and 7.48 ppm) in our experiments, but found no detectable amounts of it under any of the conditions used. Our observations instead suggest that **5** derives from **4**. A hypothetical route involving reaction of **4** with benzenethiol could be ruled out since **4** remained unaffected upon prolonged treatment with excess benzenethiol in 2-PrOH-d_8.[6] Support for the proposal that **4** is involved in the production of intermediate **5** came from a crossover experiment in which 1 equiv of *N*-(4-bromophenyl)hydroxylamine was added to a solution of **i** freshly prepared by mixing **1** (7 mM) with 1.2 equiv of benzenethiol. GC-MS analysis of the resulting solution revealed the presence of 4,4′-bromochloroazoxybenzene and 4,4′-dibromoazoxybenzene besides the usual reaction products. It also indicated the presence of **5** already after 3 h as opposed to the longer reaction time required in the absence of added external hydroxylamino reagent.

Finally, an important result concerns sulfinamide **6**, which was never observed ("doublets" at 7.38 and 7.42 ppm) at any stage in any of the various experiments performed with [C_6D_5SH]/[**1**] ratios ranging from 0.15 to 5. Interestingly, the sulfinamide is a major product of reaction in aqueous media[6,8] and, to a certain extent, also in benzene.[16]

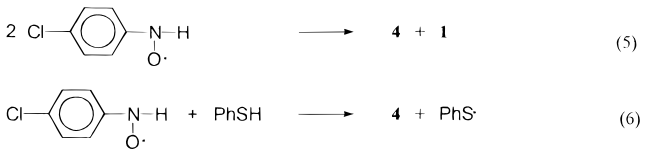
Discussion

The results described above establish the sequence of steps which account for the 2-propanol reaction of nitrosobenzenes with benzenethiol. A proposal consistent with our observations is presented in Scheme 1.

The process is initiated by fast condensation of the NO and SH functionalities to form a covalent adduct, the *N*-(4-chlorophenyl)hydroxybenzenesulfenamide **i**, the ^1H NMR spectrum of which is shown in trace b of Figure 1. In an earlier investigation[19] of a solution of **1** and benzenethiol in glycerol by means of FAB mass spectrometry, we observed signals due to species $[MH]^+$, corresponding in mass to the sum of the two reagents plus one proton, and $[MH - H_2O]^+$. In contrast, the FAB mass spectrum of an authentic sample of sulfinamide **6**, recorded under the same experimental conditions, contained no signal due to water loss. These observations, consistent with earlier reports[13,11] clearly indicate that **i** is an isomer of **6**. Deeper insight into the FAB-MS process was achieved by analysis of the time dependence of these signals coupled to structural analysis by the MIKE technique. It was concluded that the adduct formed upon mixing the two reagents in glycerol reacts according to two independent paths (i) FAB-induced protonation (presumably on oxygen) to an unstable $[MH]^+$ followed by water elimination to give the ionic species 4-$ClC_6H_4-N{=}^+S-Ph$; (ii) isomerization[8] to **6** which, under FAB conditions, undergoes protonation to give a stable $[MH]^+$ species.[19]

As for the fate of the initial addition product **i**, however, our observations and conclusions differ considerably from those made in related studies carried out in aqueous solvents and in benzene. Our NMR data suggest that, although the final stable product composition and the time required to reach it depend on the reactants molar ratio, reaction of **i** is always initiated by its conversion to the corresponding *N*-arylhydroxylamine **4**. *N*-Arylhydroxylamines were also observed in reactions in aqueous media. Their formation was attributed to reaction of the primary adduct *N*-arylhydroxysulfenamide, ArN(OH)SR, with free thiol, but no suggestion was provided about the mechanism involved. In our system, however, any reaction requiring the involvement of free thiol is not sufficient to account for experimental observations such as the following: the reaction mixture composition after 1 h of experiments run with benzenethiol in equimolar (Figure 4, trace b) and in 5-fold excess (Figure 3, trace b) concentrations with respect to the nitrosobenzene are very similar.

