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The chemistry of nitrosamine formation, inhibition and destruction

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Synopsis

N-Nitroso compounds are formed from the interaction of many types of organo-nitrogen compounds and nitrosating agents. Ease of nitrosation is determined by compound structure, nature of the medium and the presence of catalysts. The two categories, nitrosamines and nitrosamides, differ mainly in their CHEMICAL stability and mechanism of biological activity. NITROSAMINES are more stable and difficult to DESTROY, but their FORMATION can be INHIBITED by substances which react preferentially with the nitrosating agent. The carcinogenic activity of these compounds in laboratory animals varies widely from highly potent to innocuous.

I. INTRODUCTION

Advances in analytical techniques allow modern industrial society to detect trace amounts of undesirable substances in its physical environment. There has been legitimate concern that we are creating conditions that have serious adverse effects on human health. Recently, minute levels of nitrosamines have been found in some consumer products, including cosmetics (1). While not attempting to judge whether these substances at parts-per-billion levels have a significant physiological effect, we are presenting a review of nitrosamine chemistry to aid workers in the cosmetic and allied industries in their research on the subject.

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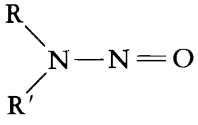
II. TYPES OF *N*-NITROSO COMPOUNDS

N-Nitroso compounds are formed by the interaction of a nitrogen-containing organic compound—such as an amine, amide, urea, guanidine, urethane or cyanamide—and a nitrosating agent, such as a nitrogen oxide.

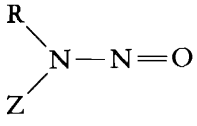
These compounds can be divided into two categories—nitrosamines and nitrosamides—which differ in their chemical stability, the mechanism of their carcinogenicity and their mutagenicity (2–4).

N-Nitrosamines



R,R′ = alkyl or aryl

N-Nitrosamides



R = alkyl or aryl

Z = $R'\overset{\overset{\displaystyle O}{\|}}{C}-$ nitrosamide

$R'_2N\overset{\overset{\displaystyle O}{\|}}{C}-$ nitrosourea

$R'_2N\overset{\overset{\displaystyle NH}{\|}}{C}-$ nitrosoguanidine

$R'O\overset{\overset{\displaystyle O}{\|}}{C}-$ nitrosourethane

$NC-$ nitrosocyanamide

$R'SO_2-$ nitrososulfonamide

The nitrosamines are very stable once they are formed. They require chemical modification in an enzyme-catalysed reaction before they exhibit carcinogenic and mutagenic activity (2, 3, 5). By comparison the nitrosamides can be hydrolysed, especially in neutral and alkaline solution. They exhibit carcinogenic and mutagenic activities without modification and malignant tumors are produced at the site of their application (2–5).

III. CARCINOGENICITY OF *N*-NITROSO COMPOUNDS

The first report that nitrosamines cause cancer in laboratory animals was that rats fed low levels (50 ppm) of dimethylnitrosamine in their diet developed liver cancer (6, 7). Since then more than 120 nitrosamines and nitrosamides have been examined for

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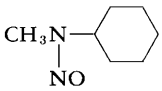
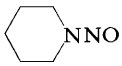
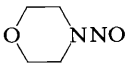
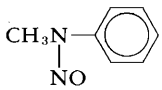
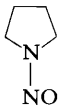
Table I
Varying Carcinogenic Activity of Nitrosamines

Classification by Range of log (l/D_{50})[a]	Structure	D_{50}[a]	log (l/D_{50})
Highly Potent, >3.0			
	$(CH_3CH_2)_2NNO$	0.00063	3.2
	$CH_3N(NO)CH_2CH_2Cl$	0.00061	3.2
	$CH_3N(NO)CH_2C_6H_5$	0.00080	3.1
Potent, 2.1 to 3.0			
		0.0010	3.0
	$CH_3N(NO)CH_2CH_2N(NO)CH_3$	0.0039	2.4
	$(CH_3)_2NNO$	0.0054	2.3
	$(n\text{-}C_3H_7)_2NNO$	0.0088	2.1
Intermediate Activity, 1.1 to 2.0			
	$(NCCH_2)_2NNO$	0.012	1.9
		0.012	1.9
		0.011	1.9
	$CH_3CH_2N(NO)CH_2CH_2OH$	0.016	1.8
	$(n\text{-}C_4H_9)_2NNO$	0.025	1.6
		0.025	1.6
	$n\text{-}C_4H_9N(NO)(CH_2)_4OH$	0.031	1.5
		0.039	1.4
Minimal Activity, ≤1.0			
	$(i\text{-}C_3H_7)_2NNO$	0.11	1.0
	$(CH_3COCH_2CH_2)_2NNO$	0.18	0.7
	$(n\text{-}C_5H_{11})_2NNO$	0.26	0.6
	$CH_3N(NO)CH_2CO_2H$	0.24	0.6
	$(HOCH_2CH_2)_2NNO$	0.89	0.05

continued on p 584

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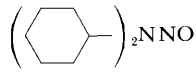
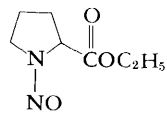
Table I (continued)
Varying Carcinogenic Activity of Nitrosamines

Classification by Range of log (l/D_{50})[a]	Structure	D_{50}[a]	log (l/D_{50})
No Detectable Activity			
	$(C_6H_5)_2NNO$	—	—
	$(C_6H_5CH_2)_2NNO$	—	—
		—	—
		—	—
	$(HO_2CCH_2)_2NNO$ (12)	—	—

[a] D_{50} = mean total carcinogenic dose, expressed in mol/kg body wt, for production of tumors in 50% of the animals.

carcinogenic activity in animals. Comprehensive reviews of the results have been published (2, 4, 5).

Although there is no direct evidence that *N*-nitroso compounds cause cancer in man, their carcinogenicity has been demonstrated in many other animal species including mice, rats, hamsters, fish, rabbits, guinea pigs, dogs and monkeys (4, 5, 9).

About 80% of the *N*-nitroso compounds tested are carcinogenic to some degree. Their potency varies widely, from compounds where a single dose is sufficient to induce tumors to those where large doses given repeatedly produce no malignancy (2, 5). To illustrate the range of activity representative nitrosamines are classified in Table I according to carcinogenic potency (10). The carcinogenic dose is expressed in the way suggested by Wishnok et al. (11) so that larger numbers indicate higher carcinogenicity.

Wishnok and coworkers (11) recently demonstrated that the carcinogenic potency of many nitrosamines correlates quantitatively with a combination of their hexane-water partition coefficients and the electronic inductive effects of substituents on the α-carbon. Earlier Wishnok and Archer (13) showed that carcinogenicity is inversely related to the number of carbon atoms of acyclic dialkyl nitrosamines. Lijinsky (14) found that the reverse is true for cyclic nitrosamines, where the larger molecules are more potent, and that there are major changes in target organs with a change in ring size.

