Addition, Reduction, and Oxidation Reactions of Nitrosobenzene

Petr Zuman* and Bhavdeep Shah

Department of Chemistry, Box 5810, Clarkson University, Potsdam, New York 13699-5810

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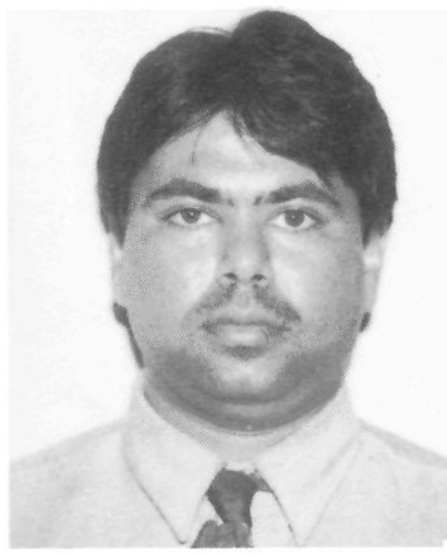
Contents

Petr Zuman was born in Prague, Czechoslovakia, where he graduated from Charles University with an RNDr degree in chemistry in 1950. In 1960 he was awarded a DrSc degree by the Czechoslovak Academy of Sciences, and in 1968 a D.Sc. degree by the University of Birmingham, U.K. From 1950 until 1966 he was associated with the J. Heyrovský Institute of Polarography in Prague, where he became the head of the organic division. From 1966 until 1970 he was a Senior Visiting Fellow at the University of Birmingham, England, and since 1970 he has been a Professor of Chemistry at Clarkson University at Potsdam, NY. His research interests involve studies of organic polarography and its applications, in particular for structure–reactivity relationships, for investigation of mechanisms of some organic reactions, and for following the interactions of xenobiotic substances with biological materials.



Bhavdeep B. Shah was born in Bombay, India, in 1965. He received his B.Sc. in Chemistry from University of Bombay, India, in 1985 and his Ph.D. in Physical Organic Chemistry from Clarkson University in 1994 working with Professor Petr Zuman. His work at Clarkson University involved studying the mechanism of biologically important reactions of nitrosoarenes based on kinetic investigation and product identification. His research interest is in investigation kinetics and elucidating mechanism of reactions involving acid base equilibria. He is a member of the American Chemical Society, American Association of Pharmaceutical Scientist, and Phi Sigma Epsilon. He is currently with BERTEK, Inc., in St. Albans, VT.

1. General Background

Aromatic C-nitroso compounds can be formed as reactive intermediates in biological systems. Their formation can occur either by metabolic N-oxidation of arylamines,[1,2] leading to methemoglobinemia, carcinogenesis, or mutagenesis, or by reduction of aromatic nitro compounds, introduced into organisms as a toxin. Such introduction can occur for example by inhalation of volatile aromatic nitro compounds during their manufacture, by contact with some agrochemicals, particularly pesticides, or by contact with explosives or agents of chemical warfare containing nitro groups. Alternatively some nitro compounds can enter organisms administered as drugs, for example antibiotics such as chloramphenicol, nitroimidazoles used in cancer treatment, or nitrofurans or nitrothiazoles used as antifungicidal agents. On the other hand the intercellular lifetime of C-

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nitroso drugs is short, estimated to be about 30 min. At low concentrations their cytotoxic effects are negligible[3] and they are converted to nontoxic species.[3,4]

As reactive intermediates, aromatic nitroso compounds exhibit a high reactivity of the nitroso group. The polarization of the nitrogen—oxygen bond, resembling that of the carbon—oxygen bond in carbonyl groups, results in a susceptibility of the —N=O group to additions of nucleophiles. On the other hand, the free electron pair on nitrogen enables nitrosobenzenes to act as nucleophiles and add to carbon—oxygen, carbon—nitrogen, or activated carbon—carbon double bonds. One of the manifestations of the presence of this lone pair is the largest ^{15}N chemical shift anisotropy measured to date,[5] as observed by solid-state ^{15}N NMR. Other evidence comes from a multinuclear solution NMR studies[6,7] and from ab initio SCF MO calculations.[8] The nitroso group can also participate in cycloadditions. Furthermore, the nitroso group can also be reduced to a hydroxyamino or even to an amino group or can be oxidized to a nitro group. Nitrosobenzenes coordinate to many metal ions. Nitrogen of nitroso group is included in coordination for six of seven known types of such complexes.[9]

In addition to processes involving participation of electron pairs mentioned above, nitrosobenzenes are also susceptible to one-electron processes, involving radicals and radical ions. Nitrosobenzenes can be converted into radicals or radical ions by some oxidizing or reducing agents, photochemically, or by electrochemical processes. They also react readily with other free radicals and act as radical traps. In some instances, participation of one-electron steps has been assumed even for reactions involving negatively charged nucleophiles.

In this review nucleophilic additions to nitrosobenzenes will be discussed first, followed by a discussion of the reduction of the nitroso group. This is followed by a discussion of the addition of nitrosobenzene to various double bonds and the oxidation of the nitroso group. The added nucleophiles were arbitrarily divided according to the atom bearing the free electron pair or the negative charge into oxygen-, sulfur-, carbon-, and nitrogen-containing nucleophiles. In some instances only the decrease in concentration of nitroso compound was reported and the attribution of the process to addition or reduction may be arbitrary.

Before discussing individual reactions of nitrosoarenes, some properties of their solutions will be mentioned. Whereas aliphatic C-nitroso compounds show a strong tendency to form dimers,[10-12] the importance of dimerization in solutions of nitroso arenes strongly depends on concentration of the nitroso compound, on temperature and on the presence of substituents on the aromatic ring.

At concentrations of the order of 10^{-4} M commonly studied by spectrophotometry or electroanalytical methods and at ambient temperatures, the majority of nitrosobenzenes are predominantly present in solutions as monomers.[13] At concentrations of the order of 10^{-1} M typically used in NMR studies,[6,7,13-17] on the other hand, dimers are found in concentrations comparable with those of monomers, especially at low temperatures.[18,19] In such solutions, both cis and trans isomers of dimers may be present.

The positions of the monomer—dimer equilibria are also strongly affected by the nature, but in particular by the position of substituents.[13,19] The dimer formation is most favored in the presence of substituents in the 2-position and particularly in the 2,6-positions. This indicates the role of steric hindrance of coplanarity. The compounds with diminished resonance interaction between the aromatic system and the NO group readily form dimers,[13,19] similar to aliphatic nitroso compounds. This type of interaction between two nitroso groups with limited conjugation with the aromatic ring is reflected even in the solid state.[13] In solid-state molecules with a strong interaction between the NO group and the aromatic system form green, relatively low melting crystals attributed to monomers. Compounds with bulky ortho substituents, on the other hand, form colorless crystals with higher melting points, assumed to consist of dimers. For 2,3,4,5,6-pentafluoronitrosobenzene crystallographic analysis indicated[20] the presence of areas consisting of monomeric species and areas where a cis dimer predominates.

In addition to the weak absorption band with a maximum at about 750 nm (which was exclusively used in the studies of dimerization), electronic absorption spectra of nitrosobenzenes show two absorption bands,[21-24] at about 280 and 306 nm, of comparable molar absorptivity. In a given solvent the ratio of molar absorptivities at these two wavelengths is independent of concentration of the nitroso compound in solutions containing 10^{-5} to 10^{-3} M nitrosoarene. This excludes the possibility that one of these bands could be attributed to a monomer and the other to a dimer. Changes in these two bands observed when a hydroxylic solvent was replaced by a nonpolar one do not follow a pattern expected for a nonhydrated and a covalently hydrated form. The ratio of absorbance at wavelengths corresponding to absorption maxima of these two bonds changes, nevertheless, with the polarity of the solvent. The molar absorptivity at both wavelengths is a linear function of Dimroth's solvent constant (E_T),[25] but whereas the band at 305 nm increases with increasing solvent polarity, that at 280 nm decreases.[26] The attribution of these two bands is currently being investigated. As absorbances at both wavelengths are a linear function of concentration of the nitroso compound, either of these bands can be used for analytical purposes or kinetic studies.

2. Reactions of Nitrosobenzenes with Nucleophiles

2.1. Oxygen Nucleophiles

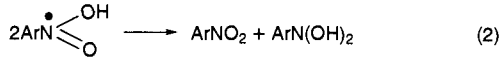
2.1.1. Water and Hydroxide Ions

The equilibrium shown in eq 1 is shifted strongly

$$ArNO + H_2O \rightleftharpoons ArN(OH)_2 \quad (1)$$

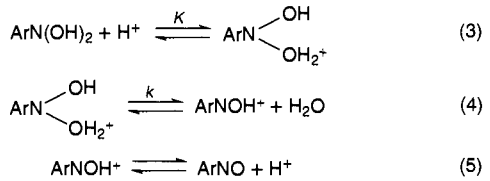
in favor of the parent compound. Attempts to follow

concentration of the hydrated form using ^{18}O exchange reaction between nitrosobenzene and $H_2{}^{18}O$ were unsuccessful.[27] In the electrochemical four-electron reduction of nitrobenzenes the hydrated form of nitrosobenzenes must occur as the primary product of a two-electron reduction. The formation of the hydrated form of nitrosobenzenes as unstable intermediates has been assumed in several electrochemical studies.[28-32] Since the acceptance of two electrons by the unhydrated nitrosobenzene occurs very rapidly at the potentials where nitrobenzene is reduced, the lifetime of the hydrated form is usually very short. Darchen and Moinet proposed that the hydrated form $ArN(OH)_2$ occurs as a relatively stable intermediate both in the reduction of mononitrobenzenes[29,30] and of *p*-dinitrobenzene.[31] The dehydration of the dihydroxyamino species is assumed to be acid and base catalyzed with the slowest rate of dehydration at pH about 2.5. It is estimated that for *p*-(dihydroxyamino)nitrosobenzene, the half-life at pH 2.5 and at −20 °C is about 20 s.[31] The experimental data presented by these authors do indicate a presence of an acid−base consecutive reaction in the course of reduction of the nitro group, but fail to offer convincing proof that this reaction is dehydration of the dihydroxyamino form. Nevertheless, when the reduction is carried out as a one-electron process using pulse radiolysis,[33] it is possible to prove the existence of the hydrate, on the basis of kinetic and spectroscopic evidence. In the reaction which occurs in acidic media the primary reduction product is a radical $ArNO_2H^{\bullet}$. This radical can undergo disproportionation (eq 2) in which a hydrate of the nitroso compound is formed:



$$2ArN(\bullet)(OH)(O) \longrightarrow ArNO_2 + ArN(OH)_2 \qquad (2)$$

The hydrate undergoes an acid-catalyzed dehydration (eqs 3−5):



$$ArN(OH)_2 + H^+ \overset{K}{\rightleftharpoons} ArN(OH)(OH_2^+) \qquad (3)$$

$$ArN(OH)(OH_2^+) \overset{k}{\rightleftharpoons} ArNOH^+ + H_2O \qquad (4)$$

$$ArNOH^+ \rightleftharpoons ArNO + H^+ \qquad (5)$$

In solutions containing varying concentrations of perchloric acid, 10^{-4} M nitrobenzene, and 10^{-1} M 2-propanol pulse radiolysis resulted in formation of hydrated electrons, H atoms and $OH^{\bullet}$ radicals. The latter two species abstract H from 2-propanol, and resulting 2-propanol radicals reduce the nitro compound. Kinetics was studied by following the absorbance of the formed unhydrated nitrosobenzene by measuring the absorbance in the 300-nm range.[34] Analysis of the absorbance−time curves enabled determination of the first-order rate constant k_b. Dependence on pH enabled separation of the rate constant of dehydration (k) that is practically irreversible and of the protonation constant (K). The protonation equilibrium constant (K) shows a dependence on substituents on the benzene ring in meta- and para-position, which can be expressed by constants σ, in accordance with the Hammett equation. The rate constant of dehydration (k) shows a small susceptibility to substituent effects.

Polarographic and voltammetric studies[35] indicated that nitrosobenzene reacts at pH > 11 with hydroxide ions in a reversible reaction (eq 6) yielding an adduct:

$$ArNO + OH^- \rightleftharpoons ArN(OH)O^- \qquad (6)$$

This reaction has an equilibrium constant $K = 1.58$ and is followed by a slower reaction. This consecutive reaction involves a second hydroxide ion, is irreversible, and leads in the absence of oxygen to the formation of azoxybenzenes and in its presence to generation of nitrobenzene. The decrease in concentration of nitrosobenzene with time has in both reactions the same value of rate constant and shows the same dependence on pH. This indicates that the formation of a common intermediate, such as $ArN(O^-)_2$, is in both cases the rate-determining step.