Conceivable radical pathways to **4** were then considered, based on known processes adapted as in eqs 5[20] and 6.[15]

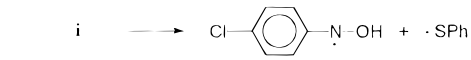


Both involve reaction of the arylhydronitroxide radical, a species which has been detected in 2-propanol solutions of nitrosobenzenes and PhSH.[16] Both can be ruled out, reaction 6 for the reasons expressed in the preceding paragraph (it does not account for the production of **4** in experiments run in the absence of excess free benzenethiol), and reaction 5 because it produces equimolar

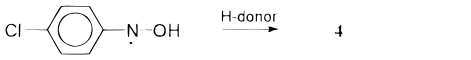
(20) Aurich, H. G. In *Supplement F: The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; J. Wiley & Sons: New York, 1982; Part 1, Ch. 14.

amounts of **4** and **1**, which should, as shown in a control experiment, undergo condensation to **3**.

A third radical process can be envisioned based on unimolecular reaction of **i** via homolytic S−N fission, a process which occurs readily in sulfenamides, in some cases simply upon exposure to diffuse sunlight.[21] If one assumes similar lability for **i** then the sequence of eqs 7 and 8 could account for the formation **4**.



(7)



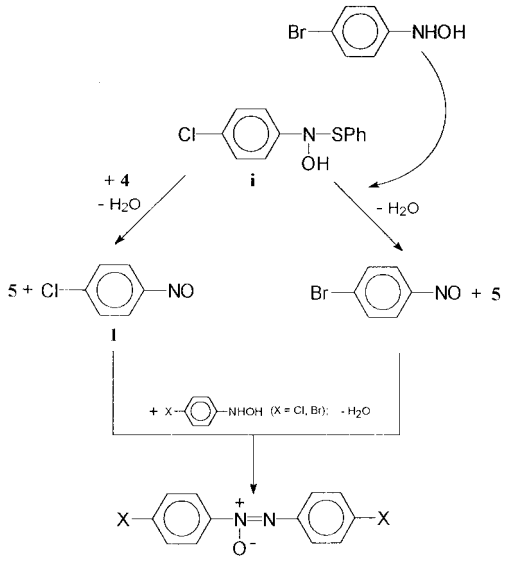
(8)

As for the nature of the H-donor species in eq 8, in experiments run with free benzenethiol, this reagent would obviously be involved in such a step. On the other hand, since the **i** → **4** conversion (Scheme 1, path b) was observed under any of the conditions used, including the case in which reaction of **i** was initiated in the absence of free benzenethiol and nitrosobenzene reagents ([C_6D_5-SH]/[**1**] = 1), we believe that the solvent itself must be involved in this step. It could intervene directly in eq 8 to produce the strongly reducing $(CH_3)_2(HO)C\bullet$ radical. Alternatively, an undissociated molecule of **i** could act as the H-donating species in eq 8, leading to **4** and to the 4-$ClC_6H_4N(O\bullet)SPh$ radical, which in turn could be reduced to **i** by a molecule of 2-propanol. Notably, such radical was not detected in 2-propanol solutions of **1** and benzenethiol.[16]

Depending on the experimental conditions used, the next NMR signals to appear are due to benzenesulfenamide **5** and/or to the azoxy compound **3**. When a [C_6D_5-SH]/[**1**] ratio ≥ 1 is used, the former is observed as a reaction intermediate which accumulates to significant concentrations before decaying to aniline **4** (see traces c and d of Figure 4). The build-up and decay of **5** is also quite evident in additional traces, not shown, pertinent to the experiment of Figure 3. In contrast, the azoxy compound **3** prevails when the nitroso reagent is used in excess with respect to benzenethiol—notably, the benzenesulfenamide **5** was never detected under these conditions.