The frequently proposed mechanism of action (2, 3, 15) shown below accounts for the enzymatic activation required by nitrosamines, but not nitrosamides, and indicates that only nitrosamines containing an α-hydrogen are carcinogenic.

The requirement for activation of nitrosamines is defined as an enzyme-catalysed hydroxylation of an α-carbon. This step is supported by correlations of the degree of carcinogenicity with α-carbon substituents (11) and by recent work showing that preformed α-acetoxy nitrosamines are direct acting carcinogens not requiring enzymatic modification for activity (16).

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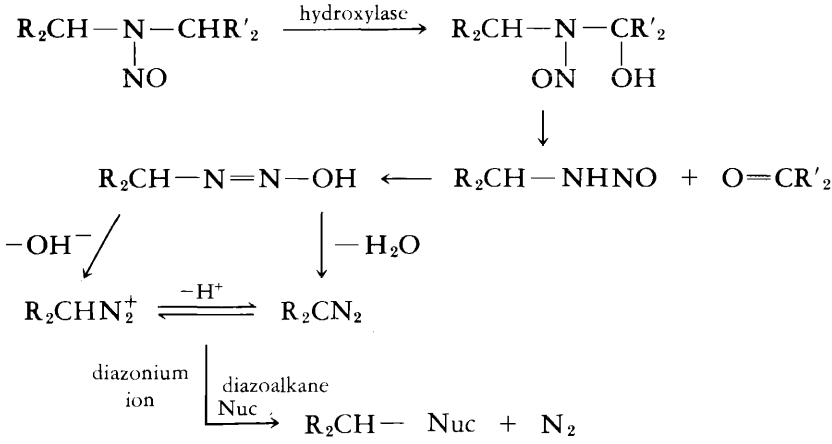
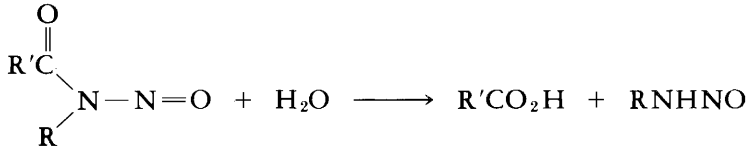


The hydroxyalkyl group is eliminated as an aldehyde or ketone leaving an unstable primary nitrosamine. The latter tautomerizes to a diazonium hydroxide.

Alkylation of nucleophilic sites (Nuc) in DNA, RNA and proteins by *N*-nitroso carcinogens has been demonstrated (5), but the evidence conflicts as to whether a diazonium ion or the diazoalkane is the alkylating agent (2, 4, 5, 17). In nucleic acids the principle site of alkylation is at N(7) of guanine. Alkylation of nucleic acid oxygens has also been demonstrated (18).

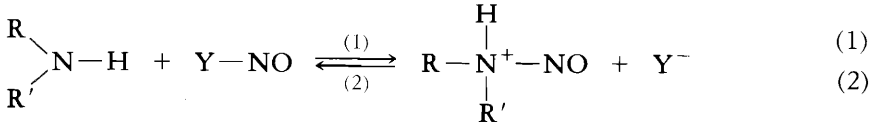
Nitrosamides do not require metabolic activation because they can be hydrolysed in vivo to an unstable primary nitrosamine (2, 3), the proposed precursor of the alkylating agent.



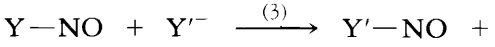
IV. CHEMISTRY OF *N*-NITROSO COMPOUNDS

A. INTRODUCTION

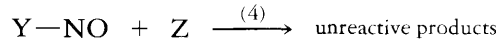
Much of the chemistry of *N*-nitroso compounds in aqueous solution can be summarized by the following scheme.



(1)
(2)



(3)



(4)

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Nitrosation of secondary amines and amides is described by eq 1. The effectiveness of the nitrosating agent Y—NO depends on the nature of Y. *Catalysis of nitrosation* by Y′ species results from its prior reaction with Y—NO (eq 3), which produces the more active nitrosating agent Y′—NO. When Y is a secondary amine function, eq 1 describes *transnitrosation* as it is defined in this paper.

Inhibition of nitrosation occurs by reaction of inhibitor Z with nitrosating agent Y—NO in the irreversible eq 4, which is much faster than 1 and produces unreactive products. *Destruction* of *N*-nitroso compounds by denitrosation is described by eq 2. Addition of Z, in this case called a trap or scavenger, is necessary to prevent via 4 the reversal of denitrosation, eq 1.

Details of these reactions and the chemistry of *N*-nitroso compounds not included in this scheme are described below.

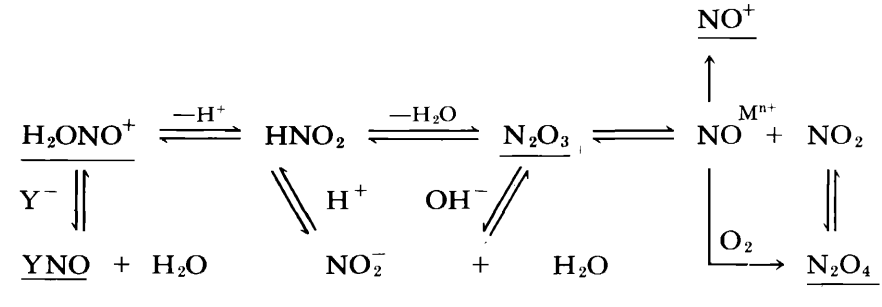
B. FORMATION

1. Nitrosating Agents

a. Inorganic Species. Several nitrogen oxide species are nitrosating agents, but nitrous acid (HONO) and the nitrite ion (ONO^-) are themselves inactive (19). Known inorganic nitrosating species are:

Substance	Medium
N_2O_3	gas (20, 21)
	water (19, 22–27)
	organic solvent (2)
NO_2/N_2O_4	water (25–27)
	organic solvent (28, 29)
	gas (21, 30)
YNO	water (19, 22, 23, 31–37)
H_2ONO^+	water (19, 22, 38–40)
NO	plus O_2 (25, 27, 36)
	anaerobic, M^{n+} (19, 27)

The interrelationship between active nitrosating agents (underlined) and inactive species is summarized below. For simplicity, the equations are not balanced.



In moderately acidic aqueous nitrite solutions the nitrosating agent is nitrous anhydride, N_2O_3 (19, 22–24), formed from nitrous acid, $pK_a = 3.138$ at 25° (41, 42), after protonation of nitrite ion according to eqs 5 and 6.

