AMINE OXIDES

1. Introduction

Amine oxides, known as *N*-oxides of tertiary amines, are classified as aromatic or aliphatic, depending on whether the nitrogen is part of an aromatic ring system or not. This structural difference accounts for the difference in chemical and physical properties between the two types.

The higher aliphatic amine oxides are commercially important because of their surfactant properties and are used extensively in detergents. Amine oxides that have surface-acting properties can be further categorized as nonionic surfactants; however, because under acidic conditions they become protonated and show cationic properties, they have also been called cationic surfactants. Typical commercial amine oxides include the types shown in Table 1.

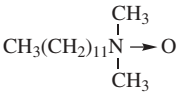
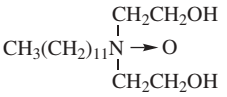
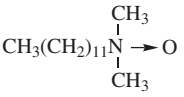
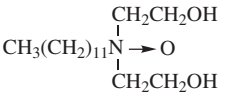
Aromatic amine oxides, produced on a much smaller scale and having some pharmaceutical importance, do not demonstrate the surface-acting properties that the aliphatic amine oxides do.

2. Physical Properties

The physical properties of amine oxides are attributed to the semipolar or coordinate bond between the oxygen and nitrogen atoms with high electron density residing on oxygen.

$$(CH_3)_3\overset{+}{N}-O^-$$

Table 1. **Commercial Amine Oxides**

Name	Molecular formula	CAS Registry Number	Structural formula
dimethyldodecylamine oxide	$C_{14}H_{31}NO$	[1643-20-5]	
dihydroxyethyldodecylamine oxide	$C_{16}H_{35}NO_3$	[2530-44-1]	
dimethyltetradecylamidopropyl amine oxide	$C_{20}H_{40}NO_2$		
N-dodecylmorpholine *N*-oxide	$C_{16}H_{33}NO_2$	[2530-46-3]	
1-hydroxyethyl-2-octa-decyl imidazoline oxide	$C_{23}H_{46}N_2O_2$		
N,N′,N′-hydroxy ethyl-*N*-octadecyl-1,3-propylenediamine oxide	$C_{27}H_{58}N_2O_5$		

The N–O bond distances, found to be 0.133 to 0.139 nm for trimethylamine oxide (1), are somewhat shorter than the single N–C bond distance of 0.147 nm in methylamine. The N–C bond distance of 0.154 nm in trimethylamine oxide approaches that of the C–C bond. This is in agreement with the respective absorptions in the infrared region; valence vibrations of N–O bonds of aliphatic amine oxides are found between 970 – 920 cm^{-1} (2).

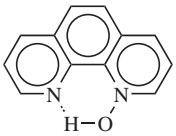
A dipole moment of 1.46×10^{-29} C·m (4.38 D) for the nitrogen–oxygen bond is larger than the moments of other semipolar bonds (3). The spatial arrangement around nitrogen in amine oxides is tetrahedral as in quaternary ammonium salts. Tetrahedral configuration was demonstrated by Meisenheimer, who separated *N*-ethyl-*N*-methylaniline *N*-oxide [825-19-4] into its optical isomers (4), and later confirmed by electron diffraction studies (1).

For the aromatic amine oxides, the trigonal nitrogen forces the oxygen into the same plane as the aromatic ring and permits resonance structures involving the nonbonded electrons on oxygen. This is largely responsible for the distinction between aliphatic and aromatic amine oxides and accounts for the added stability and special properties of aromatic amine oxides. Although amine oxides are

Table 2. **pK_a Values of Protonated Amines and Their *N*-Oxides**

Parent amine	Amine Registry Number	pK_a amine	Oxide molecular formula	Oxide Registry Number	pK_a *N*-oxide
$(CH_3)_3N$	[75-50-3]	9.74	C_3H_6NO	[1184-78-7]	4.65
$(C_2H_5)_3N$	[121-44-8]	10.76	$C_6H_{15}NO$	[2687-45-8]	5.13
$C_6H_5N(CH_3)_2$	[121-69-7]	5.06	$C_8H_{11}NO$	[874-52-2]	4.21
$C_6H_5N(C_2H_5)_2$	[91-66-7]	6.56	$C_{10}H_{15}NO$	[826-42-6]	4.53
o-$CH_3C_6H_4N(CH_3)_2$	[609-72-3]	5.86	$C_9H_{13}NO$	[6852-47-7]	4.78
p-$CH_3C_6H_4N(CH_3)_2$	[99-97-8]	5.50	$C_9H_{13}NO$	[825-85-4]	4.32

weaker bases than the amines from which they are derived, there is a base leveling effect in the oxides that is not found in the amines. This leveling effect is probably caused by the decreased effect of substituents which are further removed from the basic oxygen center (Table 2). Aromatic amine oxides are generally weaker bases than aliphatic amine oxides. However there are exceptions, eg, 1,10-phenanthroline monoxide [1891-19-6] is a stronger base than most aliphatic amine oxides because of stabilization of the conjugate acid through intramolecular hydrogen bonding (5).