Three different mechanisms have been proposed to account for the production of sulfenamides ArNHSR in the reaction of nitrosobenzenes (ArNO) with thiols (RSH) in aqueous media: (1) reaction of the original adduct ArN(OH)SR with a molecule of thiol, a molecule of [RSOH] being the side product;[6] (2) two-step reaction, each step requiring one molecule of thiol, of the original adduct ArN(OH)SR via the intermediacy of dithioketal $ArN(SR)_2$;[9] (3) reaction of ArNHOH with thiol.[12] All three require free thiol as reagent and appear therefore inadequate to accommodate our finding that **5** forms also in the absence of free thiol. In addition, evidence against the operation of mechanism 3 in our system was obtained in an independent experiment which proved the stability of **4** upon prolonged treatment with excess benzenethiol, a finding matching some earlier observations.[6] Lack of detection of the dithioketal **7** in all of our experiments, on the other hand, speaks against mechanism 2. Such a mechanism proved unlikely also for reactions in aqueous media since only ArNHSR and no ArNHSR′ formed when ArN(OH)SR was treated with R′SH.[13]

Scheme 2



Alternative routes to **5** had therefore to be considered. One, consistent with all the experimental data collected so far, is that of step d of Scheme 1, in which reduction of **i** to **5** is accompanied by oxidation of **4** to the nitroso precursor **1**: the latter can either be trapped by excess benzenethiol and recycle as **i** or compete for **4** and enter path c. Route d, therefore, accounts for the formation of the azoxy compound in reactions of the intermediate **i** initiated in the absence of free nitroso compound, i.e., when an original [C_6D_5SH]/[**1**] ratio ≥ 1 is used. Azoxybenzenes can also be produced via dimerization of arylnitroxide radicals, $ArN(O\bullet)H$.[20]

Step d is also consistent with the results of a crossover experiment in which addition of *N*-(4-bromophenyl)-hydroxylamine to a solution of **i** stimulated the production of **5** and led to, besides the usual products, also some 4,4′-bromochloroazoxybenzene and 4,4′-dibromoazoxybenzene, as summarized in Scheme 2.

For the absence of the sulfinamide **6**, the 2-propanol reaction differs remarkably from that in aqueous media for which sulfinamides are major products of reaction.[6,8] Notably PhNHS(O)Ph was also isolated (17% yield) from the reaction of nitrosobenzene with PhSH in benzene,[16] and **6** was detected by FAB-MS analysis of a solution of 4-chloronitrosobenzene and benzenethiol in glycerol.[19] Certainly the role of the solvent on the stability and reactivity of the various intermediates and, therefore, on the outcome of these reactions is of major importance. This was clearly demonstrated in the present study also for the reaction first step: in sharp contrast with the behavior in 2-propanol, no indication was obtained by in situ NMR analysis for the presence of **i** in benzene solution, the first detectable product being in this case **5**.

Finally, it should be pointed out that no evidence was collected, in any of our many different NMR runs, for the occurrence of radical species. Thus, although radicals have been detected by EPR spectroscopy in different solvents[14−16] including 2-propanol,[16] and their involvement in some of the elementary steps comprised in the proposed complex reaction scheme (Scheme 1), such as

(21) (a) Horspool, W. H. In *The Chemistry of Sulphenic Acids and Their Derivatives*; Patai. S., Ed.; J. Wiley & Sons: Chichester, 1990; Ch. 11, p 517. (b) Bayfield, R. F.; Cole, E. R. *Phosphorous Sulphur* **1976**, *1*, 19.

step b, is very likely, their concentration and/or lifetime is evidently not sufficient to produce any appreciable line-broadening phenomena in the NMR signals.