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$$H^+ + ONO^- \rightleftharpoons HONO \quad (5)$$

$$2HONO \rightleftharpoons ONNO_2 + H_2O \quad (6)$$

At lower pH, more rapid nitrosation by the nitrous acidium ion (19, 22, 38–40) becomes important, especially for weakly basic aryl amines and amides.

$$HONO + H^+ \rightleftharpoons H_2ONO^+ \quad (7)$$

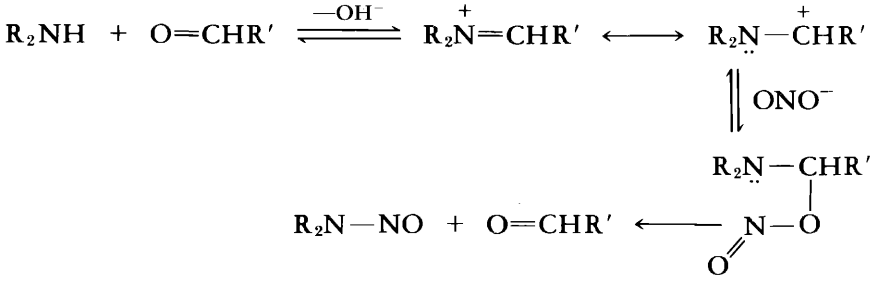
Certain anions, Y^-, catalyse the reaction in water by forming nitrosating species Y—NO which are more reactive than N_2O_3.

$$HONO + Y^- + H^+ \rightleftharpoons Y{-}NO + H_2O \quad (8)$$

Of the anionic catalysts studied thiocyanate has the greatest effect (23, 31–37). Halide ions are also catalytic in the order SCN^-, $I^- >> Br^- > Cl^-$ (19, 22, 23, 31, 33, 35). The equilibrium concentration of YNO (eq 8) mainly determines the order of the catalytic effect, rather than the actual reactivities of YNO (36). As the pH is lowered below 2, rapid nitrosation by Y—NO dominates over that by N_2O_3, lowering the pH at which the nitrosation rate is maximum compared to the uncatalysed reaction (23, 32–34, 37). Perchlorate and sulfate ions are not catalytic (22, 31, 33). Hydrogen phosphate and carboxylate anions may catalyse nitrosation (31), but only weakly (19, 33).

Substances capable of forming micelles exert a catalytic effect on the nitrosation of amines in acid solution. The rate of nitrosation of dihexylamine at pH 3.5 increases 800-fold in the presence of decyltrimethylammonium bromide micelles (43). Other cationic and nonionic substances at levels higher than their critical micelle concentrations are also catalytic (43, 44). The magnitude of the catalytic effect is smaller for secondary amines with alkyl chain lengths shorter than C_6. Some nitrosation rate enhancements observed in the presence of microorganisms have been explained as due to an analogous hydrophobic interaction between amine and a cellular constituent (45).

In aqueous solution at pH > pK_a of HNO_2 the rate of nitrosation drops rapidly with increasing pH, because the concentrations of active nitrosating species generated in situ decrease. No nitrosation by aqueous nitrite has been observed above pH 7.5. When formaldehyde (equimolar with amine) is added to neutral or basic solutions, nitrite can nitrosate secondary amines, but at a slower rate than in acid solutions (46, 47). Nitrosamine yields vary with steric accessibility of the nitrogen atom. Chloral (46, 47), pyridoxal and various benzaldehydes (48) are also catalytic, but less so than formaldehyde. Acetone and acetaldehyde are inactive. The proposed mechanism (eq 9) involves nucleophilic attack by nitrite on an iminium ion intermediate following by collapse of the adduct releasing the carbonyl catalyst.



(9)

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In organic solvents NOCl, N_2O_3, N_2O_4 and $NOBF_4$ have been used as preparative nitrosation reagents (23, 25). Use of N_2O_3 (2) or N_2O_4 (28) in carbon tetrachloride or acetic acid gives high yields of nitrosamides. With secondary amines N_2O_4 in methylene chloride reacts cleanly either as a nitrosating agent at 0° or as a nitrating agent at −80° (29). Since NO_2 is in equilibrium with N_2O_4 (49), statements in the literature on effects of either substance must be critically viewed.

Nitrosation of amides occurs faster in two-phase systems composed of an organic solvent and aqueous HNO_2 solution at pH 1 or in methylene chloride extracts of 2 *M* aqueous HNO_2 than in water alone at pH 1 (50). Nitrosation of amines dissolved in methylene chloride in contact with solid sodium nitrite occurs by a reaction which involves the solvent (51).

Recent studies have shown that secondary amines react with N_2O_3 and N_2O_4 gases dissolved in aqueous alkaline solutions (pH 6–14) at a rate greater than in acidified nitrite (25–27). Although both nitrogen oxides might be expected to undergo rapid hydrolysis at pH > 5 to yield unreactive NO_2^- and NO_3^-, amines of widely different reactivity compete effectively with water and OH^- for dissolved N_2O_3 and N_2O_4.

Nitric oxide (NO) alone is inactive but is oxidized by oxygen to NO_2 and thus to the reactive nitrosating agents N_2O_3 and N_2O_4 (25, 27, 36). Rapid nitrosation by NO under anaerobic conditions occurs in the presence of iodine or Ag(I), Cu(I), Cu(II), Zn(II), Fe(III) or Co(II) salts (19, 27).

b. Organic Species. *N*-Nitrosamines themselves act as nitrosating agents. Aromatic nitrosamines, such as nitrosodiphenylamine, transnitrosate secondary amines under neutral conditions in organic solvents (52, 53) probably by a free radical mechanism (53). The process is more rapid in acidic aqueous solution and occurs by a heterolytic mechanism (53, 54). The slower transnitrosation between aliphatic secondary amines requires more extreme conditions or catalysis by nucleophilic agents, such as thiocyanate and halide ions (23, 55, 56).

Nitrosation of morpholine by aromatic and aliphatic *C*-nitro compounds in tetrahydrofuran at 70°C has recently been reported (57). Further work is required to ascertain whether nitrosation occurs by direct reaction of amine with the C-nitro function or is caused by agents derived from inorganic nitrite present as a synthetic contaminant or decomposition product. Primary and secondary nitroalkanes decompose to nitrite in dilute alkaline solutions (58).