Amine oxides show either nonionic or cationic behavior in aqueous solution depending on pH. In acid solution the cationic form (R_3N^+OH) is observed (2) while in neutral and alkaline solution the nonionic form predominates as the hydrate $R_3NO{\cdot}H_2O$. The formation of an ionic species in the acidic pH range stabilizes the form generated by the most studied commercial amine oxide, dimethyldodecylamine oxide (6).

Aliphatic amine oxides behave as typical surfactants in aqueous solutions. Below the critical micelle concentration (CMC), dimethyldodecylamine oxide exists as single molecules. Above this concentration micellar (spherical) aggregates predominate in solution. Aliphatic amine oxides are similar to other typical nonionic surfactants in that their CMC decreases with increasing temperature.

Temperature, °C	CMC, mol/L
1	0.0028
27	0.0021
40	0.0018
50	0.0017

Wetting times of *N,N*-dimethyl-*n*-alkylamine oxides as a function of the alkyl chain length show a minimum with dimethyldodecylamine oxide

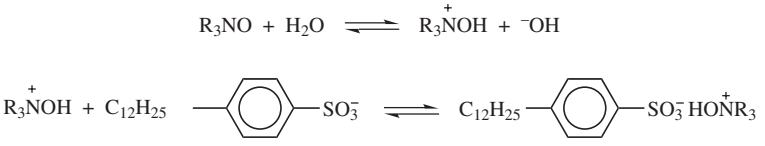
Table 3. **Surfactant Properties of *N,N*-Dimethylalkylamine Oxides**

Amine oxide	CAS Registry Number	Alkyl chain length	Wetting time, s	Foam height[a], mm
dimethyloctylamine oxide	[2605-78-9]	8	900	
dimethyldecylamine oxide	[2605-79-0]	10	150	138
dimethyldodecylamine oxide	[1643-20-5]	12	37	175
dimethyltetradecylamine oxide	[3332-27-2]	14	225	185
dimethylhexadecylamine oxide	[7128-91-8]	16	900	30
dimethyloctadecylamine oxide	[2571-88-2]	18		17

[a] Concentration = 3 g/L at 20°C.

(Table 3). Foam generation of dimethyl-*n*-alkylamine oxides solutions show a maximum when the alkyl group contains 14 carbons.

In the presence of an anionic surfactant such as sodium dodecyl-benzenesulfonate [25155-30-0] any protonated amine salt present forms an insoluble salt (4). Salt formation results in an increase in the pH of the solution.



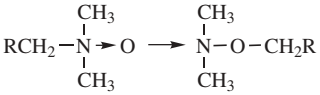
The effect of added inorganic salts on the micellar properties of the nonionic and cationic forms of dimethyldodecylamine oxide has been determined (2).

Aliphatic amine oxides form charge-transfer complexes with iodine (7) because of the asymmetric electron distribution in the N–O bond with oxygen being the electron donor. Complexes of aliphatic amine oxides are stronger than those of aromatic ones (8). Amine oxides form hydrogen bonds with strong acids (9) and weak acids such as phenols (10). Trimethylamine oxide dihydrate contains strongly bound tricoordinated water and the hydrate water forms with the oxygen of the amine oxide is a structure similar to the water–fluoride cluster in tetraethylammonium fluoride dihydrate [63123-01-3] (11). Aliphatic amine oxides form complexes with metals or metallic salts (12).

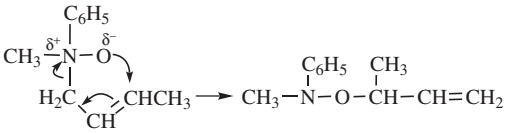
3. Chemical Properties

3.1. Decomposition. Most amine oxides undergo thermal decomposition between 90 and 200°C. Aromatic amine oxides generally decompose at higher temperatures than aliphatic amine oxides and yield the parent amine.