Similar reaction seems to be involved in alkaline solutions of 4-nitrosobenzaldehyde which yields, 4,4′-diformylazoxybenzene rather than the expected products of Cannizzaro reaction.[36]

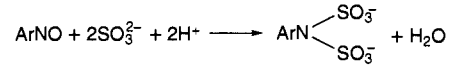
2.1.2. Alcohols and Alkoxide Ions

No evidence is available for a reaction of aromatic nitroso compounds with alcohols and the information on addition of alkoxide ions to nitroso group is rather limited. Existence of adducts of the type $ArN(OR)O^-$ was only deduced on the basis of identification of products of their further conversion, in particular azoxybenzenes[37,38] or their precursors, *N,N′*-dihydroxy-*N,N′*-diphenylhydrazines.[39,40] These consecutive reactions involve radical formation.[37,38,41]

2.2. Sulfur Nucleophiles

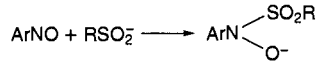
2.2.1. Sulfites and Sulfinates

Preparative studies[42,43] indicate formation of $ArN(SO_3^-)_2$ in the presence of excess SO_3^{2-} (eq 7).



$$ArNO + 2SO_3^{2-} + 2H^+ \longrightarrow ArN(SO_3^-)_2 + H_2O \qquad (7)$$

Sulfinates on the other hand react[44,45] in ratio 1:1 (eq 8):



$$ArNO + RSO_2^- \longrightarrow ArN(SO_2R)(O^-) \qquad (8)$$

The conjugate acid of the product is stable in acidic media and the reaction can be used for protection of C-nitroso group against reduction and condensation at pH 0−3. Deprotection can be achieved by making the solution alkaline. Addition of sulfite probably plays a role in the Piria reaction, involving reaction of sulfite with aromatic nitro compounds.[46]

The early kinetic investigation[47] of the reaction of nitrosobenzene with sulfite was carried out in 50% methanol−water mixtures containing acetate buffers pH 4.9−6.1. The decrease in concentration with time was followed colorimetrically, using relatively high (10^{-2} M) concentrations of both nitrosobenzenes and sulfite. It was assumed[47] that the initial reaction (which is first order in both nitrosobenzene and sulfite) is not an addition, but a one-electron transfer

resulting in a formation of a pair of radical anions (eq 9) and not a diradical proposed in ref 47.

$$ArNO + SO_3^{2-} \rightarrow Ar\dot{N}-O^- + SO_3^{\bullet-} \quad (9)$$

By the using measurement of absorbance at 300 nm[48] it was possible to follow concentration changes of nitrosobenzene in reaction mixtures 100−1000x more diluted than when colorimetry was used. The low concentrations used enabled studies of purely aqueous solutions. Furthermore, slower reaction rates in more dilute solutions enabled extension of the investigated pH range to 5.4−8.0. The measured second-order rate constant k' decreases with decreasing pH as corresponds to the equation $k' = kK_a/(K_a + [H^+])$ [where K_a is the second dissociation constant of sulfurous acid ($pK_a = 7.3$) and k is the intrinsic second-order rate constant]. Such dependence indicates that sulfite rather than bisulfite is the nucleophile participating in the reaction (eq 10):

$$HSO_3^- \underset{K_a}{\rightleftharpoons} SO_3^{2-} + H^+ \quad (10)$$

$$SO_3^{2-} + ArNO \xrightarrow{k} ArN(SO_3^-)O^- \quad (11)$$

The formation of the nucleophile SO_3^{2-} in equilibrium 10 is rapid, and reaction 11 is the rate-determining step. The reaction sequence (eqs 10 and 11) does not manifest general acid catalysis and is irreversible, as proved by the absence of regeneration of nitrosobenzene after acidification of the reaction mixture. Such irreversibility was observed for additions of other nucleophiles containing sulfur.[49] The irreversibility is attributed to a consecutive reaction of the adduct $ArN(O^-)SO_3^-$, probably involving isomerization to $Ar\bar{N}\ OSO_3^-$ that can be at pH 6−8 protonated to yield $ArNHSO_3^-$. Rate constants for the initial reaction of nitrosobenzene substituted by m-NO_2, p-Cl, and p-CH_3 with sulfite groups carried out in a 70% methanol−water mixture containing acetic acid and acetate in a ratio 3:2 at $\mu = 0.4$ followed Hammett equation $\log k_x = \varrho\sigma$ for $\varrho = 2.65$.[47] This indicates that reaction of sulfite with these substituted nitrosobenzenes follows the same mechanism. The deviating value of p-nitroso-N,N-dimethylaniline indicates that for this compound another reaction path is followed.

In more concentrated solutions,[47] the initial reaction is followed by slower consecutive processes which the German authors attributed to a transfer of the second electron yielding the adduct which they presented as follows (eq 12):

$$Ar\dot{N}-\bar{O}| \quad \bullet SO_3^{2-} \longrightarrow ArN(O^-)SO_3^- \quad (12)$$

but rather involves (eq 13)

$$Ar\dot{N}-O^- + SO_3^{\bullet-} \xrightarrow{k} ArN(SO_3^-)O^- \quad (13)$$

In view of the confirmed sequence (eqs 10 and 11), this attribution is incorrect and another, unidentified process is involved. The German authors[47] also assumed occurrence of a reaction of the adduct with a sulfite ion, but recent investigation[48] was unable to find any proof for participation of the second sulfite ion.

2.2.2. Thiols

As with other reactions in which thiols act as nucleophiles, in their interactions with nitrosoarenes the thiolates (RS^-) are considerably more active than the thiols (RSH). The interpretation of experimental evidence was complicated by the fact that thiolate was considered either as a nucleophile or as a reducing agent. Conclusions were sometimes made only on the basis of the identification of the species desired from nitrosobenzene rather than on identification of disulfides generated by oxidation of thiolates.

The first communications[50,51] dealing with interaction of aromatic C-nitroso compounds with thiols reported formation of an adduct in the reaction of 2-nitrosofluorene with glutathione. More recent studies investigated reactions of nitrosobenzenes with glutathione,[48,52−59] because of its biological importance, and with 1-thioglycerol,[48,60] chosen as a suitable model compound, which is well soluble in aqueous solutions, stable, non volatile, and does not contain additional acid−base centers.

The reaction between nitrosobenzene and thiols occurs in several steps: As in other nucleophilic additions involving bivalent sulfur, the nucleophile attacking the nitroso group is a thiolate anion. It is formed from a thiol in a rapidly established acid−base equilibrium (eq 14). The thiolate adds to nitrosobenzene in a rapid reaction (eq 15). The adduct $ArN(SR)O^-$ undergoes a slower rearrangement (eq 16), followed by a reaction with another thiol (eq 17); the reaction with the second thiol can also occur as a competitive reaction (eq 18).

$$RSH \rightleftharpoons RS^- + H^+ \quad (14)$$

$$RS^- + ArNO \overset{k_B}{\rightleftharpoons} ArN(SR)O^- \quad (15)$$

$$ArN(SR)O^- \xrightarrow{k_{16}} IM \quad (16)$$

$$IM + RS^- \xrightarrow{k_{17}} P \quad (17)$$

$$ArN(SR)O^- + RS^- \xrightarrow{K_{18}} P \quad (18)$$

When comparable and low initial concentrations of the thiol and nitrosobenzene are used, it was possible using polarographic analysis[48] to prove that neither in reaction 15 nor 17 is the thiolate oxidized to a disulfide, nor nitrosobenzene reduced to phenylhydroxylamine.

Kinetics of the first step, involving reactions 14 and 15, was studied using a stop-flow method.[52] No attempts were made to confirm the reaction rate equation, and only the initial rate (v_o) was measured. This rate corresponds to the forward reaction with constant k_B (eq 15), as under conditions used, the contributions of the reverse reaction may be neglected. When the reported values of v_o[52] for the reaction of nitrosobenzene with glutathione were

plotted as a function of pH,[48] v_o increased with increasing pH and the plot had a shape of a dissociation curve with an inflexion point at pH about 8.4. This is smaller than the pK_a of glutathione (9.2)[61] but comparable with the intrinsic value of pK_a of the thiol group, reported[62,63] to be 8.7.

The best insight so far into kinetics of the slower reactions (eqs 16 and 17) was achieved by following the decrease in concentration of nitrosobenzene using the absorbance at 308 nm and that in concentration of the thiol by measuring the decrease in the height of the anodic polarographic wave of this group.[48] When an excess either of the thiol or of the nitrosobenzene was used, the rate of reactions 16 and 17 becomes, over a considerable range of pH, too fast to be followed by conventional methods. Studies covering a wide range of pH values were therefore carried out at comparable concentrations of thiols and nitrosobenzenes, both of the order of 10^{-4} M.[48] Under such conditions for reaction of nitrosobenzene with glutathione and 1-mercaptoglycerol at pH smaller than about 5, the reaction follows second-order kinetics. At pH about 5 to 6.5, concentration changes of nitrosobenzene and thiol follow the kinetics of two consecutive second-order reactions. Finally in more alkaline solutions, at pH greater than about 7, third-order kinetics is observed—first in nitrosobenzene and second in the thiol used.

Such behavior indicates that the rate of both reactions (eqs 16 and 17) increases with increasing pH. The rate of the reaction with the second thiolate (eq 17) increases with increasing pH more than the rate of reaction 16. The rate of the second reaction (eq 17) also increases more with increasing initial concentrations of the thiol and nitrosobenzene than the rate of reaction 16, which involves consumption of the first thiolate.[48] Consequently, e.g. at pH 4.5 where at $[ArNO]_o = [RSH]_o = 10^{-4}$ M the reaction is first order in thiol, at $[ArNO]_o = [RSH]_o = 10^{-3}$ M the reaction is second order in the thiol.

The structure of the adduct ArN(SR)OH formed in reaction 15 has been elegantly confirmed when the reaction was carried out in a solvent of low polarity and high initial concentrations of both nitrosobenzene and the thiol were used at low temperature. The adduct absorbed in UV at 262 nm and its structure was confirmed using a low-temperature ^{13}C NMR and FAB mass spectra.[60] Alternatively, the structure of the adduct was confirmed in a glycerol matrix inside a FAB mass spectrometer.[59]

Initial attempts[51-57] to identify the intermediate and products were marred by the attempts to use GLC and HPLC for product identification as well as by the ignorance about the affect of the rate on pH and initial concentration on the course of reaction. Labile species formed can undergo changes during chromatography. Due to the relatively high initial concentration and usually higher pH (typically pH 7.4), isolated compounds were probably products P formed in reaction 17 with overall assumption of two thiol molecules per one nitrosobenzene rather than the intermediate IM formed in reaction 16. Hence the isolated compound with structure ArNHSOR with an absorption maximum at 230 nm attributed to a product of rearrangement of $ArN(SR)O^-$ (eq 16) is more probably a species formed after interaction with two thiol molecules. GLC-MS of such products[48] yielded mostly aniline derivatives, probably products of a cleavage of product P.

The rate of the initial reaction depends on the nature of substituents on the nitrosobenzene ring and on the structure of the thiol.[55] The rate of the reaction of substituted nitrosoarenes with glutathione at pH 7.4 increases with increasing electronegativity of the substituent in para- and meta-position to the nitroso group. This effect is quantitatively described by the Hammett equation $\log(k/k_o) = \varrho\sigma$ for $\varrho = 2.1$.