2. Nitrogen Compounds

a. Primary Amines. The well-known deamination of primary aliphatic amines with nitrite in cold aqueous acid yields a variety of products (22). The rapid reaction proceeds through unstable primary nitrosamine and diazonium ion intermediates. The latter reacts with nucleophiles present to form substitution, elimination and rearrangement products.

$$\begin{array}{lcl} RNH_2 + NO_2^-, H^+ & \longrightarrow & R-\underset{\underset{H}{|}}{\ddot{N}}-N=O \longrightarrow R\ddot{N}=N-OH \\ & & \qquad\qquad\qquad\qquad\qquad\qquad \Big\downarrow H^+ \\ \text{alcohols, alkenes} & \xleftarrow[-N_2]{\text{Nuc}} & R-N\equiv N^+ + H_2O \end{array} \qquad (10)$$

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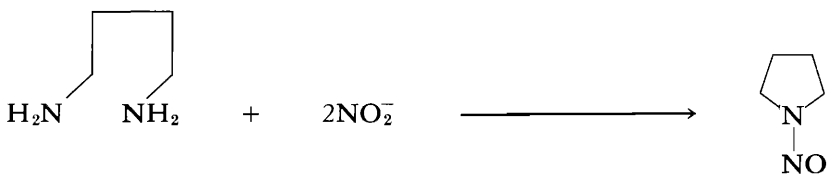
Secondary amines and subsequent nitrosamines formed by reaction of the diazonium ion with the primary amine starting material (eq 11) have been isolated (22). This reaction occurs in low yield because the amine is largely protonated and unreactive under the strongly acidic and low temperature conditions commonly used.

$$R{-}N{\equiv}N^+ + RNH_2 \xrightarrow{-N_2} R_2NH \xrightarrow{NO^-_2,H^+} R_2NNO \qquad (11)$$

Diamines with a second primary amine function appropriately located for intramolecular reaction with the diazonium ion form secondary nitrosamines at high temperatures or long reaction times as illustrated by the following examples (59).



HCl salt	moist	160°C, 2 hr	22% yield
0.025 *M*	0.050 *M*	in citrate-phosphate buffer, pH 3.4	
		100°C, 1 hr	1.6%
		22°C, 6 days	0.39%

Under similar conditions *n*-butylamine, a monoamine, gave much lower yields of *N*-nitrosodibutylamine.

Higher levels of stable α-alkoxynitrosamines are produced from the reaction of primary amines with aldehydes in the presence of alcohols and nitrite under mildly acidic conditions (60, 61).

$$RNH_2 + CH_2O + R'OH + NO^-_2, H^+ \longrightarrow R{-}\underset{\underset{NO}{|}}{N}{-}CH_2OR' \qquad (12)$$

However, mixtures of primary amines and aldehydes without alcohol do not react with nitrite at pH 3 (62).

b. Secondary Amines. Nitrosamines formed directly from secondary amines are stable. In moderately acidic aqueous nitrite solutions N_2O_3, formed from two molecules of HNO_2 (eq 6) is the nitrosating agent. The rate-determining step in the reaction is electrophilic attack by N_2O_3 on the free electron pair of the unprotonated amine (eq 13). Rate equation 14 describes the kinetics.

$$R_2NH + N_2O_3 \rightarrow R_2NNO + HNO_2 \qquad (13)$$

$$\text{rate} = k[R_2NH][HNO_2]^2 \qquad (14)$$

Thus, two factors determine the effect of pH on the rate of nitrosation:

(i) extent of conversion of NO_2^- to HNO_2 and thus to N_2O_3 (favored by lower pH)

(ii) concentration of unprotonated amine (favored by higher pH).

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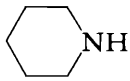
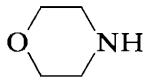
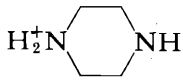
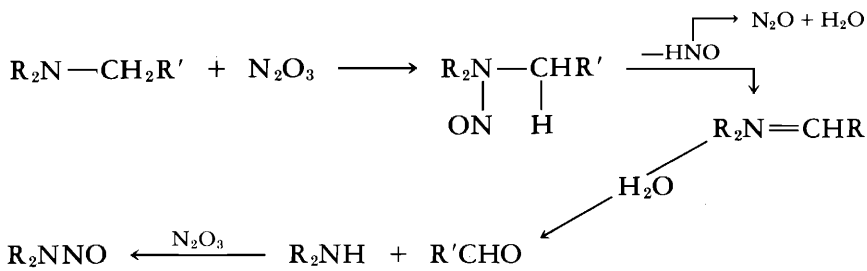
As predicted by the rate equation (33) for simple basic amines ($pK_a > 5$), the nitrosation rate in water is maximum at $pH_{max} = 3$ to 3.4 (23, 24, 40, 63, 64) near the pK_a of HNO_2. For a given amine as the pH increases above pH_{max} the rate decreases, because the concentration of HNO_2 decreases. As the pH decreases below pH_{max} the rate decreases, because the concentration of unprotonated amine decreases. At a given pH the rate of nitrosation increases as the basicity of the amine decreases, because of the higher relative concentration of unprotonated amine present. Thus, the following order of reactivity is found at pH 3.0:

Amine			
pK_a	11.2	8.7	5.57
Relative rate (23, 33)	1	930	180,000

Nitrosation of secondary amino acids (65, 66) occurs at an optimum $pH_{max} = 2.25$ to 2.5 (34, 40). The reaction follows rate eq 14, but the pH-rate profile is changed by the fact that two amine species react—$RNHCHR'CO_2^-$ and $RNHCHR'CO_2H$.

c. Tertiary Amines and Related Compounds. Tertiary amines have generally been regarded as inert to nitrosation, even though their conversion to secondary nitrosamines was reported over 100 years ago (67). Because dealkylation is required, the reaction occurs to a significant extent only at elevated temperatures in weakly acidic media (68–70). At 25°C and pH 3.4 nitrosation of tertiary amines is about 10,000 times slower than that of related secondary amines (23).

The following mechanism has been proposed (23, 68, 69) for nitrosative dealkylation and nitrosamine formation:



(15)

With mixed tertiary alkyl aryl amines ring C-nitrosation also occurs (19).

Two related compounds—the nitrogen acetal hexamethylenetetramine (71) and the drug antipyrine which has an eneamine structure (23, 72)—undergo *N*-nitrosation much more rapidly and extensively than normal tertiary amines. In both compounds at least one of the three *N*-substituents is in a higher oxidation state than in typical tertiary amines and nitrosation undoubtedly occurs by a different mechanism (70).

d. Quaternary Amines and Amine Oxides. Quaternary ammonium compounds apparently react slowly with nitrite in acidic media. The initial dealkylation required accounts for their lower activity compared to tertiary amines and may not involve the nitrosating agent (73). The relative reactivity of secondary, tertiary and quaternary

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amines is indicated by the following data gathered for reaction of a ratio of 5 mol $NaNO_2$/mol amine at 78°C and pH 5.6 for 4 hr (73).