Rearrangement. Aliphatic amine oxides without an aliphatic hydrogen atom β to the nitrogen undergo Meisenheimer's rearrangement when heated to give trisubstituted hydroxylamines.

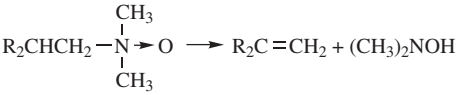


Allyl or benzyl groups on the nitrogen facilitate the process. The rearrangement appears to be intramolecular (13), proceeding by a cyclic mechanism as in the case of *N*-2-butenyl-*N*-methylaniline oxide giving *N*-methyl-*O*-1-methylallyl-*N*-phenyl-hydroxylamine.

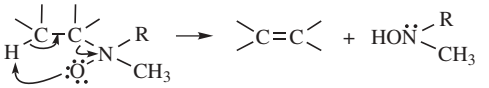


The rate of rearrangement increases as the basicity of the parent tertiary amine decreases (14). Strong support for a free-radical mechanism has been demonstrated (15,16).

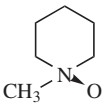
Elimination. Aliphatic amine oxides having an aliphatic hydrogen β to the nitrogen form olefins and dialkyl hydroxylamines when heated. This reaction is known as the Cope elimination (17)



and proceeds through a planer five-center intermolecular mechanism (18,19):



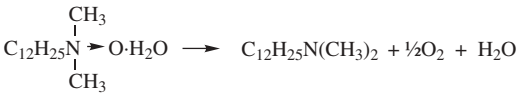
N-methylpiperidine oxide [17206-00-7] does not undergo the reaction because of its inability to achieve the highly strained transition configuration, whereas the



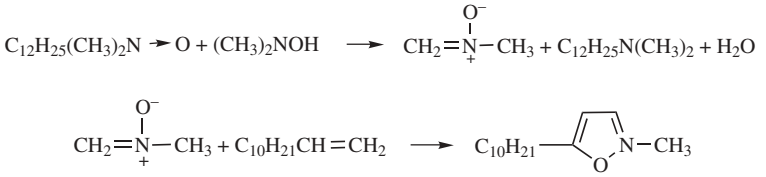
corresponding seven- and eight-membered ring compounds yield respectively 57% and 78% of the elimination product (18). When more than one possibility for elimination exists, it occurs predominantly toward the alkyl group having the most β-hydrogens, or one having an electron withdrawing group attached to the β-carbon (20). Stereoselectivity for this elimination reaction is predominantly cis (21) and allows for the preparation of certain olefins that could not otherwise be made using other elimination reactions that follow either the Hoffmann rule or the Saytzeff rule (19).

In the pyrolysis of pure amine oxides, temperature has a significant effect on the ratio of products obtained (22). The principal reaction during thermal

decomposition of *N,N*-dimethyllaurylamine oxide [1643-20-5] at 80–100°C is deoxygenation to *N,N*-dimethyllaurylamine [112-18-5] (lauryl = dodecyl).



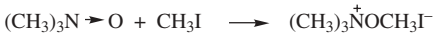
However, when the temperature is increased to 120°C, the principal reaction is the elimination to olefin. The thermal decomposition of dimethyldodecylamine oxide at 125°C in a sealed system, as opposed to a vacuum used by Cope and others, produces 2-methyl-5-decylisoxazolidine, dimethyldodecylamine, and olefin (23). The amine oxide oxidizes *N,N*-dialkylhydroxylamine to the nitrone during the pyrolysis and is reduced to a tertiary amine in the process.



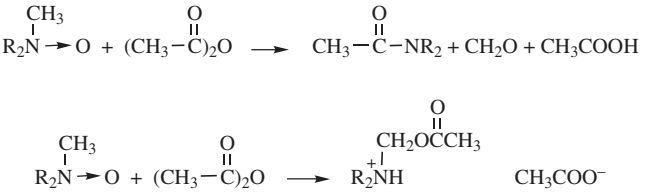
Metal Catalysis. Aqueous solutions of amine oxides are unstable in the presence of mild steel and thermal decomposition to secondary amines and aldehydes under acidic conditions occurs (24,25). The reaction proceeds by a free-radical mechanism (26). The decomposition is also catalyzed by V(III) and Cu(I).