When the rate of the initial reaction of nitrosobenzene with various thiols was compared at pH 7.4, at 37 °C, in nitrogen atmosphere, the following sequence has been observed for the reactivity of thiols $HSCH_2Y$:

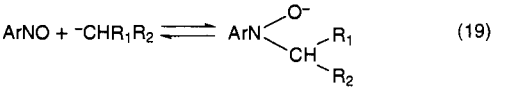
Y	CH_2OH	C_6H_5	GSH	$CHNH_2COOH$	CH_2NH_2
k L mol^{-1} s^{-1}	1300	1500	5000	12000	12000

A need for further investigation of processes following the initial addition step is thus strongly indicated. The importance of a better understanding of the processes involved is manifested by the confirmation of the occurrence of such reactions in biological systems,[53,64-66] in particular for reactions of nitrosobenzene with glutathione and thiol groups of hemoglobin and of nitrosochloramphenicol.[67,68] The rate of the addition of the thiolate to the nitroso group depends on the nature of the substituent in the nitrosobenzene ring in a similar way for the reactions of glutathione ($\varrho = 2.1$) as for the reactions of the thiol group of hemoglobin ($\varrho = 1.7$).[64]

Reaction of nitrosobenzene with thiophenol carried out in benzene involved predominantly reduction and subsequent reactions of the reduction products.[69] In partly aqueous solutions, reduction and substitution are competing reactions.[48]

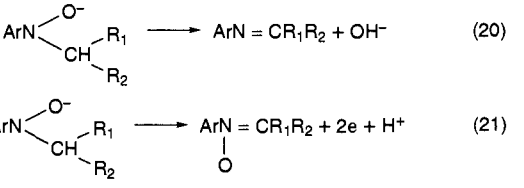
2.3. Carbon Nucleophiles

When nucleophilic addition to nitrosobenzenes involves carbanion derived from active methylene compounds (eq 19) the reaction is denoted Ehrlich–Sachs reaction:[70]



(19)

The adduct can be either dehydrated to an azomethine derivative (eq 20) or oxidized to a nitrone (eq 21), for example by an excess of nitroso compound:



Participation of nitrosobenzene in the formation of nitrone was confirmed by the presence of azoxybenzene among reaction products.[71] The carbanion can be generated electrochemically by reaction of the radical anion $ArNO^{\bullet-}$ with a C-acid such as fluorene

or indene. The rate constants of reaction 19 for the reaction of carbanion derived from fluorene [$(5.7 \pm 0.4) \times 10^3$ L mol^{-1} s^{-1}] and for that from indene [$(8.3 \pm 0.2) \times 10^3$ L mol^{-1} s^{-1}] were found.[71] The factors influencing the competition between the dehydration and nitrone formation include the structure of the methylene compound, the acidity of the methylene hydrogen, and reaction conditions. As the detailed mechanisms of these reactions are not well understood, it is not possible for a given C-acid to predict which of the two reaction paths will be preferred. As a broad generalization, based only on identification of reaction products, it is indicated that reactions of carbanion enolates derived form 1,3-dicarbonyl compounds and aryl aralkyl ketones yield predominantly azomethine derivatives,[72-78] but some exceptions are known.[78,79]

Limited information is available on systems where the methylene group is a part of a cyclic system, as for fluorene[71,80] or 3,3-diphenyl-1-hydrinone[81] where nitrone is formed, or for 4-chromanones[82] and 2,5-piperazinedione[83] where the reaction following the formation of an adduct have not been examined. 4,6-Diamino-5-nitroso-2-phenylpyrimidine reacts with phenylacetaldehyde or phenylacetone to yield a nitrone, which can be cyclized to yield pteridine derivatives.[84]

Compounds in which the acidity of the methylene group is increased by a presence of a cyano group, such as phenylacetonitrile,[85,86] cyanoacetamide,[87] and malonitrile[88] yield azomethine derivatives.

A nitrone can be formed in reactions analogous to eqs 19–21 even in compounds where the carbanion is formed from a methyl group, if its acidity is sufficiently increased as for 2,4-dinitrotoluene,[89] 2,4,6-trinitrotoluene,[90] 9-methylacridine,[91,92] or α-(hydroxyethyl)thiamine[93,94] or nitroalkanes[95] including nitromethane,[88] in the first step consecutive to the addition of the carbanion.

With respect to reaction conditions it has been shown[71] that in the reactions of nitrosobenzene with fluorene and indene the relative proportions of azomethines and nitrones depend on temperature used.

In related Kröhnke reaction, the carbanion is formed from compounds having one acidic hydrogen and a good leaving group, of the type R_2CHL. The leaving group (L) can be a halide,[96] a pyridinium ring,[97,98] a sulfonium group,[99-101] or a cyano group in diarylacetonitriles or arylaminoacetonitriles.[102-104] In all these cases a nitrone is the predominant product (eq 22):

$$R_2CHL + ArNO \xrightarrow[\text{Base}]{} R_2C{=}N(O){-}Ar + HL \qquad (22)$$

The reaction of nitrosobenzene with phosphorus ylides could give a nitrone in Kröhnke reaction (by elimination of the triarylphosphine), but gives an azomethine in a Wittig type of reaction[105] (eq 23):

$$Ar'_2\bar{C}{-}\overset{+}{P}Ar''_3 + ArNO \rightarrow ArN{=}CAr'_2 + Ar''_3PO \qquad (23)$$

Finally, cyanide ion is added to methyl *p*-nitrosobenzoate or nitrosobenzene, if both components are present in equimolar concentrations in an aprotic solvent like DMSO or DMF. The product, ArN(OH)-CN, can be converted into a stable species by methylation with methyl iodide, producing $ArN(OCH_3)$-CN.[106] In solutions containing methyl iodide and an excess of the nitroso compound, so that its molar concentration was double that of cyanide ions, consecutive reactions occur, yielding $ArN(CH_3)CN$, $ArNO_2$ and ArN(O)=NAr with $ArN(O^-)ON(CN)Ar$ as an assumed intermediate. In methanol, reaction of ArNO and CN^- produced ArN(O)=NAr and $ArNO_2$ as main products.[106] In 48% ethanol, formation of ArN=NAr was reported.[107]

Limited information is available on reactions of organometallic compounds with nitrosobenzene. For phenyllithium, reduction seems to predominant,[108] yielding diphenylamine and phenol. But for phenyl magnesium bromide, *N*,*O*-diphenylhydroxylamine is formed,[109-111] indicating nucleophilic addition (eq 24):

$$ArNO + PhMgBr \longrightarrow ArN(O^-)(Ph)MgBr^+ \qquad (24)$$

Formation of free radicals during the course of the reaction between nitrosobenzene and a Grignard reagent has been reported,[112] but as their yields are relatively small it remains an open question if they are a primary product of a one-electron process. The same alternative is to be considered for other reactions of nucleophiles assumed to occur by one-electron processes.[113]

All the above studies were carried out under preparative conditions and the only information available is identification of products. No data concerning position of the addition equilibria, the rates of their establishment, and the nature and the rates of consecutive reactions have been reported. The only exception is the kinetic study of the reaction of active methylene derivatives with nitrosobenzene.[114] In the presence of triethylamine as a base in nonaqueous solvents, the reaction was first order in nitrosobenzene and first in carbanion:

$$CH_2R^1R^2 + N(C_2H_5)_3 \underset{K_z}{\rightleftharpoons} (C_2H_5)_3NH^+ + {}^-CHR^1R^2 \qquad (25)$$

$$ArNO + {}^-CHR^1R^2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArN(O^-)CHR^1R^2 \qquad (26)$$

$$ArN(O^-)CHR^1R^2 \xrightarrow{k_3} ArN{=}CR^1R^2 + OH^- \qquad (27)$$

$$(C_2H_5)_3NH^+ + OH^- \rightleftharpoons (C_2H_5)_3N + H_2O \qquad (28)$$

Assuming that $k_3 \gg k_1 < k_{-1}$, the measured rate constant $k' = k_1K_zC_2/(K_E + 1)$ (where C_2 is the concentration of the amine catalyst used, K_z the equilibrium constant for the reaction of the catalyst base with the methylene compound, and $K_E = C_K/C_E$ where C_K is the concentration of the ketone, C_E of the enol form of the methylene compound used). Solvent polarity strongly affects the reaction rate. For example, a replacement of ethylene glycol as a solvent by *tert*-butyl alcohol results in a decrease of the measured rate constant by 3 orders of magnitude.[114]

The predominance of formation of azomethine derivatives in the Ehrlich–Sachs reaction seems to be mainly caused by the electronic effects of the

activating groups, which destabilize the adduct and favor rapid elimination of OH^- or H_2O. Stronger C-acids favor Ehrlich–Sachs reaction and production of azomethine derivatives, whereas weaker C-acids favor Kröhnke's synthesis yielding nitrones.

2.4. Nitrogen Nucleophiles

2.4.1. Reaction of Nitrosobenzenes with Alkyl- and Aralkylamines

Alkylamines and aralkylamines add to nitrosoarenes, when present in reaction mixture in an unprotonated form with a free electron pair on nitrogen (eqs 29 and 30):

$$R^1R^2CHNH_3^+ \rightleftharpoons R^1R^2CHNH_2 + H^+ \quad (29)$$

$$R^1R^2CHNH_2 + ArNO \rightleftharpoons ArN(OH)NHCHR^1R^2 \quad (30)$$

This reaction hence follows a pattern analogous to the addition of amines to carbonyl compounds. Also the possible stabilization in the second step (eq 31) can occur in a complete analogy with the formation of azomethine bonds, with elimination of water producing an arylazoalkane:

$$ArN(OH)NHCHR^1R^2 \rightleftharpoons ArN{=}NCHR^1R^2 + H_2O \quad (31)$$

But unlike the carbon–nitrogen bond in the corresponding carbonyl derivatives, the N–N bond in the adduct to nitroso group can also undergo cleavage (eq 32):

$$ArN(OH)NHCHR^1R^2 \longrightarrow ArN(OH)H + HN{=}CR^1R^2 \quad (32)$$

The resulting arylhydroxylamine can react with nitroso compound and yield diarlyazoxy derivatives (eq 33):

$$ArNHOH + ARNO \rightarrow ARN(O){=}NAr + H_2O \quad (33)$$

Kinetic details of individual steps are not known, and the preferred reaction paths are deduced on the basis of yields. The main factor seems to be the structure of the amine. Straight-chain alkyl amines favor dehydration of the adduct (eq 31) and yield arylazoalkanes,[115] whereas isopropylamine,[115] *tert*-butylamine,[115] and benzylamines[115–117] do not form any azo compounds. Formation of azoxybenzenes following eqs 32 and 33 was observed for isopropylamine and benzylamine but not for *tert*-butylamine.[115–117] Aldimine $HN{=}CR'R^2$ formed in eq 31 was also isolated.[118] Any azobenzene found[119,120] is attributed to a reduction of azoxybenzene probably by the arylhydroxylamine present. Formation of azoxybenzene was reported[121] also for reactions of nitrosobenzene with seconary amines. For the reaction of diphenylmethylamine with nitrosobenzene[118] the time dependence of yields indicates that azoxybenzene and ketimine (A) are intermediates in a sequence (eqs 34–36) in which ketimine (B) is the final product:

$$ArNO + (C_6H_5)_2CHNH_2 \rightleftharpoons ArN(OH)NHCH(C_6H_5)_2 \quad (34)$$

$$ArN(OH)NHCH(C_6H_5)_2 \rightleftharpoons ArNHOH + HN{=}C(C_6H_5)_2 \quad (35)$$

$$ArNHOH + ArNO \longrightarrow ArN(O){=}NAr + H_2O \quad (36)$$

$$\underset{A}{HN{=}C(C_6H_5)_2} + H_2NCH(C_6H_5)_2 \longrightarrow \underset{B}{(C_6H_5)_2CH{-}N{=}C(C_6H_5)_2} + NH_3 \quad (37)$$

2.4.2. Reaction of Nitrosobenzenes with Arylamines

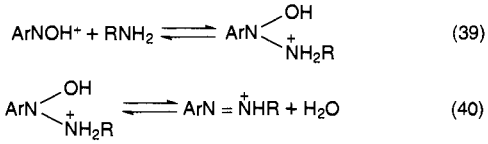
The condensation of aromatic nitroso compounds with arylamines can proceed either in acidic[122–127] or in basic[128,129] media.