Amine	% Yield of $(CH_3)_2NNO$
$(CH_3)_2NH$	9.6
$(CH_3)_3N$	0.9
$(CH_3)_4N^+$	0.6
$(CH_3)_2NCH_2CH_2OH$	1.6
$(CH_3)_3N^+CH_2CH_2OH$	0.0002

Several naturally occurring quaternary ammonium compounds were found to be much less reactive than the tetramethylammonium ion (73). The tribenzylmethylammonium ion is reported to be unreactive under similar conditions (68). No nitrosation of 10^{-3} *M* hexadecyltrimethylammonium bromide by a 20-fold excess of nitrite at 25°C and pH 3.5 was observed after 40 min (44).

Tertiary amine oxides in the presence of excess nitrite at pH 1 to 3 and temperature 25 to 75°C are converted to secondary nitrosamines to a greater extent than are tertiary amines (74). However, at 90 to 100°C and pH 4 to 5 both classes show similar reactivity (68, 70, 74). Two mechanisms that account for the change in relative reactivity with conditions have been proposed (70, 74).

e. Secondary and Tertiary Amides. For secondary amides, as with amines, the nitrosation condition most widely investigated has been nitrite in aqueous acid.

N-Alkyl ureas and carbamates are rapidly nitrosated at pH 1 to 2. The nitrous acidium ion is the main nitrosating agent for these and other amides (eq 16) and the reaction rate follows eq 17 (23, 39, 40).

$$ZNHR + H_2ONO^+ \rightarrow ZN(NO)R + H_2O + H^+ \quad (16)$$

$$\text{rate} = k[ZNHR][HNO_2][H^+] \quad (17)$$

The reaction rate increases about ten times for each 1-unit drop in pH from 3 to 1 and does not show a pH maximum. At pH > 2.5 nitrosation by N_2O_3 contributes (39).

In acidic aqueous media nitrogen substrates decrease in propensity toward nitrosation in the order 2-imidazolidone > acyclic *N*-alkylurea > *N*-arylurea > *N*-alkylcarbamate > less basic dialkyl and secondary aromatic amines ($pK_a < 9$) and tertiary eneamines > more basic dialkyl amines > *N*-alkylamides, *N*-acylureas, *N*-alkylguanidines and tertiary amines (23).

High yields of nitrosamides are obtained from reactions of amides with N_2O_3 (2) or N_2O_4 (28) in organic solvents. However, *N*-methylacetamide in aqueous solution at pH 13 does not react with added N_2O_4, conditions under which secondary amines are rapidly nitrosated (27). Apparently the weakly basic amide is too unreactive to compete with hydrolysis of the nitrosating agent.

Nitrosation of tertiary amides in acidic aqueous solutions of nitrite at high concentrations and temperatures produce either nitrosamides or nitrosamines (23, 70, 75). Nitrosation of trialkylureas gives the corresponding nitrosoureas. Dialkylnitrosamines are the major product from dialkyl- or trialkylthioureas, 1,1-dialkylureas, 1,1-dialkyl-3-phenylureas and tetraalkylureas.

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C. INHIBITION OF NITROSATION

Studies of nitrosamine inhibition have consisted of the use of substances which compete with the amine for nitrosating species. The reduction potentials of various nitrogen oxides (76) listed below can aid in selecting appropriate oxidizing and reducing agents for destruction of nitrite.

In acid solution:

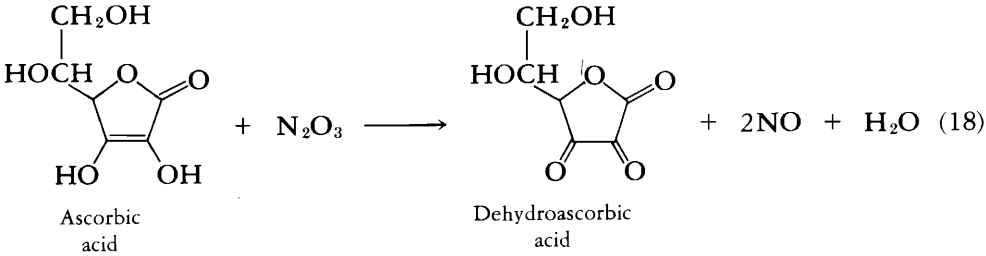
	E° (volts)
$HNO_2 + H_2O \rightleftharpoons NO_3^- + 3H^+ + 2e^-$	−0.94
$NO + H_2O \rightleftharpoons HNO_2 + H^+ + e^-$	−0.99
$N_2O + 3H_2O \rightleftharpoons 2HNO_2 + 4H^+ + 4e^-$	−1.29

In basic solution:

$NO_2^- + 2OH^- \rightleftharpoons NO_3^- + H_2O + 2e^-$	−0.01
$NO + 2OH^- \rightleftharpoons NO_2^- + H_2O + e^-$	+0.46
$N_2O + 6OH^- \rightleftharpoons 2NO_2^- + 3H_2O + 4e^-$	−0.15

1. Inhibition by Ascorbic Acid

Ascorbic acid inhibits nitrosamine formation by rapid reduction of the nitrosating agent (77). Since the product NO can be air-oxidized to



the nitrosating agent N_2O_4, excess ascorbic acid must be added to inhibit nitrosation in systems exposed to air.

Literature reports describing ascorbic acid inhibition of nitrosamine formation in amine-nitrite systems are summarized in Table II. Under in vitro conditions ascorbic acid inhibited nitrosamine formation. It inhibited the toxic and carcinogenic effects attributable to in vivo nitrosamine formation with two exceptions. In one case adenoma induction by *N*-nitrosomorpholine and mononitrosopiperazine increased with added ascorbic acid (78). In another it inhibited in vivo synthesis of *N*-nitrosomorpholine in rats and consequent liver tumors, but enhanced forestomach papillomas and carcinoma (79).