Conclusions

In 2-propanol at room temperature nitrosobenzenes are trapped by benzenethiol to form adducts of *N*-arylhydroxysulfenamide structure. This reaction is fast and quantitative, and its product is relatively stable, thus allowing for convenient monitoring of subsequent complex transformations by in situ NMR analysis. In contrast to the reaction in aqueous media, which involves several competing steps for the decay of this primary intermediate, our data suggest one single path leading to the corresponding *N*-arylhydroxylamine. A new mechanism is suggested for this conversion, based on homolytic N−S fission and reduction of the resulting aminyl radical. The *N*-arylhydroxylamine reacts according to either of two courses, leading to azoxybenzene (step c) and to *N*-arylbenzenesulfenamide (step d), respectively, the partitioning depending on the initial reagents molar ratio. When PhSH is used in excess, path d prevails since the nitroso precursor generated as a side product in this step is trapped by PhSH and recycled. When the nitroso reagent is used in excess, path c prevails due to the efficient condensation between the NO and NHOH functionalities. Another striking difference concerns the absence in the 2-propanol reaction of benzenesulfinamides (ArNHS(O)Ph), major products of the reaction in aqueous media. The present investigation highlights the crucial role played by the solvent on the reactivity in these complex systems. It also shows that, in contrast with what suggested for reaction in aqueous media, reaction of the adduct does not require free benzenethiol.

Experimental Section

^{1}H NMR experiments were performed on Bruker AC200 and AC400 spectrometers. A Hewlett-Packard 5890 GC5970 MSD was used for GC-MS analysis, with a 15-m fused silica column of poly(dimethylsiloxane)−bonded phase.

Materials. Reagent grade 2-propanol was fractionally distilled from Mg turnings. 2-Propanol-d_8 and the other deuterated solvents (chloroform, benzene-d_6, methanol-d_4, acetone-d_6, and DMSO-d_6) were the products of Cambridge Isotope Laboratories. They were used as received and stored over molecular sieves. Benzenethiol was freshly distilled before use and stored under argon. 4-Chloronitrosobenzene (**1**) was prepared and purified as reported earlier.[22] *N*-(4-chlorophenyl)-hydroxylamine (**4**),[23] *N*-(4-bromophenyl)hydroxylamine,[23] *N*-(4-chlorophenyl)benzenesulfenamide (**5**),[24] *N*-(4-chlorophenyl)-benzenesulfinamide (**6**),[25] *N*-(4-chlorophenyl)-*N*-(phenylthio)-benzenesulfenamide (**7**),[26] 4,4′-dichloroazossibenzene (**3**),[27] and 4,4′-dichloroazobenzene (**9**)[28] were prepared and purified according to published procedures. Perdeuterated thiophenol, PhSH-d_5, was prepared from bromobenzene-d_5 (≥99.5%-D, Fluka) by a literature method[29] and purified by vacuum-distillation (Kugelrohr Büchi GKR-51).

Product Isolation. A deoxygenated solution of 0.3 g (2.1 mmol) of 4-chloronitrosobenzene and 1.25 mL (10.6 mmol) of benzenethiol in 25 mL of 2-propanol was stirred at 25 °C for 3 days. After addition of 25 mL of water, the mixture was extracted with diethyl ether (3 × 50 mL). Flash chromatography (petroleum ether/toluene 1:1) of the residue obtained after evaporation of the solvent yielded 4-chloroaniline (0.19 g, 70% yield) and 4,4′-azoxybenzene (0.07 g, 25% yield).

NMR Experiments. Most spectra were conducted at 400 MHz (a few at 200 MHz), with a probe temperature of 25 °C and a sweep width of 5000 Hz. Complete sets of reference spectra in 2-propanol-d_8 recorded both at 200 and at 400 MHz were acquired for peak attribution. The general procedure was as follows. A 1 mL aliquot of a 7 mM solution of 4-chloronitrosobenzene in 2-propanol-d_8 was transferred into a 5 mm diameter NMR tube fitted with a screw-cap equipped with a septum. After sonication and gentle bubbling of Ar through the solution, the NMR spectrum was recorded to provide the "time zero" data point. By means of a graduated microsyringe, a small volume of a degassed concentrated (0.39 M) C_6D_5SH solution in 2-propanol-d_8 was quickly added to obtain the desired final concentration, the tube inverted a few times to ensure thorough mixing, and the time count started. Spectra were recorded at desired times either by means of an automated procedure or manually. Automated aquisition was especially useful to monitor the initial stages of the process. The same procedure was used with the aliphatic thiols, except with MeSH, the concentration of which was not determined. In this case the reagent was bubbled directly through the nitrosobenzene solution for a short time.

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