The condensation at pH smaller than about 9 follows second-order kinetics, first order each in nitrosobenzene and in aniline.[130–137] The reaction is general acid catalyzed[131,135–137] and involves reaction with water and hydronium ions. Brønsted plots of logarithms of catalytic constants as a function of pK_a of the carboxylic acid components of the buffer used are linear and their slopes correspond to Brønsted coefficient α varying from 0.39 to 0.34 for reactions of anilines with substituted nitrosobenzenes and from 0.34 to 0.28 for reactions of nitrosobenzenes with para-substituted anilines.[136] Values of the Brønsted coefficient α for the general catalysis of reactions of *p*-chloroaniline, aniline, and *p*-methylaniline with nitrosobenzene are linearly related to the values of pK_a for the conjugate acids of the nucleophilic reagents.[137] Introduction of a substituent on the aromatic amine, as manifested in reactions of nitrosobenzene with substituted anilines,[131–135] results in an increase in reactivity with increasing basicity of the amine. Quantitatively, the substituent effects on aniline can be expressed by the Hammett[131,132] or the Yukawa–Tsuno[134,135] equation with a reaction constant $\varrho = -2.14$. Substituents on nitrosobenzene have an opposite effect and the condensation is aided by the presence of electron-withdrawing groups,[130–131] and the Hammett reaction constant ϱ has the value +1.22. Hammett reaction constants ϱ^- for the general acid catalyzed attack of aniline on substituted nitrosobenzenes increase linearly with increasing pK_a of the catalyst.[137]

The most striking aspect of the kinetics of azobenzene formation is its similarity to the kinetics of addition of weakly basic amines to benzaldehydes. As in the latter case, the reaction of nitrosobenzenes can be considered to occur in the following step:

$$ArNO + H^+ \rightleftharpoons ArNOH^+ \quad (38)$$

Alternatively, the proton transfer may not be complete and the activation of the nitrosobenzene molecule toward a nucleophilic attack can be achieved by formation of a complex involving formation of a hydrogen bond between a molecule of the catalytically active acid and the oxygen of the nitroso group. The activated species (here denoted as $ArNOH^+$) is then exposed to an attack by the amine:



(39)

(40)

The following similarities between addition of anilines to benzaldehydes and nitrosobenzenes can be pointed out:

(1) The similarity of the dependences of rate constants on pH for reactions of benzaldehydes and nitrosobenzenes indicates that in the latter the formation of the adduct is in most cases the rate-determining step, at least in mildly acidic solutions.

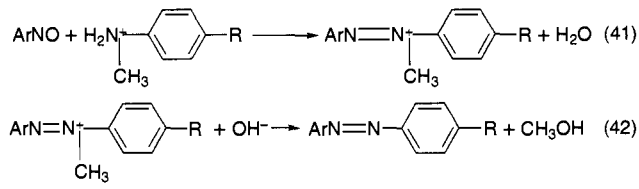
(2) The formation of the adduct as the rate-determining step is in agreement with the above-described substituent effects and the existence of general acid catalysis. The better fit of the logarithm of the rate constant to substituent constant $\sigma^-_{p\text{-}NO_2}$ than $\sigma_{p\text{-}NO_2}$ indicates that the transition state is stabilized more by substituents capable of accepting electrons by resonance than the ground state. The break on the log k vs pH plot for p-nitronitrosobenzene formation may indicate a change in the rate-determining step from attack of the amine on nitrosobenzene to dehydration of the adduct at higher pH values. Nevertheless, the role of the addition of hydroxide ions to the nitroso group of p-nitronitrosobenzene at pH > 9 cannot be excluded (cf. ref 35).

(3) The reactions of benzaldehydes and nitrosobenzenes with weakly basic amines show similarity in the nature of the acid catalysis. This is a true general acid catalysis, in which substrate protonation and covalent bond formation may principally occur as concerted. The ratios of rate constants for the reactions with water and with protons are for both reactions similar, and so are the values of Brønsted coefficients α, which in both cases do not vary significantly with the reactivity of the substrate.

(4) For amine attack on both C=O and N=O, the reactions become more susceptible to the effects of polar substitutents with decreasing strength of the catalyzing acid, in accord with the Hammond postulate.

Reaction between nitrosobenzene and aniline has also been studied in a mixture containing 80% pyridine and 20% water, containing 0.1 M $N(CH_3)_4OH$.[138] The course of this reaction was followed spectrophotometrically, after extraction of individual samples with toluene. Since the behavior of solutions containing in a similar alkaline solution only nitrosobenzene has not been reported for comparison and the role of extraction on possibly established equilibria has not been investigated, the physical meaning of the reported values of rate constants is questionable. In anhydrous pyridine azobenzenes are formed by condensation of nitrosobenzenes and anilines in solutions saturated with KOH.[118] For such reactions rate-determining dehydration of the tetrahedral adduct is assumed.[136,139]

The product of the reaction of N-methylaniline with nitrosobenzene in acidic media is azobenzene. This indicates[140] hydrolysis of the quaternary azo compound (eq 41) formed in the first step (eq 42):



(41)

(42)

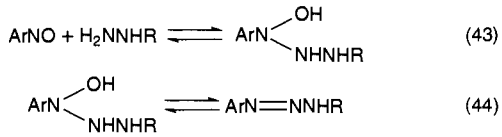
In reactions of anilines with p-nitrosobenzaldehyde, condensation with aldehydic group occurs in addition to condensation to the nitroso group.[141]

The reaction of p-nitrosobenzoic acid with a mixture of aniline derivatives can be used for determining of traces of m-aminophenol in the presence of excess of p-aminosalicyclic acid.[142]

2.4.3. Reactions of Nitrosobenzenes with Hydrazines

No information is available concerning kinetics of reactions between nitrosobenzene with hydrazine and its derivatives. As reported studies were restricted to product identification with occasional information on yields and as complex reactions are involved as manifested by a variety of reported products with composition dependent on the structure of the hydrazine derivative, only a brief summary of data can be presented here.

A simple addition of hydrazine to nitrosobenzene would yield an adduct (eq 43); that could subsequently yield a triazine on dehydration (eq 44):



(43)

(44)

But formation of triazenes either with hydrazines or with arylhydrazines was not observed. Only when nitrosobenzene was reacted with benzhydrazide (R = COC_6H_5), the corresponding 1-phenyl-3-benzoyltriazene ($ArN{=}NNHCOC_6H_5$) was prepared.[143]

Reaction of nitrosobenzene with hydrazine yields aniline, nitrogen, and some azobenzene[144] and diarylamine.[145,146] Phenylhydrazine in the presence of large excess of nitrosobenzene yields azobenzene,[147] and excess of phenylhydrazine leads in addition to azobenzene also to benzene and nitrogen gas.[148,149] Reaction of nitrosobenzene with phenylhydrazine in methanolic solutions produced azoxybenzene, azobenzene, diarylamine, and benzene. Formation of azoxybenzene indicates the presence of phenylhydroxylamine as intermediate, with azobenzene being a product of consecutive reactions of azoxybenzene. Formation of benzene is attributed to a generation of phenyldiazine ($ArN{=}NH$), yielding nitrogen and phenyl radical:

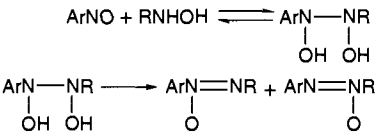
$$ARN{=}NH \rightarrow AR^{\bullet} + N_2 \qquad (45)$$

Of the two aryl groups in diarylamine formed, one originates from $ArNHNH_2$, the other from ArNO.[146] Benzenesulfonyl hydrazide in the presence of a base yields azoxybenzene.[150]

2.4.4. Reactions of Nitrosobenzenes with Hydroxylamines

It would be possible to assume that addition of arylhydroxylamines to nitrosobenzene might follow

a simple pattern (eqs 46 and 47):



(46)

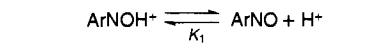
(47)

but reaction mixtures often contain also ArN(O)=NAr, RN(O)=NR, and even ArN=NAr and similar products.[151-153] A similar mixture of products was observed when starting materials were tagged by ^{15}N,[154] ^{18}O,[155] or by a deuterated benzene ring.[156]

To interpret these observations it would be necessary to understand in detail the operating reaction mechanisms of what is evidently a complex system. One of the reasons preventing better understanding of processes involved is the fact that some of the initial kinetic studies were carried out in unbuffered solutions in organic or mixed solvents[157-159] or in alkaline solutions.[160-164] In alkaline solutions the situation is complicated by the reactivity of both components of the reaction mixture. In alkaline solutions both in the absence of oxygen, one containing nitrosobenzene, and the other containing arylhydroxylamine, azoxybenzene is spontaneously generated. This reaction then competes with formation of azoxybenzene by condensation. Moreover, it has been shown[35] that at pH greater than about 10 the predominating species in solutions of nitrosobenzene is ArN(OH)O$^-$. Furthermore, it is this adduct, rather than the parent ArNO, which is a precursor of azoxybenzene and the rate-determining step is preceded by another acid–base process, possibly involving formation of ArN(O$^-$)$_2$.

The reaction is first order in nitrosobenzene and first in arylhydroxylamine,[157,159] and the pH dependence of rate constants was first interpreted[165] as due to a specific acid and specific base catalysis in ethanolic buffers. The role of general catalysis was first recognized in an acetate buffer[166] and later extended to other buffers.[167] The reaction exhibits general acid catalysis with Brønsted coefficient $\alpha = 0.29$, general base catalysis with $\beta = 0.15$, and specific base catalysis by hydroxide ions.

The specific acid catalysis can be described by the sequence of reactions 48–51:



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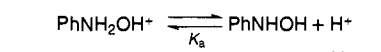

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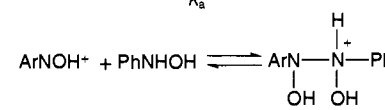

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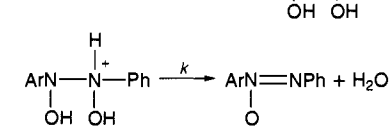


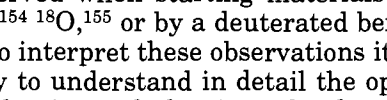
(51)

If equilibrium (eq 48) is rapidly established, then for the reaction rate followed by concentration change of the azoxy product with time the observed pseudo-first-order rate constant k_{obs} can be expressed as

$$k_{obs} = k\frac{S_{ArNO}K_a}{(K_a + [H^+])}\frac{[H^+]}{(K_1 + [H^+])} \qquad (52)$$

For $K_1 \gg [H^+] \gg K_a$ this expression simplifies to $k_{obs} = k_H S_{ArNO} K_a$ (where S_{ArNO} is the analytical concentration of the nitrosobenzene present in excess and $k_H = k/K_1$). Hence in an acidity range where log a_H is smaller than pK_1 but larger than pK_a, the rate constant k_{obs} will be independent of acidity, as observed.

For the specific base catalysis by hydroxide ions the authors[167] propose sequence shown in eqs 53–55:



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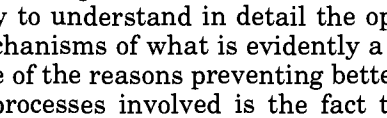

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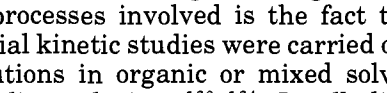
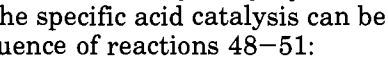


(55)

Formation of azoxybenzene in alkaline solutions, prepared only from nitrosobenzene, in which the adduct ArN(OH)O$^-$ predominates, involves an interaction with a second hydroxide ion. The reaction is complex, as indicated by the fact that the decrease in concentration of nitrosobenzene with time does not follow simple kinetics, first order in ArNO.[35,161] The formation of azoxybenzene in the absence of air oxygen and the formation of a nitro compound observed in the same solution containing dissolved oxygen have the same value of rate constant and show the same dependence of observed rate constant on pH.[35] This indicates that both reactions share the same intermediate and that the formation of this intermediate is the rate-determining step. It is presumed that the dianion ArN(O$^-$)$_2$ might be the intermediate yielding both azoxybenzene (in absence of oxygen) and nitrobenzene (in its presence).