Table II
Inhibition of In Vitro and In Vivo Nitrosamine Formation by Ascorbic Acid in the Presence of Nitrite

Amine (or Amide)	System Investigated	Effect of Ascorbic Acid	Reference
Aminopyrine	Hepatic necrosis, Mice	2 *M* excess of ascorbate prevented necrosis. Equimolar ascorbate gave incomplete protection.	80

continued on p 593

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Table II (continued)

Amine (or Amide)	System Investigated	Effect of Ascorbic Acid	Reference
Aminopyrine	Hepatotoxicity, Rats	Inhibits elevation of GPT, Ala. aminotransferase, nitrosodimethylamine serum levels.	81, 82
Aminopyrine	Carcinogenesis, Rats	Greater incidence of cancer in rats in absence of ascorbic acid.	83
Chlordiazepoxide	In vitro	Inhibits nitrosamine formation.	84
Chlordiazepoxide	Toxicity, Rats	Ascorbate protected against increases in liver and spleen wt.; decrease in adrenal wt., increases in GPT, LDH.	85
Dimethylamine	Acute tox., Rats	Hepatic necrosis inhibited. GOT, GPT elevation inhibited.	86
Dimethylamine	In vitro	Low conc. of ascorbate *enhanced* nitrosamine formation. High concentrations inhibited such formation. Formation and inhibition are a function of pH.	87
Ethylurea	Pregnant rats	Prevents carcinoma in offspring.	88
Morpholine	In vitro	Amount of ascorbate required depends on the presence or absence of O_2.	89
Morpholine	In vitro	Inhibits nitrosamine formation.	90
Morpholine	Nitrosomorpholine formation and tumorgenesis in rats	Inhibits nitrosomorpholine formation and liver tumors. *Enhanced* forestomach papillomas and carcinoma.	79
Piperazine	In vitro, human gastric juice	Inhibits nitrosamine formation.	91
Proline	Fried, nitrite-cured bacon	Formation of nitrosopyrrolidine from proline is inhibited.	92
Dimethylamine Pyrrolidine Proline	Model food systems	Inhibits nitrosamine formation.	93
Dimethylamine, Pyrrolidine, Piperidine	Meat-curing mixtures	Inhibits nitrosamine formation.	94
Morpholine Piperazine Methylurea	Adenoma, lung, in mice	Ascorbate decreased adenoma frequency in some cases. Increases adenoma frequency when given with the nitrosamines.	78
Morpholine, Oxytetracycline, Piperazine, N-Methylaniline, Methylurea, Dimethylamine	In vitro	Inhibits nitrosamine and nitrosamide formation.	95
Piperazine, Aminophenazone	In vitro, human gastric juice	Inhibits nitrosamine formation.	96
—	—	Review	97

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Table III
Effect of Phenols on Nitrosamine Formation In Vitro and In Vivo

Phenol	Amine	System	Effects of the Phenol	Reference
Phenol	—	In vitro	Phenol reacts with nitrite 10^4 X as rapidly as dimethylamine.	98
Gallic Acid	Morpholine	Adenoma induction, Mice	Adenoma strongly inhibited.	78
Gallic Acid	Diethylamine	In vitro	Inhibited or catalysed depending on pH and rel. conc. of reactants.	99
Gallic Acid	Diethylamine	In vitro	Catalyses nitrosamine formation (see text).	100
Gallic Acid	Piperazine Aminophenazone	In vitro, human gastric juice	Inhibited nitrosamine formation.	96
Propyl Gallate	Proline	Oil/water system	Inhibited nitrosamine formation.	93
Propyl Gallate	Proline	Fried, nitrite-treated bacon	Inhibited nitrosopyrrolidine formation.	92
Propyl Gallate	Dimethylamine	Hepatotoxicity, Rats	Inhibited liver pathol. GOT, GPT and ornithine carbamoyl transferase.	101
Tannic Acid	Dimethylamine	In vitro	Inhibited nitrosamine formation.	93
Tannin	Piperazine, Aminopherazone	In vitro, human gastric juice	Inhibited nitrosamine formation.	96
α-Tocopherol	Dimethylamine	In vitro	Inhibited nitrosamine formation.	93
α-Tocopherol	Dimethylamine	Cigarettes	Inhibited dimethylnitrosamine formation.	102, 103
	Proline	Bacon	Inhibited nitrosopyrrolidine formation.	
	Aminopyrine	Hepatotoxicity, Rats	Inhibited hepatotoxicity.	
t-Butyl-hydroquinone	Pyrrolidine	In vitro, Oil/Water	Inhibited nitrosamine formation.	93
t-Butyl-hydroquinone	Dimethylamine	Hepatotox., Rats	Inhibited hepatox. GOT, GPT, ornithine carbamoyl transferase.	101
2,6-Di-*t*-butyl-*p*-cresol (BHT)	Dimethylamine	Hepatotox., Rats	Relatively ineffective.	101
Butylated Hydroxyanisole (BHA)	Dimethylamine	Hepatotox., Rats	Relatively ineffective.	101
4-Methyl-catechol	Piperidine	In vitro	Catalysed nitrosamine formation.	104
Chlorogenic Acid	Piperidine	In vitro	Catalysed nitrosamine formation.	104
Vanillin	Dimethylamine	In vitro	Inhibited nitrosamine formation.	93
Hydroquinone	Dimethylamine	In vitro	Inhibited nitrosamine formation.	93
Thymol	Dimethylamine	In vitro	Inhibited nitrosamine formation.	93

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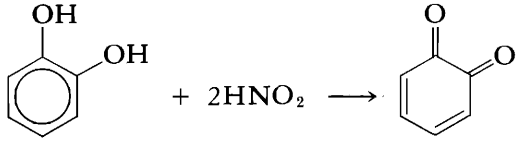
2. Effect of Phenols on Nitrosamine Formation

In Table III are summarized literature reports of the effect of phenols on the formation of nitrosamines in amine—nitrite systems. In most cases phenols inhibited nitrosamine formation, but sometimes their presence intensified nitrosamine production.

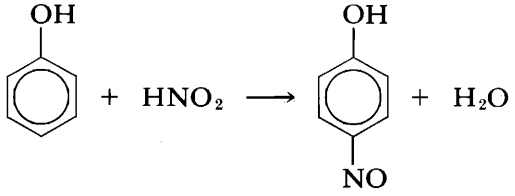
In systems containing nitrite, phenols and secondary amines several reactions compete:
—formation of quinones (eq 19)
—formation of *C*-nitrosophenols (eq 20)
—direct formation of *N*-nitrosamines
—phenol-catalysed formation of *N*-nitrosamines
—aerobic oxidation of *C*-nitrosophenols to noncatalytic nitrophenols (105).

Inhibition of nitrosamine formation by phenols occurs by reduction of nitrite to unreactive nitric oxide (104)



(19)

or by removal of nitrite via *C*-nitrosation (98):



(20)

Under some conditions phenols can catalyse nitrosamine formation. In the presence of excess nitrite 4-methylcatechol catalyses the nitrosation of dimethylamine and piperidine (104) and both *p*-cresol and *p*-nitroso-*o*-cresol catalyse the nitrosation of pyrrolidine (105).

Walker, Pignatelli and Castegnaro (100) investigated the effects of 0–65 m*M* gallic acid on the formation of nitrosodiethylamine from 75 m*M* nitrite and 500 m*M* diethylamine. Figure 1 and Table IV are adapted from their data obtained at pH 4.2 where maximum nitrosamine formation occured. In the absence of gallic acid 0.39 m*M* nitrosamine was formed. At the lowest level of gallic acid added, 12.5 m*M*, nitrosamine formation increased nine-fold. However, further increases in gallic acid concentration *decreased* nitrosamine formation linearly. Extrapolation of the linear relationship (Figure 1) indicates that addition of 144 m*M* gallic acid would result in complete inhibition of nitrosamine formation. This is equivalent to approximately 2 mol of gallic acid per mol of nitrite.