3.2. Reduction. Just as aromatic amine oxides are resistant to the foregoing decomposition reactions, they are more resistant than aliphatic amine oxides to reduction. Aliphatic amine oxides are readily reduced to tertiary amines by sulfurous acid at room temperature; in contrast, few aromatic amine oxides can be reduced under these conditions. The aliphatic amine oxides can also be reduced by catalytic hydrogenation (27), with zinc in acid, or with stannous chloride (28). For the aromatic amine oxides, catalytic hydrogenation with Raney nickel is a fairly general means of deoxygenation (29). Iron in acetic acid (30), phosphorus trichloride (31), and titanium trichloride (32) are also widely used systems for deoxygenation of aromatic amine oxides.

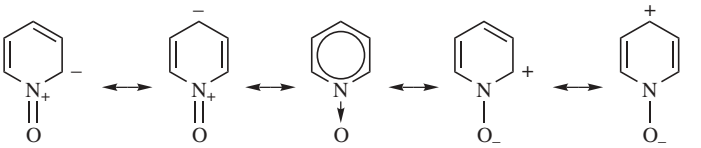
3.3. Alkylation. Alkylating agents such as dialkyl sulfates and alkyl halides react with aliphatic amine oxides to form trialkylalkoxyammonium quaternaries. For example (33), methyl iodide reacts with trimethylamine oxide to form trimethylmethoxyammonium iodide



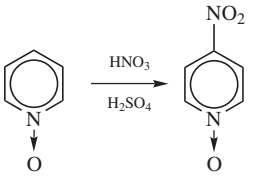
3.4. Acylation. Aliphatic amine oxides react with acylating agents such as acetic anhydride and acetyl chloride to form either *N,N*-dialkylamides and aldehyde (34), the Polonovski reaction, or an ester, depending upon the polarity of the solvent used (35,36). Along with a polar mechanism (37), a metal-complex-induced mechanism involving a free-radical intermediate has been proposed.



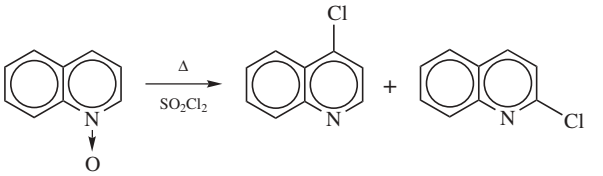
3.5. Substitution Reactions. Aromatic heterocyclic *N*-oxides undergo both electrophilic and nucleophilic substitution because the dipolar *N*-oxide group is both an electron donor and an electron acceptor, giving rise to the resonance structures:



Pyridine oxide [694-59-7] is converted to 4-nitropyridine oxide in 80–90% yield on heating with concentrated sulfuric acid and fuming nitric acid at 100°C (38).



Nucleophilic substitution occurs in positions α and γ to the *N*-oxide group. In nearly all these reactions deoxygenation occurs giving the substituted heterocyclic amine.



Heterocyclic *N*-oxides can react at the oxygen atom with a variety of electrophilic reagents to give adducts which, according to the reagent and reaction conditions, may be stable or react further (39). Heterocyclic *N*-oxides are reduced by reaction of nucleophiles at the *N*-oxide oxygen.

4. Manufacturing and Processing

Linear alpha-olefins are the source of the largest volume of aliphatic amine oxides. The olefin reacts with hydrogen bromide in the presence of peroxide catalyst, to yield primary alkyl bromide, which then reacts with dimethylamine to yield the corresponding alkyldimethylamine. Fatty alcohols and fatty acids are also used to produce amine oxides (Fig. 1).