An alternative mechanism for the formation of azoxybenzene from nitrosobenzene and phenylhydroxylamine involves one-electron processes, yielding radicals or radical anions. On the basis of ESR studies indicating presence of radicals, the following scheme was proposed (eqs 56–59):[163,164]



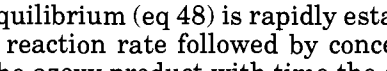
(56)

(57)

(58)

(59)

Alternatively[165] the one-electron processes are assumed to yield *N'*-hydroxy *N*-oxide that can undergo dehydration (eqs 60–62):



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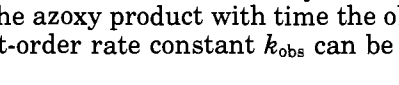
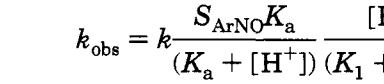


(61)



(62)

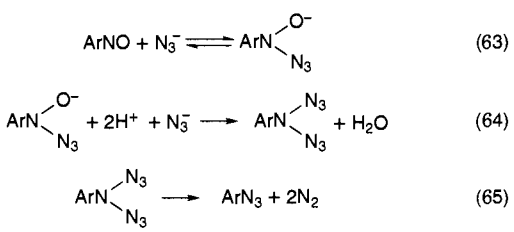
There are two problems with these interpretations: First, even when the presence of radical anions or radicals has been proved by ESR, the concentration of these species has not been determined. Thus it is difficult to distinguish whether comparable concentrations of radicals and ionic species, or only traces of the former are present in reaction mixtures. Second, the presence of the radicals has been demonstrated either only in alkaline solutions containing nitrosobenzene and arylhydroxylamine[162,164] or in the presence of one-electron reducing agents, such as Fe^{2+} or Ti^{3+}.[162,168] In alkaline solutions the form ArNO assumed to participate in reactions 57 or 61 does not predominate in the reaction mixture. Since the addition of hydroxide ions (eq 6) is a rapidly established equilibrium, ArNO can, nevertheless, be the reducible form. It is indicated that radicals can be generated by reactions subsequent to tne formation of $ArN(OH)O^-$ or $ArN(O^-)_2$.

For o-nitrosobenzaldehyde the formation of a stable intermediate of the type ArN(OH)N(OH)Ar was assumed.[169,170] More recently,[171] it has been shown that the product formed results in a condensation of the hydroxyamino groups of one molecule with aldehydic group of the other molecule, resulting in an intermediate of the type ArN(OH)CH(OH)Ar, which can undergo cyclization.

For the reaction of nitrosobenzene with *N*-benzyl-*N*-phenylhydroxylamine[172] in carbon tetrachloride, benzene, THF, DMF, and ethanol as solvent the nucleophilic addition mechanism was excluded. For this mechanism large solvent effects would be expected, whereas only small solvent effects were obtained experimentally. A mechanism in which a pair of nitroxyl radicals is formed in a cyclic process is proposed.

2.4.5. Reactions of Nitrosobenzenes with Other Nitrogen-Containing Nucleophiles

The reaction of nitrosobenzene with azide ion (N_3^-) yields an aryl azide and N_2.[173-175] One possible sequence is eqs 63–65:



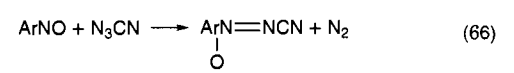
$$ArNO + N_3^- \rightleftharpoons ArN(O^-)N_3 \quad (63)$$

$$ArN(O^-)N_3 + 2H^+ + N_3^- \longrightarrow ArN(N_3)N_3 + H_2O \quad (64)$$

$$ArN(N_3)N_3 \longrightarrow ArN_3 + 2N_2 \quad (65)$$

If the original HN_3 contained N^{15} in the two end atoms of the N_3 group, the resulting ArN_3 has two terminal nitrogen atoms tagged with N^{15} and the first nitrogen adjacent to the ring is N^{14}.[175] The principal route of the reaction passes through a cyclic pentazene. The main route is facilitated by the electrophilicity of the substituent on benzene and accounts for 92% for *p*-NO_2 and 53% *p*-$(CH_3)_2N$ substituted nitrosobenzene.

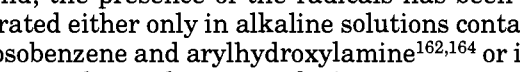
Cyanoazide (N_3CN) adds to nitrosobenzene[176] (eq 66):



$$ArNO + N_3CN \longrightarrow ArN(O)NCN + N_2 \quad (66)$$

With *N,N*-dichloroamines, C-nitrosoarenes yield alkylazoxy arenes.[177] As the reaction is carried out in methanolic solutions of potassium hydroxide, a formation of an intermediate[35] of the type $ArN(OR)O^-$ cannot be excluded.

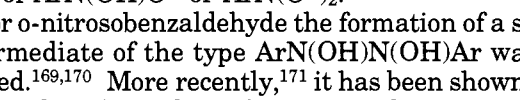
Reaction of aryl azides (ArN_3) with nitrosoarenes (RNO) yields azoxybenzenes:[178,179]



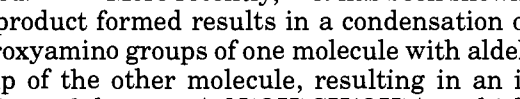
$$RNO + ArN_3 \longrightarrow RN(O)NAr + N_2 \quad (67)$$

Nitrogen monoxide reacts with nitrosobenzene in ammoniacal ether to yield $ArN(NO)ONH_4$.[180] Bromide ions in solutions of HBr in carbon tetrachloride add to nitrosobenzene.[181]

Nucleophilic addition of phenylhydrazones to nitrosobenzenes yields nitrones in benzene as a solvent:[182]



$$Ar_1CH{=}NNHAr_2 + Ar_3NO \longrightarrow Ar_1CH(O{-}N{-}Ar_3){-}N{=}\dot{N}HAr_2 \quad (68)$$



$$Ar_1CH(O{-}N{-}Ar_3){-}N{=}\dot{N}HAr_2 \longrightarrow Ar_1CH{=}N(O)Ar_3 + N_2 + Ar_2 \quad (69)$$

The reaction is first order in hydrazone and first in nitrosobenzene[183] and the effects of substituents on all three rings Ar_1, Ar_2, and Ar_3 (eqs 68 and 69) on reaction rate constants follow Hammett equation $\log k/k_o = \varrho\sigma$. The reaction is facilitated by electron-donating substituents in the meta- or para-position on either ring Ar_1 ($\varrho = -0.3$) or ring Ar_2 ($\varrho = -2.2$) of the benzaldehyde phenylhydrazone and by electron-withdrawing substituents on ring Ar_3 of nitrosobenzene ($\varrho = 3.0$). These effects are in agreement with a mechanism involving in the first step formation of an adduct (eq 68) resulting from an attack of the nitroso group nitrogen on the carbon of the azomethine bond.

3. Reduction of Nitrosobenzenes

Reduction of nitrosobenzenes can occur electrochemically, by hydrated electrons, or by chemical reducing agents. Some reducing agents can potentially act as single-electron donors. To distinguish between reduction and nucleophilic addition (which also can occur competitively) the fate of the reducing agent must be understood. In numerous examples of studied reactions, analytical methods for the determination of the oxidized form of the reagent were either not available or not used.

3.1. Electrochemical Reduction of Nitrosobenzenes

Electrochemical reduction of nitrosobenzenes involves in the first step a two-electron or a one-electron transfer, depending on whether the reduction is carried out in protic or aprotic solvents.

3.1.1. Reduction in Aqueous and Water-Containing Solvents

In buffered aqueous solutions, nitrosobenzenes undergo a two-electron reduction to arylhydroxylamines.[184,185] The establishment of the equilibrium

between nitroso and hydroxyamino forms is rapid, and the system satisfies all the criteria for a reversible system. This has been verified experimentally with the DME[186-190] at pH 4.0–10.0 and with a graphite electrode[191] at pH 1.6–12.5. As the system is reversible, oxidation–reduction potentials can be determined also potentiometrically.[192-194] Another consequence of the reversibility of the system is that only the overall scheme (eq 70) can be presented

$$ArNO + 2e^- + 2H^+ \rightleftharpoons ArNHOH \qquad (70)$$

The observed shifts of about 0.06 V/pH do not allow one in such cases to distinguish whether the proton transfer occurs before, between, or after electron transfers.

In acidic media the two-electron step is followed at more negative potentials by another irreversible two-electron process corresponding to the reduction of protonated form of arylhydroxyamine to amine:

$$ArNH_2OH^+ + 2e + H^+ \rightarrow ArNH_2 + H_2O \qquad (71)$$

As long as the protonation (eq 72) at the electrode surface remains fast, the height of the two-electron wave at negative potentials remains unchanged:

$$ArNHOH + H^+ \rightleftharpoons ArNH_2OH^+ \qquad (72)$$

With increasing pH, usually at pH greater than about 4.0, the rate of protonation following reaction 71 decreases due to a decrease in a_{H^+}. In this pH range the limiting current of the more negative wave is governed by the rate of protonation and decreases gradually with increasing pH. The slope of the plot of current as a function of pH does not allow one to exclude the possibility that transfers of more than one proton are involved. The large slope of the $E_{1/2} = f(pH)$ plot, often more than 0.1 V/pH, also indicates participation of several proton transfers.

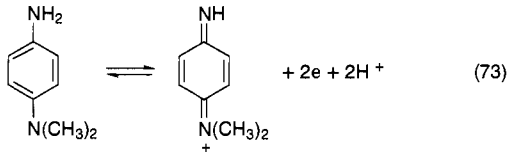
The influence of substituents in meta- or para-position in nitrosobenzene on half-wave potentials can be expressed by Hammett equation. Values for *p*-nitrosophenols and *p*-nitrosoanilines are excluded from this correlation, because their reduction follows another mechanism (see below). Furthermore, the effects of electronegative substituents in the para-position, which can be involved in resonance interaction with the nitroso group, are characterized by substituent constants $\sigma^-_{p\text{-}X}$. The reaction constant ϱ_{NO} characterizing the susceptibility of the nitroso group to substituent effects is small (ϱ = 0.06 V), in agreement with the relatively positive reduction potential of unsubstituted nitrosobenzene.[195] The wavelengths of the weak absorption maxima at 700–750 nm, corresponding to an n → π^* transition, are a linear function of Hammett substituent constants $\sigma^-_{p\text{-}X}$. Consequently, the half-wave potentials are a linear function of the frequency of absorption maxima.[196]

A similar pattern of reduction, involving a single two-electron step accompanied in acidic media by a consecutive reduction of the protonated hydroxyamino group (at more negative potentials) has been observed for all meta-substituted nitrosobenzenes and most of the ortho- and para-substituted ones. Notable exceptions are o- and *p*-hydroxy- and -amino-nitrosobenzenes,[196-204] for which the arylhydroxylamine, formed in the first two-electron uptake, undergoes dehydration. The quinonimines or quinonediimines resulting in this reaction are more easily reducible than the parent nitroso compound. Hence at the potential where the nitroso group undergoes reduction into hydroxyamino group, a further two-electron reduction takes place. In this process quinonimines derived from o- and *p*-nitrosophenols yield o- and *p*-aminophenols and quinonediimines derived from o- and *p*-nitroanilines yield o- and *p*-phenylenediamines. The rate of dehydration is acid and base catalyzed. In the medium pH range where the rate of dehydration is relatively slow, the reduction in the first step occurs with the uptake of two electrons. At pH below about 6 at a more negative potential a reduction wave of the unconverted protonated form of the arylhydroxyamine occurs. With decreasing pH the rate of dehydration increases and governs the height of the first wave, which increases with decreasing pH and the plot of the limiting current as a function of pH has the shape of a dissociation curve. At sufficiently low pH values the rate of dehydration is sufficiently fast to convert all of the hydroxyamino derivative into the quinonoid species. Hence at a low pH value (e.g. pH 2.0) the limiting current reaches a maximum value which corresponds to an overall transfer of four electrons. Similarly the base-catalyzed dehydration results in a gradual increase in the limiting current with increasing pH in the alkaline region. At a sufficiently high pH the rate of the base-catalyzed dehydration of o- and *p*-hydroxy or o- and *p*-(aminophenyl)-hydroxylamines is fast enough to convert all of the hydroxyamino derivative into a quinone-like species, which is immediately reduced. So above a sufficiently high pH, the current of the single wave observed also corresponds to a four-electron process. An analogous behavior was observed also for 4-nitrosodiphenylamine[205] and 5-nitroso-6-aminouracils.[205] For nitroso naphthols[198] and *p*-nitrosodialkylanilines[200,204] presence of a single four-electron wave was reported over the entire pH range, indicating fast dehydration even in the medium pH range. On the other hand, for 2,4-dinitrosoresorcinol presence of two two-electron waves has been reported[206] for pH 2.0–12.0.

The basic reduction pattern, involving reduction of nitrosobenzene to phenylhydroxylamine, which in acidic media can be further reduced to amine, has been observed also in buffered solutions containing between 10% and 70% ethanol, acetone, or dioxane.[207] The simplest information about the reduction process can be obtained when DME is used, as under conditions used in polarography the surface renewal prevents accumulation of electrolysis products at the electrode surface and their participation in homogenous chemical reactions. More complex processes occur when the electrolysis of nitrosobenzenes is carried out using electrodes with a larger surface area with limited surface regeneration.