This result is consistent with that obtained by Davies and coworkers (105) who found that the rate of nitrosation of pyrrolidine by nitrite *increased* linearly with the concentration of *p*-nitroso-*o*-cresol. They demonstrated that the nitrosating species responsible for catalysis is an adduct of nitrite and a tautomer of the nitrosophenol. A similar mechanism probably operates with gallic acid where a large excess of nitrite would lead to catalysis by *C*-nitrosogallic acid.

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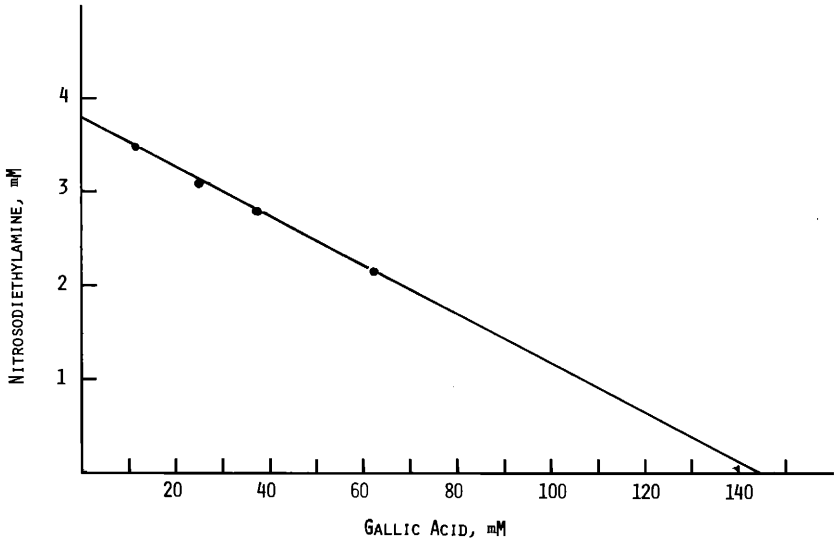

Figure 1. Effect of gallic acid on *N*-nitrosodiethylamine synthesis

Thus, whether a phenol inhibits or catalyses nitrosamine formation largely depends on the relative concentration of nitrite and phenol. Excess nitrite *C*-nitrosates the phenol and subsequently forms the catalytic species. A large excess of phenol removes nitrite so that it is unavailable for reaction with amine, either directly or catalytically. No catalysis should occur with phenols such as α-tocopherol, which are not *C*-nitrosated because the ring is fully substituted.

Table IV
Effect of Gallic Acid Concentration on Nitrosodiethylamine (NDEA) Synthesis from 75 m*M* Nitrite and 500 m*M* Diethylamine at pH 4.2

	m*M* NDEA	
m*M* Gallic Acid (g)	Found (N)	Calc. (N^a)
62.5	2.15	2.15
37.5	2.81	2.80
25.0	3.10	3.13
12.5	3.48	3.46
0.0	0.39	—

$N^a = -0.0263\ g + 3.79$, the least squares line of best fit.

3. *Inhibition by Sulfur Compounds*

Bisulfite reduces nitrite in two steps (106)—first to nitric oxide (eq 21) and then to nitrous oxide (eq 22). Sulfamate reduces nitrite to molecular nitrogen (107) (eq 23). These substances inhibit nitrosamine formation (Table V).

$$SO_2 + 2HNO_2 \rightarrow 2NO + H_2SO_4 \quad (21)$$

$$SO_2 + 2NO + H_2O \rightarrow N_2O + H_2SO_4 \quad (22)$$

$$NaNO_2 + H_2NSO_3H \rightarrow NaHSO_4 + N_2 + H_2O \quad (23)$$

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Table V
In Vitro Inhibition of Nitrosamine Synthesis by Sulfur Compounds

Sulfur Compound	Amine	System	Effect of Sulfur Compound	Reference
Sodium Bisulfite	Dimethylamine	Model food systems	Inhibits nitrosamine formation.	93
Ammonium Sulfamate	Dimethylamine, morpholine, piperazine	In vitro	Inhibits nitrosamine formation.	93
Sulfamic Acid	Piperazine Aminophenazone	Human gastric juice, in vitro	Inhibits nitrosamine formation.	108
Cysteine	Dimethylamine	In vitro	Inhibits nitrosamine formation.	93
Cysteine	Piperazine Aminophenazone	Human gastric juice, in vitro	Inhibits nitrosamine formation.	108
Glutathione	Dimethylamine	In vitro	Inhibits nitrosamine formation.	93
Glutathione	Piperazine	Human gastric juice, in vivo	Inhibits nitrosamine formation.	91
Methionine	Dimethylamine	In vitro	Inhibits nitrosamine formation.	93

The thiols cysteine and glutathione also inhibit nitrosamine formation. The thioether methionine is less effective. It is postulated that nitrite oxidizes methionine to the sulfoxide or sulfone and is in turn reduced to nitric oxide (93).

Thiols react with nitrite to form *S*-nitroso compounds (109). In the absence of nitrite preformed nitrosocysteine reacts with *N*-methylaniline, morpholine and pyrrolidine to form *N*-nitrosamines (105). In contrast catalysis of nitrosation by *p*-nitroso-*o*-cresol does not occur in the absence of nitrite. One would suggest transnitrosation of secondary amines by nitrosothiols, except that molecular oxygen appears to be necessary (105).

4. *Miscellaneous Inhibitors*

The ammonium ion reacts with nitrite to form molecular nitrogen (107) by the following sequence:

$$NH_4^+ \rightleftharpoons NH_3 + H^+ \tag{24}$$
$$2H^+ + NO_2^- \rightleftharpoons H_2ONO^+$$
$$H_2ONO^+ + NH_3 \rightarrow H_2O + NH_3NO^+ \rightarrow N_2 + H^+ + H_2O$$

Hydroxylamine reduces nitrite to nitrous oxide (107).

$$NH_2OH + HNO_2 \rightarrow N_2O + 2H_2O \tag{25}$$

Vitamin A reacts with nitrite in acid solution but not under neutral conditions (108). Presumably oxidation of the vitamin involves its double bonds.

Table VI summarizes literature indicating that urea, caffeine and ethanol are relatively ineffective inhibitors, but reduced nicotinamide adenine dinucleotide (NAD) is effective.

In alkaline solution even weak oxidants such as O_2 convert nitrite to nitrate (110).