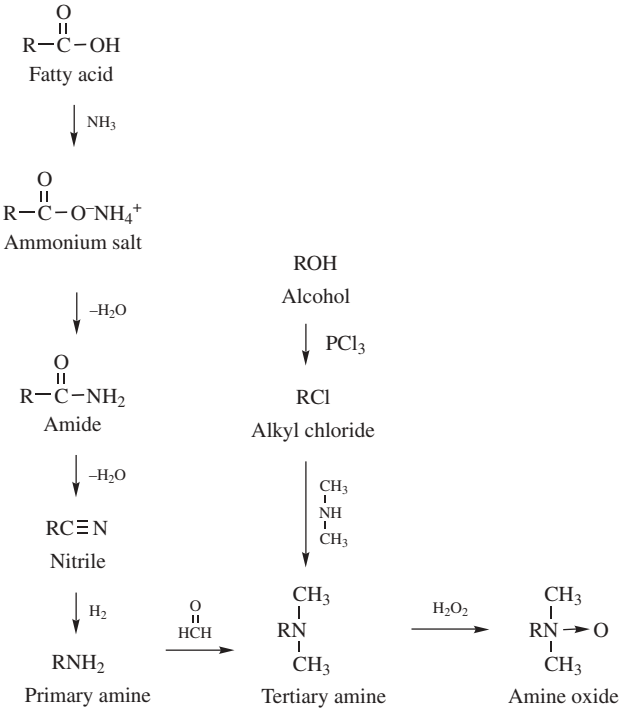


Fig. 1. Routes to tertiary amines from fatty acids or fatty alcohols.

Amine oxides used in industry are prepared by oxidation of tertiary amines with hydrogen peroxide solution using either water or water and alcohol solution as a solvent. A typical industrial formulation is as follows:

N,*N*-dimethyltetradecylamine [112-75-4]	1475 kg
hydrogen peroxide (35%)	640 kg
EDTA	1.5 kg
water	3225 kg

A process for preparation of high quality amine oxides using secondary and tertiary amines with hydrogen peroxide has been reported (40).

EDTA (ethylenediaminetetraacetic acid, [60-00-4]) chelates any trace metals that would otherwise decompose the hydrogen peroxide [7722-84-1]. The amine is preheated to 55–65°C and the hydrogen peroxide is added over one hour with agitation; the temperature is maintained between 60–70°C. The reaction is exothermic and cooling must be applied to maintain the temperature below 70°C. After all the peroxide has been added, the temperature of the reaction mixture is raised to 75°C and held there from three to four hours until the unreacted amine is less than 2.0%. The solution is cooled and the unreacted hydrogen peroxide can be destroyed by addition of a stoichiometric amount of sodium bisulfite. This may not be desirable if a low colored product is desired, in which case residual amounts of hydrogen peroxide enhance long-term color stability.

Primary and secondary amines are oxidized to the respective hydroxyl amines, and further oxidation to the nitro compound occurs in the case of primary amines.

$$RNH_2 + H_2O_2 \longrightarrow RNHOH + H_2O$$

$$RNHOH + 2\ H_2O_2 \longrightarrow RNO_2 + 3\ H_2O$$

Owing to the lower basicity of the parent amines, aromatic amine oxides cannot be formed directly by hydrogen peroxide oxidation. These compounds may be obtained by oxidation of the corresponding amine with a peracid; perbenzoic, monoperphthalic, and monopermaleic acids have been employed.

5. Economic Aspects

Demand for amines in the United States is expected to grow to $\$\ 1.9 \times 10^9$ in 2004. Specialty amines, the group in which amine oxides are categorized, will lead the demand because of strong performance characteristics. A major use for amine oxides is as surfactants in a variety of soaps, detergents and personal care products, Multifunctionality and mildness of ingredients are reasons for the demand (41).

Global demand for cationic and amphoteric surfactants is projected to grow at a rate of 5.4% to 1.97×10^6 t for a value of $\$3.26 \times 10^9$ in 2005. Europe is the largest consumer of cationic surfactants (about 36% of total), the United States is the second largest at approximately 27% of total. Asia (25%), South America (8%), and Mexico (4%) follow (42).

6. Specifications

Industrial specifications for aliphatic tertiary amine oxides generally require an amine oxide content of 20–50%. These products may contain as much as 5% unreacted amine, although normally less than 2% is present. Residual hydrogen peroxide content is usually less than 0.5%. The most common solvent systems employed are water and aqueous isopropyl alcohol, although some amine oxides are available in nonpolar solvents. Specifications for individual products are available from the producers.

7. Analytical Methods

Analytical methods include thin-layer chromatography (43), gas chromatography (44), and specific methods for determining amine oxides in detergents (45) and foods (46). Nuclear magnetic resonance (47–49) and mass spectrometry (50) have also been used. A frequently used procedure for industrial amine oxides (51) involves titration with hydrochloric acid before and after conversion of the amine to the quaternary ammonium salt by reaction with methyl iodide. A

simple, rapid quality control procedure has been developed for the determination of amine oxide and unreacted tertiary amine (52).