Cyclic voltammetry with HMDE[208] and stationary pyrolytic graphite electrode[191] confirmed the reversibility of the couple nitrosobenzene–phenylhydroxylamine, but at pH > 10 a much more negative

wave of azoxybenzene was observed. Azoxybenzene was probably formed by a homogeneous reaction[35] rather than by reaction of electrolysis products. Cyclic voltammetry of *N,N*-dimethyl-*p*-nitrosoaniline with a carbon paste electrode[201] allowed observation of the reversible process (eq 73):



$$+ 2e + 2H^+ \qquad (73)$$

p-(Dimethylamino)aniline was formed in the forward sweep by the reduction of *N,N*-dimethyl-*p*-nitrosoaniline, so that its oxidation peak was observed on the reverse sweep at potentials more positive than that of the $ArNO + 2e + 2H^+ \rightleftharpoons ArNHOH + H_2O$ couple. On the second sweep from positive to negative potential the reduction peak of the quinonediimine cation was observed.

When controlled potential electrolysis was carried out with mercury pool electrodes at pH 7.0, the decrease in concentration of nitrosobenzene with time followed strictly first-order kinetics,[209] but the increase in concentration of the arylhydroxylamine with time was smaller than would correspond to the decrease in nitrosobenzene. Formation of reduction waves of azoxybenzene and azobenzene in the course of electrolysis indicates the occurrence of parallel or consecutive reactions of phenylhydroxylamines or nitrosobenzenes or both. This type of processes seems to play largest role in acidic media. Mercury can also participate in a chemical reduction of nitrosobenzene, if an anion is present which shifts the potential of mercury dissolution to sufficiently negative potentials.[210] In a short circuited system in the presence of 0.5 M chloride ions in 0.5 M H_2SO_4 and 50% ethanol, 10^{-2} M solution of nitrosobenzene yields azoxybenzene.

An attempt was made to study the condensation of nitrosobenzene with electrochemically generated phenylhydroxylamine using thin-layer linear sweep voltammetry[161] and chronopotentiometry.[211] These studies were, nevertheless, carried out at pH > 11 where the adduct $ArN(OH)O^-$ predominates and where azoxybenzene can also be formed in a reaction involving only nitrosobenzene as the starting material.[35]

3.1.2. Reduction in Organic Solvents

The reduction in nonaqueous solutions follows patterns analogous to those observed for the majority of reducible organic compounds: The first step involves a transfer of one electron and formation of a radical anion. This step is usually much simpler than the first step of reductions in protic media. On the other hand, the subsequent processes are usually not only more complex in nonaqueous systems, but also more difficult to study. The complexity of these consecutive processes is partly due to the high reactivity of radical anions formed in one-electron uptake, resulting in various dimerization and disproportionation processes and acid–base reactions, including those involving parent compounds, solvent molecules as well as components of supporting electrolytes. Alternative complications result from ion-pair formation and similar reactions with components of the supporting electrolyte used, the role of which is so far only partly understood. The methodology of the study of these processes is limited by the difficulty to control the acidity in the vicinity of the electrode surface.

Polarographic reduction of nitrosobenzene in DMF containing 0.2 M $NaNO_3$ was reported[212] to occur irreversibly, which was attributed to the instability of the radical anion formed. The half-wave potentials in DMF containing 0.2 M $NaNO_3$ did not differ substantially from those in ethanol containing 0.2 M $LiClO_4$,[213] but depend on the nature and concentration of the cation of the supporting electrolyte used,[214] indicating formation of ion pairs: $R^{\bullet -} + pM^+ \rightleftharpoons (R^{\bullet -}pM^+)$. NH_4^+ ion acts in DMF as a proton donor and in its presence, a two-electron reversible reduction of nitrosobenzene to arylhydroxylamine is observed.[215] In the presence of Mg^{2+} ions, the reduction also occurs in a single two-electron step, the shape of which indicates occurrence of an irreversible process. In methanolic solutions, reduction of *p*-nitrosodimethylaniline, containing lithium chloride, is affected by addition of proton donors: A prewave at more positive potentials forms, shifts to more positive potentials, and increases in height with increasing concentration of the added proton donor.[216]

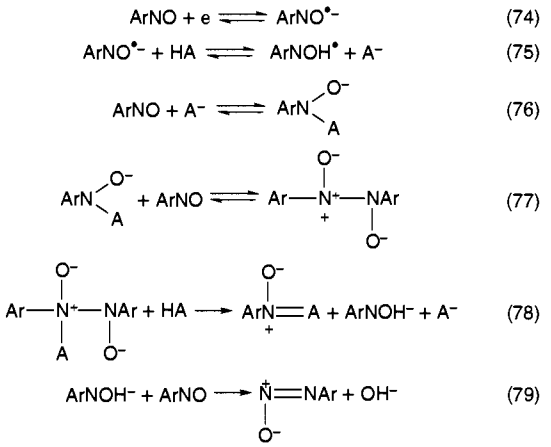
Cyclic voltammetry in DMF containing 0.2 M $NaNO_3$ at a HMDE indicated irreversibility of the process at lower scanning rates,[212,217,218] but in the presence of $N(C_2H_5)_4ClO_4$ and $NaClO_4$, a reversible system was observed.[215] In tetrahydrofuran containing 0.15 M Bu_4NPF_6 the one-electron process is also reversible.[71] The rate of the first electron transfer has been found[219] to depend on the nature and position of substituents on the nitrosobenzene ring. When an appropriate potential was found using cyclic voltammetry on a rotating disk electrode, the radical anions were generated by a controlled potential electrolysis and identified by ESR.[220]

A one-electron reduction of nitrosobenzenes has also been reported in 50%acetic acid containing 0.2 M CH_3COONa, at a potential of more than 0.5 V more positive than in DMF or ethanol.[213]

Among consecutive and/or competitive processes of the reduction of nitrosobenzene, the most important seems to be formation of azoxybenzene.[71,212,215,217,218,220] Initially[212,213,217,218] its formation was considered to occur as a consecutive reaction, resulting in dimerization of two radical anions. Nevertheless, controlled potential experiments[221] indicated that the decrease in concentration of nitrosobenzene with time in the course of electrolysis is much faster than would correspond to a one-electron process. This was observed both in DMF and acetonitrile, both with platinum and mercury electrodes. This indicates that nitrosobenzene is consumed in a chemical reaction with an electrolysis product. The rate of this reaction increased with increasing concentration of nitrosobenzene. The rate of the decrease in nitrosobenzene concentration was, at the same initial concentration of the nitroso compound, faster in acetonitrile than in DMF. But the most revealing

experiment was a comparison of the amount of azoxybenzene after electrolysis with yields of the same compound in a homogenous reaction in the absence of electrolysis which occurred when tetraethylammonium hydroxide was added[221] to the solution containing the same initial concentration of nitrosobenzene. When initial concentrations of nitrosobenzene and hydroxide ions were equal in DMF or in ratio of 1:0.3 in acetonitrile, comparable yields of azoxybenzene were obtained as when electrolysis (in the absence of hydroxide) was carried out. This indicates that in the course of electrolysis, nitrosobenzene reacts with a base such as OH^- ions, generated by electroreduction in the unbuffered system, probably forming in the first step an adduct of the type $ArN(OH)O^-$, consuming further hydroxide ions in subsequent steps, and regenerating some OH^- ions.[35]

An alternative interpretation[71] involves a chain reaction of the type:



The species generated in the reduction of nitrosobenzenes in aprotic media can be utilized in preparative procedures as reagents. Thus electrogenerated nitrosobenzene ions can react with alkyl halides to yield *N,O*-dialkylphenylhydroxylamines,[222] whereas radical anions of nitrosobenzene underwent competitive reactions. Attempts to use nitrosocyclohexane to generate reactive reagents in a similar way were unsuccessful, as the nitroso compound was converted by base into an oxime.

When nitrosobenzene is reduced electrochemically in aprotic media in the presence of acetic anhydride, *N,O*-diacetylated hydroxylamines are formed.[223,224] On the basis of the changes of cyclic voltammograms of nitrosobenzene in the presence of acetic anhydride the following scheme (eqs 80–84) was proposed:

$$ArNO + e \rightleftharpoons ArNO^{\bullet -} \quad (80)$$

$$ArNO^{\bullet -} + Ac_2O \rightarrow Ar\dot{N}OAc + AcO^- \quad (81)$$

$$Ar\dot{N}OAc + e \rightleftharpoons Ar\bar{N}OAc \quad (82)$$

$$Ar\bar{N}OAC + Ac_2O \rightarrow ArN(OAc)_2 + AcO^- \quad (83)$$

$$Ar\bar{N}OAc + H^+ \rightleftharpoons ArNHOAc \quad (84)$$

The reversible couple of peaks, observed in the absence of acetic anhydride, corresponding to reaction 80, is in the presence of acetic anhydride replaced by an irreversible peak at a more positive potential corresponding to a two-electron process. It is relatively common that a reduction of a radical (conjugate acid) occurs at more positive potentials than the reduction of the corresponding radical anion. In the studied system the effect of the acetyl group results in the reduction (eq 82) at potential E_2, which is even more positive than potential E_1 corresponding to the reduction of the parent compound. Hence the reaction of the radical anion $ArNO^{\bullet -}$ with acetic anhydride (eq 81) results in a formation of a more easily reducible species $ArNOAc^{\bullet -}$ and the overall process results in a two-electron transfer. The anion $ArNOAc^-$ formed in the two-electron process is either converted (eq 83) into the *N,O*-diacetylarylhydroxylamine or in a competitive reaction (eq 84) into *N*-acetylhydroxylamine. The rates of these two reactions are sufficient to cause the two-electron reduction to be irreversible.

In the presence of acetyl chloride, $Ar\dot{N}OAc$ is formed in reactions analogous to eqs 73 and 74 and reduced in eq 75 in a wave more positive than that of nitrosobenzene.[225] But with increasing concentration of acetyl chloride an even more positive wave is observed, attributed to the reduction of a cation $ArNOAc^+$ (eq 86) resulting from the reaction (eq 85) between acetyl chloride and the parent nitroso compound:

$$ArNO + ClAc \rightarrow Ar\overset{+}{\dot{N}}OAc + Cl^- \quad (85)$$

$$Ar\overset{+}{\dot{N}}OAc + e \rightleftharpoons Ar\dot{N}Ac \quad (86)$$

3.1.3. Electrochemical Generation of the Reducing Agent

Unipositive magnesium was generated anodically in sodium iodide–pyridine solutions.[226] In the presence of nitrosobenzene, 85% *trans*-azobenzene and 15% azoxybenzene was produced. It is assumed that nitrosobenzene is reduced by Mg^+ to phenylhydroxylamine, which reacts with nitrosobenzene to yield azoxybenzene. Further reduction with Mg^+ results in *trans*-azobenzene.

3.2. Chemical Reduction of Nitrosobenzene

Reduction of nitroso compounds can be accomplished with a variety of chemical reagents,[227] including zinc and tin[228] in acidic media, sodium in diethyl ether,[229,230] diborane and trialkylborane,[231] disodium decacarbonyldichromate[232] and hydrazine hydrate.[233] Reduction can also be carried out by catalytic hydrogenation[227] and by pulse radiolysis.[234] Using the latter technique, it has been shown that a radical anion $ArNO^{\bullet -}$ can be produced by the reduction of ArNO by a hydrated electron, $OH^\bullet$ radical and radical anions $R_1R_2CO^{\bullet -}$ or $CO_2^{\bullet -}$ (from formate), whereas alcohol radicals $R_1R_2COH^\bullet$ yield radical $ArNOH^\bullet$. The pK_a of the reaction $ArNOH^\bullet \rightleftharpoons ArNO^{\bullet -} + H^+$ is 11.7.