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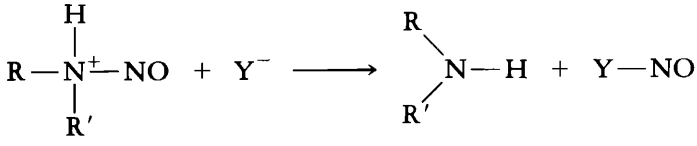
Table VI
Miscellaneous Nitrosamine Inhibitors

Inhibitor	Amine	System	Effect of Inhibitor	Reference
Urea	Dimethylamine	In vitro	Relatively ineffective in inhibiting.	93
Urea	Piperazine Morpholine	In vitro	Inhibitory effect decreases with time.	95
Reduced NAD	Dimethylamine Pyrrolidine Piperidine	In vitro	Inhibits nitrosamine formation.	93
Caffeine	Morpholine	Lung adenoma, Mice	Moderately inhibited.	78
Ethanol	Chlordiazepoxide	In vitro	Slight inhibitory effect.	99

D. DESTRUCTION OF *N*-NITROSO COMPOUNDS

N-Nitrosamines are stable compounds and are difficult to destroy once they are formed. They are stable in neutral and strong alkaline solutions in the absence of light (2, 5). Denitrosation (eq 2) occurs slowly in acid solution (1 to 5 *M*) and is catalysed by nucleophiles in the order of effectiveness $Y = I^- > SC(NH_2)_2 > SCN^- > Br^- > Cl^-$ (36, 111). To prevent reversal of the reaction a substance, which reacts irreversibly with YNO (eq 4) and more rapidly than amine, must be added. Relative efficiency of various nitrite traps in 5 *M* H_2SO_4 was found to be hydrazoic acid and hydrazine > sulfamic acid > aniline > hydroxylamine > urea (112). Ease of denitrosation varies in the order R,R′ = aryl > R = aryl,R′ = alkyl > R,R′ = alkyl (53, 113).



(2)

$$Y{-}NO + Z \rightarrow \text{unreactive products} \qquad (4)$$

Quantitative denitrosation of nitrosamines can also be achieved at room temperature using a solution of HBr (5 to 10%) in glacial acetic acid if water is excluded. Analysis of the nitrite released provides a measure of the original nitrosamine concentration (114).

When exposed to ultraviolet light nitrosamines decompose either to aldehydes, nitrogen and nitrous oxide or quantitatively to amine and nitrous acid depending on the wavelength used. The reaction is fastest in acid and faster in neutral than basic solutions. Apparatus and conditions for the photochemical destruction of nitrosamines in solution in the presence of a HNO_2 scavenger have been described (115, 116).

Nitrosamines can be reduced by zinc in acetic acid, sodium amalgam, tin in hydrochloric acid, lithium aluminum hydride and catalytic hydrogenation (4, 117). A reduction procedure for destruction of nitrosamines in alkaline solution with aluminum has been published (118). The corresponding hydrazines are usually formed (eq 26), but other products can be produced depending on the reducing agent and experimental conditions (119). Many hydrazines are carcinogenic, but about 100 times less so than the corresponding nitrosamines (2).

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$$R_2NNO \xrightarrow{\text{reduction}} R_2NHNH_2 \tag{26}$$

N-Nitrosamides are hydrolytically unstable. In aqueous acid they decompose by both denitrosation and deamination pathways (120, 121). Hydrogen bromide in carbon tetrachloride has been used for synthetic conversion of nitrosamide to amide (28).

At alkaline pH nitrosamides decompose to diazoalkanes (eq 27) (2, 4, 17, 23, 122).

$$\begin{array}{ccccccc} RCH_2N{-}Z & + & H_2O & \xrightarrow{OH^-} & RCH_2NHNO & + & ZOH \\ | & & & & \downarrow & & \\ NO & & & & & & \\ RCH{=}N{=}N & + & H_2O & \longleftarrow & RCH_2N{=}NOH & & \end{array} \tag{27}$$

The rate of decomposition increases with increasing pH and varies with amide structure (2). At pH 9 the order of stability was found to be nitrosourea < nitrosamide < nitrosourethane < nitrososulfonamide < nitrosoguanidine (2).

In the solid state *N*-nitrosamides sometimes decompose explosively (2). Nitrosourea samples should be frozen, not merely refrigerated (123). Nitrososulfonamides are stable only if kept cool and dry (124).

V. PRACTICAL CONSIDERATIONS

The basic problem in minimizing nitrosamine formation is prevention of the reaction between nitrosating species and amines. The nitrosating species are ubiquitous in the environment. Roughly 50 ppb of nitrous oxide and nitrogen dioxide are present in the atmosphere of our cities (125). In soils, streams and rivers, organisms of the genus nitrosomonas oxidize ammonia to nitrite (126). Some foods have a high nitrate content. These can be reduced in vivo after ingestion of the food. Nitrites are added to some foods to prevent growth of botulinus organisms. Nitrites are also widely used as metal corrosion inhibitors.

Removal of nitrosating species from our environment is a sociological task not amenable to immediate solution. In certain cases, steps can be taken to minimize such contamination. Already industry is moving to replace nitrite as a corrosion inhibitor in some applications and reduce its use as an additive in meat.

A more likely general approach to preventing the reaction of nitrosating species and amines is the inclusion of appropriate scavengers into raw materials and finished products. For example, in the production of organic raw materials, where a nitration step occurs in the synthesis, a small amount of SO_2 can be added before solvent removal in the final step to destroy any traces of nitrite. The excess SO_2 would be eliminated by the drying process. Alternatively, a nontoxic nitrite scavenger, such as ascorbic acid, can be incorporated into the raw material or finished product.

Scavengers which reduce nitrosating species can be classified into those which convert nitrite to NO and those which reduce it further. Most inhibitors described here reduce nitrite to NO. In the presence of molecular oxygen NO is readily oxidized to N_2O_4 which is a good nitrosating agent. Thus, a sufficient excess of these inhibitors should be incorporated to scavenge oxidized NO. Sulfamates and sulfites reduce the nitrites to

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N_2 and N_2O, respectively, which are not reoxidized by molecular oxygen. These inhibitors are not as innocuous as some of the weaker reducing agents, however.

Cosmetics are frequently in the form of emulsions. Mirvish has shown that lipids readily extract nitrosating species from water. Under these conditions, nitrosation reactions are very fast. Since amines are also more soluble in the oil phase of emulsions, it is appropriate to incorporate oil soluble inhibitors, such as ascorbyl palmitate and α-tocopherol, into such products for maximum inhibition of nitrosamine formation.

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Solvent	$K \times 10^5$
Gas Phase	382
CCl_4	8.05
$CHCl_3$	5.53
C_6H_6	2.23

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Editor's Note:

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Editor

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