8. Health and Safety Factors

Aliphatic amine oxides such as alkyldimethylamine oxides and alkylbis (2-hydroxylethyl)amine oxides range from practically nontoxic to slightly toxic (53). Reported LD_{50}s range from 1.77 g/kg to 6.50 g/kg. The commercial concentrated products are primary skin and eye irritants. At concentrations of 2%, these products may be considered as nonirritating to the skin or eye.

Test	Result
bacterial toxicity, Bringmann-Kuhn	$EC_{10} = 80$ ppm
algae toxicity, growth inhibition 72 h	$EC_{50} = 0.66$ ppm NOEC = 0.25 ppm
daphnia toxicity, acute 48 h	$EC_{50} = 9.5$ ppm NOEC = 4.6 ppm
fish toxicity (zebra fish), acute 96 h	$LC_{50} = 42.0$ ppm NOEC = 33.5 ppm
biodegradation, Closed Bottle, 28 d	readily = 93%

Among the aromatics, it was found that 4-nitroquinoline *N*-oxide [56-57-5] is a powerful carcinogen producing malignant tumors when painted on the skin of mice (54). It was further established that the 2-methyl, 2-ethyl, and 6-chloro derivatives of 4-nitroquinoline oxide are also carcinogens (55).

9. Uses

9.1. Detergents. Aliphatic amine oxides find wide use in the detergent and personal care industries. A comparison of detergents and admixtures with other surfactants in a light duty liquid detergent revealed that the most effective performance came from a blend of ammonium ether sulfate and an alkyldimethylamine oxide where the alkyl group contained 14 carbon atoms (56). Amine oxides improve the stability and amount of foam generated in light liquid detergents and because of this they are used extensively in shampoos, dishwashing liquids, and liquid soaps. A high foaming, grease cutting, light duty liquid detergent has been described (57). Other uses for amine oxides are found in paper and textile production, electroplating, oil and petroleum, plastics and rubber, metal and mining, polymerization, and photographic industries.

Amine oxides compete with alkanolamides as foam boosters in the detergent and personal care industry. Although amine oxides are more expensive than alkanolamides they have the advantage of being milder to the skin and eyes and are more effective surfactants, so that on a cost performance basis they are a better buy than alkanolamides in many cases (see ALKANOLAMINES FROM OLEFIN OXIDES AND AMMONIA). As well as being excellent foam stabilizers in

liquid detergents, alkyl amine oxides also increase viscosity, emolliency, detergency, and antistatic properties in many detergent and cosmetic formulas (58).

The surface active properties of aliphatic amine oxides were discovered in the 1930s and the wetting, detergent, emulsion, and foam stabilizing properties were published shortly thereafter (59). However, the use of amine oxides was not significant until Procter and Gamble started using them in household products around 1960 (60–63).

9.2. Organic Reagents. Amine oxides are used in synthetic organic chemistry in the preparation of olefins, or phase-transfer catalysts (64), in alkoxylation reactions (65), in polymerization, and as oxidizing agents (66,67).

9.3. Textiles. In the area of textile and synthetic fiber processing, amine oxides have been used as dyeing auxiliaries as well as wetting agents (68,69), as antistatic agents (qv) (70–72), and as bleaching agents (73,74).

Selected amine oxides in textile technology as dye receptors and for aesthetic purposes has been described (75).

9.4. Pharmaceutical Uses. The biochemistry of heteroaromatic amine oxides has been extensively explored and has led to the synthesis of many biochemically and pharmaceutically important compounds (76). Aromatic amine oxides are useful as analgesics, antihistamines, antitussives, diuretics, tranquilizers, and drug potentiators. In many cases, the *N*-oxides of pharmacologically active tertiary amines have added benefits, ranging from lower toxicity and better solubility to enhanced therapeutic behavior. The biological activity of these materials has led to patented uses as bactericides, fungicides, insecticides, nematocides, filaricides, amoebicides, anthelmintics, antiparasitics, and disinfectants. The pharmacology and biochemistry of amine oxides has been reviewed (77). Earlier references covering these and other applications were reported in a survey on amine oxides by the Du Pont Company (78).

9.5. Other. Other uses of aliphatic amine oxides are as corrosion inhibitors for nonferrous metals (79) and in aqueous systems (80), as fuel oil antiicing and pourpoint additives that also depress combustion chamber fouling (81–83), in the plastic industry as molecular weight regulators in ethylene and propylene copolymerization (84), in photography to prevent waterspots in drying photographic films (85), as complexing developers and dyes (86), and as asphalt emulsifiers (87).

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