Among organic reducing agents thiourea dioxide reduces nitrosobenzenes to hydrazo compounds[235] and trimethylammonium formate to azoxybenzenes.[236] For compounds bearing divalent sulfur, addition competes with reduction. Ion HS^- reduces nitrosobenzenes to amines,[237,238] and oxidation of mercap-

tans to disulfides by oxygen is catalyzed in alkaline media by small amounts of o- or *p*-nitrosophenols or anilines.[239] In the reaction of nitrosobenzene with thiophenol in a benzene solution,[69] diphenyl disulfide was the predominating product. 2-Naphthalenethiol reacts in DMSO-*tert*-butyl alcohol mixture 2:1 containing potassium butoxide with nitrosobenzene, yielding 79% disulfide, azobenzene, and azoxybenzene.[240] Radical anions detected in reaction mixture by ESR may result from consecutive reactions of ArN(OR)(O^-).[35]

Nitrosoanilines and nitrosonaphthols are reduced by HSe^- ion,[241] and nitrosobenzenes are assumed to be reduced by selenophenol to arylhydroxylamines and arylamines.[242] Considerable attention has been paid to reductions of nitrosobenzenes by biologically important compounds. Thus a nitroso analog of chloramphenicol is reduced by glutathione to a hydroxylamine derivative,[243] 4-nitrosophenetol to *N*-hydroxy-4-phenetidine and 4-phenetidine,[244] and nitrosobenzene to phenylhydroxylamine by dihydroflavin.[245] Reductions of nitrosobenzene with NADH, NADPH, and other dihydropyridine derivatives yield predominantly arylhydroxylamines[246-250] and products of their reaction with the starting material, azobenzenes.[251] The reduction was shown[247] to be acid catalyzed. A large kinetic isotope effect is interpreted as an indication that reduction occurs by a direct hydride transfer from the C4 carbon atom of the dihydronicotinamide ring to the nitroso nitrogen of the reduced species, thus excluding a radical mechanism.[250] When 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine reacts with nitrosobenzene, *O*-acetylphenylhydroxylamine is assumed to be formed.[252] Reduction of nitrosoarenes can also occur enzymatically.[253]

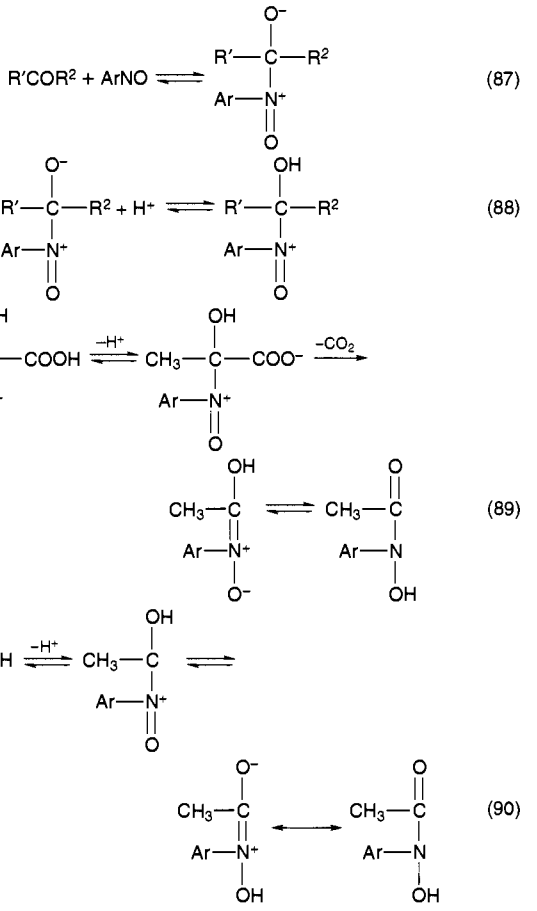
Nitrosobenzene interacts also with hemoglobin.[254-256] It is bound by coordination to the iron in hemoglobin and is reduced to azo- and azoxybenzene. Reduction of the nitroso group occurs also by perfusion of isolated liver by nitrosobenzene,[244,257] yielding phenylhydroxylamine, aniline, and other metabolites. The supernatant of rats liver (at 100000*g*) reduced nitrosobenzene to phenylhydroxylamine.[257]

4. Additions of Nitrosobenzenes

4.1. Nitrosobenzenes as Nucleophiles

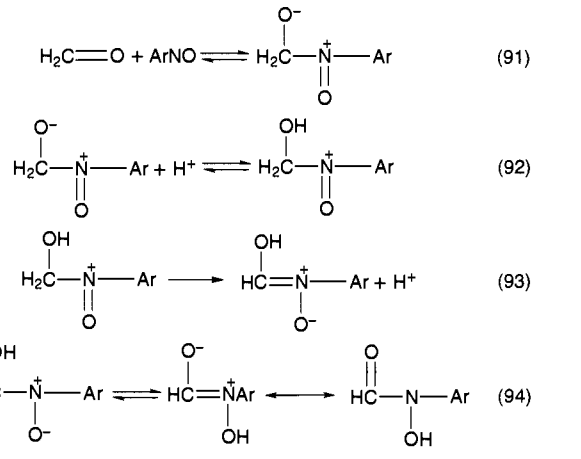
Due to the free electron pair on nitrogen, nitrosobenzenes can act in some instances as nucleophiles.

For the addition of nitrosobenzene to a carbonyl group, the presence of a leaving group capable of heterolytic cleavage adjacent to the carbonyl carbon is essential,[94,258] or the reaction must be carried out in the presence of a powerful catalyst. An example is the reaction of benzaldehyde with nitrosobenzene in the presence of aluminum propoxide.[259] In such cases, hydroxamic acids RCON(OH)Ar are formed. In acid-catalyzed reactions, nitrosobenzenes add to formaldehyde,[260,261] acetaldehyde,[262,263,264] trifluoroacetaldehyde,[262] glyoxylic acid,[265] and pyruvic acid[262,266] to give corresponding *N*-phenylhydroxamic acids. The first step is a nucleophilic attack of the nitroso group on the carbonyl group (eq 87), followed by a protonation of the intermediate (eq 88). This intermediate in the case of pyruvic acid undergoes decarboxylation (eq 89) or elimination of a proton from the carbon of the nitrosocarbinolic group in the case of acetaldehyde (eq 90):



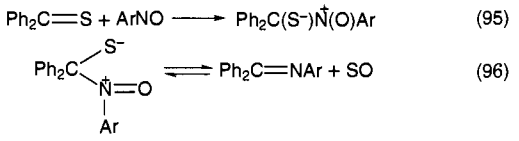
The reaction of pyruvic acid includes, along with the acid-catalyzed one, also an intramolecular reaction pathway.

In the reaction of formaldehyde, the nucleophilic attack of the nitroso group on the carbonyl group (eq 91) yields an unstable zwitterionic intermediate. The protonated form of this intermediate forms a more stable nitrosocarbinolic cation intermediate (eq 92). This intermediate undergoes a rate-controlling elimination of the proton from the C-atom of the nitrosocarbinolic group (eq 93) to yield the hydroxamic acid (eq 94):



This mechanism was confirmed by the observed kinetics, by the Hammett reaction constant $\varrho = -1.74$ for substituted nitrosobenzenes, by the observation of general acid–base catalysis, by the inverse solvent deuterium isotope effect of about 1.8, by the kinetic primary deuterium isotope effect of about 8 related to the "water" reaction, and by kinetic primary deuterium isotope effect of about 2.1 for the acetate-catalyzed reaction.[261]

Thioketones add nitrosobenzene and yield anils (eqs 95 and 96):

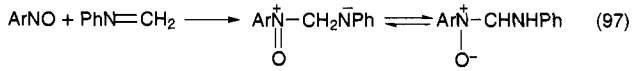


(95)

(96)

where SO undergoes disproportionation to SO_2 and S.[267] Reaction of nitrosobenzene with carbon disulfide in the presence of hydrogen sulfide yields 2-mercaptothiazole.[268] The first step of this reaction probably involves a nucleophilic attack of the nitrogen of nitrosobenzene on the carbon of the carbon disulfide.

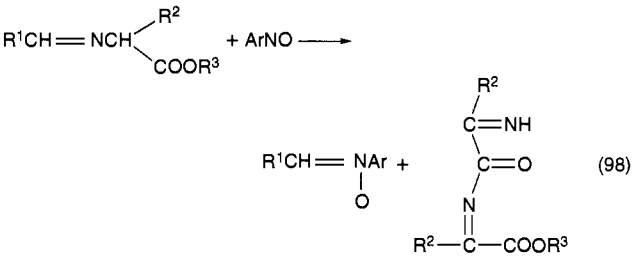
Somewhate more information is available about addition of nitrosobenzene to azomethine bonds. Thus the reaction with methyleneanilines yields nitrones[269,270] (eq 97):



(97)

Nitrones are predominant products, if equimolar amounts of starting materials or an excess of the azomethine compound is used. In the presence of excess of nitrosobenzene formanilides and azoxybenzene are formed, indicating that nitrone undergoes oxidation–reduction process. The previously[271] assumed formation of oxadiazetidine as intermediate was ruled out.

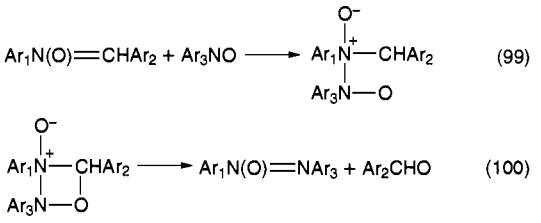
Arylidineimines of α-amino esters also react with nitrosobenzene and form nitrones[272] (eq 98):



(98)

The reaction is assumed to involve concerted cycloaddition, but the evidence is limited.

Reactions of nitrones with nitrosobenzenes resulted in formation of azoxybenzene.[273,274] The reaction was assumed to follow a pattern (eqs 99 and 100):



(99)

(100)

The reaction occurred in chloroform, DMF, DMSO, acetonitrile, or benzene,[274] but only in the presence of an acid catalyst, like traces of HCl in chloroform or added trifluoroacetic acid in the other solvents. An alternative mechanism considered was hydrolysis of the mixture, followed by a reaction of resulting phenylhydroxylamine with nitrosobenzene.

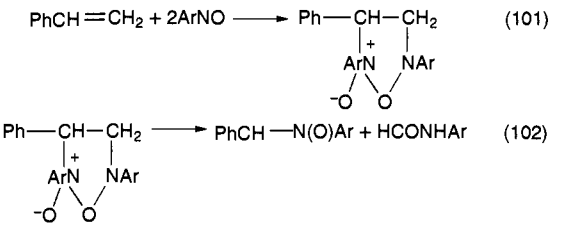
Distribution of products from nitrones substituted either on ring Ar_1 or Ar_2 lead to the conclusion[274] that the mechanism (eqs 99 and 100) involving the cyclic intermediate is highly unlikely. Without investigation of hydrolysis of nitrones under conditions used in the absence of nitrosobenzene, it remains questionable whether this hydrolysis is sufficiently fast to produce the phenylhydroxylamine needed for condensation with nitrosobenzene to yield azoxybenzene. It remains to decide whether the acid catalysis involves the hydrolysis of the nitrone or formation of azoxybenzene (cf. section 2.4.4).

4.2. Reactions of Nitrosobenzenes with Olefins—Additions and Cycloadditions

It was recognized early[275–277] that nitrosobenzenes add to olefins and yield unsaturated nitrones and azoxybenzenes. Cycloaddition of nitrosobenzene with diethyl methylenemalonate and 1,1-diphenylethylene, yielding oxazetidines has been reported.[278] Product structures were proposed[279,280] as ArN(OH)CH=C-$(COOC_2H_5)_2$ and ArN(O)=CPh_2. These structures are thought to be confirmed by chemical[281,282] and NMR studies.[283]

A kinetic study,[284] where the concentration changes of nitrosobenzene were followed spectrophotometrically, lead to the conclusion that a dimeric form of nitrosobenzene reacts with styrene. Benzylidinemalonaldehyde reacts with nitrosobenzene and forms a hydroxylamino derivative[285] which is reduced by a second molecule of nitrosobenzene to ArC(NHPh)=C-(CHO)COOH.

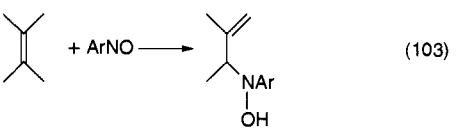
In ethanolic solutions, reactions of nitrosobenzenes with olefins yield azoxybenzene.[286] At 0 °C, in the absence of a solvent or in pyridine solutions, nitrosobenzene reacts with styrene to yield α,*N*-diphenylnitrone.[287] It was assumed that the reaction involves two molecules of nitrosobenzene and formation of a cyclic intermediate (eqs 101 and 102):



(101)

(102)

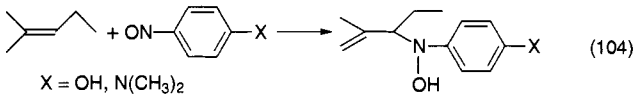
As an alternative reaction path an "ene" addition of nitrosobenzene yielding an unsaturated hydroxylamine has been proposed (eq 103):



(103)

When the reaction of olefins was carried out with

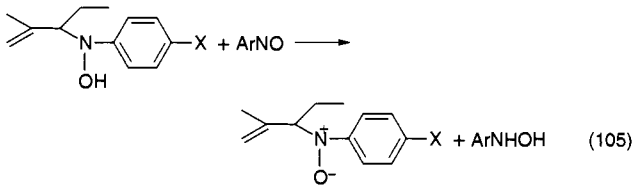
nitrosobenzene,[288] azoxybenzene was the only product either because the "ene" reaction does not occur or because the adduct is unstable and eliminates arylhydroxyamine. On the other hand, *p*-nitrosoanilines,[289,290] imines,[291] and *p*-nitrosophenol[292] yielded reduction products of the adduct (eq 104):



(104)

In the reactions of allylic olefins with nitrosobenzene, *N*-alkenyl-*N*-phenylhydroxylamines were isolated.[293,294] The "ene" reaction is further confirmed by the effect of the structure of the olefin on the rate of its reaction with nitrosobenzenes and on the nature of alkenyl groups generated in the product.[293] The reaction path depends on the structure of the olefin: Olefins which do not possess α-methylenic hydrogen atoms react with nitrosobenzene to form an adduct.[288]

Reaction of nitrosobenzene with 2-methyl-2-pentene results in a radical $C_2H_5C(NOAr)C(CH_3)=CH_2$ in about 40% yield. The second-order rate constant of the formation of this radical is of the order of 10^{-3} L mol^{-1} s^{-1} at 23 °C. Attempts to isolate the addition product were unsuccessful, only azoxybenzene was recovered. Simple olefins containing methylenic hydrogen atoms react in the initial stage with nitrosobenzenes in an "ene" addition with rearrangement of the double bond to give alkenylhydroxylamines[295] which are oxidized by another nitrosobenzene molecule (eqs 105 and 106):



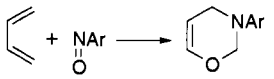
(105)

$$ArNHOH + ArNO \longrightarrow ArN(O)=NAr + H_2O \qquad (106)$$

When the nitrosobenzene carries electron-withdrawing substituents, nitrones and azoxybenzenes are the predominant products. When the parent nitrosobenzene carries electron-donating substituents, the rate of the reaction with the second nitrosobenzene molecule is slower and a thermal decomposition yielding amines and nitrones predominates.

Two molecules of nitrosobenzene add to the carbon–carbon double bond in 3-phenyl-1-indanone.[296] Addition of nitrosobenzene to the double bond in 1,3-dimethyl-6-(alkylamino)uracil yields in the presence of acetic anhydride 7-phenyltheophylline.[297] Examples of other reaction partners of nitrosobenzene are acetylenes[298–300] and allenes.[301] Addition of nitrosobenzene to quinones results in a formation of a 1:1 or 2:1 adduct. The later can be converted into a dinitrone.[302,303] To explain its formation, a single-electron transfer involving generation of radical anions was suggested.[304]

The Diels–Alder reaction of C-nitroso compounds with conjugated dienes[304–306] was first reported by Wichterle[307] and Arbuzov.[308] Their findings were later confirmed and extended.[309] Nitrosoarenes react with simple dienes in good yield, for example 1,3-butadiene gives 1,2-oxazine derivatives[310] (eq 107):



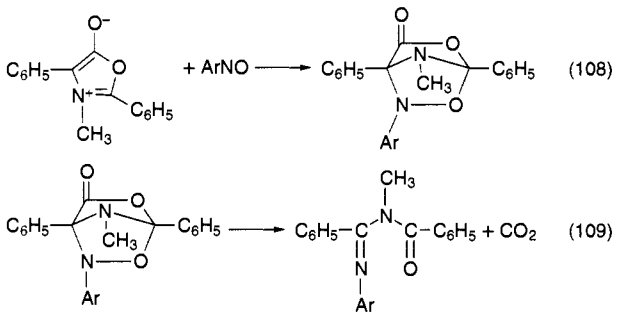
(107)

Kinetic studies of second-order reactions of 1,3-cyclohexadiene and 2,3-dimethyl-1,3-butadiene with para-substituted nitrosobenzenes[311,312] indicated acceleration of the cycloaddition by electron-withdrawing substituents. Quantitative investigations of such substituent effects[313,314] both on reaction rates and relative yields of regioisomers[315] lead to the conclusion[304,313,314] that the rates and ratios of regioisomers depend on relative stabilization of dipolar transition states by substituents on nitrosobenzene. Addition of nitrosobenzene to some dienones and dienols[316] manifested regioselectivity, which can be rationalized by FMO theory,[317] provided that the interaction of dienone HOMO with the LUMO of nitrosobenzene is considered. For permethyl-2,4-cyclohexadiene-1-one, no stereoselectivity was observed and this was attributed to steric factors.

Addition of *p*-chloronitrosobenzene to 1,3-cyclohexadiene-5,6-diyl diacetate yields a single adduct,[318] whereas that to 5-methoxy-1,3-cyclohexadien-6-ol yields two. For these findings, no interpretation is available,[306]

Addition of nitrosobenzenes to thebaine is a reversible reaction which at 25 °C is shifted in favor of products.[319] Electron-withdrawing substrates on nitrosobenzene favor the shift toward products, electron-donating substituents act in the opposite direction. Addition of nitrosobenzenes to *N*-acyldihydropyridines[320] yields a single regioisomer, in accord with the prediction of the FMO theory.[317]

Among the 1,3-dipolar cycloadditions reported, addition of nitrosobenzene to 3-methyl-2,4-diphenyloxazolium-5-olate yields[321] *N*-benzoylbenzamidine (eqs 108 and 109):



(108)

(109)

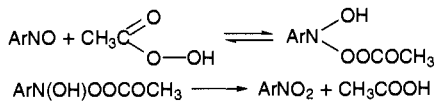
In another example of the 1,3-dipolar cycloaddition[322] the mesoionic form of Δ^2-oxazolin-5-one forms, with nitrosobenzene, Δ^4-1,2,4-oxazolidine-3-carboxylic acid.

5. Oxidation of Nitrosobenzenes

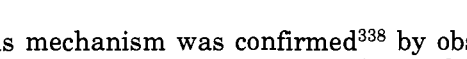
Oxidation of nitrosobenzenes to nitro compounds can be achieved by numerous oxidizing agents, such as permanganate, chromate, hexacyanoferrate, Caro's acid,[323] nitric acid,[324–327] nitrogen dioxide and nitrogen monoxide,[328] by hypochlorite and hydrogen peroxide in alkaline media,[35,329–332] and in a mixture of hydrogen peroxide with nitric acid in glacial acetic acid as a solvent.[323]

Some attention has been paid to the oxidation of nitrosobenzene with peroxocarboxylic acids. Thus peroxotrifluoroacetic acid[333] reacts in a methylene chloride solution under refluxing with nitrosobenzene to yield nitrobenzene, whereas at 5-10 °C, *p*-nitroso-*N*,*N*-diphenylhydroxylamine formed by self-condensation is the predominant product. 5-Nitrosopyrimidine is oxidized to 5-nitropyrimidine by hydrogen peroxide using trifluoroacetic acid as the solvent.[334]

Contrary to an earlier report,[335] both peroxochloroacetic and peroxoacetic acids oxidize nitrosobenzene.[336] The oxidation of nitrosobenzene by peroxoacetic acid follows second-order kinetics, first in nitrosobenzene and first in peroxoacetic acid.[337] The rate of the oxidation, which is not acid catalyzed, is increased by electron-donating substituents in para-position on nitrosobenzene; electron-withdrawing ones decrease it. The reaction rate constants follow Hammett equation with $\varrho = -1.6$. Addition of nitrobenzene as a radical trap does not inhibit the rate of the reaction. The proposed mechanism involves a nucleophilic attack of the peroxo acid upon the substrate (eq 110), followed by oxidation (eq 111):



$$ArNO + CH_3C(=O)(O-OH) \rightleftharpoons ArN(OH)(OOCOCH_3) \quad (110)$$



$$ArN(OH)OOCOCH_3 \longrightarrow ArNO_2 + CH_3COOH \quad (111)$$

This mechanism was confirmed[338] by observed solvent effects on rate constants for oxidation of nitrosobenzene by *m*-chloroperoxobenzoic acid. Observed effects parallel those found for oxidation of *p*-nitrophenyl phenyl sulfide by peroxobenzoic acid. In both these reactions oxidation is assumed to occur in a single step. The different solvent effects were observed, on the other hand, for oxidation of *p*-nitrophenyl phenyl sulfoxide by peroxobenzoic acid, for which a two-step mechanism involving protonation of oxygen was proposed. For oxidation of nitrosobenzene a two-step mechanism does not need to be considered. Absence of correlation of the rate constants of nitrosobenzene oxidation with solvent polarity indicates formation of a transition state avoiding a charge separation by protonation either internal or, in hydroxylic solvents, external.

The oxidation of nitrosobenzenes in cyclohexane or benzene solutions by *tert*-butyl peroxide is initiated by di-*tert*-butyl peroxooxalate or by hydrocarbon-soluble β-diketonates of transition metals.[339] The peroxooxalate-initiated reaction follows a radical chain mechanism which involves both *t*-BuO$^\bullet$ and *t*-BuOO$^\bullet$. The radical *t*-BuO$^\bullet$ reacts with PhNO to form Ph(BuO)NO$^\bullet$, conversion of PhNO into $PhNO_2$ occurs by an oxygen-atom transfer from *t*-BuOO$^\bullet$. The principal mode of termination is the reaction of *t*-BuOO$^\bullet$ with Ph(BuO)NO$^\bullet$.

In a solution, composed of 80% DMSO and 20% *tert*-butyl alcohol containing potassium *tert*-butoxide, nitrosobenzene was converted into azoxybenzene in the presence of dioxygen.[340] It has been proposed that azoxybenzene is formed by condensation of nitrosobenzene radical anion with nitrosobenzene rather than by coupling of nitrosobenzene radical anions. This view is supported by the rate of the decay of the nitrosobenzene radical anion followed by ESR as compared with the rate of oxygen absorption, followed manometrically. Rate of oxygen consumption increased with the increasing concentration of the base. Formation of azoxybenzene was accompanied by a competitive oxidation to nitrobenzene. The yield of the latter decreases in the presence of an excess of the base.

In a reaction of *N*-arylhydroxylamines with dioxygen at pH 5.3–7.8, 2–12% $ArNO_2$, 70–95% ArNO, and 1–20% of ArN(O)=NAr are formed.[341] Direct attack of dioxygen on ArNHOH was postulated.

In solutions, to which only nitrosobenzene was added, at pH > 11, where the adduct $ArN(OH)O^-$ predominates,[35] azoxybenzene is the predominant product in the absence of dioxygen. On the other hand, when dioxygen is dissolved in the reaction mixture (protected from illumination), a considerable amount of nitrobenzene is formed. The rate of decrease in concentration of nitrosobenzene in both reactions in the absence and presence of dioxygen is not only equal at given pH, but increases in both cases equally with increasing pH. This indicates that rates of both reactions yielding azoxybenzene and nitrobenzene are governed by a formation of the same intermediate. This intermediate, which is formed following an interaction of the adduct $ArN(OH)O^-$ with another hydroxide ion, is assumed to be the dianion $ArN(O^-)_2$ or a product of its conversion.[35]

Finally, nitrosobenzene can be both oxidized and reduced in a reaction of the disproportionation type.[342] Thus in cyclohexane solutions at 70–100 °C nitrosobenzene reacts to yield nitrobenzene and an azoxy compound (eqs 112 and 113):

$$2ArNO \rightarrow ArNO_2 + ArNHOH \quad (112)$$

$$ArNHOH + ArNO \rightarrow ArN(O)=NAr + H_2O \quad (113)$$

The second reaction (eq 113) is slower than the first (eq 112), and the decrease in nitrosobenzene concentration hence follows second-order kinetics. Ineffectiveness of addition of a radical scanvanger indicated absence of radical reactions. Correlation of log *k* with σ^- constants is poor, with σ^+ considerably better with a slope of $\varrho = 1.46$. Authors[342] consider the role of a dimer–monomer equilibrium, but whereas aliphatic nitroso compounds readily form dimers, there is no evidence for dimerization of nitrosoarenes at room or higher temperatures (cf. section 1).[11,12]

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